Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with Type 2 diabetes and microalbuminuria  

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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 study compared two treatment options for patients with Type 2 diabetes and microalbuminuria. The treatment options were the angiotensin II receptor blocker valsartan (Diovan) and the calcium-channel blocker amlodipine (Norvasc).

Type of intervention  
Treatment.

Economic study type  
Cost-utility analysis.

Study population  
The study population comprised patients with Type 2 diabetes and microalbuminuria. The characteristics of the target population were not described in full detail. The reader is referred to the original clinical study, the MicroAlbuminuria Reduction with VALsartan (MARVAL) study (see 'Other Publications of Related Interest' below for bibliographic details).

Setting  
The setting was not explicitly specified. The economic study was carried out in the USA.

Dates to which data relate  
The effectiveness evidence was derived from studies published between 1993 and 2003. The cost data were derived from sources published between 2001 and 2002. All costs were reported for the price year 2001.

Source of effectiveness data  
The effectiveness data were derived from the MARVAL study, other completed studies and government documents.

Modelling  
The authors constructed a Markov model to explore the distribution of patients to seven possible health states, and to investigate the possible effects and costs of the treatment options in the long term. The following health states of renal disease were included in the model:

Stage 0 disease, normal albumin levels;

Stage 1 disease, microalbuminuria;
Stage 2 disease, nephropathy;
Stage 3 disease, kidney failure (end-stage renal disease, ESRD);
cardiovascular disease;
death; and
withdrawal from the study due to any reason.

The time horizon of the model was 8 years. The outcomes were calculated on a quarterly (3-month) basis and were reported by the authors on an annual basis.

Outcomes assessed in the review
Input parameters for the model were the following transition probabilities, applied to both treatment arms:

in Stage 0, the probabilities for staying healthy, to relapse and to stop treatment;
in Stage 1, the probabilities of recovering, receiving routine care, progressing to Stage 2, developing cardiovascular disease, death, and stopping treatment;
in Stage 2, the probabilities of improving with treatment, receiving routine care, progressing to Stage 3, developing cardiovascular disease, and death;
in Stage 3, the probabilities of having dialysis, transplant, and ESRD complications.

Input parameters for transplantation were the success and failure rate of transplantation. Those for ESRD complications were the probability of dialysis and the probability of death, while those for cardiovascular disease were the probability of having the disease and the probability of dying. The probability of patients returning to normoalbuminuria, the probability of patients reaching ESRD, and the mortality rate were assessed as the summary measures of outcomes.

Study designs and other criteria for inclusion in the review
The outcomes were derived from the MARVAL study, recently published longer-term studies and government documents. The MARVAL study was a 6-month clinical trial of 332 patients with Type 2 diabetes and microalbuminuria, who received either valsartan (n=169) or amlodipine (n=163).

Sources searched to identify primary studies
Not reported.

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
It seems that, overall, the authors have used 6 primary studies as sources of effectiveness evidence.

Methods of combining primary studies
It appears that the results of the primary studies have not been combined.

**Investigation of differences between primary studies**
The authors do not seem to have investigated any differences between the primary studies.

**Results of the review**
Over the 8-year time horizon, more than twice as many patients in the valsartan group as the amlodipine group showed normal albuminuria (29.9% versus 14.5%; \( p = 0.001 \)).

In the valsartan group, 9.1% of patients reached ESRD. The equivalent percentage was 18.6% in the amlodipine group.

Mortality outcomes reached 8.5% in the valsartan group and 17.3% in the amlodipine group.

The proportion of patients progressing to cardiovascular disease was 1.9% in the valsartan group and 2.3% in the amlodipine group.

The rates of withdrawal from treatment were 21.5% in the valsartan group and 23.7% in the amlodipine group.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the years (or equivalent months) of QAS (i.e. quality-adjusted life-years, QALYs). The QAS was estimated by multiplying the time patients spent in each health state by the equivalent health utility. The health utilities assigned to each health state were derived from the literature, and were reported in detail. The health benefits were discounted at an annual rate of 3%.

**Direct costs**
From the third-party payer perspective, the costs included in the analysis were for the drugs (valsartan and amlodipine), renal disease, cardiovascular disease, death, and withdrawal (calculated as the average for Stages 0 to 3 renal disease costs). The costs of renal disease considered normal albuminuria, elevated microalbuminuria, advanced nephropathy and ESRD. The costs and the quantities were not reported separately. The costs were reported at an aggregate level, making it impossible to know which costs and which resources were included. All quantities were derived from the model, while all costs were derived from official published sources. All the costs were appropriately adjusted to reflect 2001 prices (future costs were assumed to increase at a rate of 2.8% per year). As the time horizon of the model was 8 years, discounting was appropriately carried out at an annual rate of 3 years.

**Statistical analysis of costs**
The authors conducted a bootstrap analysis to define the statistical significance of differences in costs between the two groups.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was performed on key model parameters to test variability in the data. Although the type of sensitivity analysis was not explicitly reported, it seems to have been a one-way sensitivity analysis. The key parameters
tested in the sensitivity analysis were health state transition probabilities, costs, utilities, medical cost inflation and the discount rate. The health state transition probabilities were varied according to the lower and upper 95% confidence interval values reported in the literature. Generic prices were tested for the cost of the drugs.

**Estimated benefits used in the economic analysis**
The estimated benefits were discounted and reported as the mean discounted QALYs per patient for each year of the 8-year time horizon. The mean discounted QALYs were:

- In the first year, 0.957 in the valsartan group and 0.946 in the amlodipine group;
- In the second year, 1.861 in the valsartan group and 1.819 in the amlodipine group;
- In the third year, 2.715 in the valsartan group and 2.622 in the amlodipine group;
- In the fourth year, 3.525 in the valsartan group and 3.363 in the amlodipine group;
- In the fifth year, 4.294 in the valsartan group and 4.048 in the amlodipine group;
- In the sixth year, 5.025 in the valsartan group and 4.684 in the amlodipine group;
- In the seventh year, 5.723 in the valsartan group and 5.278 in the amlodipine group;
- In the eighth year, 6.390 in the valsartan group and 5.835 in the amlodipine group;

The eighth year yielded a difference of 0.555 QALYs per patient, which is equivalent to 7 months per patient of additional survival in full health.

**Cost results**
The costs were reported per patient and an incremental analysis was performed.

In general, for both treatment arms, the aggregated discounted mean medical costs per patient increased over time.

At the end of the first year, the medical costs per patient were $11,909 in the valsartan group compared with $12,915 in the amlodipine group. The difference of $1,006 favoured valsartan. This difference increased to $11,339 by the end of the fourth year and to $32,412, (p<0.01), by the end of the eighth year of analysis.

**Synthesis of costs and benefits**
The cost-effectiveness ratios (CERs) were calculated by dividing the costs by years of QAS. The CER expresses the relative cost to purchase the equivalent of 1 full year of QAS.

In the first year of analysis, the average CER was $12,444 per QALY gained in the valsartan group and $13,653 per QALY gained in the amlodipine group. At the end of the 8 years, the cost increased to $14,407 per QALY gained in the valsartan group, and to $21,332 per QALY gained in the amlodipine group.

Valsartan was less costly and more effective in terms of QAS than amlodipine. This gave the incremental CER a negative value (i.e. -$58,400 per QALY gained; p<0.01).

The sensitivity analysis conducted demonstrated the robustness of the results to wide variability in key parameters.

**Authors' conclusions**
Important health benefits and costs-savings could be obtained by adopting the valsartan treatment for patients with Type 2 diabetes and microalbuminuria.
CRD COMMENTARY - Selection of comparators
Sufficient justification was provided for the comparators used. You should decide if these represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
A systematic review of the literature was not undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors appear to have used data from the available studies selectively, and the impact of differences between the studies identified were not considered when estimating effectiveness. In addition, the target population characteristics were not reported in detail in the current study, thus limiting the generalisability of the results. However, the authors carried out several sensitivity analyses relating to the efficacy estimates. These analyses improve both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates.

Validity of estimate of measure of benefit
The measure of benefit was QAS. It was estimated on a quarterly basis and reported by the authors on an annual basis. The health utilities assigned at each health stage were reported. Although they were derived from published literature, no specific details on their derivation were reported in the current study, thus making it difficult to comment on the quality of the estimates used.

Validity of estimate of costs
The economic analysis adopted the perspective of a third-party payer. As such, it seems that all the necessary costs have been included. However, the use of aggregated summary costs makes it impossible to know what aspects of costs were included and which health care resources were used. The costs and the quantities were not reported separately, which does not allow the analysis to be easily reworked for other settings. All the costs were derived from official published sources, and appropriate statistical analysis and extensive sensitivity analyses were undertaken to assess the robustness of the estimates used. Discounting, inflation of costs and the price year were appropriately reported.

Other issues
The authors compared their results with findings of published studies, and reported consistency in their findings. The authors felt that the greater cost-savings reported in their study were due to the longer time horizon of their analysis, the selection of a higher-risk group of patients, different success rates for both treatments, and the use of more favourable model parameters. The issue of generalisability of the results was partially addressed through the sensitivity analysis. The authors do not appear to have presented their results selectively, although the results from the statistical tests were not reported.

The authors reported a number of limitations to their study. First, the transition probabilities were extrapolated from a 6-month clinical trial conducted in the UK and were projected over an 8-year horizon. Second, aggregate costs for each health state were used, whereas the use of actual costs for different practice settings might have been more representative of local conditions. Thus, the authors recommended caution when evaluating aggregate model results with respect to a particular setting. Finally, the health utilities were obtained from the literature and do not capture variation of preferences over time and between people.

Dean Smith, Anh Nguyen and Corey Peak are paid consultants for Novartis, while Feride Frech is an employee of Novartis.

Implications of the study
The authors did not make any specific recommendations for changes in policy or practice. They suggested that future research should try to further compare the use of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors, especially generic angiotensin-converting enzyme inhibitors.
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14720103

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Albuminuria /drug therapy; Amlodipine /economics /therapeutic use; Angiotensin-Converting Enzyme Inhibitors /economics /therapeutic use; Calcium Channel Blockers /economics /therapeutic use; Cost-Benefit Analysis; Diabetes Mellitus, Type 2 /drug therapy /economics; Health Services Research; Humans; Markov Chains; Outcome and Process Assessment (Health Care); Tetrazoles /economics /therapeutic use; Treatment Outcome; United States; Valine /analogs & derivatives /economics /therapeutic use; Valsartan

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