Losartan Reduces the Costs Associated With Diabetic End-Stage Renal Disease

The RENAAL study economic evaluation

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OBJECTIVE — To evaluate the within-trial effect of losartan and conventional antihypertensive therapy (CT) compared with placebo and CT on the economic cost associated with end-stage renal disease (ESRD).

RESEARCH DESIGN AND METHODS — The Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) study was a multinational double-blind randomized placebo-controlled clinical trial designed to evaluate the renal protective effects of losartan on a background of CT (excluding ACE inhibitors and angiotensin II receptor agonists [AIIAs]) in patients with type 2 diabetes and nephropathy. The primary composite end point was doubling of serum creatinine, ESRD, or death. Data on the duration of ESRD were used to estimate the economic benefits of slowing the progression of nephropathy. The cost associated with ESRD was estimated by combining the days each patient experienced ESRD with the cost of ESRD over time. The cost of ESRD for individuals with diabetes was estimated using data from the U.S. Renal Data System. Total cost was estimated as the sum of the cost associated with ESRD and the cost of study therapy.

RESULTS — We estimated that losartan and CT compared with placebo and CT reduced the number of days with ESRD by 33.6 per patient over 3.5 years ($P = 0.004$, 95% CI 10.9–56.3). This reduction in ESRD days resulted in a decrease in cost associated with ESRD of $5,144 per patient ($P = 0.003$, 95% CI $1,701 to $8,587). After accounting for the cost of losartan, the reduction in ESRD days resulted in a net savings of $3,522 per patient over 3.5 years ($P = 0.041$, $143 to $6,900).

CONCLUSIONS — Treatment with losartan in patients with type 2 diabetes and nephropathy not only reduced the incidence of ESRD, but also resulted in substantial cost savings.

Diabetes Care **26:683–687, 2003**

Diabetes is the leading cause of end-stage renal disease (ESRD) in the U.S., accounting for 40% of all new cases between 1994 and 1999 (1). In 1999, 350,000 individuals in the U.S. suffered from ESRD and the Medicare ESRD program incurred $12.7 billion in costs (1). This cost is expected to increase to $28 billion a year by 2010 (2). Health care programs aimed at preventing the onset of ESRD may substantially reduce the economic burden of ESRD. Recently, the Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that in patients with type 2 diabetes and nephropathy who were for the most part hypertensive, treatment with losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25%; $P = 0.006$) and ESRD (risk reduction, 29%; $P = 0.002$) and that these benefits exceeded those attributable to measured reductions in blood pressure (3). No differences were observed between treatment groups in overall mortality or in the incidence of reported adverse experiences. However, 24% of patients in the placebo group and 19% of patients in the losartan group discontinued study therapy because of side effects. The American Diabetes Association has stated that angiotensin II receptor antagonists are the initial agent of choice for the treatment of nephropathy in hypertensive type 2 diabetic patients (4) based in part on results of the RENAAL study. In this article, we extend the RENAAL study findings by examining the effect of losartan and conventional antihypertensive therapy (CT) compared with placebo and CT on ESRD-related costs.

RESEARCH DESIGN AND METHODS

Study design

The RENAAL study design and results were reported by Brenner et al. (3). Briefly, the RENAAL study was an investigator-initiated multinational double-blind randomized placebo-controlled clinical trial designed to evaluate the renoprotective effects of losartan in 1,513 patients with type 2 diabetes and nephropathy. Patients were randomized to losartan or placebo on a background of non–ACE inhibitor conventional antihypertensive therapy (e.g., diuretics,

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Received for publication 19 July 2002 and accepted in revised form 3 December 2002.

W.H.H., S.S., G.W.C., E.J.D., W.C.G., C.M.A., J.R.C., and B.M.B. hold stock in Merck & Company. W.H.H. is a paid consultant for Merck & Company. B.M.B. is a paid consultant for Merck & Company, BMS, and Genzyme and has received grant support from Merck & Company and Novartis.

Abbreviations: CT, conventional antihypertensive therapy; ESRD, end-stage renal disease; RENAAL, Reduction of End Points in Type 2 Diabetes With the Angiotensin II Antagonist Losartan.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics*

	Losartan (+ CT)	Placebo (+ CT)
n	751	762
Age (years)	60 ± 7	60 ± 7
Male	462 (61.5)	494 (64.8)
Race		
Asian	117 (15.6)	135 (17.7)
Black	125 (16.6)	105 (13.8)
Caucasian	358 (47.7)	378 (49.6)
Hispanic	140 (18.6)	136 (17.8)
Other	11 (1.5)	8 (1.0)
Medical history		
Duration of diabetes ≥5 years	676 (90.0)	686 (90.0)
BMI (kg/m^2)*	30 ± 6	29 ± 6
Systolic blood pressure (mmHg)	152 ± 19	153 ± 20
Diastolic blood pressure (mmHg)	82 ± 10	82 ± 11
Use of antihypertensive drugs	693 (92.3)	721 (94.6)
Currently smoking	147 (19.6)	130 (17.0)
Lipid disorders	234 (31.2)	271 (35.6)
Angina pectoris	65 (8.7)	75 (9.8)
Myocardial infarction	75 (10.0)	94 (12.3)
Coronary revascularization	1 (0.1)	1 (0.1)
Stroke	0	1 (0.1)
Retinopathy	494 (65.8)	470 (61.7)
Neuropathy	375 (50.0)	379 (49.7)
Amputation	65 (8.7)	69 (9.1)
Laboratory		
Urine albumin:creatinine ratio (median, mg/g)†	1,237	1,261
Serum creatinine (mg/dl)‡	1.9 ± 0.5	1.9 ± 0.5
HbA_{1c} (%)	8.5 ± 1.7	8.4 ± 1.6
Serum cholesterol (mg/dl)§		
Total	227 ± 56	229 ± 55
LDL	142 ± 47	142 ± 45
HDL	45 ± 16	45 ± 15
Serum triglycerides (mg/dl)‖	213 ± 180	225 ± 200

Data are means ± SD or *n* (%). *BMI was calculated as weight (kilograms) divided by square of height (meters squared); †to convert to mg/mmol, multiply by 0.113; ‡to convert to μmol/l, multiply by 88.4; §to convert to mmol/l, multiply by 0.02586; ‖to convert to mmol/l, multiply by 0.01129.

calcium-channel antagonists, α- or β-blockers, centrally acting agents, or some combination of these types of medications). Patients enrolled had type 2 diabetes and a urinary albumin:creatinine ratio of at least 300 mg/g on a first morning specimen and serum creatinine between 1.3 to 3.0 mg/dl. Of the patients, 97% were either receiving antihypertensive therapy or were noted as having had hypertension but were not receiving antihypertensive therapy at baseline. Baseline characteristics of the study population are summarized in Table 1. The study protocol was approved by the Institutional Review Board of each center, and all patients gave written informed consent. The primary efficacy end point was a composite of the time to first event of doubling of serum creatinine, ESRD, or death.

Economic evaluation

The objective of the economic evaluation was to evaluate the effect of losartan and CT compared with placebo and CT on health care resource use and costs. The prespecified primary hypothesis was that therapy with losartan compared with placebo would reduce within-trial cumulative ESRD-related costs after 3.5 years of follow-up. As supportive analyses, we examined the effect of therapy on total cost.

Health economic measures

ESRD-related costs. The cost associated with ESRD was calculated for each patient by combining the number of days the patient experienced ESRD with the cost of ESRD over time. To adjust for both differential length of follow-up and death, we estimated the number of days with ESRD 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. Although there were a small number of kidney transplantations performed (three losartan, five placebo), for the purpose of the cost analysis, we assumed that all individuals with ESRD were treated with hemodialysis. Given that the cost of ESRD is greater at the onset of ESRD (5) and greater among individuals with diabetes (1), we estimated the longitudinal cost of ESRD for patients with diabetes using 1997 and 1998 data from the U.S. Renal Data System (1). The average daily cost attributable to ESRD for individuals with diabetes was estimated to be $267 per day the first 90 days after onset of ESRD and $147 per day thereafter.

Total cost. Total cost was defined as the sum of the cost attributable to ESRD and the cost of losartan therapy. The cost of losartan was estimated based on the average wholesale price multiplied by the days on therapy by dose. The 2001 average U.S. wholesale price for losartan at 25-, 50-, and 100-mg doses was $1.43, $1.43, and $1.95 per tablet, respectively. We assumed that patients who discontinued study therapy incurred no additional medication costs. We did not include the costs associated with monitoring serum creatinine and potassium because this monitoring would be performed routinely in individuals with diabetes and renal disease (4). Given that there were no differences in the incidence of side effects between treatment groups (3), we assumed that the difference in the cost of side effects between treatment groups was zero. We also conservatively assumed that there were no differences in the cost of nonstudy medications between treatment groups because there was a small but not significantly greater use of nonstudy medications in the placebo group (3).

Analyses

To estimate costs, we adopted the perspective of a health care system responsible for all direct medical costs. All randomized participants were included in the analysis on an intention-to-treat basis.

Table 2—*Mean number of ESRD days and days saved per patient*

Follow-up (years)	Losartan (+ CT) (n = 751)	Placebo (+ CT) (n = 762)	Difference	95% CI of difference	P
2.0	19.2	24.9	5.7	−2.7 to 14.1	0.191
2.5	34.7	46.9	12.2	−0.7 to 25.1	0.064
3.0	53.6	74.7	21.1	3.5 to 38.7	0.019
3.5	76.1	109.7	33.6	10.9 to 56.3	0.004
4.0	102.0	148.9	46.9	19.1 to 74.7	0.009

The null hypothesis was that there is no difference between treatment groups in mean ESRD-related cost at 3.5 years of follow-up. We compared the 3.5-year mean ESRD-related cost between treatment groups using a regression-based method (6). This method accounts for administrative censoring brought about by staggered entry into the trial and involves two stages: *1*) estimation of the mean relationship between cost and survival time and *2*) weighting of this mean relationship by the Kaplan-Meier probabilities of survival. The bootstrap method (7) was used to construct a 95% CI on the treatment difference (placebo-losartan). All costs were discounted at an annual rate of 3% and are reported in 2001 U.S. dollars. Sensitivity analyses were performed on the cost of ESRD and the cost of losartan.

RESULTS — Table 2 and Fig. 1*A* show the mean number of days with ESRD by treatment group and follow-up time. Among individuals with type 2 diabetes and nephropathy, losartan compared with placebo on a background of non–ACE inhibitor/non–angiotensin II receptor agonist (AIIA) antihypertensive therapy reduced the number of days with ESRD by 33.6 days (95% CI 10.9–56.3) or 31% per patient over 3.5 years. Over 4 years, the number of ESRD days saved increased to 46.9 per patient (19.1–74.7). Table 3 and Fig. 1*B* show the mean ESRD-related cost by treatment group and follow-up time. The reduction in ESRD days resulted in a decrease in cost associated with ESRD of $5,144 ($P$ = 0.003) per patient over 3.5 years. The reduction in cost associated with ESRD increased to $7,058 ($P$ = 0.002) per patient over 4 years. Figure 1*C* shows the ESRD-related cost savings per patient by follow-up time. Table 4 and Fig. 1*D* show the estimated net cost savings per patient by follow-up time. After accounting for the cost of losartan, the reduction in ESRD days resulted in a net savings of $3,522 (95% CI $143 to $6,900) per patient over 3.5 years. This saving increased to $5,298 ($954 to $9,643) per patient over 4.0 years.

Sensitivity analyses indicate that treatment with losartan saves on cost under a variety of scenarios. For example, treatment with losartan would still save on costs after 3.5 years if the cost of ESRD decreased by 68% or if the cost of losartan increased threefold.

CONCLUSIONS — The RENAAL economic evaluation has demonstrated that, in individuals with type 2 diabetes and nephropathy, treatment with losartan resulted in substantial cost savings from the perspective of a health care system responsible for all direct medical costs. These results are meaningful from many perspectives.

From a managed care perspective in the U.S., these savings are notable because they accrue during the 30-month period when the managed care organiza-

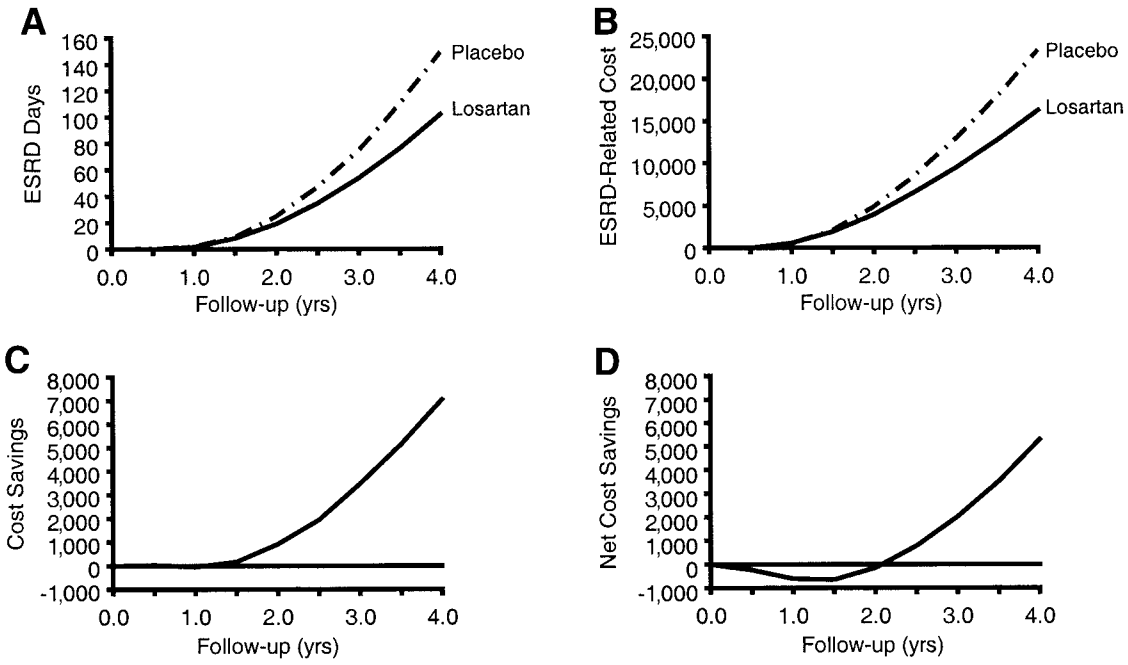

Figure 1—*Cumulative number of days with ESRD* (A)*, ESRD-related costs (U.S. dollars)* (B)*, ESRD-related cost savings* (C)*, and net cost savings* (D) *per patient by duration of follow-up.*

Table 3—*Mean ESRD-related cost and cost-savings per patient (in U.S. dollars)*

Follow-up (years)	Losartan (n = 751)	Placebo (n = 762)	Difference	95% CI	P
2.0	3,956	4,878	922	−541 to 2,386	0.217
2.5	6,509	8,560	2,051	−23 to 4,125	0.053
3.0	9,457	12,931	3,474	758 to 6,190	0.012
3.5	12,714	17,858	5,144	1,701 to 8,586	0.003
4.0	16,253	23,311	7,058	2,632 to 11,484	0.002

tion is responsible for the health care costs of a person developing ESRD before that person is eligible for Medicare coverage (8). For example, we found that for every dollar spent treating patients with type 2 diabetes and nephropathy, $3.17 in ESRD-related cost savings would be realized over 3.5 years. For the Medicare program in the U.S. where ESRD accounts for 5% of the total Medicare budget, treatment with losartan could potentially reduce a portion of these expenditures in patients with characteristics similar to the RENAAL study population. This could also be the case outside the U.S., where ESRD represents a significant line item on many national health care system budgets (9,10).

From the perspective of the public health system in the U.S., the results of the RENAAL study are consistent with the goals of Healthy People 2010 (11), where objective 4.1 is aimed at "reducing the rate of new cases of end-stage renal disease." In particular, the addition of losartan to the treatment regimens of 100 patients with type 2 diabetes, nephropathy, and characteristics similar to those of the RENAAL patients could be expected to lead to a reduction of 6.3 cases of ESRD and 9.2 person-years with ESRD over 3.5 years. This reduction in years with ESRD would translate into a $514,000 reduction in the cost of ESRD and a $352,000 net savings over 3.5 years for these 100 patients. From a societal perspective, these savings represent an underestimate, given that the costs do not include patient out-of-pocket costs or productivity losses.

These savings are noteworthy for a number of other reasons. First, few medical interventions in health care actually save on costs (12). However, many health programs aimed at reducing ESRD have been shown to be cost-effective and even cost-saving. For example, Rodby et al. (13) demonstrated that treatment of individuals with type 1 diabetes and nephropathy using the ACE inhibitor captopril saves on costs. These results are consistent with the findings of this study given both populations studied were at high risk for a high-cost outcome (i.e., ESRD). Second, and unlike the Rodby economic evaluation (13), the effect of therapy on net costs was statistically significant (P = 0.041). This finding is unique to losartan given no other antihypertensive or angiotensin II antagonist agent has demonstrated a significant reduction in the incidence of ESRD in individuals with type 2 diabetes and nephropathy. Third, sensitivity analyses indicate this net cost savings is robust across a wide range of values for the cost of ESRD and losartan.

A reasonable question is whether these within-trial savings would be sustained over the long-run. This question is beyond the scope of this analysis, as this analysis would require developing a model that projects the long-term consequences of therapy. However, the data shown in Fig. 1*D* demonstrate that the cost savings increase over time between 2.5 and 4.0 years. Moreover, given that the competing mortality rate is so high in this population, it is likely that these savings would persist because individuals would likely die from other causes before reaching ESRD. Regardless, for many decision makers, these near-term savings are meaningful.

In summary, losartan reduced the estimated number of days with ESRD for patients with type 2 diabetes and nephropathy by 33.6 days over 3.5 years. This reduction in ESRD days resulted in a decrease in cumulative ESRD-related cost of $5,144 per patient after 3.5 years. After accounting for the cost of losartan, the reduction in ESRD days resulted in a net savings of $3,522 per patient after 3.5 years. These savings increased with greater duration of follow-up during the trial. These findings demonstrate that treatment with losartan in patients with type 2 diabetes and nephropathy not only reduced the incidence of ESRD, but also resulted in substantial cost savings.

Table 4—*RENAAL: estimated net cost savings per patient (in U.S. dollars)*

Follow-up (years)	Net cost savings	95% CI	P
2.0	−137	−1,552 to 1,277	0.849
2.5	782	−1,238 to 2,801	0.448
3.0	2,016	−623 to 4,655	0.134
3.5	3,522	143 to 6,900	0.041
4.0	5,298	954 to 9,643	0.017

Acknowledgments— This study was funded by Merck & Company.

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