Effect of amlodipine on systolic blood pressure

CRD summary
This manufacturer-funded review concluded that amlodipine given alone is effective for reducing systolic blood pressure in people with hypertension. The conclusions should be treated with caution because of methodological and reporting limitations in the review.

Authors' objectives
To examine the effectiveness of amlodipine in lowering systolic blood-pressure (SBP).

Searching
MEDLINE was searched from January 1980 to June 2001. The search terms were ‘Amlodipine’ and ‘Norvasc’. Current Contents (Clinical Medicine) and the Cochrane Library were also searched. The reference lists from all accepted studies and recent reviews were checked. Abstracts, letters, comments and reviews were excluded, as was articles written in languages other than English, French German, Italian or Spanish.

Study selection
Study designs of evaluations included in the review
Parallel-group randomised controlled trials (RCTs) with at least 10 participants were eligible for inclusion.

Specific interventions included in the review
Studies that used amlodipine as monotherapy for a minimum duration of 8 weeks were eligible for inclusion. In the included studies, the doses were fixed or were titrated to achieve the targeted BP. The median daily dose was 5 mg in both fixed and titrated dose studies (range: 1.25 to 15 mg). The duration of the treatment ranged from 8 to 260 weeks. Some studies were placebo-controlled.

Participants included in the review
Studies of adults with baseline hypertension (SBP of at least 140 mmHg and/or diastolic BP of at least 90 mmHg) were eligible for inclusion. The participants in the included studies had a mean age of less than 60 years, were either white, black, Hispanic or Asian, and more than half were male.

Outcomes assessed in the review
The primary outcome of interest was the mean change in SBP. In the included studies this was measured in a variety of ways: office, ambulatory, sitting supine, standing, during exercise, daytime or night-time.

How were decisions on the relevance of primary studies made?
Study inclusion required the agreement of two reviewers, who applied the inclusion criteria independently.

Assessment of study quality
The authors stated that they evaluated the studies for levels and quality of evidence. No further details were reported. The authors did not state how the evaluation was performed.

Data extraction
The data extraction forms were designed specifically for this review. One reviewer conducted the data extraction and another reviewer checked it. The mean baseline, end point and change in SBP were extracted for each amlodipine-treated group in each study. If only the baseline and end point, or the baseline and change were reported, the missing parameter was calculated by subtraction. If SBP was measured by more than one method in a study, data were extracted...
for only one method in the following descending order of preference: sitting, supine, standing, during exercise. Data were also extracted from placebo-controlled trials to calculate the mean difference in the baseline-to-end point change in SBP between amlodipine and placebo. All extracted data were based on the number of participants analysed, not the number randomised.

**Methods of synthesis**

How were the studies combined?

Simple pooling (adding up and taking the average) was used to combine the baseline, end point and change in SBP data from all the amlodipine-treated groups in all studies. The overall mean values and range were reported. Mean values were also calculated for subgroups of participants based on age, race or co-morbidity (isolated systolic hypertension, diabetes mellitus, renal insufficiency). The placebo-controlled trials were combined by a meta-analysis, using a fixed-effect model. The weighted mean difference in SBP was reported with the 95% confidence interval (CI) shown on the graph. For other studies, the authors only used data from the amlodipine-treated arms.

How were differences between studies investigated?

The Q statistic was calculated to test for heterogeneity in the meta-analysis of placebo-controlled studies. In the simple pooling of amlodipine-treated groups, differences between the studies were not investigated.

**Results of the review**

Eighty-five studies (13,293 participants) were included. Twelve of these were placebo-controlled RCTs (1,051 participants), 11 of which were included in the meta-analyses.

Heterogeneity was not statistically significant in the meta-analyses of studies that compared amlodipine with placebo. Treatment with amlodipine brought about a mean reduction in SBP of 12.2 mmHg (from the graph, 95% CI: 10.3, 14.0) compared to placebo (P<0.001).

In the analyses of all study arms of participants treated with amlodipine, the office-measured SBP was reduced by a mean of 17.5 mmHg (range: -5.3,-35). Amlodipine reduced SBP to a greater degree in black participants (n=74; mean decrease 23.9 mmHg), those aged 60 years or over (n=497; mean decrease 24.1 mmHg), those with isolated systolic hypertension (n=178; mean decrease 25.9 mmHg), those with diabetes (n=240; mean decrease 19.1 mmHg) and those with renal insufficiency (n=91; mean decrease 19.1 mmHg).

**Authors' conclusions**

Amlodipine monotherapy is effective in reducing SBP.

**CRD commentary**

The inclusion criteria were clearly defined and the search strategy appears good, although there may be publication and some language bias. Methods to reduce bias and errors in the study selection and data extraction processes were reported. The authors analysed the data in order to estimate the difference between amlodipine treatment and placebo. However, for other included studies, no information on the comparator treatments was given; the authors only analysed the data from the amlodipine treatment arms of these studies. No analyses to assess the difference between amlodipine and these comparator treatments were conducted.

Details of the studies were generally lacking and the characteristics of the individual studies were not reported. The results of the quality assessment were also not reported and study quality was not considered when interpreting the results. The reliability of the results from the simple pooling of amlodipine-treated groups is questionable: combining studies by simply adding up treatment effects in single treatment arms from different trials and taking the average is not a valid method for pooling data from RCTs. The results from the meta-analysis of the placebo-controlled trials are likely to have been more reliable; however, bias may have been introduced because the analysis was not by intention-to-treat (loss to follow-up, withdrawals, etc. were not taken into account), and the effect of study quality on the result was not investigated (poor-quality RCTs may inflate treatment effects). In addition, since the data for each trial were not
shown, we cannot tell whether pooling the weighted mean difference was appropriate.

The review was conducted by a consulting firm whose clients include the pharmaceutical industry. The review was funded by Pfizer, the manufacturer of amlodipine.

**Implications of the review for practice and research**
Practice: The authors stated that antihypertensive agents, such as amlodipine, warrant consideration for the management of patients with inadequately controlled SBP.

Research: The authors did not state any implications for further research.

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