Health economic implications of irbesartan plus conventional antihypertensive medications versus conventional blood pressure control alone in patients with type 2 diabetes, hypertension, and renal disease in Switzerland


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 irbesartan, 300 mg daily, plus conventional antihypertensive therapy in patients with Type 2 diabetes, hypertension and microalbuminuria.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with Type 2 diabetes, hypertension and microalbuminuria. The latter was defined as a urinary albumin excretion (UAE) of 20 to 199 microg/minute on two out of three consecutive occasions.

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

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 2000 and 2004. No dates for the majority of the resource use data were reported. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors’ opinions.

Modelling
A published Markov model was used to simulate the long-term progression of renal disease in patients with Type 2 diabetes and the impact of the two treatments under investigation. Patients could move across the following health states:

- microalbuminuria (UAE 20 to 199 microg/minute),
- early overt nephropathy (UAE 200 microg/minute to median UAE 1,900 mg/24 hours),
- advanced overt nephropathy (median UAE on entry >/= 1,900 mg/24 hours),
doubling of serum creatinine (DSC),

ESRD treated with dialysis,

ESRD treated with renal transplant, and

dead.

A simplified version of the model was presented. The time horizon was 25 years and the cycle length appears to have been 1 year.

**Outcomes assessed in the review**
The outcomes estimated from the literature were the transition probabilities across health states and the mortality rates.

**Study designs and other criteria for inclusion in the review**
It was not stated whether a systematic review of the literature was undertaken to identify the primary studies. The clinical data were mainly derived from two clinical trials, the Irbesartan in Reduction of Microalbuminuria-2 study and the international Irbesartan in Diabetic Nephropathy Trial. The first study included 590 patients with Type 2 diabetes or microalbuminuria, while the second enrolled 1,715 patients with Type 2 diabetes, hypertension or advanced overt nephropathy. Mortality for transplant patients was obtained from a European transplant register and a German dataset. All-cause mortality was based on Danish data. No information on the other studies was provided.

**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 stated.

**Number of primary studies included**
Nine primary studies provided the clinical evidence.

**Methods of combining primary studies**
A narrative approach appears to have been used to combine the primary estimates.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The clinical estimates derived from the literature were reported selectively. Transition probabilities were reported for very few health states. For example, the rate of transition from transplant to dialysis was 17.1% in the first year and 5% in subsequent years.

It was stated that 0.35% of patients diagnosed with ESRD received renal transplantation.
Approximately 95.2% of patients started haemodialysis and 4.8% received peritoneal dialysis.

The annual rate of dialysis patients receiving a transplant was 4.2%.

The relative risk (RR) of mortality for patients with Type 2 diabetes, hypertension and microalbuminuria was 2.03.

The RR for mortality in patients with Type 2 diabetes, hypertension and overt nephropathy was 4.4 compared with the general population.

Annual mortality in dialysis patients was 16.91%.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model when published data were not found.

**Estimates of effectiveness and key assumptions**
The rate of progression from early overt nephropathy to advanced overt nephropathy was assumed to be the same in both treatment arms. The RRs for all-cause mortality in the early overt nephropathy, advanced overt nephropathy and DSC states were conservatively assumed to be the same.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were life expectancy, years free of ESRD and the cumulative incidence of ESRD. All measures were estimated using the modelling approach. An annual discount rate of 5% was used.

**Direct costs**
The analysis was carried out from the perspective of the third-party payer. It included the costs of irbesartan and the treatment of ESRD, which included resources associated with renal transplant and dialysis. The costs of other medications were not considered since they were assumed to have been comparable between treatment arms. The unit costs were not presented separately from the quantities of resources used. The unit costs for renal transplant and follow-up treatment because of ESRD were estimated from Swiss national insurance data, while the unit costs of haemodialysis were obtained from Swiss national tariffs. The cost of peritoneal dialysis was derived from published data and expert opinion. Resource use associated with medications was taken directly from the clinical trial, while the sources of other resource consumption were not explicitly stated. Discounting was relevant, as the long-term costs were evaluated, and an annual rate of 5% was used. The price year was 2003.

**Statistical analysis of costs**
No statistical analyses of the costs were performed.

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

**Currency**
Swiss francs (CHF).

**Sensitivity analysis**
A univariate sensitivity analysis was carried out to assess the robustness of the expected costs and benefits to variations in three key model assumptions. First, the UAE threshold for advanced overt nephropathy was set to the minimum required (585 mg/24 hours). Second, recent UK mortality data for no renal disease, microalbuminuria, or overt
nephropathy were used. Third, the RR of mortality in the states leading up to ESRD was set to 1.0 in order to simulate only the effects of treatment on delaying the onset of ESRD and its increase in associated mortality.

Estimated benefits used in the economic analysis
The discounted life expectancy was 9.80 years in the control group and 10.37 years in the irbesartan group (difference 0.57).

The undiscounted life expectancy was 14.39 years in the control group and 15.61 years in the irbesartan group (difference 1.22).

The analysis of life-years saved with irbesartan showed that survival benefits were observed after 7 years of treatment.

The years free of ESRD were 12.90 in the control group and 15.04 in the irbesartan group.

The cumulative incidence of ESRD was 26.6% in the control group and 10.7% in the irbesartan group.

Cost results
The total costs per patient would be CHF 46,956 in the control group and CHF 25,469 in the irbesartan group (cost-difference CHF 21,487).

The extra cost of irbesartan treatment was more than offset by savings associated with a reduction in ESRD treatment.

Synthesis of costs and benefits
The incremental costs and benefits were not combined in a cost-effectiveness ratio since irbesartan was the dominant strategy (being both more effective and less expensive than the comparator).

The sensitivity analysis showed that the base-case results were unchanged when variations in key assumptions were made. In other words, irbesartan remained the dominant strategy in all cases.

Authors' conclusions
Compared with conventional therapy, the use of irbesartan to treat Type 2 diabetes patients with hypertension and microalbuminuria improved life expectancy and reduced total costs from the perspective of the Swiss health system.

CRD COMMENTARY - Selection of comparators
The choice of the comparators was appropriate because a new medication was compared with the conventional therapy for patients with Type 2 diabetes, hypertension and microalbuminuria. Doses and frequency of administration were reported. Angiotensin-converting enzyme inhibitors, other angiotensin-2-receptor antagonists and dihydropyridine calcium-channel blockers were excluded because of contrasting evidence on their efficacy. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from published studies. The authors did not report the methods and conduct of a systematic review, so it is possible that the primary studies might have been identified selectively. Different sources of data were used, including clinical trials and international registries. In general, the use of clinical trials ensures a high internal validity of the primary estimates. Similarly, the European registry should have provided good-quality data. Some assumptions were also made, owing to the lack of published evidence. The authors acknowledged the uncertainty surrounding some clinical estimates, which were varied in the sensitivity analysis. The issue of heterogeneity among the primary studies was not addressed.
Validity of estimate of measure of benefit
Both disease-specific and generic benefit measures were used in the analysis. Life expectancy represents a valid
measure as the disease in question has a strong impact on mortality. It has the further advantage of being comparable
with the benefits of other health care interventions. The effect of the treatments under examination on quality of life
was not explicitly assessed, but the use of a summary measure such as years free of ESRD captures, in part, this aspect
of patient health. Discounting was performed in accordance with international recommendations.

Validity of estimate of costs
The costs included were appropriate given the perspective adopted in the analysis. The authors justified the choice of
excluding some categories of costs. However, a detailed breakdown of the cost items was not provided and all costs
were presented as macro-categories. In addition, details of the unit costs and quantities of resources used were not
given. This represents a limitation of the analysis as it will prevent its replication in other settings. The sources of the
costs were reported and most costs were derived from national databases. However, less detailed information on the
source of resource use was provided. No statistical analyses of the costs were carried out, and the cost estimates were
specific to the authors' setting as sensitivity analyses were not carried out. The price year was reported, thus facilitating
reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue
of the transferability of the study results to other settings. Limited sensitivity analyses were carried out but these were
restricted to the clinical side of the analysis. Therefore, caution will be required if extrapolating the results of the study
to other contexts. The authors acknowledged some limitations of their study. First, owing to the lack of direct clinical
comparisons, it was not possible to compare the projections for irbesartan treatment with those of angiotensin-
converting enzyme inhibitors or other angiotensin-2-receptor antagonists. Second, there was a lack of published data
about the distribution of treatment of ESRD with haemodialysis, continuous ambulatory peritoneal dialysis or transplant
in Switzerland, so data from other countries were needed to populate the decision model.

Implications of the study
The study results support the use of irbesartan for the treatment of Type 2 diabetes patients with hypertension and
microalbuminuria. The authors pointed out that head-to-head clinical trials comparing angiotensin-converting enzyme
inhibitors and angiotensin-2-receptor antagonists should be carried out.

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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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