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Profile of People Initiating Oral Semaglutide for the Treatment of Type 2 Diabetes in Japan:

Results of a Cross-Sectional Study Using a Large Nationwide Database

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● **Abstract**

Background: Oral semaglutide (Rybelsus®) – the first oral glucagon-like peptide 1 receptor agonist (GLP-1RA) – has been approved for the treatment of type 2 diabetes (T2D) in Japan since 2020. This cross-sectional study utilized data extracted from the Medical Data Vision database to evaluate the profile of people with T2D initiating oral semaglutide compared with people receiving an injectable GLP-1RA or dipeptidyl peptidase 4 (DPP-4) inhibitor in Japan.

Methods: Adults (≥ 20 years) with T2D and a first prescription for oral semaglutide or new/first prescription for an injectable GLP-1RA or DPP-4 inhibitor (index date) between February 2021 – July 2022 were eligible. Patient characteristics, comorbidities, treatment/s, and diabetic complications were evaluated according to treatment group.

Results: Of 83,211 people, 6,838 (8.2%) received oral semaglutide, 9,792 (11.8%) received an injectable GLP-1RA, and 66,581 (80.0%) received a DPP-4 inhibitor. People initiating oral semaglutide tended to be younger (age 45 – 64: 44.2%) and have a higher body mass index (BMI) (> 25: 61.6%) compared with patients prescribed a DPP-4 inhibitor (15.4% and 34.8%, respectively) or injectable GLP-1RA (29.2% and 47.7%, respectively). In contrast, elderly people (aged ≥ 75 years) were more frequently prescribed a DPP-4 inhibitor (53.4%) compared with oral semaglutide (17.2%). People prescribed a DPP-4 inhibitor were more frequently treatment-naïve (64.3%) and had a lower mean (95% CI) baseline HbA1c (7.4% [7.4, 7.5]) versus those initiating oral semaglutide (8.9% and 8.0% [7.9, 8.1], respectively) or an injectable GLP-1RA (21.1% and 8.4% [8.3, 8.5], respectively).

Conclusions: People with T2D initiating oral semaglutide were typically younger and had a higher BMI and higher number of previous diabetes medications versus those receiving GLP-1RAs or DPP-4 inhibitors. These data show the characteristics of people initiating oral semaglutide compared with people receiving an injectable GLP-1RA or DPP-4 inhibitor in real-world practice in Japan and identify treatment gaps.

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Keywords: glucagon-like peptide-1 receptor agonist; oral semaglutide; type 2 diabetes

INTRODUCTION

Diabetes is a major public health problem worldwide.[1)] In Japan, approximately 11.8% of adults aged 20 – 79 years have diabetes, equivalent to approximately 11.0 million people in 2021.[2)] Treatment goals for type 2 diabetes (T2D) include glycemic control and modification of risk factors (e.g. body weight, blood pressure and lipid metabolism) to prevent the development and progression of diabetic complications and maintain quality of life and life expectancy at levels comparable to those in healthy individuals.[3)] Management typically includes lifestyle modifications, with sequential addition of oral antidiabetic drugs (OADs) and injectable drugs as the disease progresses. Although metformin is considered the preferred first-line therapy for T2D in most international guidelines,[4)5)] no specific therapy is endorsed by the Japanese Diabetes Society (JDS).[6)] Instead, the latest JDS (2023) consensus statement proposes an individualized treatment approach, with the choice of antidiabetic agent selected based on relevant patient characteristics, such as glycemic target, diabetes pathology, safety considerations (e.g. age, renal impairment, heart failure), and additional medication benefit for comorbidities.[6)]

Several classes of antidiabetic drugs are routinely available for T2D in Japan, including oral (biguanides,

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sulfonylureas [SUs], imeglimin, dipeptidyl peptidase-4 [DPP-4] inhibitors, thiazolidinediones, sodium glucose cotransporter-2 [SGLT2] inhibitors, and α-glucosidase inhibitors) and injectable (insulin and glucagon-like peptide-1 receptor agonists [GLP-1RAs]) agents. In a large database study evaluating OAD utilization patterns in 25,751 Japanese people with T2D, DPP-4 inhibitors were used by over half (56.9%) of people in 2019.[7] SGLT2 inhibitors were prescribed less frequently (23.6%), and were predominantly used in patients with a body mass index (BMI) ≥ 30 kg/m^2.[7] GLP-1RAs have been shown to possess significantly greater antihyperglycemic and weight loss effects compared with DPP-4 inhibitors[8] and semaglutide has demonstrated significantly greater reductions in HbA1c and weight reduction compared with SGLT2 inhibitors[9][10] in head-to-head clinical trials, and have beneficial effects on cardiovascular and renal outcomes,[11][12] and a low risk of hypoglycemia.[13] However, most GLP-1RAs are administered by subcutaneous injection, and therefore have typically been initiated later in clinical practice as a result, with only 8.4% of people with T2D receiving GLP-1RA therapy in Japan in 2021.[14]

Oral semaglutide (Rybelsus®) – the first oral GLP-1RA – has been approved in the United States since 2019, and in Japan and Europe since 2020 for the treatment of T2D.[15][16] The efficacy and safety of oral semaglutide in T2D has been established against a broad range of OADs in the randomized phase III PIONEER (Peptide Innovation for Early Diabetes Treatment) clinical trial program, which included eight global and two Japan-specific (PIONEER 9 and 10) studies.[17]-[19] Although evidence exists detailing the characteristics of people enrolled in the phase III PIONEER program[20] and the early use of semaglutide in clinical practice in the United States,[21] data is lacking regarding the demographics and clinical characteristics of people with T2D initiating oral semaglutide in clinical practice in Japan. Insights into the real-world use of oral semaglutide are necessary to understand the reasons underlying clinician treatment selection in Japan and identify important knowledge gaps.

We therefore conducted a cross-sectional study utilizing data from a large national database, Medical Data Vision (MDV), to determine the profile of people initiating oral semaglutide for T2D in clinical practice from when it became available in Japan. The primary objective of this analysis was to determine the profile, including sociodemographics, clinical characteristics, and diabetes-related characteristics, of people initiating oral semaglutide in local clinical practice in Japan, and the secondary objective was to compare the profile of people initiating oral semaglutide to those treated with injectable GLP-1RAs and DPP-4 inhibitors during the study period. The findings from this analysis will provide better understanding of the real-world utilization of T2D treatment and treatment intensification, and factors associated with these prescribing patterns in Japan.

METHODS

Study Design

This was a cross-sectional database study involving secondary use of data extracted from the MDV database in Japan. People initiating oral semaglutide between February 2021 (availability of oral semaglutide in Japan) and July 2022 (the last data collection point in the MDV database) for T2D were included, with those prescribed an injectable GLP-1RA and/or DPP-4 inhibitor during this period included as comparators. The index date was defined as the date of first prescription of oral semaglutide, or new/first prescription for an injectable GLP-1RA or DPP-4 inhibitor. Registration in the database was required for at least one year prior to the index date, defined as the pre-index period (−1 year to +7 days' post index date).

Participants

People were eligible if they had a confirmed diagnosis of T2D prior to the index date, were aged ≥ 20 years at the index date, and had a first prescription for oral semaglutide or first/new prescription for an injectable GLP-1RA and/or DPP-4 inhibitor during the study period (February 2021 to July 2022).

Exclusion criteria included those previously prescribed oral semaglutide at any time point, or an injectable GLP-1RA or DPP-4 inhibitor during the pre-index period. People who had previously been treated with a DPP-4 inhibitor or injectable GLP-1RA prior to the pre-index period and were reinitiated on this treatment during the study period were permitted. Additional exclusion criteria included type 1 diabetes, gestational diabetes, pregnancy, and previous bariatric surgery.

Data Source

The MDV database is an administrative Diagnosis Procedure Combination (DPC) database containing records from 40 million people from over 460 acute phase treatment hospitals in Japan, including a large proportion of elderly people. The coding of diagnoses and disease names was standardized using the International Classification of Diseases, tenth revision (ICD-10) and the disease codes of the Medical Information System Development Center (MEDIS-DC), respectively.

Data Collection

Details regarding patient characteristics (age, sex, body weight, and BMI), disease characteristics (comorbidities), treatment (antidiabetic medication/s prior to the study period, and other concomitant medications) and diabetic complications of interest were collected during the pre-index period. Concomitant medications captured included use of oral (including

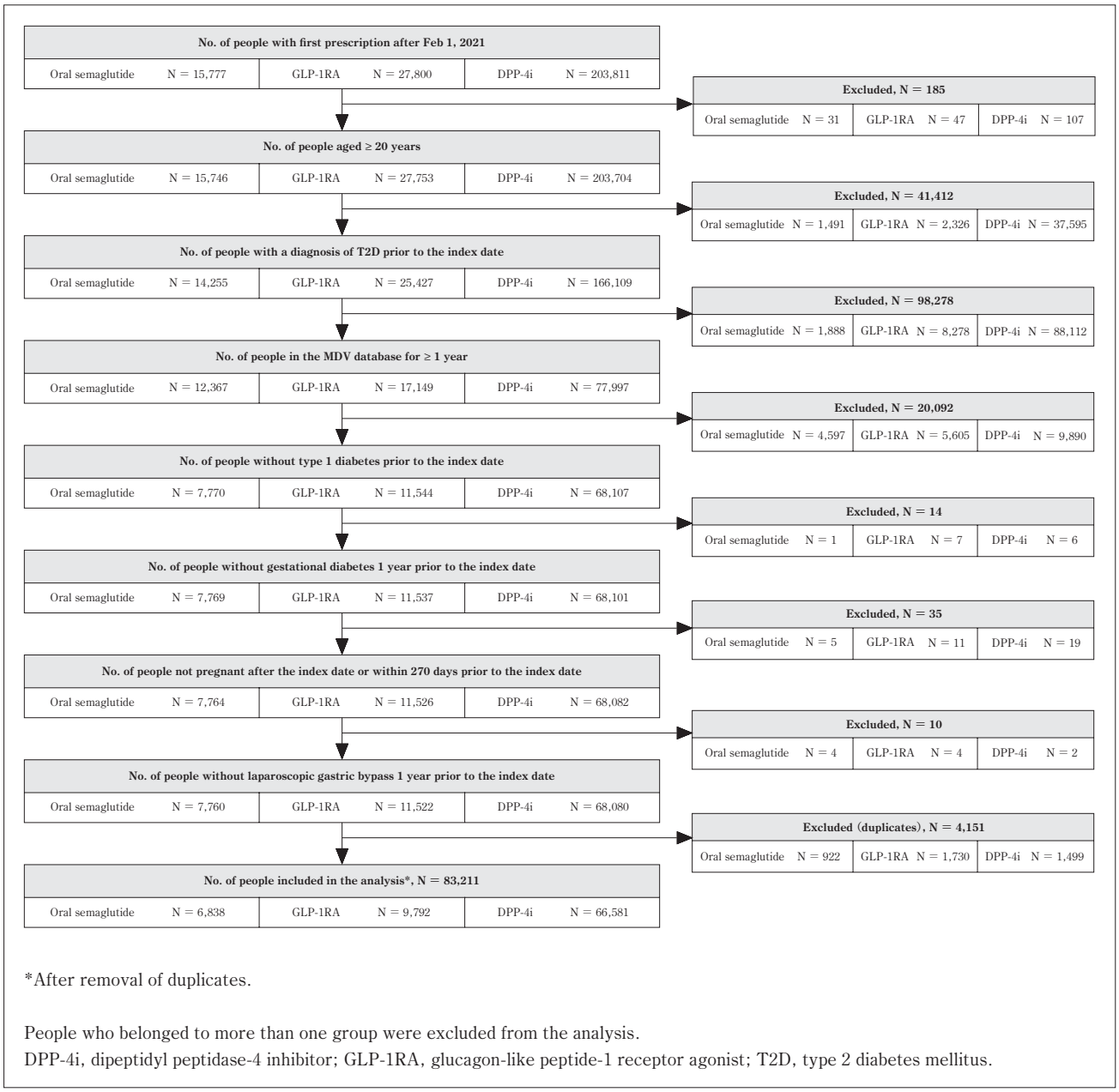

Figure 1　Flow Chart

metformin, SUs, alpha-glucosidase inhibitors, imeglimin, thiazolidinediones, SGLT2 inhibitors, DPP-4 inhibitors) and injectable (insulin, GLP-1RAs) antidiabetic drugs, hypertensive drugs (including angiotensin receptor blockers, beta blockers, calcium antagonists, thiazides, angiotensin-converting enzyme inhibitors), lipid-lowering drugs (e.g. statins, fibrates), weight loss agents, and antithrombotic drugs. Complications of interest included diabetic-related complications (retinopathy, neuropathy, and nephropathy), established cardiovascular disease, hypertension, and stroke.

Statistical Analysis

Data were summarized descriptively, with the mean (95 % confidence interval [CI]) and median (Q1, Q3) calculated for continuous variables, and the frequency number and proportion (with 95% CI) calculated for categorical variables.

As there is a 14-day prescription limit for one year for new drugs listed in Japan, a subgroup analysis was also conducted to examine patient profiles before (Feb 2021 − Nov 2021) and after (Dec 2021 − Jul 2022) the 14-day prescription limit for oral semaglutide.

Ethical Considerations

As only de-identified secondary data was used for this study, approval by an ethics committee was not required.

Table 1 Baseline Demographics and Clinical Characteristics

	Oral Semaglutide (N = 6,838)	Injectable GLP-1RA (N = 9,792)	DPP-4 inhibitor (N = 66,581)
Age at index date			
Mean (95% CI)	62.1 (61.8, 62.4)	68.6 (68.3, 68.9)	74.2 (74.1, 74.3)
Median (Q1, Q3)	63.0 (53.0, 72.0)	71.0 (59.0, 79.0)	76.0 (69.0, 82.0)
Age category at index date, n (%)			
< 45 years	639 (9.3)	460 (4.7)	1,118 (1.7)
45 − 64 years	3,024 (44.2)	2,863 (29.2)	10,240 (15.4)
65 − 74 years	1,997 (29.2)	2,850 (29.1)	19,643 (29.5)
≥ 75 years	1,178 (17.2)	3,619 (37.0)	35,580 (53.4)
Sex, female, n (%)	2,901 (42.4)	3,800 (38.8)	25,932 (38.9)
No. of days between first and last prescription			
< 60 days	3,039 (44.5)	4,421 (45.1)	40,580 (60.9)
≥ 60 days	3,799 (55.5)	5,371 (54.9)	26,001 (39.1)
No. of prescriptions (on different days), mean (95% CI)	4.1 (4.0, 4.3)	5.7 (5.5, 5.8)	9.2 (9.1, 9.3)
HbA1c at baseline (−90 days/ + 7 days), mean (95% CI)	8.0 (7.9, 8.1)	8.4 (8.3, 8.5)	7.4 (7.4, 7.5)
HbA1c at baseline (−90 days/ + 7 days)			
< 7%	119 (18.4)	167 (15.2)	2,810 (41.4)
7% − < 8%	237 (36.6)	315 (28.6)	2,366 (34.8)
8% − < 9%	179 (27.6)	298 (27.0)	905 (13.3)
≥ 9%	113 (17.4)	322 (29.2)	710 (10.5)
Missing	6,190	8,690	59,790
Weight at baseline (−90 days/ + 7 days), kg, mean (95% CI)	71.9 (70.6, 73.1)	65.8 (65.3, 66.3)	60.6 (60.5, 60.7)
BMI at baseline*, (−90 days/ + 7 days), kg/m^2, mean (95% CI)	27.4 (26.9, 27.8)	25.5 (25.3, 25.7)	24.2 (23.7, 24.7)
BMI at baseline* (90 day period), kg/m^2, mean (95% CI)			
< 18.5	19 (2.7)	289 (6.8)	3,534 (8.2)
18.5 − 25	249 (35.7)	1,935 (45.5)	24,724 (57.1)
> 25	430 (61.6)	2,028 (47.7)	15,067 (34.8)
Time in database, years, mean (95% CI)	10.4 (10.2, 10.5)	9.5 (9.4, 9.7)	8.0 (7.9, 8.0)

BMI, body mass index; DPP-4, dipeptidyl-peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin A1c.

RESULTS

Disposition

A total of 83,211 people met eligibility criteria and were included in the analysis, including 6,838 (8.2%) initiating oral semaglutide, 9,792 (11.8%) receiving an injectable GLP-1RA, and 66,581 (80.0%) receiving a DPP-4 inhibitor (**Figure 1**).

Baseline Demographics and Clinical Characteristics

Details of the baseline demographics and clinical characteristics of the study cohort of people with T2D are presented in **Table 1**.

Those initiating oral semaglutide tended to be younger, and a higher proportion were female (42.4%) compared with those receiving an injectable GLP-1RA (38.8%) or DPP-4 inhibitor (38.9%) (**Table 1**). By age category, a higher proportion (44.2%) of people initiating oral semaglutide were aged 45 − 64 years compared with those receiving an injectable GLP-1RA (29.2%) or DPP-4 inhibitor (15.4%). A smaller proportion (29.2%) of people initiating oral semaglutide were aged 65 − 74 years, and the rate was similar to those receiving an injectable GLP-1RA (29.1%) or a DPP-4 inhibitor (29.5%). In contrast, elderly people (aged ≥75 years) were less frequently initiated on oral semaglutide (17.2%) compared with those receiving a DPP-4 inhibitor (53.4%) or an injectable GLP-1RA (37.0%).

People initiating oral semaglutide had a higher mean (95% CI) BMI (27.4 [26.9, 27.8]) at baseline compared with those receiving an injectable GLP-1RA (25.5 [25.3, 25.7]) or DPP-4 inhibitor (24.2 [23.7, 24.7]). Over half (61.6%) of people initiating oral semaglutide had a BMI >25, which was greater than those initiating an injectable GLP-1RA (47.7%) or DPP-4 inhibitor (34.8%), and 35.7% had a BMI 18.5 − 25 (vs 45.5% and 57.1%, respectively) (**Table 1**).

HbA1c Level at Baseline

The mean (95% CI) HbA1c at baseline was comparable between those prescribed oral semaglutide (8.0% [7.9, 8.1]) and an injectable GLP-1RA (8.4% [8.3, 8.5]) but was higher compared with those prescribed a DPP-4 inhibitor (7.4% [7.4, 7.5]). Similarly, the proportion of people with a HbA1c between 8 − 9% and ≥ 9% was

Table 2　Dose Details of Oral Semaglutide

	Oral Semaglutide (N = 6,838)	Injectable GLP-1RA (N = 9,792)	DPP-4 inhibitor (N = 66,581)
Index dose, n (%)			
3 mg	5,870 (85.8)	0	0
7 mg	410 (6.0)	0	0
14 mg	105 (1.5)	0	0
3 mg and 7 mg	425 (6.2)	0	0
3 mg and 14 mg	1 (0.0)	0	0
7 mg and 14 mg	5 (0.1)	0	0
3 mg and 7 mg and 14 mg	22 (0.3)	0	0
Missing	0	9,792	66,581
Highest dose, n (%)			
3 mg	2,711 (39.6)	0	0
7 mg	3,329 (48.7)	0	0
14 mg	798 (11.7)	0	0
Missing	0	9,792	66,581

DPP-4, dipeptidyl-peptidase 4; GLP-1, glucagon-like peptide 1.

similar between those prescribed oral semaglutide (27.6 % and 17.4%, respectively) and an injectable GLP-1 agonist (27.0% and 29.2%, respectively) and higher compared with those prescribed a DPP-4 inhibitor (13.3 % and 10.5% , respectively) (**Table 1**).

Prescription Details and Dose

The number of days between the first and last prescription was < 60 days in 44.5% of people prescribed oral semaglutide, 60.9% of people prescribed a DDP-4 inhibitor, and 45.1% of people prescribed an injectable GLP-1RA, and ≥ 60 days in 55.5% of people prescribed oral semaglutide, 39.1% of people prescribed a DDP-4 inhibitor, and 54.9% of people prescribed an injectable GLP-1RA.

Most (85.8%) people in the oral semaglutide treatment group were prescribed the 3 mg dose at the index date; 6.2% received a prescription for both the 3 mg and 7 mg dose, and 6.0% were prescribed the 7 mg dose (**Table 2**).

Nearly half (48.7%) of people increased their dose to 7 mg, which is the maintenance dose in Japan. The remainder were prescribed the 3 mg dose (39.6%) as the highest dose, followed by the 14 mg dose (11.7%).

Prior Diabetes Medications During the Pre-Index Period

A summary of the previous diabetes medications used during the pre-index period is presented by treatment group in **Table 3**.

The majority (64.3%) of people prescribed a DPP-4 inhibitor were treatment-naïve compared with 21.1% prescribed an injectable GLP-1RA and 8.9% initiated on oral semaglutide.

Overall, 45.8% of people had a prescription for any diabetes medication during the pre-index period, with the most common prescription being for insulin (27.6%), followed by metformin (14.5 %), and a SGLT2 inhibitor (12.8 %). When analyzed by treatment group, 92.1% of people in the oral semaglutide group, 79.4% of people in the injectable GLP-1RA treatment group, and 36.1% of people in the DPP-4 inhibitor treatment group were prescribed diabetes medication in the pre-index period. In the oral semaglutide treatment group, the most common previous medication was metformin (58.8%), followed by a SGLT2 inhibitor (54.0%), DPP-4 inhibitor (35.0%), sulfonylurea (24.4%) and insulin (22.4%). In the injectable GLP-1RA treatment group, the most common previous medication was insulin (48.0%), followed by a DPP-4 inhibitor (38.7%), metformin (34.5%), and a SGLT2 inhibitor (31.2%). In the DPP-4 inhibitor treatment group, the most common previous medication was insulin (25.1%), followed by metformin (7.0%), and an SGLT2 inhibitor (5.8%), although the proportions were smaller.

A total of 17.9% of people initiating oral semaglutide received combination therapy during the pre-index period compared with 10.9% of people receiving an injectable GLP-1RA and 3.1% of people receiving a DPP-4 inhibitor. Nearly a third (31.2%) of people initiating oral semaglutide had received ≥ 3 different OADs, compared with only 15.8% of people receiving an injectable GLP-1RA and 0.9% of people receiving a DPP-4 inhibitor.

Diabetic Complications of Interest

The incidence of diabetic nephropathy (5.0%), neuropathy (1.1%), and retinopathy (2.0%) diagnosed during the pre-index period was low overall (**Table 4**).

Table 3 Summary of Previous Treatments in the Pre-Index Period by Treatment Group

Previous Treatment	Oral Semaglutide (N = 6,838)	Injectable GLP-1RA (N = 9,792)	DPP-4 inhibitor (N = 66,581)
GLP-1 RA, n (%) [a]	1,231 (18.0)	0 (0)	404 (0.6)
Exenatide (Byetta®/Bydureon®)	0 (0)	14 (0.1)	0 (0)
Lixisenatide (Lyxumia®)	0 (0)	17 (0.2)	0 (0)
Semaglutide (Ozempic®)	0 (0)	1,641 (16.8)	0 (0)
Dulaglutide (Trulicity®)	0 (0)	6,645 (67.9)	0 (0)
Liraglutide (Victoza®)	0 (0)	1,475 (15.1)	0 (0)
Missing	0 (0)	0 (0)	0 (0)
Metformin, n (%) [a]	4,022 (58.8)	3,374 (34.4)	4,681 (7.0)
Sulfonylurea, n (%) [a]	1,666 (24.4)	1,856 (19.0)	2,374 (3.6)
Thiazolidinedione, n (%) [a]	718 (10.5)	537 (5.5)	717 (1.1)
Alpha glucosidase inhibitor, n (%) [a]	1,078 (15.8)	1,390 (14.2)	2,123 (3.2)
SGLT-2 inhibitor, n (%) [a]	3,695 (54.0)	3,059 (31.2)	3,867 (5.8)
DPP-4 inhibitor, n (%) [a]	2,396 (35.0)	3,794 (38.7)	0 (0)
Insulin, n (%) [a]	1,531 (22.4)	4,702 (48.0)	16,716 (25.1)
Other blood glucose-lowering agent, n (%) [a]	802 (11.7)	1,325 (13.5)	1,430 (2.1)
Any antidiabetic medication, n (%) [a]	6,298 (92.1)	7,772 (79.4)	24,023 (36.1)
Combination treatment, n (%) [a]	1,221 (17.8)	1,072 (10.9)	2,033 (3.1)
Number of different OADs, n (%) [a]			
0	813 (11.9)	3,074 (31.4)	54,896 (82.4)
1	1,247 (18.2)	1,700 (17.4)	7,643 (11.5)
2	1,759 (25.7)	2,059 (21.0)	2,851 (4.3)
≥ 3	3,019 (44.1)	2,959 (30.2)	1,191 (1.8)
Antidiabetic medication, n (%) [a]			
Naïve	611 (8.9)	2,066 (21.1)	42,791 (64.3)
1 OAD only	783 (11.5)	612 (6.2)	4,680 (7.0)
2 OADs only	1,043 (15.3)	861 (8.8)	1,626 (2.4)
≥ 3 OADs only	2,132 (31.2)	1,551 (15.8)	619 (0.9)
GLP-1 switch ± OAD ± insulin	1,231 (18.0)	0 (0)	404 (0.6)
Insulin ± OAD	1,038 (15.2)	4,702 (48.0)	16,461 (24.7)

OAD, oral antidiabetic drug; DPP-4, dipeptidyl-peptidase 4; GLP1, glucagon-like peptide 1 receptor agonist; SGLT-2, sodium glucose cotransporter-2.

[a]Prescribed during the 365 days baseline period.

A total of 31.0% of people had hypertension, 21.9% had disorders of lipoprotein metabolism, and 12.9% experienced a stroke during the pre-index period. A slightly higher proportion of people with hypertension, disorders of lipoprotein metabolism, and stroke received an injectable GLP-1RA or a DPP-4 inhibitor versus oral semaglutide (**Table 4**). The proportion of people treated with lipid-modifying medication was higher in the oral semaglutide (60.5%) and injectable GLP-1RA (48.4%) treatment groups compared with the DPP-4 inhibitor (22.1%) treatment group.

Over a third (38.6%) of people were diagnosed with cardiovascular disease during the pre-index period, including 39.6% of people receiving an injectable GLP-1RA, 39.4% of people receiving a DPP-4 inhibitor, and 28.7% of people initiated on oral semaglutide.

Subgroup Analysis

When baseline demographics and clinical characteristics were analyzed before (Feb 2021－Nov 2021) and after (Dec 2021－Jul 2022) the 14-day prescription limit, no notable differences were observed in age, sex, HbA1c at baseline, weight, BMI, or time in the database (**Supplementary Table 1**). Predictably, the number of days between the first and last prescription was considerably longer before the 14-day prescription limit compared with after the prescription limit, overall and in each treatment group (**Supplementary Table 1**). Similarly, no notable differences were observed when previous antidiabetes treatments were analyzed before and after the 14-day prescription limit, with a few exceptions (**Supplementary Table 2**). Before the 14-day prescription limit, 42.1% had increased their dose to

Table 4　Comorbidities Diagnosed During the Pre-Index Period

	Oral Semaglutide (N = 6,838)	Injectable GLP-1RA (N = 9,792)	DPP-4 Inhibitor (N = 66,581)
Diabetic nephropathy, n (%)	509 (7.4)	1,102 (11.3)	2,552 (3.8)
Diabetic nephropathy, Stage			
1	58 (0.9)	94 (1.0)	156 (0.2)
2	198 (3.0)	227 (2.5)	290 (0.4)
3	38 (0.6)	104 (1.1)	123 (0.2)
4	10 (0.2)	46 (0.5)	102 (0.2)
5	2 (0)	13 (0.1)	55 (0.1)
Missing	203	618	1,826
Diabetic neuropathy, n (%)	86 (1.3)	221 (2.3)	609 (0.9)
Diabetic retinopathy, n (%)	126 (1.8)	356 (3.6)	1,172 (1.8)
Hypertension, n (%)	843 (12.3)	2,825 (28.9)	22,103 (33.2)
Disorders of lipoprotein metabolism and other lipedemias, n(%)	1,022 (14.9)	2,439 (24.9)	14,798 (22.2)
Myocardial infarction, n (%)	280 (4.1)	731 (7.5)	5,010 (7.5)
Stroke, n (%)	321 (4.7)	931 (9.5)	7,866 (11.8)
Coronary artery disease, n (%)	924 (13.5)	2,202 (22.5)	13,370 (20.1)
Procedures and surgeries for CAD, n (%)	118 (1.7)	325 (3.3)	1,642 (2.5)
Heart failure, n (%)	1,172 (17.1)	2,459 (25.1)	16,253 (24.4)
Peripheral artery disease, n (%)	706 (10.3)	1,137 (11.6)	5,182 (7.8)
Atrial fibrillation, n (%)	141 (2.1)	562 (5.7)	4,790 (7.2)
Cardiovascular disease[a], n (%)	1,961 (28.7)	3,877 (39.6)	26,255 (39.4)

CAD, coronary artery disease; DPP-4, dipeptidyl-peptidase 4; GLP1, glucagon-like peptide 1 receptor agonist.
ICD-10 diagnosis codes for: myocardial infarction, I21.x; stroke, I60.x-I64.x; coronary artery disease, I20.x-I25.x; procedures and surgeries for CAD, 150374910, 150375010, 150375110, 150260350, 150284310, 150359310, 150375210, 150375310, 150375410, 160107550, 150318310, 150145910, 150146010, 150302770, 150318410, 150318510; heart failure: I50.x; peripheral artery disease: I70.x, I71.x, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959; atrial fibrillation: I48.x.
[a] "Cardiovascular disease" includes any of the above.

7 mg, 29.9% had increased their dose to 14 mg, and 28.1 % remained on the 3 mg dose. After the 14-day prescription limit, 49.7% had increased their dose to 7 mg, 8.9% had increased their dose to 14 mg, and 41.4% remained on the 3 mg dose.

DISCUSSION

In this large cross-sectional study of 83,211 people with T2D utilizing data from the MDV database, we describe the characteristics of people initiating oral semaglutide for T2D in clinical practice after its introduction in Japan. Initiators of oral semaglutide for T2D in our study tended to be younger, were more likely female (42.4% vs 38.8 % and 38.9%, respectively), and had a higher rate of obesity (mean BMI [95% CI]: 27.4 [26.9, 27.8] vs 25.5 [25.3, 25.7] and 24.2 [23.7, 24.7], respectively) and previous diabetes medication use (92.1% vs 79.4% and 36.1%, respectively) compared with those receiving GLP-1RAs or DPP-4 inhibitors. Elderly people (aged ≥ 75 years) were more frequently prescribed a DPP-4 inhibitor (53.4%) compared with oral semaglutide (17.2 %), which may explain the lower body weight observed in this treatment group. People prescribed a DPP-4 inhibitor were also more likely to be treatment-naïve (64.3%) compared with those initiating oral semaglutide (8.9%), most (31.2%) of whom had received at least 3 prior OADs in the pre-index period.

Although the reasons underpinning treatment selection were not explored in our study, prescription of DPP-4 inhibitors as a first-line treatment in our study may be due to several reasons. For example, several studies have shown that incretin-based medications such as DPP-4 inhibitors can reduce HbA1c more effectively in east Asian people compared with Caucasian and black people.[22)-24)] Also of note, genome-wide association studies have suggested that many east Asians possess a specific genetic variation (SNP) in the GLP-1 receptor gene, which promotes insulin secretion in response to GLP-1.[25)] Further, the low risk of hypoglycemia with DPP-4 inhibitors and increased incidence of gastrointestinal adverse events (AEs) associated with metformin may further explain this finding.[6)26)27)] DPP-4 inhibitors are also considered a preferred treatment for older adults with

T2D[28)29)] due to their convenient oral administration and good safety profile. In addition, some DPP-4 inhibitors are prohibited for people with liver dysfunction and the dose of DPP-4 inhibitors should be adjusted for people with renal dysfunction. In contrast, no dosage adjustments are required for oral semaglutide in people with renal or liver conditions. Oral semaglutide provides an effective treatment option in older people and/or those with comorbidities.[30)-32)]

In this study, people prescribed an injectable GLP-1RA tended to be older compared with those prescribed oral semaglutide. A total of 37.0% of people prescribed an injectable GLP-1RA were aged ≥ 75 years compared with only 17.2% of people prescribed oral semaglutide. BMI was also lower in those prescribed an injectable GLP-1RA versus oral semaglutide（BMI＜18.5: 6.8% vs 2.7%, respectively; BMI＞25: 47.7% vs 61.6%, respectively）. Although the exact reasons for this are unknown, our results and those of others suggest that most people in Japan are initiated on dulaglutide as their first injectable GLP-1RA therapy（**Table 3**）,[33)] and approximately 50% of people treated with an injectable GLP-1RA have already received pretreatment with insulin therapy.[34)] Although the duration of diabetes was unable to be investigated in this database, the findings from the current study suggest that GLP-1RA therapy is also introduced at a later stage in the treatment of T2D in Japan, as we expected.

Several post-hoc analysis have been conducted evaluating the effect of various baseline characteristics on the efficacy and safety of oral semaglutide in both global and domestic PIONEER studies.[35)~38)] Across these studies, consistent and dose-dependent reductions in Hb1Ac and body weight were demonstrated with oral semaglutide, irrespective of age, BMI, and background medication.[35)-38)] In a post-hoc analysis evaluating the effect of baseline age on efficacy and safety of oral semaglutide across the global Phase III PIONEER 1－5, 7, and 8 studies,[38)] consistently greater HbA1c and body weight reductions were observed with oral semaglutide versus comparators, irrespective of age（＜45 years; ≥ 45-＜65 years; ≥ 65 years）, and safety was similar between elderly（≥ 65 years）and non-elderly（＜65 years）people. These findings have subsequently been confirmed in Japanese people, with two separate post-hoc analyses of the PIONEER 9 and 10 studies demonstrating comparable glycemic efficacy with oral semaglutide, irrespective of age（＜65 years vs ≥ 65 years）[31)] or baseline HbA1c, BMI, or background medication.[36)] In both the global PIONEER studies[30)] and the domestic PIONEER 9 and 10 studies,[18)31)] the incidence of AEs and AEs leading to treatment discontinuation were slightly higher in people aged ≥ 65 years versus＜65 years, but the incidence of serious AEs was low overall, and was similar between groups.[31)] Baseline HbA1c, BMI and background medication did not appear to affect the proportions of people reporting AEs.[36)] Furthermore, reductions in HbA1c have been shown to be greater in Asian and Japanese people compared with the overall population and other races.[20)35)]

Oral semaglutide was well-tolerated across Phase III studies, with a safety profile that is consistent with the GLP-1RA drug class.[39)] Gastrointestinal events（constipation, nausea, diarrhea, abdominal discomfort）are generally the most frequently observed class of AE.[31)] The incidence of hypoglycemia was very low across the PIONEER studies, including the PIONEER 9 and 10 studies, and was similar between age subgroups.[31)] However, when used in combination with a sulfonylurea or insulin, a reduction in the dosage of these medications may be considered to decrease the risk of hypoglycemia.

In our study, people initiating oral semaglutide were more likely to be overweight（BMI＞25）（61.6%）compared with those prescribed an injectable GLP-1RA（47.7%）or DPP-4 inhibitor（34.8%）and had a higher mean BMI（27.4 kg/m^2 vs 25.5 kg/m^2 and 24.2 kg/m^2, respectively）. Consistent with all agents in the GLP-1RA class, sustained and significant weight loss effects have been demonstrated with oral and subcutaneous semaglutide in obese people with T2D in the PIONEER and SUSTAIN clinical trial programs.[40)] It is expected that oral semaglutide was preferentially selected by physicians for overweight/obese people with T2D in our study to leverage its well-established weight loss benefits.

Peptide-based drugs such as GLP-1RAs are not typically administered via the oral route as significant degradation by proteolytic enzymes in the stomach and poor absorption across the gastrointestinal mucosa lead to low bioavailability. As such, administration has typically required daily or weekly injections, which has restricted their use, with only 8.4% of people with T2D receiving GLP-1RA therapy in Japan in 2021.[14)] Oral semaglutide is a long-acting GLP-1RA with 94% homology to human GLP-1 which is co-formulated with an absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, to overcome these issues and facilitate once daily oral absorption.[41)42)] Oral semaglutide has specific dose administration instructions and should be taken on an empty stomach upon waking with ≤ 120 mL of water at least 30 minutes before the first intake of food/liquid or other daily medications. Given the 14-day limitation in the first year of the study, we anticipated that there may be some bias in patient characteristics between periods. However, no notable differences were observed between patient characteristics during the 14-day limitation period and after December 2021（**Table S1** & **Table S2**）. Preliminary insights suggest that baseline patient characteristics are less important determinants of oral semaglutide efficacy than dosage.[31)35)-38)]

The recommended starting dose of oral semaglutide is 3 mg once daily, followed by escalation to 7 mg once daily

after at least 4 weeks, which can be further increased to 14 mg once daily if additional glycemic control is required after 4 weeks. Interestingly, although oral semaglutide was increased to the 7 mg maintenance dose in 48.7% of people, a relatively large proportion (39.6%) remained on 3 mg as their highest dose, with only 11.7% increased to the 14 mg dose. Reasons for this likely include adequate blood glucose control with the 3 mg or 7 mg dose, as well as cost considerations and pre-emptive avoidance of gastrointestinal side effects with the higher dose. However, dose escalation to 14 mg in line with the clinical trial program and prescribing information has been shown to provide greater improvements in glycemic control.[16] In subgroup analyses of the PIONEER 9 and 10 studies, dose-dependent reductions in HbA1c and body weight were observed irrespective of various patient characteristics (HbA1c, body weight, age and background medications), but were consistently greatest with the 14 mg dose.[31)36)] In PIONEER 7 and its extension trial, which were conducted under similar conditions to clinical practice and employed a flexible-dose adjustment method (3, 7, or 14 mg) based on HbA1c level, 63.6% of participants were on the 14 mg dose at 52 weeks and there was less need for additional glucose-lowering agents.[43)44)] These findings and those of others suggest that oral semaglutide may be able to decrease the number of concomitant antidiabetic agents, and thus polypharmacy.[43)-45)]

At baseline, approximately 40% of people initiating oral semaglutide used ≥ 3 different OADs, which was higher than in people prescribed DPP-4 inhibitors (1.8%) and even injectable GLP-1RA (30.2%). Further, mean (95% CI) HbA1c and the proportion of people with a baseline HbA1c ≥ 9% was higher in people initiating oral semaglutide compared with those prescribed a DPP-4 inhibitor, and was comparable to those prescribed GLP-1RAs. These findings suggest that people initiating oral semaglutide in clinical practice in Japan tended to do so later in the treatment schedule.

The results of this analysis were strengthened by the large sample size (N = 83,211) and use of a large national database, which permitted collection of robust and up-to-date data from clinical practice. Further, the eligibility criteria was minimal in order to facilitate the inclusion and characterization of a broad population of people with T2D initiating treatment with oral semaglutide. Limitations of the analysis included the cross-sectional study design, which prevented evaluations on the effectiveness of oral semaglutide. Secondly, due to the nature of the MDV database, the availability of HbA1c data was limited to approximately 10% of the sample population. Thirdly, MDV is a hospital-based database, which means that data was biased towards people that are in later stages of their disease and may not adequately represent the entire population of people initiating oral semaglutide. Treatments prescribed outside of the hospital system were also not captured. As prescription of oral semaglutide was restricted to 14 days' duration from February 2021 to November 2021 for safety reasons, this may have impacted the type of treatments selected by healthcare prescribes. Thus, these analyses were exploratory in nature and no formal statistical comparisons were made.

Nevertheless, this, to our knowledge, is the first large-scale study to analyze the profile of people initiating oral semaglutide in clinical practice in Japan and provides valuable insights into treatment practices following its introduction. Our findings showed that the first initiators of oral semaglutide clinical practice in Japan were typically younger, with a high rate of obesity and previous treatments compared with those prescribed an injectable GLP-1RA or DPP-4 inhibitor.

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DISCLOSURES

All authors are employees of Novo Nordisk.

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Supplementary Table 1 Baseline Demographics and Clinical Characteristics by Time Period (Subgroup Analysis)

	Feb 2021 − Nov 2021				Dec 2021 − Jul 2022			
	Oral Semaglutide (N = 891)	GLP-1RA (N = 6,133)	DPP-4 inhibitor (N = 41,759)	Total (N = 48,783)	Oral Semaglutide (N = 5,947)	GLP-1RA (N = 3,659)	DPP-4 inhibitor (N = 24,822)	Total (N = 34,428)
Age at index date								
Mean (95% CI)	61.5 (60.6, 62.4)	68.0 (67.6, 68.3)	74.0 (73.9, 74.1)	73.0 (72.9, 73.1)	62.2 (61.8, 62.5)	69.7 (69.2, 70.1)	74.6 (74.4, 74.7)	71.9 (71.8, 72.1)
Median (Q1, Q3)	62.0 (52.0, 72.0)	70.0 (59.0, 78.0)	75.0 (68.0, 82.0)	74.0 (67.0, 81.0)	63.0 (53.0, 72.0)	72.0 (61.0, 79.0)	76.0 (69.0, 82.0)	74.0 (65.0, 81.0)
Age category at index date, n (%)								
< 45 years	102 (11.4)	319 (5.2)	739 (1.8)	1,160 (2.4)	537 (9.0)	141 (3.9)	379 (1.5)	1,057 (3.1)
45 − 64 years	386 (43.3)	1,866 (30.4)	6,558 (15.7)	8,810 (18.1)	2,638 (44.4)	997 (27.2)	3,682 (14.8)	7,317 (21.3)
65 − 74 years	253 (28.4)	1,800 (29.3)	12,608 (30.2)	14,661 (30.1)	1,744 (29.3)	1,050 (28.7)	7,035 (28.3)	9,829 (28.5)
≥ 75 years	150 (16.8)	2,148 (35.0)	21,854 (52.3)	24,152 (49.5)	1,028 (17.3)	1,471 (40.2)	13,726 (55.3)	16,225 (47.1)
Sex, female, n (%)	438 (49.2)	2,427 (39.6)	16,232 (38.9)	19,097 (39.1)	2,463 (41.4)	1,373 (37.5)	9,700 (39.1)	13,536 (39.3)
No. of days between first and last prescription								
< 60 days	224 (25.1)	2,094 (34.1)	21,447 (51.4)	23,765 (48.7)	2,815 (47.3)	2,327 (63.6)	19,133 (77.1)	24,275 (70.5)
≥ 60 days	667 (74.9)	4,039 (65.9)	20,312 (48.6)	25,018 (51.3)	3,132 (52.7)	1,332 (36.4)	5,689 (22.9)	10,153 (29.5)
No. of prescriptions (on different days), mean (95% CI)	11.2 (10.6, 11.9)	7.0 (6.8, 7.2)	10.3 (10.2, 10.5)	9.9 (9.8, 10.0)	3.1 (3.0, 3.2)	3.5 (3.3, 3.6)	7.3 (7.2, 7.5)	6.2 (6.1, 6.3)
HbA1c at baseline (−90 days/+7 days), mean (95% CI)	8.0 (7.7, 8.3)	8.4 (8.3, 8.5)	7.4 (7.4, 7.4)	7.6 (7.5, 7.6)	8.0 (7.9, 8.1)	8.3 (8.2, 8.5)	7.5 (7.4, 7.6)	7.7 (7.6, 7.7)
HbA1c at baseline (−90 days/ + 7 days)								
< 7%	14 (17.1)	109 (14.6)	1,858 (41.8)	1,981 (37.6)	105 (18.6)	58 (16.3)	952 (40.5)	1,115 (34.1)
7% − < 8%	33 (40.2)	218 (29.2)	1,574 (35.4)	1,825 (34.6)	204 (36.0)	97 (27.3)	792 (33.7)	1,093 (33.4)
8% − < 9%	21 (25.6)	197 (26.4)	579 (13.0)	797 (15.1)	158 (27.9)	101 (28.5)	326 (13.9)	585 (17.9)
≥ 9%	14 (17.1)	223 (29.9)	430 (9.7)	667 (12.7)	99 (17.5)	99 (27.9)	280 (11.9)	478 (14.6)
Missing	809	5,386	37,318	43,513	5,381	3,304	22,472	31,157
Weight at baseline (−90 days/+7 days), kg, mean (95% CI)	71.7 (69.1, 74.3)	66.1 (65.5, 66.8)	60.7 (60.5, 60.8)	61.2 (61.0, 61.4)	71.9 (70.4, 73.4)	65.2 (64.4, 66.0)	60.5 (60.3, 60.7)	61.3 (61.1, 61.5)
BMI at baseline*, (−90 days/+7 days), mean (95% CI)	27.5 (26.6, 28.5)	25.6 (25.4, 25.8)	24.4 (23.6, 25.1)	24.5 (23.8, 25.2)	27.4 (26.9, 27.9)	25.4 (25.0, 25.8)	23.9 (23.8, 24.0)	24.2 (24.1, 24.2)
BMI at baseline* (90-day period)								
< 18.5	3 (1.9)	181 (6.8)	2,162 (8.0)	2,346 (7.9)	16 (2.9)	108 (6.8)	1,372 (8.4)	1,496 (8.1)
18.5 − 25	54 (34.8)	1,186 (44.6)	15,402 (57.0)	16,642 (55.8)	195 (35.9)	749 (47.1)	9,322 (57.1)	10,266 (55.7)
> 25	98 (63.2)	1,295 (48.6)	9,448 (35.0)	10,841 (36.3)	332 (61.1)	733 (46.1)	5,619 (34.4)	6,884 (36.2)
Missing	736	3,471	14,747	18,954	5,404	2,069	8,509	15,982
Time in database, years, mean (95% CI)	10.1 (9.6, 10.5)	9.5 (9.3, 9.6)	8.0 (8.0, 8.1)	8.3 (8.2, 8.3)	10.4 (10.3, 10.6)	9.7 (9.5, 9.9)	7.9 (7.8, 8.0)	8.5 (8.5, 8.6)
Index dose								
3 mg	825 (92.6)	0	0	825 (92.6)	5,045 (84.8)	0	0	5,045 (84.8)
7 mg	49 (5.5)	0	0	49 (5.5)	361 (6.1)	0	0	361 (6.1)
14 mg	14 (1.6)	0	0	14 (1.6)	91 (1.5)	0	0	91 (1.5)
3 mg and 7 mg	2 (0.2)	0	0	2 (0.2)	423 (7.1)	0	0	423 (7.1)
3 mg and 14 mg	1 (0.1)	0	0	1 (0.1)	0	0	0	0
7 mg and 14 mg	0	0	0	0	5 (0.1)	0	0	5 (0.1)
3 mg and 7 mg and 14 mg	0	0	0	0	22 (0.4)	0	0	22 (0.4)
Missing	0	6,133	41,759	47,892	0	3,659	24,822	28,481
Highest dose								
3 mg	250 (28.1)	0	0	250 (28.1)	2,461 (41.4)	0	0	2,461 (41.4)
7 mg	375 (42.1)	0	0	375 (42.1)	2,954 (49.7)	0	0	2,954 (49.7)
14 mg	266 (29.9)	0	0	266 (29.9)	532 (8.9)	0	0	532 (8.9)
Missing	0	6,133	41,759	47,892	0	3,659	24,822	28,481

BMI, body mass index; DPP-4, dipeptidyl-peptidase 4; GLP1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c.

Supplementary Table 2 Summary of Previous Treatments in the Pre-Index Period by Time Period (Subgroup Analysis)

	Feb 2021 − Nov 2021				Dec 2021 − Jul 2022			
	Oral Semaglutide (N = 891)	GLP-1RA (N = 6,133)	DPP-4 inhibitor (N = 41,759)	Total (N = 48,783)	Oral Semaglutide (N = 5,947)	GLP-1RA (N = 3,659)	DPP-4 inhibitor (N = 24,822)	Total (N = 34,428)
GLP-1RA								
No	717 (80.5)	6,133 (100.0)	41,482 (99.3)	48,332 (99.1)	4,890 (82.2)	3,659 (100.0)	24,695 (99.5)	33,244 (96.6)
Yes	174 (19.5)	0	277 (0.7)	451 (0.9)	1,057 (17.8)	0	127 (0.5)	1,184 (3.4)
Metformin								
No	434 (48.7)	3,952 (64.4)	38,886 (93.1)	43,272 (88.7)	2,382 (40.1)	2,466 (67.4)	23,014 (92.7)	27,862 (80.9)
Yes	457 (51.3)	2,181 (35.6)	2,873 (6.9)	5,511 (11.3)	3,565 (59.9)	1,193 (32.6)	1,808 (7.3)	6,566 (19.1)
Sulfonylureas								
No	715 (80.2)	4,946 (80.6)	40,266 (96.4)	45,927 (94.1)	4,457 (74.9)	2,990 (81.7)	23,941 (96.5)	31,388 (91.2)
Yes	176 (19.8)	1,187 (19.4)	1,493 (3.6)	2,856 (5.9)	1,490 (25.1)	669 (18.3)	881 (3.5)	3,040 (8.8)
Thiazolidinediones								
No	810 (90.9)	5,764 (94.0)	41,319 (98.9)	47,893 (98.2)	5,310 (89.3)	3,491 (95.4)	24,545 (98.9)	33,346 (96.9)
Yes	81 (9.1)	369 (6.0)	440 (1.1)	890 (1.8)	637 (10.7)	168 (4.6)	277 (1.1)	1,082 (3.1)
α glucosidase inhibitors								
No	748 (84.0)	5,273 (86.0)	40,453 (96.9)	46,474 (95.3)	5,012 (84.3)	3,129 (85.5)	24,005 (96.7)	32,146 (93.4)
Yes	143 (16.0)	860 (14.0)	1,306 (3.1)	2,309 (4.7)	935 (15.7)	530 (14.5)	817 (3.3)	2,282 (6.6)
SGLT-2 inhibitors								
No	458 (51.4)	4,163 (67.9)	39,633 (94.9)	44,254 (90.7)	2,685 (45.1)	2,570 (70.2)	23,081 (93.0)	28,336 (82.3)
Yes	433 (48.6)	1,970 (32.1)	2,126 (5.1)	4,529 (9.3)	3,262 (54.9)	1,089 (29.8)	1,741 (7.0)	6,092 (17.7)
DPP-4 inhibitors								
No	600 (67.3)	3,686 (60.1)	41,759 (100.0)	46,045 (94.4)	3,842 (64.6)	2,312 (63.2)	24,822 (100.0)	30,976 (90.0)
Yes	291 (32.7)	2,447 (39.9)	0	2,738 (5.6)	2,105 (35.4)	1,347 (36.8)	0	3,452 (10.0)
Insulin								
No	682 (76.5)	3,203 (52.2)	31,624 (75.7)	35,509 (72.8)	4,625 (77.8)	1,887 (51.6)	18,241 (73.5)	24,753 (71.9)
Yes	209 (23.5)	2,930 (47.8)	10,135 (24.3)	13,274 (27.2)	1,322 (22.2)	1,772 (48.4)	6,581 (26.5)	9,675 (28.1)
Combinations								
No	724 (81.3)	5,432 (88.6)	40,506 (97.0)	46,662 (95.7)	4,893 (82.3)	3,288 (89.9)	24,042 (96.9)	32,223 (93.6)
Yes	167 (18.7)	701 (11.4)	1,253 (3.0)	2,121 (4.3)	1,054 (17.7)	371 (10.1)	780 (3.1)	2,205 (6.4)
Other blood glucose-lowering drugs								
No	763 (85.6)	5,314 (86.6)	40,895 (97.9)	46,972 (96.3)	5,273 (88.7)	3,153 (86.2)	24,256 (97.7)	32,682 (94.9)
Yes	128 (14.4)	819 (13.3)	864 (2.1)	1,811 (3.7)	674 (11.3)	506 (13.8)	566 (2.3)	1,746 (5.1)
Any antidiabetic medication								
No	115 (12.9)	1,229 (20.0)	27,250 (65.3)	28,594 (58.6)	425 (7.1)	791 (21.6)	15,308 (61.7)	16,524 (48.0)
Yes	776 (87.1)	4,904 (79.9)	14,509 (34.7)	20,189 (41.4)	5,522 (92.9)	2,868 (78.4)	9,514 (38.3)	17,904 (52.0)
Number of different OADs								
0	164 (18.4)	1,848 (30.1)	34,761 (83.2)	36,773 (75.4)	649 (10.9)	1,226 (33.5)	20,135 (81.1)	22,010 (63.9)
1	162 (18.2)	1,052 (17.2)	4,538 (10.9)	5,752 (11.8)	1,085 (18.2)	648 (17.7)	3,105 (12.5)	4,838 (14.1)
2	198 (22.2)	1,336 (21.8)	1,754 (4.2)	3,288 (6.7)	1,561 (26.2)	723 (19.8)	1,097 (4.4)	3,381 (9.8)
≥ 3	367 (41.2)	1,897 (30.9)	706 (1.7)	2,970 (6.1)	2,652 (44.6)	1,062 (29.0)	485 (2.0)	4,199 (12.2)
Antidiabetic medication								
Naïve	123 (13.8)	1,260 (20.5)	27,382 (65.6)	28,765 (59.0)	488 (8.2)	806 (22.0)	15,409 (62.1)	16,703 (48.5)
1 OAD only	93 (10.4)	373 (6.1)	2,785 (6.7)	3,251 (6.7)	690 (11.6)	239 (6.5)	1,895 (7.6)	2,824 (8.2)
2 OADs only	119 (13.4)	569 (9.3)	994 (2.4)	1,682 (3.4)	924 (15.5)	292 (8.0)	632 (2.5)	1,848 (5.4)
3 OADs only	241 (27.0)	1,001 (16.3)	361 (0.9)	1,603 (3.3)	1,891 (31.8)	550 (15.0)	258 (1.0)	2,699 (7.8)
GLP-1RA, + / − OAD, + / − insulin	174 (19.5)	0	277 (0.7)	451 (0.9)	1,057 (17.8)	0	127 (0.5)	1,184 (3.4)
Insulin + / − OAD, no GLP-1RA	141 (15.8)	2,930 (47.8)	9,960 (23.9)	13,031 (26.7)	897 (15.1)	1,772 (48.4)	6,501 (26.2)	9,170 (26.6)

BMI, body mass index; DPP-4, dipeptidyl-peptidase 4; GLP1, glucagon-like peptide 1; HbA1c, glycated hemoglobin A1c; OAD, oral antidiabetic drug.