A comparison of nisoldipine ER and amlodipine for the treatment of mild to moderate hypertension

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of two long-acting dihydropyridine calcium antagonists, amlodipine and nisoldipine extended-release, for the treatment of mild to moderate hypertension.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients with Stage I or II hypertension, as defined by diastolic blood pressure (DBP) criteria of the Sixth Report of the Joint National Committee. Patients were excluded if they had any known form of secondary hypertension, a systolic blood pressure (SBP) of greater than 200 mmHg or a DBP of greater than 110 mmHg, or bradycardia (heart rate less than 45 beats per minute, bpm) or tachycardia (heart rate greater than 100 bpm). Also excluded were patients who had had a stroke or myocardial infarction in the last 6 months. Other criteria for exclusion were congestive heart failure (left ventricular ejection fraction less than 40%), clinically significant hepatic or renal disease, uncontrolled diabetes mellitus, and a history of allergy or intolerance to the study medications.

Setting
The setting was not explicitly reported but it was likely to have been primary care. The economic study was carried out in the USA.

Dates to which data relate
The dates during which the effectiveness and resource use data were gathered were not reported. The price year was not given.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was performed prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The use of power calculations was not reported. Of the 228 eligible patients identified initially, 161 received the study
medications. However, the study sample comprised 146 patients because 15 were excluded due to treatment noncompliance, refusal to continue, or noncompletion of the trial due to adverse events. There were 73 patients in each group. The mean age was 52.9 (+/- 14.6) years in the nisoldipine group and 56.3 (+/- 10.1) years in the amlodipine group. Women comprised 53% of the nisoldipine group and 52% of the amlodipine group.

**Study design**

This was a prospective, randomised, double-blind, double-dummy parallel-group trial that was carried out in 9 centres. The methods of randomisation and blinding were not reported. After a 3-week, single-blind, placebo lead-in period, patients with a sitting trough DBP in the range of 90 to 109 mmHg inclusive (mean of 3 consecutive measurements) were randomised to the study groups for an 8-week period. The outcomes were assessed at weeks 2, 4 and 8 after randomisation. As reported already, 15 patients were not included in the final study sample. However, 157 patients had at least one valid assessment during the study.

**Analysis of effectiveness**

The analysis of effectiveness was restricted to those patients who completed the protocol (per protocol analysis, PPA; n=146). However, an intention to treat (ITT) analysis was also performed on the 157 patients with at least one valid assessment. The primary health outcome used in the analysis was efficacy, measured in terms of changes in SBP, DBP and heart rate. The secondary outcome measures were the percentage of treatment responders and the tolerability profile (occurrence of adverse events). A responder was defined as either a sitting trough DBP below 90 mmHg for those patients with an entry DBP of 90 to 100 mmHg, or a DBP that decreased by 10 mmHg or more and below 95 mmHg in patients whose entry DBP was 100 to 109 mmHg. The study groups were comparable at baseline in terms of the gender distribution, age, race and mean weight.

**Effectiveness results**

Results of the PPA.

The baseline SBP was 148.9 (+/- 14) mmHg in the nisoldipine group and 151.8 (+/- 13.9) mmHg in the amlodipine group. The mean changes after 8 weeks' treatment were -11.7 (+/- 1.4) mmHg (nisoldipine) and -14.3 (+/- 1.4) mmHg (amlodipine), respectively (difference 2.7, 90% confidence interval, CI: -0.1 - 5.5).

The baseline DBP was 97.5 (+/- 5) mmHg in the nisoldipine group and 97.6 (+/- 5.2) mmHg the amlodipine group. The mean changes after 8 weeks' treatment were -9.3 (+/- 0.8) mmHg (nisoldipine) and -142 (+/- 0.8) mmHg (amlodipine), respectively (difference 2.7, 90% CI: 1.1 - 4.3). This difference was statistically, but not clinically, significant.

The baseline heart rate was 75.4 (+/- 9.5) bpm in the nisoldipine group and 73.6 (+/- 8.2) bpm in the amlodipine group. The mean change after 8 weeks' treatment were 1 (+/- 1.2) bpm (nisoldipine) and 0.7 (+/- 1.1) bpm (amlodipine), respectively (difference 0.3, 90% CI: -2.1 - 2.6).

The percentage of treatment responders was 38% in the nisoldipine group and 37% in the amlodipine group at 2 weeks, 67% and 59% at 4 months, and 79% and 60% at 8 months, (p=0.004).

Similar results were observed in the ITT analysis.

Adverse events were comparable between both groups.

**Clinical conclusions**

The effectiveness study showed that amlodipine and nisoldipine were equally effective for the treatment of mild to moderate hypertension.

**Measure of benefits used in the economic analysis**

The summary benefit measure was the mean decrease in DBP. This was obtained directly from the effectiveness study.
**Direct costs**
Discounting was not relevant because the costs were estimated during one year. The unit costs and the quantities of resources used were not presented separately. The economic evaluation considered only the costs of the drugs. The cost/resource boundary adopted in the study was not reported. Resource use was estimated from the actual drug consumption that was observed in the effectiveness study. The costs were estimated from drug acquisition costs. The price year was not reported.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
In the PPA, the average daily drug acquisition cost per 100 patients was $74.26 in the nisoldipine group and $134.32 in the amlodipine group. The corresponding figures in the ITT analysis were $74.26 (nisoldipine) and $133.65 (amlodipine), respectively.

In the PPA, the total annual drug costs per 100 patients were $27,105 in the nisoldipine group and $49,027 in the amlodipine group (cost-difference $21,922). The corresponding figures in the ITT analysis were $27,105 (nisoldipine) and $48,782 (amlodipine), respectively (cost-difference 21,677).

**Synthesis of costs and benefits**
Average cost-effectiveness ratios were calculated to combine the costs and benefits of the study medications. In the PPA, the average daily cost per mean decrease in DBP in 100 patients was $7.98 in the nisoldipine group and $11.19 in the amlodipine group. Similar results ($7.98 versus $12.04) were obtained in the ITT analysis.

**Authors' conclusions**
Amlodipine and nisoldipine were equally effective for the treatment of mild to moderate hypertension. However, despite a similar safety profile, the drug acquisition costs were far lower in the group of nisoldipine patients.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparators was clear. The authors stated that amlodipine and nisoldipine represented two widely used calcium-channel blockers. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The analysis of effectiveness used a randomised trial, which was appropriate for the study question. The study sample appears to have been representative of the study population. The double-blind and multicentre design, the use of PPA and ITT as the basis for the effectiveness analysis, and the baseline comparability of the study groups further enhanced the internal validity of the study. The method used to select the sample was reported, but details on randomisation and blinding were not. A limitation to the internal validity of the study was the lack of power calculation and the fact that no evidence about the appropriateness of the sample size was reported.

Validity of estimate of measure of benefit
The reduction in DBP was used as the summary benefit measure. This was derived from the effectiveness study. Since it a measure specific to the disease considered in the study, it could be difficult to compare it with the benefits of other health care interventions. No summary benefit measure was used in the cost-minimisation analysis due to the equal effectiveness of the study drugs.

Validity of estimate of costs
The authors did not state explicitly which perspective was adopted in the study. In addition, only the costs of the drugs were considered in the economic evaluation. The inclusion of other cost categories, such as hospitalisations, would have been helpful. Few details on the cost analysis, namely source of data, were provided. Other pieces of information, such as the unit costs, quantities of resources used and price year, were not reported. These would have been useful for replicating the study in other settings. The costs were treated deterministically and the estimates were specific to the study setting. Sensitivity analyses were not carried out.

Other issues
The authors compared their findings with those from a published study that showed the comparable efficacy of the two drugs. However, the issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not performed. Consequently, the external validity of the analysis was low. The study referred to patients with mild to moderate hypertension and this was reflected in the authors' conclusions. The costs and benefits were combined using an average cost-effectiveness ratio, despite the cost-minimisation design.

Implications of the study
The study results suggested that nisoldipine represents a more economical treatment for mild to moderate hypertension than amlodipine, although the two drugs were equally effective.

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Other publications of related interest
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