Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials

Coleman C I, Baker W L, Kluger J, White C M

CRD summary
The review concluded that commonly used antihypertensive drugs were not associated with increased odds of developing cancer. Evidence appeared to support the authors’ conclusions, but lack of reporting of differences between studies and reliance upon short-term studies may have weakened the strength of the evidence.

Authors' objectives
To determine the association between commonly used antihypertensive agents and the incidence of cancer.

Searching
MEDLINE, EMBASE, CINAHL and Web of Science databases were searched to June 2007. Search terms were reported. Reference lists from reports of clinical trials or review articles were searched. Internet searches were conducted of www.theheart.org and www.cardiosource.com for additional studies.

Study selection
Randomised controlled trials (RCTs) evaluating antihypertensive drug classes thiazide diuretic, β-blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or calcium channel blocker (CCB) in comparison with placebo, active or untreated control were eligible for inclusion. The primary outcome of interest was incidence of cancer.

Antihypertensives used in the included studies included CCBs ACEIs, diuretics, β-blockers, β-blockers with diuretics (“conventional therapy”) and ARBs. The majority of participants in the included studies were being treated for hypertension only. The remaining studies included participants with chronic kidney disease and hypertension, pre-hypertension, heart failure, coronary artery disease or myocardial infarction. The duration of follow-up ranged from six months to five years.

Three reviewers independently selected studies for inclusion. Any methods used to resolve disagreements were not reported.

Assessment of study quality
Validity was assessed using the Jadad scale, which assesses randomisation, blinding and handling of withdrawals and dropouts with a maximum possible score of 5 points. Two reviewers independently assessed validity and resolved disagreements through discussion.

Data extraction
The percentage of patients who developed cancer was extracted for each treatment group and used to calculate Odds Ratios (ORs) and 95% confidence intervals (CIs). Data were extracted onto a standardised form independently by three reviewers with disagreements resolved through discussion.

Methods of synthesis
A random-effects model was used to combine ORs and 95% CIs. Statistical heterogeneity was assessed using the Q Statistic. In addition, studies were combined in a mixed treatment comparison (MTC) meta-analysis to compare different antihypertensive agents. The MTC meta-analysis used direct, within-trial and between-drug comparisons together with indirect evidence from trials with one treatment in common. All MTC analyses were conducted using a Bayesian Markov Chain Montel Carlo method and produced credible intervals.

Several sensitivity analyses were conducted including: exclusion of studies with a Jadad score less than 3; "conventional treatment" arms which allowed use of either a β-blocker or a thiazide diuretic; exclusion of studies with less than three
years of mean patient follow-up; and only studies which evaluated hypertension.

Conventional therapy arms were not used in the primary analysis, but were included in the sensitivity analyses.

Results of the review
Twenty seven RCTs (56 treatment arms, n=126,137) were included in the primary analysis and 28 RCTs (n=136,821) in the MTC meta-analysis, individual pair-wise meta analysis and sensitivity analysis. Seven RCTs scored 5 points on the Jadad scale, five scored 4 points, and 15 scored 3 points or less.

Primary analysis (27 RCTs, n=126,137) reported that the overall incidence of cancer averaged 4.7 per cent (number with cancer n=5,868 and total at risk n=126,137) for trials lasting on average 3.3 years. The incidence of cancer was reported as 6.5 per cent for ACEIs, 6.6 per cent for ARBs, 3.2 per cent for β-blockers, 6.7 per cent for diuretics, 3.9 per cent for CCBs and 3.0 per cent for placebo/control.

MTC meta-analysis found no statistically significant differences between placebo/no treatment control and ACEIs, ARBs, β-blockers, diuretics and CCBs. Individual meta-analyses for each pair-wise comparison also found no statistically significant differences between any of the drug classes compared. No significant changes to the results were reported by any of the sensitivity analyses.

Authors' conclusions
Commonly used antihypertensive drugs were not associated with increased odds of developing cancer.

CRD commentary
The review question was clear and supported by detailed inclusion criteria. Several relevant sources were searched and some handsearching was conducted. It was not clear whether any language limitations had been applied and so the potential for language bias could not be assessed. Methods were used to minimise reviewer errors and bias in study selection, assessment of validity and extraction of data. Validity was assessed using an established checklist, although only the composite score was presented making it difficult to judge the study validity. Most included studies were of low methodological quality, however, the authors conducted sensitivity analysis to explore the influence on results of the validity. Duration of follow-up was relatively short term for cancer studies. Characteristics of the included studies were presented in tables, although there was limited data reported on study participants. The authors reported assessing statistical heterogeneity, but the results of that analysis were not reported and it was, therefore, unclear whether it was appropriate to pool the studies. Evidence appeared to support the authors' conclusions, but lack of reporting of differences between studies and reliance upon short-term studies may have weakened the strength of the evidence.

Implications of the review for practice and research
Practice: The authors stated that based on the findings, the risk of developing cancer should not be a factor in the selection of one antihypertensive class over another.

Research: The authors did not state any implications for research.

Funding
Not stated.

Bibliographic details

PubMedID
18327066
DOI
10.1097/HJH.0b013e3282f3ef5e

Indexing Status
Subject indexing assigned by NLM

MeSH
Antihypertensive Agents /therapeutic use; Humans; Hypertension /drug therapy /epidemiology; Incidence; Neoplasms /epidemiology; Randomized Controlled Trials as Topic; Risk Factors

AccessionNumber
12008104591

Date bibliographic record published
03/02/2009

Date abstract record published
20/05/2009

Record Status
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.