Economic evaluation of the use of irbesartan and amlodipine in the treatment of diabetic nephropathy in patients with hypertension in Canada

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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
Irbesartan (an angiotensin-II-receptor antagonist) was compared with amlodipine (a calcium-channel blocker) and standard care for the treatment of patients with Type 2 diabetes, with hypertension and proteinuria. Standard care concerned antihypertensive treatment, excluding angiotensin-II-receptor antagonists, calcium-channel blockers and angiotensin-converting enzyme inhibitors.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical study population comprised patients with Type 2 diabetes and hypertension and proteinuria.

Setting
The setting was not stated explicitly, but it is likely that treatment was initiated in a secondary care setting. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were taken from the Irbesartan in Diabetic Nephropathy Trial (IDNT) published in 2001. Additional data were derived from a study that used data from the United States Renal Data System published in 1997. The use of drug therapies and the required dosages were taken from the IDNT study. Other resource use was taken from Canadian studies published between 1995 and 1999. The cost estimates were adjusted to year 2001 Canadian dollars.

Source of effectiveness data
The majority of the effectiveness data were derived from a single study, supplemented with data from a US data system.

Modelling
The economic study was performed using a Markov model. This enabled data from the trial to be combined with additional data. In addition, the effectiveness data were extrapolated to a time horizon of 25 years to capture the major long-term health effects. Hence, the model allowed postponement of end-stage renal disease (ESRD), prolonged survival and the potential for cardiovascular events. Five primary health states were included in the model. These were survive (the entry state relating to proteinuria), doubling of serum creatinine (DSC), ESRD managed with dialysis.
(ESRD/dialysis), ESRD treated with renal transplant (ESRD/transplant) and death. Further, nonfatal cardiovascular events were included as temporary states within the survive and DSC states.

The transition probabilities for amlodipine and irbesartan beyond the end of the trial were taken to be the weighted averages (by cohort size) of the transition probabilities for each therapy and standard care during the trial.

Outcomes assessed in the review
The primary health outcomes presented were the transition probabilities using one of the alternative treatments to move from one health state to another. The probabilities were derived as hazard rates from the IDNT data and data from the US Renal Data System.

Study designs and other criteria for inclusion in the review
Not stated.

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
Two studies were included in the review.

Methods of combining primary studies
Not relevant.

Investigation of differences between primary studies
Not stated.

Results of the review
The transition probabilities from survive to death were 0.0518 - 0.1808 for irbesartan, 0.0505 - 0.1802 for amlodipine, and 0.0564 - 0.1831 for standard care.

The probabilities from survive to ESRD/transplant were 0.0010 for irbesartan, 0.0015 for amlodipine, and 0.0014 for standard care.

The probabilities from survive to ESRD/dialysis were 0.0234 for irbesartan, 0.0354 for amlodipine, and 0.0335 for standard care.

The probabilities from survive to DSC were 0.0295 for irbesartan, 0.0468 for amlodipine, and 0.0401 for standard care.

The probabilities from survive to DCS with cardiovascular event were 0.0026 for irbesartan, 0.0069 for amlodipine, and 0.0084 for standard care.
The probabilities from survive to survive with cardiovascular event were 0.0556 for irbesartan, 0.0617 for amlodipine, and 0.063 for standard care.

The probabilities from DSC to DCS with cardiovascular event were 0.0192 for irbesartan, 0.0147 for amlodipine, and 0.0152 for standard care.

The probabilities from DCS to ESRD/dialysis were 0.5161 for irbesartan, 0.5458 for amlodipine, and 0.58 for standard care.

The probabilities from DCS to ESRD/transplant were 0.0215 for irbesartan, 0.0227 for amlodipine, and 0.0242 for standard care.

**Methods used to derive estimates of effectiveness**
The authors made assumptions to derive estimates of effectiveness.

**Estimates of effectiveness and key assumptions**
The authors assumed that the transition probabilities from ESRD/dialysis and ESRD/transplant were the same for each therapeutic option. The transition probabilities from DCS to death were assumed to be the same as those from survive to death.

The transition probability from ESRD/dialysis to transplant was 0.04.

The probability to death was 0.2563 to 0.5671.

The probability from ESRD/transplant to ESRD/dialysis was 0.118 and from ESRD/transplant to death 0.0932 - 0.1876.

**Measure of benefits used in the economic analysis**
The benefit used in the economic analyses was the life-years gained (LYG). Two thresholds were used for the cost-benefit analysis, indicating alternative monetary values of maximum willingness to pay for a life-year.

**Direct costs**
The quantities and cost were estimated though use of the model. The direct medical costs included were for drug therapy, concomitant medications, monitoring during the survive and DSC states (e.g. urine tests, blood counts and physician visits), and inpatient and outpatient care for a cardiovascular event, dialysis and renal transplant. The daily costs of therapy with irbesartan and amlodipine were reported separately. The costs of medication were derived from the Ontario Drug Benefit Formulary. Resource use of amlodipine and irbesartan, including the required dosages, were derived using actual data from the IDNT and were adjusted for assumed rates of compliance. The costs of the drug therapy in standard care were not reported.

Canadian costs for cardiovascular events, dialysis and transplant were obtained from economic studies. The cost estimates were adjusted to year 2001 Canadian dollars, but the method used was not described. A discount rate of 5% was used.

**Statistical analysis of costs**
The mean values and distributions were used for the cost parameters. The distributions were not described.

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

Univariate analyses were performed using estimates from the results of the Monte Carlo simulation.

One-way sensitivity analyses were conducted for parameters with no probability distribution (transition probabilities from ESRD/dialysis end ESRD/transplant). Alternative fixed values (base values multiplied by 0.5 and 2), discount rates (0% and 3%) and time horizon (3 years) were used. The relative importance of each parameter in contributing to the uncertainty of the results was assessed using the rank correlation technique.

Estimated benefits used in the economic analysis

From the results of the probability analyses, the LYG were 6.82 (95% confidence interval, CI: 6.2 - 7.44) for the irbesartan group, 6.48 (95% CI: 5.90 - 7.06) for the amlodipine group, and 6.40 (95% CI: 5.68 - 7.17) for the standard therapy group. (The figures were discounted at a rate of 5%).

Cost results

The total costs were Can$89,304 for the irbesartan group, Can$109,280 for the amlodipine group, and Can$101,688 for the standard care group.

From the results of the probability analyses (Monte Carlo simulation), the total costs were Can$89,158 (95% CI: 61,771 - 124,160) for the irbesartan group, Can$109,086 (95% CI: 75,351 - 150,117) for the amlodipine group, and $101,424 (95% CI: 68,193 - 143,564) for the standard care group.

A 5% discount rate was used. Undiscounted figures were not presented. The incremental costs were not reported separately.

Synthesis of costs and benefits

The costs were combined with the LYG. The results of the deterministic analysis and the probability analyses indicated that amlodipine and standard care were dominated by irbesartan. Treatment with irbesartan resulted in more LYG at a lower total cost. The results of the univariate sensitivity analyses showed that irbesartan always dominated the alternative treatments.

The net benefits of irbesartan compared with amlodipine were Can$30,000 (95% CI: 2,000 - 62,000) when assuming a maximum willingness to pay of Can$30,000 for a life-year, and Can$37,000 (95% CI: -5,000- 80,000) when assuming $50,000 for a life-year. The net benefits of irbesartan compared with standard care were Can$25,000 (95% CI: -5,000 - 53,000) and Can$33,000 (95% CI: -6,000 - 73,000), respectively.

The most sensitive parameters related to net monetary benefits were probabilities relating to the transition from the initial health state and to cost of dialysis (from survive to ESRD/dialysis). For example, using a threshold of Can$30,000 (irbesartan versus amlodipine), a rank correlation of the probability from survive to ESRD/dialysis was 0.47 when using amlodipine and -0.44 when using irbesartan. The lowest correlation that was found in this scenario was the probability from survive to ESRD/transplant using amlodipine (0.09).

Authors' conclusions

The analysis provided strong evidence that, compared with amlodipine and standard care, irbesartan led to a reduction in the medical costs and an increase in life expectancy.

CRD COMMENTARY - Selection of comparators
The two therapies in the analysis had demonstrated efficacy. Standard care is always a relevant comparator, although it could have been better described. You should decide if these comparators represent all relevant alternatives in your own setting.

Validity of estimate of measure of effectiveness
The majority of the effectiveness data were derived from a randomised controlled clinical trial, which is an appropriate study design for the study question. To fully understand the trial and the validity of these effectiveness data, the reader should read the original trial publication.

Assumptions were made when extrapolating transition probabilities over a longer time horizon than that used in the trial. These were not justified with reference to the medical literature. The authors acknowledged this limitation and it seems likely that a conservative approach was taken. In addition, sensitivity analyses were performed to assess the impact of the different parameters. Transition probabilities from ESRD/dialysis and ESRD/transplant were derived from the US Renal Data System. The authors did not consider any possible implication of using these data for populations outside the US setting. This may limit the generalisability of the results.

Validity of estimate of measure of benefit
The estimation of benefit (LYG) was modelled. The use of a Markov model to estimate the benefits was appropriate in this situation.

Validity of estimate of costs
A third-party payer perspective was adopted in the study. All the costs relevant to this perspective were included in the analysis. The costs were reported separately, but specific information on the quantities and prices of the different components of the cost parameters were not reported. This may affect the generalisability of the results obtained. Resource use for drug therapies was derived using actual data from the trial. In order to generalise the drug use to daily practice, adjustments were made for compliance. Although a justification was not given explicitly, the figures applied were reported separately. The cost of drug therapy for standard care was not estimated, and it was unclear whether the authors corrected for this in the annual cost of amlodipine and irbesartan. Further, the information on standard care was limited. Given this, the generalisability of the results obtained is limited.

Other resource use was taken from economic studies and was based on Canadian resource use patterns. It was not stated whether charges or real costs were used to estimate the cost. Sensitivity analyses of the cost and quantities were not reported. Discounting was appropriately carried out since the time horizon was longer than one year. The price year was reported, which will aid any future reflation exercises.

Other issues
The authors did not compare their results with findings from other studies. The values of the individual model parameters were presented, which facilitates replication of the model in other settings. Except for adjustments of compliance, the issue of generalisability was not discussed. The authors acknowledged the limitations of the study. For example, the lack of available data on transitions beyond the follow-up period of the clinical study and the use of a model. This was addressed by using a conservative approach for effectiveness after the follow-up period of the trial, and by performing probability and sensitivity analyses. The results were not reported selectively.

Implications of the study
The analysis provided evidence that, compared with amlodipine or standard care, irbesartan led to a reduction in the medical costs and an increase in life expectancy. However further trials might be required to confirm the relative differences between amlodipine and irbesartan.

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**Other publications of related interest**


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