

# Influence of angiotensin II receptor blocker combination tablet prescription on drug number and cost

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## Abstract

**Objectives:** Combination therapy using an angiotensin II receptor blocker is expected to promote medication adherence and alleviate economic burden among patients by reducing the number of drugs taken, and thereby to lower associated medical costs. In the present retrospective study, we conducted a survey on the use of angiotensin II receptor blocker-containing combination tablets as anti-hypertensive drugs, in particular angiotensin II receptor blocker/diuretic and angiotensin II receptor blocker/calcium channel blocker combinations, in order to investigate the number of prescribed drugs and drug cost.

**Methods:** We performed a retrospective study of patients who visited the outpatient clinic of GifuMunicipalHospital and received anti-hypertensive agents between June 2006 and December 2011.

**Results:** No reductions in the number of prescribed drugs or drug cost were seen following a change in prescription to an angiotensin II receptor blocker/diuretic. Patients receiving an angiotensin II receptor blocker/calcium channel blocker had a significant reduction in the number of prescribed drugs and a slight decrease in drug cost.

**Conclusion:** In this study, a reduction in the number of prescribed drugs and a decrease in economic burden were not observed after prescription of angiotensin II receptor blocker-containing combination tablets. In order to assess the usefulness of angiotensin II receptor blocker combination tablets, further studies are necessary to investigate their hypotensive effects, safety profile, and other factors.

## Keywords

Angiotensin II receptor blocker, combination therapy, hypertension

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## Introduction

The number of patients with hypertension increases annually in Japan. According to the National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare in 2010, 60.0% of men and 44.6% of women aged greater than 30 years suffer from hypertension. Current trends suggest that these numbers will increase in the future.

As stated in the 2009 Guideline for Hypertension Therapy of the Japanese Society of Hypertension (JSH 2009),<sup>1</sup> in order to control the onset, progress, and recurrence of cardiovascular diseases, young and middle-aged patients should maintain blood pressure below 130/85 mmHg, whereas elderly patients should maintain blood pressure below 140/90 mmHg. In addition, patients with diabetes mellitus (DM), chronic kidney disease, and myocardial infarction have a strict target blood pressure value of 130/80 mmHg.

However, it is often reported that target blood pressure values are difficult to achieve using monotherapies.<sup>2</sup> Therefore, it is often necessary to combine various anti-hypertensive agents when treating patients with hypertension. Based on

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the strength of their anti-hypertensive effects and good safety profiles, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCB), and combinations of diuretic agents are recommended in JSH 2009 for hypertension therapy. However, prescription of multiple drugs may reduce patient compliance and increase economic burden.

To solve the problems associated with prescribing multiple drugs to patients with hypertension, combination tablets, which contain two components, have been developed. In December 2006, the first combination tablet for hypertension containing both an ARB (losartan potassium; Banyu Pharmaceutical Co., Ltd., currently MSD Co.) and a low-dose thiazide diuretic agent (hydrochlorothiazide) was developed in Japan (Preminent<sup>®</sup>; referred to as an ARB/diuretic). Subsequently, various ARB-containing combination tablets, such as ARB/CCB agents, have been marketed by various pharmaceutical companies. The use of ARB-containing combination tablets reduces the number of drugs that patients are required to take, which increases patient adherence to dosing regimens and reduces the economic burden of treatment and related medical costs.<sup>3</sup> However, when combination tablets that are used in hospitals and pharmacies cause adverse effects, it can be difficult to determine the causative component, and this difficulty has resulted in arguments to postpone the use and adoption of ARB-containing combination tablets.

Therefore, we conducted a study to evaluate the usage status of ARB-containing combination tablets.

## Methods

### Subjects

The study included patients who met the inclusion criterion of visiting the outpatient clinic of GifuMunicipalHospital and receiving anti-hypertensive agents between June 2006 and December 2011. The target population was residents of Japan.

### Measured factors

Medical data extracted from the digital medical records of Gifu Municipal Hospital were retrospectively investigated to analyze (1) usage status of anti-hypertensive agents before and after the adoption of ARB-containing combination tablets, (2) drugs prescribed before use of ARB-containing combination tablets, (3) changes in drug combinations and the number of anti-hypertensive agents used before and after prescription of ARB-containing combination tablets, and (4) the cost of the prescribed ARB-containing combination tablets to patients. The standard price of the drugs at the time of administration was used in the analysis.

### Statistical analyses

The difference in the average number of anti-hypertensive agents prescribed before and after prescription of the ARB-

**Table 1.** The usage status of anti-hypertensive agents before and after the adoption of the ARB-containing combination tablets.

	June 2006 to December 2006 (before adoption)		June 2011 to December 2011 (after adoption)	
	Number	%	Number	%
All anti-hypertensive agents	5694		4472	
CCB	3423 <sup>a</sup>	60.1	2281	51.0
ARB	1757	30.9	1832	41.0
ACEI	571	10.0	280	6.3
$\alpha$ blocker	250	4.4	217	4.9
$\beta$ blocker	293	5.1	328	7.3
Thiazide diuretic	79	1.4	104	2.3
Other diuretic	908	15.9	691	15.5
ARB/HCTZ	–	–	156	3.5
ARB/CCB	–	–	123	2.8
Other	84	1.5	109	2.4

CCB: calcium channel blocker; ARB: angiotensin II receptor blocker; ACEI: angiotensin converting enzyme inhibitor; HCTZ: hydrochlorothiazide.

<sup>a</sup>Patients who received CCB from June to December 2006.

containing combination tablets was confirmed using two-tailed paired t-tests with a significance threshold of  $p < 0.05$ .

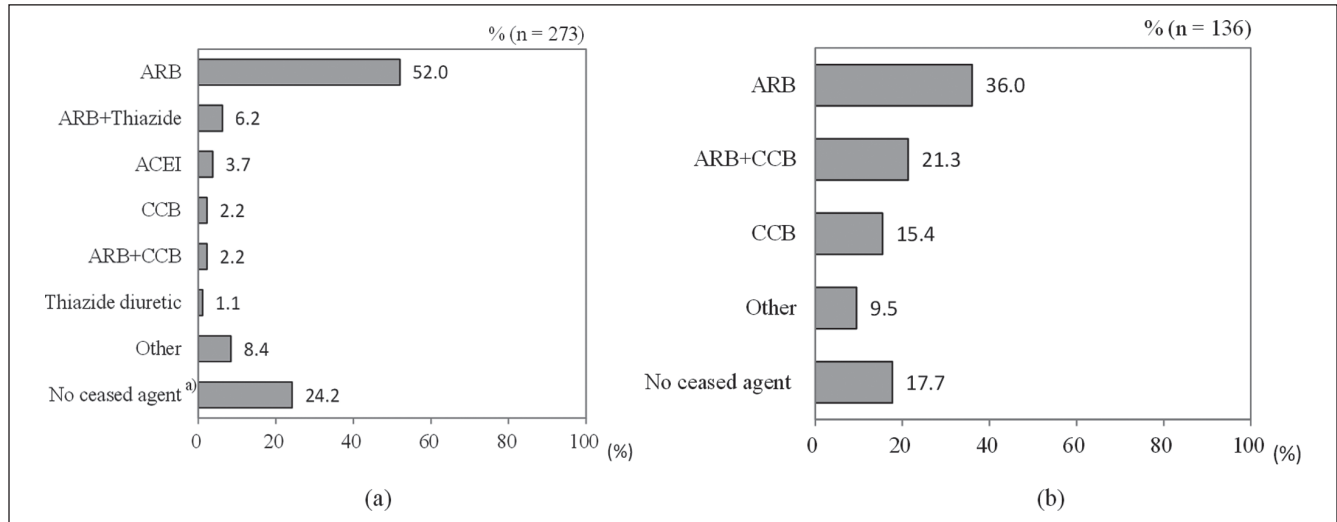
### Ethical considerations

This study was performed in accordance with the Ethics Guidelines of Gifu Pharmaceutical University and GifuMunicipalHospital, and consent was waived in this study.

## Results

Table 1 shows the usage status of anti-hypertensive agents before (from June to December 2006) and after (from June to December 2011) the adoption of ARB-containing combination tablets at GifuMunicipalHospital. Before the adoption of ARB-containing combination tablets, CCBs and ARBs accounted for 60.1% and 30.9%, respectively, of all hypertensive agents. However, after the adoption of ARB-containing combination drugs, CCB use decreased to 51.0% and ARB use increased to 41.0%. A thiazide diuretic agent was used by 1.4% of patients before the ARB-containing combination tablets were adopted, whereas the thiazide diuretic usage rate increased to 2.3% after they were adopted. The usage rate of ARB-containing combination tablets was 3.5% for the ARB/diuretic group and 2.8% for the ARB/CCB group.

The percentage of patients who ceased using anti-hypertensive agents when the ARB-containing combination tablets were adopted, as well as the anti-hypertensive agents they stopped using, are shown in Figure 1. During the study



**Figure 1.** Cessation of anti-hypertensive agents and the percentage of patients taking such agents when the ARB-containing combination tablets were prescribed: (a) ARB/HCTZ and (b) ARB/CCB.

ARB: angiotensin II receptor blocker; HCTZ: hydrochlorothiazide; ACEI: angiotensin converting enzyme inhibitor; CCB: calcium channel blocker.

<sup>a</sup>Shows the percentage of patients who did not stop taking anti-hypertensive agents when the ARB-containing combination tablets were prescribed.

**Table 2.** The usage status of combination anti-hypertensive agents before and after the prescription of the ARB-containing combination tablets.

(1) Average number of anti-hypertensive agents before and after the prescription of the ARB-containing combination tablets

	Average number of combination anti-hypertensive drugs		Paired t-test
	Before prescription	After prescription	
ARB/HCTZ (n = 226)	2.52	2.50	NS
ARB/CCB (n = 117)	2.06	1.76	p < 0.0001

(2) Changes in the number of anti-hypertensive agents before and after the prescription of the ARB-containing combination tablets

	Changes in the number of combination anti-hypertensive drugs					
	Two-drug increase	One-drug increase	No change	One-drug decrease	Two-drug decrease	Three-drug decrease
ARB/HCTZ (n = 226)	0.4% <sup>a</sup>	13.7%	70.8%	13.7%	1.3%	–
ARB/CCB (n = 117)	0.9%	5.1%	60.7%	30.8%	1.7%	0.9%

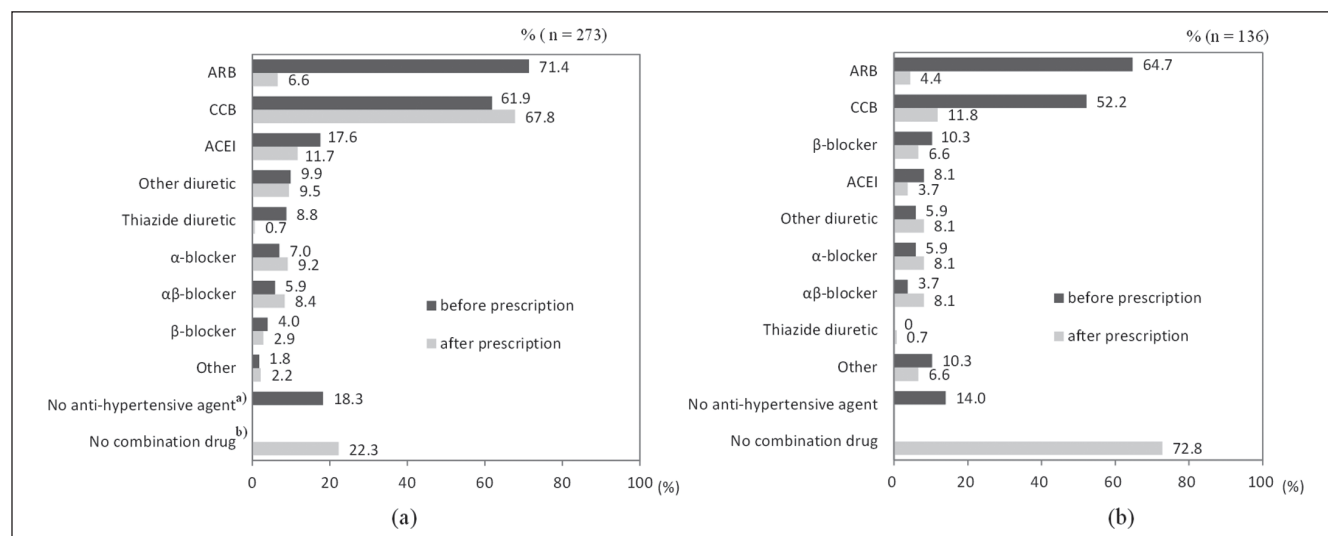
ARB: angiotensin II receptor blocker; HCTZ: hydrochlorothiazide; CCB: calcium channel blocker.

period, an ARB/diuretic was prescribed to 273 patients and an ARB/CCB was prescribed to 136 patients. In the ARB/diuretic group, 52.0% of patients ceased using ARBs alone when they received the ARB/diuretic, whereas 6.2% of patients stopped using the ARB and thiazide combination. In the ARB/CCB group, 36.0% of patients ceased using ARBs alone when they received the ARB/CCB, and 21.3% of patients ceased using the combination of ARBs and CCBs.

Table 2 shows the numbers of patients receiving combinations of anti-hypertensive agents before and after prescription of the ARB-containing combination tablets. The patients who did not receive anti-hypertensive agents before prescription

of the ARB-containing combination tablets (47 patients receiving an ARB/diuretic and 19 patients receiving an ARB/CCB) were excluded.

The average number of anti-hypertensive agents in the ARB/diuretic group prescribed the ARB-containing combination tablet was 2.52 agents before the prescription and 2.50 agents after the prescription, and this difference was not significant. However, the ARB/CCB group received 2.06 agents before the prescription of ARB-containing combination tablets and 1.76 agents after they were prescribed, which was a significant reduction (p < 0.0001). In addition, analysis of changes in combinations of anti-hypertensive agents taken by



**Figure 2.** The types of prescribed anti-hypertensive agents and the percentage of patients taking such agents before and after the prescription of the ARB-containing combination tablets:(a) ARB/HCTZ and (2) ARB/CCB.

ARB: angiotensin II receptor blocker; HCTZ: hydrochlorothiazide; CCB: calcium channel blocker; ACEI: angiotensin converting enzyme inhibitor.

<sup>a)</sup>“No anti-hypertensive agent” shows the percentage of patients who did not receive any anti-hypertensive agent prior to the prescription of the ARB-containing combination tablets.

<sup>b)</sup>“No combination drug” shows the percentage of patients not using any drug combinations following the prescription of the combination tablets. For example, when a patient taking an ARB changed to an ARB/diuretic combination tablet, “ARB” was recorded before the prescription and “no combination drug” was recorded after the prescription.

the patients after the prescription of ARB-containing combination tablets showed that among those given the ARB/diuretic, 70.8% of patients did not change their combination of anti-hypertensive drugs, and 15.0% of patients reduced the number of drugs in their drug combinations. Among those who were given the ARB/CCB, 60.7% did not make changes in their drug combination, whereas 33.4% of patients reduced the number of drugs in their drug combinations.

Changes in the percentages of patients prescribed various hypertensive drugs before and after prescription of the ARB-containing combination tablets are shown in Figure 2. Before prescription of the ARB/diuretic, ARBs were given to 71.4% of patients and a thiazide diuretic was given to 8.8% of patients. However, after prescription, the percentage of patients who were given ARBs decreased to 6.6% and that of the patients who were given thiazide diuretics decreased to 0.7%. In contrast, the number of patients who were given a CCB,  $\alpha$  blocker, and  $\alpha\beta$  blocker increased after prescription of the ARB/diuretic. In the ARB/CCB group, ARBs were given to 64.7% of patients before prescription of the ARB/CCB, and a CCB was given to 52.2% of patients. However, after prescription of the ARB/CCB, there was a marked reduction in the number of patients who received an ARB or a CCB (4.4% and 11.8%, respectively). In addition, after prescription of the ARB-containing combination tablets, the percentage of patients who received only ARB-containing combination tablets was 72.8% in the ARB/CCB group and 22.3% in the ARB/diuretic group, indicating that the ARB/diuretic monotherapy was prescribed to fewer patients.

The effect of the prescription of ARB-containing combination tablets on the economic burden of medical treatment is shown in Table 3. In the ARB/diuretic group, the average price of prescribed anti-hypertensive agents per patient per day before the switch to the ARB/diuretic was 146.1 Yen; however, after the switch, the cost increased to 18.0–164.1 Yen. There was also a case in which a daily cost of 393.0 Yen before the switch increased to 395.1 Yen after the switch. However, the average price per patient per day of anti-hypertensive agents was 150.6 Yen before the switch to the ARB/CCB and 141.5 Yen after the switch, indicating an average reduction of 9.2 Yen. There was another case in which the daily cost was reduced from 240.3 Yen to 129.0 Yen after the switch to the ARB/CCB.

## Discussion

No studies have been conducted regarding the usage status of anti-hypertensive agents following the availability of ARB-containing combination tablets in Japan. Thus, we evaluated the usage status of anti-hypertensive agents before and after the adoption of ARB-containing combination tablets in order to evaluate changes in the prescription status of anti-hypertensive agents, including ARBs, CCBs, and thiazide diuretics. In our study, data were extracted from digital medical records. Analysis of medical data extracted from the digital medical records in our study is considered to be sufficient to evaluate the usage status of ARB-containing combination tablets. Patient interviews are required if information

**Table 3.** The effect of the prescription of the ARB-containing combination tablets on the cost of drugs per day.

Before prescription, average (range)	Drug price (per patient per day)		
	After prescription, average (range)		Difference, average (range)
ARB/HCTZ (n=207) (Yen)	146.1 (4.9–541.8)	164.1 (130.6–557.2)	18.0 (–393.0 to +395.1)
Drugs before prescription			
ARB (n=144)	148.2 (75.8–243.2)	163.7 (130.6–557.2)	15.5 (–88.9 to +395.1)
Thiazide diuretic (n=3)	8.1 (4.9–9.7)	171.1 (171.1–171.1)	163.0 (+161.4–+166.3)
ARB + thiazide diuretic (n=19)	162.0 (84.8–294.4)	157.8 (139.3–219.8)	–4.3 (–74.6 to +95.9)
The others (n=41)	141.4 (23.4–541.8)	133.5 (130.6–234.4)	–7.9 (–393.0 to +146.6)
ARB/CCB (n=112) (Yen)	150.6 (14.8–384.1)	141.5 (130.1–170.1)	–9.1 (–240.3 to +129.0)
Drugs before prescription			
ARB (n=49)	136.3 (71.2–225.5)	141.3 (130.1–170.1)	5.0 (–81.7 to +72.6)
CCB (n=19)	67.0 (14.8–133.2)	140.5 (130.1–150.3)	73.5 (–3.1 to +129.0)
ARB + CCB (n=28)	208.8 (137.6–348.8)	141.2 (130.1–170.1)	–67.6 (–205.0 to +32.5)
The others (n=16)	192.1 (57.3–384.1)	143.5 (130.1–170.1)	–48.5 (–240.3 to +72.8)

ARB: angiotensin II receptor blocker; HCTZ: hydrochlorothiazide; CCB: calcium channel blocker.

on compliance is evaluated, but our study focused on the number and cost of anti-hypertensive drugs, and thus, interviews were not performed.

In the ARB/diuretic and ARB/CCB groups, CCBs, followed by ARBs, were the most prescribed anti-hypertensive agents before and after the adoption of the ARB-containing combination tablets. However, after adoption of the ARB-containing combination tablets, the percentage of patients using CCBs decreased, whereas the percentage of patients using ARBs increased. Compared to angiotensin converting enzyme inhibitors (ACEIs), ARBs have fewer reported adverse events<sup>4,5</sup> and have a renal protective effect,<sup>6</sup> and these are perhaps the factors leading to their increased use. In addition, the use of thiazide diuretics also increased after adoption of the ARB-containing combination tablets, although the change was modest. In the Seventh Report of the American Joint Committee (JNC7),<sup>7</sup> diuretics and diuretic combination therapies were recommended as first-line drugs for hypertension. Thiazide is widely used in many countries, but its use is often avoided in Japan because of adverse events such as glucose tolerance abnormalities and hyperuricemia.<sup>8,9</sup> However, because the combination of ARBs and thiazide enhanced anti-hypertensive effects and reduced adverse events in Japanese patients with high salt intake or salt sensitivity hypertension,<sup>10</sup> thiazide diuretic combination therapy, which accelerates sodium excretion, is considered to be therapeutically useful.<sup>11,12</sup> In addition, in the Gauging Albuminuria Reduction With Lotrel in Diabetic Patients (GUARD) study of patients with type 2 DM hypertension associated with albuminuria, albuminuria was significantly reduced in subjects given a combination of an ACEI and a diuretic, in comparison with that of patients given a combination of an ACEI and a CCB.<sup>13</sup> Furthermore, because thiazide diuretics are effective treatments for hypertension, their use has been reviewed in recent years.

Accordingly, along with the increase in the use of ARB/diuretic combinations, the use of thiazide diuretics has also increased.

The recommendations for numbers of prescription treatment days for the combination tablets were released on 10 December 2010. Combined with the Japanese Pharmacopoeia product list of drugs used in the clinic for more than 1 year, drugs were limited to those with similar efficacy, dosage, and administration regimens to products on the existing product list. Thus, it is thought that there was no effect of the limited number of drug administration days that was possible in the present survey.

One of the effects of ARB-containing combination tablets is expected to be increased patient compliance. It has been reported that the use of ARB-containing combination tablets reduces the number of drugs taken each day, resulting in increased adherence to administration regimens.<sup>14</sup> In this study, there was no significant change in the number of prescribed anti-hypertensive agents before and after prescription of the ARB/diuretic. This might be because the prescription frequency of the thiazide diuretic was low, and as such, there were very few patients who switched from a combination of an ARB and a thiazide diuretic, but many patients who switched from taking an ARB only. Therefore, the effect on the number of prescribed anti-hypertensive drugs was small. However, a reduction in the numbers of prescribed anti-hypertensive drugs was observed in the ARB/CCB group. ARBs and CCBs are commonly prescribed in Japan. The two-drug combination of an ARB and a CCB is recommended in JSH 2009, and in practice, such combinations predominantly consist of a renin angiotensin system inhibitor and a CCB.<sup>15</sup> Therefore, there were many patients who switched from receiving an ARB and CCB combination, resulting in a reduced number of drug combinations.

Combination tablets are usually distributed at a lower price than are single agents. It has been reported that the use of ARB-containing combination tablets reduces the cost of medications to patients.<sup>16</sup> However, we found no reductions in medicine cost in the ARB/diuretic group. As explained above, there were only a few patients who switched from the use of two agents (ARBs and thiazide diuretics). Therefore, the cost of thiazide might have affected the treatment cost. In contrast, after prescription of the ARB/CCB, a small decrease in medicine cost was observed. The most likely explanation is that there were some patients who switched from the ARB and CCB combination to a different treatment regimen.

However, the large reduction in cost that we expected to observe in the ARB/CCB group did not occur. Similar to the ARB/diuretic group, there were many patients in the ARB/CCB group who switched from single ARB therapy. This study has some limitations. There is no information on patient characteristics and the exact number of pills taken by hypertensive patients. The general blood pressure target for the studied patients is 140/90 mmHg according to current 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) and 2014 Joint National Committee (JNC) guidelines, but in our study, anti-hypertensive drugs are prescribed to reach the more rigorous target of 130/80 mmHg provided in the JSH 2009. Because data from the medical affairs section were used, we were unable to evaluate the anti-hypertensive effects of ARB-containing combination tablets and their safety. In addition, it was only possible to evaluate the economic burden from the point of view of the patient. It is not possible to draw conclusions on the usefulness of the combination tablets from the results of this study; therefore, in future studies, it will be important to evaluate the anti-hypertensive effects of ARB-containing combination tablets and their safety, in order to evaluate their usefulness.

## Conclusion

In the present retrospective study, a reduction in the number of prescribed drugs and a decrease in economic burden were not observed after prescription of ARB-containing combination tablets.

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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