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Original Article

Losartan reduces the costs of diabetic end-stage renal disease: An Asian perspective

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SUMMARY:

Objective: To evaluate losartan and conventional antihypertensive therapy (CT) compared with CT alone on the cost associated with end-stage renal disease (ESRD) in Hong Kong, Japan, Korea, Malaysia, Singapore and Taiwan.

Methods: Reduction of end-points in non-insulin-dependent diabetes mellitus with the angiotensin II antagonist losartan (RENAAL) was a multinational, double-blind, randomized, placebo-controlled trial to evaluate the renal protective effects of losartan on a background of CT in patients with type 2 diabetes and nephropathy. The primary composite end-point was a doubling of serum creatinine, ESRD or death. Data on the duration of ESRD for the Asian subgroup of patients enrolled in RENAAL were used to estimate the economic benefits of slowing the progression of nephropathy. The cost associated with ESRD was estimated by combining the number of days each patient experienced ESRD with the average daily cost of dialysis from the third-party payer perspective in Hong Kong, Japan, Korea, Malaysia, Singapore and Taiwan. Total cost, converted to US dollars, was the sum of ESRD and losartan costs.

Results: Losartan plus CT reduced the number of days with ESRD by 37.9 per patient over 3.5 years compared with CT alone. This reduction in ESRD days resulted in a decrease in the cost associated with ESRD, which ranges from $910 to $4346 per patient over 3.5 years across the six countries or regions. After accounting for the cost of losartan, the reduction in ESRD days resulted in net savings in each of the six countries or regions, ranging from $55 to $515 per patient.

Conclusion: Treatment with losartan in patients with type 2 diabetic nephropathy not only reduced the incidence of ESRD among Asian patients, but resulted in direct medical cost savings in countries or regions representing Asia.

KEY WORDS: **angiotensin II receptor antagonist, Asia, cost-effectiveness, cost, end-stage renal disease, losartan, type 2 diabetes mellitus.**

The use of dialysis services represents a significant share of country or regional health care budgets around the world.[1] In Taiwan, the government spends approximately 6% of their annual health care budget on the reimbursement of dialysis therapy.[2] Diabetic nephropathy is generally the most common cause of end-stage renal disease (ESRD), accounting for 34–50% of ESRD cases in Hong Kong, Korea, Japan Malaysia, Singapore and Taiwan.[3–5] The absolute number of ESRD cases attributable to diabetic nephropathy is expected to rise with the increasing prevalence of type 2 diabetes mellitus in this region. The International Diabetes Federation (IDF) has predicted the prevalence of type 2 diabetes in the Western Pacific region will increase 76% between 2003 and 2025.[6] Health care programmes aimed at preventing or delaying the onset of ESRD in patients with type 2 diabetes might substantially reduce the economic burden of ESRD in this region.

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The reduction of end-points in non-insulin-dependent diabetes mellitus (NIDDM) 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.[7] A subgroup analysis of the Asian patients enrolled in RENAAL revealed that the primary end-point was 35% lower and the ESRD incidence was 38% lower for losartan-treated patients.[8] Thus, the robust losartan treatment effect in the Asian subgroup was consistent with the results of the main study.

In the present paper, we compare the effect of losartan and conventional antihypertensive therapy (CT) compared with CT alone on the economic cost associated with ESRD in Hong Kong, Japan, Korea, Malaysia, Singapore and Taiwan using data from the Asian subgroup of patients enrolled in RENAAL.

METHODS

Study design

The RENAAL study design and results have been reported by Brenner *et al.*[7] The RENAAL study was a double-blind, randomized, placebo-controlled study that compared the renal protective effects of the angiotensin II (AII) antagonist losartan plus conventional antihypertensive therapy with a placebo plus CT in 1513 patients with type 2 diabetes and nephropathy.

In RENAAL, 252 patients were of Asian ethnicity; most resided in Asia ($n = 220$). Of these 220 patients, 96 were from Japan and the remainder were predominantly Chinese from Hong Kong ($n = 92$), Malaysia ($n = 21$) and Singapore ($n = 11$). The remaining 32 Asian patients were geographically located worldwide. The study results from these 252 patients of Asian ethnicity have been recently published.[8] Briefly, type 2 diabetic patients aged 31–70 years with nephropathy (presence, on two occasions, of urinary albumin-to-creatinine ratio from first morning specimen ≥300 mg/g or rate of urinary protein excretion of ≥0.5 g/day) and serum creatinine level of 115–265 μmol/L (133–265 μmol/L for men weighing >60 kg) were studied.

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 over 3.5 years from the perspective of a national or regional health care system responsible for all direct medical costs in Hong Kong, Japan, Korea, Malaysia, Singapore and Taiwan.

Health economic measures

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.

The costs of dialysis therapy (2004 US dollars) are shown for each country in Table 1. Dialysis costs were based on the reimbursed price of haemodialysis and peritoneal dialysis services in Hong Kong (Health Authority).[9] Dialysis costs from Taiwan were based on an analysis of claims data for haemodialysis ($n = 4744$) and continuous ambulatory peritoneal dialysis ($n = 162$) patients from the Kao-Pin branch of the Bureau of National Health Insurance (BNHI).[10] The results from a microcosting study conducted at 44 haemodialysis and 11 continuous peritoneal dialysis centres was the source for Malaysian dialysis costs.[4] For Japan, Korea and Singapore, the results from a survey of nephrologists were used to estimate dialysis costs, while subtracting the 20% patient copayment in Korea and Singapore.[11] There is no patient copayment in Japan. Estimates of the annual number of haemodialysis sessions per patient were used to convert the costs per session costs to annual costs in Malaysia (153 annually).[4] A single dialysis cost was determined by creating an average of the haemodialysis and peritoneal dialysis costs, which was weighted by the proportion of patients using the two treatment modalities within a given country or region.[3–5,12–14]

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 number of days on therapy by the dose (50 mg, 100 mg) within each country as of November 2004.

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. We compared the 3.5 year mean ESRD-related cost between treatment groups using a regression-based method.[15] This method accounts for administrative censoring brought about by staggered entry into the trial and involves two stages: (i) estimation of the mean relationship between cumulative cost and survival time; and (ii) weighting of this mean relationship by the Kaplan-Meier probabilities of survival. The bootstrap method was used to construct 95% confidence intervals on the treatment difference (losartan-placebo).[16] All costs were discounted at an annual rate of 3% and are reported in 2004 values in US dollars, thereby allowing the use of a single currency.

Table 1 Per patient monthly cost of haemodialysis and peritoneal dialysis (PD) by country or region

	Hong Kong	Japan	Korea	Singapore	Malaysia	Taiwan
Hemodialysis cost ($)†	2167	3803	1020	880	795	1534
Peritoneal dialysis cost ($)†	500	3497	967	543	787	1137
Proportion on dialysis using PD	0.81	0.04	0.24	0.15	0.19	0.06
Weighted dialysis cost ($)†	817	3791	1007	830	793	1510

†Costs are in 2004 US dollars (USD).

RESULTS

Table 2 shows the mean number of days with ESRD by treatment group and follow-up time. By 3.5 years, there were 37.9 ESRD days (95% confidence interval (CI): –24.3, 100.0) saved per patient among Asian people with type 2 diabetes and nephropathy. The result is consistent with the 33.6 day (95% CI: 10.9, 56.3) reduction with losartan based on the overall trial population.[17]

Table 3 shows the ESRD-related costs and ESRD cost savings. By 3.5 years of follow up, the ESRD-related cost savings ranged from $910 (Malaysia) to $4346 (Japan) per patient over 3.5 years (see Table 3). Table 4 shows the net cost savings after factoring in the cost of losartan therapy. After 3.5 years of follow up, losartan reduced the total cost from $55 (Korea) to $515 (Hong Kong) per patient over 3.5 years.

Table 2 Mean number of end-stage renal disease (ESRD) days and days saved per patient – Asian population in reduction of end-points in non-insulin-dependent diabetes mellitus (NIDDM) with the angiotensin II antagonist losartan (RENAAL)

Follow up (years)	Losartan (n = 117)	Placebo (n = 135)	ESRD days saved	95% CI
2.0	14.0	15.7	1.7	–14.8, 18.3
2.5	33.1	37.3	4.1	–25.3, 33.6
3.0	54.7	70.7	16.0	–28.5, 60.5
3.5	79.8	117.7	37.9	–24.3, 100.0

CI, confidence interval.

DISCUSSION

This economic evaluation has shown that among individuals with type 2 diabetes and nephropathy, losartan treatment resulted in substantial cost savings from the perspective of six different health care systems in the Asian region. For many countries, the use of dialysis services represents a significant percentage of their total health care spending, and the use of losartan could potentially reduce a portion of these expenditures in patients with characteristics similar to the RENAAL study population. Approximately eight type 2 diabetic nephropathy patients would need to be treated with losartan for 3.5 years to prevent or delay one case of ESRD, based on the 13.3% ESRD risk difference at 3.5 years for the Asian subgroup in RENAAL.

The use of losartan in the type 2 diabetic nephropathy patient population has the potential to have a significant effect on the number of individuals with ESRD and ESRD person years. Wong *et al.* projected that there are 485 612 individuals with type 2 diabetic nephropathy in the six countries or regions represented in the present study (Hong

Table 3 Estimated mean end-stage renal disease (ESRD)-related cost and cost savings per patient by country or region and years of follow up

	Follow up (years)	Losartan (n = 117)	Placebo (n = 135)	ESRD cost savings†
Hong Kong	2.0	354	399	45
	2.5	827	933	106
	3.0	1348	1749	402
	3.5	1944	2881	937
Japan	2.0	1645	1852	208
	2.5	3837	4330	493
	3.0	6255	8118	1863
	3.5	9023	13369	4346
Korea	2.0	437	492	55
	2.5	1019	1150	131
	3.0	1661	2156	495
	3.5	2396	3551	1154
Malaysia	2.0	344	388	44
	2.5	803	906	103
	3.0	1309	1699	390
	3.5	1888	2798	910
Singapore	2.0	360	406	46
	2.5	840	948	108
	3.0	1369	1777	408
	3.5	1976	2927	952
Taiwan	2.0	655	738	83
	2.5	1528	1725	196
	3.0	2491	3234	742
	3.5	3594	5325	1731

†Costs are in 2004 US dollars (USD).

Table 4 Estimated net cost savings per patient by country or region and years of follow up

	Follow up (years)	Net cost savings†	95% CI
Hong Kong	2.0	–202	–601, 197
	2.5	–196	–897, 503
	3.0	33	–1014, 1080
	3.5	515	–943, 1974
Japan	2.0	–1867	–3714, –20
	2.5	–2114	–5352, 1124
	3.0	–1504	–6344, 3335
	3.5	505	–6271, 7280
Korea	2.0	–555	–1045, –65
	2.5	–629	–1488, 230
	3.0	–467	–1752, 818
	3.5	55	–1742, 1854
Malaysia	2.0	–326	–712, 61
	2.5	–354	–1032, 323
	3.0	–182	–1196, 831
	3.5	255	–1160, 1671
Singapore	2.0	–388	–793, 16
	2.5	–426	–1135, 283
	3.0	–247	–1308, 813
	3.5	202	–1279, 1683
Taiwan	2.0	–822	–1574, –70
	2.5	–940	–2291, 410
	3.0	–727	276, –451
	3.5	56	–2643, 2755

†Costs are in 2004 US dollars (USD). CI, confidence interval.

Kong, 25 210; Japan, 293 692; Korea, 81 343; Malaysia, 24 346; Singapore, 11 589; Taiwan, 49 432).[18] The addition of losartan to the treatment regimen to these individuals can be projected to lead to a reduction of 64 586 ESRD cases over 3.5 years, based on the 13.3% absolute ESRD risk difference observed among Asian subgroup results from RENAAL.

The results from economic evaluations have a limited generalisability across national borders when unit costs and practice patterns vary considerably between countries. For instance, the weighted costs of dialysis were considerably lower in Hong Kong, which might be attributed to a government policy mandating that all patients be placed on continuous ambulatory peritoneal dialysis as an initial dialysis regimen unless a medical contraindication exists. Furthermore, governments are not the only third-party payer for dialysis services. In Singapore and Malaysia, charitable organizations finance dialysis services by providing subsidies for patients undergoing dialysis.[4,19] A reduced incidence of ESRD might free up subsidies to extend patient access to dialysis services, or to improve the quality of care for patients undergoing dialysis.

The economic analysis of the losartan treatment effect identified patients based on Asian ethnicity, not the region or country in which the patient resides. Most patients of Asian ethnicity included in the RENAAL subgroup analysis resided within Asia (87%). Among these, all resided in one of the six countries or regions considered in this economic evaluation. Thus, our assumption was that the losartan treatment effect on ESRD days and study medication use was independent of the region and country, and the same treatment effect was applied to each of the six countries or regions. In addition, there are quality of life benefits associated with reducing the incidence of ESRD, non-direct medical costs (e.g. commuting to dialysis centres) and lost productivity that have not been incorporated into the analysis, which, if incorporated, would further enhance the value of losartan. The reduction in the number of days with ESRD for losartan was based on the Asian subgroup from RENAAL. As a consequence, the precision of the estimate for days with ESRD was substantially reduced compared with an analysis based on the full number enrolled in RENAAL. Finally, the economic analysis did not include all countries in Asia, and the six countries or regions should not be considered a representative sample of all Asian countries or regions. The six countries included were selected based on the level of interest for such an evaluation.

In summary, losartan reduced the estimated number of days with ESRD for Asian patients with type 2 diabetes and nephropathy by 37.9 days over 3.5 years. This reduction in ESRD days resulted in a decrease in the cumulative ESRD-related cost ranging from $910 to $4346 per patient after 3.5 years in six Asian countries. After accounting for the cost of losartan, the reduction in ESRD days resulted in a net saving of $55 to $515 per patient after 3.5 years. These findings show that treatment with losartan in Asian patients with type 2 diabetes and nephropathy reduces the incidence of ESRD and results in cost savings.

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