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An Asian Regional Analysis of Cost-Effectiveness of Early Irbesartan Treatment versus Conventional Antihypertensive, Late Amlodipine, and Late Irbesartan Treatments in Patients with Type 2 Diabetes, Hypertension, and Nephropathy

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ABSTRACT

Objective: The prevalence of type 2 diabetes, often leading to diabetic nephropathy, has increased globally, especially in Asia. Irbesartan treatment delays the progression of kidney disease at the early (microalbuminuria) and late (proteinuria) stages of nephropathy in hypertensive type 2 diabetics. This treatment has proven to be cost-effective in Western countries. This study assessed the cost-effectiveness of early irbesartan treatment in Asian settings.

Methods: An existing lifetime model was reprogrammed in Microsoft Excel to compare irbesartan started at an early stage to irbesartan or amlodipine started at a late stage, and standard treatments from a health-care perspective in China, Malaysia, Thailand, South Korea, and Taiwan. The main effectiveness parameters were incidences of end-stage renal disease, time in dialysis, and life expectancy. All costs were converted to 2004 US$ using official purchasing power parity. Local data were obtained for costs, transplantation, dialysis, and mortality rates. Probabilities regarding disease progression after treatment with the investigated drugs were extracted from two published clinical trials. A probabilistic sensitivity analysis was performed.

Results: Early use of irbesartan yielded the largest clinical and economic benefits reducing need for dialysis by 61% to 63% versus the standard treatment, total costs by 9% (Thailand) to 42% (Taiwan), and increasing life expectancy by 0.31 to 0.48 years. Early irbesartan had a 66% (Thailand) to 95% (Taiwan) probability of being dominant over late irbesartan.

Conclusion: Although the absolute results varied in different settings, reflecting differences in epidemiology, management, and costs, early irbesartan treatment was a cost-effective alternative in the Asian settings.

Keywords: amlodipine; cost-effectiveness; hypertension; irbesartan; nephropathy; type 2 diabetes.

Introduction

The World Health Organization (WHO) has highlighted the rapidly growing burden of diabetes worldwide. Globally, an estimated 30 million people were diagnosed with diabetes in 1985; this value increased to 135 million in 1995, and in the year 2000, it reached 177 million. More importantly, diabetes is expected to affect more than 300 million people by 2025 [1]. This epidemic can be attributed to demographic aging and changes in lifestyle (e.g., globalization, rural-to-urban shifts, and changes in diet and physical activity). In the West, awareness regarding this phenomenon is widespread. Nevertheless, although Asia is also dramatically affected by diabetes, the awareness levels remain relatively low [1–3]. In Malaysia, for instance, the overall prevalence of diabetes (types 1 and 2) drastically increased from 0.65% in 1960 to approximately 8% to 12% in the mid-1990s; moreover, a 1998 study conducted in rural and semiurban Malaysia revealed that the prevalence was 14.0%, ranging between 7.1% and 20.3% [4]. In China, diabetes prevalence increased from 1.0% in 1979 to 3.21% in 1996 [5]. By 2025, China will have the highest number of diabetics worldwide, second only to India [1,3].

Diabetic nephropathy is a common and serious complication of diabetes [6]. Among patients starting dialysis in Malaysia, diabetic nephropathy was found to be the responsible cause in 51.7% of all end-stage renal disease (ESRD) cases [7]. Therefore, with the increasing prevalence of diabetes, the incidence of

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ESRD is also expected to increase in Asian regions. This correlates well with the fact that Malaysia already has one of the highest diabetic dialysis rates in the world [8].

Several trials have established the renoprotective effects of angiotensin receptor blockers (ARBs) on the progression of renal disease in patients with hypertension and type 2 diabetes [9–11]. Two prospective clinical trials—the Irbesartan in Reduction of Microalbuminuria-2 (IRMA-2) study [12] and the Irbesartan in Diabetic Nephropathy Trial (IDNT) [13]—specifically investigated the effect of irbesartan, an ARB, on type 2 diabetic hypertensive patients with microalbuminuria (MAU) (early diabetic nephropathy) and proteinuria (late diabetic nephropathy), respectively.

The results of these two trials were utilized as primary data to investigate the clinical and economic impact of different therapeutic strategies for patients with type 2 diabetes, hypertension, and nephropathy (e.g., early irbesartan treatment versus late irbesartan treatment) through a Markov model. In the United States, France, United Kingdom, Hungary, Italy, Spain, and Germany, this model established the cost-effectiveness (i.e., greater improvements in projected life expectancy and lowest overall costs) of initiating irbesartan treatment in type 2 diabetics with MAU as compared to initiating either irbesartan or amlodipine treatment in type 2 diabetics with proteinuria or treating patients with standard therapies (i.e., antihypertensive therapy that excludes drugs affecting the renin-angiotensin system and dihydropyridine calcium-channel blockers) [14–18].

These conclusions can, however, be challenged when adapting the Markov model to different healthcare settings because of the variability of certain factors such as epidemiology, disease evolution, treatment patterns, and the associated cost.

Therefore, the objective of this work was to assess the health and economic effects of the initiation of early irbesartan treatment compared either to late irbesartan or amlodipine treatment or to standard therapies in five Asian settings (China, Malaysia, South Korea, Taiwan, and Thailand) by adapting the existing Markov model to each specific setting.

Methods

Model Description

The model used in this analysis explores long-term costs from a third-party payers' perspective and the health consequences for patients with type 2 diabetes, hypertension, and MAU through the following seven stages on a 25-year time horizon (Fig. 1) [14–18].

- MAU (24-hour urinary albumin excretion [(UAE]), 20–199 μg/minute);
- Early diabetic nephropathy (UAE ranging from 200 μg/minute to a median value of 1900 mg/24 hours);
- Advanced diabetic nephropathy (median UAE on admission, 1900 mg/24 hours);
- Doubling of serum creatinine (DSC);
- ESRD treated by dialysis;
- ESRD treated by renal transplant;
- Death.

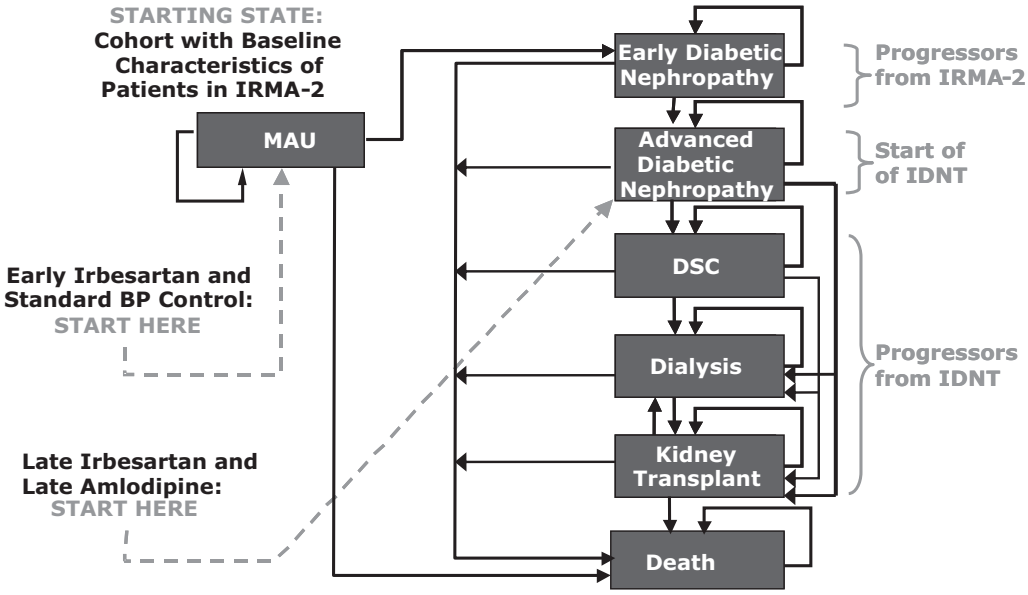

Figure 1 Model structure. BP, blood pressure; DSC, doubling of serum creatinine; IDNT, Irbesartan in Diabetic Nephropathy Trial; IRMA-2, Irbesartan in Reduction of Microalbuminuria-2; MAU, microalbuminuria.

Table I Baseline characteristics of patients in the IRMA-2 study (adapted from [10])

	Standard blood pressure control ($n = 201$)	Irbesartan, 300 mg ($n = 194$)
Demographic characteristics		
Age (year)	58.3 ± 8.7	57.3 ± 7.9
Male (%)	68.7	70.6
Clinical characteristics		
Body-mass index (kg/m^2)	30.3 ± 4.4	30.0 ± 4.3
Known duration of diabetes (year)	10.4 ± 8.6	9.2 ± 6.9
Any type of retinopathy (%)	44.6	35.8
Nonsmokers (%)	47.8	41.2
Laboratory variables		
Blood pressure (systolic) (mmHg)	153 ± 15	153 ± 14
Glycosylated hemoglobin (%)	7.1 ± 1.6	7.1 ± 1.7
Urinary albumin excretion (μg/minute)	54.8 ± 2.5	53.4 ± 2.2
Serum creatinine (mg/dL)		
Male patients	1.1 ± 0.1	1.1 ± 0.2
Female patients	0.9 ± 0.1	1.0 ± 0.2
Triglycerides (mmol/l)	1.9 ± 1.2	2.1 ± 1.3
Total cholesterol (mmol/l)	5.8 ± 1.1	5.8 ± 1.2

IRMA-2, Irbesartan in Reduction of Microalbuminuria-2.

This model simulates a hypothetical cohort of 59-year-old patients with type 2 diabetes, hypertension, and MAU (UAE = 20–199 μg/minute on two of three consecutive occasions), presenting characteristics similar to that of the baseline population in the IRMA-2 study [12] (see Table 1), and following one of the following four treatment strategies:

Standard treatment. Standard antihypertensive therapy alone, excluding the use of acetylcholine esterase (ACE) inhibitors, ARBs, and dihydropyridine calcium-channel blockers.

Early irbesartan treatment. Standard antihypertensive therapy plus administration of 300 mg/day irbesartan at the onset of MAU.

Late irbesartan treatment. Standard antihypertensive therapy plus administration of 300 mg/day irbesartan once the patients reach the advanced diabetic nephropathy stage.

Late amlodipine treatment. Standard antihypertensive therapy plus administration of 10 mg/day amlodipine once the patients reach the advanced diabetic nephropathy stage.

Given the age of the patients at entry of the model, the 25-year time horizon was to be approximating a lifetime horizon. This seminal model [14–18] was reprogrammed in Microsoft Excel 2003® (Microsoft, USA) format to facilitate adaptations to five different Asian settings, namely, China, Thailand, Taiwan, South Korea, and Malaysia, while also increasing transparency for the model user.

Transition Probabilities

The transition probabilities between the health states of disease progression (from MAU to ESRD) were those used in the adaptations of the seminal model [14–18]. These reflected the disease progression as reported in the IRMA-2 study and the IDNT for a patient under each specific treatment investigated. These transition probabilities, presented in Table 2, were assumed to apply to the Asian setting investigated.

In the case of advanced nephropathic stages (i.e., ESRD), the treatment pattern was assumed, after validation with local experts in each settings, to be identical regardless of the initial treatment strategies and was established based on the probabilities of dialysis, transplantation, and death in each stage. Since ESRD management differed across regional health-care settings, the transition probabilities for these stages (i.e., transplantation probability and dialysis) were obtained for each setting from available local data (i.e., peer-reviewed articles, expert opinions, national registries, chart reviews, and/or national statistics) (see Table 3 for the data sources used in each setting and Table 4 for transition probabilities specific to each setting).

The mortality rates for patients with MAU, early and advanced diabetic nephropathy, and DSC were setting and age-dependent. These were calculated by adjusting the age- and sex-specific all-cause mortality values that were published by the WHO for Malaysia, China, South Korea, and Thailand [19] or by using the official statistics [20] for Taiwan, by health state-dependent relative risks (RRs) reported in the seminal model [14–18]. The MAU and overt nephropathy RR were, respectively, valued at 2.03 and 4.4. These were determined, based on Danish data, by comparing mortality

Table 2 Transition probabilities, determined from the IRMA-2 and IDNT study, applied to all Asian settings

	Irbesartan (300 mg daily)	Standard blood pressure control alone	Amlodipine (10 mg daily)
Progression from MAU to early diabetic nephropathy			
Year 1	0.025	0.095	NA
Years 2+	0.036	0.083	NA
Progression from early diabetic nephropathy to advanced diabetic nephropathy			
Year 0		0.068	
Year 1		0.455	
Year 2		0.367	
Year 3		0.526	
Year 4		0.667	
Year 5		0.667	
Year 6		0	
Year 7		0	
Years 8+		1	
Progression from advanced diabetic nephropathy to DSC			
Year 1	0.007	0.014	0.014
Year 2	0.045	0.049	0.051
Year 3	0.042	0.064	0.087
Years 4+	0.032	0.042	0.051
Progression from advanced diabetic nephropathy to ESRD			
Year 1	0.031	0.025	0.027
Year 2	0.021	0.045	0.048
Year 3	0.025	0.04	0.041
Years 4+	0.026	0.036	0.038
Progression from DSC to ESRD			
Years 1+	0.538	0.604	0.56

DSC, doubling of serum creatinine; ESRD, end-stage renal disease; IDNT, Irbesartan in Diabetic Nephropathy Trial; IRMA-2, Irbesartan in Reduction of Microalbuminuria-2; MAU, microalbuminuria; NA, not available.

rates in specific health states to mortality among the general population [21,22]. Because of the absence of data for the DSC state, the RR of overt nephropathy was conservatory used. For the sex adjustment the 68.7% male proportion observed in the IRMA-2 study was used.

Costs Included in the Model

Costs were expressed in 2004 US$ after conversion of setting specific cost data using the health-care product price index for update to 2004 values, and official purchasing power parity for conversion from local currency to US$ [23,24]. Cost data were retrieved from different sources depending on local availability (published data in China and Malaysia; insurance or hospital databases in Taiwan, Thailand, and South Korea) (see Table 2). The costs of concomitant medication, including all other antihypertensive agents, were assumed to be similar between treatment regimens and were excluded from the cost calculation. The specific costs in each Asian setting are presented in Table 5.

Effectiveness Parameters

The model investigated the impact of the four treatment options on the cumulative incidence of ESRD, the number of years the patients lived free of ESRD, the number of days in dialysis, and the number of life-years saved.

Discount Rate

An annual discount rate of 3% was applied for both future costs and outcomes. This corresponds to the discount rate that is generally recommended for health economic evaluations [25,26] and applied in health economic studies performed from an Asian perspective [27–30].

Sensitivity Analysis

Sensitivity analysis was conducted using two complementary approaches: deterministic and probabilistic sensitivity analyses. One-way deterministic sensitivity analysis was performed to individually assess the sensitivity of both cost and outcomes calculated by the model to the uncertainty around each key input parameter and to determine which specific parameter had the largest effect on the results after assigning extreme values (defined as $\pm 50\%$ of the values obtained in the base-case analysis) to key input parameters (drug costs, transplantation probability, mortality, and RRs). The time horizon was also included in this analysis in the form of a threshold analysis and by assessing overall cost after varying the time horizon from 0 to 30 years. The probabilistic sensitivity analysis (second-order Monte Carlo simulation) was used to assess the effect of uncertainty around the model results given uncertainty around each input parameter. From this analysis, 95% confidence intervals round the overall costs and health outcomes investigated in the model were produced [26] and the probability that the incremental cost-effectiveness ratio (ICER) of a given treatment would be below a threshold ICER (cost-effectiveness acceptability) was determined.

Table 3 Sources used to collect data from the different Asian regions

	China	Malaysia	South Korea	Taiwan	Thailand
Transition probabilities	• National statistics [1] • Published peer-reviewed data [2] • Expert opinion	• National Dialysis and Transplant Registry [3]	• Chart review of 2311 ESRD patients newly identified at University Hospital Kidney Center during the periods of 1997–2002	• National statistics [1,4] • Published peer-reviewed data [2]	• Published peer-reviewed data [5] • Thailand Renal Replacement Therapy Registry 2003 [6] • Thailand Renal Transplantation Registry 2004 [7]
Costs	• Published peer-reviewed data [8–10]	• Published peer-reviewed data [27] • Average costs in the private and NGO sectors • Malaysian medical association schedule of fees, 2002	• Health Insurance Review Agency database • Pharmaceutical and Medical Care Benefit Schedule of the National Health Insurance in Korea	• Local database • Taiwan Bureau of National Health Insurance 2004 [11] • Veteran General Hospital Taichung, 2000 statistics national [12]	• Thailand Renal Replacement Therapy Registry 2003 [6] • Thailand Renal Transplantation Registry 2004 [7] • Drug and medical supplies information center [13]

ESRD, end-stage renal disease; NGO, non-governmental organization.

To perform this probabilistic analysis, a specific distribution was attributed to each parameter around the point estimate used in the principal analysis. A triangular distribution, ranging from −30% to +30% of the mean value, was used for the cost variables given no distribution could be retrieved for these parameters, and a binomial distribution was used for the transition probability variables. Thereafter, 1000 cost and health outcome estimates were computed by drawing a specific value from each distribution allowing the quantification of the uncertainty around the model outcomes given the existing uncertainty around each input parameter. The analysis was conducted using @risk 4.5® (Palisade, London, UK).

Results

Cumulative Incidence of ESRD and Number of Cases Prevented

For all the health-care settings, the cumulative incidence of ESRD, defined as the proportion of the patient population that develops ESRD over time, was the lowest when the early irbesartan treatment strategy was used, and it ranged between 9% in Malaysia and 14% in Taiwan. In comparison, the cumulative incidence of ESRD when the late irbesartan treatment strategy was used ranged between 18% in South Korea and 25% in Taiwan. The incidence ranged between 22% in South Korea and 31% in Taiwan when the standard therapy strategy was used. Finally, the model indicated that the late amlodipine treatment strategy yielded the highest cumulative incidence rates in all settings (ranging between 24% in South Korea and 30% in Thailand) (see Fig. 2). The magnitude of reduction in the cumulative ESRD incidence per 1000 patients was investigated. The model indicated that the early irbesartan treatment strategy reduced the number of ESRD incident cases for 1000 patient treated by 85 (South Korea) to 118 (Taiwan) when compared to the late irbesartan treatment strategy, by 128 (South Korea) to 177 (Taiwan) when compared to the standard treatment strategy, and by 144 (South Korea) to 198 (Taiwan) when compared to the late amlodipine treatment strategy. Although the magnitude of reduction was comparable between countries, the maximal reduction was reported in Taiwan, where the incidence was the highest.

Number of Days in Dialysis

Across the settings, the number of days in dialysis per patient was the lowest with the early irbesartan treatment strategy, followed by the late irbesartan, standard, and late amlodipine treatment strategies in that order. The number of days in dialysis was substantially reduced when the early irbesartan treatment strategy was used (the most dramatic reduction was reported in

Table 4 Annual transition probabilities used for each Asian setting

	China [32,33]	Malaysia [34]	South Korea*	Taiwan [32,33,35]	Thailand [36–38]
Transition from dls to tpt over year 1	0.062	0.001	0.024	0.009	0.010
Transition from dls to tpt over year 2	0.062	0.001	0.038	0.009	0.021
Transition from dls to tpt over year 3	0.062	0.003	0.022	0.009	0.004
Transition from dls to tpt over year 4	0.062	0.001	0.018	0.009	0.005
Transition from dls to tpt year 5 and after	0.062	0.003	0.031	0.009	0.008
Mortality from dls over year 1	0.102	0.140	0.107	0.149	0.090
Mortality from dls over year 2	0.102	0.151	0.119	0.124	0.099
Mortality from dls over year 3	0.102	0.178	0.069	0.111	0.110
Mortality from dls over year 4	0.102	0.167	0.071	0.101	0.123
Mortality from dls over year 5 and after	0.102	0.180	0.025	0.099	0.141
Mortality after tpt over year 1	0.042	0.070	0.017	0.021	0.028
Mortality after tpt over year 2	0.042	0.011	0.004	0.021	0.009
Mortality after tpt over year 3	0.042	0.033	0.007	0.021	0.009
Mortality after tpt over year 4	0.042	0.011	0.018	0.021	0.003
Mortality after tpt over year 5 and later	0.042	0.057	0.015	0.021	0.003
Transition from tpt to dls over year 1	0.015	0.000	0.017	0.015	0.096
Transition from tpt to dls over year 2	0.015	0.010	0.003	0.015	0.023
Transition from tpt to dls over year 3	0.050	0.010	0.005	0.050	0.024
Transition from tpt to dls over year 4	0.050	0.031	0.012	0.050	0.029
Transition from tpt to dls over year 5 and later	0.060	0.021	0.013	0.060	0.030
Immediate tpt upon ESRD	0.015	0.010	0.095	0.001	0.033

*Based on a chart review of 2311 ESRD patients newly identified at University Hospital Kidney Center during the periods of 1997–2002.
dls, dialysis; ESRD, end-stage renal disease; tpt, transplantation.

Taiwan, where the early irbesartan treatment strategy yielded a reduction of 245.3 days per patient from the number of days with the standard treatment strategy). The reduction was fairly similar across all the health-care settings—the early irbesartan treatment strategy lowered the number of days in dialysis by 62%, 51%, and 63% as compared to the standard, late irbesartan, and late amlodipine treatment strategies, respectively.

Number of Years Free of ESRD

According to the model, the number of years free of ESRD per patient (see Fig. 2) was the highest across the health-care settings investigated when the early irbesartan treatment strategy was used, ranging between 10.5 years in South Korea and 12.4 years in Taiwan. The number of years free of ESRD ranged between 9.8 in South Korea and 11.5 in Taiwan when the late irbesartan treatment strategy was used. This value was still lower when the standard and late amlodipine treatment strategies were used, with estimates ranging between 9.6 and 11.2 years, and 9.5 and 11.1 years in South Korea and Taiwan, respectively. Interestingly, when the early irbesartan treatment strategy was used, the onset of ESRD was 1.5 and 1.8 years later in South Korea and Taiwan, respectively, than that when the standard treatment was used. This represents a 16% increase in the ESRD-free duration.

Projected Effects on Life Expectancy

Finally, the life expectancy was the highest across all settings investigated when the early irbesartan treatment strategy was used; this was followed by the late irbesartan, late amlodipine, and standard treatment strategies in that order (see Fig. 2). The early irbesartan treatment strategy yielded life expectancies ranging between 10.8 years in South Korea and 12.8 years in Taiwan. When the early irbesartan treatment strategy was used, the life expectancy was an average of 4% to 6% higher than that reported for any other treatment strategy.

Table 5 Costs per year in each Asian setting ($)

	China [39–41]	Malaysia [27]*	South Korea†	Taiwan [42,43]	Thailand [37,38,44]
Cost of amlodipine	2,018	322	619	355	779
Cost of irbesartan	1,660	258	593	461	1,340
Cost of a dbt patient on dls	56,584	19,054	40,254	21,852	31,651
Cost of renal tpt of a dbt patient in the first year	54,886	70,022	41,823	22,382	45,953
Cost (post index year) of a transplanted dbt patient	27,259	14,111	21,639	9,559	19,349

*Average costs in the private and NGO sectors and Malaysian medical association schedule of fees, 2002.
†Health Insurance Review Agency database and Pharmaceutical and Medical Care Benefit Schedule of the National Health Insurance in Korea.
All costs are presented in terms of 2004 US$ values, taking into account purchase power parities.
dbt, diabetic; dls: dialysis; tpt, transplantation.

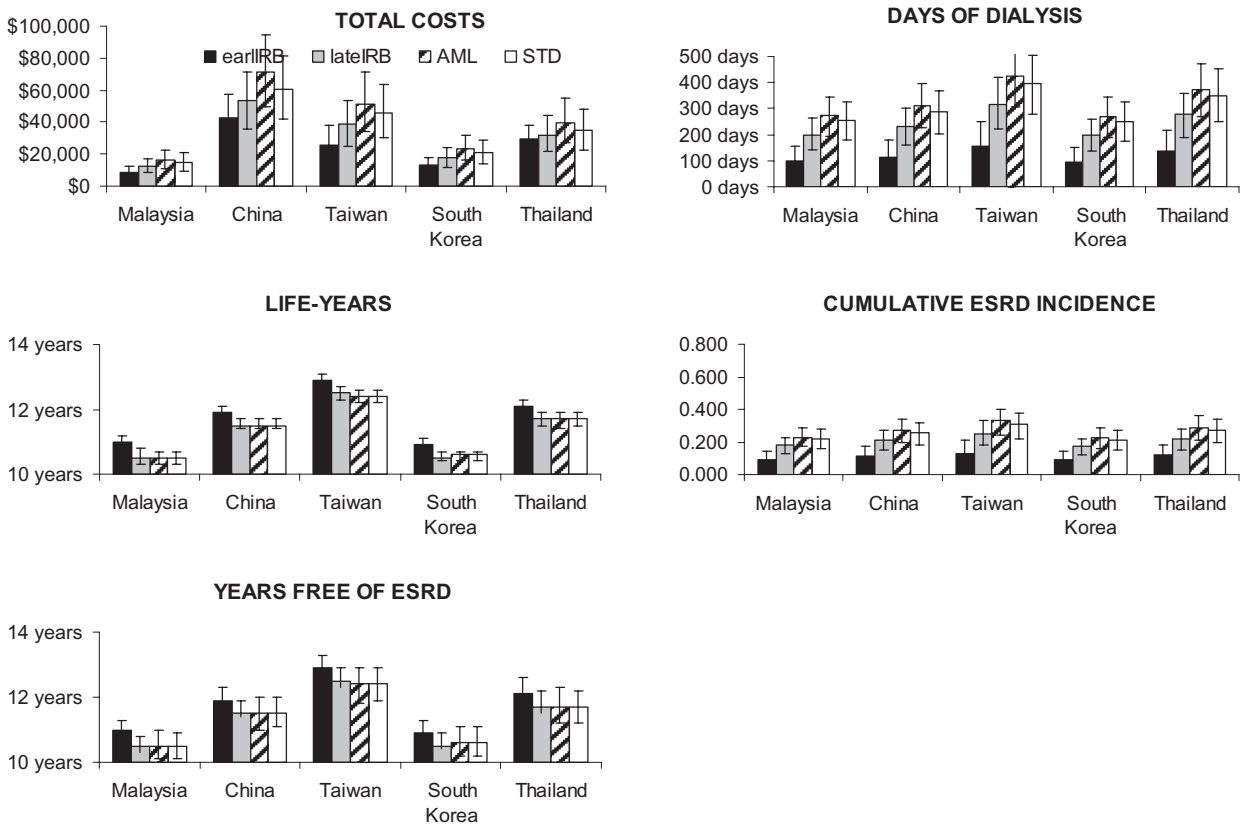

Figure 2 Summarized results of models operated in a 25-year time frame and 3% discount rate for both costs and outcomes. Mean and 95% confidence intervals are displayed. AML, amlodipine; earlIRB, early irbesartan; ESRD, end-stage renal disease; lateIRB, late irbesartan; STD, standard therapy.

Projected 25-Year Costs

The total costs per patient, expressed in terms of 2004 US$, differed greatly among the settings, with an approximately fourfold difference between Malaysia and China (see Fig. 3). Although the costs associated with the early irbesartan treatment strategy were initially higher than those with other treatment strategies (due to the higher cost of irbesartan), the model established that the early irbesartan treatment strategy was eventually cost-saving—after 11 years in Malaysia, Taiwan, 13 years in South Korea, 16 years in China, and 20 years in Thailand. At the end of the time horizon of the model (25 years), the early irbesartan treatment strategy was consistently found to be the least expensive across the health-care settings, with costs of $8,455 in Malaysia, $12,961 in South Korea, $29,737 in Thailand, $25,790 in Taiwan, and $42,990 in China. The costs for the late irbesartan, standard, and late amlodipine treatment strategies were, respectively, $2,980 to $13,484, $6,189 to $21,148, and $8,200 to $29,732 higher than that of early irbesartan treatment.

Sensitivity Analysis

One-way deterministic sensitivity analysis was conducted to evaluate the effect of uncertainty in key parameters on the results. When the annual probability of death in the early stages (i.e., during MAU, early diabetic nephropathy, and advanced diabetic nephropathy) varied between –50% and +50% of the values in the base-case analysis, results remain in favor of early irbesartan in all settings. More specifically, both increasing MAU mortality and decreasing diabetic nephropathy mortality reduced the beneficial effect of early irbesartan treatment in terms of decreased life-years gained compared to the base case. Nevertheless, the early irbesartan treatment strategy remained dominant over the other treatment alternatives. The sensitivity analyses also indicated that the results were not impacted by changes in the transplantation probability.

Finally, the model's cost results appeared to be sensitive to changes in the cost of irbesartan. When the irbesartan cost increased by 50%, irbesartan remains dominant in all settings except in Thailand. Similar results were obtained by reducing the costs of dialysis by 50%. In all the other settings the dominance of irbesartan is maintained with extreme input data.

In addition, the second-order Monte Carlo sensitivity analysis established that the early irbesartan treatment strategy presented a higher probability of dominance (higher clinical benefits and lower costs)

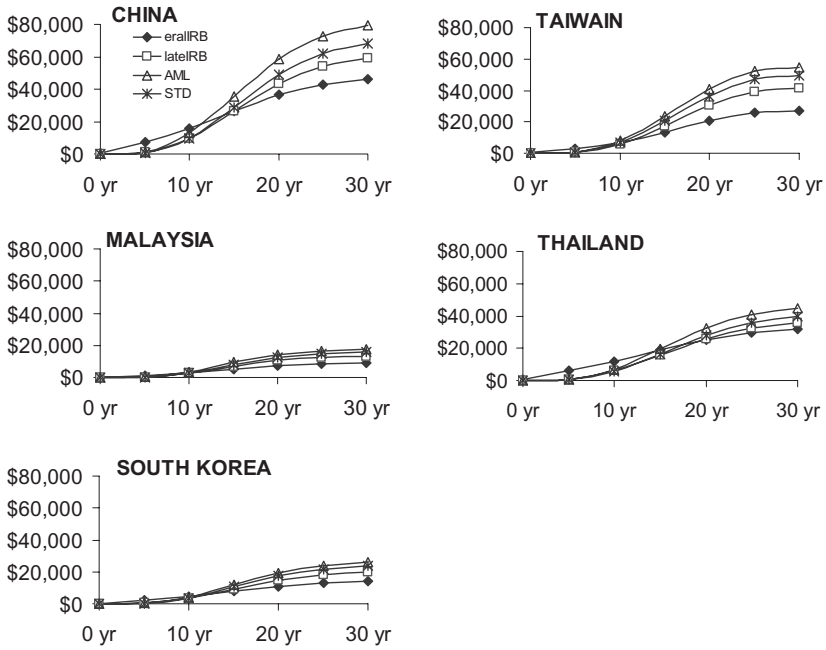

Figure 3 Cumulative total costs over time in US$ per region. AML, amlodipine; earlIRB, early irbesartan; lateIRB, late irbesartan; STD, standard therapy.

than the standard treatment strategy. The 1000 cost and health outcome estimates computed by drawing a specific value for each parameter's distribution showed life-year gained and cost savings for irbesartan compared to standard treatment strategy in at least 66% of the cases in Thailand and up to 95.3% of the cases in Taiwan. Compared to the other treatment strategies, the early irbesartan treatment strategy had a 78% and 93% probability of dominance in Thailand over the late irbesartan and the late amlodipine treatment strategies, respectively. The 1000 second-order Monte Carlo estimates computed when the early irbesartan treatment strategy was used compared to when the standard treatment strategy was used are graphically presented for all Asian settings in the cost-effectiveness planes (Fig. 4).

Discussion

This analysis aimed at adapting a Markov model that was previously developed for Western countries to different Asian health-care settings (China, Thailand, Taiwan, South Korea, and Malaysia). In all five settings, the model indicated that treating patients by standard hypertension treatment plus 300 mg/day irbesartan administered at the onset of MAU could result in cost savings as early as 11 years after the onset of MAU in some Asian settings such as Malaysia or Taiwan. More importantly, this treatment strategy was associated with longer life expectancy and a shorter duration of dialysis as compared to the other treatment options (61% to 63% shorter duration of dialysis compared to the standard hypertensive treatment strategy). Furthermore, the sensitivity analysis established the probability that early irbesartan treatment would predominate over the standard treatment, and it ranged between 66% in Thailand (where the beneficial effect was the lowest) and 95% in Taiwan (where the beneficial effect was the highest).

Some limitations of this study have been identified. The model excluded the costs of comedication for diseases other than diabetic nephropathies. In light of the impact of combination therapies used for hypertension control and their associated costs, this exclusion might, however, be considered conservative. In fact, a higher degree of blood pressure control may be achieved by these treatment strategies, thus reducing the need for additional treatment for comorbidities other than diabetic nephropathies [15]. Further, comparison between the different settings could be reviewed in light of the differences in data sources used to operate the model but also lack of Asian-specific data for some of the transition probabilities. Critical analysis of the input data, however, revealed that there were no major differences among input data obtained from literature, databases, or expert opinion; this underlined the relevance of the comparisons performed in this study.

Finally, this model uses a unique disease pattern across the settings, which may undermine the local differences in the clinical management of these patients among the different settings. Nevertheless, it is well accepted that economic evaluations simplify disease progression to cover most cases in a given setting. Furthermore, for patients with ESRD, dialysis and transplantation are the main treatment alternatives, and both these alternatives were considered by the model in a country-specific manner. Moreover, the

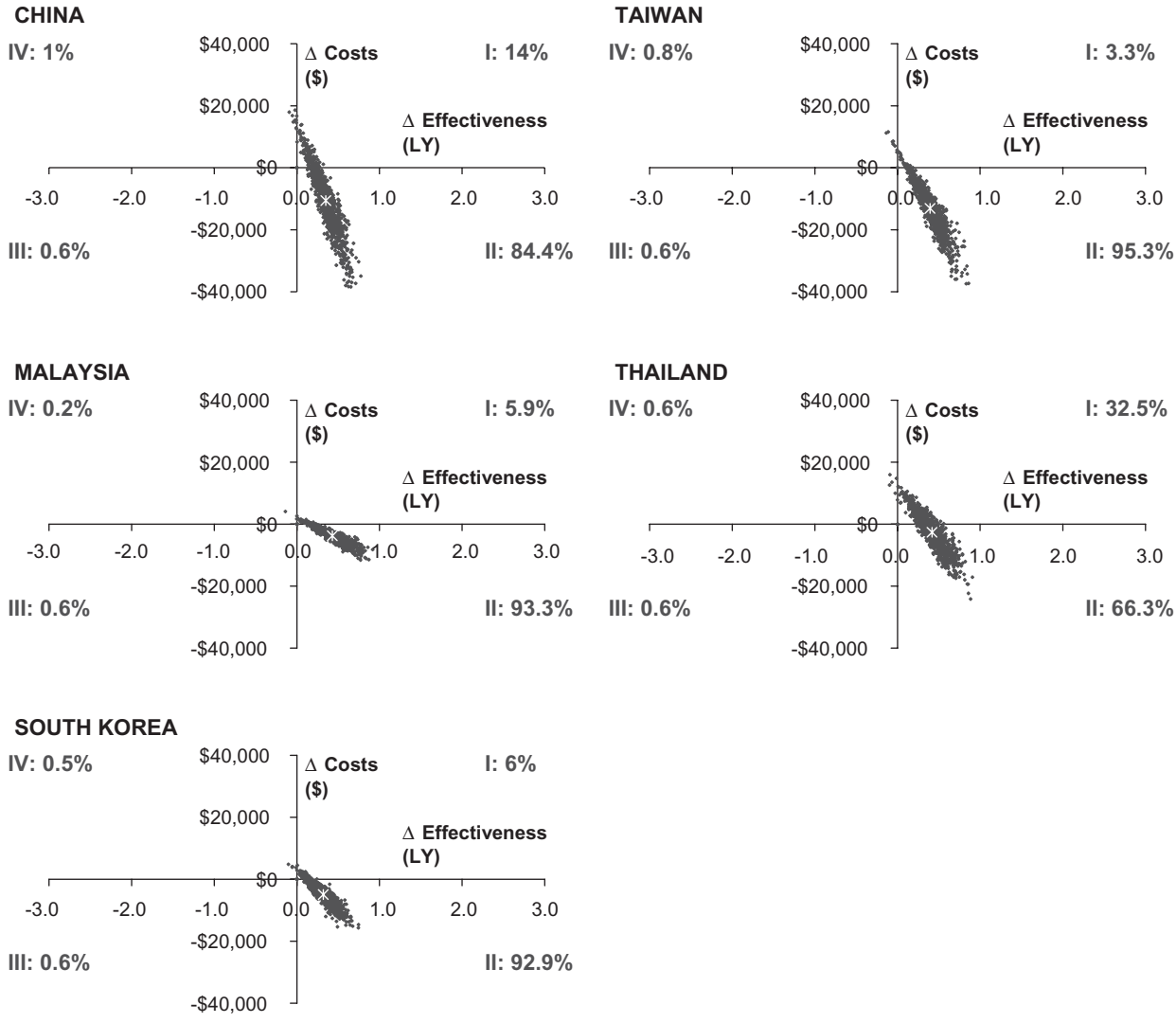

Figure 4 Cost-effectiveness plane (difference in incremental costs vs. difference in incremental life expectancy [LY]) with Monte Carlo simulation for each Asian setting comparing early irbesartan treatment to the standard treatment (*base-case value).

model structure was further validated in each specific setting by local experts.

With regard to the results, the gain in life expectancy for the five settings investigated with early irbesartan ranged between 0.31 and 0.48 life-years over the standard treatment strategy, between 0.33 and 0.44 life-years over the late irbesartan strategy, and between 0.30 and 0.49 life-years over the late amlodipine treatment strategy. These results are in the same range as those obtained in other adaptations of this model. For instance, the US version of this analysis yielded a gain of 0.96 discounted life-years over the standard treatment and 0.92 life-years over the late irbesartan treatment strategies [14], while the Belgian and French models yielded life-year gains ranging between 0.62 and 0.61 years over the standard treatment and between 0.46 and 0.45 years over the amlodipine treatment strategies [14].

Such comparable results can be explained by the method used in the seminal model to adapt to the different settings. The transition probabilities between the different health stages originate from the same clinical trials, except for the mortality-related transition probabilities that were obtained from local sources for each adaptation. Therefore, the impact of modifying mortality-related transition probabilities was included in the sensitivity analysis. Although increasing MAU mortality or reducing overt nephropathy mortality did reduce the reported difference in life expectancy with regard to the base-case scenario for the early irbesartan treatment strategy, varying the mortality-related probabilities did not impact the model's conclusion.

Contrary to the reported outcomes, the economic results of the model are extremely different from those reported in Europe and the United States, with differences being up to 11 times higher in the United States [14] than in Malaysia.

To further investigate the cause of such variations, the results of this adaptation were compared to the gross domestic products (GDPs) of the countries involved in this analysis expressed in 2004 US$. These five settings presented very different characteristics in terms of the GDP per capita ($5600 in China, $8100 Thailand, $9700 in Malaysia, $19,200 in South Korea, and $25,300 in Taiwan).

Overall, the differences in the results observed between the different Asian settings correlate well with the GDPs, with Malaysia showing the lowest costs and among the lowest GDP and Taiwan the highest costs and GDP. In this crude comparison, China appeared to be an outlier, perhaps because of the fact that the costs used in this analysis were mainly from urban regions, whereas GDP of China ($5600 per capita) reflects the costs in both rural and urban settings.

Interestingly, previous analysis of health economic evaluations for many countries, although focusing on Western countries, already highlighted that resource use and therefore cost data were the main drivers of between-country variation [31]. Therefore, the current analysis and previous studies highlight the relevance of adapting international models to local settings since the transferability of economic analyses from one setting to another is challenged by disease management and access to health care.

The conclusion of the current adaptation did not differ from the previous European or US versions of the model for the five Asian settings analyzed. Early irbesartan treatment was indeed a better alternative to standard, late irbesartan, or late amlodipine treatments. Nevertheless, it is evident that the results of health economic analyses cannot be generalized for different countries since the variations in results are not systematic [31].

In conclusion, this Asian adaptation of a peer-reviewed health economic model confirmed the advantage of initiating irbesartan therapy in hypertensive type 2 diabetics as early as the MAU stage. This treatment strategy increased life expectancy, reduced the occurrence of ESRD and the resulting need for dialysis, and thereafter reduced the overall cost in the five Asian settings investigated.

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