Blood pressure reduction and renin-angiotensin system inhibition for prevention of congestive heart failure: a meta-analysis


CRD summary
This review concluded that a reduction in blood pressure from angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and calcium-channel blockers was beneficial. ACEIs and ARBs had the greatest benefit in patients with hypertension or high cardiovascular risk. The authors' conclusions should be interpreted with caution given the lack of study details and potential for bias in the review.

Authors' objectives
To assess blood pressure-related and other unrelated effects of renin-angiotensin system inhibiting drugs for the prevention of congestive heart failure in patients with hypertension or high cardiovascular risks.

Searching
MEDLINE and The Cochrane Library were searched for publications up to September 2008. The review was restricted to studies published in peer-reviewed journals indexed on MEDLINE. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) or calcium-channel blockers (CCBs) with old antihypertensive drugs (diuretics and β-blockers) or placebo were eligible for inclusion. Studies had to include 100 or more patients with hypertension or high cardiovascular risk. Patients with overt heart failure were excluded at study entry. Eligible studies were required to measure systolic blood pressure at baseline and follow-up; median or mean follow-up of at least two years was required. The outcome of interest was congestive heart failure.

Most included studies were of patients with hypertension and also included patients with coronary artery disease, diabetes mellitus, abnormal glucose tolerance or high cardiovascular risk. Some studies included patients with one additional cardiovascular risk factor.

The authors did not state how many reviewers screened the studies for inclusion.

Assessment of study quality
Validity was assessed in accordance with the Jadad scale of criteria on randomisation, blinding and withdrawals. Studies were assigned a score between 0 and a maximum of 5. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data on the incidence of congestive heart failure on an intention-to-treat basis to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Where treatment arms had no events, corrections were made using values of various sizes (such as $10^{-8}$, 0.01). Data were extracted on blood pressure at follow-up for treatment and control groups, and used to calculate the mean difference between the groups. Discrepancies were resolved by consensus.

Methods of synthesis
Fixed-effect and random-effects models were used to pool odds ratios and their 95% CIs. The weighted mean difference in blood pressure was calculated weighted on sample size. Statistical heterogeneity was assessed using the Q test and $I^2$ statistic.

Subgroup analyses were conducted by intervention type and comparator type. Sensitivity analyses were performed by excluding one study at a time. Meta-regression was undertaken to assess the effect of various modifying variables (such as...
as drug regimen and study quality) on outcomes. Only variables that reduced between-study heterogeneity were included in the model.

Publication bias was assessed using funnel plots and a modified regression test based on sample size.

Results of the review
Thirty one RCTs (seven randomised open blinded endpoint trials) (n=225,764) were included in the review. Sample sizes ranged between 414 and 24,309 participants. Follow-up ranged between two and 8.4 years. Twenty two RCTs received a quality score of 4 or 5. The following results were based on a random-effects model.

ACEIs significantly reduced the risk of congenital heart failure compared with placebo (OR 0.79, 95% CI 0.66 to 0.94). There was no evidence of statistical heterogeneity ($I^2=31.8\%$). CCBs were associated with a significantly increased risk of congenital heart failure compared to diuretics/β-blockers (OR 1.18, 95% CI 1.00 to 1.39; 11 RCTs). There was evidence of significant statistical heterogeneity ($I^2=61.2\%$).

The following comparisons showed no significant differences using a random effect model: ACEIs compared to diuretics/β-blockers (five RCTs, $I^2=60.4\%$); ARBs versus placebo (three RCTs, $I^2=62.5\%$), ARBs versus β-blockers (one RCT) and CCBs versus placebo (eight RCTs, $I^2=51.9\%$).

There were no significant differences in mean blood pressure for any comparison.

Meta-regression showed that larger differences in systolic blood pressure predicted greater reduction in the risk of CHF: for each 5mmHg reduction there was a 24% reduction in the risk of CHF (p<0.001). The risk of congenital heart failure was significantly lower in studies of ACEIs/ARBs compared to studies of CCBs. The regression model accounted for most of the between study heterogeneity and the residual between study variance was no longer significantly different from zero.

Subgroup analyses and sensitivity analyses were reported in the review. There was no evidence of publication bias.

Authors’ conclusions
ACEIs and ARBs had greater benefits compared to CCBs over and beyond the blood pressure reduction achieved by these drugs in patients with hypertension or high cardiovascular risk, but without established coronary heart failure.

CRD commentary
The review question and inclusion criteria were clearly stated. The literature search was based on only two electronic databases. The search was restricted to peer-reviewed studies, but funnel plots and tests showed no evidence of publication bias. Validity was assessed using the Jadad scale. Most studies were reported to be of moderate or high quality. However, only summary scores were reported and it was unclear which criteria had not been fulfilled. Data extraction was carried out in duplicate. The authors did not state whether this was the case for study selection and validity assessment, thus reviewer error and bias could not be ruled out. Appropriate methods were used to combine the data and investigate statistical heterogeneity. Although various variables were assessed to identify their effect on outcomes (for example, drug regimen), details on patient characteristics and study methodology (for example, dosing regimens) were limited. Confidence intervals appeared wide for a number of studies and affected the robustness of the results. The authors’ conclusions should be interpreted with caution due to the lack of details on included studies and quality assessment, restricted searches and potential for bias in the review.

Implications of the review for practice and research
The authors did not state any implications for research or practice.

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