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Improving Drug Adherence Using Fixed Combinations Caused Beneficial Treatment Outcomes and Decreased Health-Care Costs in Patients with Hypertension

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Abstract

We enrolled 196 patients with hypertension who were already being treated with free-drug combinations of angiotensin-II receptor blocker (ARB) and amlodipine. The free-drug combinations of ARB and amlodipine were replaced with the same dose of the fixed-dose combinations. The average home blood pressure (BP) in all patients receiving fixed-dose combinations was significantly lower than those receiving free-drug combinations (131 ± 10/75 ± 8 vs. 136 ± 11/77 ± 9 mm Hg, $P < .01$) accompanied with increasing drug adherence. After lowering BP by fixed-dose combinations, the costs for medications decreased by 31% over the 3 months.

Keywords: adherence, fixed-dose combinations, hypertension, blood pressure control, health-care cost, antihypertensive drug

INTRODUCTION

Hypertension is one of the most common risk factor for cardiovascular disease, and treatment and control of hypertension will reduce these risks. However, in the United States, national surveys demonstrate that controlling hypertension in a clinical setting is suboptimal, with only about 50% of hypertensive patients achieving the blood pressure (BP) goal, despite recent improvements (1). Adequate BP control rates are reported to be less than 50% and hypertensive patients receiving a combination of two or more antihypertensive agents are reported to be 35.3% (2). The number of single doses to be taken daily is an important contributor to drug adherence and compliance (3,4). Poor drug adherence is associated with increased mortality in patients receiving polypharmacy (5). Improving drug adherence is critical in order to achieve and maintain BP control for patients with hypertension (6).

Fixed-dose combinations in the treatment of hypertension can contribute to the reduction of the number of single doses, and, therefore, also drug adherence. Although the efficacy of taking at least one or more antihypertensive drug at bedtime has been reported in patients with resistant hypertension (7), it has also been reported that the prescribed number of doses per day is inversely related to adherence (3). The efficacy of fixed-dose combinations of a single morning dose on morning BP was unclear, especially in patients with early morning hypertension.

Accordingly, we performed a prospective, multicenter, observational study to investigate the impact of treatment of fixed-dose combinations on drug adherence, home BP, and health-care costs.

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METHODS

Patient Population

The study was conducted at the Mie University Graduate School of Medicine, Onishi Heart Clinic, Nagai Hospital, Iwasaki Hospital, Yazu Naika Clinic, Oota Clinic, Ueda Clinic, Hiraoka Clinic, and Heartful Clinic Kitai between December 2010 and November 2011. In this study, outpatients with essential hypertension were recruited. Inclusion criteria required self-measurement of home BP and the prescribed free-drug combinations of angiotensin-II receptor blocker (ARB) (8 mg candesartan, 80 mg valsartan, or 40 mg telmisartan) and 5 mg amlodipine during a 3-month period. Patients with severe renal or liver dysfunction, severe heart failure, and prescription of the time-specific packs were excluded. With these inclusion criteria, 196 patients were enrolled in this study.

Protocol

Each subject was provided with informed and written consent to the protocol approved by the review board of Mie University Graduate School of Medicine. All patients performed self-measurements of morning BP and pulse rate (PR) at home using an upper arm cuff oscillometric device, HEM-7080IC (Omron, Healthcare Co., Ltd., Kyoto, Japan) according to the 2009 Japanese Society of Hypertension Guidelines for Management of Hypertension (JSH 2009) (8). Patients were instructed to place the cuff on the same arm throughout the measurements and to measure BP in a seated position. Measurements were performed within 1 hour of waking, after urination, after 2 minutes rest, before taking antihypertensive drugs, and before breakfast in the morning. All BP and PR values were recorded and reported to their own physician. The mean values of the first measurement taken each morning during the final month of a 3-month treatment were obtained. Clinical BP values were measured at the office by a method similar to that used for self-measured BP at home, and blood samples were collected. We evaluated the adherence of home BP measurements by calculating the number of days of self-home BP measurement per month. After the measurements, prescriptions of free-drug combinations of ARB and amlodipine were exchanged for the same dose of the fixed-dose combinations with ARB and amlodipine in the morning. As the fixed-dose combinations with ARB and amlodipine, the trade name Unisia® combination tablet HD (Takeda Pharmaceutical Co. Ltd., Osaka, Japan) contains 8 mg of candesartan cilexetile and 5 mg of amlodipine besilate, Exforge® combination tablet (Novartis Pharmaceuticals Corp., Basel, Switzerland) contains 80 mg valsartan and 5 mg of amlodipine besilate, and Micamlo® combination tablet AP (Astellas Pharma Inc., Tokyo, Japan and Boehringer Ingelheim Co. Ltd., Tokyo, Japan) contains 40 mg of telmisartan and 5 mg of amlodipine besilate were used. All patients were divided into two groups based upon the dosing time of free-drug combinations of ARB and amlodipine. Group 1 consisted of patients receiving the morning prescriptions of free-drug combinations of ARB and amlodipine. Group 2 consisted of patients receiving the morning prescriptions of ARB and the bedtime prescriptions of amlodipine. The same BP measurements were recorded for 1 month after the 3-month treatment period was completed, and blood samples were collected. The other antihypertensive medications were not changed during the treatment period. We evaluated drug adherence by measuring the ratio of the number of self-reported ingestion of medications, as measured by tablet counts, to the number of prescribed medications. Furthermore, we investigated the effects on health-care costs by calculating the difference in drug costs between free-drug combinations and fixed-dose combinations.

Statistical Analysis

Patient characteristics and results were reported as mean ± SD or percentages, and results of drug adherence were reported as median with interquartile range (25th–75th percentile). Differences between free-drug combinations and fixed-dose combinations were evaluated with paired t test or Wilcoxon signed-rank test. All analyses were performed with SPSS software (SPSS version 19.0; SPSS, Inc., Chicago, IL, USA), and the level of significance was taken as $P < .05$.

RESULTS

Patient Characteristics

Baseline patient characteristics in this study are shown in Table 1. Among the 196 patients, 136 patients were in

Table 1. Patient characteristics ($n = 196$)

Age (y)	69 ± 11
Male (%)	57
Comorbidities	
Diabetes mellitus (%)	28
Chronic kidney disease (%)	28
Dyslipidemia (%)	60
Ischemia heart disease (%)	17
Chronic heart failure (%)	9
Cerebral vascular disease (%)	8
Atrial fibrillation (%)	2
Smoking (%)	6
Medications	
ARB; candesartan 8 mg (%)	48
Valsartan 80 mg (%)	46
Telmisartan 40 mg (%)	6
Calcium channel blockers; Amlodipine 5 mg (%)	100
Beta-blockers (%)	13
ACE inhibitors (%)	1
Diuretics (%)	11
Alpha-blockers (%)	2
NSAIDs (%)	2
Statins (%)	32
Average number of tablets taken daily (tablets)	5.5 ± 3.8
Average number of antihypertensive tablets taken daily (tablets)	2.3 ± 0.5
Average number of doses per day (times)	2.2 ± 1.1

Abbreviations: ARB – angiotensin-II receptor blocker; ACE – angiotensin-converting enzyme; NSAIDs – non-steroidal anti-inflammatory drugs.

Table 2. Comparison of laboratory tests between free-drug combinations and fixed-dose combinations ($n = 196$)

	Free-drug combinations	Fixed-dose combinations	P value
White blood cells count (/mm^3)	5800 ± 2100	6100 ± 2000	.146
Hemoglobin (g/dL)	13.6 ± 2.9	13.4 ± 1.7	.474
Platelet counts (×10^4/mm^3)	21.7 ± 6.1	23.0 ± 10.2	.201
Aspartate aminotransferase (IU/L)	26 ± 9	25 ± 10	.651
Alanine aminotransferase (IU/L)	25 ± 16	26 ± 17	.622
Uric acid (mg/dL)	6.1 ± 1.9	6.1 ± 1.6	.703
Creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.4	.886
Potassium (mEq/L)	4.4 ± 0.4	4.3 ± 0.4	.692
Glucose (mg/dL)	122 ± 45	120 ± 47	.738

group 1 and 60 patients were in group 2. The mean age was 69 ± 11 years for all patients. Regarding patient comorbidities, 60% of patients had dyslipidemia, 28% had diabetes mellitus or chronic kidney disease, 17% had ischemic heart disease, 9% had heart failure, and 8% had cerebral vascular disease. Among ARB prescriptions, 48% of patients were taking candesartan, 46% of patients were taking valsartan, and 6% of patients were taking telmisartan. The average number of tablets taken daily was 5.5 ± 3.8, and specifically, the average number of antihypertensive tablets taken was 2.3 ± 0.5. The average number of doses per day was 2.2 ± 1.1. Table 2 shows the results of laboratory tests before and after the replacement to fixed-dose combinations of ARB and amlodipine. There were no significant differences in laboratory tests between free-drug combinations and fixed-dose combinations.

In patients overall, the average of self-monitoring BP measurements taken during early morning for fixed-dose combinations was significantly lower compared with the free-drug combinations (131 ± 10/75 ± 8 mm Hg vs. 136 ± 11/77 ± 9 mm Hg, $P < .01$) (Figure 1A). The average of clinical BP for fixed-dose combinations was also significantly lowered compared with free-drug combinations (132 ± 12/75 ± 8 mm Hg vs. 137 ± 12/77 ± 9 mm Hg, $P < .01$). Similar results were obtained in group 1 (130 ± 10/74 ± 8 mm Hg vs. 135 ± 10/77 ± 9 mm Hg, $P < .01$) and group 2 (132 ± 11/75 ± 8 mm Hg vs. 138 ± 13/79 ± 9 mm Hg, $P < .01$) (Figure 1B and C). Home PR was not changed in all patients for fixed-dose combinations compared with free-drug combinations (67 ± 8 per min vs. 67 ± 9 per min, $P = .2$). There is no significant difference in the adherence of home BP measurements between the free-drug combinations and the fixed-dose combinations.

Figure 2A shows that the box-and-whisker plots of the calculated drug adherence from the valid answers for the number of self-reported ingestion of medications. Drug adherence improved significantly fixed-dose combinations compared with free-drug combinations. Dividing into groups based upon improved drug adherence, the mean value of home systolic BP was significantly lower in the group with improved drug adherence compared with the group without the improved drug adherence (Figure 2B).

Figure 3 shows that patient's BP taken at home improved significantly and was more consistent with the target home BP recommended in JSH 2009 by fixed-dose combinations (8). The target home BP improved from 24% to 39% in all subjects; from 14% to 24% in nonelderly patients (younger than 65 y); from 50% to 71% in elderly patients; and from 7% to 31% in patients with diabetes mellitus, chronic kidney disease, or a history of myocardial infarction.

The drug costs were lowered by about 60 yen per tablet when changing from free-drug combinations to fixed-dose combinations of ARB and amlodipine. The healthcare costs were decreased by 31% per patient from 17 075 yen to 11 815 yen over the 3-month treatment period (Figure 4).

DISCUSSION

In this prospective, multicenter, observational study, fixed-dose combinations of ARB and amlodipine were shown to significantly reduce home BP resulting from improved drug adherence. This effect was also shown in group 2 that was prescribed ARB at morning and amlodipine at bedtime. Reasonable interpretations of these results indicate that patients often miss taking doses of their medicines particularly at bedtime, and so morning BP is better controlled by prescribing fixed-dose combinations, rather than by adding more antihypertensive agents at bedtime. Gupta et al. (9) reported in a meta-analysis study that compared with free-drug combinations, fixed-dose combinations of antihypertensive agents are associated with a significant improvement in compliance without beneficial trends in BP. In their selected studies, BP lowering efficacy is assessed based upon the clinical BP, but not home BP. According to the NICE clinical guideline 127 update in August 2011, home BP monitoring is more accurate than clinical BP measurement for the diagnosis and treatment of hypertension (10). In this study, we clearly showed the BP-lowering effects of fixed-dose combinations by assessing home BP.

According to JSH 2009 for the management of patients with hypertension, the target home BP is strictly defined: less than 125/80 mm Hg in nonelderly patients (younger than 65 years), 135/85 mm Hg in elderly patients, 125/75 mm Hg of patients with diabetes mellitus, chronic kidney disease, or a history of myocardial infarction (8). In this study, the achieved rate to the target home BP before exchange to the fixed-dose combinations was low because patients had various comorbidities, which affected BP and led to an

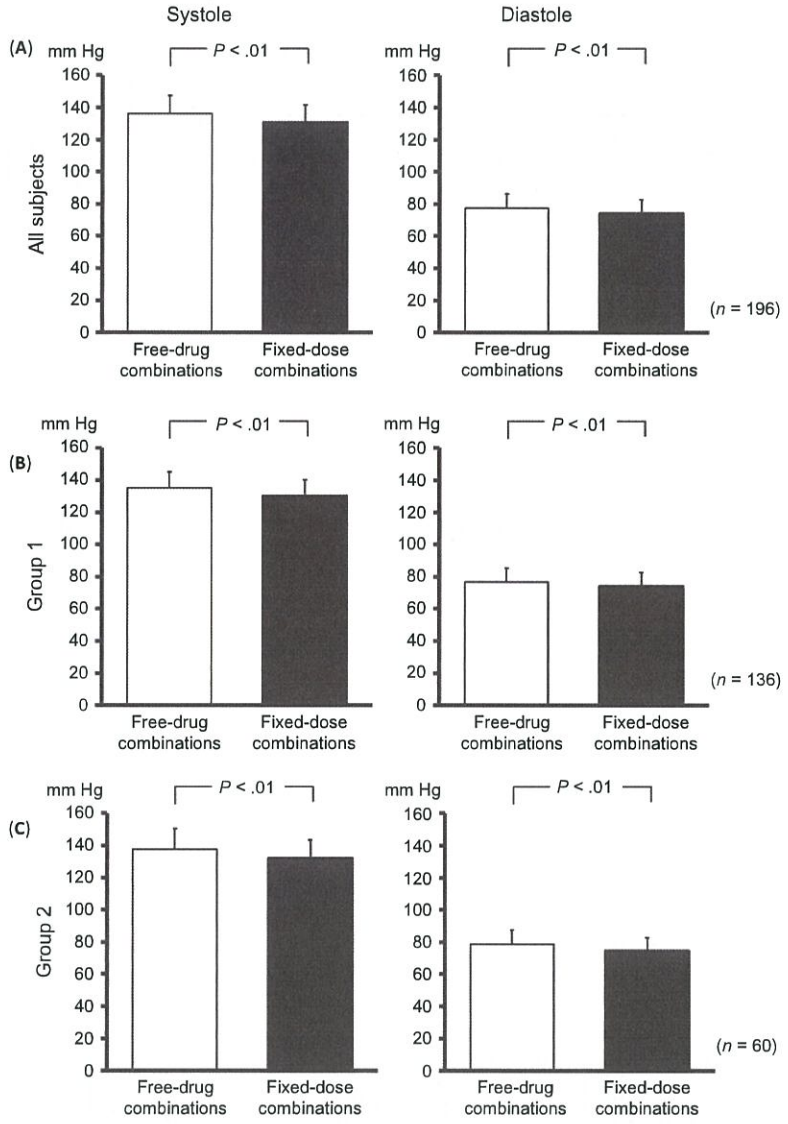

Figure 1. Average of self-monitoring blood pressure at home in early morning with fixed-dose combinations was significantly lower than that of free-drug combinations in each group. (**A**) Overall patients. (**B**) Group 1 included the prescriptions of both ARB and amlodipine taken at morning that were then changed to fixed-dose combinations at morning. (**C**) Group 2 included the prescriptions of ARB taken at morning and amlodipine taken at bedtime that were changed to fixed-dose combinations taken at morning. (**D**) Drug adherence improved significantly after changing to fixed-dose combinations from free-drug combinations among all patients. Abbreviation: ARB – angiotensin-II receptor blocker.

increase in average number of tablets taken daily. After exchange to the fixed-dose combinations, the rate at which target home BP was significantly improved in all categories. Particularly, high-risk patients such as elderly patients, or those with diabetes mellitus, chronic kidney disease, or a history of myocardial infarction tended to achieve target home BP partly due to the reduction in the number of single doses. Thus, simplifying the therapy by using fixed-dose combinations may be particularly important for elderly patients, who are more likely to have comorbid conditions and are taking multiple medications.

Generally, the price for fixed-dose combinations of medications is lower than for separate combinations of medications. Reducing health-care costs will result in further improvement of drug adherence. Most patients were satisfied with the replacement to the fixed-dose combinations, because they obtained better BP control with lower drug costs and less number of tablets compared with those prior to replacement.

Limitations regarding the method for measuring adherence should be acknowledged in this study. The available methods for measuring adherence can be divided into direct and indirect methods. Each method

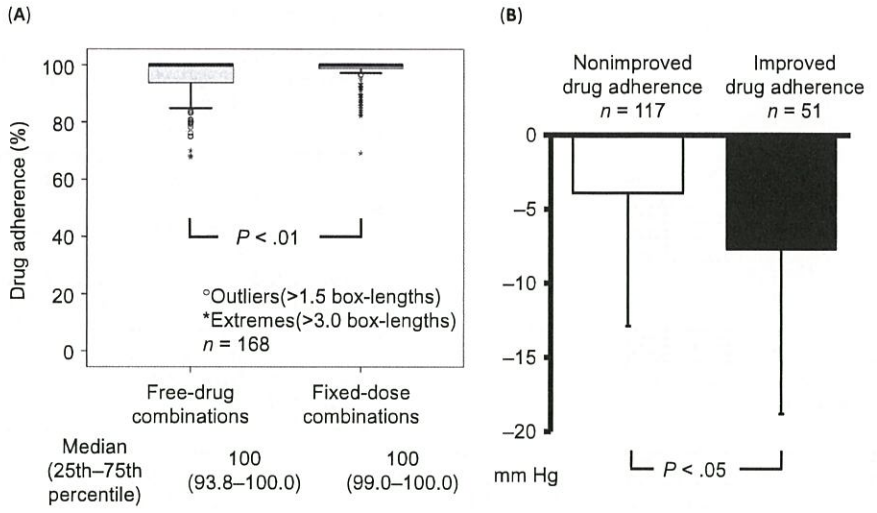

Figure 2. (**A**) Box-and-whisker plots of the calculated drug adherence from valid answers for the number of self-reported ingestion of medications. Drug adherence improved significantly fixed-dose combinations compared with free-drug combinations. °Values more than 1.5 box-lengths from the box but not extremes (outliers). *Values more than 3.0 box-lengths from the box (extremes). (**B**) Dividing into groups based upon improved drug adherence, the value of mean home systolic blood pressure was significantly lower in the group with improved drug adherence than in the group without.

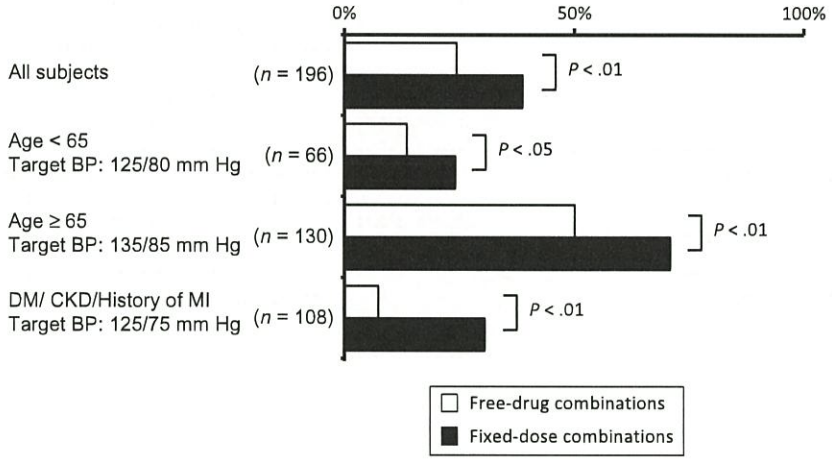

Figure 3. Patient BP taken at home was significantly improved and was more consistent with the target home BP recommended in the 2009 guidelines of the Japanese Society of Hypertension for the management of hypertension (JSH 2009) by fixed-dose combinations. Abbreviations: BP – blood pressure; DM – diabetes mellitus; CKD – chronic kidney disease; MI – myocardial infarction.

has advantages and disadvantages, and no method is considered as the gold standard (11). Direct methods include measurement of concentrations of a drug or its metabolite in blood or urine. However, this approach is difficult in daily clinical practice, because the time between taking pills and collecting blood sample is different in each patient. Indirect methods include patient questionnaires, patient self-reports, pill counts, rates of prescription refills, and electronic medication monitors. We chose the method of patients' self-reported medication consumption, as measured by tablet counts, to the number of prescribed medications. Because this is a simple method of measuring adherence and it is reported that patients' self-reports is the most useful method in the clinical setting (11,12). Although high-adherence patients are reported to be as high as 75% among patients receiving antihypertensive therapy (13), our results indicated an extremely high drug adherence rate. The reason for this result may be due to patient inclusion criteria as requiring self-measurement of home BP. However, among such populations, it is interesting that drug adherence significantly improved through the use of fixed-dose combinations. In clinical practice, fixed-dose combinations may be more effective for patients without home BP monitoring, and so future research is needed in this regard.

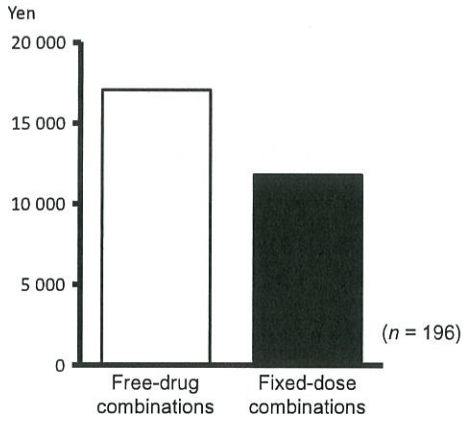

Figure 4. The drug costs were lower by about 60 yen per tablet when changing from free-drug combinations to fixed-dose combinations of angiotensin-II receptor blocker and amlodipine. The health-care costs decreased by 31% per patient over the 3-month treatment period.

In conclusion, fixed-dose combinations of ARB and amlodipine improve drug adherence and are a very effective means of lowering BP. Additionally, fixed-dose combinations reduce the health-care costs of patients with hypertension.

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