Treatment of elderly hypertensive patients with epithelial sodium channel inhibitors combined with a thiazide diuretic reduces coronary mortality and sudden cardiac death

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CRD summary
The authors concluded that use of an epithelial sodium channel inhibitor combined with hydrochlorothiazide for treatment of hypertension in elderly patients resulted in favourable effects on coronary mortality or sudden cardiac death. The reliability of the conclusions is uncertain given a number of weaknesses in the review methods (risk of error and bias, unclear quality of included studies).

Authors’ objectives
To assess the effect of hydrochlorothiazide (HCTZ) combined with an epithelial sodium channel (ENaC) inhibitor on coronary mortality and sudden cardiac death.

Searching
PubMed (from 1985), Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2006) and related reviews on the consequences of treating hypertension were searched.

Study selection
Randomised controlled trials (RCTs) that compared the effects of diuretic-based antihypertensive treatment (of at least one year) with placebo (or usual care) on coronary mortality or sudden cardiac death were eligible for inclusion. Trials that used concomitant interventions that could potentially confound the effects of thiazides were excluded. For ENaC inhibitor/hydrochlorothiazide combination therapy, eligible trials were those in which the protocols specified that an ENaC inhibitor was to be used routinely in combination with a thiazide diuretic (those that did not meet this criterion were considered as trials that did not mandate use of potassium-sparing diuretics).

ENaC inhibitors administered were triamterene and amiloride. The daily dose of hydrochlorothiazide was 25mg. Thiazide doses in trials that did not mandate use of a potassium-sparing drug ranged from 12.5mg to 50mg daily. Included studies enrolled elderly patients: the mean age of patients in trials that mandated use of an ENaC inhibitor in combination with a thiazide ranged from 70 to 76 years; the meanaged of patients in trials that did not mandate use of a potassium-sparing drug ranged from 38 to 84 years.

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

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently abstracted data on the number of events to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for coronary mortality or sudden cardiac death.

Methods of synthesis
Pooled odds ratios for coronary deaths and sudden cardiac deaths (with 95% CIs) were calculated using fixed-effects meta-analysis. Statistical heterogeneity was assessed using $\chi^2$. The linear trend between the risk of coronary mortality and thiazide dose was assessed using metaregression.

Results of the review
Nineteen RCTs (n=70,385) were included.

Three trials (n=5,761) mandated ENaC inhibitor-hydrochlorothiazide combination therapy. ENaC inhibitor-hydrochlorothiazide combination therapy, compared to controls, was associated with significant reduction in both
coronary mortality and sudden cardiac death in elderly patients: coronary mortality (OR 0.59, 95% CI 0.44 to 0.78); sudden cardiac death (OR 0.60, 95% CI 0.38 to 0.94).

Sixteen trials (n=64,624) did not mandate concomitant ENaC inhibitors. Thiazide diuretic therapy was not associated with significant reductions in coronary mortality or sudden cardiac death: coronary mortality (OR 0.94, 95% CI 0.81 to 1.09); sudden cardiac death (OR 1.27, 95% CI 0.93 to 1.75).

Meta-regression showed no significant effect of age (p=0.57) or blood pressure reduction (p=0.706) on outcomes in thiazide alone trials.

Authors’ conclusions
Use of an epithelial sodium channel (ENaC) inhibitor combined with hydrochlorothiazide for treatment of hypertension in elderly patients resulted in favourable effects on coronary mortality or sudden cardiac death.

CRD commentary
The review addressed a clearly stated question. Two relevant databases were searched; search terms and search end dates were not reported. The search for unpublished studies was limited and a number of relevant publications may have been missed. Data extraction was performed in duplicate, which minimised risks of error and bias; it was unclear whether similar efforts were used in study selection. The quality of included studies was unclear as no validity assessment was performed. Statistical heterogeneity was assessed using an appropriate method, but results were not reported and so the appropriateness of the meta-analysis was unclear.

Given a number of weaknesses in review methods (risk of error and bias, unclear quality of included studies and incomplete reporting of aspects of statistical analysis) the reliability of the authors' conclusion is uncertain.

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

Research: The authors stated that further randomised controlled trials were needed to identify a diuretic regimen that reduces sudden cardiac death in middle-aged patients. Further randomised controlled trials were needed to determine whether an aldosterone antagonist combined with a thiazide was equivalent or superior to an ENaC inhibitor/hydrochlorothiazide combination.

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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.