Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials

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Authors' objectives
To summarise the current evidence from randomised controlled trials (RCTs) of diuretics in patients with congestive heart failure (CHF).

Searching
MEDLINE and EMBASE were searched between 1966 and 1999. The keywords were listed in the paper. In addition,, pertinent journals were handsearched and the reference lists of papers were inspected. Book chapters and editorials were also scanned.

Study selection
Study designs of evaluations included in the review
The included studies were parallel or crossover RCTs with a duration of 4 to 24 weeks, with the exception of one trial which lasted 52 weeks.

Specific interventions included in the review
Loop or thiazide diuretic therapy for CHF. Loop diuretics (e.g. furosemide) were used in most studies. In 12 studies most patients were treated concomitantly with digoxin. In 6 studies the patients were taking angiotensin-converting enzyme inhibitors. In one study 21% were taking amiodarone, while in another study 88% were taking vasodilators. The specific interventions included were furosemide-hydrochlorothiazide, pertanide, amiloride, spironolactone, furosemide, furosemide-sironolactone, frumil, hydrochlorothiazide-triamterene, pertamide and hydroclorothiazide.

Participants included in the review
Patients with CHF. The patients were selected on the basis of symptoms, clinical and radiological findings, parameters of ventricular function or haemodynamics, or if pre-existing diuretic treatment for heart failure was required. The exclusion criteria in the included studies were clinically unstable conditions such as recent myocardial infarction, unstable angina pectoris and arrhythmias, hypotension or hypertension, valvular heart diseases, right heart failure or pulmonary oedema. The mean age of the patients in the included studies was 59 and 39% were women. Twenty-seven per cent of the patients were New York Heart Association class I, 40% were class II, 29% class III and a few class IV. Where reported, the ejection fraction was 46% (range: less than 20 to 65) and the end-diastolic dimension was increased at 68 mm (range: 63 to 77). Where reported, the pulmonary capillary wedge pressure was 26 mmHg.

Outcomes assessed in the review
The authors aimed to obtain data on mortality and morbidity, but as this information was often not specified, other possible outcomes were evaluated: the effect of diuretic withdrawal on worsening of heart failure; the effect of diuretics on exercise capacity; the effect of diuretics on symptoms and quality of life; the haemodynamic effect; and the neuroendocrine effect of diuretics. The outcomes included in the review were mortality, worsening heart failure, and exercise capacity. For exercise capacity, it was unclear which definition was used.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors state that methodological quality was assessed, but they do not report a method for assessing validity. Two reviewers assessed the methodological quality of each paper.
Data extraction
Two reviewers independently abstracted the data using a standardised protocol

Methods of synthesis
How were the studies combined?
The authors used the Mantel-Haenszel method and estimated combined odds ratios (ORs) using the fixed-effect model.

How were differences between studies investigated?
Chi-squared tests for heterogeneity were reported in three of the four main analyses, but were not discussed in the text of the paper. The studies were grouped according to design, i.e. the placebo-controlled trials were tabulated and pooled separately from the active-controlled trials. The authors conducted a sensitivity analysis to calculate the effect of including a large trial.

Results of the review
Seventeen studies were included in the primary analyses of the review: 7 randomised placebo-controlled trials (n=431) and 10 randomised active-controlled trials (n=383). A further analysis included one additional large study.

Mortality: 3 placebo-controlled trials (n=221) reported data; the OR was 0.25 (95% confidence interval, CI: 0.07, 0.84, P=0.03), representing an absolute risk reduction of 8% in mortality in patients treated with diuretics compared to placebo.

Worsening of heart failure: 4 placebo-controlled trials (n=448) and 4 active-controlled trials (n=177) reported data. The OR was 0.31 (95% CI: 0.15, 0.62, P=0.001) for the placebo-controlled trials and 0.34 (95% CI:0.10, 1.21, P=0.10) for the active-controlled trials.

Exercise capacity: 6 active-controlled trials (n=174) reported data; the OR was 0.37 (95% CI: 0.10, 0.64, P=0.007). It should be noted that this result was reported in the text as an OR, but in the figure as the standardised mean difference. It was not always clear which outcomes were studied. The inclusion of the large excluded study did not alter the direction or statistical significance of the treatment effects.

Authors' conclusions
Compared with active control, diuretics appeared to reduce the risk of worsening disease and improve exercise capacity. The available data from small studies showed that, in CHF, conventional diuretics reduce the risk of death and worsening heart failure in comparison with placebo.

CRD commentary
The review question, inclusion criteria, search strategy and data from the primary studies were clearly presented. However, there was some discrepancy between the numbers of patients included in the review, as reported in the text and in the tables. Only English language trials were searched and so some studies may have been missed. The authors do not appear to have searched for unpublished material. Two authors assessed the quality of the included studies, but the authors do not state how they assessed validity. In addition, validity assessment data were not reported nor used in interpreting the results of the trials. The authors noted that the included population were considerably younger (59 years) than patients with CHF in the population (74 years).

The outcomes that the authors used were not stated clearly, in particular for exercise capacity. The meaning of the results were reported in two different ways in the paper (OR and standardised mean difference) and were not at all clear.

The authors noted several limitations. All the randomised trials were small and there was great variability in the type of intervention, clinical characteristics, assessment of severity, aetiology of heart failure, study duration, concomitant medications, outcome measures and drop-out rates. Methods of masking and the assessment of outcome measures were
not reported clearly in many studies. The inclusion of crossover studies was a statistical weakness. There was also heterogeneity in the mechanism of action of loop diuretics and thiazides, and the dose of diuretics. Given these limitations, the results of the review should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors state that the evidence from trials is insufficient to justify widespread use of diuretics to influence clinical outcomes (e.g. to reduce mortality). Despite this, diuretics will continue to be used routinely in the management of CHF for symptom relief.

**Research:** The authors state that diuretics have not been tested in long-term trials evaluating survival, mainly because of ethical difficulties. The authors state that it is unlikely that diuretics will be the subject of future trials to evaluate effects on clinical outcomes in compensated heart failure, especially in patients stabilised on angiotensin-converting enzyme inhibitors and beta-blockers.

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