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ORIGINAL ARTICLE

Persistence of oral antidiabetic treatment for type 2 diabetes characterized by drug class, patient characteristics and severity of renal impairment: A Japanese database analysis

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Aim: To evaluate the persistence with oral antidiabetic drug (OAD) treatment characterized by drug class, patient characteristics and severity of renal impairment (RI) in patients with type 2 diabetes (T2DM) in Japan.

Materials and Methods: This retrospective, observational study extracted data from a large-scale hospital database (April 2008 to September 2016). Patients with T2DM aged ≥40 years on the day of their first prescription (index date) of any OAD (biguanides [BGs], thiazolidinediones [TZDs], sulphonylureas [SUs], glinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, or α-glucosidase inhibitors [α-GIs]) available between January 1, 2014 and September 30, 2016 were identified. Sodium-glucose co-transporter-2 inhibitors were not available at study initiation. Treatment persistence was assessed by Kaplan–Meier survival curves. Patients were also categorized by RI status using estimated glomerular filtration rate: ≥90 mL/min/1.73 m^2 (G1); 60 to <90 mL/min/1.73 m^2 (G2); 30 to <60 mL/min/1.73 m^2 (G3); and <30 mL/min/1.73 m^2 (G4+).

Results: We identified 206 406 index dates from 162 116 eligible patients. The largest number of index dates (91634) was observed for DPP-4 inhibitors, followed by BGs, SUs, α-GIs, glinides and TZDs. Treatment persistence was longest for DPP-4 inhibitors (median 17.0 months, 95% confidence interval [CI] 16.4-17.5) and BGs (median 17.3 months, 95% CI 16.6-18.2), and shortest for α-GIs (median 5.6 months, 95% CI 5.4-5.9) and SUs (median 4.3 months, 95% CI 4.2-4.6). Persistence was longest with DPP-4 inhibitors at all RI stages (G1–G4+), followed by BGs at stages G1/G2.

Conclusions: The longest OAD persistence was observed for BGs and DPP-4 inhibitors at RI stages G1/G2, and for DPP-4 inhibitors at RI stages G3/G4+.

KEYWORDS

antidiabetic drug, database research, DPP-4 inhibitor, observational study, pharmacoepidemiology, type 2 diabetes

1 | INTRODUCTION

The worldwide prevalence of diabetes is rising, and Japan ranks among the top 10 countries in terms of the number of adults with diabetes.[1] The Japan Ministry of Health, Labour and Welfare estimated that in 2014, 3.2 million patients had diabetes and were receiving continuous treatment,[2] equating to 1.22 trillion yen in annual medical expenditure.[3] Based on a systematic sub-analysis of the Global Burden of Disease Study 2015, diabetes was the 28th leading cause of death and 14th leading cause of disability-adjusted life years in Japan in 2015.[4]

The Japan Diabetes Society recommends oral antidiabetic drugs (OADs), insulin and glucagon-like peptide-1 receptor agonists for patients with non-insulin-dependent type 2 diabetes mellitus (T2DM) with poorly controlled blood glucose levels after 2 to 3 months of diet and exercise.[5] The choice of OADs depends on disease status, with consideration of the characteristics and side effects of each drug. Based on the underlying cause of T2DM, patients may be prescribed insulin-sensitizing agents (biguanides [BGs] or thiazolidinediones [TZDs]), insulin secretagogues (sulphonylureas [SUs], glinides or dipeptidyl peptidase-4 [DPP-4] inhibitors), or carbohydrate absorption/excretion-modulating agents (α-glucosidase inhibitors [α-GIs] or sodium-glucose co-transporter-2 [SGLT2] inhibitors). Notably, although no recommended guidelines exist for their concurrent use, DPP-4 inhibitors were the most frequently prescribed OAD class during the last decade in Japan.[6]

In patients with T2DM and renal impairment (RI), all drugs, including OADs, and particularly those that affect renal metabolism and excretion, should be used according to their prescribing information with due consideration to the patient's glomerular filtration rate (GFR).[5] In general, all OADs can be used in patients with mild RI; however, treatment options for patients with moderate-to-severe chronic kidney disease or end-stage renal disease (ESRD) are limited because reduced GFR may lead to drug or metabolite accumulation and subsequent side effects.[7]

Because T2DM requires long-term treatment, patients must remain adherent to and persistent with their prescribed OADs to optimize clinical benefits.[8] According to the World Health Organization, non-adherence to long-term medications for diseases such as hypertension, dyslipidaemia and diabetes is common, leading to compromised clinical outcomes and major economic consequences.[9] Patients' likelihood of maintaining adherence to and persistence with treatment is important, therefore, when choosing from a complex array of OADs.[8–11] According to a literature review of six retrospective observational studies from the United States, Canada and Europe between January 2000 and November 2005, the mean estimated OAD persistence over 6 to 24 months was 56% (95% confidence interval [CI] 46-66), with estimates ranging from 41% to 81%.[12] Although treatment adherence and persistence may be assessed as part of rigorously controlled clinical trials involving specific patient populations with diabetes,[13] reports of real-world OAD adherence and persistence rates are limited, particularly in Japan.[14,15]

To our knowledge, this is the first large-scale, real-world evaluation of treatment persistence, patient characteristics and severity of RI among classes of OADs in T2DM patients in Japan.

2 | MATERIALS AND METHODS

2.1 | Study objectives

The study objectives were to analyse treatment persistence and patient characteristics stratified by OAD class, individual DPP-4 inhibitors, RI category at index date, and lines of therapy (1, 2 and 3+).

2.2 | Study design and data source

This retrospective, observational cohort study collected data from a large-scale hospital database provided by Medical Data Vision (Tokyo, Japan) to determine the persistence with OADs in patients with T2DM in Japan. The details of the database are provided in the Supporting Information. The study period for individual patients consisted of a look-back period (6 months before the index date) for history of drug prescription,[16] index date (date of first OAD prescription), and administration/observation period (assessment of persistence). The study protocol was reviewed and approved by the Keio University Faculty of Pharmacy Ethics Committee for Research Involving Humans (170217-1) and was registered with ClinicalTrials.gov (NCT03092752).

2.3 | Patient eligibility

Eligible patients had a diagnosis of T2DM (International Classification of Diseases 10th Revision [ICD-10] code E11–E14),[17] had received any OAD prescription, and had data available during the look-back period. Index date for an OAD was defined as the date of first prescription of that OAD for a patient and was determined between January 1, 2014 and September 30, 2016. January 1, 2014, was selected as the start date for data retrieval in this study to enable assessment of all seven DPP-4 inhibitors, which could be prescribed starting from a similar time point. In Japan, prescriptions are limited to 2 weeks for a period of 1 year after product launch; therefore, patients who visit the hospital every 2 weeks are able to access the necessary prescription. Seven DPP-4 inhibitors had entered the Japanese market in succession by July 2013. Multiple OADs in the first OAD prescription contributed to multiple index dates. Additional eligibility criteria were age ≥40 years at the time of T2DM diagnosis, no diagnosis of type 1 diabetes mellitus (ICD-10 code E10), no prescription for the OAD during the look-back period, and average of <92 days between hospital visits (excluding periods of inpatient hospitalization). Detailed information regarding the data source used in this study, study drugs prescribed to patients, and determination of index dates for comparison of drugs are provided in the Appendix S1.

2.4 | Analyses and statistical methods

Treatment persistence was defined as the duration of time from the index date to the first occurrence of discontinuation for each OAD class. OAD treatment was considered to be discontinued when there was a treatment gap of ≥30 days between two subsequent visits and days of drug supply.

For between-OAD class analysis, continuation was defined as continuing the same drug or switching drugs within a class; switching to another drug class was defined as discontinuation. Estimated GFR (eGFR) was calculated based on sex, age at index date, and the most recent serum creatinine value at the index date or during the look-back period using the following formula recommended by the Japanese Society of Nephrology,[18] where Cr is serum creatinine (mg/dL).

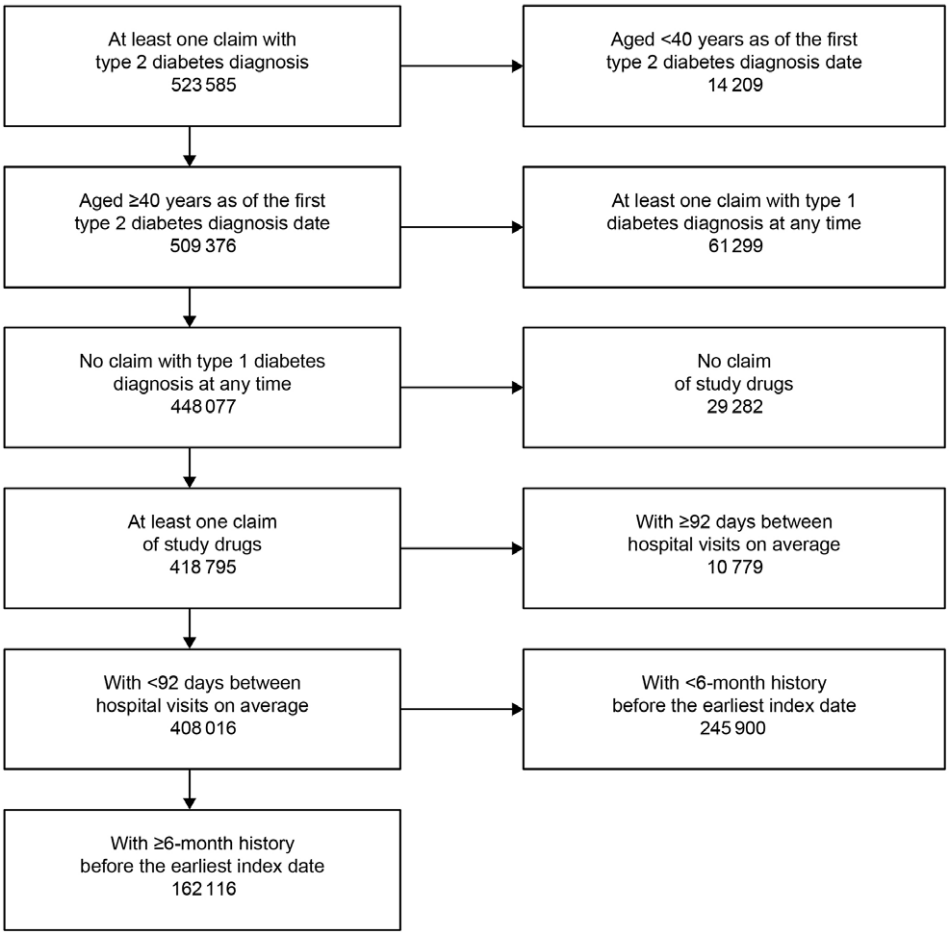


FIGURE 1 Flowchart of patient eligibility criteria

$$eGFR\left(\frac{\frac{mL}{min}}{1.73m^2}\right) = 194 \times Cr^{-1.094} \times age(years)^{-0.287} (\times 0.739 if\ female)$$

Categories of eGFR/RI were defined by the following stages: G1 (eGFR ≥90 mL/min/1.73 m^2; normal or high kidney function), G2 (60 to <90 mL/min/1.73 m^2; normal or mildly decreased kidney function), G3a (45 to <60 mL/min/1.73 m^2; mildly or moderately decreased kidney function), G3b (30 to <45 mL/min/1.73 m^2; moderately to severely decreased kidney function), G4 (15 to <30 mL/min/1.73 m^2; severely decreased kidney function), and G5 (<15 mL/min/1.73 m^2; ESRD). Comorbidities were defined by ICD-10 code (Table S1, Appendix S1) and categorized by baseline RI at the index date (Table S2, Appendix S1).

Descriptive statistics were used for patient demographics and characteristics stratified by OAD class and RI stage. Treatment persistence for each OAD class by RI stage, and for RI stage by OAD class, was determined using Kaplan–Meier survival curves. The median survival time representing median persistence was estimated from the Kaplan–Meier plot. Sensitivity analyses were performed by re-evaluating baseline patient characteristics for OAD class and individual DPP-4 inhibitors by reducing the duration of the look-back period from 6 to 3 months, thereby increasing the number of index dates, and by re-evaluating OAD persistence by modifying the definition of discontinuation from a treatment gap of ≥30 to ≥60 days. Data analyses were performed using Excel 2010 (Microsoft, Redmond, Washington) and SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Between-OAD class analyses: patient characteristics and OAD prescribing patterns

Of 523 585 patients with a T2DM diagnosis identified from the database, 162 116 met the eligibility criteria (Figure 1). Overall, 206 406 OAD index dates were identified, most commonly for DPP-4 inhibitors (91 634; 44%), followed by BGs, SUs, α-GIs, glinides and TZDs (Table 1). Among SUs, 24 101 index dates were identified for glimepiride, 2903 for gliclazide, 1202 for glibenclamide, and five for tolbutamide.

Most patients (61%) were men, and the proportions of men were similar (61%-63%) across all OAD classes. The mean (SD) age of patients at the index date was 70.7 (11.2) years; 73% of patients were aged ≥65 years and 40% were aged ≥75 years. Patients who were prescribed BGs were younger than those prescribed other OAD classes (mean [SD] 66.5 [11] years vs 69.7 [11.4] to 72 [11.1] years). The mean (SD) follow-up duration was 363 (282) days. The mean (SD) glycated haemoglobin (HbA1c) levels were similar between classes. The mean (SD) eGFR was 65.2 (28.1) mL/min/1.73 m^2 at the

TABLE 1 Characteristics of patients categorized by index dates in each oral antidiabetic drug class

	Total	DPP-4 inhibitors	BGs	SUs	α-GIs	Glinides	TZDs
Number of index dates	206 406	91 634	33 238	28 211	26 192	16 787	10 344
Men, %	61	61	62	61	62	61	63
Age at index date							
Mean ± SD age, years	70.7 ± 11.2	71.6 ± 11.0	66.5 ± 11.0	72 ± 11.1	71.4 ± 10.8	71.4 ± 10.8	69.7 ± 11.4
≤64 years, %	27	24	39	23	24	24	30
65 to 74 years, %	33	33	36	31	33	34	33
≥75 years, %	40	43	24	45	43	42	37
Mean ± SD follow-up duration, days	363 ± 282	360 ± 283	370 ± 281	357 ± 286	361 ± 281	361 ± 270	383 ± 284
Mean ± SD HbA1c, %	7.5 ± 1.5	7.4 ± 1.5	7.7 ± 1.6	7.6 ± 1.5	7.5 ± 1.5	7.6 ± 1.5	7.7 ± 1.6
eGFR at index date							
Mean ± SD eGFR, mL/min/1.73 m^2	65.2 ± 28.1	63 ± 28.8	74 ± 23.9	67.4 ± 26.4	60.1 ± 29.4	59.5 ± 30.2	69.7 ± 23.7
G1 (≥90 mL/min/1.73 m^2), *n* (%)	3868 (15)	1592 (14)	838 (19)	530 (16)	429 (14)	252 (13)	227 (17)
G2 (60 to <90 mL/min/1.73 m^2), *n* (%)	11 188 (44)	4877 (43)	2373 (55)	1446 (44)	1175 (37)	691 (37)	626 (48)
G3 (30 to <60 mL/min/1.73 m^2), *n* (%)	7776 (31)	3566 (31)	1045 (24)	1090 (33)	1055 (34)	610 (32)	410 (31)
G4+ (<30 mL/min/1.73 m^2), *n* (%)	2554 (10)	1411 (12)	67 (2)	208 (6)	488 (16)	337 (18)	43 (3)
Comorbidities at index date, %							
Hypertension	68	69	66	66	70	73	68
Ischaemic heart disease	30	30	27	29	33	33	28
Myocardial infarction	14	14	13	14	15	14	12
Heart failure	24	25	19	23	27	28	19
Stroke	25	26	22	26	26	27	25
RI	18	19	10	14	23	26	11
Diabetic foot	3	4	3	3	4	5	3
Previous treatment[a], %							
DPP-4 inhibitors	1	0	3	2	1	3	8
BGs	1	2	0	1	2	3	2
SUs	4	3	2	0	3	19	2
α-GIs	2	2	2	1	0	8	1
Glinides	1	1	1	3	2	0	0
TZDs	1	2	2	1	1	1	0
Insulin	9	9	7	12	10	12	8
Concomitant treatment at index date[b], %							
DPP-4 inhibitors	23	3	40	32	37	56	34
BGs	10	9	0	11	12	20	19
SUs	10	9	17	1	13	4	21
α-GIs	8	8	9	6	2	16	10
Glinides	3	2	3	1	4	4	4
TZDs	3	2	4	2	3	6	1
Insulin	27	27	23	25	31	37	24
Number of concomitant treatments at index date[b] in class, %							
0	45	55	38	45	38	20	38
1	34	33	37	37	34	37	29
2+	21	12	26	19	28	43	34

Abbreviations: α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; RI, renal impairment; SU, sulphonylurea; TZD, thiazolidinedione.

[a] Previous treatment was defined as medications prescribed before, but not after, the index date.

[b] Concomitant treatments were defined as medications prescribed with the first oral antidiabetic drug prescription at the index date or prescribed during the administration and were analysed as individual drugs.

index date; eGFR was highest in patients prescribed BGs (74 [23.9] mL/min/1.73 m^2) and lowest in those prescribed α-GIs (60.1 [29.4] mL/min/1.73 m^2) and glinides (59.5 [30.2] mL/min/1.73 m^2). The percentages of patients with index dates for DPP-4 inhibitors, BGs, SUs, α-GI, glinides and TZDs among patients with RI stage G4+ (12%, 2%, 6%, 16%, 18% and 3%) were lower than for those with RI stage G3 (31%, 24%, 33%, 34%, 32%, and 31%), respectively. The most common comorbidity at the index date was hypertension (68%); 18% of patients had RI. Comorbidities were more common among patients who were prescribed glinides and α-GIs, and less common among

TABLE 2 Characteristics of patients categorized by index dates for each generic DPP-4 inhibitor

	DPP-4 inhibitor						
	Sitagliptin	**Vildagliptin**	**Alogliptin**	**Linagliptin**	**Teneligliptin**	**Anagliptin**	**Saxagliptin**
Number of index dates	39 576	22 592	10 930	31 353	18 284	2051	3134
Men, %	60	60	61	62	61	60	60
Age at index date							
Mean ± SD age, years	71.7 ± 11.0	70.3 ± 11.2	71 ± 10.9	72.5 ± 10.8	70.9 ± 10.9	68.6 ± 10.8	69.3 ± 10.5
≤64 years, %	24	28	26	22	26	33	30
65 to 74 years, %	33	33	34	31	34	34	37
≥75 years, %	43	39	40	47	40	32	33
Mean ± SD HbA1c, %	7.4 ± 1.5	7.4 ± 1.3	7.3 ± 1.3	7.2 ± 1.4	7.3 ± 1.3	7.5 ± 1.4	7.4 ± 1.4
eGFR at index date							
Mean ± SD eGFR mL/min/1.73 m^2	69.3 ± 26.2	62.5 ± 30.8	64.2 ± 26.4	50.9 ± 29.2	60.6 ± 28.2	69 ± 21.5	61.7 ± 25.5
G1 (≥90 mL/min/1.73 m^2), *n* (%)	800 (16)	324 (14)	262 (14)	323 (8)	239 (12)	44 (15)	52 (12)
G2 (60 to <90 mL/min/1.73 m^2), *n* (%)	2496 (50)	966 (41)	845 (46)	1104 (29)	764 (40)	148 (51)	203 (47)
G3 (30 to <60 mL/min/1.73 m^2), *n* (%)	1479 (30)	774 (33)	538 (29)	1411 (37)	636 (33)	94 (32)	127 (29)
G4+ (<30 mL/min/1.73 m^2), *n* (%)	223 (4)	311 (13)	205 (11)	985 (26)	276 (14)	7 (2)	54 (12)
Comorbidities at index date, %							
Hypertension	66	70	70	77	75	72	75
Ischaemic heart disease	27	31	32	37	34	31	33
Myocardial infarction	13	14	14	17	15	12	14
Heart failure	22	26	26	34	30	25	25
Stroke	26	25	26	29	27	26	25
RI	12	20	16	31	24	11	22
Diabetic foot	3	4	3	5	4	2	4
Previous treatment[a], %							
DPP-4 inhibitors	6	28	15	20	32	42	32
BGs	1	5	2	3	2	1	1
SUs	3	3	3	4	4	3	3
α-GIs	2	2	2	2	3	3	3
Glinides	1	1	1	1	1	1	1
TZDs	1	1	5	2	2	2	1
Insulin	9	7	7	8	6	3	5
Concomitant treatment at index date[b], %							
DPP-4 inhibitors	1	2	2	2	2	3	2
BGs	10	18	16	11	16	32	21
SUs	10	18	15	13	19	24	20
α-GIs	7	12	11	11	14	17	14
Glinides	2	4	3	3	4	7	6
TZDs	3	4	4	3	4	7	4
Insulin	26	27	20	31	25	15	22
Launch	Dec 2009	Apr 2010	Jun 2010	Sep 2011	Sep 2012	Nov 2012	Jul 2013

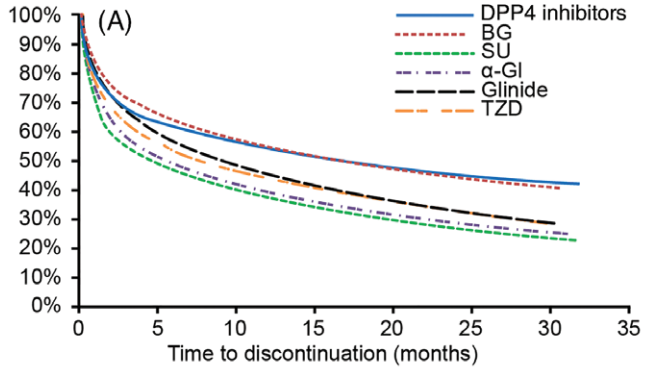
Abbreviations: α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; RI, renal impairment; SU, sulphonylurea; TZD, thiazolidinedione.

[a] Previous treatment was defined as medications prescribed before, but not after, the index date.

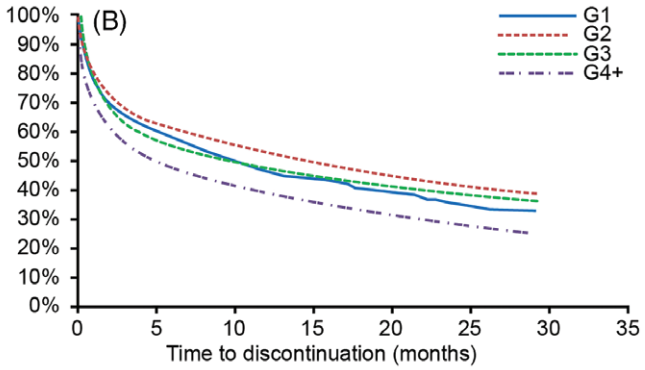
[b] Concomitant treatments were defined as medications prescribed with the first oral antidiabetic drug prescription at the index date or prescribed during the administration and were analysed as individual drugs.

those prescribed BGs and TZDs. For example, compared with those prescribed other OADs, fewer patients prescribed BGs or TZDs had comorbid heart failure (23%-28% vs 19%) and RI (14%-26% vs 10% and 11%).

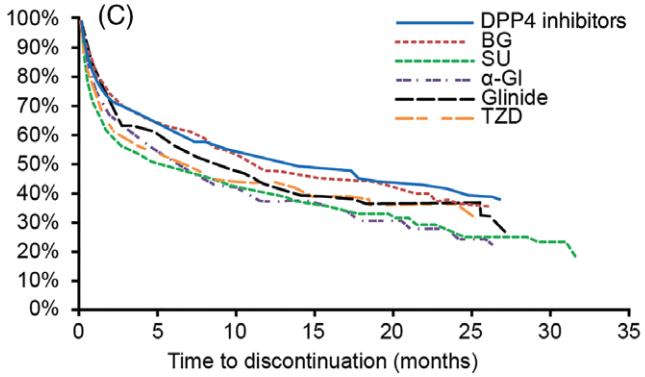
Previous treatment was noted in 0% to 19% of index dates categorized by drug class (Table 1); 19% of glinide prescriptions resulted from switching from SUs. Overall, 8% to 12% of all OAD prescriptions resulted from switching from insulin. The relative frequency of prescribing a concomitant treatment in each OAD class was similar to the relative number of index dates; DPP-4 inhibitors were the highest (23% overall) and were prescribed for 56% of patients taking glinides and 40% of patients taking BGs. The rate of added use of concomitant treatments was lowest for DPP-4 inhibitors (45%) and SUs (55%) and was highest for glinides (80%); glinides also contributed to the highest



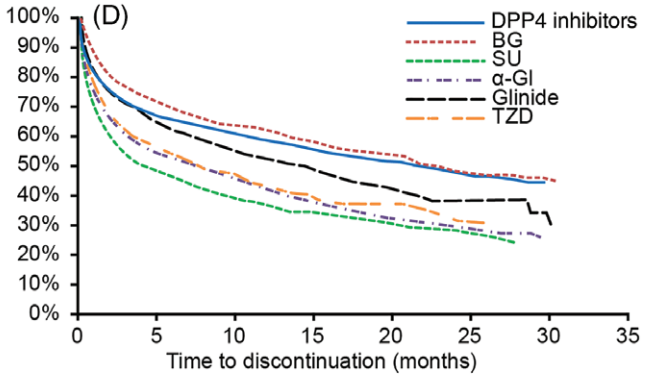
	Median (95% CI) months	Index dates (*n*)
DPP4I	17.0 (16.4–17.5)	91 634
BG	17.3 (16.6–18.2)	33 238
SU	4.3 (4.2–4.6)	28 211
α-GI	5.6 (5.4–5.9)	26 192
Glinide	9.2 (8.8–9.7)	16 787
TZD	8.2 (7.7–8.9)	10 344



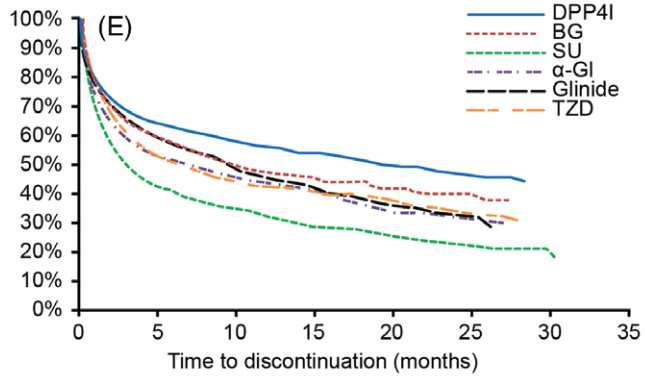
	Median (95% CI) months	Index dates (*n*)
G1	10.1 (8.8–11.2)	3868
G2	15.1 (13.8–16.2)	11 188
G3	10.3 (9.4–11.4)	7776
G4+	5.2 (4.3–6.2)	2554



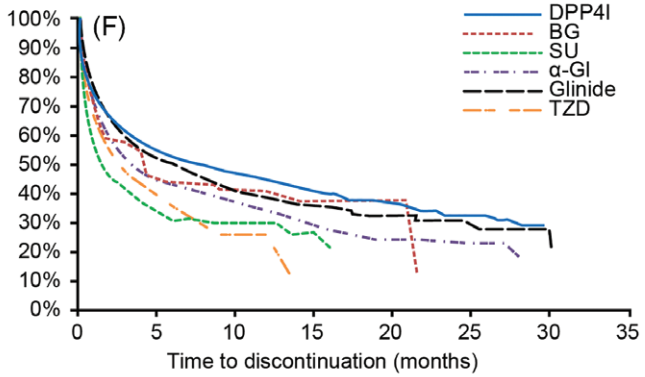
	Median (95% CI) months	Index dates (*n*)
DPP4I	13.7 (11.1–17.7)	1592
BG	11.1 (9.6–14.2)	838
SU	5.5 (3.5–8.3)	530
α-GI	6.3 (4.9–8.7)	429
Glinide	8.4 (5.8–12.1)	252
TZD	6.2 (3.9–14)	227



	Median (95% CI) months	Index dates (*n*)
DPP4I	21.9 (19.7–23.6)	4877
BG	21.8 (20.7–26.1)	2373
SU	4.1 (3.3–5.7)	1446
α-GI	7.4 (5.6–8.6)	1175
Glinide	13.3 (10.0–17.1)	691
TZD	7.9 (5.6–10.5)	626



	Median (95% CI) months	Index dates (*n*)
DPP4I	19.0 (17.1–22.3)	3566
BG	9.5 (7.7–12.6)	1045
SU	3.0 (2.3–3.8)	1090
α-GI	6.4 (4.7–9.6)	1055
Glinide	9.6 (7.0–11.2)	610
TZD	6.3 (4.2–9.1)	410



	Median (95% CI) months	Index dates (*n*)
DPP4I	7.4 (6.0–9.8)	1411
BG	4.0 (1.4–21.5)	67
SU	1.4 (1.0–2.5)	208
α-GI	3.0 (2.3–5.0)	488
Glinide	6.0 (3.9–8.8)	337
TZD	2.3 (1.2–7.0)	43

FIGURE 2 Persistence rates A, by oral antidiabetic drug (OAD) class in all patients, B, by estimated glomerular filtration rate (eGFR) stage of renal impairment (RI) and by OAD class for each eGFR stage of RI, C, stage G1, D, stage G2, E, stage G3 and F, stage G4+. α-GI, α-glucosidase inhibitor; BG, biguanide; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; SU; sulphonylurea; TZD, thiazolidinedione

concomitant treatments with ≥2 OAD classes for 43% of patients, followed by TZDs (34%).

3.2 | Within-OAD class analyses: patient characteristics and DPP-4 inhibitor prescribing patterns

In total, 91 634 DPP-4 inhibitor index dates were identified, most commonly for sitagliptin, followed by linagliptin, vildagliptin, teneligliptin and alogliptin. Anagliptin and saxagliptin, the last two DPP-4 inhibitors to be launched, were not commonly prescribed (Table 2). The mean age and ratio of men to women were similar across different DPP-4 inhibitor groups; however, within each group, prescribing patterns differed by age, level of RI, and rates of comorbidities. For example, almost half of the patients who were prescribed linagliptin were aged ≥75 years with eGFR <60 mL/min/1.73 m^2 (G3/G4+), whereas almost half the patients prescribed other DPP-4 inhibitors had eGFR ≥60 mL/min/1.73 m^2 (G1/G2). Also, patients prescribed linagliptin showed the highest rate of comorbidities and concomitant insulin use. DPP-4 inhibitors were the most commonly prescribed previous treatment for each individual drug in this class. The proportion of patients switching from another DPP-4 inhibitor was consistent with the timing of the launch of these new drugs, except for vildagliptin and saxagliptin.

In the sensitivity analyses with the look-back period shortened from 6 to 3 months, the number of index dates increased by 23 820 (10%), with DPP-4 inhibitors accounting for 7784 (33%) of the total increase (Table S3, Appendix S1). No remarkable differences were observed against the primary analysis in patient characteristics, comorbidities and relative distribution of index dates in each OAD class, proportion of previous treatments, or proportion of concomitant treatments. Across DPP-4 inhibitors, the number of index dates increased relative to the timing of new drug launches, with sitagliptin—the earliest DPP-4 inhibitor to be released—accounting for over half of the new index dates (4157/7784; 53% [Table S4, Appendix S1]).

3.3 | RI stage analyses: patient characteristics

The mean (SD) age of patients at RI stages G1, G2, G3 and G4+ was 65.6 (12.2), 69.5 (10.7), 75.0 (9.8) and 73.2 (10.8) years, respectively. In general, HbA1c level decreased and the proportions of patients with each comorbidity increased with severity of RI (Table S2, Appendix S1). Among patients without available serum creatinine data, age and proportions of patients with each comorbidity were in the range of values for patients at RI stages G2 and G3, except for myocardial infarction and diabetic foot.

3.4 | Between-OAD class analyses: treatment persistence

Treatment persistence was longest for DPP-4 inhibitors (median 17.0 [95% CI 16.4-17.5] months) and BGs (median 17.3 months [95% CI 16.6-18.2]) and shortest for α-GIs (median 5.6 months [95% CI 5.4-5.9]) and SUs (median 4.3 months [95% CI 4.2-4.6]; Figure 2A). In the sensitivity analyses with a less stringent definition of persistence, treatment persistence was extended by ~70% for all OAD classes; the relative order of persistence rates among drug classes was maintained (Figure S1, Appendix S1). Irrespective of the number of concomitant drugs (or line of treatment) at the index date, treatment persistence was longest for DPP-4 inhibitors and BGs and shortest for α-GIs and SUs (Figure S2, Appendix S1).

3.5 | RI stage analyses: treatment persistence

In general, treatment persistence (assessed as time to discontinuation) for OADs was longest in patients at RI stage G2, similar between patients in stages G1 and G3, and shortest at stage G4+ (Figure 2B). Persistence with each drug class varied by RI stage, and was longest for DPP-4 inhibitors at all RI stages, followed by BGs at RI stages G1 and G2 (Figure 2C-F).

4 | DISCUSSION

The results of the present retrospective, real-world database analysis show that, among the OADs evaluated, DPP-4 inhibitors and BGs were the most frequently prescribed OAD classes, with the longest treatment persistence. These findings are similar to those from previous reports in Japan.[6,19,20] TZDs and glinides were the least frequently prescribed OADs, and treatment persistence was shortest for α-GIs and SUs. We believe treatment persistence is a result of several factors, including a balance of effectiveness, tolerability, safety, superior utility and cost. Specifically, the increased risk of hypoglycaemia associated with SUs[5,21] and reduced quality of life linked to α-GIs in comparison with DPP-4 inhibitors[13,22] may have been related to the poor persistence observed for these OADs.

When treatment persistence was evaluated by severity of RI at the index date, persistence was shortest in patients at RI stage G4+ and varied for each OAD drug class by the RI stage. The longest persistence was observed with DPP-4 inhibitors across all RI stages (G1-G4+), followed by BGs at stages G1 and G2, and subsequently by glinides across all stages (G1-G4+). The number of index dates for BGs (208), SUs (67) and TZDs (43) was lowest for RI stage G4+, suggesting that OADs are generally prescribed properly by physicians, in accordance with the Guidelines for the Treatment of Diabetes in Japan.[5]

Considering patient baseline characteristics, the increasing severity of RI was consistent with ageing and higher rates of comorbidities.[23,24] The younger average age of patients at RI stage G1 could explain why persistence appears lower than for those at stage G2 in our analysis[15]; however, in general, treatment persistence rates declined with increasing severity of RI. This could be attributed to switching to other drugs without prescription restrictions in patients with increasing severity of RI, a reduced requirement for OADs because of a decline in blood sugar, and an increased risk of hypoglycaemia.[25] Although we observed similar (but longer) persistence for DPP-4 inhibitors and BGs compared with other OAD classes at RI stages G1 and G2, a longer persistence was observed for DPP-4 inhibitors than for BGs at RI stages G3 and G4+.

Evaluation of prescribing patterns showed that no concomitant OADs were prescribed with DPP-4 inhibitors 55% of the time at the index date, suggesting that DPP-4 inhibitors were most frequently prescribed as first-line monotherapy. This observation is consistent with a study concluding that DPP-4 inhibitors were the most frequently prescribed OAD class during the last decade in Japan.[6] In the present study, BGs—which are widely endorsed as first-line treatment in Western countries[26,27]—were used in younger patients with relatively stable renal function (G3, 24%; G4+, 2%). BGs such as metformin are contraindicated in patients with eGFR <30 mL/min/1.73 m^2, and their use should be avoided in patients with eGFR between 30 and 45 mL/min/1.73 m^2 according to the Japan Diabetes Society[28] and the US Food and Drug Administration.[29] Patients who were prescribed SUs had better renal function despite their older age, suggesting that patients who had previously been prescribed SUs switched to glinides when their renal function declined. Similarly, α-GIs were prescribed to patients who were older, had reduced renal function, and more comorbidities. Many patients who were prescribed glinides at the index date had concomitant treatments, implying a tendency to prescribe this OAD class for patients with poor blood sugar control.[30] Notably, 19% of patients prescribed BGs and TZDs had comorbid heart failure despite contraindications.[5]

Within the class of DPP-4 inhibitors, linagliptin was preferentially prescribed for patients at RI stage G4+ and for those who were older, had higher complication rates, and concomitant insulin use. Among patients prescribed other DPP-4 inhibitors at the index date, differences in baseline characteristics were negligible, indicating the potential for interchangeability of DPP-4 inhibitors in the sample. Further, more patients who were prescribed linagliptin as first-line treatment had baseline cardiac, renal and urinary disorders, an observation that was also reported in a previous post-marketing surveillance study.[31] Linagliptin is excreted via the biliary route rather than the renal route like other DPP-4 inhibitors; therefore, it can be prescribed regardless of RI stage.[32] Teneligliptin, which has the second highest rate of biliary excretion (34%),[33] was also frequently prescribed in patients with RI stage G4+. Notably, teneligliptin-treated patients had higher average eGFRs than linagliptin-treated patients.

For patients with DPP-4 inhibitor prescriptions at the index date, previous treatment with other DPP-4 inhibitors was common (15%-42%) except for sitagliptin (6%), which was the first DPP-4 inhibitor launched in Japan in December 2009. A high rate of previous treatment with other DPP-4 inhibitors was observed for drugs that were launched later.

Since prescription of DPP-4 inhibitors has increased rapidly in Japan, the study period is likely to impact this type of real-world data analysis. Tanabe et al[14] reported that DPP-4 inhibitors were stopped for 2 years in ~80% of cases in a study using the same database (2008-2013) in 7108 patients with T2DM. Although those data cannot be compared with our results because of differences in data analysis methods, it might be worth noting that DPP-4 inhibitors became available in Japan in December 2009 with a 2-week prescription limitation until December 2010, indicating that only a limited number of patients could have been assessed for 2 years until the end of their study period in March 2013.

The present study has several strengths, including its real-world setting, the data evaluation from a recognized, large database covering 300 Japanese hospitals providing care for acute-phase diseases to >20 million patients,[34] and a distribution of age of patients with T2DM similar to national patient statistics provided by the statistics bureau of the Ministry of Health, Labour and Welfare.[2] Some limitations are also worth noting. The treatment persistence observed in this study might be underestimated, as persistence could only be measured within the same hospital in the database and patients who changed hospitals were not followed up. Factors affecting treatment persistence, such as changes in biometric values (e.g. body weight), reasons for starting or terminating a treatment, duration of diabetes, social background, and compliance with diet, exercise and drug treatment could not be evaluated given the lack of these data in the study database. Furthermore, the results of the sensitivity analysis showed an extension in persistence with a prescription gap of ≥60 days vs ≥30 days; this indicates continuation of treatment beyond the prescribed days of supply, possibly because of poor adherence and consequent leftover tablets, which we did not consider. Because the relative persistence between OAD classes was maintained in the sensitivity analysis, we considered our comparisons of treatment persistence to be valid. Data from Diagnosis Procedure Combination hospitals included patients with multiple moderate-to-severe diseases and may not reflect the general patient population with T2DM in Japan, resulting in limited generalizability. Additionally, the 6-month look-back period may have enabled time for patients to be evaluated for other diseases, leading to higher rates of comorbidities, especially myocardial infarction, heart failure and stroke, than those in previous reports.[35,36] Differences between patient characteristics among the OAD classes were not adjusted for using propensity-score matching; however, stratification by baseline renal function was applied for persistence analysis. Our results reflect the treatment status of patients mostly at RI stages G2 to G4+, including those without serum creatinine values categorized by comorbidity. Factors affecting treatment persistence, such as changes in biometric values (e.g. body weight), reasons for starting or terminating a treatment, duration of diabetes, social background and compliance with diet, exercise and drug treatment, could not be evaluated given the source of data. Patients with available serum creatinine data to calculate eGFR were limited; consequently, analyses based on RI included fewer data points than the other analyses. Also, the durability/persistence of each drug or drug combination as first- and second-line therapy was not evaluated. The post-discontinuation treatment pattern was also not evaluated. Finally, DPP-4 inhibitors are widely used in Japan[37]; however, their use may be restricted in other countries. This might be partly attributable to differences in approach while formulating treatment guidelines,[38] the health insurance reimbursement system, as well as differences in diabetes pathophysiology.[39,40]

Nevertheless, the results reflect a long-term, real-world scenario in a large number of patients from numerous centres and provide a comprehensive description of the characteristics of present treatment with OADs in Japanese patients with T2DM.

Overall, DPP-4 inhibitors were the most frequently prescribed OAD class, accounting for half of the index dates, followed by BGs, SUs, α-GIs, glinides and TZDs. Treatment persistence was longest for

DPP-4 inhibitors and BGs. Notably, persistence was highest with DPP-4 inhibitors in patients with severely decreased renal function. Most OADs were prescribed appropriately by practitioners in Japan; however, contrary to recommendations, BGs were prescribed for patients at RI stage G3 and G4, and SUs and TZDs for patients at stage G4. We believe that the appropriate use of OADs can be improved to achieve the goals of long-term, effective treatment of patients with T2DM. An open question is whether the higher persistence seen for certain classes was associated with improvements in health outcomes.

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Conflict of interest

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Author contributions

All named authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, take responsibility for the integrity of the work as a whole, and provided the final approval for the version to be published.

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