Losartan reduces the costs associated with nephropathy and end-stage renal disease from Type 2 diabetes: economic evaluation of the RENAAL study from a Canadian perspective

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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 use of losartan (50 to 100 mg once daily) taken in addition to conventional antihypertensive therapies (e.g. calcium-channel antagonists, diuretics, alpha-blockers, beta-blockers, and centrally acting agents) for the treatment of Type 2 diabetes patients with nephropathy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with nephropathy from Type II diabetes.

Setting
The setting was secondary care. The economic study was conducted in Canada.

Dates to which data relate
The effectiveness evidence and most resource use data were taken from a study published in 2001. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study, the REENAL study, which was reported elsewhere (see Other Publications of Related Interest).

Link between effectiveness and cost data
The costing was mainly conducted prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Limited information on the sample size was reported since the main details of the clinical study had been published elsewhere. A sample of 1,513 patients (age range: 31 - 70 years) was included in the analysis. There were 751 patients in the losartan group and 762 in the placebo group.

Study design
This was a prospective, randomised, double-blind, placebo-controlled clinical trial. The mean duration of the study was 3.4 years (range: 2.3 - 4.6). Other information on the follow-up and outcome assessment was not provided.

**Analysis of effectiveness**

The outcome measures used were:

- the reduction in the incidence of a doubling of serum creatinine concentration and end-stage renal disease (ESRD; defined as initiation of dialysis or renal transplantation) with losartan over placebo; and
- the reduction in the estimated ESRD days over a 4-year period.

The number of hospitalisations was also reported. The baseline comparability of the study groups was not discussed. Similarly, the approach used to analyse the effectiveness (e.g. intention to treat) was not reported.

**Effectiveness results**

The reduction in the incidence of a doubling of serum creatinine concentration with losartan over placebo was 25%, (p=0.006).

The reduction in the incidence of ESRD with losartan over placebo was 29%, (p=0.002).

The ESRD days saved with losartan over placebo were:

- 0.1 (95% confidence interval, CI: -0.1 - 0.4) after 0.5 years;
- 0.5 (95% CI: -0.9 - 2.1) after 1 year;
- 1.2 (95% CI: -3 - 5.4) after 1.5 years;
- 5.7 (95% CI: -2.7 - 14.1) after 2 years;
- 12.2 (95% CI: -0.7 - 25.1) after 2.5 years;
- 21.1 (95% CI: 3.5 - 38.7) after 3 years;
- 33.6 (95% CI: 10.9 - 56.3) after 3.5 years; and
- 46.9 (95% CI: 19.1 - 74.7) after 4 years.

The mean number of hospitalisations per patient for renal or cardiovascular-related causes was lower with losartan (0.82) than with placebo (1.00), as was the mean number of hospitalisations per patient for all causes (1.92 versus 2.05, respectively). However, none of these differences reached statistical significance.

**Clinical conclusions**

The effectiveness analysis showed that, compared with placebo, losartan was effective in reducing ESRD days in Type 2 diabetes patients with nephropathy. In particular, a statistically significant reduction in ESRD days was observed after 3 years of follow-up.

**Measure of benefits used in the economic analysis**

The summary benefit measure was the number of ESRD days saved with losartan over placebo. This was derived directly from the effectiveness analysis.
Direct costs
Discounting might have been relevant since the costs and resource use were incurred over a long timeframe. However, no discount rate was reported. The unit costs were not presented separately from the quantities of resources used. The health services included in the economic evaluation were ESRD treatment costs and losartan. The costs of treating ESRD were for haemodialysis, peritoneal dialysis, and renal transplantation. The costs of losartan included the drug, prescription fee, and mark-up minus patient copayment. The net ESRD-related costs were estimated by subtracting the drug costs of losartan from the mean ESRD-related costs per patient. The cost/resource boundary of the health care payer was adopted. Hospitalisation costs were also considered and were based on renal-related, cardiovascular-related, or other hospitalisations by a study investigator who was blinded to the treatment group allocation. Resource use was estimated mainly from trial data. Some assumptions about the categories of costs excluded (i.e. the costs associated with monitoring serum creatinine and potassium, or the costs of non-study medications) were made. The treatment costs came from published studies, while the drug costs were obtained from public sources. The price year was not explicitly reported, but it appears to have been 2001.

Statistical analysis of costs
Statistical analyses were conducted to test the statistical significance of differences in the cost estimates.

Indirect Costs
The indirect costs were not included.

Currency
Canadian dollars (Can$).

Sensitivity analysis
A univariate sensitivity analysis, in which the daily costs of ESRD were varied by +/- 10%, was conducted to assess the robustness of the estimated cost-savings. A bootstrap method was also used to determine the CIs for days saved and the cost-savings with losartan over placebo.

Estimated benefits used in the economic analysis
As shown in the effectiveness analysis, losartan reduced the estimated number of days with ESRD by 33.6 (95% CI: 10.9 - 56.3) over 3.5 years, and by 46.9 (95% CI: 19.1 - 74.7) over 4 years.

Cost results
When the drug costs were not considered, the cost-savings with losartan over placebo were:

- Can$28 after 0.5 years, (p=0.413);
- Can$83 after 1 year, (p=0.423);
- Can$168 after 1.5 years, (p=0.574);
- Can$797 after 2 years, (p=0.191);
- Can$1,705 after 2.5 years, (p=0.064);
- Can$2,949 after 3 years, (p=0.019);
- Can$4,695 after 3.5 years, (p=0.004); and
- Can$6,554 after 4 years, (p=0.009).
Substantial cost-savings pertaining to hospitalisation expenses were also observed after the third year.

When the cost of losartan was also included in the analysis, net cost-savings with losartan were observed after 2 years' follow-up (Can$130), 2.5 years (Can$908), 3 years (Can$2,033), 3.5 years (Can$3,675) and 4 years (Can$5,445).

The cost-difference was statistically significant only after 3.5 years' follow-up.

The sensitivity analysis revealed that changes in the daily cost of ESRD did not affect the estimated cost-savings. Further, the cost of ESRD would have to decrease by 78% before the net cost-savings with losartan therapy would reach zero.

**Synthesis of costs and benefits**
The costs and benefits were not combined because losartan dominated placebo (less effective and more costly).

**Authors' conclusions**
Compared with placebo, the use of losartan reduced days of end-stage renal disease (ESRD) and treatment costs in patients with nephropathy from Type 2 diabetes, in Canada.

**CRD COMMENTARY - Selection of comparators**
The rationale for the choice of the comparator was clear. Placebo was used in the clinical trial that provided the evidence. In addition, placebo was also likely to represent an actual treatment option for Type 2 diabetes patients with nephropathy who were taking conventional antihypertensive therapies. You should decide whether it is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The internal validity of the analysis was likely to have been high due to the robust design of the primary trial, which was randomised and double-blinded. However, limited information on the methods of sample selection and outcome assessment was provided. Further details of the primary source were reported elsewhere (see Other Publications of Related Interest).

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the disease considered in the study and is hardly comparable with the benefits of other health care interventions. It was derived directly from the effectiveness analysis.

**Validity of estimate of costs**
The authors stated explicitly which perspective was adopted in the study. As such, it appears that all the relevant categories of costs have been considered in the analysis. A detailed breakdown of the costs was not provided, and information on the unit costs and quantities of resources used was not reported. This reduces the possibility of replicating the study. Discounting was relevant due to the long time horizon of the study, but was not reported. The source of the data was reported for most items. Some statistical tests were conducted. These assessed the significance of differences in the estimated cost-savings.

**Other issues**
The authors did not compare their findings with those from other studies since they stated that their study was the first one to assess the economic impact of losartan. The issue of the generalisability of the study results to other settings was not explicitly addressed and few sensitivity analyses were conducted. This reduced the external validity of the analysis. The authors highlighted the unique advantages of losartan but also the limitations of their study. First, the outcomes were not actually assessed after the 4-year period considered in the analysis. Second, the issues of patient
compliance and tolerability is likely to affect heavily the benefits of the therapy. Finally, ethnic differences could reduce the benefits of antihypertensive therapies.

**Implications of the study**
The study results suggested that, from the perspective of the Canadian health care payer, losartan represents a cost-effective treatment for Type 2 diabetes patients with nephropathy.

**Source of funding**
Supported by a grant from Merck Frosst Canada Ltd.

**Bibliographic details**

**PubMedID**
15152291

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Angiotensin Receptor Antagonists; Canada; Cost Savings; Diabetes Mellitus, Type 2 /drug therapy /economics; Diabetic Nephropathies /drug therapy /economics; Double-Blind Method; Drug Costs; Female; Health Care Costs; Health Expenditures; Humans; Kidney Failure, Chronic /economics; Losartan /antagonists & inhibitors /therapeutic use; Male; Middle Aged

**AccessionNumber**
22004000730

**Date bibliographic record published**
28/02/2005

**Date abstract record published**
28/02/2005