Effects of losartan-based therapy on the incidence of end-stage renal disease and associated costs in type 2 diabetes mellitus: a retrospective cost-effectiveness analysis in the United Kingdom

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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 - 100 mg once daily) for the prevention or delay of progression of diabetic nephropathy to end-stage renal disease (ESRD) in patients with Type 2 diabetes mellitus (DM-2) and nephropathy.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with DM-2 and nephropathy. Inclusion and exclusion criteria may be found in the primary publication.

Setting
The setting was primary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were derived from a study published in 2001. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that used in the effectiveness analysis.

Study sample
Limited information on sample selection was provided. Overall, 1,513 adult patients were included. There were 751 patients in the losartan group and 762 in the control group.

Study design
This was a prospective, double-blind, randomised clinical trial. The mean length of follow-up was 3.4 years. Other details on follow-up, randomisation and the number of centres involved were not reported.
Analysis of effectiveness
It was not stated whether the analysis was conducted on an intention to treat basis or on treatment completers only. The primary outcome measure was a composite end point consisting of a 2-fold increase in serum creatinine concentration (SCr), development of ESRD (defined as the need for dialysis or transplantation), or death. The relative risk (RR) of developing ESRD was also presented separately. No information on the comparability of the study groups was provided, but the randomisation methods employed should have ensured that the patients in the two groups were not statistically significantly different.

Effectiveness results
The RR for the composite outcome was 25% less in the losartan-treated group than in the control group, (p=0.006). Similarly, the RR for ESRD was 28% less in the losartan-treated group, (p=0.002).

Clinical conclusions
The effectiveness analysis showed that losartan was significantly more effective than control treatments for the prevention of ESRD in patients with DM-2 and nephropathy.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic evaluation was the number of life-years saved (LYS). These were obtained by combining data on the RR of ESRD obtained from the clinical trial with the life expectancy differences between individuals with and without ESRD. The long-term analysis assumed that losartan did not provide any additional clinical benefits in ESRD risk reduction beyond the trial period. An annual discount rate of 3.5% was applied. The cumulative incidence of ESRD at 4 years was also reported.

Direct costs
The analysis of the costs was carried out from the perspective of the NHS. It included the costs of losartan, haemodialysis and peritoneal dialysis. The unit costs were not presented separately from the resource quantities. The costs of non-study medications were assumed to have been similar between the two treatment groups. It was also assumed that patients who discontinued study medication incurred no additional costs. The costs associated with monitoring SCr and potassium concentration were not included because this monitoring would be performed routinely in patients with DM-2 and renal disease. The costs of treating complications associated with dialysis were also excluded from the analysis. Resource use was estimated retrospectively from the actual resource consumption observed in the RENAAL study. In the base-case, the costs of haemodialysis and peritoneal dialysis were derived from the UK Transplant website, where costs relevant to the NHS were considered. The lifetime cost of ESRD was based on an annual average cost for haemodialysis and peritoneal dialysis, weighted according to the distribution of first renal replacement therapy and the median survival time of patients undergoing diabetic renal replacement therapy (age-matched to the RENAAL population). In a secondary analysis, the costs of haemodialysis and peritoneal dialysis were taken from the UK 2-Center European Dialysis and Cost-Effectiveness (EURODICE) study. The price year was 2004. Discounting was relevant and an annual rate of 3.5% was used.

Statistical analysis of costs
Statistical analyses were carried out to test the statistical significance of cost-differences between the groups by generating confidence intervals (CIs) around mean values using the bootstrapping method.

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

Currency
UK pounds sterling (\(\)). The exchange rate from UK pounds sterling to US dollars (\(\$\)) was 1 = \$1.75.

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the robustness of the costs and benefits to variations in the cost of daily renal replacement therapy and life expectancy (increased by 50%) with losartan when on dialysis. Alternative cost estimates were based on different costing approaches (bottom-up and top-down approaches from the EURODICE study). A bootstrapping approach was also used to generate CIs around the costs and benefits.

**Estimated benefits used in the economic analysis**
The expected LYS were 7.82 with losartan and 7.38 with the control treatments (difference 0.44, 95% CI: 0.16 to 0.71; \(p=0.002\)).

The cumulative incidence of ESRD at 4 years was 0.193 with losartan and 0.296 with the control treatments (difference -0.102, 95% CI: -0.157 to -0.047; \(p<0.001\)).

**Cost results**
The medication costs per patient were 768 with losartan and 0 with the control treatments (difference 768, 95% CI: 707 to 820; \(p<0.001\)).

The ESRD-related costs per patient were 14,009 with losartan and 21,399 with the control treatments (difference -7,390, 95% CI: -11,366 to -3,414; \(p<0.001\)).

Thus, the total costs per patient were 14,777 with losartan and 21,399 with the control treatments (difference -6,622, 95% CI: -10,591 to -2,653; \(p=0.001\)).

**Synthesis of costs and benefits**
A synthesis of costs and benefits was not required since losartan dominated the control treatments, which were both less effective and more expensive. The costs and benefits estimated in the base-case analysis remained robust to variations in clinical and economic factors. Therefore, losartan remained the preferred treatment even under unfavourable scenarios (i.e. when the cost of renal replacement therapy was reduced by 50%).

**Authors’ conclusions**
A losartan-based regimen in patients with Type 2 diabetes mellitus (DM-2) and nephropathy was cost-saving from the perspective of the National Health Service (NHS) in the UK because it reduced the incidence of end-stage renal disease (ESRD) in comparison with a non angiotensin-converting enzyme inhibitor or non angiotensin II antagonist antihypertensive regimen.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which represented a range of possible therapies for patients with DM-2 and nephropathy. You should decide whether they are valid comparators in your own setting. The authors stated that angiotensin-converting enzyme inhibitors and angiotensin II antagonists were not included because of the lack of reliable data from clinical trials.

**Validity of estimate of measure of effectiveness**
The effectiveness evidence was extracted from a published clinical trial, which was appropriate for the study question. The randomised design should have reduced the potential impact of selection bias, while double masking was appropriate to control for performance bias and assessment bias. The length of follow-up appears to have been appropriate. Most of the information on sample selection, patient follow-up and the use of power calculation was not
reported in this paper, thus the reader is referred to the primary publication. However, in general, the use of a large clinical trial ensures robust clinical estimates.

**Validity of estimate of measure of benefit**
The use of LYS as the summary benefit measure was appropriate as the impact of the interventions on survival is a key aspect of patient health. LYS are comparable with the benefits of other health care interventions. However, since quality of life is also a relevant aspect of health for patients with DM-2 and nephropathy, the use of quality-adjusted life-years would have been helpful.

**Validity of estimate of costs**
The analysis of the costs was consistent with the authors' stated perspective. Typical NHS sources were used to derive the costs, but details of the unit costs and resource quantities were not presented. A detailed breakdown of the cost items was not given and some costs were presented as macro-categories, which will not help any attempt to replicate the analysis in other settings. The cost estimates were specific to the study setting and alternative costing approaches were used in the sensitivity analysis. Statistical analyses of the costs were carried out and CIs around the cost estimates were calculated. This represented a strength of the cost analysis. The price year was reported, which will facilitate reflation exercises in other time periods. The authors stated that some costs were excluded on the basis of specific assumptions. However, they also stated that the use of these assumptions biased the analysis in favour of the comparators, thus the base-case analysis gave conservative results.

**Other issues**
The authors stated that their findings were similar to those obtained in previous cost studies of losartan. The issue of the generalisability of the study results to other settings was not explicitly addressed and only limited sensitivity analyses were carried out. Thus, the external validity of the study was low. The authors noted that median life expectancy as opposed to mean life expectancy was applied to extrapolate clinical data and this should bias the analysis against losartan, making the results of the study conservative. The study referred to patients with DM-2 and nephropathy and this was reflected in the authors' conclusions.

**Implications of the study**
The study results supported the use of losartan for the treatment of patients with DM-2 and nephropathy. The authors stated that future studies should assess the relative cost-effectiveness of losartan versus angiotensin-converting enzyme inhibitors or angiotensin II antagonists in patients with DM-2 and nephropathy. In effect, there is a lack of data on the extent to which angiotensin-converting enzyme inhibitors delay the need for renal replacement therapy in this specific patient population.

**Source of funding**
None stated.

**Bibliographic details**

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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