Cost-effectiveness of early irbesartan treatment versus control (standard antihypertension medications excluding ACE inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium channel blockers) or late irbesartan treatment in patients with Type 2 diabetes, hypertension, and renal disease


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
Three treatment strategies for patients with Type 2 diabetes, hypertension and microalbuminuria were compared. Microalbuminuria was defined as a urinary albumin excretion of 20 to 199 microg/minute on two of three consecutive occasions. The three strategies were control treatment, late irbesartan treatment and early irbesartan treatment.

Control treatment was the use of standard antihypertensive medications to achieve a target blood pressure of less than 135/85 mmHg, started when patients were in the state of microalbuminuria. The standard antihypertensive medications included diuretics, beta-blockers, alpha/beta-blockers, peripheral vasodilators, peripheral adrenergic blockers and central adrenergic blockers, but excluded angiotensin-converting enzyme (ACE) inhibitors, other angiotensin-2 receptor antagonists, and dihydropyridine calcium-channel blockers.

Early irbesartan treatment comprised 300 mg irbesartan daily, started when patients were in the state of microalbuminuria.

Late irbesartan treatment referred to control therapy (as described already) when patients were in the states of microalbuminuria and early overt nephropathy, with 300 mg irbesartan daily added once patients reached the state of advanced overt nephropathy.

Type of intervention

Economic study type
Cost-effectiveness analysis.

Study population
The target population for the model was a hypothetical cohort of 1,000 patients with Type 2 diabetes, hypertension and microalbuminuria, similar to the baseline characteristics of patients in the IRMA-2 study (Parving et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details).

Setting
The setting was secondary and tertiary care. The economic study was carried out in the USA.

Dates to which data relate
Studies providing effectiveness evidence dated from 1993 to 2004. For cost data, the studies dated from 2000 and 2001. The price year was 2000.
Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on authors' assumptions.

Modelling
A Markov (state transition) decision model was used to simulate the progression of patients with Type 2 diabetes. The model was described in detail. The disease states modelled were microalbuminuria, early overt nephropathy, advanced overt nephropathy, doubling of serum creatinine (DSC), ESRD treated with dialysis, ESRD treated with renal transplant, and death. A distinction was made between early and advanced overt nephropathy to bridge the gap that existed between patients reaching the end point of the IRMA-2 study and patients included in the IDNT trial (Lewis et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details). The cohort was followed yearly over a 25-year horizon.

Outcomes assessed in the review
The parameters used in the model included:

- the annual transition probabilities for disease state progression;
- the age- and gender-specific all-cause mortality rates adjusted by state-dependent relative risks (RRs) for all-cause mortality in each state; and
- the ESRD outcome data, including mortality rates in the ESRD states.

Study designs and other criteria for inclusion in the review
The authors used randomised controlled trials (RCTs), cohort studies and published literature.

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
Two RCTs supplied much of the data.

Methods of combining primary studies
A narrative method was used to combine the studies.

Investigation of differences between primary studies
Not reported.

Results of the review
The results of the review were not completely reported in the article, although RRs and transition probabilities over a
25-year horizon were reported in a detailed online appendix.

The RR of progression from microalbuminuria to early overt nephropathy was 0.30 (95% confidence interval, CI: 0.14 - 0.61; p<0.001);

from advanced overt nephropathy to DSC, 0.71 (95% CI: 0.54 - 0.92; p=0.009); and

from advanced overt nephropathy or DSC to ESRD, 0.83 (95% CI: 0.62 - 1.11; p=0.19).

The RR of mortality for patients with Type 2 diabetes, hypertension and microalbuminuria was calculated to be 2.03.

The RR of mortality for patients with Type 2 diabetes, hypertension and overt nephropathy was calculated to be 4.4 in comparison with the general population.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
The authors stated that when published estimates were not available, they assumed a conservative estimate of the parameter. The rate of progression from early overt nephropathy to advanced overt nephropathy was the same in both treatment arms. The RRs for all-cause mortality in the early and the advanced overt nephropathy states, as well as the DSC state, were assumed to be the same.

Measure of benefits used in the economic analysis
The authors used life-years gained (LYG) as a measure of benefit. They also reported years free of ESRD. Life expectancy was discounted at an annual rate of 3% and projected over 25 years.

Direct costs
Only the incremental costs of adding irbesartan therapy to the control treatment arm and the costs of ESRD treatment were considered. The costs of other medications, including all other antihypertensive agents, were not included in the analysis because it was assumed that they did not differ between treatment regimens. The costs of ESRD treatment (dialysis and transplantation) were taken from the U.S. Renal Data Service. The annual costs of 300 mg irbesartan daily were taken from the Drug Topics Red Book, using the average wholesale price. Estimations of the quantities and the costs were derived by modelling. All the costs were discounted at a rate of 3% per year. The quantities and the costs were not analysed separately and were not reported in full. The costs were not reflated. The price year was 2000.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
No indirect costs were reported.

Currency
US dollars ($).

Sensitivity analysis
A second-order Monte Carlo analysis was performed to calculate the mean, median and 95% CI of the total costs and
life expectancy. A distribution for the RR with irbesartan, taken from the IRMA-2 and IDNT trials (Parving et al. 2001 and Lewis et al. 2001), was used in the model.

Further sensitivity analyses investigated a large variety of assumptions about the structure of the model.

**Estimated benefits used in the economic analysis**

The mean number of discounted LYG was:

- 0.96 per patient for early irbesartan treatment versus the control;
- 0.05 per patient for late irbesartan treatment versus the control; and
- 0.92 per patient for early versus late irbesartan treatment.

Undiscounted results were also reported. Improvements in life expectancy were seen after 4 years for early irbesartan versus control, and after 10 years for late irbesartan versus control. Improvements in life expectancy were seen after 5 years for early versus late irbesartan.

After 25 years, early irbesartan led to the avoidance of approximately 130 cases of ESRD per 1,000 patients treated versus the control, and 86 cases per 1,000 patients treated versus late irbesartan. Late irbesartan led to 45 cases of ESRD avoided per 1,000 patients treated versus the control. The onset of ESRD was delayed by 2.1 years with the early use of irbesartan compared with the control, by 0.3 years with late irbesartan versus the control, and by 1.8 years for early versus late irbesartan.

**Cost results**

The total costs per patient were $16,859 for early irbesartan treatment, $25,529 for late irbesartan treatment and $28,782 for the control strategy. The cost-savings became evident after 10 years with early irbesartan treatment versus the control, after 5 years with late irbesartan treatment versus the control, and after 11 years for early versus late irbesartan.

The mean 25-year discounted costs were decreased by $11,900 per patient for early irbesartan versus the control, and by $3,252 per patient for late irbesartan versus the control. The incremental cost per patient for early irbesartan versus late irbesartan was $8,670.

**Synthesis of costs and benefits**

The early irbesartan treatment strategy was dominant, meaning that it saved both lives and money in comparison with the other treatments. Also, the late irbesartan treatment strategy dominated the control strategy with 0.05 discounted LYG and $3,252 saved per patient. Undiscounted results were also reported.

In the sensitivity analyses, the relative results remained stable under all conditions tested. Both early and late irbesartan treatments were projected to be cost- and life-saving compared with the control, with early irbesartan treatment having a more positive impact than late irbesartan.

**Authors' conclusions**

The model supported the use of irbesartan in hypertensive Type 2 diabetic patients with microalbuminuria (early intervention) or overt nephropathy (late intervention). Both treatments were life- and cost-saving. However, early intervention with irbesartan was predicted to lead to the greatest decreases in the incidence of end-stage renal disease (ESRD), as well as prolongation of life and monetary savings. These findings were robust under a wide range of assumptions.

**CRD COMMENTARY - Selection of comparators**

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The authors justified their choice of the comparators used. Several trials have recently reported on the blood pressure-independent renoprotective effects of angiotensin-receptor antagonist treatment on the progression of various stages of renal disease in patients with hypertension and Type 2 diabetes. These trials showed that renal events could be postponed considerably, which could have impacts on both life expectancy and health care costs. You should judge whether these strategies are relevant in your own setting, or whether other comparators could also be relevant (e.g. ACE inhibitors or others drug members of the irbesartan class).

**Validity of estimate of measure of effectiveness**
The main source of the effectiveness evidence was two trials (Parving et al. 2001 and Lewis et al. 2001). Much of the effectiveness evidence was derived from these two trials and studies from different countries, which were adequate sources. However, it was unclear whether a systematic review of the literature had been 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 used data from the available studies selectively. One cannot be sure that all relevant literature was identified, although it is certain that RCTs were used to derive the effectiveness of the strategies. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources and their own assumptions, justifying their assumptions with reference to the medical literature. The estimates were investigated in sensitivity analyses, using ranges from the literature.

**Validity of estimate of measure of benefit**
The authors used life-years as the measure of benefit. This measure of benefit enables comparisons across health technologies. When estimating uncertainty in the study results, the authors did not describe the probability distributions incorporated in the Monte Carlo simulation. Thus, these results are difficult to interpret.

**Validity of estimate of costs**
The authors reported that the costs were estimated from a third-party payer perspective, therefore the indirect costs (loss productivity) were appropriately not included. Although some costs might have been omitted from the analysis, these were unlikely to have affected the authors' conclusions since they were common to both strategies. The resource use quantities and prices were taken from published sources but they were not reported separately. Statistical analyses of the costs were not conducted. Discounting was carried out, which was appropriate since the time horizon exceeded 2 years. The price year was reported. The costs were not reflated and this will not aid any future reflation exercises.

**Other issues**
The authors' conclusions reflected the scope of the analysis. The authors did not explicitly address the generalisability of the results, and they recognised certain limitations. In particular, the lack of direct clinical comparisons and limited ability to make comparisons with ACE inhibitors, or other angiotensin-2 receptor antagonists, led to the exclusion of a treatment arm containing an ACE inhibitor that had shown benefits and possible cost-savings in Type 1 diabetes and nondiabetic nephropathy in a number of country-specific settings.

**Implications of the study**
Although the study showed irbesartan to be beneficial and cost-saving in hypertensive Type 2 diabetic patients with microalbuminuria or overt nephropathy, the authors stated that future health economic comparisons between ACE inhibitors and angiotensin-2 receptor antagonists would be of great interest if evidence-based data derived from direct comparative clinical trials become available.

**Source of funding**
None stated.

**Bibliographic details**

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Other publications of related interest


Indexing Status
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MeSH
Angiotensin-Converting Enzyme Inhibitors /therapeutic use; Antihypertensive Agents /economics /therapeutic use; Biphenyl Compounds /economics /therapeutic use; Calcium Channel Blockers /therapeutic use; Cost-Benefit Analysis; Creatinine /blood; Diabetes Mellitus, Type 2 /economics /mortality /physiopathology; Diabetic Angiopathies /drug therapy; Diabetic Nephropathies /complications; Disease Progression; Humans; Hypertension /drug therapy /economics; Markov Chains; Models, Theoretical; Reimbursement Mechanisms; Survival Analysis; Tetrazoles /economics /therapeutic use; United States

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