
Modelling and costing the consequences of using an ACE inhibitor to slow the progression of renal failure in type I diabetic patients

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Summary

Antihypertensive drugs slow the progressive decline in renal function seen in patients with insulin-dependent diabetes and nephropathy. In a recent study, the ACE inhibitor captopril protected against this deterioration in renal function. We developed an economic model to analyse the cost impact of ACE inhibitor treatment on progression to end-stage renal failure (ESRF) in diabetic patients over 4 years. Two scenarios were compared: one describing the progression of a cohort of 1000 patients receiving 25 mg captopril three times daily, and the other for an equivalent cohort without such prophylactic treatment. Previously published data were

used to estimate the transition rates for each stage from the onset of renal failure until death. All direct costs were discounted by an annual rate of 6%, and were subjected to sensitivity analysis. The discounted cost saving of ACE inhibitor treatment for a cohort of 1000 patients was estimated as £0.95 million over 4 years. Under sensitivity analysis, these results were very robust to variations in the costs of ESRF treatment. Prophylactic treatment with ACE inhibitors was predicted to provide substantial increases in life expectancy and reduction in the incidence of ESRF, while also providing significant economic savings.

Introduction

Diabetic nephropathy is a relatively common microvascular complication of both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM), and poses a major threat to survival and quality of life in people with diabetes.¹ It is clinically defined by the presence of persistent proteinuria in a diabetic patient with concomitant retinopathy and elevated blood pressure, but without urinary-tract infection, other renal disease, or heart failure.² In established diabetic nephropathy, glomerular filtration rate declines relentlessly towards end-stage renal failure (ESRF), necessitating dialysis or transplantation in many cases.

Studies in the UK have indicated that approximately 600 new cases of ESRF occur in diabetic patients every year (about 10 cases per million population).³ Throughout the world, over half a million patients are registered as being on renal

replacement therapy (RRT), and diabetic nephropathy is the cause in nearly one-fifth of them.⁴ In the US, the total cost of caring for diabetic patients with renal failure approached US\$2 billion in 1989, and continues to rise rapidly.⁵ Many other costs are not included in this total, such as the cost of most out-patient drugs, and lost production. Table 1 outlines the major direct and indirect costs of diabetic nephropathy to society.⁶

Patients with diabetic nephropathy almost invariably suffer from raised arterial blood pressure.² A progressive rise in blood pressure occurs with declining renal function.⁷ Treatment of hypertension has been shown to slow the rate of loss of renal function, and several studies have used angiotensin-converting enzyme (ACE) inhibitors.²

The Diabetic Nephropathy Collaborative Study Group (DNCSG) carried out a trial to determine

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Table 1 Major costs of diabetic nephropathy to society

Direct costs	Indirect costs
Drug therapy	Premature mortality
Renal transplantation and maintenance	Premature retirement
Hospital care	Absenteeism from work
Dialysis	Poor work performance
Nursing-home care	
Surgery (e.g. amputation) and physiotherapy	
GP consultations	
Retinopathy	
Dietician consultations	
Cardiovascular events and care	

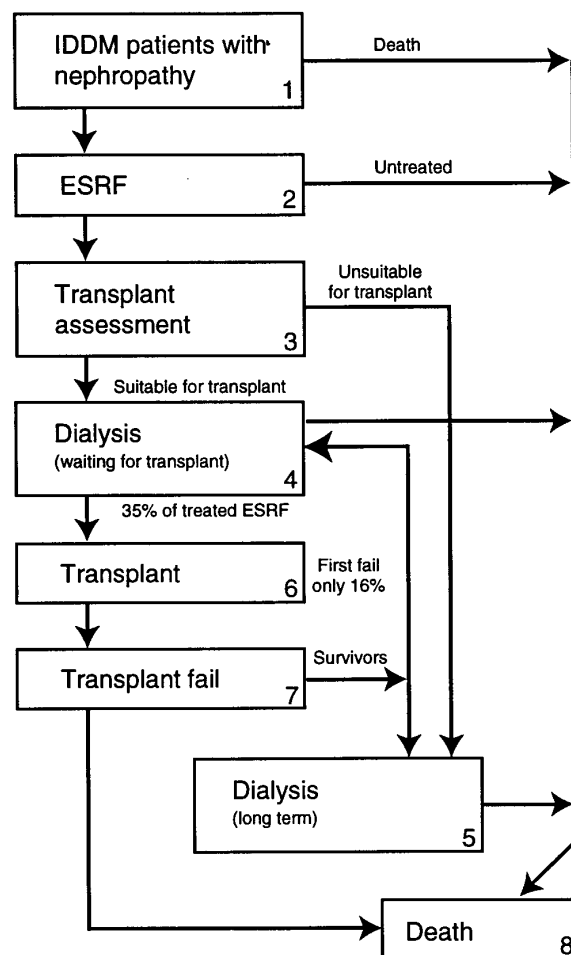
Adapted from reference 6.

whether the ACE inhibitor captopril was more effective in slowing progression to ESRF than other anti-hypertensive agents.⁸ In this placebo-controlled, multicentre, randomized trial involving 409 patients with IDDM in the USA, the risk of a doubling of the serum creatinine concentration was reduced by 48% in the ACE inhibitor group. Thus, ACE inhibitor therapy was shown to have a beneficial kidney-protecting effect, with few serious side-effects. Lewis *et al.*⁸ concluded that ACE inhibitor therapy should be used in normotensive and hypertensive patients with diabetes and clinically evident nephropathy.

We have developed an economic model using the results of the DNCSG to simulate the likely long-term outcome of ACE inhibitor treatment in IDDM patients with nephropathy. Our aim was to estimate the effectiveness of ACE inhibitor treatment in terms of survival and the need for kidney transplantation, and also to assess the cost savings and benefits by considering all direct costs of medical care. We compared two simulated cohorts of patients with diabetic nephropathy, one cohort treated prophylactically with an ACE inhibitor (25 mg captopril three times daily) and the other not so treated.

Methods

Figure 1 shows the treatment paths used in the economic model for a simulated group of patients with diabetic nephropathy, from the development of ESRF to death. The model covers a period of 4 years, the duration of the DNCSG trial.⁸ The group of patients were aged 18–49 years, had had IDDM for at least 7 years, with an onset before the age of 30 years, and had diabetic retinopathy.⁸ Comorbidity conditions included in the model are not shown in Figure 1, and are discussed later.

**Figure 1.** Diabetic nephropathy event and treatment paths.

The model starts with a cohort of patients with diabetic nephropathy⁸ (Figure 1, box 1). The user can select an initial cohort size (for example, 1000) or the size of the population to be considered. In the latter case, the model calculates the size of the cohort from the incidence rates of diabetic nephropathy.

Some patients in the initial cohort will go on to develop ESRF (box 2). It is this progression that was delayed by prophylactic treatment with an ACE inhibitor. Progression rates to ESRF and death for patients treated with and without the ACE inhibitor were taken from a similar study carried out in the US, which derived these figures from the DNCSG trial data.⁹ In the subsequent analysis, it was assumed that 10% of those who develop ESRF will not be treated because of major comorbidities, and will die within a short period of time.

The majority of patients who are recommended for ESRF treatment will be assessed to determine their suitability for kidney transplant (box 3). We have assumed that this assessment may include an echocardiogram (90%), cardiac consultation (30%), and cardiac catheterization (15%).

As a result of the transplant assessment, some patients will be on dialysis and waiting for a suitable transplant to become available (box 4), whilst others will be on permanent dialysis (box 5). For costing purposes, the model includes the three most common modes of dialysis in the UK: hospital (35%), home (5%), and continuous ambulatory peritoneal dialysis (CAPD, 60%).¹⁰ Over a period of two and a half years, up to 35% of patients will receive a kidney transplant (box 6). However, 15% of patients waiting for a transplant die annually.¹⁰

Patients whose transplants fail (box 7) are categorized into 'early' and 'late' graft failures according to whether the transplant failed in the first year post-transplant, or subsequently. This allows different survival parameters to be used for early and late graft failure patients, to take account of the average additional life years already enjoyed by late graft failure patients.¹⁰ Some patients who survive a transplant failure will be regrafted, although it is extremely rare for a diabetic patient to have more than two grafts, the maximum assumed in the model.

Comorbidities

Comorbid conditions are included in the model as average incidence or prevalence rates for a group of patients. The probabilities were derived from literature where possible, or clinical judgement was used. Comorbidities where the same rates were used for all patients include diabetic retinopathy, and ketoacidosis or hypoglycaemic episodes. Different rates were used for patients before progression to ESRF, on dialysis, or post-transplant, for peripheral vascular disease (ulcers and amputations) and cardiovascular events and conditions (stroke, angina, myocardial infarction, congestive heart failure, and revascularization).

Treatment

Typical treatment pathways for diabetic nephropathy in the UK were used in the model. Most of the data relating to dialysis and transplants were obtained from the Report of the Review of the London Renal Services,¹⁰ which is based mainly on UK and European EDTA data. The long-term survival rates of patients with diabetic nephropathy may be underestimated, as data from 1978 onwards were used to achieve reasonable sample sizes, and survival rates are likely to have improved since then.

Drug treatment and specific procedure costs

Costs for procedures and other hospital treatments were obtained from a variety of hospitals in England. Drug costs were derived from published NHS sources,¹¹ ACE inhibitor treatment being costed on the basis of 25 mg captopril three times daily, giving

an annual cost of £249. Costs for GP care and cardiology treatments, and procedures included in the model, were taken from 'Costing of Cardiology Services',¹¹ which also gives more detail of the costing methodology.

Indirect costs and savings

In this analysis, only direct costs have been incorporated. Indirect costs, such as loss of working capacity due to dialysis, or benefits such as increased fitness for work (see Table 1) have been omitted. This has been done for two reasons. Firstly, the indirect costs are notoriously difficult to quantify and are, at best, subjective. Secondly, the paper is written from an NHS perspective, and the only relevant costs in such a context are direct NHS costs. However, from a community standpoint, the use of direct costs and savings in these calculations probably underestimates the true benefit of prophylactic treatment.

Discounting

All costs and benefits have been discounted by 6% per year to take into account the general preference to incur costs in the future rather than in the present.¹²

Sensitivity analysis

A sensitivity analysis was performed by varying key parameters to investigate the effect of uncertainties in the data on the results of the study. The sensitivity of the direct cost savings achieved by treating patients with an ACE inhibitor was examined in relation to the two key study parameters—the rates of progression of the two cohorts to ESRF and death, and the difference in the costs of care for diabetic care alone compared with the costs of treating ESRF.

Further program details

Further details of the program used to make the calculations can be obtained from the York Health Economic Consortium.

Results

The annual costs of treating different patient groups, as well as the total costs for each cohort, were calculated.⁶ The total cost over 4 years for a cohort of 1000 patients treated with an ACE inhibitor was £8 334 500 compared with £9 287 300 for the untreated group (Table 2). This shows an immediate saving of £952 800 on direct costs, equivalent to a saving of £953 per patient.

In the first year, the cost of the cohort of ACE inhibitor patients is greater than the untreated cohort,

Table 2 Total undiscounted costs over 4 years for an initial cohort of 1000 patients with and without ACE inhibitor treatment

	Total costs over 4 years (without ACE inhibitor)	Total costs over 4 years (with ACE inhibitor)
Pre-ESRF	£4 394 700	£4 761 700
Untreated ESRF	£3200	£2100
ESRF entry	£19 600	£12 700
Transplants	£171 200	£104 200
Post-transplant (year 1)	£353 900	£209 100
Post-transplant (year 2 +)	£113 000	£50 500
Dialysis (year 1)	£3 138 000	£2 025 400
Dialysis (year 2 +)	£2 112 300	£1 078 800
ACE inhibitor	£0	£977 700
Total	£10 305 900	£9 222 200

due to the additional cost of the treatment itself (£977 700 over 4 years). However, by the second year, the medical benefits of reducing the number of patients developing ESRF are reflected in the reduced costs of care (Figure 2). The costs saved in not having to treat so many patients for ESRF more than compensate for the cost of the ACE inhibitor and the costs of treating the extra patients kept alive.

Figure 3 shows the costs of caring for ESRF patients, either with transplants or with dialysis, relative to the cost of diabetic care alone. The cost of caring for a patient on dialysis is over 18 times the cost for diabetic care alone, at approximately £23 000 per year.

Results applied to different populations

This economic model can also be used in ‘population mode’ to establish the cost consequences of treating diabetic patients with nephropathy for a given population. The incidence of diabetic nephropathy in the UK has been estimated using EDTA figures

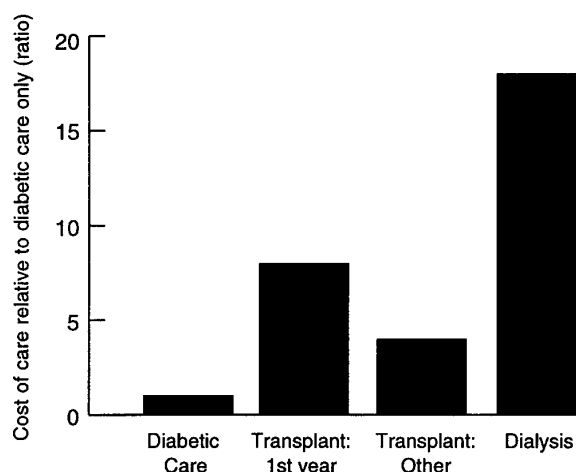


Figure 3. Cost of ESRF care relative to the cost of diabetic care only.

for IDDM patients starting renal replacement therapy¹³ and data from the Lewis trial of the percentage of patients with diabetic nephropathy

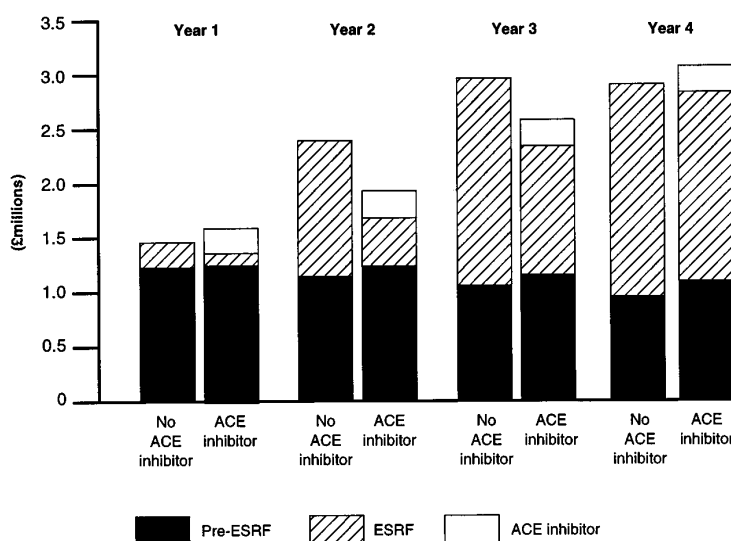


Figure 2. Comparison of treatment costs by year with and without ACE inhibitor treatment.

reaching ESRF or dying each a year. Examples of results are shown in Table 3, using the UK population and illustrated population sizes of small districts (200 000) and large districts (500 000) in the model to calculate discounted cost savings and life years saved. These figures indicate the savings arising from each cohort of patients entering the model each year.

These are treatment costs for the number of patients developing diabetic nephropathy in any year, over the following four years, and can also be interpreted as the total costs for four successive cohorts in any one year.

Sensitivity analysis

The calculated progression rates to ESRF and death appear erratic from year to year, presumably as a result of the relatively small number of patients with diabetic nephropathy affected. Two issues of relevance are: how the costs of treating either cohort are affected by the timing of progression to ESRF, and the confidence limits on the overall progression rates over the four years.

Regression lines were fitted to each of the cumulative progression rates to ESRF and death. The result of smoothing these progression rates was to increase slightly the costs of both the ACE-inhibitor-treated group and the untreated group. However, the absolute cost saving for the ACE-inhibitor-treated cohort of 1000 patients over four years is increased to £1.0m, but the life years saved are reduced very slightly from 195 to 191.

Proportional-hazards regression analysis was used to estimate the 95% CIs of the risk reduction for death/ESRF in the DNCSG study.⁸ These CIs were applied to the cumulative progression rates, using the untreated group results as a baseline. In the worst case, if a risk reduction of only 18% is assumed (compared with the trial result of 50%), a cost of £71 000 is incurred over 4 years and 52 life-years are saved; the cost per life-year saved is £1360. The upper 95%CI (70%) on risk reductions suggests a cost

saving of £2.3m, with 211 life years saved over 4 years.

The key variable in this economic analysis was the ratio of the cost of treating patients for ESRF compared with that of treating patients for diabetes alone. A sensitivity analysis was done by leaving the costs of diabetic care constant and underestimating the costs of all procedures and treatment for ESRF by 10% and 20%; and also overestimating the costs by 10% and 20%.

It can be seen that even if the costs of ESRF treatment have been overestimated by 20%, there is a resultant cost saving using ACE inhibitor therapy of £517 200 over 4 years (Figure 4). If the ESRF costs have been underestimated by 20%, the cost saving over 4 years is increased to almost £1.4m.

Discussion

The DNCSG has shown that ACE inhibitor therapy protects against deterioration in renal function in insulin-dependent diabetic nephropathy, and is significantly more effective than blood pressure control alone over a period of four years.⁸ ACE inhibitor treatment was also associated with a 50% reduction in risk of the combined endpoints of death, dialysis, and transplantation that was independent of a small disparity in blood pressure between the groups.

In this study, the cost saving of prophylactic treatment with an ACE inhibitor over 4 years for an initial cohort of 1000 has been estimated as £0.95m, with 195 life-years saved. For the UK population (58.4 m), this represents a cost saving of almost £400 000 per year. As indirect costs were not considered in this analysis, total cost savings would probably be even greater. Sensitivity analysis has shown that the most pessimistic scenario from the trial results, of only 18% reduction in risk progression to death or ESRF, would still yield 52 life-years saved at a cost of £71 000. The results are robust to variations in the costs of ESRF treatment.

Table 3 Discounted cost savings and life-years saved for sample population

	Population (millions)		
	58.4	0.5	0.2
Initial cohort size	413	3.5	1.4
Life-years saved	80.5	0.69	0.28
Total costs* (without ACE inhibitor)	£3,835,700	£32,840	£13,140
Total costs* (with ACE inhibitor)	£3,442,200	£29,470	£11,790
Cost saving	£393,500	£3,370	£1,350

* Total discounted costs for cohort over four years.

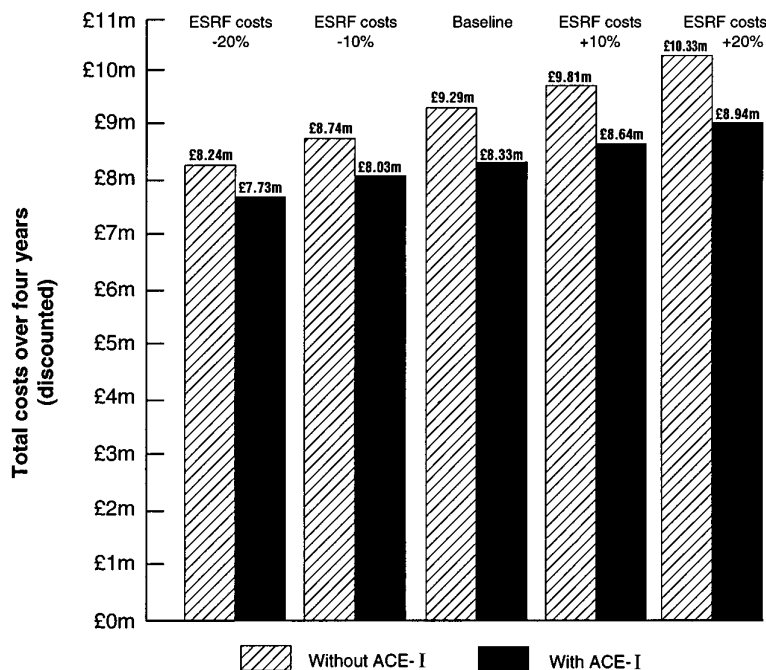


Figure 4. Sensitivity analysis on costs of ESRF treatment.

Clinically, prophylactic treatment of this group of patients with an ACE inhibitor significantly slows the rate of loss of renal function, by a mechanism independent of its antihypertensive properties.⁸ ACE inhibitors are known to decrease urinary protein excretion in patients with diabetes and other glomerulopathies, as shown in the Lewis study.⁸ This decrease could be explained by a beneficial effect of the drug on glomerular haemodynamics and glomerular pathology. Remuzzi and Bertani¹⁴ have suggested that proteinuria levels might be linked with the rate of progression of kidney damage, and are therefore relevant to the lower levels of urinary protein in patients treated with the ACE inhibitor in this study.

In conclusion, the clinical benefits of ACE inhibitor therapy appear to be combined with significant cost benefits.

Acknowledgements

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