


ORIGINAL ARTICLE

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Treatment patterns of antihypertensive fixed-dose combinations according to age and number of agents prescribed: Retrospective analysis using a Japanese claims database

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Aim: To determine the real-world use of fixed-dose combinations (FDC) of antihypertensive agents using data collected from a nationwide medical database of acute hospitals in Japan.

Methods: We carried out a retrospective analysis of data from the Medical Data Vision database for patients with hypertension who received an antihypertensive drug prescription between April 2014 and March 2015. The prescription rate of antihypertensive FDC were assessed by class, age and according to combinations.

Results: In total, data from 59 867 patients aged 70.0 ± 11.9 years (mean \pm SD) were analyzed. Patients were prescribed 1.9 ± 1.0 oral antihypertensive agents (mean \pm SD). Overall, 58.6% of patients were prescribed two or more antihypertensive agents, and the most frequently prescribed classes were calcium channel blockers (CCB) and angiotensin II receptor blockers (ARB). As the number of concomitant antihypertensive agents prescribed increased, the prescription rate of a CCB + an ARB FDC decreased, whereas the prescription rate of an ARB + a diuretic FDC increased. This trend was the same regardless of age. Of the 12 222 patients who were prescribed a CCB + an ARB, 26.0% received a FDC. In contrast, of the 922 patients prescribed an ARB + a thiazide diuretic, 80.6% received a FDC. Medium doses of both CCB and ARB agents, and low doses of diuretics were the most frequently prescribed for each class.

Conclusions: Our analyses show that the real-world use of FDC varies depending on the combination of agent class and the number of prescriptions; the latter was similar regardless of age. *Geriatr Gerontol Int* 2019; 19: 1077–1083.

Keywords: antihypertensive drugs, fixed-dose combinations, hypertension, Japan, prescription status.

Introduction

Hypertension is an established, preventable risk factor for cardiovascular diseases and mortality. In 2010, an estimated 43 million people in Japan had a diagnosis of hypertension,¹ highlighting the importance of controlling blood pressure in this large patient population.¹ Hypertension predominantly affects older people^{1–3} with one study reporting a prevalence of 66%/62% in men/women aged 60–69 years and 81%/71% in men/women aged 70–79 years.¹ Consequently, the number of patients with hypertension in Japan is expected to rise along with the aging population.^{1,2,4}

The mean blood pressure in Japan has decreased over the past 50 years due to the improved management of high blood pressure and the development of multiple classes of antihypertensive.¹ Patients often require two or more antihypertensive agents, with different mechanisms of action, to control hypertension.^{5,6} This has led to the development of fixed-dose combinations (FDC),

which combine two different classes of antihypertensive agents in a single pill.⁷ It is common for multiple agents to be used to treat older patients with hypertension, as they often have comorbid conditions.⁸ Simplifying the prescriptions for older patients through the use of FDC might improve treatment compliance and lower treatment costs versus individual agents used together (i.e. multi-pill combinations).^{7,9,10}

In older patients in Japan, treatment guidelines recommend beginning antihypertensive treatment at half the standard dose for a monotherapy, and if this does not sufficiently control blood pressure, to add a second agent; that is, commence combination therapy.^{2,4} Furthermore, guidelines suggest that if polypharmacy is a contributor to the lack of treatment adherence, then patients should be given a stronger dose of a single agent or a FDC; the FDC should be provided in one-dose packaging, which should simplify the dosing schedule.¹¹ Prescribing of FDC antihypertensive agents has increased in Japan, and a retrospective cost analysis showed that switching to a FDC reduces the annual cost of antihypertensive treatment.⁷ However, real-world use of FDC has not been adequately studied in Japan.

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Using a nationwide medical database, we previously carried out a retrospective study of the use of antihypertensive agents in patients with hypertension in Japan according to patient age. In that study, we found that there was a difference in the prescription rates of angiotensin II receptor blockers (ARB), calcium channel blockers (CCB) and loop diuretics between patients aged ≥ 75 years and those aged < 75 years.⁴

Here, we report a retrospective analysis of the real-world use of FDC classified by class, age and according to combinations.

Methods

Study design and patients

Detailed methods of the present retrospective analysis have been reported in full previously.^{4,12} Briefly, we analyzed data from the Medical Data Vision (MDV; Tokyo, Japan) database for patients who were entered into the system with hypertension and who were dispensed an antihypertensive agent prescription within the target selection period of April 2014 to March 2015. The MDV contains claims and administrative data on inpatients or outpatients treated at 174 hospitals in Japan participating in the Diagnostic Procedure Combination payment system (constituting 11% of all Diagnostic Procedure Combination hospitals).

The first day of prescription of the first antihypertensive agent within the target selection period formed the index date. Data were collected for 12 months before and 12 months after the index date. Eligible patients had to have had an outpatient visit or hospitalization (for any indication) in the 12 months before the index date. Patients with no history of attendance during this timeframe were excluded from the analysis. Patients who had been prescribed a loop diuretic or aldosterone antagonist as monotherapy or combination therapy were also excluded, as these agents can be prescribed for congestive heart failure or other edematous diseases. Patients who were prescribed a combination of three or more agents that included a loop diuretic, an aldosterone antagonist, and at least one other antihypertensive agent were included.

Assessments

The prescription rates of antihypertensive agents were assessed by class and according to combinations. The fixed-dose, two-agent combinations of a CCB + an ARB and an ARB + a thiazide diuretic were analyzed, as well as the three-agent drug combinations of a CCB + an ARB and a β -blocker or a thiazide diuretic. Patient background information, including age, sex, comorbidity and number of antihypertensive agents, was also collected, and the impact of background factors on the prescription rates of different combinations and FDC was determined. Patients with diabetes as a comorbidity were defined as those with the appropriate International Classification of Diseases-10 code and who were prescribed antidiabetic medicine. Comorbid diseases and antihypertensive agents were defined using the International Classification of Diseases, International Classification of Diseases-10¹³ and/or Anatomical Therapeutic Chemical Classification System codes.¹⁴ In order to assess the dose distribution of the antihypertensive agents, the dose of antihypertensive was classified into three or four categories based on different concentration cut-offs for individual agents within the combinations. Association between age groups (age < 74 vs ≥ 75 years) and sex, comorbidities, hospitalization and number of antihypertensive agents prescribed was tested using Pearson's χ^2 -test.

Ethical considerations

Data within the MDV database are anonymized. According to Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Welfare and Labor, ethics approval and informed consent were not applicable. Data were analyzed by IQVIA Solutions Japan K.K. (Tokyo, Japan) and stored in standalone (not connected to a local area network) personal computers that could be locked with a password.^{4,12}

Statistical analysis

Demographics, baseline comorbidities and the number of antihypertensive agents prescribed were summarized using descriptive statistics, and presented as the mean and standard deviation (SD) for continuous data, and as the number and percentages for categorical data.^{4,12} Prescription rates for each class of antihypertensive agent were presented as percentages for the overall population and for patient subgroups according to age, and according to combinations of interest as individual agents or FDC.^{4,12} Analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Overall, 123 414 patients were diagnosed with hypertension between April 2014 and March 2015. Of these, 62 080 patients were prescribed, and had an outpatient claim for, one or more antihypertensive agents (index date), were aged ≥ 20 years and had at least one claim for any condition in the 1 year period before the index date. A further 2213 patients were excluded due to receiving a loop diuretic or aldosterone antagonist alone or in combination on the index date, giving a total analysis population of 59 867. The mean age \pm SD of patients was 70.0 ± 11.9 years, and patients were prescribed a mean of 1.9 ± 1.0 oral antihypertensive agents. The most common comorbidities were dyslipidemia (56.8%) and heart diseases (52.0%; Table 1). Overall, 58.6% of patients were prescribed two or more antihypertensive agents, and the most frequently prescribed classes of agent were CCB and ARB with rates of approximately 35%.^{4,12}

Patients who were prescribed a FDC of a CCB + an ARB or an ARB + a diuretic tended to be younger, were more likely to be male and less likely to be hospitalized than those who were prescribed multi-pill combinations (Table S1). Among patients who were prescribed an ARB + a diuretic, FDC patients had a numerically higher prevalence of diabetes (26.2% vs 19.2%) and dyslipidemia (61.2% vs 53.6%), and a lower prevalence of kidney disease (4.2% vs 8.6%) and osteoporosis (6.5% vs 12.6%) than multi-pill patients.

The frequency of use of a CCB + an ARB FDC or an ARB + a diuretic FDC were stratified according to the total number of antihypertensive drugs prescribed (Fig. 1). Overall (all patients who were prescribed two or more antihypertensive agents), a CCB + an ARB FDC (14.0%) were more frequently prescribed for patients with hypertension than an ARB + a diuretic FDC (9.1%). As the number of concomitant antihypertensive agents used increased, the prescription rate of ARB + diuretic FDC increased, whereas there was a trend toward a decrease in the prescription rate of a CCB + an ARB FDC (Fig. 1). This trend for FDC prescription rates was the same regardless of age when analyzed according to patients aged ≤ 75 years (Fig. 2a) and patients aged ≥ 75 years (Fig. 2b). However, for patients aged ≥ 75 years, a lower proportion of FDC (20.2%) were used compared with patients aged < 75 years

Table 1 Patient baseline characteristics

Background factor	Overall population		Age < 75 years		Age ≥ 75 years		P-value (age <75 years vs ≥75 years) [†]
	(n = 59 867)		(n = 37 015)		(n = 22 852)		
Age distribution, n (%)							
20–44 years	1872	3.1%	1872	5.1%	0	0.0%	
45–54 years	4465	7.5%	4465	12.1%	0	0.0%	
55–64 years	10 868	18.2%	10 868	29.4%	0	0.0%	
65–74 years	19 810	33.1%	19 810	53.5%	0	0.0%	
>75 years	22 852	38.2%	0	0.0%	22 852	100.0%	
Sex, n (%)							
Male	34 044	56.9%	22 703	61.3%	11 341	49.6%	<0.001
Comorbidities [‡] , n (%)							
Diabetes	14 548	24.3%	9506	25.7%	5042	22.1%	<0.001
Dyslipidemia	34 001	56.8%	20 967	56.6%	13 034	57.0%	0.347
Gout/hyperuricemia	10 886	18.2%	6612	17.9%	4274	18.7%	0.010
Kidney disease	5966	10.0%	3252	8.8%	2714	11.9%	<0.001
Heart disease accompanied by hospitalization	31 106	52.0%	16 978	45.9%	14 128	61.8%	<0.001
Cerebrovascular disease accompanied by hospitalization	11 596	19.4%	6133	16.6%	5463	23.9%	<0.001
Osteoporosis	6312	10.5%	2883	7.8%	3429	15.0%	<0.001
Hospitalization, n (%)							
Patients with hospitalization	11 403	19.1%	5922	16.0%	5481	24.0%	<0.001
No. antihypertensive agents prescribed, n (%)							
1 agent	24 786	41.4%	16 296	44.0%	8490	37.2%	<0.001
2 agents	20 499	34.2%	12 491	33.7%	8008	35.0%	
3 agents	9879	16.5%	5627	15.2%	4252	18.6%	
4 agents	3662	6.1%	2032	5.5%	1630	7.1%	
≥5 agents	1041	1.7%	569	1.5%	472	2.1%	

[†]Calculated using Pearson's χ^2 -test. [‡]Definitions of comorbidities (previous observation period): diabetes, diagnosis (International Classification of Diseases [ICD]-10; E10, E11) + prescription of diabetes remedy (Anatomical Therapeutic Chemical code); dyslipidemia, diagnosis (ICD-10; E78); gout/hyperuricemia, diagnosis (ICD-10; E79, M10); kidney disease, diagnosis (ICD-10; I12, N08, N18, N19, N26, N28); heart disease, diagnosis (ICD-10; I20-25, I47-50, I51.7, I11); cerebrovascular disease, diagnosis (ICD-10; I60-63, I67-68, G45); osteoporosis, diagnosis (ICD-10; M80-82).

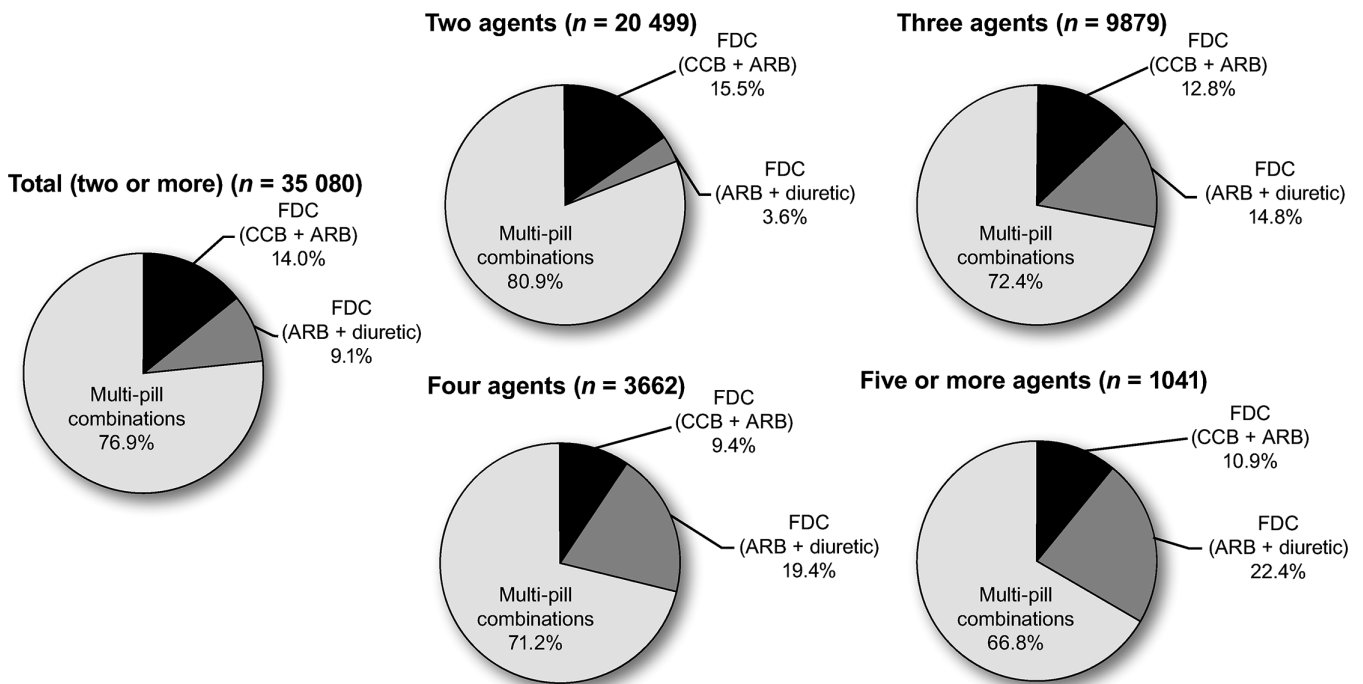


Figure 1 The frequency of fixed-dose combination use according to the number of antihypertensive agents prescribed. ARB, angiotensin II receptor inhibitor; CCB, calcium channel blocker; diuretic, thiazide diuretic; FDC, fixed-dose combination.

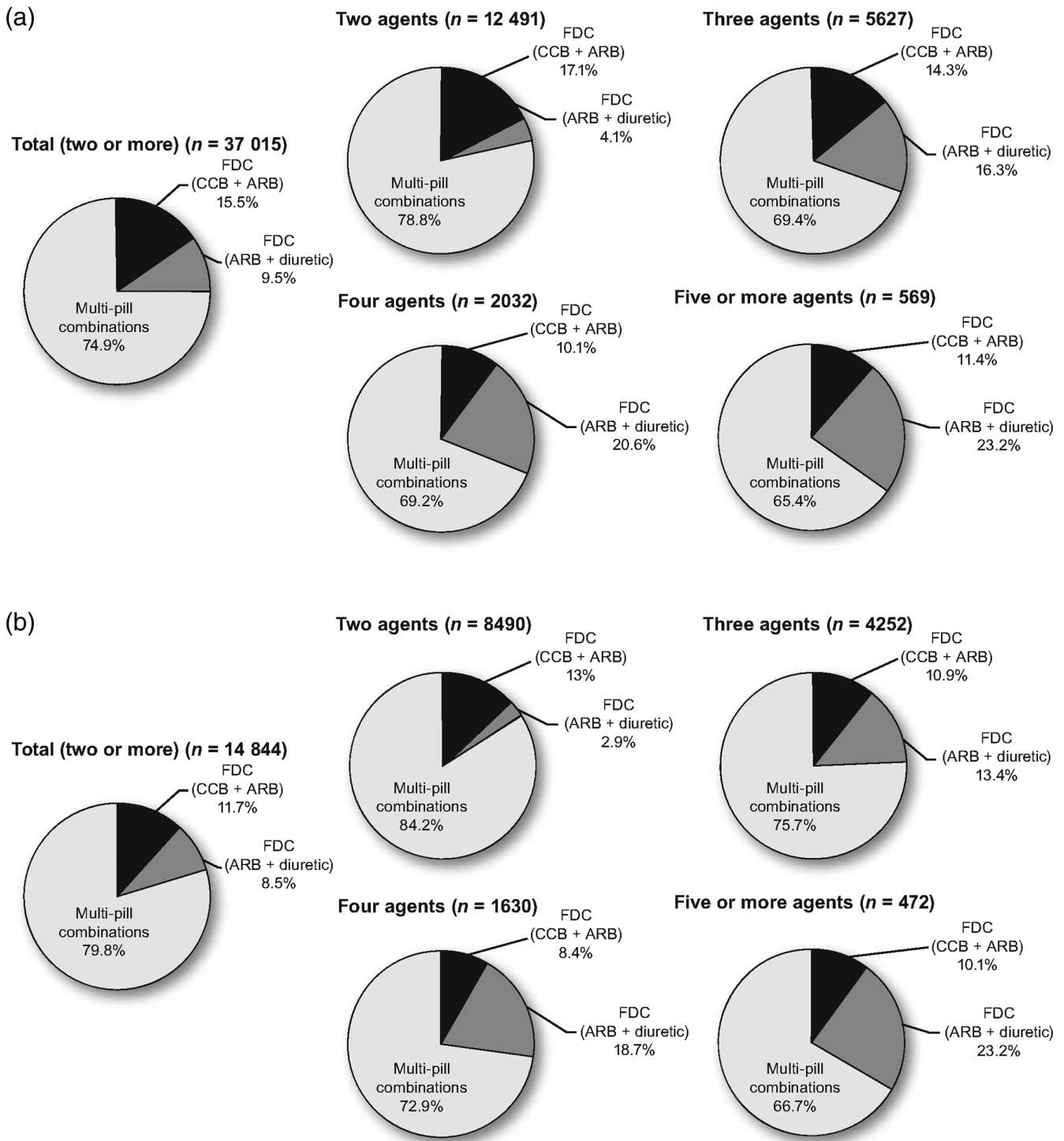


Figure 2 The frequency of fixed-dose combination use according to age and the number of agents prescribed: (a) <75 years and (b) ≥75 years. ARB, angiotensin II receptor inhibitor; CCB, calcium channel blocker; diuretic, thiazide diuretic; FDC, fixed-dose combination.

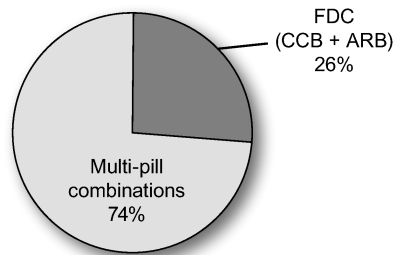
(25.0%). The presence of comorbidities (kidney disease, gout/hyperuricemia or diabetes) did not affect FDC prescription rates in patients aged <75 years (Fig. S1a). Diabetes also had no apparent impact on FDC utilization rates in patients aged ≥75 years (Fig. S1b). However, among older patients, the FDC prescription rate was numerically lower in patients with

gout/hyperuricemia (for the CCB ± ARB FDC) or kidney disease (for the CCB ± ARB and ARB ± diuretic FDC) than in the overall population.

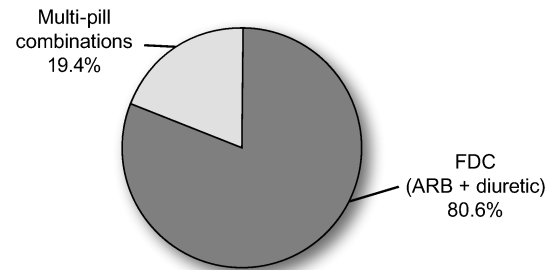
Next, we analyzed the proportion of FDC used by agent type and according to whether two or three agents were prescribed (Fig. 3). Overall, 12 222 patients were prescribed a CCB + an ARB

Two agents prescribed

CCB + ARB (n = 12 222)

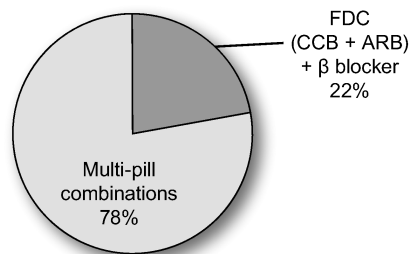


ARB + diuretic (n = 922)



Three agents prescribed

CCB + ARB + β -blocker (n = 2790)



CCB + ARB + diuretic (n = 2067)

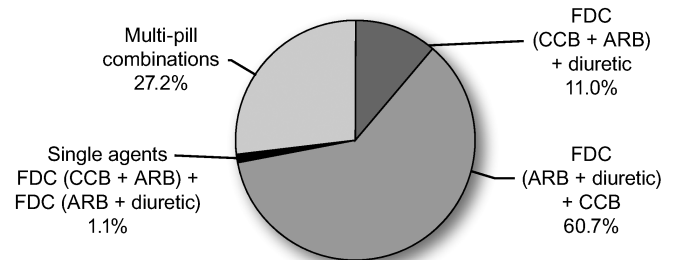


Figure 3 The frequency of fixed-dose combination use by drug type and according to the number of drugs prescribed. ARB, angiotensin II receptor inhibitor; CCB, calcium channel blocker; diuretic, thiazide diuretic; FDC, fixed-dose combination.

and, of these patients, 26.0% received these drugs as a FDC, with the remaining patients receiving multi-pill combinations. In contrast, 922 patients were prescribed an ARB + a thiazide diuretic, and 80.6% of these patients received these medications as a FDC (Fig. 3). Similar to the overall population, 22.9% of patients aged ≥ 75 years received a CCB + an ARB as a FDC with the remaining patients receiving multi-pill combinations. Additionally, 74.5% of patients aged ≥ 75 years were prescribed an ARB + a thiazide diuretic as a FDC (data not shown). When a CCB + an ARB were prescribed as part of a three-agent combination, the CCB + ARB FDC was used in 22.0% of patients in combination with a β -blocker, and in 11.0% in combination with a thiazide diuretic. In our previous analysis, of all patients who received three-agent combinations, approximately 50% received a CCB + an ARB + a β -blocker or a CCB + an ARB + a thiazide diuretic.¹² However, in the current study, the ARB + diuretic FDC was used in 60.7% of patients when prescribed in the three-agent combination with CCB (Fig. 3). Finally, we analyzed the dose distribution of these antihypertensive agent combinations, except for β -blockers, which were not divided according to dose (Fig. 4). Most dose concentrations were classified as medium for CCB and ARB agents, as low for diuretics, and there were no combinations of high and very low dosages (Fig. 4).

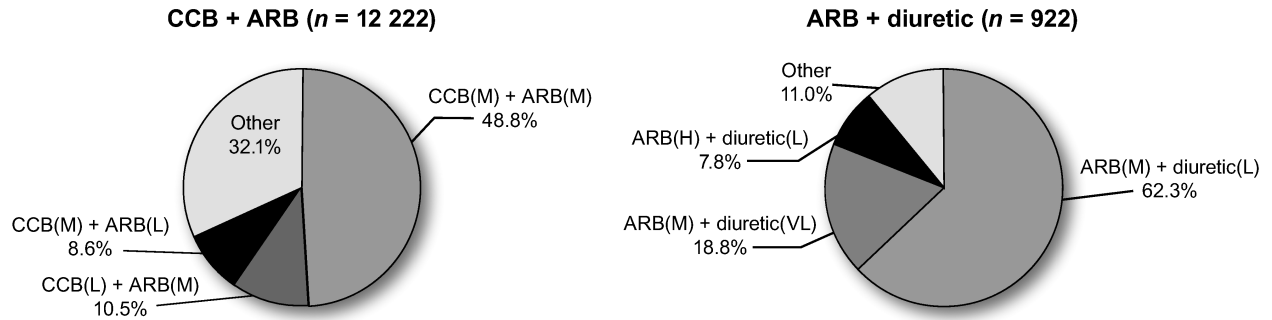
Discussion

We carried out a retrospective analysis of patients with hypertension to analyze the real-world prescription status of FDC of antihypertensive agents classified by class, age and according to agent combinations using the data collected from a nationwide medical database of acute hospitals in Japan. In contrast to

European recommendations, antihypertensive combinations are only recommended in Japan if single-agent treatment does not provide adequate blood pressure control (for hypertension without compelling indications).^{2,5} The present analyses show that the real-world use of FDC varies depending on the desired combination and number of agents prescribed. Overall, the majority of patients in the present study were prescribed one or two antihypertensive agents, and the most frequently prescribed classes of agents were CCB and ARB,¹² consistent with similar analyses carried out in Japan using pharmacy prescription data.¹⁵ We found that the prescription rate of CCB + ARB FDC was relatively low overall, and did not increase depending on the total number of antihypertensive agents prescribed. In contrast, the prescription rate of ARB + diuretic FDC increased as the number of concomitant antihypertensive agents used increased. This is in contrast to the pharmacy prescription data study in which the proportions increased for both FDC.¹⁵ In the same study, the prescription rate of a CCB + an ARB FDC was also higher than we found in the present study, although the frequencies of an ARB + a diuretic prescriptions were similar.¹⁵ This might be due to differences in sampling of the databases (local non-acute hospitals *vs* national acute hospitals). Although some differences in comorbidities were noted among patients who were prescribed an ARB \pm a diuretic FDC or multi-pill combination, small sample sizes in these subgroups prevented meaningful comparisons, and further investigation of these findings is required.

The results for the changes in proportion of FDC were similar regardless of age; however, for patients aged ≥ 75 years, a lower overall proportion of FDC was used compared with patients aged < 75 years. This might be because older patients may require more frequent adjustment of dosage; however, this cannot be verified,

Two agents prescribed



Three agents prescribed

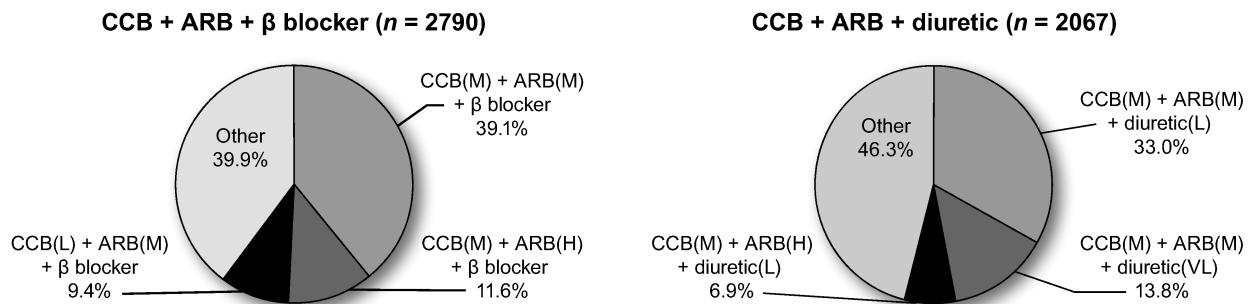


Figure 4 The dose distribution of antihypertensive drugs. ARB, angiotensin II receptor inhibitor; CCB, calcium channel blocker; diuretic, thiazide diuretic; H, high; L, low; M, middle; VL, very low.

as the database does not include blood pressure data. Older patients with kidney disease also had a lower utilization rate of the CCB \pm ARB and ARB \pm diuretic FDC, which might reflect a requirement for antihypertensive dose adjustment to control blood pressure and improve renal function, including a need to increase the diuretic dose as kidney function worsens to achieve a natriuretic response.

When analyzing the proportion of typical two- or three-agent combination therapies that were prescribed as FDC, the use of a CCB + an ARB FDC was much lower than an ARB + a diuretic FDC. This might suggest that dose adjustments are often required for the CCB + ARB combination, as, with FDC, the concentrations of the individual components cannot be altered. Indeed, we found that the 62.3% of doses used (regardless of whether it was a multi-pill combination or a FDC) were medium for ARB and low for diuretics, which is reflected in the fact that a high proportion of patients were able to be prescribed a FDC of an ARB and a diuretic (80.6%).

As well as not being able to make dose adjustments when using FDC, another disadvantage might be cost when compared with the use of generic multi-pill combinations. In a retrospective study carried out in the USA, investigating Medicare spending on brand-name combination medications *vs* their generic constituents, it was found that medical expenses were higher for brand-name combinations compared with generic constituents.¹⁶ A similar study in Japan would be required to confirm whether the findings are applicable. Another disadvantage to FDC is the fact that the agents are taken simultaneously, which means that chronotherapy with a particular agent cannot be used. Studies have shown that bedtime hypertension chronotherapy of one or more antihypertensive agent is more effective at controlling sleeping blood pressure, and reduces the overall and major

cardiovascular disease events.¹⁷ We cannot assess whether chronotherapy was carried out with either multi-pill combinations or the FDC, as data on the timing of medication were not collected. One of the main advantages of FDC is that they can improve adherence for patients who need to take multiple agents to control their hypertension, or as a result of comorbidities.^{18,19} However, a recent study on adherence in Japan using a claims database found that there was no benefit in terms of improved adherence when comparing multi-pill combinations versus FDC, with the exception of the CCB + ARB FDC.²⁰ As such, it might be necessary to carefully select treatments based on individual patient suitability for multi-pill combinations versus FDC. Fixed-dose triplet combination therapy was not included in the present study, as it has only been in use since 2017. Recently, antihypertensive fixed-dose triple combination therapy was shown to be well tolerated in Japan; and in Sri Lanka, it was reported to result in an increased proportion of patients achieving their target blood pressure goal versus usual care.^{16,21,22} It might be necessary to investigate fixed-dose triplet combination therapy differences in hypertension treatment in future.

There were several limitations to the present retrospective study. No data on blood pressure were collected, making it impossible to assess a patient's clinical status and treatment effects. There was also no information on when the agents were taken during the day, and it can be difficult to track patient data if they are transferred between healthcare providers. Additionally, as the MDV database only covers approximately 20% of all Diagnostic Procedure Combination hospitals, the results might not be representative of the overall Japanese hypertensive patient population, and so cannot be generalized. Given the target selection period of April 2014 to March 2015, the results might also not reflect current prescription patterns of FDC. Finally, some patients might be prescribed antihypertensive agents

for reasons other than hypertension, and the relatively high incidence of heart disease in the patients sampled might have influenced the prescribing patterns.^{4,12}

Results from this retrospective analysis show that the real-world use of FDC varies according to the combination of agent classes and the total number of agents prescribed, and that the latter was similar regardless of age. The data presented here along with previous analyses from this database (including adherence findings) might help in selecting optimal treatments for individual patients, including their suitability for multi-pill combinations versus FDC, and should be considered alongside clinical and health economic data.^{4,12,20}

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Disclosure statement

TI was formerly employed by Takeda Pharmaceutical Company. AO and NN are employees of Takeda Pharmaceutical Company. TT received speech fees from MSD, Sanwa Chemical Research Institute, Shionogi Pharmaceutical, Sumitomo Dainippon Pharmaceutical, Takeda Pharmaceutical, Teijin Pharma, Terumo Corporation and Pfizer.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1 Frequency of fixed-dose combination use according to age and number of antihypertensive agents prescribed to patients with kidney disease, gout/hyperuricemia and diabetes, and overall: (a) aged <75 years and (b) ≥75 years. ARB, angiotensin II receptor inhibitor; CCB, calcium channel blocker; diuretic, thiazide diuretic; FDC, fixed-dose combination.

Table S1 Patient baseline characteristics according to drug combinations of interest.

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