Cost-effectiveness of using angiotensin-converting enzyme inhibitors to slow nephropathy in normotensive patients with diabetes type II and microalbuminuria


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 an angiotensin-converting enzyme (ACE) inhibitor, enalapril, at a dose of 10 mg/day.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of normotensive patients with Type II diabetes and microalbuminuria, who were aged 44 years.

Setting
The setting appears to have been secondary care, although the authors did not explicitly state this. The economic study related to the situation in Thailand.

Dates to which data relate
The effectiveness data were taken from studies and government figures published between 1993 and 1998. The dates during which the resource data were collected were not reported. All of the costs were reported as 1999 values.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies, and from estimates of effectiveness based on expert opinion.

Modelling
A Markov model was used to calculate the lifetime medical costs and life expectancy in patients treated with or without ACE inhibitors. The number of one-year cycles was 25.

Outcomes assessed in the review
The outcomes included microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD), and death.

Study designs and other criteria for inclusion in the review
Different study designs were included in the review. These included a randomised controlled trial (RCT) and
longitudinal studies. In addition, the mortality rate was derived from public health statistics published by the Ministry of Public Health in Thailand. The authors did not specify any inclusion or exclusion criteria for the studies selected.

Sources searched to identify primary studies
The authors simply stated that the data were derived from the medical literature. No further details were provided.

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

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

Number of primary studies included
There were three primary studies included in the review. The other study was a RCT.

Methods of combining primary studies
Not applicable as only one study was used per parameter estimate.

Results of the review
The transition probabilities (tp) per year, taken from the review, were:

for microalbuminuria to macroalbuminuria, with drug therapy (tp1a), 0.02795;
for microalbuminuria to macroalbuminuria, without drug therapy (tp1b), 0.12269;
for macroalbuminuria to ESRD (tp2), 0.0498; and
for ESRD to death (tp5), 0.36754.

Methods used to derive estimates of effectiveness
Estimates of effectiveness for mortality rates were also derived from the opinions of five senior nephrologists from the Nephrology Society of Thailand. These experts were individually asked two questions. First, "how much of an increase or decrease in the mortality rate would be expected in type II diabetic patients with microalbuminuria treated with or without ACE inhibitors?". Second, "how much of an increase or decrease in the mortality rate would be expected in type II diabetic patients with macroalbuminuria?". The median value of each set of data was then used as an estimate of the mortality rate in each circumstance. The authors also made the assumption that the tp values remained constant over time.

Estimates of effectiveness and key assumptions
The tps per year, taken from expert opinion and national statistics, were:

for microalbuminuria to death, with drug therapy (tp3a), 0.01013;
for microalbuminuria to death, without drug therapy (tp3b), 0.0152; and
for macroalbuminuria to death (tp4), 0.05065.

**Measure of benefits used in the economic analysis**
The health benefit measure used in the economic analysis was the life-years saved, which were discounted at 8%.

**Direct costs**
The costs were determined from the direct medical expenses paid by the patients. Only the costs associated with renal complications were included. The costs of other disorders affected by the intervention, including metabolic abnormalities, were assumed to be equal for each alternative. The two main costs included were for drug therapy and for treating ESRD. The drug price was marked up by approximately 20% from the wholesale price, in order to account for hospital fees and drug monitoring costs. The costs associated with treating drug side-effects were not included in the study. As the majority of ESRD patients in Thailand undergo haemodialysis, the cost of haemodialysis was used to represent the cost of treating ESRD. This included the dialysis fee, equipment and medications used by the patients.

All of the costs were assessed at 1999 values. The unit costs were not reported separately from the resource quantities, although the wholesale price for enalapril 5 mg was given as US$0.196 per tablet. All of the costs were discounted at 8% per annum (discounting was relevant as the time period for the model was 25 years). The incremental costs used in the cost-effectiveness analysis included additional direct medical costs relative to the new programme, and the savings in medical care costs because of the reduced morbidity associated with the new programme.

**Statistical analysis of costs**
Deterministic costs were presented. Sensitivity analyses were used to identify areas of uncertainty associated with the estimates.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was carried out on three parameters to test for variability in the data. These were the cost of the drug, the cost of the ESRD treatment (haemodialysis), and the effectiveness of the drug.

**Estimated benefits used in the economic analysis**
In the patients not treated with ACE inhibitors, the model predicted an undiscounted life expectancy of 14.3 years per patient, i.e. survival to the age of 58 (44 plus 14.3 years) on average.

With ACE inhibitor treatment, the model gave a life expectancy of 19.39 years per patient, i.e. survival to the age of 63 (44 plus 19.39 years) on average. Thus, overall, 509 undiscounted life-years were saved in the drug therapy group compared with those not receiving drug therapy.

In the patients not treated with ACE inhibitors, the model predicted a discounted (8% per annum) life expectancy of 7.54 years per patient, i.e. survival to the age of 51 years on average.

With ACE inhibitor treatment, the model gave a life expectancy of 9.06 years per patient, i.e. survival to the age of 53
years on average. Thus, overall, 152 discounted life-years were saved in the drug therapy group compared with those not receiving drug therapy.

**Cost results**
For a cohort of 100 patients treated with ACE inhibitors, the discounted lifetime cost was $281,470 ($132,283 drug costs and $149,187 ESRD costs). Compared with the costs of $401,302 for the untreated group, the use of ACE inhibitors would result in savings of $119,832.

**Synthesis of costs and benefits**
The incremental cost-effectiveness ratio was given as -$788.37 per life-year saved. In other words, treatment with enalapril dominated placebo (higher benefit and lower cost). The sensitivity analysis showed that ACE inhibitor therapy would cause the programme to incur additional costs when the cost of ACE inhibitors was increased more than 90%, when the cost of haemodialysis was decreased more than 48%, or when the efficacy of the treatment was reduced until the cumulative incidence of macroalbuminuria was increased from 18 to 48%.

**Authors' conclusions**
The use of angiotensin-converting enzyme (ACE) inhibitor therapy (enalapril) in this group of patients resulted in cost-savings of $788.37 per life-year gained.

**CRD COMMENTARY - Selection of comparators**
An ACE inhibitor, enalapril, was compared with no drug treatment. The authors did not explicitly state why this comparison was made, and you must consider whether there would have been better comparators, for example, established practice.

**Validity of estimate of measure of effectiveness**
The validity was compromised by the lack of explanation in the paper on how the primary studies were selected. The review of the literature and the selection of relevant studies do not seem to have been conducted using systematic methods. The authors do not appear to have considered the impact of differences between the primary studies when estimating the effectiveness. Although expert opinion was also used to derive measures of effectiveness, it did not involve the use of a Delphi panel. The estimates were investigated by a sensitivity analysis, which should improve the generalisability of the results.

**Validity of estimate of measure of benefit**
Similar comments to those in the previous section apply when considering the quality of the parameters used as inputs into the model, from which the measure of benefit was derived. Accounting for individual preferences over quality of life attributes would have been useful.

**Validity of estimate of costs**
The authors provided good explanations of the costs used and where they were derived from. Also, the sensitivity analysis tested the variability in cost data, which should have improved the generalisability to other settings. However, the costs and the resources were not reported separately. The authors did not specify the perspective from which the economic analysis was conducted. The omission of indirect costs from the analysis will have a significant impact on the final results, as the benefits in terms of survival infer up to five extra years of working life for patients in the drug therapy group, compared with the group not receiving drug therapy. No justification was provided for the use of 8% as the discount rate. The authors reported an incremental cost-effectiveness ratio. However, it would have been more succinct and appropriate to have stated that treatment dominated no treatment, i.e. lower cost and higher benefit. Thus, it would be clear that if these results are valid, this technology should replace no treatment.
Other issues
The authors made appropriate comparisons of their results with the findings from other studies, and the sensitivity analysis should improve the generalisability of their findings. The authors acknowledged that further studies of ACE inhibitors are required, both in clinical trials and in real clinical settings.

Implications of the study
The authors stated that the use of ACE inhibitors in this group of patients is likely to have a favourable cost-effectiveness ratio and should, therefore, be part of any preventive treatment programme. However, further research is required both in clinical trials and in real clinical settings.

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