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 study examined several antihypertensive therapies for the first-line treatment of mild-to-moderate (uncomplicated) hypertension. In particular, chlorthalidone, propranolol, amlodipine, enalapril and losartan. Defined daily dosages for the antihypertensive agents were assumed. These were 25 mg for chlorthalidone, 160 mg for propranolol, 5 mg for amlodipine, 10 mg for enalapril and 50 mg for losartan.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of adult patients with uncomplicated hypertension who received a single agent at a low dose as monotherapy.

Setting
The setting was secondary care. The economic study was carried out in Greece.

Dates to which data relate
The effectiveness data were derived from studies published between 1999 and 2003. Some resource use data were derived from studies published between 1997 and 2003. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and experts' assumptions.

Modelling
A decision model was constructed to simulate clinical decisions and outcomes in the treatment of mild-to-moderate uncomplicated hypertension in a hypothetical cohort of patients. Patients not achieving adequate control were given a higher dose of the same agent, but if they still did not achieve control or experienced intolerable side effects, a different single agent was prescribed. The patients had an initial evaluation visit and then a follow-up visit 1 month after the drug therapy began. However, for those patients who changed medication, monthly visits were scheduled until hypertension control was achieved. The patients were then re-evaluated every 4 months for the remainder of the simulation. The time horizon of the model was 5 years.
Outcomes assessed in the review

The outcomes estimated from the literature were:

- the relative risk (RR) of total mortality, cardiovascular disease (CVD) mortality, major CVD events (e.g., coronary heart disease (CHD), stroke, congestive heart failure), CHD and stroke for any antihypertensive drug treatment versus no treatment;
- the number-needed-to-treat (NNT);
- compliance rates for each agent; and
- the probability of hypokalaemia for each agent.

Study designs and other criteria for inclusion in the review

A systematic review of the literature was undertaken to identify the primary studies. Treatment efficacy came from a published meta-analysis of 25 trials. These involved a total of 69,185 patients who were followed for a mean of 4.1 years.

Sources searched to identify primary studies

The primary studies were identified from searches of MEDLINE, previous meta-analyses, and journal reviews from January 1999 through December 2003.

Criteria used to ensure the validity of primary studies

Only randomised clinical trials (RCTs) with a minimum of 200 person-years of observation were included.

Methods used to judge relevance and validity, and for extracting data

Not stated.

Number of primary studies included

Seven studies (6 RCTs and a meta-analysis) provided clinical evidence.

Methods of combining primary studies

The efficacy data were combined in a random-effects meta-analysis. Other clinical data were not combined since they were derived from single studies.

Investigation of differences between primary studies

The homogeneity between the primary studies was addressed using chi-squared tests. These showed that the primary clinical trials were comparable in terms of most end points.

Results of the review

The RR for any antihypertensive drug treatment versus no treatment was:

- 0.90 (confidence interval, CI: 0.85 - 0.95) for total mortality,
- 0.84 (95% CI: 0.76 - 0.92) for CVD mortality,
- 0.79 (95% CI: 0.74 - 0.85) for major CVD events,
0.68 (95% CI: 0.61 - 0.77) for stroke, and
0.87 (95% CI: 0.80 - 0.94) for CHD.

The 5-year NNT was:
143 (95% CI: 97 - 833) for total mortality,
134 (95% CI: 96 - 556) for CVD mortality,
34 (95% CI: 30 - 66) for major CVD events,
65 (95% CI: 57 - 123) for stroke, and
348 (95% CI: 213 - not applicable) for CHD.

The compliance rate was 0.623 with chlorthalidone and with propranolol, 0.662 with amlodipine, 0.613 with enalapril and 0.840 with losartan.

The rate of hypokalaemia was 0.080 in the chlorthalidone group, 0.040 in the amlodipine group and 0.020 in the enalapril group.

**Methods used to derive estimates of effectiveness**

Some assumptions were made to derive specific clinical estimates. Expert opinion was based on a panel of three clinical hypertension researchers.

**Estimates of effectiveness and key assumptions**

The rate of hypokalaemia was 0.010 in both the propranolol and losartan groups.

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

No summary benefit measures were used in the economic analysis since a cost-minimisation analysis was carried out. However, the authors considered the reductions in mortality and other CVD events as benefit measures (as they were common to all strategies). These were discounted at an annual rate of 5%.

**Direct costs**

The analysis of the costs was carried out from the perspective of the Greek social security system. It included drugs, clinical visits (plus electrocardiogram), routine and extra laboratory tests, and serum potassium levels. Routine laboratory tests were plasma glucose, serum total cholesterol, high-density lipoprotein, triglycerides, uric acid, creatinine, potassium, haemoglobin, haematocrit and urinalysis. Extra laboratory tests for the chlorthalidone group included serum potassium, creatinine, urea, total cholesterol and triglycerides, while extra tests for the propranolol group included serum total cholesterol and triglycerides. Resource consumption associated with adverse events and switching between treatments was taken into consideration. The unit costs were presented separately from the quantities of resources used. The drug costs came from the Greek National Formulary, while other costs were estimated from the Fee Schedule of the Greek Ministry of Health. Drug dosages were based on the defined daily dose. Other resource use data were estimated from published sources. Given the long time horizon of the study, an annual discount rate of 5% was applied. The price year was 2004.

**Statistical analysis of costs**

The costs were treated deterministically.
Indirect Costs
The indirect costs were not included.

Currency
Euros (Euro). In 2004, Euro1 = 1.25 US dollars.

Sensitivity analysis
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the model results to variations in clinical and economic inputs. The ranges of values used were either set by the authors or derived from the literature. The effectiveness of newer medications was increased by 30% and a higher compliance rate was assumed in comparison with older therapies. Further, the price of the older antihypertensive agents was increased. Changes in other prices and discount rates for both the costs and effects were also investigated.

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

Cost results
The 5-year drug costs (excluding other cost categories) were Euro 78.4 with chlorthalidone, Euro 418.53 with propranolol, Euro 1,005.05 with amlodipine, Euro 548.41 with enalapril and Euro 1,657.10 with losartan.

When the other categories of costs (laboratory tests, clinical visits, side effects, switch to other therapies) were included, chlorthalidone was still the cheapest drug, with a 5-year cost of Euro 485.87. However, the difference between chlorthalidone and losartan was reduced to less than three-fold when the other categories of costs were also included.

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-minimisation analysis was carried out. However, the cost to prevent one death or other major cardiovascular event was calculated. The cost to prevent one death was Euro 60,230.71 with chlorthalidone, Euro 70,369.96 with propranolol, Euro 105,596.72 with amlodipine, Euro 75,301.40 with enalapril and Euro 158,659.35 with losartan. Clearly, chlorthalidone had the lowest cost-effectiveness ratio, regardless of the benefit measure used, as the effectiveness was comparable between groups but chlorthalidone cost the least.

The sensitivity analysis showed that chlorthalidone remained the most cost-effective antihypertensive strategy in most scenarios. Only changes in drug efficacy and compliance affected the conclusions of the analysis. In particular, in the unlikely case that new antihypertensive agents were 30% more effective than chlorthalidone, then enalapril would be the most cost-effective treatment. Also, enalapril had the lowest cost-effectiveness ratio in an implausible assumption of simultaneously poor compliance, reduced price of new agents and increased charges of monitoring.

Authors' conclusions
Chlorthalidone was the most cost-effective agent in the treatment of mild-to-moderate uncomplicated hypertension in Greece. Prescribing newer agents as first-line therapy for uncomplicated hypertension is not cost-effective, unless the acquisition costs of these agents become lower.

CRD COMMENTARY - Selection of comparators
The choice of the treatments examined in the study was not explicitly justified, but it appears that the most widely used old and new hypertensive medications have been included in the analysis. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness
The clinical evidence came from a review of the literature. Some information on the methods used to conduct the review was reported. For example, inclusion criteria were stated and the sources searched were given. All clinical data came from RCTs, which ensure a high internal validity. A published meta-analysis was also used. The method used to pool the primary estimates of treatment efficacy was reported. The issue of homogeneity across the primary studies was addressed and the result of the heterogeneity test was reported for all clinical end points. Several assumptions were made. The issue of uncertainty surrounding key clinical data was extensively tested in the sensitivity analysis. The clinical end points used in the analysis were typical outcome measures used for patients with hypertension.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-minimisation analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
The cost analysis was consistent with the stated perspective. A strength of the analysis was the inclusion of costs associated with side effects and switching. The authors stated that the adoption of a broader perspective, such as that of society, would not have substantially changed their conclusions. The unit costs and the quantities of resources used were presented separately, which enhances the possibility of replicating the analysis in other settings. The source of the data was reported for all items. Discounting was applied and the impact of using alternative discount rates was investigated. The costs were treated deterministically, but most cost estimates were varied in the sensitivity analysis. The price year was explicitly stated, which aids reflation exercises in other time periods.

Other issues
The authors did not report the results from other studies, but it was noted that the current findings are consistent with those from other economic evaluations. The issue of the generalisability of the study results to other settings was explicitly addressed. The authors pointed out that, despite variability in drug prices across countries, the relative difference in costs observed using Greek prices was similar to the cost-difference in the USA. Thus, it might be possible to extrapolate the results of the current study to other settings. Sensitivity analyses were performed on key estimates, and these further enhanced the external validity of the results of the analysis. The study referred to patients with uncomplicated hypertension and this was reflected in the authors’ conclusions. Some limitations of the analysis were also noted. For example, the impact of the treatments on quality of life was not investigated, although the authors stated that RCTs had failed to show statistically significant differences in quality of life between treatment groups.

Implications of the study
The study results supported the use of older hypertensive agents as first-line treatment for uncomplicated hypertension.

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None stated.

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Other publications of related interest


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