

Original Article

Comparison of Health Costs Associated with Treatment of Hypertension with a Calcium Channel Blocker and Angiotensin-Converting Enzyme Inhibitor in the United States and Japan

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Hypertension is prevalent in over 25% of populations in developed countries, and poses an increasing economic burden on health resources. Therefore it is predicted that future medical treatment of hypertension will be increasingly affected by cost considerations. Several classes of antihypertensive drugs are used as first-line agents for the treatment of hypertension, but the economic impact of using these agents in different countries remains to be addressed. In this study, we compared health costs associated with treatment of hypertension using the calcium channel blocker amlodipine and the angiotensin-converting enzyme inhibitor enalapril in the US and Japan. Pharmaceutical costs and hospitalization costs were analyzed from established databases. The data for the prevalence of myocardial infarction and stroke were derived from the Framingham study and the Hisayama study. Analysis of the economic impacts using relative risk differences between the calcium channel blocker and angiotensin-converting enzyme inhibitor together with regional hospitalization costs resulted in an apparent 11.2 billion yen health cost reduction in favor of the calcium channel blocker in the case of Japan, in contrast to an apparent 5.7 billion yen reduction in favor of the angiotensin-converting enzyme inhibitor in the case of the US. The trends in Japan for 2000 and 2004 were similar. These results suggest that there are regional differences in the health costs associated with different classes of hypertensive agents, which could affect national policies on the choice of antihypertensive drugs. It is predicted that future treatment of hypertension will be increasingly tailored to the epidemiologic profiles and medical costs of individual communities. (*Hypertens Res* 2006; 29: 333–338)

Key Words: calcium channel blocker, angiotensin-converting enzyme inhibitor, health economics

Introduction

Hypertension is a disease which has a wide prevalence worldwide and whose incidence is increasing. Recent data suggest that 26.4% of the world adult population in 2000 had hypertension, and the number was projected to increase to 29.2% by 2025 (1). Hypertension is a major risk factor for a variety of disorders, including stroke and coronary heart disease, and

thus it is an important worldwide public-health challenge both because of its high frequency and because of the concomitant risk of cardiovascular disease. Cardiovascular diseases are the leading cause of death worldwide (2); about two-thirds of the cerebrovascular disease burden and half the ischemic heart disease burden are attributable to non-optimum blood pressure (3). Moreover, hypertension is the most important component of the metabolic syndrome (4), which has become increasingly important because of the aging society. Conse-

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Received September 28, 2005; Accepted in revised form February 6, 2006.

quently, the burden to society in terms of medical costs associated with hypertension and its complications is immense.

In view of the large costs associated with this disease, it has become increasingly important to find cost-effective forms of treatment, without compromising the quality of health care. This has become recognized in national and international guidelines for the treatment of hypertension, such as the World Health Organization/International Society of Hypertension (WHO/ISH) guidelines (5), and the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC 7) in the US (6). In Japan, the Japanese Society of Hypertension guidelines committee first published the Guidelines for the Management of Hypertension for Japanese physicians in 2000 (JSH 2000) (7). In 2004, a revised version (JSH 2004) was published, and the introduction to the new guidelines stressed the importance of health economic considerations in formulating national treatment strategies (8).

The incidence of hypertension-related cardiovascular disease in Japan has several unique features. According to world vital statistics in the 1950s and 1960s, the Japanese population was characterized by the highest stroke mortality, and also by a lower coronary heart disease mortality compared with Western populations (9, 10). In an international comparison, Japan had one of the highest prevalences of hypertension in the developed world, in addition to having a rapidly aging population (1). These features may be related both to genetic background, and cultural features such as the Japanese diet.

Because of these unique epidemiological features, health economic analyses performed in Japan may yield different results than those made in other countries, including the US. Moreover, recent studies from our and other institutions have shown that the prescription patterns of Japanese physicians may be markedly different from those of the US, with Japanese physicians preferring calcium channel blockers, while American physicians prescribe more angiotensin-converting enzyme inhibitors (11, 12). In view of these differences, the aim of the present study was to compare the health costs associated with the use of the calcium channel blocker amlodipine, and the angiotensin-converting enzyme inhibitor enalapril, in order to analyze the effects of treatment of hypertension using these two agents from an economic perspective.

Methods

The comparison of health costs was performed by analyzing the treatment outcomes for theoretical cohorts of 100,000 patients administered a calcium channel blocker (amlodipine) or an angiotensin-converting enzyme inhibitor (enalapril) for 3 years. The pharmaceutical costs, inpatient costs, incidence, and relative risk for stroke and myocardial infarction were analyzed from established databases and reports. For the comparisons of pharmaceutical costs, the data from the Red Book Database Services (Updated November 2004) was used

for the US, while the *Nippon Iyakuin Johoshu* (Japanese Pharmacopoeia, 2000 and 2004 edition) (13, 14) was used for Japan. For the purposes of this study, the costs for pharmaceutical treatment were defined as the charges for the generic compounds, when available. For the estimation of costs associated with hospitalization, the data of Mullins *et al.* was used for the US (15), while the data obtained from the Japanese Diagnosis Group Rates and Shindangun Bunrui Tenshuho (Diagnostic Codes and Rates) (16, 17) were used for Japan. Outpatient costs were assumed to be equal for treatments with calcium channel blocker and angiotensin-converting enzyme inhibitor, and were not included in the calculation.

To estimate the incidence of stroke and myocardial infarction, epidemiological data from the Framingham study were used for the US (18, 19), while the data in Japan were obtained from the follow-up of the Hisayama study in Fukuoka (20). Relative risks for the incidence of stroke and myocardial infarction were based on the two meta-analyses of the Blood Pressure Lowering Treatment Trialists' Collaboration on studies comparing calcium channel blockers and angiotensin-converting enzyme inhibitors, published in 2000 and 2003 (21, 22).

Costs are expressed in yen, and adjustments for inflation were performed using the medical care component of the Consumer Price Index (US Department of Labor Bureau of Labor Statistics, Washington DC, USA) with a conversion rate of 1 dollar = 100 yen for ease of comparison.

Results

The pharmaceutical cost of amlodipine (5 mg) in the US in 2004 was 159 yen. The corresponding costs for amlodipine in Japan were 98.9 yen and 87.5 yen in 2000 and 2004, respectively. In the case of the angiotensin-converting enzyme inhibitor, the cost for enalapril maleate (10 mg) in the US was 107 yen in 2004, while the corresponding costs in Japan in 2000 and 2004 were 214.2 yen and 188.6 yen, respectively (13, 14).

The average hospitalization cost for stroke in the US was estimated to be 1,951,000 yen (not including transportation costs) vs. 407,750 yen (in patients without complications and not receiving surgical treatment) in Japan in 2004. Similarly, the hospitalization costs for myocardial infarction were 2,237,000 in the US, and 649,300 yen in Japan (15, 17).

The incidence of stroke in untreated hypertensive patients was reported to be 250 per 100,000 person years (750 per 100,000 persons per 3 years) in males, and 190 per 100,000 person years (570 per 100,000 persons per 3 years) in females in the US, resulting in a total incidence of 1,320 persons over 3 years. The values for myocardial infarction were 710 per 100,000 person years (2,130 per 100,000 persons per 3 years) in males, and 420 per 100,000 person years (1,260 per 100,000 persons per 3 years) in females in the US, resulting in a total incidence of 3,390 persons over 3 years (18, 19). In the case of Japan, the Hisayama study suggested an incidence of

Table 1. Estimation of Cost Difference Associated with the Use of Amlodipine vs. Enalapril in 100,000 Patients for 3 Years (Data for US, 2004)

	Amlodipine (C)	Enalapril (A)	Difference (C - A)
Pharmaceutical cost/day	159	107	52
Total pharmaceutical cost	17,410,500,000	11,716,500,000	5,694,000,000
Relative risk of stroke	0.89	1.00	
Estimated incidence of stroke	1,174	1,320	
Estimated stroke hospitalization cost	2,292,908,264	2,576,301,420	-283,393,156
Relative risk of myocardial infarction	1.04	1.00	
Estimated incidence of myocardial infarction	3,525	3,390	
Estimated myocardial infarction hospitalization cost	7,887,970,487	7,584,587,007	303,383,480
Estimated total cost difference (C - A)			5,713,990,324

Values in yen.

Table 2. Estimation of Cost Difference Associated with the Use of Amlodipine vs. Enalapril in 100,000 Patients for 3 Years (Data for Japan, 2004)

	Amlodipine (C)	Enalapril (A)	Difference (C - A)
Pharmaceutical cost/day	87.5	188.6	-101.1
Total pharmaceutical cost	9,581,250,000	20,651,700,000	-11,070,450,000
Relative risk of stroke	0.89	1.00	
Estimated incidence of stroke	2,448	2,751	
Estimated stroke hospitalization cost	998,331,023	1,121,720,250	-123,389,227
Relative risk of myocardial infarction	1.04	1.00	
Estimated incidence of myocardial infarction	751	723	
Estimated myocardial infarction hospitalization cost	488,221,656	469,443,900	18,777,756
Estimated total cost difference (C - A)			-11,175,061,471

Values in yen.

stroke of 4,755 per 100,000 person years, and an incidence of myocardial infarction of 1,059 per 100,000 person years in 2003 (20).

Based on the Blood Pressure Lowering Treatment Trialists' Collaboration meta-analysis published in 2003 (22), the relative risk for the onset of stroke in patients on calcium channel blockers compared to placebo was found to be 0.62, and the value in patients on angiotensin-converting enzyme inhibitor compared to placebo was 0.72. In the case of myocardial infarction, the relative risk in patients on calcium channel blocker compared to placebo was 0.78, and the value in patients on angiotensin-converting enzyme inhibitor compared to placebo was 0.80.

Using the above data, the costs associated with calcium channel blocker and angiotensin-converting enzyme inhibitor use were computed. In the case of the US (Table 1), the use of a calcium channel blocker was associated with a smaller incidence of stroke of 146 per 100,000 persons per 3 years (1,174 in the calcium channel blocker group vs. 1,320 in the angiotensin-converting enzyme inhibitor group), resulting in a decrease in stroke hospitalization costs of 283,393,156 yen. On the other hand, the incidence of myocardial infarction rose from 3,390 in the angiotensin-converting enzyme inhibitor

group to 3,525 in the calcium channel blocker group, resulting in an increase in the costs for myocardial infarction hospitalization of 303,383,480 yen in patients treated with calcium channel blocker. Consequently, the use of a calcium channel blocker was associated with an increase in hospitalization costs in the amount of 19,990,324 yen. In terms of the pharmaceutical cost associated with the use of a calcium channel blocker in preference to an angiotensin-converting enzyme inhibitor, the costs were increased by 5,694,000,000 yen. Taken together, these differences amount to an increase of 5,713,990,324 yen associated with the use of a calcium channel blocker compared to an angiotensin-converting enzyme inhibitor in the US.

When the same calculation was made using the Japanese data for 2004, the opposite conclusion was obtained (Table 2). In the case of Japan, the use of a calcium channel blocker was associated with a smaller incidence of stroke of 303 per 100,000 persons per 3 years (2,448 in the calcium channel blocker group vs. 2,751 in the angiotensin-converting enzyme inhibitor group), resulting in a decrease in stroke hospitalization costs of 123,389,227 yen. On the other hand, the incidence of myocardial infarction rose from 723 in the angiotensin-converting enzyme inhibitor group to 751 in the

Table 3. Estimation of Cost Difference Associated with the Use of Amlodipine vs. Enalapril in 100,000 Patients for 3 Years (Data for Japan, 2000)

	Amlodipine (C)	Enalapril (A)	Difference (C - A)
Pharmaceutical cost/day	98.9	214.2	-115.3
Total pharmaceutical cost	10,829,550,000	23,454,900,000	-12,625,350,000
Relative risk of stroke	0.98	1.00	
Estimated incidence of stroke	4,659	4,755	
Estimated stroke hospitalization cost	4,131,047,949	4,215,355,050	-84,307,101
Relative risk of myocardial infarction	1.23	1.00	
Estimated incidence of myocardial infarction	1,302	1,059	
Estimated myocardial infarction hospitalization cost	541,999,377	440,649,900	101,349,477
Estimated total cost difference (C - A)			-12,608,307,624

Values in yen.

calcium channel blocker group, resulting in an increase in the costs for myocardial infarction hospitalization of 18,777,756 yen in patients treated with a calcium channel blocker. Consequently, the use of a calcium channel blocker was associated with a decrease in hospitalization costs in the amount of 104,611,471 yen. In terms of the pharmaceutical cost associated with the use of a calcium channel blocker in preference to an angiotensin-converting enzyme inhibitor, the costs were decreased by 11,070,450,000 yen. Taken together, these differences amount to a decrease of 11,175,061,471 yen associated with the use of a calcium channel blocker compared to an angiotensin-converting enzyme inhibitor. A similar result (decrease of 12,608,307,624 yen) was found in the year 2000 in Japan (Table 3).

Discussion

The characteristic epidemiological structure, with a high incidence of myocardial infarctions compared to stroke, the risk reduction using an angiotensin-converting enzyme inhibitor, and above all, the unit pharmaceutical costs, together resulted in a reduction in health care costs associated with the use of an angiotensin-converting enzyme inhibitor (enalapril) as compared to a calcium channel blocker (amlodipine) in the US. However, the epidemiological profile, relative risk reduction, and, most importantly, the unit costs in Japan were different, resulting in a different estimation for the costs associated with angiotensin-converting enzyme inhibitor and calcium channel blocker use in Japan. The results for Japan in 2000 and 2004 were similar, suggesting the absence of major temporal changes during this period.

These findings suggest the conclusion that the results of the health economic analysis of hypertension may lead to contrasting outcomes in Japan and US, therefore results obtained from US economic analyses may not always be applicable to Japan. This may be important when planning future national treatment strategies for hypertension.

The comparison was based on several assumptions. Firstly, the analysis was based on the use of amlodipine and enalapril,

which are popular and representative of the classes of calcium channel blocker and angiotensin-converting enzyme inhibitor, respectively, and the dose of medication was based on the maximum dose of amlodipine and enalapril used in the US and Japan. Secondly, outpatient visit costs were not included in this study because it was assumed that these costs would not be different between calcium channel blocker and angiotensin-converting enzyme inhibitor treatments. Thirdly, extra expenses such as rehabilitation fees were not included in the calculation. Finally, the relative risks were computed based on the assumption that all the patients were taking an angiotensin-converting enzyme inhibitor.

Since 1999 many large scale morbidity and mortality trials have compared different classes of antihypertensive drugs. The data for relative risks were based on these studies, and are summarized in two major meta-analyses performed by the Blood Pressure Lowering Trialists' Collaboration. The first meta-analysis, published in 2000, compared the effectiveness of newer therapies, such as treatments based on angiotensin-converting enzyme inhibitors or calcium channel blockers, with conventional therapies (based on diuretics or β -blockers) (21). The second meta-analysis extended these findings to include 29 major trials with over 700,000 years of patient follow-up (22).

A caveat is that in both cases, the risks were presented for calcium channel blockers and angiotensin-converting enzyme inhibitors in general, and were not limited to amlodipine and enalapril. It is theoretically possible that different results would be obtained using different drugs within the same class; however, there is insufficient evidence at present to enable an assignment of reductions in relative risk for individual calcium channel blockers and angiotensin-converting enzyme inhibitors. Since the relative risks in different countries have not been specified, we assumed that the reductions in relative risk would be similar in both Japan and the US.

One limitation of our study was that our data did not take into account any differences in mortality in the patients with stroke or myocardial infarction. This is because the epidemiological data did not provide full details of the number of

patients with stroke or myocardial infarction who subsequently died during hospitalization. A major difference in the numbers of patients who died during hospitalization would result in changes in the calculation of subsequent medical costs. However, since the incidence of stroke and myocardial infarction was much smaller than the number in the whole cohort (100,000 patients), and the magnitude of the differences in hospitalized patients was not major between the calcium channel blocker and angiotensin-converting enzyme inhibitor, we assumed that any differences would not make a major difference in the final conclusion.

The results are of interest when we compare national guidelines concerning the use of calcium channel blockers and angiotensin-converting enzyme inhibitors in the US and Japan. It has been suggested that American guidelines are less favorable to the use of calcium channel blockers, for example for recurrent stroke prevention (6), or for patients with diabetes mellitus (23), compared to the corresponding Japanese guidelines. These differences are probably linked to the different epidemiological characteristics of the two countries, and may be connected to the greater popularity of calcium channel blockers in Japan compared to the US. For example, Saito *et al.* showed that calcium channel blockers were three times as popular as angiotensin-converting enzyme inhibitors amongst 447 medical doctors in Japan in 2001 (11), whereas angiotensin-converting enzyme inhibitors were more popular than calcium channel blockers in the US (12).

In comparing the efficacy of the calcium channel blockers and angiotensin-converting enzyme inhibitors, economic considerations are only one of the factors to be assessed. Other factors include tolerability, side-effect profiles, ease of use, and effects on quality of life (QOL) in general. Moreover, it is well-known that there are situations in which the preferential use of calcium channel blockers is indicated. For example, the JSH 2004 guidelines recommend the use of both calcium channel blockers and angiotensin-converting enzyme inhibitors for the treatment of cerebrovascular disease, left ventricular hypertrophy, and diabetes mellitus, and for treatment in older people (8). In contrast, the guidelines recommend the use of calcium channel blockers but not angiotensin-converting enzyme inhibitors for angina pectoris, whereas the use of angiotensin-converting enzyme inhibitors is specifically recommended for heart failure, renal disease, and post-myocardial infarction. Therefore it is very important to stress that economic considerations are only one of many factors involved in determining the optimal treatment strategy for hypertension.

A major finding of this study is that the most important component of the differences in medical economic costs was the differences in pharmaceutical costs between the US and Japan. In the US, the price of medications is based predominantly on free-market principles, whereas the prices in Japan are mainly regulated by the government. Although both methods of price setting have their advantages and disadvantages, the most rational and cost-effective approach could be to

adjust the price of medications based on their efficacy in preventing future complications and therefore in saving medical costs in the long-term. Further studies, similar to this present one, could be valuable in determining the economic efficacy of other antihypertensive agents, which could later be fed back to changes in their prices.

In conclusion, the results of this study suggest the general principle that the costs associated with the use of different antihypertensive agents may differ in different countries. These differences may be important when considering future national guidelines concerning the optimum use of antihypertensive agents and other drugs.

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