Mild-to-moderate uncomplicated hypertension: further analysis of a cost-effectiveness study of five drugs

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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 telmisartan (40 - 120 mg daily), an angiotensin-II inhibitor used for the treatment of mild-to-moderate uncomplicated hypertension.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised hypothetical patients with uncontrolled mild-to-moderate uncomplicated hypertension.

Setting
The setting was primary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence was derived from studies published between 1998 and 2001. No dates for the resource use data were reported. The price year was 1997.

Source of effectiveness data
The effectiveness evidence came from a review of published studies and experts' assumptions.

Modelling
A decision tree model was employed to evaluate the costs and consequences of using the five alternative treatments for the management of mild-to-moderate uncomplicated hypertension. Patients were seen monthly in the first 3 months, during which hypertension may be controlled or patients may switch to a second-line treatment due to adverse events or lack of efficacy. After achieving hypertension control, the patient is seen every 3 months. The overall time horizon of the model was 15 months. The structure of the model was constructed on the basis of data derived from a literature search and a Delphi panel. The model only took monotherapies into account, as the data on combination therapies were inconsistent.

Outcomes assessed in the review
The outcomes assessed in the review were the probabilities of using each drug as first-line monotherapy, and the probability of switching to a second-line therapy due to adverse events or lack of efficacy.
Study designs and other criteria for inclusion in the review
All of the primary studies included in the review were randomised double-blind trials.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Six primary studies, one of which was unpublished, were used to derive the probability values used in the model.

Methods of combining primary studies
It is not clear what methods were used to combine the primary studies, although the authors did state that they "pooled data".

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of using each drug as first-line monotherapy was 0.70 for CCB, 0.70 for BB, 0.53 for ACE, 0.71 for the diuretic, and 0.72 for telmisartan.

The probability of switching to a second-line therapy due to adverse events was 0.01 for CCB, 0.05 for BB, 0.05 for ACE, 0.11 for the diuretic, and 0.04 for telmisartan.

Methods used to derive estimates of effectiveness
The probability of switching to a second-line therapy due to lack of efficacy was 0.21 for CCB, 0.25 for BB, 0.42 for ACE, 0.18 for the diuretic, and 0.24 for telmisartan.

Effectiveness estimates derived from a Delphi panel were used in the decision model.

Estimates of effectiveness and key assumptions
The probability of being chosen as first-line therapy was 0.072 for CCB, 0.365 for BB, 0.239 for ACE, 0.311 for the diuretic, and 0.022 for telmisartan.

The probabilities of being chosen as second-line therapy after each first-line therapy were also reported in the article. The model also assumed that the remaining drugs had an equal probability of being chosen for third-, fourth- and fifth-line therapies. The adverse events were reported at a constant frequency over the model frame.

Measure of benefits used in the economic analysis
The main summary benefit measure was time to hypertension control, which was calculated on the basis of the decision model. Time to control was not discounted because the model had a time horizon of 15 months. The authors performed a secondary analysis using quality-adjusted life-years as the benefit measure. However, expert opinion rather than patient-validated values were used to estimate quality of life in the short-term period.

**Direct costs**
Discounting was not performed since the costs were incurred over 15 months. The unit costs were not reported separately from the quantities of resources used. The health service costs included in the economic evaluation were drug use, physician visits and the management of adverse events (including hospitalisation data when relevant). The costs of adverse events were divided into two groups: first-quarter adverse events (i.e. the costs incurred during the first 3 months a patient is treated with the new drug) and maintenance of adverse events (costs resulting from mild adverse events and incurred quarterly while the patient remains on medication). The cost/resource boundary of the study was that of the government of private health care provider organisation. The adverse event costs were calculated on the basis of an algorithm developed by one physician-consultant, and validated by a second physician-consultant. The authors stated that all the unit costs were derived from published data. All of the cost values were adjusted to 1997, which was the price year.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
Extensive sensitivity analyses were conducted to evaluate the robustness of the estimated costs and clinical outcome. Two scenarios were considered. First, the inclusion of telmisartan as a therapeutic option on a formulary. Second, the comparison of starting therapy with different drugs if telmisartan was available. Further one-way sensitivity analyses explored the impact on the estimated costs and benefit of variations in a number of factors. For example, the model time horizon, efficacy of telmisartan, efficacy of amlodipine, equivalent efficacy of all drugs, additional costs for diuretic monitoring, adverse event rates and cost values, comparison with losartan, Delphi panel results, and generic pricing of enalapril.

**Estimated benefits used in the economic analysis**
Time to hypertension control was 2.83 months for CCB, 3.04 months for BB, 3.75 months for ACE, 3.41 months for the diuretic, and 2.73 months for telmisartan. Thus, telmisartan had the fastest time to control. This result was maintained over a range of variations conducted in the sensitivity analyses.

The secondary analysis showed that patients may benefit from a reduction in adverse events. The results (which were not reported) were sensitive to the variations conducted in the sensitivity analyses.

**Cost results**
The total costs were $3,018 for CCB, $2,426 for BB, $2,838 for ACE, $2,057 for diuretic, and $2,392 for telmisartan.

The quarterly maintenance costs were $347 for CCB, $228 for BB, $298 for ACE, $235 for diuretic, and $309 for telmisartan.
The authors stated that the reduction in costs observed with telmisartan was mainly due to the low initial adverse event costs and the ability to avoid using amlodipine as second-line therapy (which had the highest acquisition cost).

The sensitivity analyses showed that the inclusion of telmisartan as a therapeutic option was generally both beneficial and cost-saving. The exception was the analysis where the rate or cost of severe oedemas dropped by more than 70%. The ranking of interventions did not vary in the sensitivity analyses.

**Synthesis of costs and benefits**

Although the authors calculated a summary benefit measure, the costs and benefits were not combined. Thus, a cost-consequences analysis was conducted.

**Authors’ conclusions**

The decision model used in the analysis showed that telmisartan reduced the time to hypertension control and costs, relative to other commonly prescribed therapies, for the treatment of patients with mild-to-moderate hypertension. This conclusion was robust to wide variations performed in the sensitivity analyses.

**CRD COMMENTARY - Selection of comparators**

The authors selected a specific drug within each category of therapies used for the treatment of patients with mild-to-moderate hypertension. However, they did not justify the choice of the drugs, as several active principles are available within the same category of monotherapy. Further, combined therapies were not evaluated although they are quite commonly prescribed. You should decide whether the comparators used in the present study represent valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness analysis used a review of recent randomised controlled trials, which were based on a double-blind assessment of the outcome. This should ensure that the most valid and up-to-date evidence was used. However, the primary study data were pooled and it was not clear whether the authors considered the impact of differences in sample size and study population when aggregating the data. Details on the search methods were not reported, and as such, it is unclear whether the authors have been selective in their choice of literature to use. Assumptions made on the basis of a Delphi panel were also used, but the Delphi approach was not described. The authors performed several sensitivity analyses to take into account the impact of variations in the base-case estimates.

**Validity of estimate of measure of benefit**

Time to hypertension control was the benefit measure used in the analysis. It appears as an intermediate outcome rather than a final health measure. However, the authors stated that it captured the efforts required of both physicians and patients, and it was used in another. Quality-adjusted life-years were also used in the secondary analysis, but only limited details were reported.

**Validity of estimate of costs**

The perspective adopted in the study was reported and it appears that all the relevant categories of costs have been included in the analysis. The unit costs were not reported separately from the quantities of resources used, although the authors stated that the data may be available on request. The price year was given, thus simplifying reflation exercises in other settings. The costs were treated deterministically in the base-case, but extensive sensitivity analyses were conducted on the cost side of the analysis. The source of the cost data was not reported for all items. Resource consumption was derived on the basis of experts’ opinions. Both of these facts hinder the reproducibility of the study in other settings.

**Other issues**
The authors compared their findings with those from other studies, but they did not address the issue of generalisability of the study results to other settings. Sensitivity analyses were performed on a wide range of model inputs. This improved the external validity of the analysis. The study referred to patients suffering from mild-to-moderate hypertension and this was reflected in the conclusions of the analysis.

Implications of the study
The main implication of the analysis was that telmisartan may represent an effective and efficient alternative to monotherapies actually used for the management of patients with mild-to-moderate hypertension. Thus, telmisartan should be made available on health plans’ drug formularies to increase the range of therapeutic options for patients with mild-to-moderate hypertension. The limitations of this study should be considered when using the results obtained.

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