Ramipril prolongs life and is cost effective in chronic proteinuric nephropathies
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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 ramipril to delay the progression of chronic renal disease to end-stage renal disease (ESRD) in patients with non-diabetic chronic nephropathies.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of patients with non-diabetic chronic nephropathies.

Setting
The study setting was hospital. The economic study was carried out in Italy.

Dates to which data relate
The dates during which effectiveness and resource use data were collected were not reported. Costs were collected from studies published between 1990 and 1997. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

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

Study sample
117 and 166 patients, respectively, were randomised to comparable blood pressure control with ramipril or conventional therapy in the Ramipril Efficacy in Nephropathy Trial (REIN). Patients included those with chronic, non-diabetic nephropathies and persistent urinary protein excretion rate of 3g or more per 24 hours. No power calculations were reported.

Study design
The study took the form of a prospective randomised double-blind trial carried out at 14 centres. No patients were lost
to follow-up.

**Analysis of effectiveness**
The analysis was based on intention to treat. Primary health outcomes studied included the rate of GFR decline, the reduction in proteinuria, and the risk of progression. The baseline characteristics of patients in the two treatment groups were comparable.

**Effectiveness results**
The decline in GFR per month was significantly lower in the ramipril group than the control group (0.53 (0.8) versus 0.88 (0.13) mL/min, p=0.03).

Among the ramipril patients, the percentage reduction in proteinuria was inversely correlated with the decline in GFR, (p=0.035) and predicted the reduction in risk of doubling of baseline creatinine or endstage renal failure (18 ramipril versus 40 placebo, p=0.04).

The risk of progression was still significantly reduced after adjustment for changes in systolic, (p=0.04) and diastolic, (p=0.04) blood pressure, but not after adjustment for changes in proteinuria.

**Clinical conclusions**
In chronic nephropathies with proteinuria of 3g or more per 24 hours, ramipril safely reduces proteinuria and the rate of GFR declines to an extent that seems to exceed the reduction expected for the degree of blood-pressure lowering.

**Modelling**
A lifetime decision analytic model was used to determine the cost-effectiveness of the two treatment strategies.

**Measure of benefits used in the economic analysis**
The progression to ESRD and life expectancy were used as the measures of benefit. Benefits were discounted at an annual discount rate of 5%.

**Direct costs**
Direct costs were discounted at an annual discount rate of 5%. Quantities and costs were not reported separately. Direct costs related to all direct medical costs, including those for outpatient and inpatient care, medications, medical equipment, supplies, and laboratory tests. The quantity/cost boundary adopted was that of the health service. The estimation of quantities and costs was based on actual data. Costs were collected from studies published between 1990 and 1997. The price year was not reported.

**Statistical analysis of costs**
No statistical analysis was carried out.

**Indirect Costs**
Indirect costs were not included.

**Currency**
US dollars ($).
Sensitivity analysis
Sensitivity analyses were conducted on costs, mortality rate, and discount rate to compute best and worst case results.

Estimated benefits used in the economic analysis
Both models predicted a reduced and delayed progression to ESRD and a prolonged patient survival in the ramipril group. The difference in time to ESRD between the two treatment groups was highly significant in the events-based model. At the time of progression to ESRD, ramipril patients were older as compared with controls (GFR model: 56.5 +/-1 versus 55.0 +/-0.9, p=0.19; events model: 56.9 +/-1.1 versus 54.7 +/-0.9, p<0.01), and therefore had a shorter life expectancy. Patients in the ramipril group had a longer overall survival.

Cost results
The difference in lifetime treatment costs between ramipril and the control group was $1,667 before progression to ESRD and $-18,271 on progression to ESRD, generating overall costs of $-16,605 (in the GFR model).

The difference in lifetime treatment costs between ramipril and the control group was $2,145 before progression to ESRD and $-26,000 on progression to ESRD, generating overall costs of $-23,894 (in the events model).

The difference in overall per year costs between ramipril and the control group was $-2,422 in the GFR model and $-4,203 in the events model.

Synthesis of costs and benefits
Ramipril as compared with non-ACE inhibitor treatment increased life expectancy by prolonging pre-ESRD survival and decreased direct costs. These results were robust to changes in model parameters.

Authors' conclusions
Ramipril prolongs life while saving money because of its beneficial effect on the course of non-diabetic chronic nephropathies.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparator used; namely that it represented traditional treatment. You, as a user of the database, should decide if this health technology is relevant to your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised-controlled trial, which was appropriate for the study question. The study sample was representative of the study population and patient groups were shown to be comparable at analysis. The internal validity of the effectiveness results is therefore likely to be high.

Validity of estimate of measure of benefit
The estimation of benefits was appropriately derived directly from the effectiveness analysis.

Validity of estimate of costs
Good features of the cost analysis were that all relevant direct cost categories were included, and sensitivity analysis was conducted on costs. However, quantities and costs were not reported separately, charges were used to proxy prices, and the price year was not reported. These latter features of the analysis tend to limit the generalisability of the cost results to other settings.
Other issues
The authors did make appropriate comparisons of their findings with those from other studies and did address the issue of generalisability to other settings. The authors did not present their results selectively. The study considered patients with non-diabetic chronic nephropathies and this was reflected in the authors' conclusions. The authors did not consider other clinical and laboratory parameters that may contribute towards establishing a diagnosis of ESRD, such as azotemia, and fluid overload. The authors also noted that their model did not consider the specific cardioprotective and lifesaving potential of ACE inhibitors suggested by recent studies. The authors did not consider quality-adjusted life years and indirect costs, which would be relevant for this study population.

Implications of the study
Ramipril prolongs life while saving money because of its beneficial effect on the course of non-diabetic chronic nephropathies. Future studies are needed to extrapolate these results to the entire population of patients with chronic renal disease and nephrotic range proteinuria.

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