Economic Evaluation of Angiotensin Receptor Blockers in Type 2 Diabetes, Hypertension, and Nephropathy

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There is a rising incidence and prevalence of ESRD as a result of diabetes, with poor outcome and growing costs. Recently, two large trials, the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), showed that angiotensin receptor blockers (ARB) are more effective than traditional antihypertensive therapies at reducing progression toward ESRD in hypertensive patients with type 2 diabetes and overt nephropathy, regardless of changes in BP. The results of these two trials were used to compare the costs of ARB with those of renal replacement therapy (dialysis and renal transplantation) in an effort to establish whether ARB are cost-saving because they delay ESRD. Two different pharmacoeconomic approaches were used. With regard to the RENAAL trial, the number of ESRD days on losartan as compared with the number of ESRD days on standard antihypertensive therapy was calculated, and the difference between the two was combined with the costs of ESRD. In the IDNT trial, Markov models were applied to assess the economic impact of irbesartan and to extrapolate future clinical and cost outcomes. Several economic analyses were performed in the United States and in European countries. Applying pharmacoeconomic models showed that treatment with ARB was associated with a greater improvement in life expectancy and lower total costs compared with amiodipine and standard antihypertensive therapy. Therefore, treating patients with type 2 diabetes, nephropathy, and hypertension with ARB is life- and cost-saving compared with traditional antihypertensive therapy.


The prevalence and incidence of ESRD that is treated by dialysis and renal transplantation are rising worldwide (1–3). Although 90% of treated patients with ESRD come from more developed countries that can still afford the cost of renal replacement therapy, the expenditures are dramatically rising, thus representing an economic problem even for industrialized countries (4). By 2001, the costs of the ESRD program had reached almost $23 billion in the United States—nearly three times higher than 10 yr before—with continuously increasing Medicare and non-Medicare expenditures (1). In Europe, dialysis alone takes up approximately 2% of the total health care budget, even though <0.1% of the population needs renal replacement treatment (4). Dialysis is a very expensive treatment modality, costing >$50,000 per patient per year in the United States (1). In Europe, the mean annual cost ranges from a minimum expense of 30,000 euro in the United Kingdom to a maximum of 60,000 euro in France. Renal transplantation provides ESRD care at a lower cost. Although the first-year renal transplantation costs are elevated because of surgery and hospitalization expenditures, as of the second year, costs become markedly lower than dialysis-related expenditures (5–12). However, because of the ongoing shortage of kidneys that are available for transplantation, dialysis treatment continues to be the most prevalent modality of treatment for most patients.

Diabetic nephropathy is one of the most frequent causes of ESRD. In the past few years, the number of patients who have diabetes and have begun renal replacement therapy has not increased in the United States alone, where they represent >40% of all new cases of ESRD, but also in Japan, Australia, and New Zealand, as well as in European countries. Most of these patients (>90%) have type 2 diabetes (13). The economic burden of ESRD secondary to diabetes is obviously overwhelming.

Pharmacoeconomic Analysis of Angiotensin Receptor Blockers in Type 2 Diabetes and Nephropathy

Two large trials evaluated the renoprotective role of angiotensin receptor blockers (ARB) in patients with type 2 diabetes and overt nephropathy (14,15). The Irbesartan Diabetic Nephropathy Trial (IDNT) trial showed that treatment with irbesartan was associated with a reduction of the risk for serum creatinine doubling (DSC), ESRD, and death compared with amiodipine or standard antihypertensive therapy (24% versus amiodipine and 19% versus control group, respectively). The risk for ESRD in the irbesartan group was 23% lower than in the conventional therapy and amiodipine groups analyzed together. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, treatment with losartan resulted in a 15% reduction of the risk for the same primary composite end point that was considered in the...
IDNT trial, whereas the risk for ESRD was 25% lower in the losartan group than in the conventional treatment group. It is interesting that the benefit of ARB went beyond BP control in both studies. The results of these two trials were used to compare the costs of ARB with those of ESRD (dialysis or renal transplantation) in an effort to establish whether ARB are cost-saving because they are able to delay ESRD.

A simple method was used in the RENAAL study and was based on the number of days that the patients experienced ESRD multiplied by the daily cost of ESRD. The number of days on ESRD was estimated by subtracting the area under the Kaplan-Meier survival curve for time to the minimum of ESRD or all-cause death from the area under the Kaplan-Meier survival curve for all-cause death. Losartan reduced the number of ESRD days in patients with type 2 diabetes and overt nephropathy by an average of 5.7 d over a 2-yr period. This difference was calculated between ESRD days in the losartan and the control groups. It increased during follow-up, became significant from the third year on, and became longer than 40 d over a 4-yr period. This difference then was multiplied by the mean daily cost of ESRD (weighed mean cost between dialysis and renal transplant) in each country. The cost of losartan then was subtracted, and the net cost savings were obtained. Results of this analysis in North America and in Europe are shown in Figure 1. All costs are reported in euro (exchange rate at December 31, 2004). During a 4-yr period, treatment with losartan was associated with a net cost saving that ranged from 3,500 euro in Canada to nearly 6,000 euro in France (6,7,16,17).

However, this method uses data only from the RENAAL study and did not take into consideration either the probability of receiving a renal transplant or the different mortality rates observed in the various countries. Therefore, extrapolation to all patients with type 2 diabetes is not possible. Furthermore, this method does not allow for assessment of long-term clinical outcomes and costs. Markov models were used to overcome this limitation (18). Markov models are a standard method that simulates the course of long-term, progressive disease and have been used in chronic diseases such as diabetes. These models assume that a patient is always in one of a finite number of discrete health states called Markov states. All events are represented as transitions from one state to another.

A Markov model was created in the IDNT to simulate the long-term treatment of hypertensive patients with type 2 diabetes and overt nephropathy and to extrapolate future clinical and cost outcomes. The model included three treatment strategies and five primary health states: Overt nephropathy, DSC, ESRD treated by dialysis, ESRD treated by renal transplant, and death. All patients started in the “overt nephropathy” state. The model was run over 3-, 10-, and 25-yr time horizons using 1-yr cycles. Patients transitioned to new states or remained within the same state in each cycle. For example, patients in the overt nephropathy state could either remain in the same state or reach DSC, thus moving to the DSC state, or they could reach ESRD and then move to dialysis or renal transplant or die. Transition probabilities for patients in the overt nephropathy and DSC states were calculated using the frequencies of events that were observed during the first 3 yr of the IDNT. Mean probability for the first 3 yr was used to calculate transition probabilities for the fourth year and beyond. Once a patient developed ESRD, the probabilities of death or of transition from dialysis to renal transplant and vice versa were assumed to be independent of the treatment arm. Because no studies have compared the effects of irbesartan, amlodipine, and standard therapy in ESRD patients, these probabilities were derived from country-specific ESRD management and outcome data (8–12,19,20).

Mean ESRD-free time was approximately 8.1 yr in the irbesartan cohort with a 1.41-yr gain as compared with amlodipine and a 1.35-yr gain as compared with conventional treatment. Moreover, simulated long-term treatment with irbesartan was associated with a lower incidence of ESRD as compared with amlodipine or control. At 10 yr, the cumulative incidence of ESRD was 36% in the irbesartan arm, 45% in the control arm, and 49% in the amlodipine arm. At 25 yr, it was 47, 55, and 59%, respectively. Combined with country-specific data, these figures provided life expectancy results. At 10 yr, simulated treatment with irbesartan was associated with a 6.40-yr life expectancy in the United States, with a gain of nearly 2 mo compared with amlodipine and 4 mo versus standard therapy. At 25 yr, higher life expectancy was observed for Europe than for the United States, regardless of treatment. Moreover, irbesartan was associated with higher life expectancy compared with amlodipine and standard therapy in all of the countries where the analysis was performed, with gains ranging from 7 to 10 mo (8–11,19,20).

These clinical results have important financial implications. The costs of both medication and ESRD were assessed in all three treatment arms. Costs were taken from each country-specific, third-party payer perspective (Medicare system in the United States, Ontario Health Insurance Schedule of Benefits and Fees in Canada, National Health Service in the United Kingdom, Social Security in France, Institut National d’Assurance de Maladie et Invalidité in Belgium, GKV in Germany, Sistema Nacional de Salud in Spain, and Sistema Sanitario Nazionale in Italy). The costs for patients with overt nephropathy and DSC states were calculated using the frequencies of events that were observed during the first 3 yr of the IDNT.
nephropathy and DSC included study drugs and concomitant antihypertensive agents, as reported in IDNT. Because the aim of the study was to evaluate the incremental costs among the treatment arms alone, all costs that were considered similar in the three treatment arms (e.g., visits to the general practitioner, expenditures as a result of cardiovascular events, urinary albumin determination) were excluded from the analysis. Study drug costs were calculated by dividing the number of days of exposure to each dose by the number of patients, multiplied by the mean duration of follow-up, multiplied by the cost of each daily dose (daily dose costs were taken from Average Wholesale Price in the United States, Ontario Drug Formulary in Canada, British National Formulary in the United Kingdom, VIDAL in France, INAMI in Belgium, Rote List in Germany, Catalogo de Especialidades Farmaceuticas in Spain, and Informatore Farmaceutico in Italy). The cost of drugs was assumed to remain constant for the entire simulation period. The price of the most often prescribed drugs was used for each class of concomitant antihypertensive therapy.

Figure 2 shows total costs and cost savings at 10 yr simulation for North America and Europe. In the United States, treatment with irbesartan is associated with lower costs, thus leading to cost savings of nearly 24% compared with expenditures for amlodipine and 17% compared with controls. Similar data are observed for Canada, whereas some variations among the various countries are evident in Europe. In the United Kingdom, for example, the net cost saving is nearly 18% compared with amlodipine and 12% compared with controls, whereas total costs are twice as low as in the United States. Total costs and cost savings at 25 yr are available for the United States, Belgium, and France. Net cost savings range from 20,000 to 27,000 euro versus amlodipine and 11,000 and 16,000 euro versus control (8–11,19,20). Therefore, irbesartan therapy is associated with net cost savings (nearly 25% of the expenditure for patients with type 2 diabetes and hypertension and nephropathy) in all countries, although total costs were different among countries.

**Italian Perspective**

A similar analysis was also performed in Italy (12) and showed that annual costs per patient for dialysis treatment are similar to costs in other European countries. First-year transplantation costs in Italy are as high as in North America or Germany, whereas annual costs as of the second year are similar to mean European expenditures. In Italy, simulated treatment with irbesartan was associated with a life expectancy of >10 yr at 25 yr, with a gain of 7 and 10 mo compared with amlodipine and standard therapy, respectively, consistent with what was reported in other European countries (8–11). Economic analysis showed that treatment with irbesartan was associated with lower total costs compared with both amlodipine and control. In Italy, net cost saving was nearly 13,550 euro versus amlodipine and 8,000 euro versus control. These cost savings were similar to those reported in other countries. Cost savings became evident after 3 yr of treatment with irbesartan and increased over time. A breakdown of the total cost over a 10-yr simulation period showed that the costs of ESRD represent the main expenditure (89 to 95%), whereas the cost of amlodipine, irbesartan, and concomitant antihypertensive therapy make up only 8 to 10% of the 10-yr expenditure. One-way sensitivity analysis was performed on life expectancy and total costs by varying each probability and cost by ±10% at a time while holding other parameters constant, so as to rank their impact order. In all of these analyses, it was assumed that the probabilities would return to those of the control group after the 3-yr trial period in all treatment arms. Only the within-trial effects of irbesartan and amlodipine were taken into consideration. Further sensitivity analyses were performed on the annual costs of ESRD, the annual costs of irbesartan, and the time horizon of the analysis. According to one-way sensitivity analysis of 10-yr life expectancy, the parameter with the greatest impact was the transition from overt nephropathy to death, followed by the transition from dialysis to death. One-way sensitivity analysis of 10-yr costs showed that the parameter with the greatest impact was the annual cost of dialysis, with costs for irbesartan only resulting in eighth place. We conclude that treatment with irbesartan is life and cost saving even in Italy (12).

To understand how much can be saved, we must keep in mind that expenditure for the entire population with type 2 diabetes in Italy is nearly 5 billion euro, corresponding to 6.65% of the overall national health expenditure. Mean annual costs range from 1,500 euro for a patient who has type 2 diabetes without complications to >5,000 euro for a patient with both micro- and macrovascular complications (21–23). Treating patients who have diabetes and overt nephropathy with ARB might lead to annual cost savings of 150 million euro, corresponding to a 3% decrease in the overall costs for type 2 diabetes and an 0.2% decrease in the overall national health expenditure.

One of the main limitations, however, must be acknowledged in the pharmacoeconomic approach of both the

Figure 2. Total costs and cost savings at 10 yr for hypertensive patients who have type 2 diabetes and nephropathy and are treated with irbesartan, compared with amlodipine and conventional therapy in North America and Europe (9–11,19,20).
RENAAL trial and IDNT. Indeed, the key recommendation of all of the international guidelines for economic studies is that the pharmacoeconomic profile of a drug be determined by comparing it with the current best alternative or current standard care. None of the existing economic analyses of losartan or irbesartan in type 2 diabetes with nephropathy has evaluated the potential benefits that are derived from alternative renin-angiotensin-aldosterone system blocking agents, i.e., angiotensin-converting enzyme (ACE) inhibitors, other ARB, or the association of both. Because no clinical data that have compared directly the efficacy of losartan or irbesartan with ACE inhibitors or other ARB in type 2 diabetes and overt nephropathy are available, a valuable cost-effectiveness comparison analysis of these different therapies is not possible. This comparison can be made only indirectly. Cost-effectiveness analysis that was performed in type 1 diabetic and in nondiabetic nephropathies showed that chronic treatment with ACE inhibitors is cost-effective as well (24,25). Cost-effectiveness analysis of dual blockade therapies probably would be even more effective. Preliminary results, indeed, suggest that association therapy is more renoprotective than ARB or ACE inhibitors alone, both in diabetic and nondiabetic nephropathies (26,27).

Conclusions
Optimization of available resources to maximize health will be the key challenge to health care systems, both public and private, such as managed care organizations, in the next decade. Several countries recently introduced guidelines or legislation to mandate cost-effectiveness assessment of at least some aspects of health care, particularly for the reimbursement of pharmaceuticals, and it is expected that thresholds for cost-effectiveness may be established for the acceptance of reimbursement or formulary listing. When we consider the most important renono- and cardioprotective strategies that are recommended by the international guidelines in type 2 diabetes, intensive BP reduction is the most cost-effective therapy as compared with intensive glycemic control and serum cholesterol level reduction (28). Last, treating patients who have type 2 diabetes with hypertension and overt nephropathy with ARB is renoprotective and cost saving and prolongs life.

References
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