Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events:  
systematic review and network meta-analyses  
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CRD summary  
This review and network meta-analysis concluded that chlortalidone was better than hydrochlorothiazide for preventing cardiovascular events, in patients with hypertension. There were concerns about the limited search, poor reporting, and indirect analysis, but the results and conclusions are likely to be reliable.

Authors' objectives  
To compare chlortalidone and hydrochlorothiazide for reducing the number of cardiovascular events, in patients with hypertension.

Searching  
PubMed was searched, and Ovid was used to search for English-language publications, to July 2011. Search strategies were reported. Previous systematic reviews were checked for further items.

Study selection  
Eligible were randomised controlled trials, of either chlortalidone or hydrochlorothiazide, which examined their antihypertensive effects on all-cause mortality, myocardial infraction, new coronary heart disease diagnoses, strokes, or congestive heart failure. Trials in which both the treatment and control groups received another anti-hypertensive were included.

The included trials compared hydrochlorothiazide with usual care, amlodipine or enalapril; or chlortalidone with placebo, referred care, lisinopril, amlodipine, doxazosin or lacidipine. Doses varied between trials. Where reported, the mean patient age ranged from 45 to 72 years, none to 61% were women, seven to 42% were smokers, and none to 60% had diabetes.

The authors did not report how many reviewers selected the trials.

Assessment of study quality  
The assessment of trial quality covered blinding, blind ascertainment, allocation concealment, completeness of follow-up, and early termination. The authors did not report how many reviewers performed this assessment.

Data extraction  
The results for mortality, cardiovascular outcomes, baseline blood pressure, and blood pressure targets achieved, were extracted. Relative risks were extracted or calculated, with 95% confidence intervals. Hazard ratios were assumed to be the same as relative risks.

The authors did not report how many reviewers extracted the data.

Methods of synthesis  
The results were combined in a network meta-analysis, using a weighted least squares regression. Two analyses were performed, one adjusted for the different drug types, and the other adjusted for office systolic blood pressure, by including the difference in mean blood pressure between the diuretic and non-diuretic treatments. Tests of homogeneity and model assumptions were performed, and numbers needed to treat were calculated.

Results of the review  
Nine randomised controlled trials were included, with 78,350 patients (range 785 to 24,335). Six trials evaluated chlortalidone (59,976 patients) and three evaluated hydrochlorothiazide (18,374 patients). Five trials were double-blind, seven had blinded outcome assessment, six had adequate allocation concealment, and eight had almost 100% follow-up. The average follow-up was between 2.7 and 5.6 years.
Drug adjustment: The analysis of four trials (50,946) found that chlortalidone significantly reduced the risk of congestive heart failure, compared with hydrochlorothiazide (RR 0.77, 95% CI 0.61 to 0.98) and cardiovascular events overall (RR 0.79, 95% CI 0.72 to 0.88). Chlortalidone was superior to hydrochlorothiazide, within the angiotensin-converting enzyme inhibitor and amlodipine network meta-analyses, for cardiovascular events, but not for congestive heart failure. There was no evidence of statistical heterogeneity. The estimated number needed to treat to prevent one cardiovascular event with chlortalidone, over five years, was 27. There were no statistically significant differences between the two drugs, in all-cause mortality or strokes, in any of the analyses.

Office systolic blood pressure adjustment: The analysis of all nine trials found that the relative risks with chlortalidone, compared with hydrochlorothiazide, were fairly constant over different baseline blood pressure levels. The risk of a cardiovascular event was significantly lower for chlortalidone (RR 0.82, 95% CI 0.70 to 0.97). The results for the other outcomes were not reported.

Authors' conclusions
Chlortalidone was better than hydrochlorothiazide at preventing cardiovascular events.

CRD commentary
This review reported inclusion criteria that could be independently replicated. Inclusion was limited to publications in English, so some relevant trials may have been missed. It was not clear whether adequate steps were taken to minimise reviewer error and bias. The quality of the trials was assessed, and it was generally found to be reasonable. An indirect comparison of treatments was made, in a network meta-analysis. The results from such indirect comparisons may be less reliable than those from direct comparisons between drugs.

Despite concerns over the limited search, poor reporting, and indirect analysis, the very large size of the review, and the consistency of results from different models, suggest that the results and conclusions are likely to be reliable.

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

Research: The authors stated that more research was needed into evening dosing and the duration of the effects of hydrochlorothiazide, compared with chlortalidone.

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