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Assessment of inter-rater agreement between physicians and their patients regarding medication adherence in a clinical questionnaire study

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Abstract

While it is important to treat lifestyle-related diseases for the primary and secondary prevention of cardiovascular diseases, medication adherence is still poor. Although various causes of poor adherence have been reported, the differences between physicians and their patients regarding the recognition of medication adherence have not been well-investigated.

We administered a questionnaire about medication adherence to 300 outpatients and their 23 cardiologists at the Department of Cardiology, Fukuoka University Hospital. The questionnaires for patients and physicians included acceptable total number of drug doses and dosing schedule, forgetting to take the medicine, and dose-reduction or -increase based on self-judgement. The patients were 70.6 ± 12.3 years old and 61.0% ($n = 183$) were male. Patients reported that it was acceptable to receive 0–5 doses twice daily. The patients were divided into two groups: an agreement group, in which physicians and their patients had the same answer to the question regarding forgetting medication (203 cases; 67.7%), and a disagreement group (97 cases; 32.3%). Overall, the inter-rater agreement between physicians and patients with regard to forgetting medication was significant, but slight (κ coefficient = 0.12). In a multivariate analysis, absence of hypertension [odds ratio (OR): 0.21, 95% confidence interval (CI): 0.09–0.50, $P < .001$), β-blocker usage (OR: 1.86, 95% CI: 1.11–3.12, $P = .02$), and biguanide usage (OR: 4.04, 95% CI: 1.43–11.41, $P = .01$) were independent predictors of disagreement with regard to forgetting medication.

The inter-rater agreement between physicians and patients with regard to medication adherence was slight. An increase in inter-rater agreement should improve medication adherence.

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, DPP-4 inhibitors = dipeptidyl peptidase-4 inhibitors.

Keywords: forgetting administration, hypertension, inter-rater agreement, medication adherence, self-report questionnaire

1. Introduction

While it is important to treat chronic diseases such as lifestyle-related diseases (hypertension and diabetes, etc.) for the primary and secondary prevention of cardiovascular diseases, medication adherence is still poor.[1–8] Poor medication adherence wastes medical resources,[2–5] worsens disease states and causes complications,[6–8] and increases the risk of administration[9] and the cost of medications.[2–5] Lower adherence has been associated with an increased risk of all-cause mortality and stroke in non-valvular atrial fibrillation patients with a novel oral anti-coagulant drug.[7] Non-adherence was associated with a > 2-fold increased rate of subsequent cardiovascular events in outpatients with stable coronary heart disease.[8] On the other hand, high medication adherence was associated with low hospitalization rates in patients with diabetes, hypertension, dyslipidemia, and congestive heart failure.[4]

It has been estimated that 16 to 50% of hypertensive treatments are discontinued within the first year.[10] In the US, among patients who started antihypertensive and lipid-lowering therapy in a managed care organization, 44.7%, 35.9%, and 35.8% of patients were adherent at 3, 6, and 12 months, respectively.[11] In the UK, among patients who attended a clinical hypertension center in whom medication adherence was investigated by high-performance liquid chromatography–tandem mass spectrometry urine analysis, 25% were non-adherent.[12] In Japan, 14 to 17% of outpatients with cardiovascular disease at university hospitals were non-adherent.[13,14]

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YO, MK, and YS contributed equally to this work.

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Poor medication adherence has been associated with long-term treatment, total number of drugs doses, complexity of drug usage, dementia, and a lack of understanding about the treated disease, the significance of preventive administration, a feeling of therapeutic value, and support by others. A once-daily dosing schedule was associated with higher adherence rates.[15] Medication adherence was also investigated from the perspective of both patients and physicians.[16] That study consisted of a web-based survey in Japan. For the treatment of hypertension and diabetes, 15% of patients were non-adherent. The main reason given for non-adherence was "inadvertently forgot" for 23% of physicians and 64% of patients. Only 4% of physicians were satisfied with the methods for preventing non-adherence, whereas 59% of patients felt that they could successfully avoid forgetting to take their medications. As mentioned above, there is a strong association between medication adherence and the difference in recognizing non-adherence between physicians and patients. Although various causes of poor adherence have been reported, the differences between physicians and their patients regarding the recognition of non-adherence have not been well-investigated. Therefore, we randomly selected outpatients to complete a questionnaire about medication adherence, and administered the same questionnaire to their respective physicians, and examined the differences in the recognition of adherence between physicians and their patients.

2. Methods

2.1. Study design

Three hundred outpatients who were all over 20 years old and had been prescribed at least one medication for chronic disease [lifestyle-related diseases (hypertension and diabetes, dyslipidemia or cardiovascular diseases: ischemic heart disease, heart failure, arrhythmia, cardiomyopathy, and vessel disease)] for over 6 months at the Department of Cardiology, Fukuoka University Hospital in Japan, from January 2017 to May 2017 were enrolled. A pharmacist performed screening and randomly selected study patients from their electronic medical records. The attending physicians were not involved in patient selection to avoid selection bias, and completed the questionnaire after performing a medical examination. The same self-reported questionnaire was administered to patients and their attending physicians at the same time. The patient characteristics were investigated to identify factors that could predict medication adherence. The study protocol was approved by the Ethics Committee of Fukuoka University (2016M024). Written informed consent was obtained from all patients and physicians.

2.2. Questionnaire

For patients, the acceptable total number of drug doses and dosing schedule, the person who manages drug administration (the patient themselves, a family member or nursing care staff), forgetting administration, and a dose-reduction or -increase based on self-judgement over 6 months were investigated. The method used to handle residual drugs, such as disposal at home, bringing to a hospital or pharmacy, or stored at home, was also investigated (Supplemental Table 1). The physicians answered the same questions for each patient. Responses of "Never" and "Hardly ever" were categorized as "No" and "Some of the time," respectively, and "All of the time" was categorized as "Yes." The patient's age, gender, underlying diseases, number of diseases, kinds of drugs, total number of drugs, timing of drug administration, and the availability of a one-dose package, in which all medicines that are to be taken at the same time are placed in a bag, were also investigated. The questions about the handling of residual drug and the person who manages drugs administration allowed multiple answers.

2.3. Statistical analyses

All analyses were performed using SPSS statistics 24.0 (IBM, Armonk, NY) and JMP 14 (SAS Institute Inc., Cary, NC). Continuous data with a normal distribution are reported as the mean ± standard deviation (SD), and continuous data with a non-normal distribution are reported as the median (interquartile range). Inter-rater agreement between physicians and their patients was evaluated by the κ coefficient for nominal scales and the weighted κ coefficient for ordered scales, where $\kappa < 0$ represents poor agreement, 0 to –0.20 slight agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement and 0.81–1.00 almost perfect agreement.[17] A significant agreement is present if there is no overlap with zero in the 95% confidence interval (CI) for the κ value. The logistic regression analysis was used to identify factors that could affect agreement and disagreement, including patient characteristics, complications, and medications. A simple logistic regression analysis was performed for each factor, and a multiple logistic regression analysis was performed for factors that were found to be significant ($P < .05$) in the simple analysis. A value of $P < .05$ was considered significant.

3. Results

3.1. Patient characteristics

The self-report questionnaire was administered to 300 outpatients and their 23 attending physicians. The patient characteristics are shown in Table 1. The patients were 70.6 ± 12.3 years old and 61.0% (n = 183) were male. The rates of hypertension, diabetes, dyslipidemia, angina, heart failure, and arrhythmia were 91.3%, 52.7%, 76.0%, 54.0%, 62.3%, and 52.0%, respectively. For arrhythmia, the rates of atrial fibrillation, supraventricular arrhythmia without atrial fibrillation, and ventricular arrhythmia were 32.7%, 9.0%, and 21.3%, respectively. The rates of angiotensin converting enzyme inhibitor (ACE-I), angiotensin II receptor blocker (ARB), β-blocker, calcium channel blocker (CCB), and medications for diabetes and dyslipidemia were 12.0%, 57.3%, 51.3%, 48.7%, 19.7%, and 66.3%, respectively. The average total number of drug doses and dosing schedules were 9.0 (6.0–12.0) doses and 2.0 (2.0–3.0) times per day, respectively. Only 84 patients (28.0%) had a one-dose package. The average age of the physicians was 45.6 ± 8.5 years and 91.3% were male (n = 21). Each attending physician completed 13 ± 2.8 questionnaires.

3.2. Inter-rater agreement regarding acceptable total number of drug doses and dosing schedule

We categorized the acceptable total number of drug doses into 3 groups: 0 to 5, 6 to 9, and more than 10 (Table 2). Thirty-one patients did not answer this question. One hundred eighty-three patients (68.0%) responded that it was acceptable to take 0 to 5 doses (Table 2). On the other hand, the physicians thought that more than 10 daily doses were acceptable in 132 of the cases

Table 1

Patient baseline characteristics.

Valuables	n (%)
Age, year	70.6 ± 12.3
Male	183 (61.0)
Comorbidity	
Hypertension	274 (91.3)
Diabetes mellitus	158 (52.7)
Dyslipidemia	228 (76.0)
Angina pectoris	162 (54.0)
Myocardial infarction	54 (18.0)
Heart failure	187 (62.3)
Arrhythmia	156 (52.0)
Af	98 (32.7)
Supraventricular arrhythmia without Af	27 (9.0)
Ventricular arrhythmia	64 (21.3)
Others	51 (17.0)
Valvular disease	53 (17.7)
Pericarditis/cardiomyopathy	45 (15.0)
Vessel disease	114 (38.0)
Others	38 (12.7)
Number of diseases	5.8 ± 1.97
Prescription medication	
Cardiovascular agents	
CCB	146 (48.7)
ACE-I	36 (12.0)
ARB	172 (57.3)
Diuretics	142 (47.3)
β-Blockers	154 (51.3)
Antiplatelet agents	145 (48.3)
Anticoagulant agents	106 (35.3)
Antiarrhythmic agents	47 (15.7)
Vasodilators	39 (13.0)
Cardiotonics	8 (2.7)
Others	10 (3.3)
Antidiabetic agents	59 (19.7)
Sulfonylurea (including glinide)	9 (3.0)
Biguanide	17 (5.7)
α-Glucosidase inhibitor	12 (4.0)
Thiazolidine derivatives	4 (1.3)
DPP-4 inhibitor	50 (16.7)
SGLT2 inhibitor	2 (0.7)
Insulin	1 (0.3)
Dyslipidemia agents	199 (66.3)
HMG-CoA reductase inhibitor	179 (59.7)
NPC1L1 inhibitor	36 (12.0)
Fibrate	4 (1.3)
EPA or EPA and DHA	29 (9.7)
Others	2 (0.7)
Digestive organ agents	159 (53.0)
Total number of drug doses	9.0 [6.0–12.0]
Dosing schedules, times daily	2.0 [2.0–3.0]
One-dose package	84 (28.0)

ACE-I = angiotensin converting enzyme inhibitor, Af = atrial fibrillation, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, DHA = docosahexaenoic acid, DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor, EPA = eicosapentaenoic acid, HMG-CoA reductase inhibitor = hydroxymethyl-glutaryl-coenzyme A reductase inhibitor, NPC1L1 inhibitor = Niemann-pick C1 Like 1 Protein inhibitor, SGLT2 inhibitor = sodium glucose cotransporter2 inhibitor. One-dose package means that all medicines which is taken at the same timing are put into a bag.

(49.1%). Although there was a significant inter-rater agreement for the acceptable total number of drug doses between physicians and their patients, the degree of agreement was slight (weighted κ coefficient 0.12, 95% CI 0.04–0.19, $P < .01$).

We also categorized the acceptable dosing schedule into 4 groups: once-daily, twice-daily, thrice-daily, and four or more

Table 2

Inter-rater agreement about acceptable total number of doses between patients and physicians.

	Attending physician			
	0–5	6–9	10≦	Total
Patient				
0–5	58 (21.6)	42 (15.6)	83 (30.9)	183 (68.0)
6–9	2 (0.7)	20 (7.4)	27 (10.0)	49 (18.2)
10≦	5 (1.9)	10 (3.7)	22 (8.2)	37 (13.8)
Total	65 (24.2)	72 (26.8)	132 (49.1)	269 (100)

Frequency (%), weighted κ = 0.12 (95% CI = 0.04–0.19, $P < .01$).

times daily (Table 3). One hundred thirty-seven patients (46.3%) responded that a twice-daily schedule was acceptable, and the physicians thought that a twice-daily schedule was acceptable in 153 of the cases (51.7%) (Table 3). There was no inter-rater agreement regarding an acceptable dosing schedule between physicians and their patients (weighted κ coefficient 0.09, 95% CI −0.02 to 0.20, $P = .09$).

3.3. Inter-rater agreement regarding the management of drug administration and the handling of residual drugs

All of the patients answered the question about the management of drug administration (Table 4). According to the patients, in 89.1% (n = 285), 10.3% (n = 33), and 0.01% (n = 2) of cases, respectively, drug administration was managed by the patients themselves, a family member, or nursing care staff. Physicians expected that 265 patients (88.5%) would manage drug administration by themselves, a family member would manage drug administration for 41 (13.2%), and nursing care staff would manage drug administration in 4 (1.3%). There was moderate inter-rater agreement between physicians and their patients regarding the management of drug administration by patients themselves (κ coefficient 0.44, 95% CI 0.27–0.62, $P < .01$). There was also moderate inter-rater agreement regarding the management of drug administration by a family member (κ coefficient 0.42, 95% CI 0.26–0.57, $P < .01$) (Table 4).

Residual drugs were either disposed of at home, brought to a hospital or pharmacy, or stored at home for 10.0% (n = 30), 2.0% (n = 6), 4.0% (n = 12), and 65.0% (n = 195) of the patients, respectively (Table 4). For physicians, these values were 3.7% (n = 11), 8.3% (n = 25), 10.3% (n = 31), and 75.7% (n = 227), respectively. There was no inter-rater agreement regarding the handling of residual drugs, including disposal at home ($P = .36$),

Table 3

Inter-rater agreement about acceptable dosing schedule between patients and physicians.

	Attending physician				
	Once daily	Twice daily	Thrice daily	Four or more daily	Total
Patient					
Once daily	37 (12.5)	44 (14.9)	25 (8.5)	4 (1.4)	110 (37.2)
Twice daily	24 (8.1)	82 (27.7)	29 (9.8)	2 (0.7)	137 (46.3)
Thrice daily	6 (2.0)	25 (8.5)	13 (4.4)	1 (0.3)	45 (15.2)
Four or more daily	1 (0.3)	2 (0.7)	1 (0.3)	0 (0.0)	4 (1.4)
Total	68 (23.0)	153 (51.7)	68 (23.0)	7 (2.4)	296 (100)

Frequency (%), weighted κ = 0.09 (95% CI = −0.02 to 0.20, $P = .09$).

Table 4

Inter-rater agreement about medication adherence between patients and physicians in all subjects, the agreement and disagreement groups.

Questions	All subjects		Agreement group Pt./Phys.		Disagreement group Pt./Phys.		κ coefficient	95% CI	*P*-value
	Pt.	Phys.	Yes/yes	No/no	Yes/no	No/yes			
Management of drug administration									
Patient	285	265	262 (87.3)	12 (4.0)	23 (7.7)	3 (1.0)	0.44	0.27–0.62	<.01
Family	33	41	18 (6.0)	244 (81.3)	15 (5.0)	23 (7.7)	0.42	0.26–0.57	<.01
Nursing care staff	2	4	1 (0.3)	295 (98.3)	1 (0.3)	3 (1.0)	N.D.		
Handling of residual drug									
Waste at home	30	11	2 (0.7)	261 (87.0)	28 (9.3)	9 (3.0)	0.05	−0.08 to 0.17	.36
Bringing to hospital	6	25	1 (0.3)	270 (90.0)	5 (1.7)	24 (8.0)	0.03	−0.09 to 0.15	.46
Bringing to pharmacy	12	31	1 (0.3)	258 (86.0)	11 (3.7)	30 (10.0)	−0.01	−0.1 to 0.08	.82
Stored at home	195	227	148 (49.3)	26 (8.7)	47 (15.7)	79 (26.3)	0.01	−0.1 to 0.12	.9
Others	76	13	4 (1.3)	215 (71.7)	72 (24.0)	9 (3.0)	0.02	−0.06 to 0.1	.65
Drug dose- reduction or -increase									
Reduction by self-judgement	16	19	4 (1.3)	269 (89.7)	12 (4.0)	15 (5.0)	0.18	−0.01 to 0.37	<.01
Increase by self-judgement	0	8	0	292 (97.3)	0	8 (2.7)	N.D.		
Forgetting administration	95	40	19 (6.3)	184 (61.3)	76 (25.3)	21 (7.0)	0.12	0.01–0.22	.02

κ coefficient could not calculated because of sparse cells.
N.D. = not determined, Phys = physicians, Pt = patient.

brought to a hospital ($P = .46$) or pharmacy ($P = .82$), and stored at home ($P = .9$) (Table 4).

3.4. Inter-rater agreement regarding a dose-reduction or -increase based on self-judgement and forgetting administration

Only 16 patients responded that they had reduced their dose based on their own judgement; the physicians expected 19 patients (Table 4). There was a significant, but slight, inter-rater agreement regarding a dose-reduction based on self-judgement (κ coefficient 0.18, 95% CI −0.01 to 0.37, $P < .01$). None of the patients reported that they had increased their dose based on their own judgement, and the physicians expected that 8 patients had increased their dose based on their own judgement.

Ninety-five patients stated that they had forgotten to take their drugs, and the physicians expected that 40 patients had forgotten to take their drugs during the 6-month period. The physicians did not identify 76 (80%) of the total 95 patients who forgot to take their drugs. Thus, when the patients were divided into groups with regard to forgetting drug administration, 203 (67.7%) and 97 subjects (32.3%) were in the agreement and disagreement groups, respectively. There was a significant, but slight, inter-rater agreement regarding forgetting drug administration (κ coefficient 0.12, 95% CI 0.01–0.22, $P = .02$) (Table 4). In the univariate analysis (Table 5), the disagreement group showed a significantly lower rate of hypertension ($P < .001$), higher rate of biguanide use ($P = .02$), and higher rate of β-blocker usage ($P = .04$) than the agreement group. In the multivariate analysis (Fig. 1), absence of hypertension (OR: 0.17, 95% CI: 0.42–0.71, $P < .001$), use of biguanide (OR: 4.04, 95% CI: 1.43–11.41, $P = .01$), and use of β-blocker (OR: 2.04, 95% CI: 1.20–3.45, $P = .01$) were independent predictors for the recognition of disagreement with regard to forgetting drug administration between physicians and their patients.

4. Discussion

We investigated the recognition of medication adherence in both physicians and their patients to improve adherence. Although there was some consistency in the recognition of medication adherence between physicians and their patients, the degree of this consistent recognition was slight.

We investigated the factors associated with disagreement about forgetting drug administration between physicians and their patients by a multiple logistic regression analysis. As a result, the absence of hypertension, and the use of biguanide and β-blocker were independent factors that predicted forgetting drug administration.

In the disagreement group, the rate of hypertension was low. Hypertension can be easily monitored by checking blood pressure and hypertensive patients can quickly feel the effects of drugs. Physicians can ask patients to check their blood pressure in their own homes. This could help increase patients' awareness of the need to treat hypertension and they will be less likely to forget to take their medications. Physicians provide their hypertensive patients various positive interventions; they promote home blood pressure measurement, confirm the blood pressure notebook at each visit, give advice on reducing salt intake and provide exercise guidance. Therefore, it might be easy for physicians to be aware of the medication adherence, which resulted in agreement about forgetting medications between patients and their attending physicians.

The disagreement group also showed a high rate of β-blocker usage. Previous studies have reported poor β-blocker adherence in antihypertensives[18] and after myocardial infarction.[19] β-Blockers are often used for complicated cardiovascular disease and these patients may have to take a lot of drugs. As a matter of fact, 120 (77.9%) of the total 154 patients in this study who were taking β-blockers had hypertension with heart failure, and patients with β-blocker treatment (n = 154) were taking a greater total number of drugs than those without β-blocker treatment (n = 146) (data not shown). Complicated cardiovascular disease obscures the understanding of the patient's clinical condition and will lead to poor medication adherence with β-blocker. A large total number of drugs will also lead to poor medication adherence with β-blocker.

The disagreement group was more likely to be prescribed biguanide than the agreement group. According to a meta-

Table 5

The differences about forgetting drug administration between agreement and disagreement groups.

Variables	Agreement group (n = 203)	Disagreement group (n = 97)	OR	95% CI	*P*-value
Age, year	71.9 ± 11.5	67.9 ± 13.3	0.98	0.96–0.99	.01
Male	118 (58.1)	65 (67.0)	0.68	0.41–1.14	.14
Comorbidty					
Hypertension	194 (95.6)	80 (82.4)	0.22	0.09–0.51	<.001
Diabetes mellitus	106 (52.2)	52 (53.6)	1.06	0.65–1.72	.82
Dyslipidemia	155 (76.4)	73 (75.3)	0.94	0.54–1.66	.84
Angina pectoris	108 (53.2)	54 (55.7)	1.11	0.68–1.80	.69
Myocardial infarction	38 (18.7)	16 (16.5)	0.86	0.45–1.63	.64
Heart failure	123 (60.6)	64 (66.0)	1.26	0.76–2.09	.37
Arrhythmia	106 (52.2)	50 (51.5)	0.97	0.60–1.58	.91
Af	66 (32.5)	32 (33.0)	1.02	0.61–1.71	.93
Supraventricular arrhythmia without Af	20 (9.9)	7 (7.2)	0.71	0.29–1.75	.46
Ventricular arrhythmia	45 (22.2)	19 (19.6)	0.86	0.47–1.56	.61
Others	35 (17.2)	16 (16.5)	0.95	0.50–1.81	.87
Valvular heart disease	40 (19.7)	13 (13.4)	0.63	0.32–1.24	.18
Pericarditis/cardiomyopathy	27 (13.3)	18 (18.6)	1.49	0.77–2.85	.24
Vessel disease	82 (40.4)	32 (33.0)	0.73	0.44–1.21	.22
Others	27 (13.3)	11 (11.3)	0.83	0.40–1.76	.63
Number of diseases	5.9 ± 2.0	5.6 ± 1.9	0.94	0.83–1.07	.34
Prescription medication					
Cardiovascular agents					
CCB	97 (47.8)	49 (50.5)	1.12	0.69–1.81	.66
ACE-I	22 (10.8)	14 (14.4)	1.39	0.68–2.85	.37
ARB	119 (58.6)	53 (54.6)	0.85	0.52–1.39	.51
Diuretics	96 (47.3)	46 (47.4)	1.01	0.62–1.63	.98
β-Blockers	96 (47.3)	58 (59.8)	1.66	1.02–2.71	.04
Antiplatelet agents	102 (50.2)	43 (44.3)	0.79	0.49–1.28	.34
Anticoagulant agents	71 (35.0)	35 (36.1)	1.05	0.63–1.74	.85
Antiarrhythmic agents	33 (16.3)	14 (14.4)	0.87	0.44–1.71	.69
Vasodilators	23 (11.3)	16 (16.5)	1.55	0.78–3.08	.22
Cardiotonics	3 (1.48)	5 (5.15)	3.62	0.85–15.49	.08
Others	6 (3.00)	4 (4.12)	1.41	0.39–5.13	.60
Antidiabetic agent	38 (18.7)	21 (21.6)	1.20	0.66–2.18	.55
Sulfonylurea (including glinide)	6 (3.0)	3 (3.1)	1.05	0.26–4.28	.95
Biguanide	7 (3.4)	10 (10.3)	3.22	1.19–8.73	.02
α-Glucosidase inhibitor	7 (3.4)	5 (5.2)	1.52	0.47–4.92	.48
Thiazolidine derivatives	3 (1.5)	1 (1.0)	0.69	0.07–6.76	.75
DPP-4 inhibitor	33 (16.3)	17 (17.5)	1.10	0.58–2.08	.78
SGLT2 inhibitor	1 (0.5)	1 (1.0)	2.10	0.13–34.0	.60
insulin	1 (0.5)	0 (0.0)	N.D.		
Dyslipidemia agents	134 (66.0)	65 (67.0)	1.05	0.63–1.75	.86
HMG-CoA reductase inhibitor	121 (59.6)	58 (59.8)	1.01	0.62–1.65	.98
NPC1L1 inhibitor	23 (11.3)	13 (13.4)	1.21	0.59–2.51	.61
Fibrate	3 (1.5)	1 (1.0)	0.69	0.07–6.76	.75
EPA or EPA andDHA	21 (10.3)	8 (8.2)	0.78	0.33–1.83	.57
Others	1 (0.5)	1 (0.5)	2.10	0.13–34.0	.60
Digestive organ agents	111 (54.7)	48 (49.5)	0.81	0.50–1.32	.40
Total number of drug doses	9.0 [6.0–12.0]	9.0 [6.0–12.0]	1.02	0.98–1.07	.31
Dosing schedules, times daily	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.96	0.78–1.17	.67
One-dose package	57 (28.1)	27 (27.8)	0.99	0.58–1.69	.97

ACE-I = angiotensin converting enzyme inhibitor, Af = atrial fibrillation, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker, DHA = docosahexaenoic acid, DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor, EPA = eicosapentaenoic acid, HMG-CoA reductase inhibitor = hydroxymethylglutaryl-coenzyme A reductase inhibitor, N.D. = not determined, NPC1L1 inhibitor = Niemann-pick C1 Like 1 Protein inhibitor, SGLT2 inhibitor = sodium glucose cotransporter2 inhibitor. One-dose package means that all medicines which is taken at the same timing are put into a bag.

analysis of 48 studies reported by McGovern et al, medication adherence was poor for metformin compared with sulfonylureas, thiazolidinedione, and dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors).[20] In another study, low adherence was associated with biguanides compared with the sulfonylureas and DPP-4 inhibitors.[21,22] This low medication adherence for biguanides may be due to multiple doses, frequent dose changes, the high number of tablets to be taken at one time, and symptoms of digestive problems at the initial stage of administration and with increasing dosage.[22] In addition, in type 2 diabetes mellitus patients, a low recognition of a therapeutic effect, the appearance of hypoglycemia, and a complex dosing regimen are factors that influence the adherence to medication.[23]

The need for numerous doses reduces medication adherence.[11,15,24–26] In this study, 68.0% of patients responded that it was acceptable to have 0 to 5 doses. In contrast, physicians

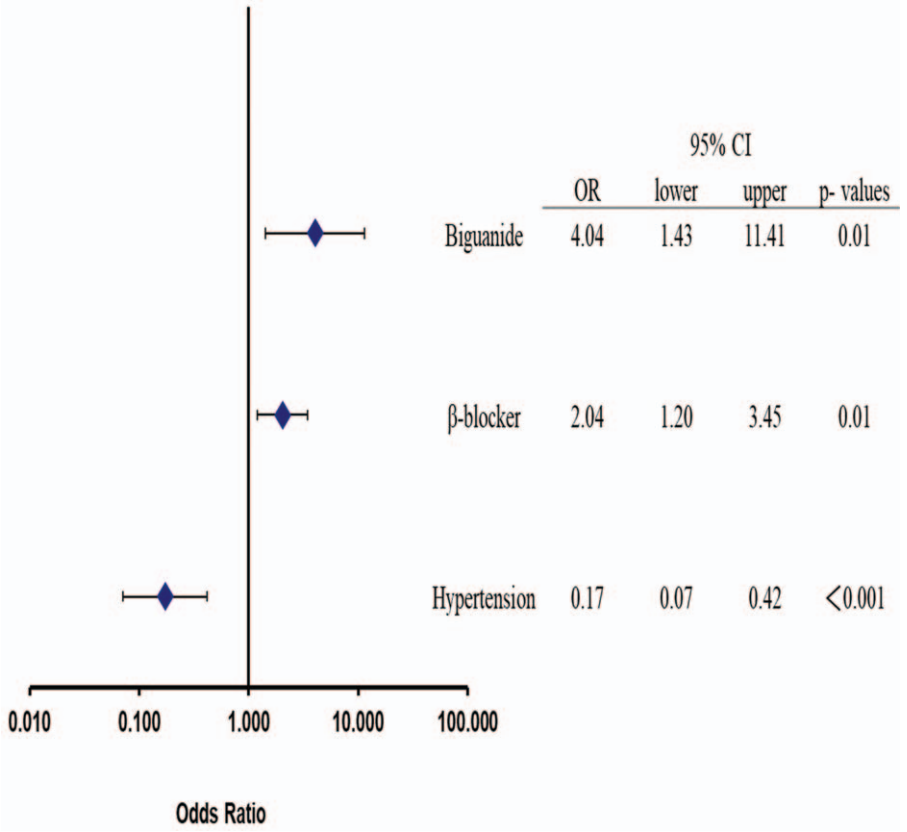

Figure 1. Factors that contributed to forgetting drug administration in the agreement and disagreement groups. A multiple logistic regression analysis was performed. Use of β-blocker and biguanide and absence of hypertension were independent factors for forgetting drug administration.

expected that 49.1% of patients would require more than 10 doses. Thus, the inter-rater agreement for acceptable total number of drug doses between patients and physicians was slight. To improve medication adherence, physicians should consider the reducing the number of drug doses or using a one-dose package. In fact, only 28.0% patients had a one-dose package. The dosing schedule is also related to medication adherence.[27–29] In addition, since there was no inter-rater agreement for an acceptable dosing schedule between physicians and patients in this study, physicians should consider using a dosing schedule that is suitable for each patient.

Patient's forgetting to take their medication is the most common cause of residual drugs. A high rate of forgotten drug administration leads to the insufficient treatment of diseases, the occurrence of adverse events, and an increase in medical costs. Patients might conceal the fact that they have forgotten to take their medications. It is important for physicians to understand why their patients forget to take their medications. In this study, although there was a significant inter-rater agreement for forgetting drug administration between patients and physicians, it was slight. The problem in this study was that physicians did not know about 80% of the patients who had forgotten drug administration. In other Japanese reports, although the rate of non-adherence was 15% and relatively low,[13,14] there may actually be more non-adherent patients. Medication adherence is indispensable for chronic drug treatment. Clinicians need to know whether or not their patients are taking their medicines in accordance with the instructions, because patients do not always report their actual medication adherence. We investigated the inter-rater agreement for forgetting administration between patients and physicians. A shared awareness concerning medication adherence between the patient and their attending physician will be helpful for improving medication adherence. Clinicians have several options available to help improve medication adherence, including educational and behavioral interventions, simplified dosing schedules, and one-dose packaging. In this study, the same self-reported questionnaire was administered to patients and their attending physicians at the same time. In addition, a pharmacist performed screening and randomly selected study patients using their electronic medical records. The attending physicians were not involved in the study design or patient selection. The use of a questionnaire in this study may have encouraged patients to provide their actual results and opinions.

This investigation has some limitations. It involved the use of a questionnaire, which contributes towards an overestimation of the level of adherence by patients.[30] However, other methods of evaluation, such as pill counts, a medication event monitoring system, prescription record, electronic monitoring, and refill frequency, are not much better. The detection of drug markers and/or metabolites is more trustworthy,[12,31] but these methods are not practical in daily practice because they are cumbersome and expensive. While previous studies have reported disagreement among doctors, patients, and their families,[32] our investigation revealed the independent predictors of disagreement regarding forgetting drug administration between physi-

cians and their patients. These results should be helpful for improving medication adherence.

In conclusion, the inter-rater agreement for forgetting administration between patients and physicians was significant, but slight. In a multivariate analysis, the absence of hypertension, and the use of biguanide and β-blocker were independent predictors of disagreement about forgetting drug administration between physicians and their patients. Based on these results, we should improve inter-rater agreement between physicians and patients to promote medication adherence.

Author contributions

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