Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double-blind studies until December 1996)

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Authors' objectives
To provide an update on the ability of different antihypertensive drugs to reduce left ventricular hypertrophy in essential hypertension.

Searching
Computer-based searches were performed as described in the previous review (see Other Publications of Related Interest), i.e. MEDLINE, DIMDI, Ringdoc, ADES (database of reports of adverse drug experiences) and EMBASE were searched through July 1995. The keywords used were: ‘cardiac’ or ‘heart’ or ‘ventricular hypertrophy’, ‘wall thickness’, ‘ventricular’ or ‘cardiac mass’, ‘arterial hypertension’, ‘man’, ‘drug treatment’, and ‘reversal/reduction’. These searches were supplemented with review articles, Current Contents and textbooks. Only articles subjected to a peer-reviewed editorial process and published in full until December 1996 were included. For control, an intensive literature search of 64 databases (including MEDLINE, BIOSIS Previews, EMBASE and SciSearch) was conducted by the independent Deutsches Institut fur Medizinische Dokumentation and Information (DIMDI) using their search engine. Studies retrieved previously were combined with results from the above searches.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled clinical trials (RCTs) with a parallel group design, which evaluated the effect of pharmacological antihypertensive therapy on left ventricular mass, were included if they fulfilled the following criteria: the drug used in at least one placebo arm was either a placebo or belonged to one of the four major antihypertensive drug classes; the treatment arms comprised at least 7 patients; the duration of treatment was at least 4 weeks; and left ventricular mass was evaluated by echocardiography.

The mean duration of treatment was 15 (SD=9) weeks for the placebo groups and 26 (SD=17) weeks for the active therapy groups. Two of the original studies were excluded from this review on the basis of criticisms made following the first review.

Specific interventions included in the review
Interventions included drugs belonging to the following four major classes of antihypertensive agents: diuretics, blockers, calcium-channel blockers and angiotensin-converting enzyme (ACE)-inhibitors.

Participants included in the review
The participants were patients in trials evaluating antihypertensive therapy. The characteristics of the participants in the placebo and active treatment groups were presented as the mean values with standard deviations (SD).

The mean age was 50 (SD=3) years in the placebo group and 56 (SD=10) years in the active group.

The mean systolic blood-pressure (BP) was 157 (SD=9) and 162 (SD=10) mmHg in the placebo and active groups, respectively.

The mean diastolic BP was 99 (SD=4) and 102 (SD=4) mmHg in the placebo and active groups, respectively.

The mean posterior wall thickness was 11.1 (SD=1.2) mm in the placebo group and 11.4 (SD=1.2) mm in the active group, whilst the mean septal wall thicknesses were 11.9 (SD=1.0) and 12.4 (SD=1.4) mm, respectively.

The mean left ventricular mass was 132 (SD=18) g/m2 in the placebo group and 136 (SD=23) g/m2 in the active group.
Outcomes assessed in the review
The primary outcome was the reduction of the left ventricular mass or the left ventricular mass index, given as the percentage change from baseline value. Other outcomes included the reduction of posterior wall and septal thickness, as percentage change from the baseline value.

How were decisions on the relevance of primary studies made?
Two investigators independently examined the identified studies, and evaluated each study for the fulfilment of all predetermined inclusion criteria using a checklist. On the basis of criticisms of the first meta-analysis, two previously accepted studies were excluded. These comments were made by Fagard (see Other Publications of Related Interest), who considered one study to have an inappropriate design and the other to have the treatment effect confounded by exercise training.

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

Data extraction
The data were extracted according to the prefixed scheme performed in the previous review, in which the following data were extracted: the number of patients (men or women); race; age; previously untreated or therapy discontinued before inclusion in the study; antihypertensive drug class; the dosage of each drug used; the duration of treatment; the number of patients evaluated; the duration of therapy (longest follow-up); pre-treatment systolic and diastolic BP; pretreatment left ventricular mass or left ventricular mass index; pretreatment posterior wall and septal wall thickness; changes in systolic and diastolic blood pressures in absolute and/or relative percentage terms; change in left ventricular mass index in absolute and/or relative terms; and changes in posterior wall and septal wall thickness in absolute and/or relative terms. Each treatment arm was taken as a separate observation.

Methods of synthesis
How were the studies combined?
Statistical methods and procedures were performed as in the first meta-analysis, in which all treatment arms of the same drug class were combined and weighted according to the number in each individual study.

How were differences between studies investigated?
The authors did not state how differences between the studies were investigated.

Results of the review
Fifty RCTs (N=1,715) with 102 study arms were used to evaluate the outcomes: 165 patients in 13 placebo arms and 1,550 patients in 89 active treatment arms.

The number of treatment arms for each drug class were: for diuretics, 15 (N=304); for blockers, 23 (N=367); for calcium-channel blockers, 26 (N=441); and for ACE-inhibitors, 25 (N=438).

A direct comparison between two hypertensive drugs was not possible due to the small numbers of studies comparing similar drugs.

The absolute decreases in the outcome parameters were as follows.
Systolic BP: placebo, 2.9 (SD=2.8) mmHg; active 11.9 (SD=4.3) mmHg; P<0.001.
Diastolic BP: placebo, 2.6 (SD=2.7) mmHg; active, 13.6 (SD=3.8) mmHg; P<0.001. Posterior wall thickness: placebo, 0.8 (SD=4.2) mm; active, 6.4 (SD=6.0) mm; P<0.01.
Septal wall thickness: placebo, 0.3 (SD=1.0) mm; active, 7.1 (SD=6.4) mm; P<0.01.
Left ventricular mass: placebo, 5.2 (SD=5.9) g/m²; active, 9.2 (SD=7.9) g/m²; P<0.001.

Differences held true after taking account of therapy, age, pre-treatment BP and decrease in BP during treatment.

The overall decrease of left ventricular mass after 26 weeks of treatment was 9.2% (95% confidence interval, CI: 7.6, 10.8) from an average pre-treatment value of 136 g/m². The decrease of left ventricular mass was more marked, the greater the pre-treatment value of left ventricular mass (correlation, r=0.53, P<0.001).

Similar relationships were found for changes in posterior and septal wall thickness (r=0.27, P<0.05 and r=0.24, P<0.06, respectively). The decrease in left ventricular mass index was greater with a greater reduction in systolic BP (partial r=0.26, P<0.05) adjusted for pre-treatment values, and with a greater reduction in diastolic BP (r=0.36, P<0.001). Left ventricular mass also decreased more with a greater fall in diastolic BP (partial r=0.28, P<0.05) adjusted for pre-treatment values. The determinants of reduction in left ventricular hypertrophy were the pre-treatment left ventricular mass index, the decrease in BP and the duration of treatment.

A significant difference was detected in the change in left ventricular mass index among the four antihypertensive drug classes (P<0.01) after accounting for systolic BP and age. After weighting for the number of patients, the decreases in left ventricular mass index were as follows: ACE-inhibitors, 11.8% (95% CI: 9.0, 14.5); calcium-channel blockers, 11.1% (95% CI: 7.8, 13.7); blockers, 4.5% (95% CI: 1.2, 7.3); diuretics, 8.6% (95% CI: 3.9, 11.1). ACE inhibitors and calcium-channel blockers led to a greater decrease in both left ventricular mass index (P<0.01 and P<0.05, respectively, after Bonferroni correction) and posterior wall thickness (P<0.05) than blockers. No difference was noted for changes in septal wall thickness.

**Authors’ conclusions**
The reduction of left ventricular hypertrophy was determined by the decrease in systolic BP, duration of antihypertensive therapy and antihypertensive drug class. ACE inhibitors and calcium-channel blockers were more potent in reducing left ventricular mass than blockers, with diuretics in the intermediate range.

**CRD commentary**
This clearly written and presented review included a comprehensive literature search, selection of studies by two investigators according to a predefined checklist of inclusion criteria, and an analysis that accounted for pre-treatment values.

The validity of included studies was not assessed, results from individual studies were not mentioned, and statistical heterogeneity among studies was not assessed. It was unclear if the analysis was performed on an intention to treat basis. The review did not include an evaluation of withdrawals, side-effects or comparative treatment costs of the therapies evaluated.

The use of each treatment arm as a separate observation in the original review was criticised by Fagard (see Other Publications of Related Interest) on the grounds that by so doing, the authors ‘gave up the major advantage of the original study design’. Schneider countered this comment by asserting that in breaking the matching of study arms with different treatments, the resulting meta-analysis was more likely to overlook moderate effects than to overestimate them. The option preferred by the authors would have been to present the results from a paired analysis by pooling the within-study differences for those trials comparing the same two drug classes. This was not possible due to the limited number of studies directly comparing drug classes within a study.

The authors present evidence of the efficacy of active drug therapy over placebo in reducing left ventricular mass.

**Implications of the review for practice and research**
The authors suggest that the superiority of any drug or class of drug, with regard to the progression of left ventricular hypertrophy, should be delineated from well-designed large scale prospective trials.
Bibliographic details
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