


# Influence of Hospital Formularies on Outpatient Prescribing Practices: Analysis of the Introduction of a Local Formulary: A Single-Center, 2-Year Follow-Up, Retrospective Cohort Study of a Local Formulary in Japan

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## Abstract

**Purpose:** The impact of a hospital formulary was evaluated to provide a guide for the establishment of local formularies to optimize patient care and healthcare costs.

**Methods:** A formulary was introduced by formulary pharmacists of the Toda Medical Group for suggesting recommended medicines to physicians based on the medication history. Patients who were hospitalized in the rehabilitation ward of the Niiza Hospital and prescribed medicines according to the formulary introduced between April 2017 and March 2018 were included and followed-up for six months.

**Results:** Of the 183 patients screened, 154 patients were enrolled as the formulary's introduction patients (76 males/78 females, median age 78 years); 92% of these patients received formulary-proposed prescriptions at the specified timepoints; and 19 patients re-consulted at the Niiza Hospital after discharge and continued the same formulary medicines. The proposed acceptance rate by physicians was 100%. Most changes suggested introduced generic formulations. The doses were equivalent for all pharmacological classes with the exception of medicines that interfere with the renin–angiotensin system, which fell from 10.7 to 7.2 mg ( $P < .0001$ ). Overall daily medication costs fell at discharge compared to admission (38.5 vs. 94.6 yen per patient, respectively,  $P < .0001$ ). This was valid for all pharmacological classes except for calcium channel blockers.

**Conclusion:** Hospital formulary-prescribed medications continued after discharge and promoted significant decreases in costs associated with outpatient prescriptions. Introducing a hospital formulary provides a basis for the introduction of local formularies and contributes to the reduction of local healthcare costs.

## Keywords

hospital formulary, local formulary, appropriate pharmaceutical care, Japan, healthcare costs

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## Highlights

### What Do We Already Know About This Topic?

Formularies, which are guidelines for effective, safe, and the economical use of medicines, are considered a tool for the appropriate use of medication.

### How Does Your Research Contribute to the Field?

Hospital formulary-prescribed medicines were continued after discharge, and can contribute to the reduction of local healthcare costs in countries with universal healthcare coverage and in countries that plan to introduce local formularies by similar approaches.

### What Are Your Research's Implications Towards Theory, Practice, or Policy?

This study validates a strategy to standardize medication prescription based on the local needs of the community and could decrease the burden on the national healthcare system while also providing improved patient care.

## Introduction

Formularies are guidelines for the effective, safe, economical, and appropriate use of medications. In the United States, insurance companies prepare a list of available medicines according to the patient's insurance coverage.<sup>1</sup> In Europe, formulary systems are linked to guidelines, protocols, and treatment pathways based on the best available evidence, including patient outcomes and pharmacoeconomic assessments.<sup>2-5</sup>

In Japan, the universal health insurance system allows free prescription of approved medicines according to the patient's insurance plan. Japan's medical system covers all citizens with public medical insurance and allows them to freely choose their medical institutions.<sup>6</sup> It is based on a social insurance system, while public funds are used to maintain universal health coverage. France is a country that has an insurance system similar to that of Japan.<sup>7,8</sup> In the United Kingdom, outpatient co-payment is free of charge in principle, which is different from Japan.<sup>7</sup> Sweden has also introduced a tax-based public health insurance service,<sup>9</sup> and the amount of co-payment for outpatients is decided independently by the local government. The U.S. insurance system is limited to public healthcare, with Medicare provided by the federal government for seniors 65 and older and the disabled, and Medicaid provided by state governments for those with low incomes. The only way for working-age people to obtain medical coverage is to purchase medical insurance from private insurance companies.

Considering cost optimization with the appropriate use of medicines, Japan falls behind other countries with formularies. As Japanese patients sometimes request cost-conscious medications, a formulary has been established in each hospital. France, which has a social security system similar to Japan's, has established a hospital formulary.<sup>5</sup> In countries that have a tax system, such as the United Kingdom or Sweden, national formularies or local formularies have been introduced. Local formularies are also more advanced in the U.S., where hospitals

cooperate with each other to set the same formulary.<sup>10</sup> In countries with national and local formularies, a national or local government system is used to coordinate the setting of the amount. The impetus in Europe and the United States is toward the creation of national formularies, similar to a universal healthcare system.<sup>1</sup> Such Japanese universal healthcare system formularies are useful for the development of the medical industry.

In Japan, the expectation of formularies had been noted since 2000 in research studies funded by the Ministry of Health, Labor and Welfare.<sup>11</sup> In 2017, a paper on the formulary system was published.<sup>12</sup> After that, reports continued to demonstrate that hospital formularies showed positive effects toward the appropriate use of drugs and a decrease in the number of adverse drug reactions.<sup>13-17</sup> Regional collaboration of formularies is also expected to reduce drug costs. Although local formularies began in some regions in 2019, a study discussing their impact on regional healthcare published in 2021 also shows expectations for their introduction.<sup>18</sup>

In Japan, hospitals are available for providing both inpatient care and outpatient prescriptions. Hospitals are classified according to the scale of their functions. Small- or medium-sized hospitals or clinics are often in charge of local medical care. Some chronic care hospitals have a community-based integrated care ward, which comprehensively ensures the provision of healthcare, nursing care, prevention, housing, and livelihood support to care for patients when they are discharged. Other hospitals have a rehabilitation ward for care after the acute phase. The Niiza Hospital has both of these facilities.

Patients are often discharged from acute-care hospitals to their homes via chronic care hospitals in Japan.<sup>19</sup> Depending on the medicines available at each hospital, it is sometimes necessary for a patient to change medications to other agents of the same class. Furthermore, when patients visit local clinics after discharge, clinic physicians can freely choose medications from among those that are approved in Japan. However, long-term treatment should be aimed at providing seamless medical care with a view to ensure treatment continuity.<sup>20</sup> To

achieve seamless, safe, effective, and economical community-based medical care, with only minor changes in the medicines taken after each hospital transfer, it is important to introduce common formularies optimized for the community (local formulary) and to provide community-based medical care.

Here, the impact of introducing a hospital-based formulary (hospital formulary) on Japan’s universal health insurance system was evaluated. The medications prescribed after hospital discharges were investigated by clarifying the impact of the hospital formulary on outpatient prescriptions and treatment cost. This study is expected to provide a model for the establishment of local formularies in Japan.

### Materials and Methods

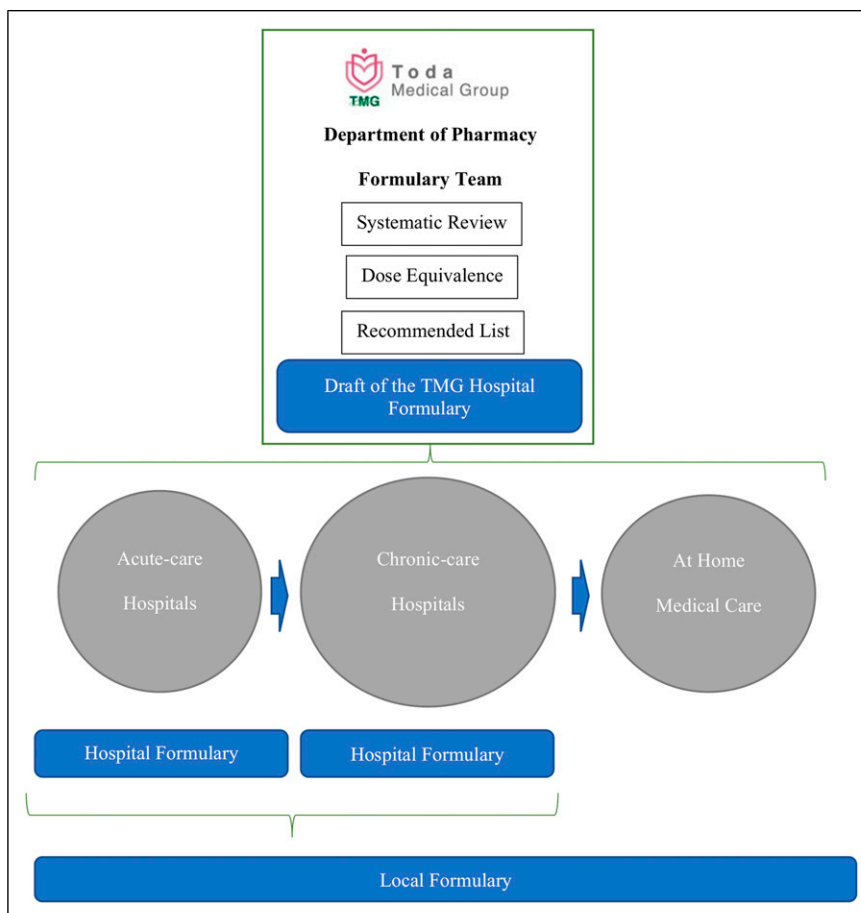
This retrospective cohort study focused on hospitalized patients who were admitted to the convalescent rehabilitation ward of the Niiza Hospital.

### Setting

Japan’s total population is 125.3 million as of 2021.<sup>21</sup> Total hospital beds per 1000 population is 12.8, which is the highest among Organisation for Economic Co-operation and Development countries.<sup>22</sup> In 2021, Japan had a total of 963 309 general hospital beds and 291 651 convalescent hospital beds.<sup>23</sup> Of those, the number of beds located among the four capital city prefectures are 213 489 and 57 966 beds, respectively.<sup>23</sup> Toda Medical Group (TMG) operates mainly in the four capital cities, and accounts for 3816 beds (1.8%) and 1170 beds (2%), respectively.<sup>24</sup>

### Formulary System

Figure 1 comprises a schematic of the system for constructing the formulary introduced by the TMG. Among 350 TMG pharmacists, those with experience in medicine information,



**Figure 1.** Hospital formularies and social network of the Toda Medical Group (TMG) in Japan. The Formulary Team of the Toda Medical Group Pharmaceutical Department conducts a systematic review of each medicine’s effect, sets equivalent doses, ranks recommendations, and prepares a draft of a formulary that can be applied at the TMG hospitals. Based on the draft formularies, each hospital constructs formularies according to the patient population of the hospital. As patients move from acute-care hospitals to chronic care hospitals, medicines used may change due to alterations in the patient’s conditions. It is possible to implement a standardized treatment by using the same draft formularies. As physicians choose medicines based on the hospital formulary, it is expected that this will lead to the establishment of a local formulary in the future.

infectious diseases, psychiatry, and community medicine, among others, were recruited to form a 10-member team to operate the formulary (formulary pharmacists). These formulary pharmacists created a draft list of medications. After the draft was approved by the Pharmaceutical Affairs Council of each hospital, the formulary was introduced. The Pharmaceutical Affairs Council consists of the hospital director, the chairman of the Pharmaceutical Affairs Review Committee (a physician), eight other physicians, the administrative director, the head of the nursing department, one head pharmacist, and two clerks in Niiza Hospital. Formulary pharmacists conducted systematic reviews or used the Cochrane Database of Systematic Reviews (CDSR) to collect comprehensive information, which was then used to objectively evaluate medicines and to create priorities for medication adoptions.<sup>25</sup> Thereafter, pharmacists at each TMG hospital introduced the system based on the formulary drafts (Table S1). Except when a high priority medicine in the formulary draft was selected due to patient differences, it was possible to provide systematic and appropriate medical care that factored in the cost based on the patients' wishes and the hospital's management practices, while ensuring effectiveness and safety. Since international comparisons are commonly used for comparative studies of drugs for efficacy and safety, the results of international comparisons are also used as evidence for formulary preparation. In terms of drug dose and genetic characteristics, it is sometimes difficult to extrapolate directly from trials that have not been conducted in Asian/Japanese populations. If the efficacy and safety is dose-dependent, we evaluate it from the viewpoint of clinical pharmacokinetics, that is, if the blood concentration is the same, the efficacy and safety are the same. Furthermore, while international comparisons are used at the approval review stage, long-term safety studies are also conducted in Japan.

Based on the formulary, the pharmacists of each TMG hospital could propose alternative medicines to physicians in cases when different medications had been previously prescribed to patients. In the Japanese healthcare system, patients can visit any medical institution of their choice. If the pharmacists decide that a change in medication is necessary, the pharmacist proposes a formulary medicine and indicates an equivalent dose to the physician. Then, the proposed medicines are confirmed by the physician, and the physicians prescribe the medicines. After the approval of the proposal, the pharmacists and nurses coordinate to monitor the patient's condition during hospitalization (mean duration 90 days)<sup>12</sup> and share the information with the medical community upon discharge.

### Data Source

The authors used the data on the medicines used at the time of admission for hospitalized patients who were admitted to the convalescent rehabilitation ward of the Niiza Hospital

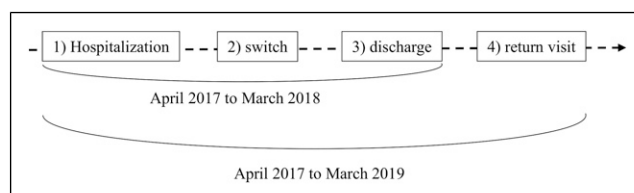
between April 2017 and March 2018. Outpatient prescription data from April 2017 to March 2019 was utilized as follow-up data (Figure 2). Data was collected using a system for drug management rather than electronic medical records.

### Cohort Study

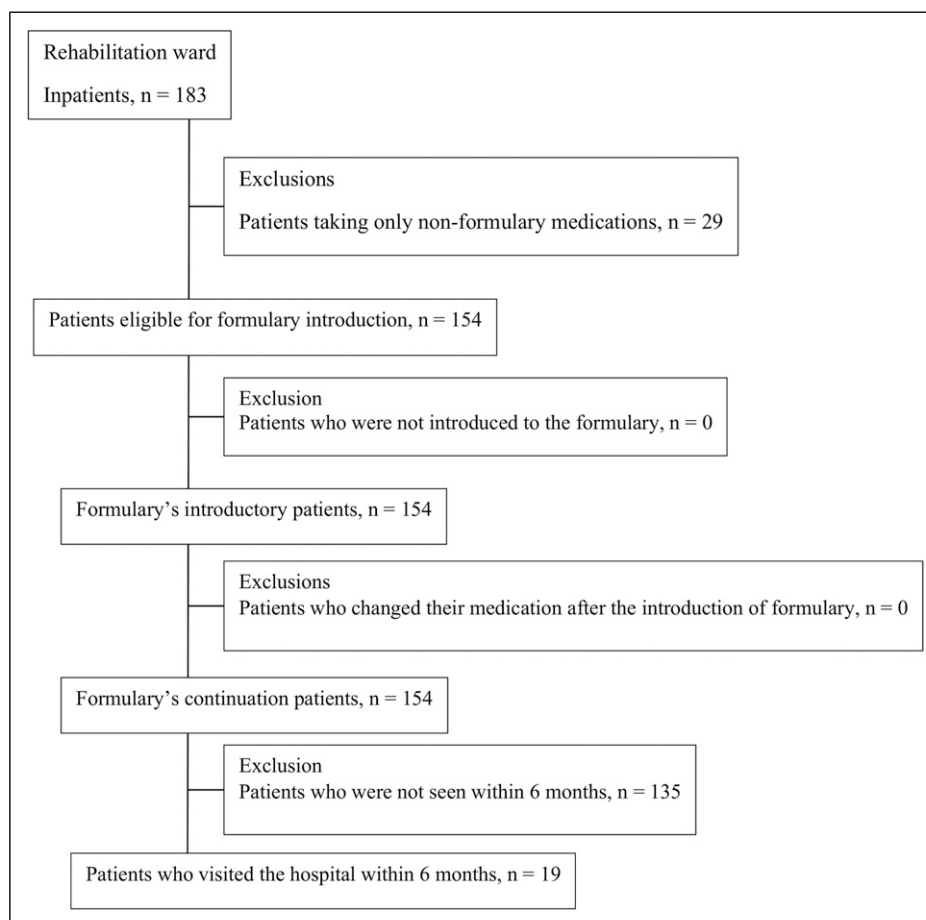
Patients hospitalized in the rehabilitation ward and prescribed medicines from the introduced formularies were selected for participation in this study. Those patients whose medications were changed based on the formularies were selected and, among them, those whose prescriptions remained unchanged at the time of discharge were defined as the formulary's introductory patients ( $n = 154$ ). The patients who returned to our hospital for outpatient visits within six months of receiving a prescription based on the formulary and those who continued to take the formulary-specified medications were defined as the formulary's continuation patients (Figure 3). Patients already taking the formulary-specified medicines at the time of admission were also included, as were patients newly introduced to the formulary-specified medications or those who discontinued the formulary-specified medications during the study period.

### Variables

The generic names and daily doses of medications were obtained. The formulary classes (recommended medications) that had been introduced in the Niiza Hospital until March 2017 included angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers (of the renin-angiotensin system [RAS]s; enalapril; or telmisartan if enalapril was not tolerated), proton pump inhibitors (PPIs; lansoprazole), xanthine oxidoreductase inhibitors (XORis; allopurinol; or febuxostat if allopurinol was not tolerated), 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors; atorvastatin), calcium channel blockers (CCBs; amlodipine or nifedipine extended-release tablets [twice-daily formulation]), and an  $\alpha$ -glucosidase inhibitor (AGI; voglibose).



**Figure 2.** Data points when medications were identified during data source creation and study period. The following points were identified: (1) At the time of hospitalization, alternative medicines were proposed for local prescriptions, (2) Whenever there were prescription changes, (3) At hospital discharge, (4) At return visits after discharge.



**Figure 3.** Flowchart of the study participant selection and evaluation timepoints.

### Statistical Analysis

The number of patients introduced to the formularies, the name of the formulary medication, and the average dosage were descriptively analyzed and dose equivalences of each medicine were proposed (Table 1).<sup>25-39</sup> Then, the medication dosages at the time of admission and discharge were converted to the recommended equivalent doses in the formulary and compared. Dose equivalences were established based on a systematic review and were determined on the basis of the corresponding doses established in trials, wherein each medicine was found to be non-inferior. For medicines without data from non-inferiority studies, clinical equivalence was determined by evaluating the adequacy of margins and the effect sizes based on non-inferiority studies that were conducted for other medicines with similar endpoints.

Medication costs were calculated based on the following factors: the Japanese National Health Insurance (NHI) price of the medications taken at the time of hospital admission, medicines listed at discharge, and those prescribed at the revisit to the Niiza Hospital after discharge. The total daily medication costs were defined as the sum of the 753

prescriptions taken by the patients (n=154). In fixed-dose combinations of RAS and CCBs, RAS cost was derived by calculating the NHI price of the combination medicine minus the lowest NHI price of the CCB generics. The data were converted at the currency rate of 104.76 JPY to \$1.00 (October 23, 2020) and listed along with the value in Japanese yen. The Wilcoxon signed-rank test was used to compare the dosages and medication costs. The significance level was set at  $P < .05$ . In this study, we did not conduct a comparative analysis between the formulary introduction group and the non-introduction group, because we assumed an imbalance between the number of two groups based on previous studies and because it is difficult to secure the number of patients to conduct a non-inferiority study.

### Results

Of the 183 admitted patients, 154 (76 males/78 females, median age 78 years [25th and 75th percentile: 69, 85], median length of stay 89 days [64, 159]) were eligible for registration in the formularies and their medications were prescribed according to the formulary (Figure 3).



**Table 1.** Dose equivalence of the medications that were proposed as substitutes by the hospital formulary.

Agents	Generic name	Dose equivalence				
		1	2	3	4	5
<b>Renin-angiotensin system (mg)</b>						
	Enalapril <sup>a</sup>	2.5	5	10		
	Imidapril	2.5	5	10		
	Perindopril		2	4	8	
	Azilsartan		10	20	40	
	Candesartan		4	8		
	Irbesartan		50	100	200	
	Losartan		25	50	100	
	Olmesartan	5	10	20	40	
	Telmisartan	10	20	40	80	
	Valsartan	20	40	80	160	
<b>HMG-CoA reductase inhibitors (mg)</b>						
	Atorvastatin <sup>a</sup>			5	10	20
	Fluvastatin	20	30	60		
	Pitavastatin			1	2	4
	Pravastatin	5	10	20		
	Rosuvastatin			2.5	5	10
<b>Calcium channel blockers (mg)</b>						
	Amlodipine <sup>a</sup>	2.5	5	7.5	10	
	Benidipine	2	4	8		
	Cilnidipine	5		10	20 <sup>b</sup>	
	Nifedipine, sustained-release (once a day)	10	20	40		
	Nifedipine, sustained-release (twice a day)	10	20	40	80 <sup>b</sup>	
<b>Xanthine oxidoreductase inhibitors (mg)</b>						
	Allopurinol <sup>a</sup>	50	100	200		
	Febuxostat	10	20	40		
<b>Proton pump inhibitors (mg)</b>						
	Esomeprazole		10	20		
	Lansoprazole <sup>a</sup>		15	30		
	Omeprazole		10	20	40	
	Rabeprazole	5	10	20	40	
	Vonoprazan		10	20		
<b><math>\alpha</math>-glucosidase inhibitors (mg)</b>						
	Voglibose <sup>a</sup>	0.6	0.6	0.9		
	Miglitol	75	100	150		

<sup>a</sup>Formulary-recommended medicines in each region.<sup>b</sup>Off-label dosage in Japan.

Of the 154 cases (324 prescriptions), 297 (92%) and 27 (8%) prescriptions were formulary-prescribed at the time when alternative medicines were proposed or when new medicines were introduced during hospitalization, respectively.

The proposal acceptance rate by physicians was 100%. None of the proposed medications was switched during hospitalization. Of the 154 patients prescribed formulary-recommended medicines during hospitalization, 19 patients re-consulted at the Niiza Hospital within six months, and the others followed-up at other local hospitals or clinics. The formulary-recommended medications prescribed to these 19 patients continued being used.

The medicine changes based on the formularies are shown in Table 2. Of the 154 patients, 67 patients were taking RAS at the time of admission, and 46/67 patients (69%) were taking brand-name ARBs. Forty patients switched to enalapril and 35 patients to imidapril, and both of these were generic formulations. Forty-six patients were taking HMG-CoA reductase inhibitors at admission, and 28 (61%) of these were taking brand-name medicines. By discharge, 22 patients were switched to the atorvastatin generic. Of the 80 patients taking CCBs at admission, 14 (18%) were taking brand-name medicines. By discharge, 74 patients were switched to the amlodipine generic. Eleven patients were taking XOIs at admission, and eight (73%) of these were taking brand-name medicines. By discharge, 15 patients were switched to the allopurinol generic, and one patient continued to receive the original febuxostat. Eighty-one patients were taking PPIs at the time of admission; of these, 24 (30%) were taking brand-name medicines. By discharge, 87 patients were switched to the lansoprazole generic. Seven patients were taking AGIs at admission, and two (29%) of these were taking brand-name medicines. By discharge, eight patients were switched to the voglibose generic, one of which was a new prescription.

The changes of dose equivalents for formulary medicines from hospitalization to discharge are shown in Table 2. For RAS, the dose of the enalapril equivalent changed from (mean  $\pm$  standard deviation)  $10.7 \pm 5.0$  to  $7.2 \pm 2.6$  mg ( $P < .001$ ). For the other pharmacological classes, there was no significant change in dose equivalents. For HMG-CoA reductase inhibitors, the doses of the atorvastatin equivalent were  $7.8 \pm 3.9$  and  $7.0 \pm 3.2$  mg ( $P = .124$ ), respectively, on hospitalization and discharge. For CCBs, the doses of the amlodipine equivalent were  $5.7 \pm 3.1$  and  $5.4 \pm 3.0$  mg ( $P = .442$ ). For XORis, the doses of the allopurinol equivalent were  $73.3 \pm 62.3$  and  $96.7 \pm 48.1$  mg ( $P = 0.086$ ). For PPIs, the doses of the lansoprazole equivalent were  $15.9 \pm 7.0$  and  $15.2 \pm 3.6$  mg ( $P = .408$ ). For the AGI, the doses of the voglibose equivalent were  $.5 \pm .2$  and  $.6 \pm .1$  mg ( $P = .317$ ).

Table 3 summarizes the total daily medication costs. At the time of discharge, the overall cost was 5930.6 yen ( $n = 154$ ; 38.5 yen per patient), whereas, at the time of admission, the cost was 14 567.5 yen ( $n = 154$ ; 94.6 yen per patient); that is, the cost at admission was 8636.9 yen [ $\$82.4$ ] (56.1 yen per patient) higher than at discharge ( $P < .001$ ). For the classes such as RAS, HMG-CoA reductase inhibitors, XORis, PPIs, and AGI, the costs at discharge were lower than at admission,

**Table 2.** Number of patients and doses taken at the time of admission and at discharge.

Agents	Generic name	Hospital admission				Hospital discharge				P-value	
		Total, n	Brand, n	Daily dose, mean (SD) (mg)		Total, n	Brand, n	Daily dose, mean (SD) (mg)			
Renin-angiotensin system					10.7	(5.0) <sup>a</sup>			7.2	(2.6) <sup>a</sup>	<.001
<b>Angiotensin-converting enzyme inhibitors</b>											
	Enalapril	5	0	8.0	(2.7)	40	0	7.8	(2.5)		
	Imidapril	1	0	5.0	(0)	35	0	6.5	(2.7)		
	Perindopril	1	0	4	(0)	0	0				
	None	4	0			0	0				
<b>Angiotensin II receptor blockers</b>											
	Azilsartan	11	11	21.8	(6.0)	0	0				
	Candesartan	4	1	5.0	(2.0)	0	0				
	Irbesartan	10	6	130	(48.3)	0	0				
	Losartan	2	0	75	(35.4)	0	0				
	Olmesartan	11	11	23.6	(11.2)	0	0				
	Telmisartan	24	16	48.3	(21.8)	0	0				
	Valsartan	2	1	80	(0)	0	0				
<b>HMG-CoA reductase inhibitors</b>											
	Atorvastatin	20	3	8.5	(3.7)	43	0	7.6	(2.5)		.124
	Fluvastatin	1	1	15	(0)	0	0				
	Pitavastatin	6	6	1.2	(.4)	0	0				
	Pravastatin	1	0	10	(0)	0	0				
	Rosuvastatin	18	18	4.4	(1.8)	0	0				
	None	1	0			4	0				
<b>Calcium channel blockers</b>											
	Amlodipine	58	10	6	(2.7)	71	0	5.5	(1.5)		.442
	Benidipine	1	1	2	(0)	0	0				
	Cilnidipine	3	2	10	(0)	0	0				
	Nifedipine, sustained-release (once a day)	7	1	50	(30)	0	0				
	Nifedipine, sustained-release (twice a day)	13	0	36.9	(14.4)	10	0				
	None	9	0			10	0				
<b>Xanthine oxidoreductase inhibitors</b>											
	Allopurinol	4	0	150	(57.7)	14	0	96.7	(48.1) <sup>a</sup>		.086
	Febuxostat	8	8	12.5	(4.6)	1	1	10	(0)		
	none	3	0			0	0				
<b>Proton pump inhibitors</b>											
	Esomeprazole	6	6	20	(0)	0	0	15.2	(3.6) <sup>a</sup>		.408
	Lansoprazole	54	0	16.4	(4.4)	86	0	15.5	(2.8)		
	Omeprazole	2	0	10	(0)	0	0				
	Rabeprazole	13	12	10.8	(2.8)	0	0				
	Vonoprazan	6	6	10	(0)	0	0				
	None	7	0			2	0				
<b>α-glucosidase inhibitors</b>											
	Voglibose	6	1	0.5	(.2) <sup>a</sup>	8	0	0.6	(.1) <sup>a</sup>		.317
	Miglitol	1	1	100	(0)	0	0	0.6	(.1)		
	None	1	0			0	0				

<sup>a</sup>Dose converted by the recommended medicine for each region (including the cases that received no medicines); SD standard deviation.

**Table 3.** Comparison of the total daily medication costs (n = 154 753 records).

Agents	Generic name	Hospital admission	Hospital discharge	Difference of medicine costs, JPY/d (\$/d)	P-value
		Total medicine costs, JPY/d (\$/d)	Total Medicine Costs, JPY/d (\$/d)		
Total		14 567.5 (139.1)	5930.6 (56.6)	-8636.9 (-82.4)	<.001
<b>Renin-angiotensin system</b>		6423.3 (61.3)	1650 (15.7)	-4773.4 (-45.6)	<.001
<b>Angiotensin-converting enzyme inhibitors</b>		149.7 (1.4)	1650 (15.7)	1500.3 (14.3)	
	Enalapril	80.8 (.8)	626.2 (6)	545.4 (5.2)	
	Imidapril	22.5 (.2)	1023.8 (9.8)	1001.3 (9.6)	
	Perindopril	46.4 (.4)	0 (0)	-46.4 (-.4)	
<b>Angiotensin II receptor blockers</b>		6273.6 (59.9)	0 (0)	-6273.6 (-59.9)	
	Azilsartan	1612.2 (15.4)	0 (0)	-1612.2 (-15.4)	
	Candesartan	181.7 (1.7)	0 (0)	-181.7 (-1.7)	
	Irbesartan	1188.7 (11.3)	0 (0)	-1188.7 (-11.3)	
	Losartan	67.6 (.6)	0 (0)	-67.6 (-.6)	
	Olmesartan	1128.1 (10.8)	0 (0)	-1128.1 (-10.8)	
	Telmisartan	1982.1 (18.9)	0 (0)	-1982.1 (-18.9)	
	Valsartan	113.2 (1.1)	0 (0)	-113.2 (-1.1)	
<b>HMG-CoA reductase inhibitors</b>		2447.6 (23.4)	646.7 (6.2)	-1800.9 (-17.2)	<.001
	Atorvastatin	477.9 (4.6)	646.7 (6.2)	168.8 (1.6)	
	Fluvastatin	38.3 (.4)	0 (0)	-38.3 (-.4)	
	Pitavastatin	339.9 (3.2)	0 (0)	-339.9 (-3.2)	
	Pravastatin	17.2 (.2)	0 (0)	-17.2 (-.2)	
	Rosuvastatin	1574.3 (15)	0 (0)	-1574.3 (-15)	
<b>Calcium channel blockers</b>		942.5 (9)	1066.8 (10.2)	124.3 (1.2)	.026
	Amlodipine	484.8 (4.6)	949.4 (9.1)	464.6 (4.4)	
	Benidipine	22.6 (.2)	0 (0)	-22.6 (-.2)	
	Cilnidipine	71.5 (.7)	0 (0)	-71.5 (-.7)	
	Nifedipine, sustained-release (once a day)	235 (2.2)	0 (0)	-235 (-2.2)	
	Nifedipine, sustained-release (twice a day)	128.6 (1.2)	117.4 (1.1)	-11.2 (-.1)	
<b>Xanthine oxidoreductase inhibitors</b>		316.7 (3)	137.4 (1.3)	-179.3 (-1.7)	.061
	Allopurinol	39 (.4)	105.3 (1)	66.3 (.6)	
	Febuxostat	277.7 (2.7)	32.1 (.3)	-245.6 (-2.3)	
<b>Proton pump inhibitors</b>		4187.8 (40)	2213.7 (21.1)	-1974.1 (-18.8)	<.001
	Esomeprazole	697.2 (6.7)	0 (0)	-697.2 (-6.7)	
	Lansoprazole	1405.4 (13.4)	2213.7 (21.1)	808.3 (7.7)	
	Omeprazole	47.6 (.5)	0 (0)	-47.6 (-.5)	
	Rabeprazole	1249.2 (11.9)	0 (0)	-1249.2 (-11.9)	
	Vonoprazan	788.4 (7.5)	0 (0)	-788.4 (-7.5)	
<b>α-glucosidase inhibitors</b>		336.4 (3.2)	250.7 (2.4)	-85.7 (-.8)	.655
	Voglibose	265.6 (2.5)	250.7 (2.4)	-14.9 (-.1)	
	Miglitol	70.8 (.7)	0 (0)	-70.8 (-.7)	

104.76 JPY=1\$ (2020/10/23).



whereas the cost of CCBs at discharge was higher than at admission.

## Discussion

We found that 89% (17/19) of patients continued to take medicines that were recommended based on the hospital formulary in cases wherein the patients revisited the same hospital. The maintenance rate of hospital formulary-recommended medication was 80%.<sup>12</sup> The adherence to the hospital formulary was therefore maintained when patients revisited the same hospital after discharge.

Here, the prescriptions for a proportion of patients who visited the same hospital were examined. Even in cases when the patients were discharged from the hospital and visited another hospital, when the patients were seen again one year later, and there was no change in the prescription contents; that is, the same medicines continued to be prescribed. If there was no change in the patient's condition and there was no need to change the prescription, then, as expected, the prescription that was proposed or changed based on the hospital formulary was maintained. The authors consider that the introduction of formularies in hospitals can be a precursor to the introduction of local formularies.

The introduction of the hospital formulary had an impact on outpatient prescriptions. As conversion of healthcare systems is difficult, integrating the method of introducing formularies in each country will be necessary. In countries with a tax system, such as the United Kingdom and Sweden, the ability of the national and local governments to determine the amount of co-payments for outpatients may have made the establishment of national or local formularies possible. In contrast, local formularies are available in the U.S., which has an insurance system limited to public healthcare. Hospitals cooperate with each other to set the same formulary.<sup>10</sup> The limitation in hospital-to-hospital formulary seems that it is assumed that non-participating hospitals will not follow the formulary. The reason why local formularies have been partially introduced even in such environments is that local physician decision-makers have been able to coordinate and modify their opinions with panel members. There are many medical institutions in Japan that provide outpatient as well as inpatient care. Introducing this system in hospitals will bring us one step closer to a local formulary in the future. France, a country with a similar medical system to Japan, has already introduced a hospital formulary. The two countries have also introduced a family doctor system. Based on the examples of countries that have successfully implemented local formularies, there needs to be a common consensus in the local districts. Local formularies will need to be coordinated and explained to the community, especially to family doctors, with the understanding that they can be modified if opinion of the doctors differs from recommendation of the Hospital formulary.

For the hospital formulary, the rate of prescription changes in response to pharmacists' suggestions was 100% in this

study. Japan has a universal health insurance system, which means that all approved medicines can be prescribed.<sup>40</sup> The high approval rate for evidence-based prescribing by physicians<sup>40</sup> implies that they approve the evidence-based suggestions made by pharmacists. This strategy has the potential to reduce the prescribing burden on physicians. In addition, 92% of the formulary medicines introduced were based on the identification of medicines available locally. The timing of suggestions for the appropriate use of medicines was important to introduce formulary medicines. Under these circumstances, all proposals based on the hospital formulary were approved and the medicines were switched after verifying the medications were available locally, indicating the hospital formulary was well managed.

Pharmacists are expected to take responsibility for the pharmacotherapy of patients for whom the prescription is proposed. Though a means of ensuring the appropriate use of medications, currently in Japan, it is not compulsory to apply a formulary for patient prescription. Here, medicines other than those recommended by the formulary were not prescribed during hospitalization when the condition of the patient remained unchanged. In cases where the patient's medication upon admission was identified, the appropriateness of the formulary medication proposal was determined while considering the patient's condition. If the prescription changed based on the formulary, then the patient was informed. Moreover, the pharmacist and nurse collaborated to monitor the patient for the effectiveness and safety of the prescribed medicines. When the patient consulted a local physician after discharge, all medication changes were noted in the discharge summary. Such a continuous approach was required in recovery and rehabilitation hospitals as well as in community-based integrated care hospitals.

Treatment according to the hospital formulary was proposed and approved for patients who could be introduced to the formulary-prescribed medications, mainly at the time of identification of medication history. The maximum dose of RAS in Japan, especially angiotensin-converting enzyme inhibitors, is lower than that approved in Europe and the United States. For example, in the case of enalapril, a dose of 10 mg per day is often prescribed. A 10 mg dose of enalapril, not 20 mg,<sup>28</sup> is prescribed instead of telmisartan 80 mg. ARBs and CCBs are often selected for the treatment of hypertension in Japan, and a fixed-dose combination of ACEIs and CCBs is not marketed.<sup>41</sup> In Japan, diuretics are not commonly prescribed as an antihypertensive medication in order to avoid the adverse drug reaction of dehydration and are not actively selected in our hospital because the median age of the patient population is 77 years and many older patients are admitted.<sup>12</sup> A reduction of the maximum RAS dose was proposed to conform to the indication of hypertension for preventing adverse drug reactions such as dry cough in hospitalized patients. This may explain why the RAS dosage decreased from an average of 10.7 mg of enalapril equivalent at the time of admission to 7.2 mg at the time of discharge. The same

trend was found in a previous study, which showed that there was no change in blood pressure even when the proposed doses were converted for older patients.<sup>12</sup> We found the dosages of CCBs were appropriately proposed, as the dosage of alternative medicines for blood pressure control were not increased. With regard to XORis, febuxostat, a new medicine that was not frequently recommended by the formulary, was selected for a patient whose uric acid level could not be controlled with allopurinol 50 mg due to renal dysfunction. This was a case of targeted administration because of reduced renal function.

The cost of medications was reduced by 56.1 yen per patient per day, which translates to an annual cost reduction of 20 476.5 yen. As the medicines brought to the hospital are those used locally, it is likely that medication costs will decrease by introducing the formulary in local hospitals. Medication use optimization in Japan has not been adequately directed toward reducing medical costs. The recent increases in antibody-based medicines and total medical costs due to an aging Japanese population have imposed pressure on the medical care system, though the equal provision of a basic level of medical treatment to all patients in the nation still occurs and is an advantage of the system.<sup>42</sup> Therefore, the concept of appropriate use of medicines to reduce the costs borne by patients and the insurer should be widely disseminated, even if the medication cost may seem small at the individual medical practitioner level. Overall, in this study, the medication costs were decreased for all pharmacological classes. Though XORi costs showed a trend to decrease, we could not demonstrate statistical significance due to the use of the expensive medicine, febuxostat. The analysis showed that the total medicine cost of XORis did not increase but decreased, as allopurinol is recommended as the standard in the formulary. This indicates the formulary did not necessarily narrow the choice of medical treatment for physicians and patients, and the medicine cost was distributed appropriately regardless of pharmacological class.

There are two limitations to this study. First, few patients returned to our hospital after discharge, and it should be noted that we were not able to track all the formulary's continuation patients. This study included patients who were introduced to the formulary in our hospital and attended our outpatient clinic (with different physicians and no restriction to prescribe from the hospital formulary). Though it was not possible to substantially track the discharged patients from our hospital who subsequently consulted at other hospitals or clinics, there were several cases where the patients did revisit our hospital and their medications had not changed, demonstrating that when hospital formularies are used, indicated medications and dosages of inpatients are often maintained by local outpatients. Therefore, a hospital formulary may help reduce medication costs in the community. Secondly, this study includes drug cost reduction partially based on the stability of the disease. The hospital formulary introduction rate was 80% in the previous study,<sup>12</sup> and the comparison between the formulary introduction and non-formulary

introduction could not be verified because the distribution of cases was assumed to be unbalanced and the number of cases was less than the required number. We expect to collect sufficient data that integrates analyzable hospital data and regional data, and will aim to show the reduction of medication costs by switching the equivalent amount of medicines through a formulary system.

## Conclusion

The development of hospital formularies influences outpatient prescribing, suggesting that collaboration among hospitals or in-hospital formularies may be an effective strategy to expand local formularies. As the number of newly approved medicines and medication costs are increasing worldwide, the introduction of formularies is just one of the necessary tools to provide appropriate pharmaceutical care to patients and facilitate better pharmacotherapy with minimized medical costs. Introducing a hospital formulary can contribute to the reduction of local healthcare costs in countries with universal healthcare coverage and in countries that plan to introduce local formularies.

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## Ethical considerations

The study was approved by the Ethics Committee of the Niiza Hospital and was undertaken in compliance with the principles evinced in the Declaration of Helsinki. Patient informed consent was not required by the ethics committee.

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## Supplemental Material

Supplemental material for this article is available online.

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