Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis

Gupta AK, Arshad S, Poulter NR

CRD summary
This review concluded that fixed-dose combinations of antihypertensive agents were associated with a significant improvement in compliance and with non significant beneficial trends in blood pressure and adverse effects. These conclusions were supported by the data presented, but their reliability is unclear due to limitations in the quality assessment.

Authors' objectives
To determine the compliance, persistence, blood pressure control and safety associated with fixed-dose combinations of antihypertensive drugs in comparison to their free-drug components.

Searching
PubMed (1966 to February 2008), Web of Science (1970 to April 2008) and Cochrane Central Register of Controlled Trials (CENTRAL) (to April 2008) were searched. Some search terms were reported. Additional studies were identified by screening bibliographies of relevant studies. The review was restricted to studies published in English.

Study selection
Studies that compared a fixed-dose combination of two antihypertensive agents in a single tablet with a free-drug combination of its components were eligible for inclusion if they reported data on compliance/adherence, persistence, blood pressure lowering effect or adverse events.

Specific interventions assessed in the review were oxprenolol combined with chlorthalidone or cyclopenthiazide, bendrofluazide (bendroflumethiazide) combined with propranolol, atenolol combined with chlorthalidone, pindolol combined with clopamide, lisinopril combined with thiazide or hydrochlorothiazide (HCTZ), enalapril maleate combined with HCTZ, amlodipine besylate combined with benazepril, candesartan cilexetil combined with HCTZ and valsartan combined with HCTZ. The proportion of men ranged from 17% to 65% and mean age ranged from 44 to 76 years, where reported.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Two reviewers independently assessed methodological quality of cohort studies with the Newcastle-Ottawa scale and clinical trials with the Delphi list. Studies were graded as poor, fair, good or excellent based on the results of the quality assessment, but it was unclear on what basis this was done.

Data extraction
Two reviewers independently extracted data for continuous outcomes (such as blood pressure) as the mean difference (MD) from baseline and dichotomous data as odds ratios (OR) together with 95% confidence intervals (CIs). Where these were not reported in the study, data necessary for their calculation were extracted. For randomised crossover trials data were extracted only for the first study period. Where necessary, authors were contacted for additional information to allow calculation of a summary statistic.

Methods of synthesis
Summary odds ratios and weighted mean differences were estimated using fixed-effects models (in the absence of heterogeneity) or random-effects models (when heterogeneity was present). Heterogeneity was assessed visually and with the I² statistic. Meta-regression was used to investigate heterogeneity based on the covariates of study design, age, gender and publication year. Publication bias was assessed with funnel plots and the Begg test.
Results of the review
Fifteen studies (n=32,331) were included in the review: one parallel group RCT; four crossover RCTs; four non-randomised crossover trials; and six retrospective cohort studies. All the cohort studies were judged to be good or better; only three trials were judged to be good and the others were categorised as fair. Duration of follow-up ranged from eight weeks to five years.

Compliance was greater for fixed-dose combinations than for free-drug combinations (OR 1.21, 95% CI 1.03 to 1.43; five studies). Results were similar when stratified according to study design.

Three cohort studies reported no significant difference in persistence with therapy between the two treatment groups, but when these studies were combined with the three cohort studies that assessed compliance there was a significant increase in compliance/persistence among those who took fixed-dose combinations (OR 1.29, 95% CI 1.11 to 1.50; six cohort studies). There was no evidence of heterogeneity.

There was no significant difference in the blood pressure lowering effect of fixed-dose combinations compared to the free-drug combinations for either systolic (p=0.15, nine trials) or diastolic (p=0.13, nine trials) blood pressure. There was strong evidence of heterogeneity. Meta-regression showed that study design that included randomisation was a significant determinant of heterogeneity (p=0.05).

There was no difference in adverse events between the two treatment groups (five trials).

There was no evidence of publication bias for any of the outcomes reported.

Authors’ conclusions
Fixed-dose combinations of antihypertensive agents were associated with a significant improvement in compliance and with non significant beneficial trends in blood pressure and adverse effects.

CRD commentary
The review addressed a clear question. Inclusion criteria were defined in terms of intervention and outcome, but were less clear for population and study design. The literature search was adequate for published trials, but restriction of the review to published English language studies raised the possibility of publication and language biases (this was assessed in the review). Appropriate steps were taken to minimise bias and errors at all stages of the review process. Study quality was assessed with published criteria, but no individual quality criteria were reported and results were simply presented as an overall rating of study quality without indications of individual quality items fulfilled or how the rating was obtained. Appropriate methods were used to synthesise studies and results were clearly presented using forest plots.

The authors’ conclusions were supported by the data presented, but their reliability is unclear due to limitations in the quality assessment.

Implications of the review for practice and research
Practice: The authors stated that use of fixed-dose combinations should be encouraged in the management of hypertension.

Research: The authors stated that more data from well-designed and conducted studies were needed to refute or corroborate the findings of this review.

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None stated.

Bibliographic details
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.