To pay or not to pay? A decision and cost–utility analysis of angiotensin-converting-enzyme inhibitor therapy for diabetic nephropathy

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Abstract

Background: Angiotensin-converting-enzyme (ACE) inhibitor therapy can significantly delay the progression of diabetic nephropathy to end-stage renal failure (ESRF). The main obstacle to successful compliance with this therapy is the cost to the patients. The authors performed a cost–utility analysis from the government's perspective to see whether the province or territory should pay for ACE inhibitors for type I diabetic nephropathy on the assumption that cost is a major barrier to compliance with this important therapy.

Methods: A decision analysis tree was created to demonstrate the progression of type I diabetes with macroproteinuria from the point of prescription of ACE inhibitor therapy through to ESRF management, with a 21-year follow-up. Drug compliance, cost of ESRF treatment, utilities and survival data were taken from Canadian sources and used in the cost–utility analysis. One-way and two-way sensitivity analyses were performed to test the robustness of the findings.

Results: Compared with a no-payment strategy, provincial payment of ACE inhibitor therapy was found to be highly cost-effective: it resulted in an increase of 0.147 in the number of quality-adjusted life-years (QALYs) and an annual cost savings of $849 per patient. The sensitivity analyses indicated that the cost-effectiveness depends on compliance, effect of benefit and the cost of drug therapy. Changes in the compliance rate from 67% to 51% could result in a swing in cost-effectiveness from a savings of $899 to an expenditure of more than $1 million per additional QALY. A 50% reduction in the cost of ACE inhibitors would result in a cost savings of $299 per additional QALY with compliance rates as low as 58% in the provincial payment strategy.

Interpretation: Provincial coverage of ACE inhibitor therapy for type I diabetes with macroproteinuria improves patient outcomes, with a decrease in cost for ESRF services.

Diabetes mellitus is a leading cause of end-stage renal failure (ESRF).[1–3] In a large randomized controlled prospective study involving people with type I diabetes, angiotensin-converting-enzyme (ACE) inhibitor therapy was found to slow the progression of nephropathy to ESRF in patients with macroproteinuria.[4] Moreover, a protective role for ACE inhibitor therapy in diabetic and nondiabetic patients has been reported by several groups.[5–9] The beneficial effect of ACE inhibitor therapy, however, is affected by poor compliance.[10–13] Patients who experience no immediate benefit and require long-term treatment, for example those taking antihypertensive agents, have been found to have noncompliance rates of 50% or greater.[10–13] Cost of therapy is another major obstacle to drug compliance and is cited as the cause of failure in 34%–46% of cases.[14,15]

This economic barrier to drug compliance may result in higher overall treatment costs. In the United States and Canada ESRF services are covered by the state or province/territory. We performed a cost–utility analysis from the government's perspective to see whether the province or territory should pay for ACE inhibitors on the assumption that cost is the main barrier to compliance with this important therapy.[13–15] Three possible outcomes were considered — dialysis, renal transplantation and death — in patients with type I diabetes and macroproteinuria with and without ACE inhibitor therapy.

Research

Recherche

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This article has been peer reviewed.

CMAJ 2000;162(2):195-8

Methods

We created a decision analysis tree to demonstrate the progression of type I diabetes with macroproteinuria (urine protein level greater than 0.5 g/d) from the point of prescription of ACE inhibitor therapy through to ESRF management, over a 21-year follow-up period. The model was analysed using Decision Maker 7.0 (Steven G. Pauker, Frank A. Sonnenberg, J.Wong, New England Medical Center, Boston). On the basis of the report of the Collaborative Study Group,[4] we assumed the following; (a) that the baseline creatinine clearance is 1.37 mL/s and that the level will decline at an annual rate of 11% in patients who comply with the ACE inhibitor therapy and of 17% in those who do not comply; (b) that patients reach ESRF when their creatinine clearance is 0.17 mL/s, which will occur in 18 years for compliers and 11 years for noncompliers; and (c) that, at an annualized death rate of 1.8%, 28% of the compliers will die over the 18 years and 72% will go on to ESRF treatment, and 18% of the noncompliers will die over the 11 years and 82% will progress to ESRF treatment. The 1996 Canadian Organ Replacement Register (CORR) provides actual survival rates among diabetic patients followed for 10 years and the disposition of their treatment modality during that period; it indicates that 79% of patients receive dialysis treatment and 21% receive transplantation. In the final nodes of the decision tree, "death" reflects the ongoing mortality while taking ACE inhibitor therapy; "long dialysis" and "long transplant" reflect the 10-year duration of these treatment modalities, based on survival data from the CORR database; and "short dialysis" and "short transplant" reflect a 3-year duration of these treatments for compliers, who have experienced 18 years of survival before the need for the treatment. For the decision analysis we presumed that longevity was similar in both the no-payment and the provincial payment groups.

We assumed that the long-term compliance rate was 50% among patients in the no-payment arm and 67% in the provincial payment arm.[10–14] The change from 50% to 67% represents a 34% cost barrier to compliance, which is similar to that noted in the study by Brand and associates.[14]

The cost of ACE inhibitor therapy was derived from a 1-year cost analysis of initial antihypertensive therapy in patients with newly diagnosed moderate hypertension.[16] We included the cost not only of the ACE inhibitor itself but also of supplemental drugs, laboratory monitoring, clinic visits and treatment because of side effects.[17]

The costs for hospital hemodialysis and continuous ambulatory peritoneal dialysis, reported by Goeree and colleagues,[18] were derived from fully allocated cost analysis in 1993 Canadian dollars for patients treated by the same dialysis modality for a full year. This measurement included in-patient and out-patient costs, overhead costs, personnel, supplies, medication costs and physician fees.[19]

The costs of ACE inhibitor therapy and ESRF treatments were converted to 1996 Canadian dollars using the Consumer Price Index for Canada.[17,19]

The transplantation costs reported in a cost-utility analysis by Laupacis and colleagues[20] for diabetics include in-patient hospitalization, out-patient visits including dialysis, transplant clinic visits, medications, laboratory tests and physician fees (nephrectomy of the living-related donor), the transplant program and patient-borne costs.[20] Costs for all subsequent years were assumed to be the same as those for the second year.[19]

The ESRF costs and utilities were corrected for annual mortality using the CORR survival curves. In the "long" dialysis and transplantation arms, a cumulative 10-year survival rate was applied to treatment costs and utilities; in the "short" dialysis

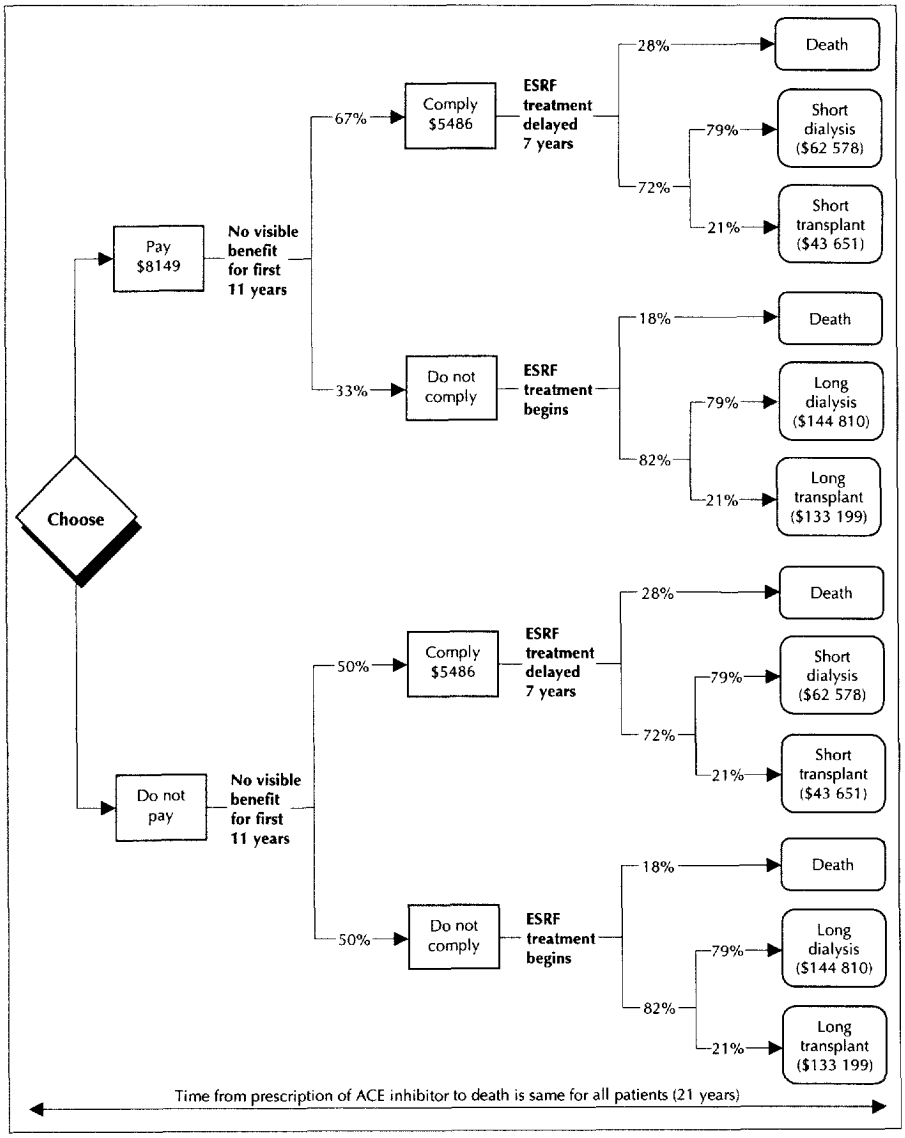

Fig. 1: Decision analysis tree, showing progression of patients with type I diabetes mellitus and macroproteinuria from start of angiotensin-converting-enzyme (ACE) inhibitor therapy through to treatment of end-stage renal failure (ESRF), with 21-year follow-up. See Methods for details.

and transplantation arms a 3-year survival rate was applied.

In our analysis, we discounted all costs and all utility values by 5% per year in accordance with Canadian guidelines for economic evaluation of pharmaceuticals.[21] Discounting attempts to correct for differential timing of costs and effects and accounts for the time value of money or the universal preference for funds now rather than later.[22]

For the basic decision analysis we used the quality-adjusted life-years (QALYs) for ESRF therapy reported by Churchill and associates[23] to quantify patient outcomes. The QALYs were constructed using the time trade-off technique determined from 272 ESRF patient interviews. Evidence for construct validity was based on correlation with the Spitzer Quality of Life Index and a provider visual analogue scale. Patients in an ESRF program were asked to estimate quality of life using the time trade-off for a year of hemodialysis, peritoneal dialysis or transplantation. The baseline time trade-off values were 1 for a year of full health and 0 for death. The terminal nodes of the decision analysis are an accumulation of the utilities (QALYs) over the time patients are taking or not taking ACE inhibitors plus the years in ESRF corrected for annual mortality.

To test the robustness of our results, we conducted cost-effective sensitivity analyses. We varied estimates of drug and treatment costs and of compliance rates from baseline values and time benefit of compliance to see if the optimal strategy changed. All of our assumptions were constructed with conservative probabilities derived from the literature, which would favour the no-payment strategy.[11–15]

Results

The decision tree (Fig. 1) indicates that 82% of diabetic patients not complying with ACE inhibitor therapy would survive for 11 years from the onset of macroproteinuria to ESRF and then undergo 10 years of ESRF treatment. Among those complying with ACE inhibitor therapy 72% would survive for 18 years from the onset of macroproteinuria to ESRF and then undergo 3 years of ESRF treatment. Our analysis showed that a provincial payment strategy with a patient compliance rate of 67% would be highly cost-effective, compared with a compliance rate of 50% in a no-payment strategy: there would be an increase in QALYs of 0.147 and a cost savings of $849 (Table 1).

In our sensitivity analysis, varying the drug compliance rate from 67% to 65% in the payment arm resulted in a marginally cost-effective strategy of $4091 per QALY gained (Table 1). With a compliance rate of less than 63% the payment strategy would cost more than Can$20 000 per QALY gained. If the drug cost were increased by 10% the provincial payment strategy would still be highly cost-effective at a compliance rate of 66%. If the drug cost were reduced by 50% the payment strategy would still be highly cost-effective at a compliance rate of 58%; at a compliance rate of 67% the cost savings would be $6761 with an additional 0.147 QALYs (Table 1). Our findings indicate that increasing the length of survival with the use of ACE inhibitor therapy before the start of ESRF would improve cost-effectiveness at lower rates of compliance; with shorter survival times, higher rates of compliance would be needed to establish cost-effective strategies.

Interpretation

The findings of the Collaborative Study Group[4] on the effect of ACE inhibitor therapy for type I diabetic nephropathy suggest major benefits for patients and significant health care cost reductions for ESRF programs. In our study we attempted to determine the most cost-effective strategy to introduce this treatment advance. We believe that the largest barrier to a successful implementation strategy is likely to be drug compliance and that the biggest obstacle to compliance is drug cost.[14,15] We chose 34% as the cost barrier to compliance because it was based on patient interviews about the purchase and use of prescribed medications.[14] This figure originated from Canadian sources and was more conservative than projections from other studies.[15,24–26] Data from the Rand health insurance experiment, a randomized controlled trial in which participants were assigned to insurance plans with varying co-insurance rates and deductibles, indicated a cost barrier of about 60%.[24] The cost sharing in that study, and in the study by Manning and colleagues,[25] was independent of health and demographic characteristics. Our baseline decision analysis indicated that a drug compliance rate of 67% in the arm in which the cost barrier is removed would result in a highly cost-effective economic strategy for provincial payment, with an increase in QALYs of 0.147 and a cost savings of $849.

The CORR database provides actual survival data for diabetic patients receiving ESRF treatments. A major drawback in the use of this database is that it does not differentiate between type I and type II diabetes. However, a recent survey of 28 hemodialysis units across Germany noted that, although there were more patients with type II diabetes than with type I diabetes (66% v. 34%), their 45-month survival rates were similar (50% and 57% respectively).[27]

Table 1: Cost-effectiveness of ACE inhibitor therapy in patients with type I diabetes mellitus and macroproteinuria, at different compliance rates and drug costs*

Compliance rate, %	Annual increase in costs (savings) per patient, $	Increase in QALYs	Cost-effectiveness ratio, $/QALY gained
Full drug cost			
51	10 201	0.009	1 176 738
63	1 913	0.113	16 978
65	1 532	0.130	4 091
66	(159)	0.140	†
67	(849)	0.147	†
Drug cost reduced by 50%			
51	4 728	0.009	545 380
57	419	0.061	6 910
58	(299)	0.069	†
67	(6 761)	0.147	†

Note: ACE = angiotensin-converting enzyme, QALY = quality-adjusted life-year.
*In comparison with a compliance rate of 50%.
†Highly cost-effective.

The costs of dialysis used in our study were reported by Goeree and colleagues[18] and applied not only to diabetic patients but to all patients with ESRF. They indicated that the variable costs were about 44% greater for diabetic patients than for average ESRF patients. Therefore, the cost-effectiveness of the provincial payment strategy in our decision analysis is likely higher for the cost-effectiveness already noted for the provincial payment arm of the decision analysis.

The drug costs for ACE inhibitor therapy are high, but they would be expected to decline as the patent for these drugs expires. In our study we used not only the cost of acquisition of the ACE inhibitor but also the cost of supplemental antihypertensive drugs.[16] Thus, the true long-term costs of ACE inhibitors are likely much lower than projected. Because we used US sources for our ACE inhibitor costs, we included the US costs for laboratory monitoring, clinic visits and treatment of side effects, which for the period 1985–1992 would have likely been greater than the comparable Canadian costs. The 50% reduction in drug cost in our sensitivity analysis may be more reflective of a Canadian analysis and would result in a highly cost-effective strategy for provincial payment at a 58% compliance rate.

In our analysis we presumed that noncompliance would be a major factor in assessing the renal protective effects of ACE inhibitor therapy in the diabetic population. Most reviews of the literature and a recent randomized controlled study have indicated that at least 50% of hypertensive patients take less than 80% of their antihypertensive therapy after 1 year.[10–13] If compliance in usual practice is less than 50%, it would further strengthen the cost-effectiveness of a provincial payment strategy for ACE inhibitor therapy.

At present we do not have direct evidence that patients who comply with ACE inhibitor therapy are more likely to comply with all parts of their medical care and thus have the potential for better health and longer survival. In our analysis we assumed that the life span was similar between the 2 groups; however, there is a strong possibility that the compliant patients have increased longevity and therefore spend more years using some type of renal replacement therapy. This would result in an increase in both discounted benefits (QALYs) and costs, which would have little overall effect on the current payment strategy.

Conclusion

We conclude that a provincial payment strategy for ACE inhibitor therapy in patients with type I diabetes and macroproteinuria is highly cost-effective and should be considered for immediate implementation to overcome a major barrier to patient benefits and health care savings.

We thank Dr. C. David Naylor for his critical review of this paper.

Competing interests: None declared for David Churchill, Lorie Forwell, Graeme Macdonald and Susan Foster. William Clark has received speaker fees from Merck Frosst Canada Inc.

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