Original Article

Cost-Effectiveness Analysis of Hypertension Treatment: Controlled Release Nifedipine and Candesartan Low-Dose Combination Therapy in Patients with Essential Hypertension—The Nifedipine and Candesartan Combination (NICE-Combi) Study—

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Societal interest in pharmaco-economic analysis is increasing in Japan. In this study, the cost-effectiveness of low-dose combination therapy with controlled release nifedipine plus candesartan and up-titrated monotherapy with candesartan was estimated, based on the results of the NICE-Combi study. The NICE-Combi study was a double-blind, parallel arm, randomized clinical trial to compare the efficacy of low-dose combination therapy of controlled release nifedipine (20 mg/day) plus candesartan (8 mg/day) vs. up-titrated monotherapy of candesartan (12 mg/day) on blood pressure control in Japanese patients with mild to severe essential hypertension who were not sufficiently controlled by the conventional dose of candesartan (8 mg/day). The incremental cost effectiveness of each cohort during the 8-week randomization period was compared, from the perspective of a third-party payer (*i.e.*, insurers). The average total cost per patient was 29,943 Japanese yen for the combination therapy group and 33,182 Japanese yen for the candesartan monotherapy group, while the rate of achievement of the target blood pressure was significantly higher in the combination therapy group than in the up-titrated monotherapy group. In the combination therapy group, higher efficacy and lower incremental treatment cost (“Dominance”) were observed when compared to the monotherapy group. The sensitivity analyses also supported the results. In conclusion, these results suggest that combination therapy with controlled release nifedipine and low-dose candesartan (8 mg) is “dominant” to up-titrated candesartan monotherapy for the management of essential hypertension. This conclusion was robust to sensitivity analysis. (*Hypertens Res* 2005; 28: 585–591)

Key Words: incremental cost-effectiveness analysis, essential hypertension, controlled release nifedipine, candesartan

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**Refer to the Appendix.

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Table 1. National Health Insurance Price (Japanese Yen) at Office-Based Physicians and Hospital with 100–200 Beds (in 2004)

	National Health Insurance price at	
	Office-based physicians for base case	Hospital with 100–200 beds for reference
Outpatient visit fee (total)	4,390	2,860
Re-visit fee	(730)	(580)
Additional fee of disease control at outpatient clinic	(520)	(520)
Additional fee of continuous disease control	(50)	(50)
Educational fee for specific disease	(2,250)	(870)
Prescription fee	(690)	(690)
Additional prescription fee for specific disease	(150)	(150)
Laboratory examination (total)	3,100	3,100
National Health Insurance price of drug (per tablet)		
Controlled release nifedipine 20 mg	46.7	46.7
Candesartan 8 mg	194.8	194.8
Candesartan 12 mg	297.6	297.6

Introduction

Strict control of blood pressure is essential to prevent organ damage, and to reduce mortality and morbidity in patients with hypertension. Among medications used for hypertension treatment, calcium channel blockers, such as controlled release nifedipine, are the most frequently used antihypertensive agents in Japan, while angiotensin II receptor blockers, which suppress the renin-angiotensin system in a manner similar to angiotensin converting enzyme inhibitors, are relatively new and seeing increasing usage. In the guidelines for the treatment of hypertension (1–4), combination therapy with multiple agents, each at low dose, is recommended rather than up-titrated monotherapy in order to minimize possible adverse reactions. Combination therapies using a calcium channel blocker plus an angiotensin converting enzyme inhibitor or a calcium channel blocker plus an angiotensin II receptor blocker have become common in Japan. However, economic evaluation of hypertension treatment, based on clinical evidence in Japanese subjects, has not yet been fully conducted.

Recently, the results of the Nifedipine and Candesartan Combination (NICE-Combi) study (5) have been presented. This study was a double-blinded, parallel arm, randomized clinical trial to compare efficacy of low-dose combination therapy of controlled release nifedipine (20 mg/day) plus candesartan (8 mg/day) vs. up-titrated monotherapy of candesartan (12 mg/day) on blood pressure control in Japanese patients with mild to severe essential hypertension who were not sufficiently controlled by the conventional dose of candesartan (8 mg/day). The results supported the use of combination therapy of a calcium channel blocker with an angiotensin II receptor blocker, demonstrating that the low-dose combination therapy is superior to the up-titrated monotherapy in terms of blood pressure control and renal protection in essen-

tial hypertensives. In the present study, we estimated the cost-effectiveness of low-dose combination therapy of controlled release nifedipine plus candesartan vs. up-titrated monotherapy of candesartan in terms of blood pressure-lowering effects in essential hypertension, based on the results of the NICE-Combi study.

Methods

DATA Source

The NICE-Combi study was a double-blinded, parallel arm, randomized clinical trial, targeting men 20–70 years of age, with mild to severe hypertension, who were not sufficiently controlled by the conventional dose of candesartan monotherapy (5). In this study, after complete discontinuation of previous antihypertensive treatments other than candesartan, 331 eligible patients were given candesartan 8 mg for 8 weeks (baseline treatment period). Then, 258 patients (males: 147; females: 111) who were not sufficiently controlled by candesartan 8 mg were randomized into 2 groups: a group receiving candesartan 8 mg + controlled release nifedipine 20 mg for 8 weeks (130 patients), or a group receiving candesartan 12 mg for 8 weeks (128 patients) (randomization period). The majority of these patients were treated at office-based clinics (office-based clinics: 228 patients; hospitals with >200 beds: 30 patients). The mean age was 55.3 years, ranging from 27.0 to 78.0 years, and there was no significant difference in gender or age between the treatment groups.

Values for the efficacy and safety of each treatment cohort (candesartan 8 mg + controlled release nifedipine 20 mg vs. candesartan 12 mg) were obtained from the results of the NICE-Combi study (5). The study was conducted in accordance with the declaration of Helsinki, the study protocol was approved by the ethics committee of each participating institute, and all patients gave their written informed consent to

Fig. 1. Difference in cost and efficacy (left: cost vs. delta decreased blood pressure; right: cost vs. achievement rate) for combination therapy relative to up-titrated monotherapy. The combination therapy was “dominant” (higher efficacy and lower incremental treatment cost) to up-titrated monotherapy. SBP, systolic blood pressure; DBP, diastolic blood pressure; JPY, Japanese yen.

Table 2. Cost of Treatment (Japanese Yen)

	Candesartan 8 mg + controlled release nifedipine 20 mg (N=130)	Candesartan 12 mg (N=130)
Average treatment cost per patient during randomization period	29,943	33,182
Outpatient visit fee (total)	(13,170)	(13,170)
Laboratory examination (total)	(3,100)	(3,100)
Cost of medication	(13,524)	(16,666)
Additional treatment costs for drug-related adverse events	(149)	(246)
Average treatment cost per patient reaching target blood pressure level		
Systolic blood pressure	105,063	192,916
Diastolic blood pressure	73,390	121,544
Both systolic blood pressure and diastolic blood pressure	134,274	474,023

participate in the study.

The NICE-Combi study is the first and currently the only clinical study to compare the efficacy of combination therapy to up-titrated monotherapy in a double-blinded, randomized clinical trial setting.

Efficacy and Safety Profile

The results demonstrated that achievement rates of target blood pressure (<130/85 mmHg for patients aged under 60 years; <140/90 mmHg for those aged 60 to 69 years; and <150/90 mmHg for those aged 70 years and over) were significantly higher in the combination therapy group (28.5% for systolic blood pressure [SBP] and 40.8% for diastolic blood pressure [DBP]), than in the up-titrated monotherapy group

(17.2% for SBP and 27.3% for DBP; $p=0.0225$ and 0.0164 , respectively). With regard to safety, adverse events related to the study drug occurred in 10 patients (7.7%) in the combination therapy group and 12 patients (9.4%) in the up-titrated monotherapy group, with no significant difference between the groups, and included discontinuation due to palpitations, headache, flushing and chest pain for one patient (0.8%) randomized to the up-titrated monotherapy group.

Cost

The cost of treatment was calculated from the perspective of insurers, based on National Health Insurance costs in April 2004, with the assumption that all patients less than 65 years old were treated by office-based physicians and were dis-

Fig. 2. Estimation of the impact of the calcium channel blocker (CCB) price. When the calcium channel blocker price was less than 510 Japanese yen, with the price of candesartan 12 mg being constant, the average treatment cost per patient reaching the target blood pressure for the combination group was less than that for the up-titrated monotherapy group. *¹The average cost per patient reaching the target blood pressure is lower in the combination therapy group. *²Current National Health Insurance (NHI) price of controlled release nifedipine 20 mg.

pensed medication at a third-party pharmacy (Ingai-Shoho) (Table 1). The cost for each treatment group during the randomization period was obtained from the data listed in Case Report Forms of the NICE-Combi study, and the following costs were included:

Outpatient visit fee = 4,390 Japanese yen $\times$ 3 times (Week 0, Week 4, Week 8)

Laboratory examination = 3,100 Japanese yen $\times$ 1 time (Week 8)

Cost of medication = controlled release nifedipine 20 mg + candesartan 8 mg or candesartan 12 mg for 8 weeks

Additional treatment costs for drug-related adverse events—Treatment cost (outpatient visit fee, laboratory examination, cost of medication and any medical procedure) was calculated from the data listed in Case Report Forms, and added to the basic treatment cost.

—The cost of over-the-counter drugs was not included, because it does not increase the expenditure of insurers.

Cost-Effectiveness

The incremental cost effectiveness of each cohort during the randomization period was compared.

Fig. 3. Estimation of the impact of the price of candesartan 12 mg. When the price of candesartan 12 mg was less than 30 Japanese yen, with the price of controlled release nifedipine being constant, the average treatment cost per patient reaching the target blood pressure in the up-titrated monotherapy group was cheaper than that in the combination therapy group. *¹The average cost per patient reaching the target blood pressure is lower in the combination therapy group. *²Current National Health Insurance price of candesartan 12 mg.

Sensitivity Analysis

The robustness of the results of cost-effectiveness analysis were estimated by sensitivity analysis.

Results

Cost-Effectiveness

The average total cost per patient was 29,943 Japanese yen for the candesartan 8 mg/controlled release nifedipine 20 mg combination therapy group and 33,182 Japanese yen for the candesartan 12 mg monotherapy group during the randomization period, while the achievement rate of target blood pressure was significantly higher in the combination therapy group than in the up-titrated monotherapy group.

During the randomization period, the average treatment cost per patient reaching the target blood pressure (average total cost for randomization period/achievement rate of target blood pressure) was as follows: 105,063 Japanese yen for the candesartan 8 mg/controlled release nifedipine 20 mg combination therapy group, and 192,916 Japanese yen for the candesartan 12 mg up-titrated monotherapy group to reach the target SBP, while 73,390 Japanese yen for the combination therapy group and 121,544 Japanese yen for the up-titrated monotherapy group to reach the target DBP.

In this sense, the combination therapy was “dominant”

Fig. 4. Estimation of the impact of the achievement rate of systolic blood pressure (SBP) in the up-titrated monotherapy group. Even when the achievement rate in the up-titrated monotherapy group was comparable to that in the combination therapy group (29%), the combination therapy showed a lower average cost per patient reaching the target blood pressure than the up-titrated monotherapy. *¹The average treatment cost per patient reaching the target blood pressure is lower in the combination therapy group.

(higher efficacy and lower average treatment cost per patient treated to target blood pressure) to the up-titrated monotherapy (Fig. 1, Table 2).

Sensitivity Analysis

Calcium Channel Blocker Price

The impact of the calcium channel blocker price on the average total treatment cost per patient reaching the target blood pressure during the randomization period was estimated to be in the range of 40 Japanese yen (the current price of controlled release nifedipine 20 mg = 46.7 Japanese yen) to 600, in order to estimate the robustness of dominance (Fig. 2). When the calcium channel blocker price was less than 510 Japanese yen, with the price of candesartan 12 mg being constant, the average total treatment cost per patient reaching the target blood pressure for the combination therapy was less than that for the up-titrated monotherapy. And once the calcium channel blocker price was higher than 510 Japanese yen, the average total treatment cost per patient reaching the target blood pressure for the combination therapy with calcium channel blocker exceeded that for the up-titrated monotherapy group.

Price of Candesartan 12 mg

The impact of the price of candesartan 12 mg on the average treatment cost per patient reaching the target blood pressure

was estimated to be in the range of 0 to 300 Japanese yen (the current price of candesartan 12 mg = 297.6 Japanese yen) (Fig. 3). When the price of candesartan 12 mg was less than 30 Japanese yen, with the price of controlled release nifedipine being constant, the average treatment cost per patient reaching the target blood pressure in the up-titrated monotherapy group was lower than that in the combination group.

Premature Discontinuation Rate

For base case, the medication cost was estimated, assuming that all patients received 8 weeks treatment (there was no difference in the premature discontinuation rate between the two groups). However, the result of the NICE-Combi study showed that there was one patient in the up-titrated monotherapy group who discontinued the study drug prematurely (within 4 weeks of the double-blinded period) due to drug-related adverse events. When taking this into account, the average total cost per patient was recalculated as 33,082 Japanese yen for the candesartan 12 mg monotherapy group during the randomization period. This did not have any significant impact on the results.

Achievement Rate of Target Blood Pressure in the Up-Titrated Monotherapy Group

Sensitivity analysis on the achievement rate of target blood pressure in the up-titrated monotherapy group was conducted. Although the adjusted difference in the achievement rate of SBP (combination therapy – monotherapy) was 11.8% (95% confidence interval: 1.7%–21.8%), combination therapy showed a lower average cost per patient reaching the target blood pressure than up-titrated monotherapy, even when the achievement rate in the up-titrated monotherapy group was comparable to that in the combination therapy group (29%) (Fig. 4).

Types of Health Care Facility

Although the treatment cost was calculated under the assumption that all patients less than 65 years old were treated by office-based physicians, the results were robust even when the treatment cost was calculated under the assumption that all patients less than 65 years old were treated at hospitals with 100–200 beds (Table 1) because the difference in treatment cost was solely attributed to the National Health Insurance price of each drug and its efficacy/safety. In hospitals with 100–200 beds, the cost was 25,353 Japanese yen per patient for the combination therapy group and 28,592 Japanese yen per patient for the up-titrated monotherapy group during the randomization period.

Incidence and Cost of Adverse Events

Neither the incidence of adverse events nor the cost of treating adverse events had any impact on the results. It was thus concluded from the sensitivity analysis that combination therapy is the dominant (higher efficacy, lower cost) treatment strategy for patients with essential hypertension.

Discussion

Evaluation of the economic cost of healthcare in Japan is becoming increasingly important due to the growing financial burden on the National Health Insurance system. However, pharmaco-economic analysis of medicinal products has not yet been fully implemented in Japan. In part, this may be because such economic analyses require a substantial database of clinical information, and there is a paucity of such information in Japan. Thus, the current study is worthwhile because the pharmaco-economic analysis was conducted based on clinical evidence—*i.e.*, that of the NICE-Combi study (5)—in Japanese patients.

Economic analysis based on the clinical results of the NICE-Combi study indicated that the combination therapy is “dominant” to the up-titrated monotherapy of candesartan. Because the guidelines for the treatment of hypertension (1–4) recommend combination therapy with multiple agents, each at a low dose, rather than up-titrated monotherapy, the current results also supported the guidelines from both a clinical and an economic viewpoint. Importantly, the results of this study were robust to sensitivity analysis, such as the cost of drugs, achievement rate of target blood pressure and incidence of adverse drug reactions. However, several points must be considered before generalizing the results.

First, the economic analysis was undertaken based on a surrogate endpoint, the achievement rate of target blood pressure after 8 weeks of treatment, instead of long-term outcome data, and thus would not be sufficient to predict the long-term economic impact on anti-hypertensive treatment. However, the possible difference in treatment costs between the two treatment regimens in the mid/long term would be greater than the difference observed in the NICE-Combi study.

Certainly, to date, no data for combination or up-titrated monotherapy have been made available for Japanese patients with regard to long-term outcome data on cardiovascular events, but in general, it is clear that a higher achievement rate of target blood pressure in the short term will contribute to the risk reduction of major vascular events in the long term. Long-term data from the PREVENT study (6) conducted in North America showed that calcium channel blocker treatment slows the progression of carotid atherosclerosis, and that patients using calcium channel blockers had significantly reduced hospitalizations for unstable angina and underwent fewer coronary revascularizations than their counterparts receiving placebo. In addition, the ALLHAT study found no difference between calcium channel blockers and angiotensin converting enzyme inhibitors in risk reduction of a primary outcome of combined fatal coronary heart disease or non-fatal myocardial infarction (7). Similar results were obtained in studies comparing these two type of antihypertensive agents in Japan (8, 9). Recently, the results of the VALUE study (10) also demonstrated that a calcium channel blocker-based regimen was better at controlling blood pressure than an angio-

tensin II receptor blocker-based regimen in the short to long term, while the incidence of cardiovascular events in a calcium channel blocker-based regimen was comparable to that in an angiotensin II receptor blocker-based regimen in long-term follow-up.

In addition, the point that not all patients reached the target blood pressure during the 8-week study period should also be considered. This indicated that additional treatment will be required in many patients. In current clinical practice, when a patient does not reach the target blood pressure by combination therapy, the next approach is up-titration of controlled release nifedipine to 40 mg (National Health Insurance price: 87.4 Japanese yen) from 20 mg. In contrast, an angiotensin converting enzyme inhibitor or a diuretic is added to the angiotensin II receptor blocker monotherapy when a patient does not achieve the target blood pressure in up-titrated angiotensin II receptor blocker treatment. Because the achievement rate of the target blood pressure in the up-titrated monotherapy group was lower than that in the combination group, more patients would require such additional treatment. Hence, in all cases, the total treatment cost for up-titrated monotherapy would always be much more expensive than that for combination therapy.

Secondly, the NICE-Combi study enrolled patients with mild to severe hypertension who were not sufficiently controlled by the conventional dose of candesartan monotherapy. According to the database of the Ministry of Health, Labor and Welfare in 2002, nearly 7 million Japanese were diagnosed with hypertension under the National Health Insurance system (Overview of Patients Survey in 2002: Section 5. Number of patients with major disease [table 11]. Database of Ministry of Health, Labour and Wealth [in Japanese]. <http://www.mhlw.go.jp/toukei/saikin/hw/kanja/02/index.html>.), and many of them considered that their blood pressure was not being well controlled. This was also implied by the results of the NICE-Combi study, which indicated that blood pressure could not be well controlled by initial treatment with candesartan 8 mg in at least 78% of patients (out of the 331 patients enrolled at the beginning of the baseline treatment period, 73 patients deviated from the randomization criteria or met the exclusion criteria) (5). Judging from the fact that the degree of blood pressure reduction observed in the NICE-Combi study (5) was significantly greater in the combination therapy group than in the up-titrated monotherapy group irrespective of complicating risk factors for cardiovascular diseases, the present economic analysis is potentially applicable to many patients with essential hypertension which is not well controlled.

Thirdly, the cost of treating adverse drug reactions may have been underestimated in this analysis, because some information could have been missed by the Case Report Forms; for example, if an adverse reaction was treated by another clinic, that might not have been counted in the study. However, the incidence of adverse drug reactions was higher in the up-titrated monotherapy group (9.4%) than in the com-

bination therapy group (7.7%) (5) (not statistically significant), despite the fact that the study subjects were limited to patients who showed good tolerability to candesartan 8 mg. Therefore, this issue was not considered to have affected the results.

Taking these points into account, the present cost-effectiveness analysis could help to significantly alleviate the long-term financial burden of both hypertensive patients and the National Health Insurance system in Japan, though another large-sized outcome study will be needed to confirm the current estimates.

In conclusion, a low-dose combination therapy of controlled release nifedipine and candesartan was “dominant” to up-titrated monotherapy with candesartan in essential hypertensives, and as a consequence, the combination treatment strategy could contribute to a decrease in the financial burden on the National Health Insurance system in Japan.

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Appendix

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