Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324168 participants from randomised trials


CRD summary
The authors suggested that the results refuted a 5% to 10% relative increased risk of cancer or cancer-related death following antihypertensive treatment, but an increased cancer risk from combination angiotensin-converting-enzyme inhibitors and angiotensin receptor-blockers could not be ruled out. This was a well-conducted review and the authors’ conclusion is likely to be reliable.

Authors’ objectives
To assess the association between antihypertensive drugs and risk of cancer.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1950 to 2010. Search terms were reported. Reference lists of reviews, meta-analyses and individual studies were scanned. Detailed information was sought from US Food and Drug Administration.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared antihypertensive treatments (angiotensin receptor-blockers (ARBs), angiotensin converting enzyme inhibitors (ACEi), beta-blockers, calcium-channel blockers (CCBs) or diuretics). Trials need at least 100 participants and follow-up of at least one year to be eligible. Primary outcomes of interest were risk of cancer and cancer-related death.

A large proportion of included participants had hypertension, often accompanied by other conditions such as coronary artery disease and diabetes. Most of the included trials contained more men than women. Participants were 48 to 76 years old. The listed drug-class treatments were compared with each other and with placebo and other controls (non-placebo active treatment). The combination of ACEi and ARBs was treated as a separate drug-class comparison.

Three reviewers independently selected trials for inclusion. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed using Cochrane-recommended criteria of randomisation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and other sources of bias. Trials that were considered to be at high or unclear risk of bias for any one of the first three criteria were designated high risk; all other trials were considered to be at low risk.

Three reviewers independently carried out the quality assessment. Disagreements were resolved by consensus.

Data extraction
Data were extracted to enable calculation of odds ratios (OR) and 95% confidence intervals (CI). Intention-to-treat data were collected. Study authors and trialists were contacted for additional data, where necessary.

Three reviewers independently carried out data extraction. Disagreements were resolved by consensus.

Methods of synthesis
Odds ratios and 95% CIs were pooled in meta-analyses using three approaches: direct comparisons (fixed-effect model, Peto OR); network meta-analysis (fixed-effect and random-effects models); and trial sequential analysis. The probability that each treatment was best (lowest event proportion) was estimated using the Bayesian Markov chain
Monte Carlo method. Vague prior distributions were used. Statistical heterogeneity for direct comparisons analyses were assessed using the I^2 statistic (I^2<25% was considered low heterogeneity and >75% was high heterogeneity).

Sensitivity and subgroup analyses were conducted in all three approaches to explore the influential effects of trials with differing characteristics, risk of bias, cancer as a pre-specified outcome, length of follow-up and trials that compared telmisartan with other comparators. Publication bias was assessed with funnel plots and Begg's and Egger's tests.

**Results of the review**
Seventy RCTs (324,168 participants) were included in the review. Risk of bias was recorded. It appeared that most trials met criteria for adequate sequence generation, allocation concealment and blinding. Mean follow-up was 3.5 years (range one to nine years). The reported drop-out rate was below 10%. Compliance rate ranged from 65% to 100%.

In the network meta-analysis, risk of cancer was found to be statistically significant for the combination of ACEi and ARBs compared to placebo (OR 1.14, 95% CI 1.02 to 1.28), but only when the fixed-effect model was used. There was no difference in risk of cancer with any of the other drugs compared to placebo. Statistically significant differences were reported for combination treatment compared to ARB alone, ACEi, beta-blockers and diuretics in terms of cancer risk and compared with ACEi for cancer-related death.

Direct comparison meta-analysis was consistent with network meta-analysis results for all comparisons except the combination of ACEi and ARBs compared to ACEis alone (OR 1.16, 95% CI 1.05 to 1.28) and CCBs compared to ARBs (OR 1.18, 95% CI 1.04 to 1.33); these comparisons were significantly associated with risk of cancer. There were no other statistically significant associations between antihypertensive drug class treatments on risk of cancer or cancer-related death.

The trial sequential analysis showed no evidence of a 5% to 10% increased risk of cancer in any individual drug class, but there was a possibility of a 10% increase in cancer risk following treatment with combination ACEi and ARB (this result was driven largely by one trial).

Sensitivity and subgroup analyses did not materially alter the main results. Statistical heterogeneity was reported as low to moderate. There was no evidence of publication bias.

**Authors’ conclusions**
The results of this review refutes a 5% to 10% relative increased in risk of cancer or cancer-related death with use of ARBs, ACEi, beta-blockers, CCBs and diuretics. An increased risk of cancer with the combination of ACEi and ARBs could not be ruled out.

**CRD commentary**
The review question was clear. Inclusion criteria were potentially replicable for all aspects except study participants. The search strategy included relevant sources. Attempts were made to minimise publication bias. The review process was carried out with substantial effort to minimise error and bias. An appropriate quality assessment tool was used to evaluate the included trials. Trial quality appeared satisfactory. Selected study characteristics were provided.

The chosen methods of synthesis appeared appropriate. Statistical heterogeneity was assessed where appropriate. Findings from the three approaches to analysis were broadly consistent and subgroup/sensitivity analyses did not materially alter the results, so the results of this review are likely to be robust.

The authors’ conclusion reflects the evidence presented. Appropriate recommendations for future research were offered.

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

**Research:** The authors stated that further trials were needed to verify the 10% increased risk of cancer associated with
combination ACEi and ARB treatment.

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