Irbesartan and amlodipine in the treatment of patients with microalbuminuria, hypertension and type 2 diabetes in Taiwan: a modelling projection over 25 years

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Summary

This modelling study aimed to evaluate the long-term cost effectiveness of four treatment strategies: early irbesartan; late irbesartan; amlodipine; and standard hypertensive treatment in patients with diabetes, hypertension and microalbuminuria in Taiwan. A Markov model was used to project costs and clinical outcomes over lifetimes.

Early irbesartan (initiated in microalbuminuric patients) yielded the largest improvements in life expectancy (0.78 years) compared with standard treatment. Late irbesartan and amlodipine (started in patients with overt nephropathy) also resulted in slight improvements in life expectancy (0.109 and 0.001 years, respectively). Both early and late irbesartan reduced lifetime costs compared with control (US$7,603 and US$3,233, respectively), whereas amlodipine increased lifetime costs by US$300. Improvements were attributed to reductions in the cumulative incidence of end-stage renal disease with early use of irbesartan.

Treating hypertensive diabetic patients with early irbesartan was projected to be life extending and cost saving, and to reduce the incidence of ESRD in Taiwan.

Keywords: irbesartan, type 2 diabetes, hypertension, microalbuminuria, nephropathy, ESRD, costs, cost effectiveness, modelling, Taiwan

Accepted for publication: 2nd October 2007

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Introduction

The increasing incidence of end-stage renal disease (ESRD) is associated with a huge healthcare burden in Taiwan. Subsequently, medical costs due to renal replacement therapy accounted for approximately 6% of the fiscal budget of the Bureau of National Health Insurance in 2001 and are therefore of major concern to healthcare decision makers in Taiwan[1]. Type 2 diabetes has been recognised as the major underlying cause of ESRD in the Western world[2] and has become a major health concern in Taiwan over the last decade, especially in childhood[3], as lifestyles have become increasingly westernised[4]. Diabetes has expanded to become the second most common cause of ESRD in Taiwan, accounting for 35.9% of newly diagnosed cases in 1997, similar to rates reported in many western countries[1]. Figures from the same year show that there were a total of 22,027 cases of ESRD in Taiwan, corresponding to a prevalence and incidence rate of 1,013 and 252 per million population, respectively[1]. With a rising number of patients who have developed renal disease and consequentially require renal replacement therapy, there remains an increasing need to identify primary and secondary interventions that delay the progression to ESRD.

Several recent clinical studies have provided evidence that treatment with angiotensin receptor antagonists for hypertension is associated with blood pressure independent benefits in terms of preserving renal function[5–7]. One of these trials, the Irbesartan in Reduction of Microalbuminuria-2 (IRMA-2) study, demonstrated a renoprotective effect of the angiotensin II receptor antagonist irbesartan in patients with type 2 diabetes, hypertension and microalbuminuria[5]. A similar renoprotective effect was observed in patients with advanced nephropathy. In the Irbesartan in Diabetic Nephropathy Trial (IDNT), treatment over 3 years with irbesartan 300 mg/day led to 23 and 20% reductions compared with amlodipine and control, respectively, in the combined endpoints of doubling of serum creatinine (DSC), ESRD or death in patients with type 2 diabetes, hypertension and overt nephropathy[6].

Both of these studies provided evidence that the development of renal complications could be considerably postponed in patients with diabetes and hypertension, thereby having positive effects on life expectancy and healthcare expenditure. As such, the use of angiotensin receptor antagonists such as irbesartan in patients with diabetes, hypertension and nephropathy may represent a good opportunity to reduce the high human and economic burden associated with renal failure.

The aim of this cost-consequence study was to evaluate the impact of treatment with irbesartan, in terms of life expectancy, costs and progression of renal disease, in patients with diabetes, hypertension and nephropathy in Taiwan. For this purpose, a previously published and peer-reviewed model has been adapted to the Taiwanese setting, which uses data from the

IRMA-2 study (early intervention) and the IDNT (late intervention) as the basis of the analysis[8].

Methods

Model structure

A peer-reviewed, published Markov model simulating progression from microalbuminuria to nephropathy, DSC, ESRD and all-cause mortality in patients with diabetes, hypertension and nephropathy was adapted to the Taiwanese setting. The model structure and the transition probabilities have been described in detail elsewhere[8]. In summary, the Markov structure consists of seven disease states that reproduce the progression of nephropathy in type 2 diabetic patients from *microalbuminuria* (24-hour urinary albumin excretion (UAE) 20–199 µg/minute) to *early overt nephropathy* (UAE 200 µg/minute to median UAE 1,900 mg/24 hours), *advanced overt nephropathy* (median UAE on entry 1,900 mg/24 hours), *DSC*, *ESRD treated with dialysis*, *ESRD treated with renal transplant* and *death* (Figure 1). As a result of differences between the endpoint of the IRMA-2 study (UAE 200 µg/minute with minimum of 30% increase in UAE from baseline) and the inclusion criteria for the IDNT (median UAE 1,900 mg/24 hours), patients within the simulated cohort were further distinguished as being in either an early or advanced stage of overt nephropathy.

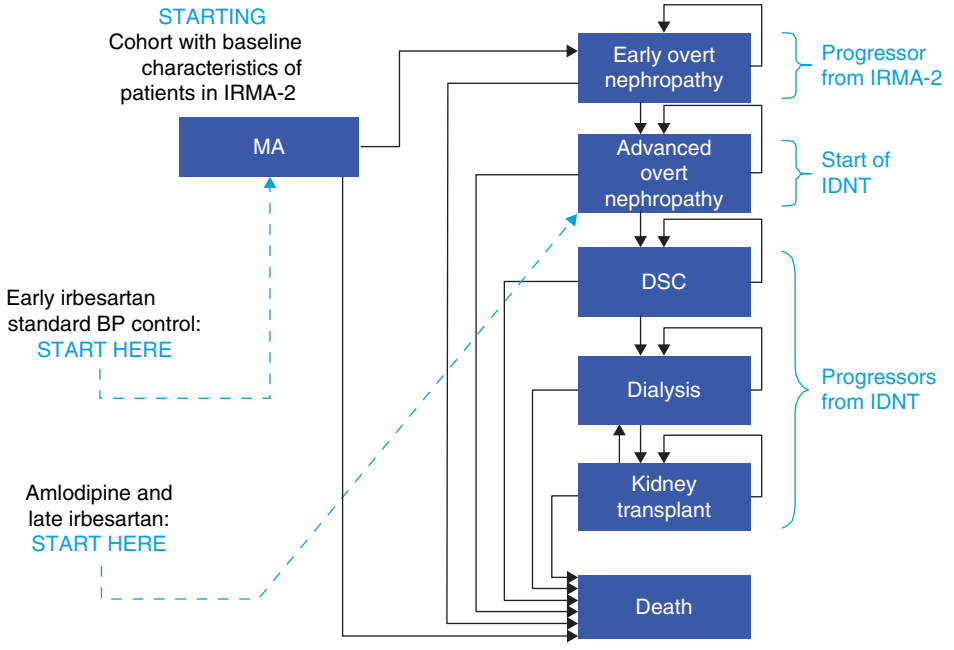
Transition probabilities for treatment-specific progression were derived from the IDNT and IRMA-2 study and have been published previously[5,6,8] (Table 1). After developing ESRD, patients were assumed to transition between the two types of renal replacement therapy (dialysis or transplantation). Transition probabilities in the state of ESRD were treatment-independent probabilities and were derived from the 2002 Annual Data Report published by the Taiwan Renal Registry[9] and the Veterans' General Hospital in Taichung (year 2000 statistics)[10] in order to further adapt the model to the Taiwanese setting.

Mortality rates were derived from multiple sources. Probabilities of death for patients who had not developed ESRD were based on published sources for type 2 diabetes patients[11,12]. Once patients reached the states of *overt nephropathy* and *DSC*, mortality rates for patients were assumed to be equal in all four treatment arms. This assumption may be conservative in light of the evidence from two previous trials suggesting that mortality may increase in line with higher levels of serum creatinine[13,14]. Mortality rates after patients had developed ESRD used values reported by the Taiwanese National Renal Registry.

Cohort and treatment groups

A cohort of patients with characteristics similar to those reported in the IRMA-2 study was simulated[5,6,15]. The simulation was performed under the assumption that patients with microalbuminuria in Taiwan are comparable with patients with microalbuminuria included in the IRMA-2

Figure 1. Model structure.



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MA, microalbuminuria; BP, blood pressure; DSC, doubling of serum creatinine; IRMA-2, Irbesartan in Reduction of Microalbuminuria-2 study[5]; IDNT, The Irbesartan in Diabetic Nephropathy Trial[6].
Control was standard antihypertensive medications (including beta blockers, alpha/beta blockers, diuretics, peripheral vasodilators, peripheral adrenergic blockers and central adrenergic blockers, but excluding angiotensin-converting enzyme inhibitors, other angiotensin II receptor antagonists and dihydropyridine calcium channel blockers) as required to achieve a target BP of <135/85 mmHg, and was started when patients were in the state of MA. Early irbesartan was irbesartan 300 mg/day started when patients were in the state of MA; late irbesartan refers to control therapy when patients were in the states of MA and early overt nephropathy, with 300-mg irbesartan daily added once patients reached the state of advanced overt nephropathy; amlodipine refers to control therapy when patients were in the states of MA and early overt nephropathy, with 10-mg amlodipine daily added once patients reached the state of advanced overt nephropathy.

trial. Although the prevalence of microalbuminuria among diabetic patients is reported to be higher in Asian countries, evidence indicating a difference in the typology of patients diagnosed with microalbuminuria has not been identified.

Four treatment choices were evaluated: (1) 'control' therapy, which included standard antihypertensive medications (including diuretics, beta blockers, alpha/beta blockers, peripheral vasodilators, peripheral adrenergic blockers and central adrenergic blockers, excluding angiotensin-converting enzyme (ACE) inhibitors) to achieve a blood pressure level of <135/85 mmHg when patients developed microalbuminuria; (2) 'early irbesartan', consisting of 300 mg of irbesartan administered to patients daily when first developing microalbuminuria; (3) 'late irbesartan', a treatment regimen that consisted of patients receiving standard antihypertensive medications while in the state of microalbuminuria, with irbesartan titrated from 75 to 300 mg/day started when patients

Table 1. Transition probabilities used in the model.

	Probability		
	Irbesartan 300 mg/day	*Amlodipine 10 mg/day*	*Control (standard blood pressure control alone)*
Progression from *microalbuminuria* to *early overt nephropathy*			
Year 1	0.0250		0.0950
Years 2+	0.0360		0.0830
Progression from *early overt nephropathy* to *advanced overt nephropathy*			
Year 0		0.0678	
Year 1		0.4545	
Year 2		0.3667	
Year 3		0.5263	
Year 4		0.6667	
Year 5		0.6667	
Year 6		0.0000	
Year 7		0.0000	
Years 8+		1.0000	
Progression from *advanced overt nephropathy* to *DSC*			
Year 1	0.0069	0.01411	0.0141
Year 2	0.0454	0.05068	0.0486
Year 3	0.0423	0.08718	0.0644
Years 4+	0.0315	0.05066	0.0424
Progression from *advanced overt nephropathy* to *ESRD*			
Year 1	0.0311	0.026063	0.0246
Year 2	0.0207	0.047999	0.0447
Year 3	0.0249	0.04045	0.0396
Years 4+	0.0256	0.038159	0.0363
Progression from *DSC* to *ESRD*			
Years 1+	0.5376	0.5602	0.6042
Probability that ESRD is initially treated with dialysis			0.998
Probability that ESRD is initially treated with transplantation			0.0014
Probability of transition from *dialysis* to *transplant*			Year 1+: 0.0087
Probability of transition from *transplant* to *dialysis*			Year 1: 0.150
			Year 2: 0.150
			Year 3: 0.500
			Year 4: 0.500
			Year 5+: 0.600

DSC, doubling of serum creatinine; ESRD, end-stage renal disease; RR, relative risk.

Table 1. Transition probabilities used in the model (continued).

	Probability		
	Irbesartan 300 mg/day	*Amlodipine 10 mg/day*	*Control (standard blood pressure control alone)*
Probability of moving from *dialysis* to *death* (all years)			Year 1: 0.149
			Year 2: 0.124
			Year 3: 0.111
			Year 4: 0.101
			Year 5+: 0.099
Probability of moving from *transplant* to *death*			Year 1+: 0.0209
Probability of death in *microalbuminuria*	Age- and gender-specific probabilities for the general population, multiplied by RR of 2.0		
Probability of death in *early overt nephropathy*, *advanced overt nephropathy* and *DSC*	Age- and gender-specific mortality probabilities for the general population, multiplied by RR of 4.4		

DSC, doubling of serum creatinine; ESRD, end-stage renal disease; RR, relative risk.

developed overt nephropathy; and (4) 'amlodipine', which consisted of control treatment, with the addition of amlodipine titrated from 5 to 10 mg/day after developing overt nephropathy.

Costs and discount rates

All costs were reported in 2004 US dollars (US$). Costs for each medication under investigation were assessed separately for patients in all four treatment groups. Costs for patients in the *overt nephropathy* and *DSC* states were based on study medication use and concomitant antihypertensive treatment reported from the IDNT. As the aim of the present study was to evaluate the incremental costs between treatment groups, costs such as those associated with cardiovascular events and standard medical examinations were not included in the analysis and were assumed to not differ between the four treatment arms.

Specific costs of the dosage for each medication (irbesartan 75, 100 and 300 mg; amlodipine 2.5, 5 and 10 mg) were calculated by determining the exposure time by dose for all patients in the IDNT. Costs of study medication were then calculated by dividing the number of days exposed at each dose by the number of patients in the trial. The proportion of patients taking the study medication was then multiplied by the mean duration of follow-up and the medication cost of the corresponding dosage. Exposure to concomitant adjunctive hypertensive medications by class was captured in the IDNT and was applied to the corresponding treatment arm. Use of non-antihypertensive medications was assumed in this model to be similar between treatment strategies. Drug costs were taken from the Taiwan Bureau of National Health Insurance (2004 values).

For patients with ESRD, costs of dialysis or transplant were taken from published sources (Table 2). In July 1996, the Taiwan Bureau of National Health Insurance adopted a capitation policy where

Table 2. Costs associated with end-stage renal disease per patient in Taiwan (US$).

Treatment	*Annual costs*		*Reference*
	TN$	*US$*	
Dialysis, Year 1+	664,108	19,533	Taiwan Bureau of National Health Insurance
Renal transplant, Year 1	690,000	20,294	Taiwan Bureau of National Health Insurance
Renal transplant, Year 2+	357,000	10,500	Taiwan Bureau of National Health Insurance
Irbesartan 300 mg (Aprovel®)	12,191	359	Taiwan Bureau of National Health Insurance
Amlodipine 10 mg (Norvasc®)	13,870	408	Taiwan Bureau of National Health Insurance

Table 3. Summary results: discounted life expectancy (years).

Time horizon	*Early irbesartan*	*Late irbesartan*	*Amlodipine*	*Control*
10 years	7.825	7.720	7.718	7.718
25 years	12.003	11.332	11.224	11.223

reimbursement was US$137 per dialysis session. The rate of reimbursement is fixed and is assumed to account for the cost of all supplies, including blood transfusion materials, medication and laboratory tests, as well as overheads, erythropoietin and renal anaemia-related medicine, and nursing and physician fees, which are adjusted for the type of dialysis received. Annual dialysis costs were calculated by multiplying the amount reimbursed for haemodialysis by the average number of times a patient receives treatment per year. A similar methodology was used to determine the cost of renal transplantation for the first and subsequent years of treatment under the assumption that treatment patterns and costs in the second year were valid for all subsequent cycles.

Lifetime outcomes (costs, life expectancy and cumulative incidence of ESRD) were calculated over a time horizon of 25 years, which was considered long enough to capture all of the long-term costs and benefits from the perspective of a third-party payer in Taiwan (Taiwan National Health Insurance Program). Discounting is commonly used in health economic analyses to adjust for the diminished value of future costs and clinical outcomes. In the present study, costs and clinical benefits were discounted at an arbitrary (but standard) rate of 3% per annum as no recommended discount rate is presently available for Taiwan[16].

Results

Projected impact on life expectancy

After 10 years of treatment, discounted life expectancy was found to be modestly higher in patients treated with early irbesartan (7.825 years) and late irbesartan (7.720 years) compared with amlodipine (7.718 years) and control therapy (7.718 years) (Table 3). After 25 years of treatment, discounted life expectancy was highest in patients treated with early irbesartan (12.003 years), followed by late irbesartan (11.332 years), amlodipine

(11.224 years) and control (11.223 years). Early irbesartan treatment resulted in improvements of approximately 0.11 and 0.78 years in life expectancy after 10 and 25 years, respectively, compared with control. These improvements correspond to 107 life years saved per 1,000 patients treated with early irbesartan after 10 years of treatment and 780 life years saved per 1,000 patients after 25 years compared with control (Table 4).

In patients treated with late irbesartan, after 10 years of treatment discounted life expectancy was projected to increase by 0.002 years and save 2 life years per 1,000 patients treated. After 25 years of treatment, life expectancy was projected to increase by 0.11 years with late irbesartan treatment compared with control, corresponding to a saving of 109 life years per 1,000 patients treated.

Projected impact on costs

Over the 25-year time horizon, treatment with early and late irbesartan were both estimated to be cost saving compared with standard antihypertensive medication, with the largest reductions seen in the early treatment group (Table 5). Projections for the early irbesartan treatment group revealed that the cumulative direct medical costs after 10 years of treatment would be US$3,181, slightly higher than costs projected for the control group (US$3,074). However, over a longer time horizon (25 years), treatment with early irbesartan was projected to reduce total costs by US$7,603 compared with control (US$8,915 vs. US$16,518, respectively). Later use of irbesartan was associated with economic savings of US$468 after 10 years of treatment compared with control therapy (US$2,606 vs. US$3,074, respectively). However, after 25 years of treatment, cost savings associated with late irbesartan treatment were US$3,233 compared with control (US$13,285 vs. US$16,518, respectively), approximately 43% lower than the cost savings of early irbesartan treatment. The cumulative costs of all four treatment options showed that treatment with early irbesartan became cost saving vs. control after 11 years and cost saving compared with late irbesartan treatment after approximately 12 years (Figure 2).

In contrast, treatment with amlodipine was associated with high costs throughout the patients' lifetimes. Compared with control, treatment with amlodipine increased costs by US$227 over 10 years and by US$300 over 25 years. Treatment with amlodipine was projected to result in higher treatment costs compared with the three other treatment options over patients' lifetimes.

Development of ESRD

In both the early and late irbesartan treatment groups, there was a projected reduction in the cumulative incidence of ESRD and an increased number of years free of ESRD compared with amlodipine and standard antihypertensive treatment (Table 6). Over patients' lifetimes, projected time free of ESRD was 15.123 years with early irbesartan, 13.310 years with late irbesartan, 13.020 years with amlodipine and 12.993 years with control. Early irbesartan patients spent on average a longer period of time free of ESRD compared with the other treatment options. The time period free of ESRD directly correlates with the lower incidence

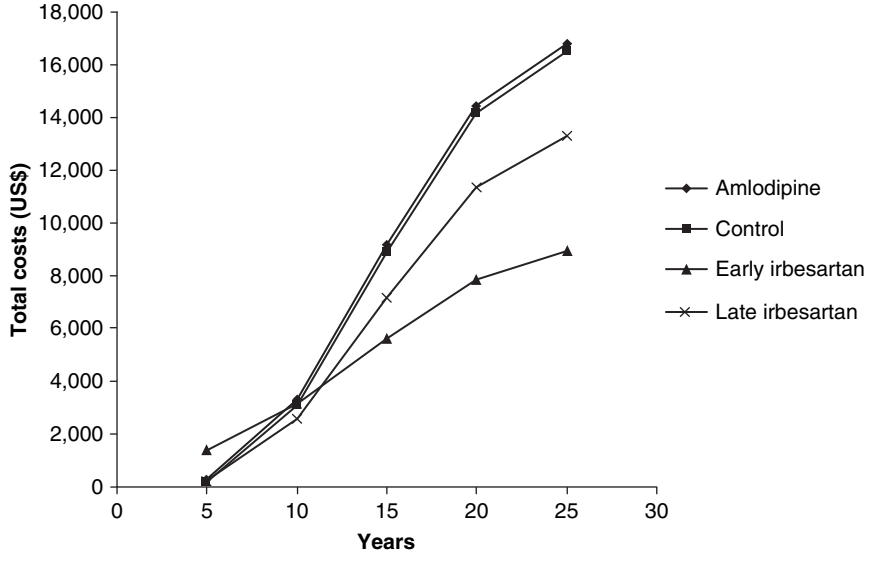
Table 4. Number of life years saved per 1,000 patients treated.

Time horizon	*Early irbesartan vs. control*	*Late irbesartan vs. control*	*Early irbesartan vs. amlodipine*	*Late irbesartan vs. amlodipine*	*Amlodipine vs. control*
10 years	107	2	0	0	0
25 years	780	109	779	109	1

Table 5. Cumulative costs and cost savings (US$).

Time horizon	*Early irbesartan*	*Late irbesartan*	*Amlodipine*	*Control*
10 years	3,181	2,606	3,301	3,074
vs. control	107	–468	227	–
25 years	8,915	13,285	16,818	16,518
vs. control	–7,603	–3,233	300	–

Figure 2. Total lifetime costs.



of ESRD in the irbesartan groups. The cumulative incidence of ESRD was almost 14% lower in the early irbesartan group compared with amlodipine and control (8.00 vs. 22.08 and 22.42%, respectively) and was also approximately 4.5% lower in the late irbesartan group (17.45%) compared with amlodipine and control.

A reduction in the cumulative incidence and delayed progression of ESRD associated with irbesartan treatment compared with amlodipine and control treatment was projected to lower the amount of renal replacement therapy required (dialysis or renal transplantation). Early treatment with irbesartan required the lowest number of days of renal

Table 6. Impact of irbesartan treatment on development of ESRD.

Time horizon	*Early irbesartan*	*Late irbesartan*	*Amlodipine*	*Control*
Number of years free of ESRD				
10 years	8.902	8.701	8.652	8.646
25 years	15.123	13.310	13.020	12.993
Cumulative incidence of ESRD (%)				
10 years	2.42	6.18	8.11	8.41
25 years	8.00	17.45	22.08	22.42
Number of days of renal replacement therapy required				
10 years	20	53	70	72
25 years	158	362	464	473

ESRD, end-stage renal disease.

replacement therapy (158 compared with 362 days with late irbesartan treatment, 464 days with amlodipine and 473 with control therapy).

Discussion

The present analysis demonstrates the importance of early treatment with a renoprotective antihypertensive medication in patients with type 2 diabetes, hypertension and microalbuminuria. Treatment with irbesartan was estimated to result in increased life expectancy and reduced incidence of ESRD and costs compared with amlodipine and standard antihypertensive treatment in Taiwan. However, the analysis also demonstrated that treatment with irbesartan should be initiated earlier rather than later to maximise potential gains in clinical and economic benefits. Early irbesartan treatment, initiated when patients first develop microalbuminuria, led to the greatest improvements in discounted life expectancy and cost savings as well as a reduction in the cumulative incidence of ESRD compared with control. Similar improvements were projected when early irbesartan was compared with amlodipine. The benefits of late irbesartan treatment, initiated when patients developed overt nephropathy, were not as great.

Treatment of ESRD with renal replacement therapy is accompanied by high costs and, as a result, any intervention with the potential to delay or prevent the development of ESRD may well prove to be cost effective or even cost saving. Promisingly, the results from this analysis predict not only substantial economic savings when irbesartan is used to treat patients with type 2 diabetes, hypertension and microalbuminuria, but also delayed progression of ESRD and improvements in life expectancy. The results may be even more remarkable given the limitations of the present analysis, as only the direct medical costs of treatment were considered. Had the analysis been performed from a societal perspective and taken into account indirect costs such as lost productivity and

Table 7. Costs of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in Taiwan (US$).

Drug	*Costs*		*Reference(s)*
	TN$	*US$*	
Enalapril 20 mg (Renitec®)	21.5	0.632	Taiwan Bureau of National Health Insurance 2007
Fosinopril 20 mg (Monopril®)	29	0.853	Taiwan Bureau of National Health Insurance 2007
Ramipril 10 mg (Tritace®)	23.3	0.685	Taiwan Bureau of National Health Insurance 2007
Irbesartan 150 mg (Aprovel®)	21.6	0.635	Taiwan Bureau of National Health Insurance 2007
Losartan 50 mg (Cozaar®)	23.9	0.703	Taiwan Bureau of National Health Insurance 2007
Valsartan 80 mg (Diovan®)	22.6	0.664	Taiwan Bureau of National Health Insurance 2007

premature death, the cost savings associated with irbesartan treatment may well have been even more dramatic.

Owing to the lack of direct clinical evidence, the present analysis is limited by the fact that it does not take into account treatment with ACE inhibitors, beta blockers or other angiotensin II receptor blockers in patients with type 2 diabetes, hypertension and microalbuminuria. Results presented from this analysis were generated from a health economic model that primarily used data from two clinical trials, both of which limited the use of antihypertensive medications in the control treatment arm to diuretics, beta blockers, calcium channel blockers (except dihydropyridines) and central alpha antagonists in order to achieve the target blood pressure of <135/85 mmHg[5]. Although international guidelines for economic studies recommend that the economic evaluation of a drug be determined by comparing it with the current best alternative or current standard of care, to date no head-to-head clinical comparisons of irbesartan and ACE inhibitors, beta blockers or other angiotensin II receptor blockers have been published in a similar population, which restricts direct comparison of these treatments using health economic models. A direct comparison of the costs of ACE inhibitors and angiotensin receptor blockers in Taiwan shows that the irbesartan tablet is the cheapest drug in its class and its price is comparable with ACE inhibitors (Table 7). Future research directly comparing ACE inhibitors and angiotensin receptor antagonists such as irbesartan would be of great interest and would almost certainly lead to health economic analyses comparing the long-term impact of both interventions.

Two large trials, namely IDNT and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, evaluated the renoprotective role of an angiotensin receptor blocker in patients with type 2 diabetes and overt nephropathy[6,7]. Economic evaluation of the RENAAL study was performed in North America and Europe showing cost saving during a 4-year period with treatment with losartan[17–21]. However, the method used in the RENAAL study does not allow for assessment of

long-term clinical outcomes and costs, whereas in this study a Markov model was used to overcome this limitation.

Previously published results based on the IRMA-2 study and the IDNT, using the same model and incorporating US economic and clinical data, presented similar results that irbesartan treatment in patients with advanced overt nephropathy, hypertension and type 2 diabetes also led to delayed onset of ESRD, improvements in life expectancy and cost savings due to the avoidance of ESRD compared with standard hypertension treatment or amlodipine[8]. Moreover, analyses using the same model in the Belgian, French, German, Hungarian, Spanish, UK and US settings provided a similar pattern of improvements in clinical and economic outcomes[22–27]. The results from the present analysis, in combination with the conclusions of similar analyses, support intervention with irbesartan at early (patients with microalbuminuria) and late (patients with overt nephropathy) stages as potentially leading to life extending and cost savings compared with amlodipine and standard antihypertensive medications.

Conclusions

This modelling study provides supportive evidence for the use of irbesartan in patients with type 2 diabetes, hypertension and microalbuminuria in a Taiwanese setting. Early intervention with irbesartan seems to be the most efficient time point to initiate therapy in terms of improving life expectancy and cost savings due to ESRD avoided. However, late intervention with irbesartan, when patients have already developed overt nephropathy, was also associated with improvements in life expectancy and cost saving compared with standard antihypertensive treatment. Both the decision makers responsible for providing healthcare and the patients whose lives are prolonged by delaying or avoiding ESRD could benefit from irbesartan use.

Acknowledgements

Declaration of interest: This study was funded by an unrestricted grant from Sanofi-Aventis.

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