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SHORT REPORT

Changes in prescription patterns and doses of oral antidiabetic drugs in Japanese patients with type 2 diabetes (JDDM70)

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ABSTRACT

We assessed the prescription patterns of oral antidiabetic drugs in Japanese patients with type 2 diabetes between 2002 and 2020 using data from the Computerized Diabetes Care database. Among 172,960 patients treated with oral antidiabetic drugs, both the sulfonylurea prescription rate and dose decreased from 2002 to 2020. Prescriptions of biguanides, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors increased; their dose and dose frequency remained relatively stable. Trends in oral antidiabetic drug prescriptions changed over time, reflecting guideline recommendations and existing evidence.

INTRODUCTION

Patient-centered care is important in type 2 diabetes management to prevent or delay complications and maintain quality of life[1]. Treatment choice should consider efficacy, safety and patient factors, including comorbidities, hypoglycemia risks and preferences[1,2]. The Japanese Clinical Practice guideline recommends evaluating factors, such as the presence and degree of complications, metabolic abnormality, and insulin secretory capacity[3].

Previous studies reported that antidiabetic drug use in Japan has evolved over time[4–6]. In Japan, first approval of dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) in 2009 and 2014, respectively, expanded type 2 diabetes treatment options. A few studies have examined oral antidiabetic drug (OAD) doses; however, these were limited to single centers or selective samples (e.g., elderly patients or focused on metformin)[7–9].

We assessed the prescription patterns, including dose and dose frequency, of OAD from 2002 to 2020 in Japanese patients with type 2 diabetes.

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MATERIALS AND METHODS

This was a retrospective, serial cross-sectional observational study of OAD prescription patterns in Japan between 2002 and 2020 using data from the Computerized Diabetes Care database. The database, established in 2001 by the Japan Diabetes Clinical Data Management (JDDM) Study Group, comprises diabetologists in Japan[10] and includes annually updated clinical data[11]. The study was carried out in accordance with the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects, and the Amended Act on the Protection of Personal Information. The protocol was approved by the Ethics Committee of the JDDM and Research Institution of Healthcare Data Science (protocol ID: 2021-10605). Informed consent was not required, because de-identified data were used; patients could 'opt out' of participation.

Patients aged ≥18 years with type 2 diabetes who were prescribed OAD between 2002 and 2020 were included. Patients with type 1 or gestational diabetes, or prescribed insulin and/or glucagon-like peptide-1 receptor agonists were excluded.

Oral antidiabetic drug prescription rates were analyzed by calculating the proportion of patients prescribed each OAD every 3 years between 2002 and 2020. OAD were categorized

according to drug class (α-glucosidase inhibitors, biguanides [BG], DPP-4i, glinides, SGLT2i, sulfonylureas [SU], thiazolidinediones) and dose (low, standard, high; Table S1). The most recent dose data between January and July of each year were extracted for each patient. Patients with data in multiple years were treated as different patients for each year. Data for OAD prescribed at a dose higher than the approved doses in Japan were excluded. For combination drugs, each component was considered as an individual drug.

Patient characteristics were summarized using descriptive statistics. Missing data were not imputed. Statistical analyses were carried out using SPSS software (version 26.0; IBM Corp., New York, NY, USA).

RESULTS

Patient selection and characteristics

Of the cumulative total of 174,528 patients identified between 2002 and 2020, 172,960 met the eligibility criteria (Figure 1). From 2002 to 2020, the median patient age increased from 62 to 68 years, duration of type 2 diabetes increased from 9.0 to 13.6 years and body mass index increased from 23.9 to 24.3 kg/m^2 (Table 1). The median hemoglobin A1c improved from 7.4% in 2002 to 7.0% in 2008, and remained stable thereafter.

OAD prescription patterns

The most common OAD prescribed between 2002 and 2011 was SU; the SU prescription rate steadily decreased from 79.8% in 2002 to 29.9% in 2020 (Figure 2). α-Glucosidase inhibitors prescription also decreased from 2002 to 2020. Thiazolidinediones prescription peaked in 2008, but decreased thereafter. BG prescription increased from 34.0% in 2002 to 63.9% in 2020. DPP-4i prescription markedly increased, then stabilized

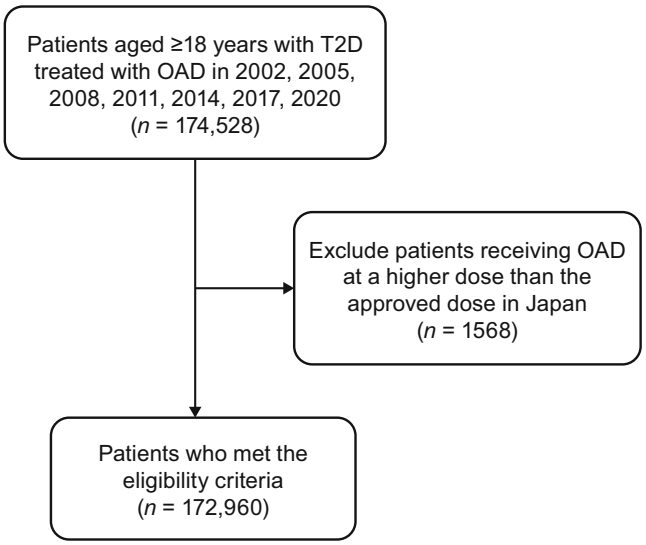

Figure 1 | Patient disposition. OAD, oral antidiabetic drug; T2D, type 2 diabetes.

Table 1 | Demographic and clinical characteristics of patients prescribed oral antidiabetic drug in the Computerized Diabetes Care database every 3 years from 2002 to 2020

Characteristic	2002 (*n* = 9,299)	2005 (*n* = 17,434)	2008 (*n* = 22,602)	2011 (*n* = 31,080)	2014 (*n* = 32,759)	2017 (*n* = 32,535)	2020 (*n* = 27,251)
Male, *n* (%)	5,820 (62.6)	10,956 (62.8)	14,417 (63.8)	19,955 (64.2)	21,138 (64.5)	20,922 (64.3)	17,505 (64.2)
Age, years (*n*)	9,299	17,434	22,602	31,080	32,759	32,535	27,251
Median (Q1–Q3)	62 (54–70)	63 (55–70)	63 (56–71)	64 (57–72)	66 (58–73)	67 (59–74)	68 (59–75)
Duration of T2D, years (*n*)	9,114	16,795	21,007	29,432	31,186	30,583	25,687
Median (Q1–Q3)	9.0 (4.5–14.5)	8.5 (4.1–14.7)	8.3 (4.1–14.2)	9.4 (5.1–15.1)	10.5 (6.2–16.5)	12.4 (7.2–18.5)	13.6 (8.1–20.3)
Height, cm (*n*)	8,481	16,137	20,145	26,702	30,880	31,044	25,553
Median (Q1–Q3)	161.0 (153.3–167.1)	161.4 (153.8–167.8)	162.0 (154.0–168.0)	162.0 (154.2–168.4)	162.2 (154.4–168.5)	162.6 (155.0–169.0)	163.0 (155.0–169.2)
Bodyweight, kg (*n*)	8,350	16,529	21,615	27,236	31,981	30,438	25,159
Median (Q1–Q3)	62.0 (54.6–69.8)	62.1 (54.7–70.4)	63.0 (55.2–71.7)	63.7 (55.4–72.7)	63.4 (55.2–72.6)	63.7 (55.6–73.0)	64.1 (55.9–73.5)
BMI, kg/m^2 (*n*)	7,669	15,600	19,317	24,675	30,674	29,775	24,396
Median (Q1–Q3)	23.9 (21.8–26.3)	23.9 (21.8–26.4)	24.2 (21.9–26.7)	24.3 (22.0–27.0)	24.2 (21.9–26.9)	24.2 (21.9–26.9)	24.3 (22.0–27.0)
HbA1c, % (*n*)	9,299	17,434	22,602	31,080	32,759	32,535	27,251
Median (Q1–Q3)	7.4 (6.7–8.1)	7.3 (6.8–8.0)	7.0 (6.6–7.7)	6.9 (6.5–7.5)	6.8 (6.4–7.3)	6.8 (6.4–7.3)	6.9 (6.6–7.4)

BMI, body mass index; HbA1c, hemoglobin A1c; Q1, first quartile; Q3, third quartile; T2D, type 2 diabetes.

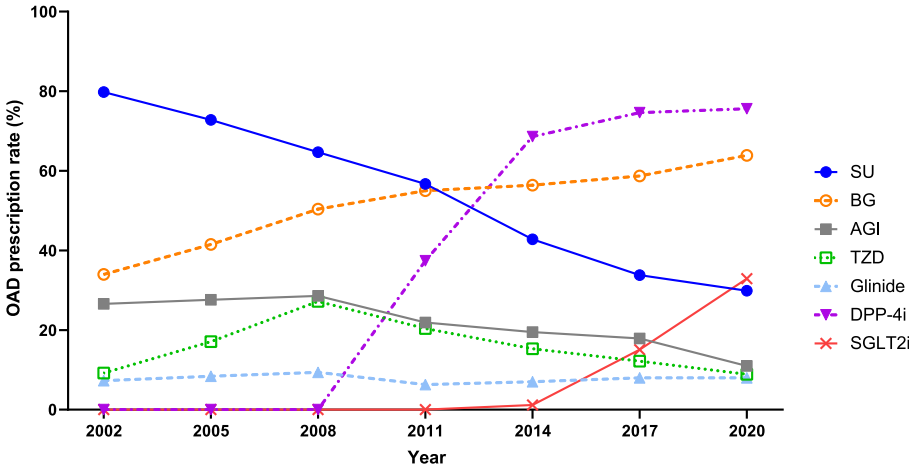

Figure 2 | Prescription patterns of oral antidiabetic drugs in patients with type 2 diabetes in Japan from 2002 to 2020. AGI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

approximately 75% after 2017, becoming the most prescribed OAD after 2014. SGLT2i prescription also markedly increased from 1.2% in 2014 to 32.9% in 2020.

OAD dose and dose frequency

Between 2002 and 2011, approximately 20–25% of SU prescriptions were for high doses; however, after 2017, high-dose SU prescriptions decreased to approximately 10%, and low-dose SU prescriptions increased to >40% (Figure 3). Low and standard doses of BG remained relatively stable, although high-dose BG prescriptions increased from 2011. Doses of other OAD remained relatively unchanged between 2002 and 2020; most thiazolidinediones, DPP-4i and SGLT2i prescriptions were for standard doses. Mean doses and dose frequencies of each OAD are shown in Tables S2 and S3.

DISCUSSION

The present study is the first to report the trends in OAD dose and dose frequency in Japanese patients with type 2 diabetes. Consistent with previous studies[4–7], SU prescription steadily decreased from 2002. Conversely, DPP-4i and SGLT2i prescription increased after 2008 and 2014, respectively, correlating with the approval of these drugs in Japan. Given that DPP-4i and SGLT2i are associated with a lower incidence of hypoglycemia and weight gain than SU[12–16], and SGLT2i have shown cardiorenal benefits in type 2 diabetes patients[17,18], these new drugs might have replaced SU for many patients. Furthermore, increased reporting of severe hypoglycemia with combined SU and DPP-4i therapy after the first approval of DPP-4i[19,20] led to a recommendation in 2010 to reduce SU doses when used concomitantly with DPP-4i[21]. Additionally, a multicenter randomized study in 2008 reported that intensive therapy (target hemoglobin A1c <6%) increased mortality without significantly reducing major cardiovascular events compared with standard therapy (target hemoglobin A1c 7.0–7.9%)[22]. Therefore, these previous studies and guideline recommendations might have affected the results observed in the present study.

In Japan, metformin's maximum approved dose was increased from 750 mg/day to 2,250 mg/day[23], when a new formulation was approved in 2010[24]. Previous Japanese studies have reported improved glycemic control, but no cases of hypoglycemia, with increased metformin doses[23,25]. Consistent with these reports and the updated metformin dose, in the present study, high-dose BG prescription increased from 2011, likely driven by the increase in mean metformin dose. Conversely, most prescriptions of DPP-4i and SGLT2i were for the standard doses. This is possibly because these drugs are associated with fewer dose-related adverse reactions, unlike other OAD, which require dose adjustments to balance the dose-dependent efficacy and safety effects[26,27], and because the cardiorenal benefits of SGLT2i do not appear to be dose dependent[28,29]. After 2011, a small decrease in dose frequencies of some SU, BG, α-glucosidase inhibitors and glinides was observed, possibly due to the increased DPP-4i and SGLT2i prescriptions. Most DPP-4i and SGLT2i were administered once daily, suggesting that OAD with lower dose frequency are preferred.

The present study provides long-term data on OAD prescription patterns for >150,000 Japanese patients with type 2 diabetes. However, data on the number of prescribed OAD (i.e., monotherapy vs combination therapy) were not analyzed, and the database only includes prescriptions issued by diabetologists.

In conclusion, over the 18-year period, both SU prescriptions and dose decreased, but DPP-4i and SGLT2i prescriptions increased, suggesting that OAD prescription patterns among Japanese patients with type 2 diabetes were consistent with guideline recommendations and existing evidence, and were altered by the availability of newer drugs.

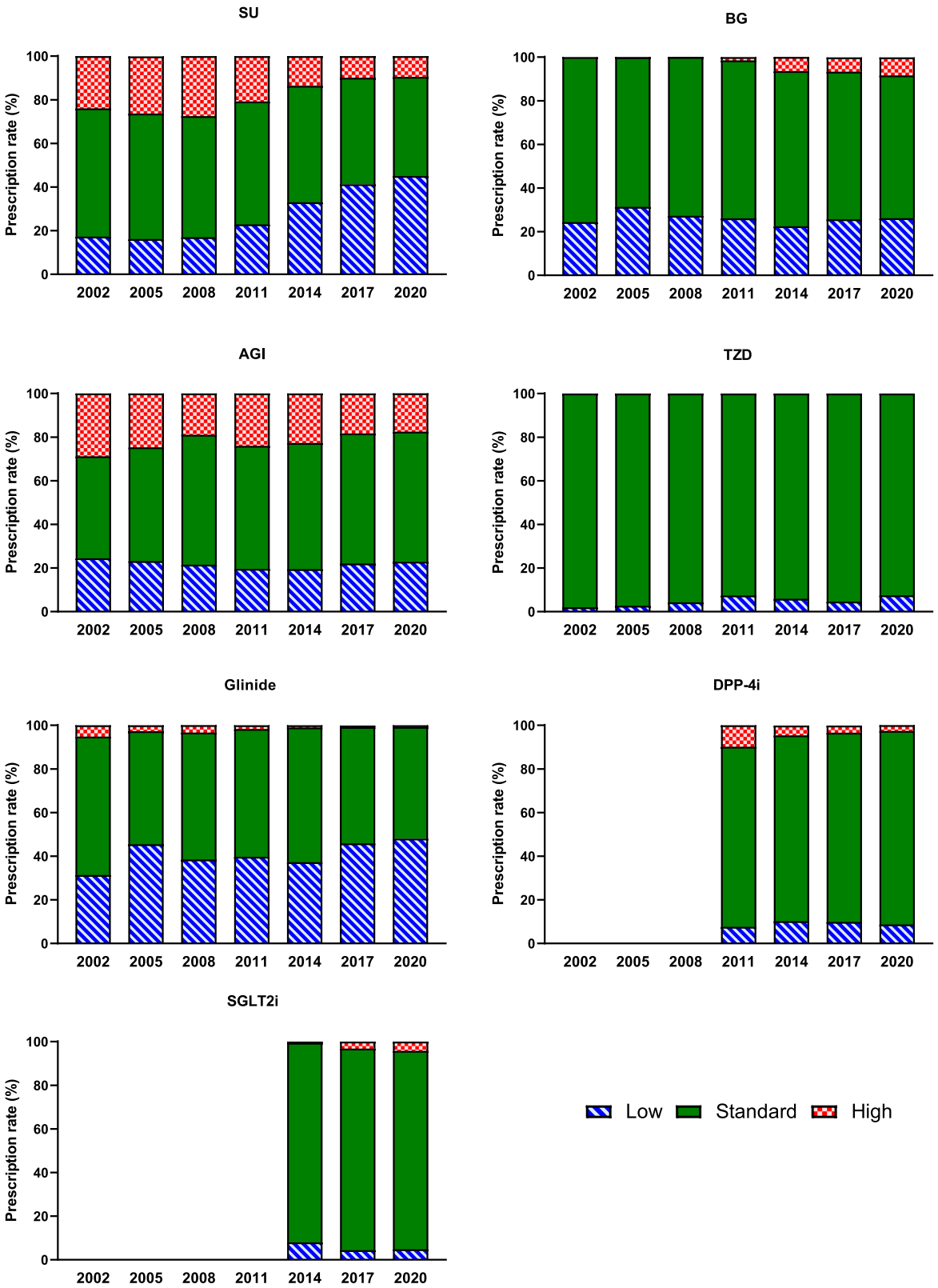

Figure 3 | Change in dose of oral antidiabetic drug (low, standard, high) used in patients with type 2 diabetes in Japan from 2002 to 2020. AGI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

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DISCLOSURE

MS, MT and TK are employees and/or shareholders of Eli Lilly Japan K.K. HM received lecturing fees from Astellas Pharma Inc., AstraZeneca K.K., Daiichi Sankyo Company, Limited, Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation and Nippon Boehringer Ingelheim Co., Ltd.; received research funding from Mitsubishi Tanabe Pharma Corporation and Nippon Boehringer Ingelheim Co., Ltd.; and received scholarships from Daiichi Sankyo Company, Limited, Mitsubishi Tanabe Pharma Corporation and Nippon Boehringer Ingelheim Co., Ltd. The other authors declare no conflict of interest.

Approval of the research protocol: Approved by the Ethics Committee of the Japan Diabetes Clinical Data Management (JDDM) and Research Institution of Healthcare Data Science (protocol ID: 2021–10,605).

Informed consent: Not required, because de-identified data were used; patients could 'opt out' of participation.

Approval date of Registry and the Registration No. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Classification of oral antidiabetic drug by drug class and doses.

Table S2 | Mean dose (mg) of oral antidiabetic drug used in patients with type 2 diabetes in Japan from 2002 to 2020.

Table S3 | Mean dose frequency of oral antidiabetic drug used in patients with type 2 diabetes in Japan from 2002 to 2020.