

# Prescription of oral hypoglycemic agents for patients with type 2 diabetes mellitus: A retrospective cohort study using a Japanese hospital database

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## ABSTRACT

**Aims/Introduction:** In treatment algorithms of type 2 diabetes mellitus in Western countries, biguanides are recommended as first-line agents. In Japan, various oral hypoglycemic agents (OHAs) are available, but prescription patterns are unclear.

**Materials and Methods:** Data of 7,108 and 2,655 type 2 diabetes mellitus patients in study 1 and study 2, respectively, were extracted from the Medical Data Vision database (2008–2013). Cardiovascular disease history was not considered in study 1, but was in study 2. Initial choice of OHA, adherence to its use, effect on glycated hemoglobin levels for 2 years and the second choice of OHA were investigated.

**Results:** In study 1,  $\alpha$ -glucosidase inhibitor, glinide and thiazolidinedione were preferentially medicated in relatively lower glycated hemoglobin cases compared with other OHAs. The two most prevalent first prescriptions of OHAs were biguanides and dipeptidyl peptidase-4 inhibitors, and the greatest adherence was for  $\alpha$ -glucosidase inhibitors. In patients treated continuously with a single OHA for 2 years, improvement in glycated hemoglobin levels was greatest for dipeptidyl peptidase-4 inhibitors. As a second OHA added to the first OHA during the first 2 years, dipeptidyl peptidase-4 inhibitors were chosen most often, especially if a biguanide was the first OHA. In study 2, targeting patients with a cardiovascular disease history, a similar tendency to study 1 was observed in the first choice of OHA, adherence and the second choice of OHA.

**Conclusions:** Even in Japanese type 2 diabetes mellitus patients, a Western algorithm seems to be respected to some degree. The OHA choice does not seem to be affected by a cardiovascular disease history.

## INTRODUCTION

In Japan, the oral hypoglycemic agents (OHAs) known as sulfonylureas (SUs), biguanides (BGs),  $\alpha$ -glucosidase inhibitors ( $\alpha$ -GIs), thiazolidinediones (TZDs), glinides, dipeptidyl peptidase-4 inhibitors (DPP-4Is) and sodium–glucose co-transporter-2 inhibitors (SGLT2-Is) are available for type 2 diabetes mellitus treatment. Such ready accessibility to all types of OHAs is unique to Japan.

Patients with type 2 diabetes mellitus carry a high risk of cardiovascular disease (CVD): 40.4% of individuals with type 2

diabetes mellitus die from CVD<sup>1</sup>. Among the seven types of OHA mentioned above, some might be beneficial for the prevention of CVD events, because they protect the cardiovascular system<sup>2–8</sup>. The SGLT2-I, empagliflozin, has been shown to significantly reduce the number of deaths among individuals with type 2 diabetes mellitus and established CVD compared with placebo<sup>9</sup>. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have issued guidelines<sup>10</sup> that incorporate information from clinical trials focusing on cardiovascular outcomes<sup>11–13</sup>. Those guidelines recommend initial treatment with a BG and emphasize a patient-centered approach to treatment rather than adherence to stricter glycemic control<sup>10</sup>. In Japan, a clear algorithm of

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OHA medication for type 2 diabetes mellitus patients has not been proposed. Also, few reliable medical databases are available in Japan. Thus, prescription of OHAs for type 2 diabetes mellitus patients in Japan is not well understood.

One way to solve this problem is to extract information from the national health insurance program in Japan, which details universal health coverage for >99% of Japanese citizens, and contains considerable medical information (including prescription patterns). The Medical Data Vision (MDV) database is a multicenter, hospital-based, medical-cost accounting database stored in hospital electronic-information systems<sup>14</sup>.

Previously, we reported that the sex and age distribution of type 2 diabetes mellitus patients extracted from the MDV database from 2013 (225,197 patients) was quite similar to The Japanese Patient Survey of 2011 (2,700,000) published by the Ministry of Health, Labor and Welfare of Japan. The MDV database could reflect the current situation of prescription patterns for patients with type 2 diabetes mellitus in Japan. Using this database, we recently showed in a 104-week retrospective cohort study that type 2 diabetes mellitus patients started first with a BG showed a significantly lower prevalence of cardiovascular (CV) events compared with those started first with a SU, and that this effect was independent of blood glucose-lowering effects<sup>14</sup>.

Next, we decided to investigate OHA prescriptions in Japan using information accumulated from the MDV database in 2008–2013. SGLT2-Is only became available in Japan in 2014, so data relating to them in the MDV database are not available.

In the present study, we focused on three aspects. First, we examined the choice of OHA and patient backgrounds, including initial control of type 2 diabetes mellitus (as denoted by glycated hemoglobin [HbA1c] levels). Second, we focused on the effect of treatment with a single OHA in type 2 diabetes mellitus patients who were treated with their first OHA continuously for 2 years. Third, we examined the second-choice OHA in addition to the first OHA when control of type 2 diabetes mellitus had not been successful during the first 2 years. These analyses were carried out in all patients irrespective of whether the CVD event was present before the first medication was prescribed. Finally, to ascertain if CVD history might affect the OHA medication, the study cohort was restricted to type 2 diabetes mellitus patients who had a history of CVD events according to the *International Classification of Diseases* (10th revision) before the medication was prescribed.

## MATERIALS AND METHODS

### Data sources

The study protocol was approved by the Review Board on Clinical Research of Fukuoka University (Fukuoka, Japan). The present retrospective observational study was carried out using a hospital-based composite database stored in hospital electronic information systems constructed by MDV. MDV data were purchased by FUJIFILM Pharma Co., Ltd. (Tokyo,

Japan). The database of patient medical information (including laboratory data) was extracted from the medical-cost account system of 103 institutions (19 hospitals with <200 beds; 66 hospitals with 200–499 beds; and 18 hospitals with ≥500 beds) in Japan. This database contains information about age, sex, diagnosis, *International Classification of Diseases* (10th revision) code, surgical history, outpatient/inpatient status, prescription and laboratory data. Analyses were carried out under a contract between FUJIFILM Pharma Co., Ltd. and Fukuoka University Hospital. Written informed consent was not obtained from patients, because all data were extracted retrospectively from the MDV database. However, patient anonymity was guaranteed.

### Study population

Two studies (study 1 and study 2) were undertaken. The patient population extracted in the present study satisfied the following conditions: (i) began treatment with a single OHA from 1 April 2008 to 30 April 2013; (ii) HbA1c level (National Glycohemoglobin Standardization Program) at baseline was available; (iii) age at baseline was 40–70 years; and (iv) the presence or absence of CVD history was not considered in study 1, but the presence of CVD history was considered in study 2.

Exclusion criteria were: (i) began treatment with insulin, glucagon-like peptide-1 (GLP-1) analog, or compounding agent at baseline; (ii) began treatment with ≥2 types of OHA; (iii) admitted to hospital at baseline; and (iv) anticancer drug was used before baseline. In 2013, the database of MDV Co., Ltd. (Tokyo, Japan) contained the data of 225,197 individuals, and among them, baseline levels of HbA1c were available for 29,074 patients. After careful adherence to inclusion and exclusion criteria, 7,108 and 2,655 individuals were subjected to cohort analyses of study 1 and study 2, respectively.

Estimated medication adherence of a single OHA prescribed first was calculated by the total sum of prescription days/total number of observation days, and expressed as ≥80, 50–80 or <50%. The second OHA was defined as an OHA chosen in addition to the single OHA prescribed first. If >2 OHAs were added at one time, they were counted as the second OHA, respectively.

### Definition of a CV event

Information regarding CV events was obtained from the MDV database. A CV event was defined as having angina pectoris (I200, I201, I208 and I209), myocardial infarction (I210–I213, I219, I220, I221 and I229), heart failure (I500, I501 and I509), cerebral infarction (I630–I635, I638 and I639), cerebral hemorrhage (I614 and I619) or subarachnoid hemorrhage (I600–I602, I604, I605 and I609).

### Statistical analysis

To verify the independence of analyses, statistical evaluation was carried out by a specialist organization (ING Corp., Tokyo,

Japan) completely unrelated to our institution or any drug company (including FUJIFILM Pharma Co., Ltd.). Statistical analyses were carried out using Sas v9.4 (SAS Institute, Cary, NC, USA). Considering type 1 errors in Student's *t*-test, patient characteristics at baseline between two groups (SU vs BG, SU vs  $\alpha$ -GI, SU vs TZD, SU vs glinide, SU vs DPP4-I) were compared using Dunnett's test. A value of  $P < 0.05$  was considered significant. Changes in HbA1c levels relative to that of a SU were evaluated by analysis of covariance (ANCOVA), and  $P < 0.05$  was considered significant.

**RESULTS**

Study 1 targeted 7,108 type 2 diabetes mellitus patients with and without a CVD history. Detailed information of initial OHA treatment and prescription course during 2 years is shown in Table 1. Among 7,108 patients, the most prevalent OHA medication given first was a BG (1,833 patients, 26.5%), followed by a DPP-4I (1,788 patients, 25.2%), SU (1,310 patients, 18.4%),  $\alpha$ -GI (1,081 patients, 15.2%), TZD (592 patients, 8.3%) and glinide (454 patients, 6.4%). However, adherence to the first medication for 2 years was highest for an  $\alpha$ -GI (27.9%), followed by a glinide (26.4%), SU (22.9%), BG (22.8%), TZD (19.9%) and DPP-4I (6.6%). Upon restriction to patients who showed medication adherence of >80%, adherence was best for a glinide and  $\alpha$ -GI (Table 2). The medication that was stopped during 2 years in  $\approx$ 80% of patients was a DPP-4I (Table 1). However, 77% of such patients prescribed with a DPP-4I showed medication adherence of >80% (Table 2). Detailed information of type 2 diabetes mellitus patients started with a single OHA is shown in Table 3. Each OHA was prescribed to almost 60% of men and 40% of women, suggesting no sex-based difference in the prescription of each OHA. In such patients ( $n = 7,108$ ), initial levels of HbA1c (%; mean  $\pm$  standard deviation) for those prescribed an  $\alpha$ -GI ( $6.8 \pm 1.1$ ), TZD ( $6.9 \pm 1.1$ ) or glinide ( $7.0 \pm 1.2$ ) were significantly lower than that of SU ( $7.6 \pm 1.5$ ), but for those prescribed DPP-4I ( $7.7 \pm 1.5$ ) and BG ( $7.6 \pm 1.6$ ) were not significantly different

from that of SU, respectively. Medication for patients with HbA1c  $\geq 6.5\%$  were more than 80% in SU, BG and DPP-4I. After continuous prescription of a single OHA for 2 years and upon showing medication adherence of >80%, HbA1c levels of all OHA groups were improved, except for those of a glinide (Figure 1). The extent of improvement in HbA1c (%; final value – initial value) by a BG ( $-0.15 \pm 0.04$ ),  $\alpha$ -GI ( $-0.11 \pm 0.06$ ) and TZD ( $-0.26 \pm 0.09$ ) was not significant compared with that of a SU ( $-0.19 \pm 0.05$ ). However, the extent of improvement in HbA1c levels by a DPP-4I ( $-0.42 \pm 0.09$ ) was much greater than that of a SU ( $P = 0.026$ ). Effects of the second OHA being added to the first OHA are shown in Table 4. Of any first OHA (including a SU, BG,  $\alpha$ -GI, TZD or glinide), a DPP-4I was the most-chosen second OHA (44.1–69.8% of second OHAs). When a BG was the first OHA, the second OHA was a DPP-4I in 69.8% of patients. When a DPP-4I was the first OHA, a BG was the second OHA in 45.2% of patients (Table 4).

Study 2 targeted 2,655 type 2 diabetes mellitus patients with a CVD history. Initial OHA treatment was highest for a DPP-4I (24.5%), followed by a SU (22.8%), BG (19.7%),  $\alpha$ -GI (17.0%), TZD (9.1%) and glinide (6.9%). However, adherence to the first medication for 2 years was highest for an  $\alpha$ -GI (31.9%), followed by a BG (30.0%), glinide (26.9%), TZD (26.0%), SU (25.7%) and DPP-4I (7.5%). In 289 patients, another OHA was added to the first OHA. For any first OHA (including a SU, BG,  $\alpha$ -GI, TZD and glinide), a DPP-4I was the most-chosen second OHA (42.9–72.2% of second OHAs; data not shown).

**DISCUSSION**

We analyzed a Japanese hospital database extracted from the MDV database (2008–2013) that targeted 7,108 patients. The two most prevalent first prescriptions of a single OHA were a BG and DPP-4I. The most-chosen second prescription in addition to the first OHA was a DPP-4I in any patient prescribed with an OHA first that was not a DPP-4I. When a DPP-4I

**Table 1** | Detailed information of a single oral hypoglycemic agent initially prescribed and its prescripational course during 2 years (study 1;  $n = 7,108$ )

	Initial OHA continued for 2 years	Initial OHA stopped during 2 years and no prescription after that	Initial OHA stopped during 2 years and new OHA began	In addition to initial OHA, another OHA combined during 2 years	Total	Ratio of medication
SU	300 (22.9%)	402 (30.7%)	389 (29.7%)	219 (16.7%)	1,310 (100%)	18.4%
BG	429 (22.8%)	708 (37.6%)	408 (21.7%)	338 (18.0%)	1,883 (100%)	26.5%
$\alpha$ -GI	302 (27.9%)	420 (38.9%)	281 (26.0%)	78 (7.2%)	1,081 (100%)	15.2%
TZD	118 (19.9%)	215 (36.3%)	227 (38.3%)	32 (5.4%)	592 (100%)	8.3%
Glinide	120 (26.4%)	96 (21.2%)	194 (42.7%)	44 (9.7%)	454 (100%)	6.4%
DPP-4I	118 (6.6%)	1,427 (79.8%)	201 (11.2%)	42 (2.4%)	1,788 (100%)	25.2%
Total	1,387 (19.5%)	3,268 (46.0%)	1,700 (23.9%)	753 (10.6%)	7,108 (100%)	100%

$\alpha$ -GI,  $\alpha$ -glucosidase inhibitor; BG, biguanide; DPP-4I, dipeptidyl peptidase-4 inhibitor; OHA, oral hypoglycemic agent; SU, sulfonylurea; TZD, thiazolidinedione.

**Table 2** | Estimated degree of medication adherence of each oral hypoglycemic agent ( $n = 7,108$ )

	Initial OHA prescription					
	Estimated medication adherence of cases who continued single OHA for 2 years			Estimated medication adherence of cases who stopped the initial OHA during 2 years		
	≥80%	50–80%	<50%	≥80%	50–80%	<50%
SU	285 (21.8%)	7 (0.5%)	8 (0.6%)	387 (29.5%)	12 (0.9%)	3 (0.2%)
BG	409 (21.7%)	14 (0.7%)	6 (0.3%)	677 (36.0%)	25 (1.3%)	6 (0.3%)
α-GI	273 (25.3%)	23 (2.1%)	6 (0.6%)	382 (35.3%)	35 (3.2%)	3 (0.3%)
TZD	112 (18.9%)	4 (0.7%)	2 (0.3%)	197 (33.3%)	16 (2.7%)	2 (0.3%)
Glinide	117 (25.8%)	1 (0.2%)	2 (0.4%)	93 (20.5%)	3 (0.7%)	0
DPP-4I	111 (6.2%)	6 (0.3%)	1 (0.1%)	1,377 (77.0%)	39 (2.2%)	11 (0.6%)
Total	1,307 (18.4%)	55 (0.8%)	25 (0.4%)	3,113 (43.8%)	130 (1.8%)	25 (0.4%)

The estimated drug compliance of a single oral hypoglycemic agent (OHA) initially medicated was calculated by the total sum of the prescription days/the total observation days and expressed as ≥80%, 50–80% and <50%, respectively. α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4I, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

**Table 3** | Clinical profiles of type 2 diabetes mellitus patients treated with oral hypoglycemic agents in study 1 ( $n = 7,108$ )

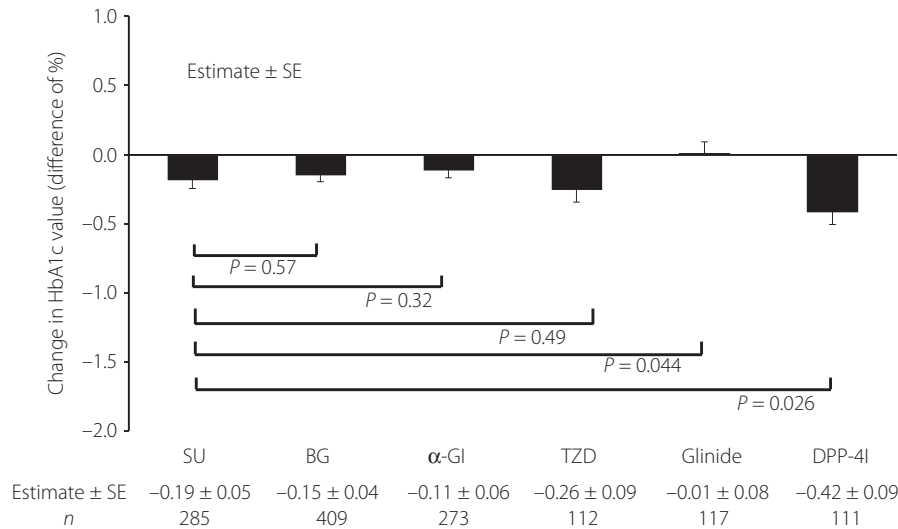
	SU		BG		α-GI		TZD		Glinide		DPP-4I	
	$n = 1,310$	$n = 1,883$	$P$ -value	$n = 1,081$	$P$ -value	$n = 592$	$P$ -value	$n = 454$	$P$ -value	$n = 1,788$	$P$ -value	
Age (years)	70 (69.3 ± 11.5)	61 (59.6 ± 13.0)	<0.001	67 (66.5 ± 12.3)	<0.001	64 (64.3 ± 11.5)	<0.001	69 (68.0 ± 11.6)	0.21	66 (65.3 ± 12.1)	<0.001	
Male	834 (63.7)	1,167 (62.0)	–	682 (63.1)	–	375 (63.3)	–	268 (59.0)	–	1,123 (62.8)	–	
Antihypertensive agent and antidiabetic agent												
None	300 (22.9)	695 (36.9)	–	282 (26.1)	–	137 (23.1)	–	129 (28.4)	–	558 (31.2)	–	
Both of them	402 (30.7)	482 (25.6)	–	383 (35.4)	–	223 (37.7)	–	125 (27.5)	–	522 (29.2)	–	
One of them	608 (46.4)	706 (37.5)	–	416 (38.5)	–	232 (39.2)	–	200 (44.1)	–	708 (39.6)	–	
HbA1c (NGSP %)	7.2 (7.6 ± 1.5)	7.1 (7.6 ± 1.6)	0.84	6.7 (6.8 ± 1.1)	<0.001	6.6 (6.9 ± 1.1)	<0.001	6.9 (7.0 ± 1.2)	<0.001	7.3 (7.7 ± 1.5)	0.15	
Minimum	4.7	4.8		4.6		4.9		4.6		4.2		
Maximum	14.5	15.1		15.5		12.2		15		17.7		
<6.5%	254 (19.4)	338 (18.0)	–	419 (38.8)	–	237 (40.0)	–	129 (28.4)	–	208 (11.6)	–	
6.5%≤	1,056 (80.6)	1,545 (82.0)	–	662 (61.2)	–	355 (60.0)	–	325 (71.6)	–	1,580 (88.4)	–	
Administration period of baseline drug (days)	583 (479 ± 269)	568 (467 ± 278)	0.62	510 (464 ± 267)	0.56	506 (459 ± 247)	0.41	554 (482 ± 254)	1.00	281 (324 ± 243)	<0.001	

Glycated hemoglobin (HbA1c) value indicates median (upper part) and mean ± standard deviation (lower part). α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4I, dipeptidyl peptidase-4 inhibitor; NGSP, National Glycohemoglobin Standardization Program; OHA, oral hypoglycemic agent; SU, sulfonylurea; TZD, thiazolidinedione.

was the first-choice OHA, the most-chosen second prescription was a BG. In patients treated continuously with an OHA first for 2 years, improvement in HbA1c levels was greatest in the DPP-4I group. Adherence to the first single OHA prescription for 2 years was highest for α-GIs. These trends of OHA prescriptions were similar, even if analyses were restricted to type 2 diabetes mellitus patients with a CVD history ( $n = 2,655$ ). The sample size for the analysis was not very large, because inclusion and exclusion criteria had to be adhered to strictly. Nevertheless, the present study might reflect (at least in part)

OHA prescription patterns in type 2 diabetes mellitus patients in Japan.

The finding that a BG is one of the two most prevalent initial prescriptions suggests that its recommendation as a first-choice OHA in an algorithm of type 2 diabetes mellitus treatment by ADA and EASD might be important even in Japan. One of the BG, metformin, has been shown to reduce CVD and improve mortality in UKPDS 34<sup>2</sup>. BGs have been reported to have favorable effects on bodyweight, lipid levels and blood pressure<sup>15</sup>, thereby providing an important rationale for using a BG as a



**Figure 1** | Changes in glycosylated hemoglobin (HbA1c) value (National Glycohemoglobin Standardization Program; mean ± standard error [SE]) between 0 weeks and 104 weeks for patients in whom a single oral hypoglycemic agent was continued for 2 years. 'n' denotes the number of patients (including patients without HbA1c data) at the week 104. The number of patients includes patients without HbA1c data at week 104. A total of 52 patients did not have HbA1c data at the final administration among 1,307 patients, so they were excluded from ANCOVA. Estimates and P-values by ANCOVA, \*P < 0.05.

**Table 4** | Second oral hypoglycemic agent added to the first single oral hypoglycemic agent

First single OHA	Second OHA							Total
	SU	BG	α-GI	TZD	Glinide	DPP-4	Other	
SU	—	54 (24.1%)	24 (10.7%)	14 (6.3%)	0	126 (56.3%)	6 (2.7%)	224 (100%)
BG	36 (10.7%)	—	20 (5.9%)	35 (10.4%)	7 (2.1%)	236 (69.8%)	4 (1.2%)	338 (100%)
α-GI	12 (15.4%)	17 (21.8%)	—	4 (5.1%)	4 (5.1%)	40 (51.3%)	1 (1.3%)	78 (100%)
TZD	5 (14.7%)	9 (26.5%)	5 (14.7%)	—	0	15 (44.1%)	0	34 (100%)
Glinide	0	11 (25.0%)	11 (25.0%)	1 (2.3%)	—	20 (45.5%)	1 (2.3%)	44 (100%)
DPP-4I	10 (23.8%)	19 (45.2%)	9 (21.4%)	3 (7.1%)	0	—	1 (2.4%)	42 (100%)
Total	63 (8.3%)	110 (14.5%)	69 (9.1%)	57 (7.5%)	11 (1.4%)	437 (57.5%)	13 (1.7%)	760 (100%)

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4I, dipeptidyl peptidase-4 inhibitor; OHA, oral hypoglycemic agent; SU, sulfonylurea; TZD, thiazolidinedione.

first-choice OHA in Western countries, where obese type 2 diabetes mellitus patients are predominant. The prevalence of a body mass index  $\geq 30$  kg/m<sup>2</sup> in Japanese individuals is <3%, whereas that in North Americans is >30%<sup>16</sup>. Nevertheless, the prevalence of type 2 diabetes mellitus patients in both countries is similar (7.4% in Japan and 8.0% in the USA), suggesting the importance of early care/intervention for mild obesity in Japan for type 2 diabetes mellitus prevention<sup>16</sup>. With a slight increase in the number of obese type 2 diabetes mellitus patients in Japan, attention to bodyweight might be reflected in selection of a BG or DPP-4I. Some reports have described trends for OHA prescription in Western countries. In a German cohort with type 2 diabetes mellitus from 2003 to 2009, metformin accounted for 63% of newly prescribed OHAs in 2003 and >80% in 2009, whereas SUs accounted for just 10%. The most commonly used second-line

OHA among metformin users were SUs (63.8%), followed by DPP-4Is/GLP-1 analogs (13.9%)<sup>17</sup>. In data dispensed from USA retail pharmacies between 2003 and 2012, use of metformin increased by 97.0% in prescription number during that decade. In 2012, the most commonly prescribed non-insulin antidiabetic drug was metformin (49.9%), followed by SUs (26.7%) and DPP-4Is (8.0%)<sup>18</sup>. Those data suggested that in Western countries, BG was the most commonly used OHA, based on ADA/EASD guidelines. However, even in USA data from 2012, despite an increasing share, DPP-4Is were prescribed not so commonly compared with the present data. The present data suggest that the use of DPP-4Is in Japan is spreading more rapidly than in Western countries.

According to the Japan Medical Information Research Institute, the share of DPP-4Is of the total OHA market reached

69% in 2015. The expanding market of DPP-4Is (even in 2013) might have resulted in the finding that DPP-4Is were one of the two most prevalent initial prescriptions and the most-chosen second prescription in addition to the first OHA. There are many benefits of incretin therapy, such as pancreatic  $\beta$ -cell preservation, lower risk of weight gain and fewer hypoglycemic attacks. In addition, incretin is a therapeutic option for the treatment of type 2 diabetes, even during end-stage renal disease<sup>19–21</sup>. In the present study, DPP-4Is were stopped during 2 years in  $\approx$ 80% of cases. Some patients might have stopped DPP-4I intake or physicians might have stopped the prescription because of relatively good glycemic control during the 2 years.

Combination therapy of a DPP-4I with a BG is rational. DPP-4Is increase GLP-1 levels, thereby stimulating insulin secretion and inhibiting secretion of glucagon<sup>22</sup>. Metformin has been shown to inhibit glucagon secretion<sup>23</sup> and increase GLP-1 levels<sup>24</sup>, which might be caused (at least in part) by inhibition of DPP-4<sup>25</sup> or increase in GLP-1 secretion from the gut<sup>26</sup>. Amplification of GLP-1 actions by metformin is also expected from increases in the numbers of GLP-1 receptors on pancreatic  $\beta$ -cells<sup>23</sup>. In the present study, when BG was the first OHA, the second OHA was a DPP-4I in 69.8% of cases. When a DPP-4I was the first OHA, the second OHA was a BG in 45.2% of cases. Good combination of a DPP-4I and an  $\alpha$ -GI is suggested from the finding that an  $\alpha$ -GI can increase GLP-1 secretion from the small intestine<sup>27</sup>, thereby possibly leading to a synergistic effect in lowering postprandial glucose levels and avoiding hypoglycemia. However, this combination was not observed frequently in the present study.

A SU was the first medication noted in 18.4% of cases. SUs have been thought to overcome the problem of low secretion of insulin in Japanese individuals compared with Western individuals<sup>28</sup>. The relatively low use of a SU in Western countries<sup>17,18</sup> can be linked to several concerns. Though not observed as often as with insulin, SUs carry a relatively higher risk of hypoglycemia<sup>29</sup> and weight gain<sup>2,30</sup>, both of which are thought to increase CVD risk. SUs bring about very effective improvement in HbA1c levels for a few years, but such improvement is not long-lived, probably owing to the failure of pancreatic  $\beta$ -cells<sup>30,31</sup>. Prescription of SUs seems to have shifted from high dose to low dose, and in combination with other OHAs.

Interestingly, adherence to the first OHA for 2 years was highest for  $\alpha$ -GIs. Low initial levels of HbA1c in  $\alpha$ -GIs among all OHAs could be (at least in part) for type 2 diabetes mellitus control being achieved for 2 years. However, initial levels of HbA1c of TZDs, glinides and BGs were not very different from those of  $\alpha$ -GIs, so the reason might be more complicated. It has been shown in Japanese type 2 diabetes mellitus patients that the larger the carbohydrate intake in food, the larger the blood glucose-lowering effect by  $\alpha$ -GIs is<sup>31</sup>. Japanese individuals are known to consume a relatively higher proportion of carbohydrates ( $\approx$ 60% of a meal) compared with Western subjects

( $\approx$ 40% of a meal). Actually,  $\alpha$ -GIs are scarcely used in Western countries<sup>17,18</sup>. Thus, certain Japanese people with type 2 diabetes mellitus might be very sensitive to treatment with  $\alpha$ -GIs, thereby resulting in good adherence to treatment. Possible prevention of CVD risk by the suppression of postprandial blood sugar as evidenced by The Study to Prevent Non-Insulin Dependent Diabetes Mellitus<sup>4</sup> might be also evaluated.

Finally, we investigated whether a CVD history could affect the initial choice of OHA medication in type 2 diabetes mellitus patients. Roumie *et al.*<sup>32</sup> analyzed the efficacy of OHAs for the prevention of CV events. It has been reported (including the present research team) that metformin can reduce the prevalence of death compared with SUs<sup>32</sup>. The Study to Prevent Non-Insulin Dependent Diabetes Mellitus showed that the prevalence of CV events or hypertension was reduced significantly in patients using one type of  $\alpha$ -GI: acarbose<sup>4</sup>. Meta-analyses of seven clinical trials focusing on acarbose showed similar results<sup>5</sup>.  $\alpha$ -GIs are also recommended in International Diabetes Federation guidelines for management of postprandial glucose published in 2008 with the highest evidence level<sup>33</sup>. The TZD, pioglitazone, has been shown to slow atherosclerosis in type 2 diabetes mellitus patients as estimated by progression of maximal carotid intima-media thickness<sup>6</sup> and by coronary atherosclerosis<sup>7</sup> compared with glimepiride. GLP-1-based therapy (which includes DPP-4Is and GLP-1 receptor agonists) has become popular treatment for type 2 diabetes mellitus patients. The DPP-4I, sitagliptin, has been speculated to lower the prevalence of CVD<sup>8</sup>. However, recent large-scale studies have reported that, among patients with type 2 diabetes mellitus who had recently experienced acute coronary syndrome, the prevalence of major adverse CV events was unchanged with the DPP-4Is, saxagliptin<sup>34</sup>, alogliptin<sup>35</sup> or sitagliptin<sup>36</sup>, as compared with a placebo, despite better control of HbA1c levels with both DPP-4Is than with a placebo. Those results suggest that some OHAs might have beneficial effects in reducing CVD events in individuals with type 2 diabetes mellitus. However, as shown in study 2, a CVD history did not affect the first choice of OHA. CVD might not be as essential for selection of the first OHA in type 2 diabetes mellitus patients. Although we could not obtain information regarding prescription of anticoagulant drugs, such kinds of drugs might be more respected than OHA selection for the secondary prevention of CVD.

The present study had limitations. First, as described above, the number of patients assessed was small. Second, the present study was not a prospective type of cohort analysis, which made evaluation of the clinical impact of each OHA on HbA1c levels difficult. Third, obtaining detailed information on the types of and dose of OHA was difficult. Fourth, the ratio of the specialty of physicians (diabetes/endocrinology/cardiology specialist or general physician) administering OHAs might have affected prescription patterns, but this information was difficult to obtain from this database. Fifth, clinical information for each patient that might affect prescription pattern was limited. Nevertheless, the present study showed the true situation of OHA

prescribing in type 2 diabetes mellitus patients in Japan to some extent.

In conclusion, treatment algorithms from the ADA and EASD for prescription of OHAs for Japanese type 2 diabetes mellitus patients seem to have been respected to some extent. Increased use of a DPP-4I as a first-line or second-line OHA seems to be characteristic. These choices of OHA do not seem to be affected by a CVD history.

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## DISCLOSURE

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