Original Article

Cost-Utility Analysis of Antihypertensive Combination Therapy in Japan by a Monte Carlo Simulation Model

Ikuo SAITO[1], Makoto KOBAYASHI[2], Yasuyuki MATSUSHITA[3),4)], Asuka MORI[4], Kaname KAWASUGI[4),5)], and Takao SARUTA[6]

The objective of the present study was to analyze the cost-effectiveness of lifetime antihypertensive therapy with angiotensin II receptor blocker (ARB) monotherapy, calcium channel blocker (CCB) monotherapy, or ARB plus CCB (ARB+CCB) combination therapy in Japan. Based on the results of large-scale clinical trials and epidemiological data, we constructed a Markov model for patients with essential hypertension. Our Markov model comprised coronary heart disease (CHD), stroke, and progression of diabetic nephropathy submodels. Based on this model, analysis of the prognosis of each patient was repeatedly conducted by Monte Carlo simulation. The three treatment strategies were compared in hypothetical 55-year-old patients with systolic blood pressure (SBP) of 160 mmHg in the absence and presence of comorbid diabetes. Olmesartan medoxomil 20 mg/d was the ARB and azelnidipine 16 mg/d the CCB in our model. On-treatment SBP was assumed to be 125, 140, and 140 mmHg in the ARB+CCB, ARB alone, and CCB alone groups, respectively. Costs and quality-adjusted life years (QALYs) were discounted by 3%/year. The ARB+CCB group was the most cost-effective both in male and female patients with or without diabetes. In conclusion, ARB plus CCB combination therapy may be a more cost-effective lifetime antihypertensive strategy than monotherapy with either agent alone. (*Hypertens Res* 2008; 31: 1373–1383)

***Key Words*: hypertension, cost-utility analysis, combination therapy, diabetes**

Introduction

In many guidelines for the treatment of hypertension, combination therapy is recommended to prevent cardiovascular diseases (*1–3*). However, the cost-effectiveness of additional blood pressure (BP) lowering by combination therapy is unknown. To accurately predict the cost-effectiveness corresponding to clinical practice, metabolic changes caused by long-term drug therapy and drug compliance should be considered in addition to the drugs' BP-lowering effects and market prices. Furthermore, observation periods in large-scale clinical trials are typically 5 years, but most patients have to take antihypertensive drugs throughout their lifetimes. Since observation periods after the development of diabetes tend to be relatively short, it is possible that individuals who develop this condition during antihypertensive drugs trials might not exhibit cardiovascular events even though it is known that

From the [1)]Health Center, Keio University, Tokyo, Japan; [2)]Health Economics Research Group, Crecon Research & Consulting Inc., Tokyo, Japan; [3)]Management Sciences Department, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan; [4)]Daiichi Sankyo Co., Ltd., Tokyo, Japan; [5)]Department of Allergy and Rheumatology, University of Tokyo School of Medicine, Tokyo, Japan; and [6)]Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

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Address for Reprints: Ikuo Saito, M.D., Health Center, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160–0016, Japan. E-mail: saito@hc.cc.keio.ac.jp

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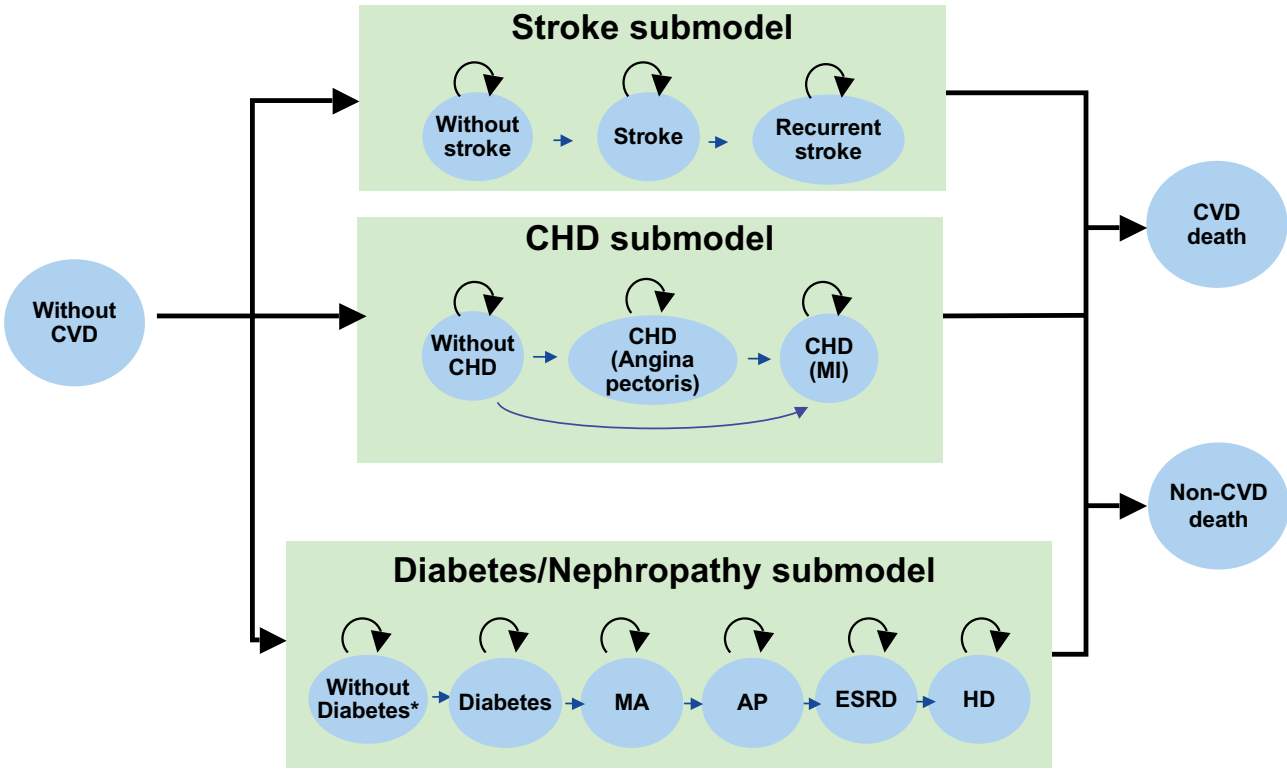

Fig. 1. *The Markov model. CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; MA, microalbuminuria; AP, apparent proteinuria; ESRD, end-stage renal disease; HD, hemodialysis. *This stage is skipped in the analysis in patients with diabetes.*

such individuals are at heightened risk (*4–9*). Thus it may not be appropriate to estimate the cost-effectiveness of lifetime antihypertensive therapy solely based on evidence obtained in large-scale clinical studies (*10*). A pharmacoeconomic approach, on the other hand, can simulate the relationship between the expected extension of survival time brought about by drugs and the cost of therapy through the construction of mathematical analytic models.

Numerous large-scale clinical studies have demonstrated that angiotensin II receptor blockers (ARBs) prevent new onset of diabetes and protect the kidney by suppressing the progression of diabetic nephropathy (*11*, *12*). Progression of diabetic nephropathy has a remarkable effect on the costs of medical care, and this factor should be included in long-term cost-utility assessment of antihypertensive drugs (*13*).

In the present study, a pharmacoeconomic analysis of combination therapy including an ARB with other antihypertensive drugs was conducted based on the rationale that such combinations are widely used in daily clinical practice (*14–16*). This study supplements similar pharmacoeconomic analyses that have been conducted to investigate combinations including an angiotensin-converting enzyme (ACE) inhibitor (*10*, *17*).

We constructed a Markov model in order to analyze the prognosis of patients with essential hypertension and evaluate the cost-effectiveness of single-drug regimens with different ARBs (*18*), and compared the cost-effectiveness of the first-line drugs with that of combination therapy in cases in which additional antihypertensive drugs were added because the first-line drugs were not sufficiently effective (*19*). Hence in the present study we pharmacoeconomically investigated the cost-effectiveness of three therapeutic regimens—ARB monotherapy, calcium channel blocker (CCB) monotherapy, and combination therapy with an ARB plus CCB (ARB+CCB)—in the presence or absence of diabetes in male and female patients. In the present analysis, prognosis of hypertensive patients was analyzed by a Monte Carlo simulation model that can repetitively simulate the prognosis of individual patients (*20*).

Methods

Analytical Model

Our Markov model took into account coronary heart disease (CHD), stroke, and progression of diabetic nephropathy submodels, as described in our previous report (Fig. 1) (*19*). CHD consisted of myocardial infarction and angina pectoris; stroke consisted of cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage.

Table 1. Probability Parameters

	ARB	CCB	ARB+CCB
Cumulative incidence of developing diabetes (%)			
First year	1.7	2.2	1.7
Fifth year	8.1	10.4	8.1
Tenth year	15.6	19.7	15.6
Fifteenth year	22.5	28.1	22.5
Twentieth year	28.8	35.6	28.8
Progression of diabetic nephropathy (%/year)			
Without nephropathy to microalbuminuria	4.6	6.0	4.6
Microalbuminuria to apparent proteinuria	4.9	6.5	4.9
Apparent proteinuria to ESRD	14.4	20.0	14.4
ESRD to hemodialysis	14.4	20.0	14.4
Hemodialysis to death	12.8	12.8	12.8

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ESRD, end-stage renal disease.

Based on this model, analysis of the prognosis of each patient was repeatedly conducted by Monte Carlo simulation. In the Markov model, CHD and stroke submodels included a risk estimation equation based on the Framingham Study (*21*) adjusted for Japanese patients (*22*). This equation incorporated several risk factors: gender; age; high-density lipoprotein (HDL) cholesterol; total cholesterol; systolic BP (SBP); diabetes; smoking; and ECG—left ventricular hypertrophy.

The mortality and care level of patients with cerebrovascular disorder were based on data stored at the Research Institute for Brain and Blood Vessels Akita (http://akita-noken.go.jp/provide/ekigaku/yobo/region/akita/akitaframe.html [accessed September 2007]). Levels of care were correlated to long-term needs based on insurance models such that cases of "disability level 1," "disability level 2," and "disability level 3" were defined as requiring "support," "care level I–III," and "care level IV–V," respectively.

The annual recurrence rate of cerebrovascular disorder was defined as 2.7% based on the results of the Perindopril Protection against Recurrent Stroke Study (PROGRESS) (*23*), and in each case the recurrent clinical entity was assumed to be the same as the previous disorder. Furthermore, the care level in recurrent patients was assumed to increase successively by one level up to the maximum level so as to reflect individual worsening conditions in 34.7% of patients based on the report by Hirai *et al*. (*24*).

The progression of diabetic nephropathy model included the following five conditions from the report by Ikeda and Kobayashi (*25*) and was constructed based on the results of the Kumamoto Study (*26*): no nephropathy, microalbuminuria, apparent proteinuria, chronic renal failure, and hemodialysis (Table 1). The mortality rate after hemodialysis was assumed to be 12.9%/year using an exponential distribution based on the 5-year survival rate reported by Nakai and Shinzato (*27*). The rates of death by causes other than CVD and dialysis were taken from the male and female data at each age range and each cause of death as described in the "Abridged Life Tables for Japan in 2004" (*28*).

The costs of medical care and nursing care were included, and quality-adjusted life years (QALYs) were used as an effectiveness index. Expected costs in the second and subsequent years and expected QALYs were discounted by 3%/year (*29*). The Monte Carlo model was constructed and simulated using TreeAge Pro 2006™ software (TreeAge Software, Inc., Williamstown, USA) and simulated 10,000 times.

Subjects and Treatment Strategies

Subjects were 55-year-old hypertensive patients with a baseline SBP of 160 mmHg. On-treatment SBP attained in patients with ARB or CCB monotherapy was assumed to be 140 mmHg; that in the ARB+CCB group was 125 mmHg. In the present analysis, dropout cases were not considered. Azelnidipine 16 mg/d and olmesartan medoxomil 20 mg/d were the CCB and ARB used, respectively.

According to Yamaguchi *et al*. (*30*), the cumulative incidence rate of diabetes in hypertensive patients during an observation period of 16.9 years was 31.2%. The annual cumulative incidence was calculated as 2.2% under an assumption of exponential distribution. This value was considered as the cumulative incidence of diabetes in patients in the CCB groups based on the findings of a recent meta-analysis (*31*), and that in the ARB group was defined as 1.7% under the assumption that the cumulative incidence of diabetes was 0.8-fold that during treatment with a CCB (*11*). In the ARB+CCB group the cumulative incidence was assumed to be the same as in the ARB group, *i.e.*, 1.7%. The cumulative incidence of developing diabetes at the end of 1, 5, 10, 15, and 20 years in each group is shown in Table 1.

ARBs have been shown to inhibit the progression of diabetic nephropathy (*12*, *32*, *33*). Before apparent proteinuria, the progression of diabetic nephropathy was assumed to be inhibited by 24% by an ARB according to the results of the Microalbuminuria, Cardiovascular, and Renal Outcomes

Table 2. Cost Parameters

Cost	Item	Cost (yen)
Coronary heart disease	Acute myocardial infarction	2,785,000
	Myocardial infarction in the chronic stage (/year)	724,000
	Angina pectoris	1,190,000
	Angina pectoris in the chronic stage (/year)	700,000
Stroke	Cerebral infarction	904,000
	Cerebral hemorrhage	1,841,000
	Subarachnoid hemorrhage	3,799,000
	Stroke in the chronic stage (/year)	213,000
Death by cause	Acute myocardial infarction	2,859,000
	Acute coronary syndrome	2,541,000
	Other	1,469,000
Long-term care (/year)	Care level I	—
	Care level II	454,277
	Care level III	1,746,010
	Care level IV–V	3,433,450
Outpatient management (/year)	Consultation/prescription fees/additional fees	58,800
	Without antihypertensive therapy	—
Antihypertensive medication (/d)	Olmesartan medoxomil 20 mg	172.4
	Azelnidipine 16 mg	80.6
Laboratory tests (/year)	On antihypertensive therapy	5,140
	Without antihypertensive therapy	—
Diabetes/diabetic nephropathy (/year)	Diabetes without nephropathy	73,940
	Microalbuminuria	76,340
	Apparent proteinuria	82,510
	End-stage renal disease	100,980
	Hemodialysis	5,765,526

(MICRO)–Heart Outcomes Prevention Evaluation (HOPE) Study (*34*). Although the test drug in MICRO-HOPE was an ACE inhibitor, from the results of the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) Study (*33*), ARBs were assumed to have similar efficacy with the same potency. After apparent proteinuria was observed, ARBs were estimated to inhibit the progression of nephropathy by 28% according to the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study (*12*). No renoprotective effect was assumed in the CCB group based on the findings of the Irbesartan Diabetic Nephropathy Trial (IDNT) (*35*). In patients of the ARB+CCB group, the efficacy was assumed to be the same as in the ARB group (Table 1).

Cost Items

The present analysis was conducted from the perspective of the payer, and direct medical and long-term care costs incurred after stroke were included in the expense items. The cost parameters used for analysis are shown in Table 2. The drug prices of azelnidipine 16 mg and olmesartan medoxomil 20 mg were defined as 80.6 and 172.4 yen/d based on the Japanese drug price list as of April 2006 (*36*). Standard medical treatment costs for hypertensive outpatients were estimated from medical treatment fees under the assumption that patients visit their medical institution once/month. Annual expenses for nursing care were calculated based on the Survey of Long-term Care Benefit Expenditures from May 2003 to April 2004 issued by the Ministry of Labour, Health and Welfare of Japan.

Other than the cost parameters described above the same values used in our previous analysis (*19*) were employed in the present study.

Utility

In the present analysis, the utility value of hypertensive patients with diabetes but not diabetic nephropathy was considered to be identical to that of hypertensive patients without any complications (utility value=1). The utility values of patients with diabetic nephropathy and CHD were taken from a utility survey of diabetic patients (*37*). The utility value of patients with ischemic heart disease was assumed to be 0.77,

Table 3. Utility Parameters

	Utility
Post coronary heart disease	0.77
Post stroke (as care level of long-term care insurance)	
Support	0.78
Care level I, II, III	0.59
Care level IV, V	0.28
Diabetic nephropathy	
Microalbuminuria	0.81
Apparent proteinuria	0.81
End-stage renal disease	0.69
Hemodialysis	0.66

and this value was also applied to patients with angina pectoris and myocardial infarction. The utility values of diabetic nephropathy were 0.81 for microalbuminuria, 0.81 for apparent proteinuria, 0.69 for end-stage renal disease, and 0.66 for hemodialysis (Table 3).

The utility value of patients after stroke was taken from the Disability Utility by Care Level Survey conducted by Kurimori *et al*. (*38*) with modification (disability level 1 = a utility value of 0.78, disability level 2 = a utility value of 0.59, and disability level 3 = a utility value of 0.28; Table 3).

Calculation of the Incremental Cost-Effectiveness Ratio

The incremental cost-effectiveness ratio (ICER) was used as an index of cost-effectiveness. ICER is defined as the cost/additional QALY. If "C_A" and "$QALY_A$" represent the expected cost and expected QALYs of treatment A, respectively, and C_B and $QALY_B$ represent these parameters for treatment B, in the case of $C_A > C_B$ and $QALY_A > QALY_B$ ICER is expressed as:

$$\text{ICER} = \frac{C_A - C_B}{QALY_A - QALY_B} \quad (1)$$

If the experimental treatment entails a lower QALY and higher expected cost than the existing therapy, or the QALYs and the costs of the treatment are equal, such treatment is excluded from the ICER assessment (*39*).

Base-Case Analysis and Sensitivity Analysis

The analysis was conducted in male and female patients both in the presence and absence of complication of diabetes, and expected QALYs and expected costs using three therapeutic strategies were calculated. Patients were divided into an ARB+CCB, an ARB, and a CCB group for analysis, and the reference group was determined as patients who received a CCB, which is the most widely used treatment in Japan (*14*). Sensitivity analysis was conducted in five cases as outlined below. 1) When SBP was assumed to have been lowered to 130 mmHg instead of 125 mmHg in the ARB+CCB group. 2) When other models were used as a model of progression of diabetic nephropathy. For diabetic nephropathy cases, a model based on the results of the United Kingdom of Prospective Diabetes Study (UKPDS) (UKPDS model) (*40*) and a model constructed based on clinical studies of ACE inhibitors conducted by Golan *et al*. (Golan model) (*41*) were used. As in the base-case analysis, progression rates before and after apparent proteinuria were decreased by 24% and 28% under treatment with an ARB or combination therapy using an ARB, respectively. 3) When the cumulative incidence of diabetes in patients without diabetes was assumed to be 50% lower or 50% higher than the assumed values in the base-case analysis. 4) When the ARB's inhibitory effect on incidence of diabetes was assumed to be 50% less effective than that in the assumption of base-case analysis. 5) When the ARB's inhibitory effect on progression of diabetic nephropathy was assumed to be 50% less effective than that in the base-case analysis.

In addition to the above cases, costs and QALYs associated with each therapy were calculated when on-treatment SBP was incrementally increased from 125 to 145 mmHg.

Results

Base-Case Analysis

In male hypertensive patients without diabetes, expected QALYs and cost/patient were 16.30 QALYs and 6.21 million yen in the ARB group, 16.16 QALYs and 6.07 million yen in the CCB group, and 16.70 QALYs and 5.98 million yen in the ARB+CCB group. Thus expected QALYs were the longest in the ARB+CCB group, followed in order by the ARB group and CCB group. The expected cost was lowest in the ARB+CCB group, followed in order by the CCB group and ARB group. Thus ARB+CCB was considered to be the dominant (less costly and more effective than comparator) therapy (Fig. 2A).

In male patients with diabetes, expected QALYs and cost/patient in the ARB, CCB, and ARB+CCB groups were 14.69 QALYs and 9.87 million yen, 14.25 QALYs and 11.01 million yen, and 15.15 QALYs and 9.58 million yen, respectively. Expected QALYs were longest in the ARB+CCB group, followed in order by the ARB group and CCB group. The expected cost was lowest in the ARB+CCB group, followed in order by the ARB group and CCB group. Thus ARB+CCB was considered to be the dominant therapy (Fig. 2B).

In female patients without diabetes, expected QALYs were the longest in the ARB+CCB group, followed in order by the ARB group and CCB group. The expected cost was lowest in the ARB+CCB group, followed in order by the ARB group and CCB group. Thus ARB+CCB was considered to be the dominant therapy (Fig. 2C).

In female patients with diabetes, expected QALYs were the

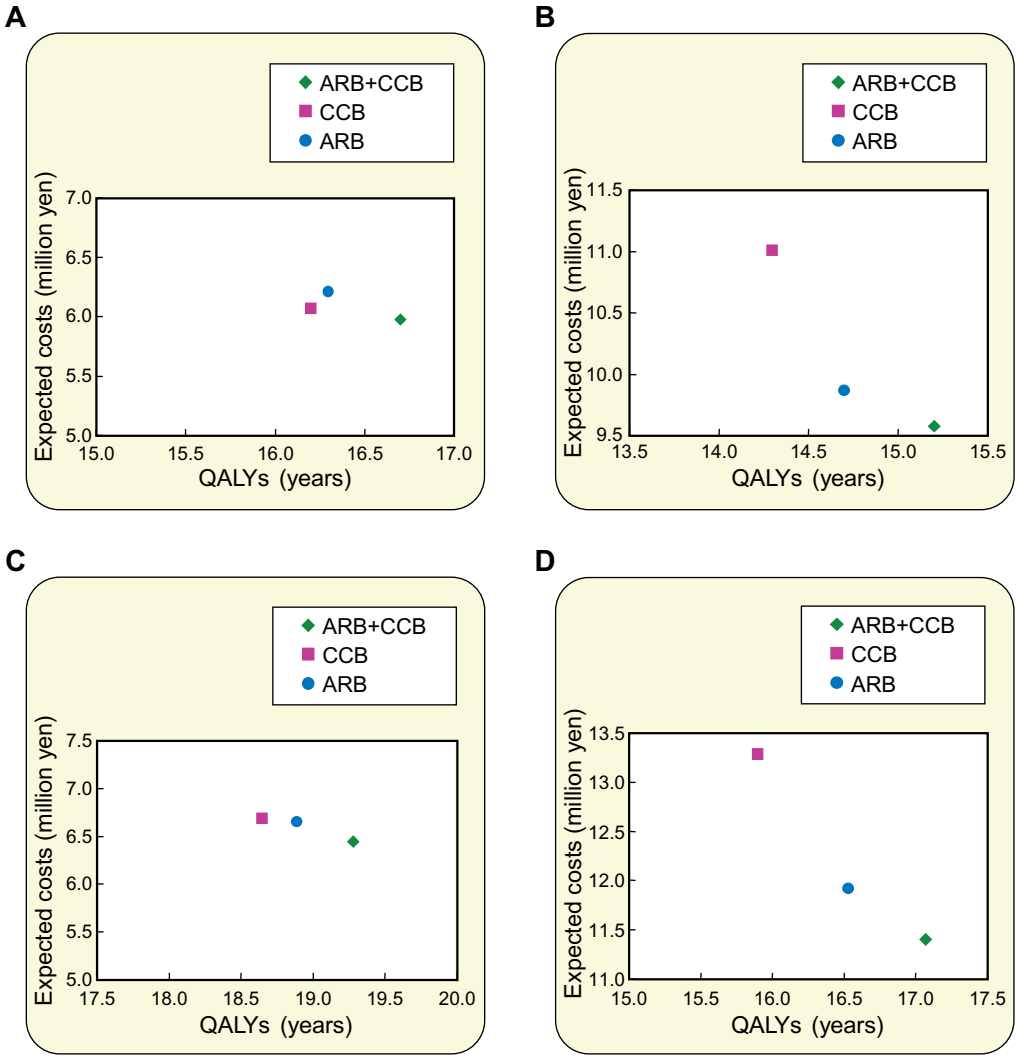

Fig. 2. *Relationship between expected costs and QALYs in male hypertensive patients without (A) and with (B) diabetes and female hypertensive patients without (C) and with (D) diabetes. Abscissa, QALYs (years); ordinate, expected costs (million yen).*

longest in the ARB+CCB group, followed in order by the ARB group and the CCB group. The expected cost was lowest in the ARB+CCB group, followed in order by the ARB group and CCB group. These results were similar to those obtained in male patients with diabetes. Thus ARB+CCB was considered to be the dominant therapy (Fig. 2D). As a result, the ICER assessment was not needed in all base-case analyses.

Sensitivity Analysis

The results of sensitivity analysis in male patients of the ARB+CCB group when SBP was assumed to have been lowered to 130 mmHg instead of 125 mmHg are shown in Table 4. The ICER in patients without diabetes in the ARB+CCB group was 0.34 million yen/additional QALY and considered cost-effective. On the other hand, in patients with diabetes the expected QALYs were longest, while the expected cost was lowest, in the ARB+CCB group. Thus ARB+CCB was the most cost-effective treatment.

The results obtained in other models of nephropathy of male patients are shown in Table 4. In the ICER assessment, ARB+CCB therapy was the most cost-effective. The results of the sensitivity analysis when the cumulative incidence of diabetes was assumed to be 50% lower and 50% higher and when the inhibitory effect of ARBs on new-onset diabetes and progression of nephropathy was assumed to be 50% lower than that in the base- case analysis are also shown in Table 4. In the ICER assessment, ARB+CCB therapy was the most cost-effective. Similar results were also obtained in female patients (data not shown).

Expected costs and QALYs in patients whose on-treatment

Table 4. Sensitivity Analyses

Condition	Treatment regimen	Male patients without diabetes		Male patients with diabetes	
		Cost (million yen)	QALYs (year)	Cost (million yen)	QALYs (year)
SBP assumed lowered to 130 mmHg instead of 125 mmHg in ARB+CCB group	ARB+CCB	6.21	16.57	9.86	15.00
	CCB	6.07	16.16	11.01	14.25
	ARB	6.21	16.30	9.87	14.69
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.34		Dominant	
UKPDS model of diabetic nephropathy	ARB+CCB	5.77	16.82	7.57	16.00
	CCB	5.54	16.33	7.47	15.35
	ARB	6.02	16.39	8.04	15.47
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.48		0.16	
Golan *et al*. model of diabetic nephropathy	ARB+CCB	5.86	16.76	8.28	15.56
	CCB	5.70	16.25	8.55	14.76
	ARB	6.08	16.35	8.63	15.06
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.31		Dominant	
Cumulative incidence of diabetes assumed 50% lower*	ARB+CCB	5.72	16.85	9.58	15.15
	CCB	5.60	16.37	11.01	14.25
	ARB	5.97	16.43	9.87	14.69
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.24		Dominant	
Cumulative incidence of diabetes assumed 50% higher*	ARB+CCB	6.18	16.56	9.58	15.15
	CCB	6.41	15.98	11.01	14.25
	ARB	6.42	16.15	9.87	14.69
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		Dominant		Dominant	
ARB's inhibitory effect on incidence of diabetes assumed 50% less effective than that in the base-case analysis*	ARB+CCB	6.08	16.66	9.58	15.15
	CCB	6.07	16.16	11.01	14.25
	ARB	6.29	16.25	9.87	14.69
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.03		Dominant	
ARB's inhibitory effect on the progression of diabetic nephropathy assumed 50% less effective than that in the base-case analysis	ARB+CCB	6.09	16.68	10.48	14.92
	CCB	6.07	16.16	11.01	14.25
	ARB	6.30	16.27	10.73	14.48
ICER (ARB+CCB *vs*. CCB; million yen/additional QALY)		0.04		Dominant	

*Due to sensitivity analyses using parameters for patients without diabetes, male patients with diabetes have the same result with the base-case analysis. QALYs, quality-adjusted life years; SBP, systolic blood pressure; ICER, incremental cost-effectiveness ratio; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; UKPDS, United Kingdom Prospective Diabetes Study.

SBP was incrementally varied from 125 to 145 mmHg at 2.5-mmHg intervals are shown in Tables 5 (patients without diabetes) and 6 (patients with diabetes). In male patients without diabetes, the costs and QALYs of the ARB+CCB group varied depending on SBP levels from 5.98 to 7.04 million yen and from 16.07 to 16.70 QALYs, respectively. In male patients with diabetes, the costs and QALYs of the ARB+CCB group varied from 9.58 to 10.55 million yen and from 14.62 to 15.15 QALYs, respectively. In female patients without diabetes, the costs and QALYs of the ARB+CCB group varied depending on SBP levels from 6.43 to 7.35 million yen and from 18.79 to 19.40 QALYs, respectively. In female patients with diabetes, the costs and QALYs of the ARB+CCB group varied from 11.29 to 12.77 million yen and from 16.33 to 17.10 QALYs, respectively.

Discussion

In the base-case analysis, ARB+CCB was more effective and less costly than the other active treatments irrespective of gender or the existence of comorbid diabetes. Furthermore, based on the results of the sensitivity analysis, the ICERs in the ARB+CCB group were far below the commonly used benchmark of US $50,000 (5 million yen)/additional QALY. ARB+CCB was considered the most cost-effective due to the combined effects of BP-lowering and the inhibitory effect of ARBs on the incidence of new-onset diabetes and progression of diabetic nephropathy, even though the cost of combined

Table 5. Costs and QALYs among Three Groups with SBP from 125 to 145 mmHg in Patients without Diabetes

SBP (mmHg)		ARB+CCB		CCB		ARB	
		Cost (million yen)	QALYs (years)	Cost (million yen)	QALYs (years)	Cost (million yen)	QALYs (years)
125	Male	5.98	16.70	5.44	16.58	5.58	16.72
	Female	6.43	19.40	5.87	19.18	5.84	19.40
127.5	Male	6.12	16.62	5.49	16.48	5.62	16.62
	Female	6.54	19.31	5.95	19.10	5.95	19.31
130	Male	6.23	16.51	5.59	16.37	5.73	16.51
	Female	6.68	19.20	6.11	18.98	6.10	19.20
132.5	Male	6.34	16.46	5.69	16.33	5.84	16.46
	Female	6.72	19.12	6.13	18.91	6.14	19.12
135	Male	6.41	16.43	5.76	16.30	5.91	16.43
	Female	6.96	19.05	6.36	18.84	6.38	19.05
137.5	Male	6.58	16.36	5.90	16.23	6.08	16.36
	Female	7.03	19.01	6.46	18.80	6.45	19.01
140	Male	6.78	16.26	6.07	16.16	6.21	16.30
	Female	7.11	18.94	6.57	18.72	6.53	18.94
142.5	Male	6.93	16.16	6.27	16.03	6.43	16.16
	Female	7.26	18.87	6.70	18.65	6.68	18.87
145	Male	7.04	16.07	6.38	15.95	6.55	16.07
	Female	7.35	18.79	6.78	18.57	6.78	18.79

QALYs, quality-adjusted life years; SBP, systolic blood pressure; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Table 6. Costs and QALYs among Three Groups with SBP from 125 to 145 mmHg in Patients with Diabetes

SBP (mmHg)		ARB+CCB		CCB		ARB	
		Cost (million yen)	QALYs (years)	Cost (million yen)	QALYs (years)	Cost (million yen)	QALYs (years)
125	Male	9.58	15.15	10.10	14.68	8.91	15.16
	Female	11.29	17.10	12.35	16.41	10.73	17.10
127.5	Male	9.62	15.00	10.30	14.50	9.13	15.00
	Female	11.45	17.00	12.48	16.32	10.89	17.00
130	Male	9.66	14.95	10.35	14.48	9.17	14.95
	Female	11.59	16.96	12.54	16.28	11.03	16.96
132.5	Male	9.77	14.93	10.42	14.47	9.28	14.93
	Female	11.75	16.85	12.64	16.19	11.19	16.85
135	Male	9.93	14.84	10.63	14.37	9.44	14.84
	Female	11.87	16.74	12.76	16.10	11.32	16.74
137.5	Male	10.10	14.80	10.76	14.33	9.61	14.80
	Female	12.10	16.66	13.03	16.02	11.55	16.66
140	Male	10.18	14.70	11.01	14.25	9.87	14.69
	Female	12.28	16.51	13.05	15.88	11.73	16.51
142.5	Male	10.39	14.63	11.04	14.18	9.91	14.63
	Female	12.43	16.40	13.29	15.79	11.89	16.40
145	Male	10.55	14.62	11.17	14.17	10.07	14.62
	Female	12.77	16.33	13.51	15.73	12.23	16.33

QALYs, quality-adjusted life years; SBP, systolic blood pressure; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

use of these two agents was increased.

Treatment costs of patients with diabetes were increased compared with patients without diabetes, because diabetes affected all therapeutic strategies. However, ARB+CCB was the most effective regimen and cost less than other treatments irrespective of gender. In these patients, the renoprotective

effects of an ARB and the BP-lowering effects of the combination of an ARB plus a CCB were considered to contribute greatly to the therapeutic efficacy, even though the drug cost was higher.

Base-case analysis was conducted under the assumption that SBP was lowered from 160 to 125 mmHg in patients of the ARB+CCB group. In addition, the sensitivity analysis was also conducted when SBP was assumed to have been lowered from 160 to 130 mmHg in the ARB+CCB group. In patients without diabetes, the ICER of ARB+CCB was small enough to be considered cost-effective, just as in the base-case analysis. In patients with diabetes, the result that the expected QALYs of patients in the ARB+CCB group were longest while the expected costs were the smallest was unaltered. Furthermore, when other models of nephropathy were used, ICER in the ARB+CCB group was considered cost-effective.

For patients who are switched to combination therapy because monotherapy for hypertension is ineffective, the data in Table 5 can be used to predict the size of the SBP reduction needed to preserve the cost-effectiveness. For example, in a nondiabetic male patient in whom SBP was lowered to 140 mmHg by CCB monotherapy, then further decreased by an additional 5 mmHg by switching to ARB+CCB therapy, the ICER may be calculated by entering the corresponding values into Eq. (1) as described above to yield $(6.41 - 6.07)/(16.43 - 16.16) = 1.26$ million yen/additional QALY, which is much lower than the US $50,000 that is generally considered acceptable. Thus an additional SBP-lowering effect of 5 mmHg is considered cost effective. This matrix could be useful for determining pharmacoeconomics based on comparative studies of monotherapy *vs*. combination therapy.

There are several limitations and matters to keep in mind in the structure or setting of parameters in the models used in the present analysis. The first is the prediction equation. Since the cumulative incidence of CHD employed in the present study was calculated based on a prediction equation derived from large-scale clinical trials and the US Framingham Study data adjusted for Japanese patients, it should be recognized that some biases might conceivably occur. In the future, such models for the analysis of cost-effectiveness should be constructed based on the results of clinical studies that include Japanese patients (*42–44*).

The second limitation is the fundamental problem that exists in any mathematical model analysis: prognosis models for hypertensive patients do not necessarily include all factors associated with antihypertensive treatment. For instance, azelnidipine has been reported to cause smaller changes in heart rate compared with other CCBs (*45*); however, the implications of this were not taken into account in the present study. Moreover, although some CCBs are reported to have similar renoprotective effects (*46–48*), this was also not taken into account.

Another point to be considered is that the pharmacoeconomics of monotherapies and combination therapies with other agents may have differed, since only two classes of antihypertensive drugs that are frequently used in Japan (*14–16*) were analyzed in the present study.

In conclusion, from a pharmacoeconomic point of view, combination therapy of an ARB plus a CCB is more favorable than monotherapy with either agent alone, irrespective of the presence or absence of comorbid diabetes.

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