Renin-angiotensin-aldosterone inhibitors in the reduction of portal pressure: a systematic review and meta-analysis

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CRD summary
This review evaluated the effectiveness and safety of renin-angiotension-aldosterone inhibitors in hepatic venous pressure gradient reduction, concluding that angiotensin receptor blockers/angiotensin-converting enzyme inhibitors reduced portal pressure in patients with Child Pugh A cirrhosis without causing adverse events. Given the poor quality of included trials, unclear reporting and substantial variation in the review, the authors’ conclusions should be treated with caution.

Authors' objectives
To evaluate the effectiveness and safety of renin-angiotension-aldosterone inhibitors in hepatic venous pressure gradient reduction.

Searching
PubMed was searched up to August 2009 for studies published in English. Search terms were reported. Google Scholar plus the bibliographies of reviews and included papers were searched for further studies.

Study selection
Eligible studies were controlled clinical trials in which patients (aged at least 18 years) with cirrhosis and clinically significant portal hypertension were treated with angiotensin receptor blockers, angiotensin-converting enzyme inhibitors or aldosterone antagonists. Clinically significant portal hypertension was defined as documented varices or hepatic venous pressure gradient of at least 10mmHg at trial inception. Eligible trials had to report hepatic venous pressure gradients at the start and end of the trial. Trials were not eligible if patients had non-cirrhotic portal hypertension or a surgical shunt or a transjugular intrahepatic portosystemic shunt was used.

The primary outcome was change in hepatic venous pressure gradient. Secondary outcomes were frequencies of adverse events and withdrawals.

In included trials, the angiotensin receptor blocker/angiotensin-converting enzyme inhibitor treatments assessed were captopril, enalapril, losartan, candesartan and irbesartan; the aldosterone antagonist assessed was spironolactone. Time between hepatic venous pressure gradient measurements (start and end of trial) ranged from one week to 52 weeks. Treatment dosages were also reported. Almost all included patients had varcies; some had previous variceal bleeds and ascites (where reported). Control treatment included placebo, no treatment and propranolol. Patient demographic details were reported, but not by trial and not so as to allow balance between treatment and control group to be checked.

One reviewer performed initial screening of abstracts. Full-text of papers not excluded at this stage were reviewed by two reviewers independently; disagreements were resolved by discussion and arbitration with a third reviewer.

Assessment of study quality
Trial quality was assessed using the Jadad scale (score between 0 and 5 points based on randomisation, allocation concealment, double blinding, and withdrawals and drop-outs), as well as whether intention-to-treat analysis was used.

Two reviewers performed the quality assessment. Disagreements were resolved by discussion and arbitration with a third reviewer.

Data extraction
Authors of included trials were contacted for individual patient data (IPD). Data required to calculate the mean change in hepatic venous pressure gradient (mean differences or percent change in hepatic venous pressure gradient between treatment and control groups) were extracted from the IPD; otherwise the IPD were extracted from graphical output within the trial paper or imputed using p-values or t-statistics. Mean differences were calculated with 95% confidence
intervals (CIs). Adverse events and withdrawals were also extracted.

The number of reviewers that extracted data was not reported.

**Methods of synthesis**

Due to differences in the treatments, trials that evaluated angiotensin receptor blockers/angiotensin-converting enzyme inhibitors were analysed separately from those that evaluated aldosterone antagonists. Trial mean differences (in hepatic venous pressure gradients between treatment and control arms) were weighted according to the inverse of their variance, and pooled using random-effects meta-analysis models to produce weighted mean differences (WMDs) with 95% confidence intervals (CIs). Trials were pooled by the comparator used. Heterogeneity was assessed using the $\Gamma^2$ and $\chi^2$ statistics.

Pre-specified subgroup analyses were performed, assessing the contribution to statistical heterogeneity of the following factors: drug class, patient weight (whether body mass index was over 25), severity of liver dysfunction, whether liver disease was due to alcohol, and whether mean arterial pressure dropped more than 10% during the trial.

Sensitivity analyses were performed to assess the effect of trial quality (with Jadad score over 3 taken to indicate high quality trials) and model type (random-effects or fixed-effect) on reported outcomes.

**Results of the review**

Eighteen trials were included in the review (n=678 patients). Eleven were randomised controlled trials and seven were controlled trials. Eight trials received a Jadad score of 4 or 5 out of 5 points; the rest scored of 2 or less. Four trials were double blinded. Eight trials had adequate reporting of allocation concealment.

**Angiotensin receptor blockers/angiotensin-converting enzyme inhibitors:** Pooled results based on six trials (n=238 patients, including one trial with available IPD) indicated statistically significantly reduced portal pressure in patients who received the treatment compared with placebo or no treatment (WMD -3.81 mmHg, 95% CI -5.85 to -1.78; $\Gamma^2=95.7\%$). Pooled results of four trials (three trials with available IPD) indicated no significant difference in portal pressure in patients who received angiotensin receptor blockers/angiotensin-converting enzyme inhibitors compared with beta-blockers ($\Gamma^2=53.3\%$); however, for the three trials with IPD, the differences were statistically significant (WMD 1.70 mmHg, 95% CI 0.45 to 2.95; $\Gamma^2=0\%$), favouring beta-blockers over angiotensin receptor blockers/angiotensin-converting enzyme inhibitors.

**Aldosterone antagonists:** Two trials that compared the aldosterone antagonist spironolactone with placebo were pooled to produce a borderline statistically significant result favouring spironolactone (WMD -1.3 mmHg, 95% CI -2.6 to 0.04). Results were not pooled for aldosterone antagonists compared with other therapies due to substantial clinical variation in the control groups. Results for individual trials were reported.

**Sensitivity analyses:** Two trials that compared angiotensin receptor blockers/angiotensin-converting enzyme inhibitors with either placebo or no treatment, and that had a Jadad score over 3, were pooled. No statistical heterogeneity was identified ($\Gamma^2=0\%$); The results were still statistically significant and in favour of angiotensin receptor blockers/angiotensin-converting enzyme inhibitors. The results were not significantly altered by using fixed-effect rather than random-effects models.

Adverse effects were reported.

**Authors' conclusions**

Angiotensin receptor blockers/angiotensin-converting enzyme inhibitors reduced portal pressure in patients with Child Pugh A cirrhosis without causing adverse events.

**CRD commentary**

This review addressed a clear research question using clear study selection criteria. Only studies published in English were included, so there was a high risk of language bias. No attempts were made to identify unpublished studies, so there was a high risk of publication bias. Measures (independent duplicate processes) to minimise the potential for reviewer error and/or bias were reported for the study selection and quality stages of the review, but the number of reviewers involved in the data extraction was not reported.
A quality assessment was performed, which showed that most included trials were of low quality (2 or fewer points out of 5), so the risk of bias involved in using such trials could not be ruled out. Few trial population details were reported, so the degree of clinical heterogeneity between trials could not be assessed, although there was high clinical heterogeneity in the treatments used. Significant statistical heterogeneity for a number of trial outcomes suggested that quantitative pooling of these results may not have been appropriate, although sensitivity analyses were performed and showed that trial quality and model type did not significantly alter the results.

Given the poor quality of included trials, unclear reporting in the review and substantial heterogeneity, the authors’ conclusions should be treated with caution.

Implications of the review for practice and research

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

Research: The authors stated that further studies should determine whether renin-angiotension-aldosterone inhibitors have the potential to be an alternative or adjunct to beta-blockers; a further study should be conducted in patients with non-alcoholic steatohepatitis, cirrhosis and obesity. The authors recommended that the effectiveness of the renin-angiotensin-aldosterone inhibitors should be evaluated as a second-line therapy in patients with compensated cirrhosis who cannot receive beta-blockers. The authors also stated that further studies with clinical endpoints are needed to determine the clinical potential of angiotensin receptor blockers and angiotensin converting enzyme inhibitors with or without a low dose mineralocorticoid in patients with Child Pugh A cirrhosis.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.