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Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study

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Abstract

Objective To determine real-world trends in antidiabetic drug use, and persistence and adherence, in Japanese patients with type 2 diabetes mellitus (T2DM).

Design Retrospective evaluation of administrative claims data (2011–2015) using the Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases.

Setting Analysis of two administrative claims databases for Japanese patients with T2DM.

Participants Adults (aged ≥18 years) with an ICD-10 code of T2DM, and at least one antidiabetic drug prescription.

Interventions Not applicable.

Main outcome measures Treatment patterns in untreated (UT) or previously treated (PT) patients receiving antidiabetic therapy; persistence with treatment at 12 months; adherence (proportion of days covered [PDC]); proportions of patients with PDC ≥0.8 (adherence rate ≥80%) at 12 months.

Results 40,908 and 90,421 patients were included from the JMDC and MDV databases, respectively. The most frequently used therapy at the index date was dipeptidyl peptidase-4 inhibitor (DPP-4i) in UT patients (JMDC: 44.0%; MDV: 54.8%) and combination therapy in PT patients (74.6%; 81.1%). Most common combinations were DPP-4i plus: biguanide (BG), sulfonylurea (SU), or BG + SU. DPP-4i was the most common add-on therapy to index BG or SU. The most common switch from an index antidiabetic drug class was to DPP-4i. 12-month persistence with index monotherapy was highest with DPP-4i and BG. 12-month persistence with index combination therapy was highest with DPP-4i plus BG. PDC was ≥0.80 for all monotherapy schedules, except insulin and glucagon-like peptide-1 agonist, and for the five most frequent 2- and 3-drug combinations. Persistence was greater in elderly UT patients and those receiving ≤5 medications, but relatively worse in UT patients with ≥3 index antidiabetic drug classes.

Conclusions The findings confirm the key role of DPP-4i in Japanese patients with T2DM and indicate high persistence and adherence to DPP-4i-containing regimens.

Trial registration Not applicable.

Strengths and limitations of this study

- This retrospective evaluation of administrative claims data (2011–2015) using the Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases was conducted to determine real-world trends in antidiabetic drug use, and persistence and adherence, in Japanese patients with type 2 diabetes mellitus (T2DM); 40,908 and 90,421 patients were included from the JMDC and MDV databases, respectively.
- The main strengths of the study are that it provides robust real-world evidence from two large administrative claims databases for patterns of antidiabetic drug use in Japanese patients with T2DM, highlighting widespread use of DPP-4i schedules (as monotherapy, add-on therapy, switch therapy, or in combination regimens) and marked persistence and adherence with DPP-4i therapy.
- The study was limited by the observational design, by the strict inclusion criteria which restricted the number of patients eligible for analysis, and by the use of prescription events rather than patient-derived data to estimate outcomes.
- Database-specific limitations were the relative scarcity of data for patients aged ≥65 years (JMDC), the absence of information as to whether patients received care in other medical facilities (MDV), and the inability to examine reasons for treatment discontinuation and potential health benefits resulting from increased persistence (JMDC and MDV).
- Uptake of SGLT2i use may not have been accurately captured given the timing of their introduction in Japan.

Introduction

The prevalence of diabetes mellitus continues to increase globally. In 2015, approximately 415 million people worldwide had diabetes, and this figure is projected to reach almost 650 million by 2040.[1] As about 20% of men and 10% of women in Japan are considered to have, or are highly likely to have, diabetes, the public health implications are enormous.[2]

Disease characteristics in Asian individuals with type 2 diabetes mellitus (T2DM) differ from those in Caucasian patients; Japanese patients with T2DM principally have pancreatic β-cell dysfunction, with less insulin resistance and adiposity than Caucasians.[1] Nevertheless, even in patients with mild metabolic dysfunction, T2DM has serious long-term consequences (i.e. nephropathy, neuropathy, and retinopathy) and is an important risk factor for atherosclerotic cardiovascular diseases.[3,4]

The benefits of early and effective intervention in T2DM are extensively acknowledged. Enhanced glycaemic control can markedly reduce micro- and macroangiopathic development and progression.[4] An intensified intervention to achieve lower treatment targets was shown to be significantly superior to conventional therapy for prevention of cerebrovascular events in patients with T2DM.[5] The Japan Diabetes Society (JDS) has developed evidence-based guidelines for management of diabetes.[6] Despite widespread availability of the guidelines and highly favourable conditions for access to health care in Japan, a 2-year longitudinal study using claims data identified that the quality of care for T2DM patients is often suboptimal.[7] Notably, screening for diabetic renal and ocular disease was less frequent than recommended in the JDS guidelines and less than half of diabetic patients were achieving the glycaemic goal (glycosylated haemoglobin [HbA1c] <7%) recommended by JDS for their circumstances.

Allied to these factors is the potential for suboptimal adherence to, and poor persistence with, treatment. Adherence is typically lower among patients with chronic conditions compared to those with acute conditions, and treatment persistence for chronic conditions is particularly low, tending to decline most dramatically within the first 6 months of treatment.[8] The reasons

for poor adherence and persistence are complex and multifactorial, involving patient- and physician-related factors as well as treatment regimen factors such as pill burden, regimen complexity, and dosing schedule.[9]

In Japan, it has been estimated that approximately 60% of patients with diabetes forget to take their medication at some stage.[10] Non-adherence to antidiabetic medications is associated with increased healthcare expenditure and higher rates of hospitalisation and death.[11,12] It has been suggested that use of a once-weekly dipeptidyl peptidase-4 inhibitor (DPP-4i), or a fixed-dose combination (FDC) therapy, may improve adherence in patients with T2DM.[13] A 10% increase in adherence has been linked with a 0.1% decrease in HbA1c.[11,14] Recent studies suggest that dual-therapy schedules containing a DPP-4i may improve persistence relative to DPP-4i monotherapy,[15] or sulfonylurea (SU)-containing schedules.[16]

Contemporary meta-analyses of studies involving incretin-based treatments (i.e. DPP-4i or glucagon-like peptide-1 [GLP-1] receptor agonists) in patients with T2DM have shown that these agents are more effective in Asian than in non-Asian populations, possibly due to greater attenuation of β-cell dysfunction.[1,17,18] Moreover, the HbA1c-reducing activity of DPP-4i has been linked with fish intake, suggesting that dietary factors may also contribute to their greater efficacy in Asian patients with T2DM.[1,19,20]

Despite widespread recognition of the deleterious long-term consequences of poorly managed T2DM, and the proven efficacy of incretin-based therapies in Asian populations with diabetes, surprisingly little is known about actual antidiabetic drug utilisation trends and persistence and adherence patterns with antidiabetic drug therapy in patients with T2DM in Japan. In the current study, data from two large administrative claims databases were used to determine real-world trends in antidiabetic drug use, and treatment persistence and adherence rates, in patients with T2DM in Japan.

Methods

Overview

This was a real-world, retrospective evaluation of data from two administrative claims databases in Japan: the Japan Medical Data Center (JMDC) database (Japan Medical Data Center Co., Ltd; Tokyo, Japan); and the Medical Data Vision (MDV) database (Medical Data Vision Co., Ltd; Tokyo, Japan). The JMDC database contains monthly claims submitted to health insurance societies from medical institutions since January 2005 and, as at July 2017, covered up to 4 million beneficiaries (employees and their dependants). MDV is a nationwide hospital-based claims database covering nearly 19 million cumulative patients since April 2008 who, as at July 2017, had been treated as inpatients or outpatients at approximately 300 hospitals in Japan that participate in the Diagnostic Procedure Combination (DPC)/Per-Diem payment system. Both databases hold anonymised information about diagnoses, patient characteristics, drug prescriptions, medical procedures, features of medical facilities, and reimbursement costs. All patient data are encrypted before entry.

Based on Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labour and Welfare, ethics approval and informed consent were not applicable for this study.

Study population

Eligible patients were adults (≥18 years) with a diagnosis of T2DM (International Classification of Diseases [ICD]-10 code: E11 or E14) and at least one prescription for an antidiabetic drug issued during the target selection period of January 2011 to December 2015.

The first prescription date for an antidiabetic drug class initiated during the selection period was the index date, and the antidiabetic drug class prescribed was designated as the index antidiabetic drug class. Only patients with a new prescription during the selection period were

included for analysis. The minimum 12-month pre-index ('look-back') period provided adequate time to observe patients' baseline characteristics and ascertain that first prescription of a given antidiabetic drug class corresponded to initiation of that drug class. The minimum 12-month post-index observational period allowed adequate time for evaluation of treatment-related outcomes of interest.

Patients were excluded for the following reasons: age <18 years at the index date; <12 months of continuous enrolment in the database before or after the index date; index prescription received in the 12 months before the index date; no T2DM diagnosis (ICD code E11 or E14) in the pre-index period (fig 1). The patient population was divided into two subgroups: 1) untreated (UT) patients, i.e. patients without a prescription for any antidiabetic drug class of interest during the pre-index period; and 2) previously treated (PT) patients, i.e. patients with a prescription for at least one non-index antidiabetic drug class during the pre-index period.

Antidiabetic drug classes of interest

Target antidiabetic drug classes of interest were DPP-4i, biguanides (BG), SU, α-glucosidase inhibitors (α-GI), thiazolidinediones (TZD), glinides, sodium-glucose cotransporter-2 inhibitors (SGLT2i), insulin and GLP-1 receptor agonists and, in PT patients, the most common combination therapy schedules (consisting of combinations of these same drug classes). Data for insulin and GLP-1 receptor agonists were excluded from persistence and adherence analyses mainly because of inconsistent database information regarding the duration of therapy for these injectable drug classes.

Objectives

The primary objectives of the study were to describe patterns of antidiabetic drug use and persistence and adherence with antidiabetic drug classes in T2DM patients, overall and by patient subgroup (UT and PT), in the JMDC and MDV database populations.

Outcomes

A treatment line was defined as the period during which a patient took a specific antidiabetic drug class or a combination of antidiabetic drug classes continuously, i.e. without addition of new class(es) or withdrawal/discontinuation of existing drug class(es). A treatment line-related event was defined as: an 'add-on' when a new antidiabetic drug class was prescribed in addition to existing drug class(es) for more than 21 days; as a 'switch' when at least one new antidiabetic drug class was prescribed within the grace period (defined as 1.5 times the median prescription duration for a given drug class).

Treatment persistence was defined as the time from the index date until discontinuation of at least one index antidiabetic drug class. The median time to discontinuation and the proportion of patients persistent with treatment at 12 months were reported. The date of discontinuation was defined as the date of the last prescription of the first discontinued drug in an antidiabetic drug combination, plus the days of supply of that prescription.

Adherence to an antidiabetic drug class of interest was defined as the proportion of days covered (PDC) or the period in which patients had the treatment in their possession, and was calculated according to the formula:

Total number of prescription days covered for defined drug class of interest /
Total number of days in the follow-up period.

Patients were considered adherent if a PDC of ≥0.8 (also expressed as an adherence rate of ≥80%) was achieved. Adherence analyses were performed for patients with at least two

prescriptions of the index antidiabetic drug class(es) during the 12-month post-index follow-up period.

The analyses reported herein focus mainly on patients who had been prescribed antidiabetic drug monotherapy, rather than those prescribed antidiabetic drug combinations, on the index date.

Statistical analyses

Analyses were performed using SAS® version 9.3 (SAS Institute; Cary, NC, USA) and were conducted on all patients who met the inclusion criteria and were stratified into the two pre-specified patient subgroups (UT and PT) on the index date. Patient demographics, clinical characteristics, treatment-related events affecting index therapy (add-on, switch) and adherence were reported descriptively. The median time to discontinuation was calculated by antidiabetic drug class using Kaplan–Meier survival analysis, with differences between patient subgroups (UT and PT) assessed by log-rank test. The first discontinuation of the index antidiabetic drug class was the survival event and patients were censored if they reached the end of follow-up without discontinuation.

Patient involvement

No patients were involved in setting the research question or outcome measures, and no patients were involved in developing plans for study implementation. Furthermore, no patients were asked for advice about interpretation or writing up of results. There are no plans to distribute the research findings to study participants or the specific patient community. Individual patient consent was not required for this study, as the trial was based on anonymised administrative claims data.

Results

Patient disposition

Between January 2011 and December 2015, 94,529 patients in the JMDC database and 721,366 patients in the MDV database with at least one prescription for an antidiabetic drug class of interest were identified. Of these, 40,908 patients (43.3%) in the JMDC database and 90,421 patients (8.0%) in the MDV database met the inclusion criteria and were included in the analyses (fig 1). The ratio of UT to PT patients was approximately 1:1 in the JMDC database and 1:3 in the MDV database.

Patient characteristics

Patient demographics and clinical characteristics are presented in table 1.

Mean duration of follow-up in UT patients was 1027.1 days in the JDMC database and 1053.7 days in the MDV database. Mean age was 51.7 years and 67.6 years, respectively. There was a higher proportion of males (72.3% *vs* 60.8%), a lower mean number of concurrent medications (2.0 *vs* 3.0), and lower incidences of comorbid hypertension (47.8% *vs* 70.1%), hyperlipidaemia (39.8% *vs* 70.0%), dementia (0.2% *vs* 1.9%), and diabetic nephropathy (3.7% *vs* 18.1%) among UT patients in the JMDC database compared with the MDV database.

Among PT patients, mean duration of follow-up was 1103.8 days in the JDMC database and 1143.9 days in the MDV database. Mean age was 54.4 years and 66.9 years, respectively. There was a higher proportion of males (73.5% *vs* 61.2%), a lower mean number of concurrent medications (2.3 *vs* 3.3), and lower incidences of comorbid hypertension (58.3% *vs* 71.3%), hyperlipidaemia (50.0% *vs* 67.2%), dementia (0.2% *vs*2.0%), and diabetic nephropathy (6.1% *vs* 15.7%) among PT patients in the JMDC database compared with the MDV database.

Index date therapy

Irrespective of database (JMDC or MDV), treatment patterns for index antidiabetic drug classes were broadly similar for UT patients and PT patients.

In UT patients (fig 2a), the most common index therapy was DPP-4i monotherapy (JMDC: 44.0%; MDV: 54.8%), followed by BG (JMDC: 17.3%; MDV: 11.2%), insulin (JMDC: 10.2%; MDV: 8.4%) and combination therapy (JMDC: 10.7%; MDV: 9.9%). Selection of antidiabetic drug classes for combination therapy was highly varied.

In PT patients (fig 2b), the most common index therapy was combination therapy (JMDC: 74.6%; MDV: 81.1%), consisting mainly of a DPP-4i plus: BG (11.4% and 10.9%, respectively); SU (8.4% and 11.0%); BG + SU (7.8% and 9.1%); α-GI (3.8% and 5.9%); or SU + α-GI (2.4% and 4.6%). The next most common index therapy in PT patients was DPP-4i monotherapy (JMDC: 11.0%; MDV: 11.7%); use of the other antidiabetic drug classes as monotherapy was low.

Changes to index therapy

In UT patients who had received a DPP-4i as the index prescription, the most frequent add-on was a BG (JMDC: 46.6%; MDV: 36.7%) or SU (JMDC: 18.9%; MDV: 23.2%). In UT patients who had received any other antidiabetic drug class as the index prescription, the most frequent add-on in all cases apart from GLP-1 receptor agonists was a DPP-4i which was added to: BG (JMDC: 67.9%; MDV: 68.6%), SU (JMDC: 57.1%; MDV: 62.9%), α-GI (JMDC: 46.2%; MDV: 60.5%), TZD (JMDC: 55.9%; MDV: 53.1%), glinide (JMDC: 42.0%; MDV: 56.8%), SGLT2i (JMDC: 44.7%; MDV: 34.3%), or insulin (JMDC: 57.1%; MDV: 50.4%) (table 2).

In UT patients who had received a DPP-4i as the index prescription, the most frequent treatment switch to another antidiabetic drug class was to a BG (JMDC: 32.7%; MDV: 26.2%), SU (JMDC: 11.8%; MDV: 11.4%), SGLT2i (JMDC: 18.6%; MDV: 11.7%), or insulin (JMDC: 14.3%; MDV: 30.5%). In UT patients whose index prescription was for any other antidiabetic drug class, the most frequent treatment switch was to a DPP-4i: from BG (JMDC: 58.8%; MDV: 76.0%), SU (JMDC: 47.3%; MDV: 72.4%), α-GI (JMDC: 57.0%; MDV: 69.2%), TZD (JMDC: 56.6%; MDV: 59.4%), glinide (JMDC: 50.0%; MDV: 51.1%), SGLT2i (JMDC: 52.0%; MDV: 30.0%), or insulin (JMDC: 34.2%; MDV: 53.7%) (table 3).

In PT patients who had received a DPP-4i as the index prescription, the most frequent add-on was BG (JMDC: 30.4%; MDV: 21.6%), SU (JMDC: 24.5%; MDV: 22.8%), or insulin, but only in the MDV population (JMDC: 0.7%; MDV: 24.6%). In PT patients who had received any other antidiabetic drug class as the index prescription, the most frequent add-on was a DPP-4i to all drug classes except GLP-1 receptor agonists in the JMDC database (BU: 50.3%; SU: 47.2%; α-GI: 43.7%; TZD: 26.5%; glinide: 42.3%; SGLT2i: 30.2%; insulin: 55.6%); and was a DPP-4i to all drug classes except α-GI and GLP-1 receptor agonists in the MDV database (BU: 40.4%; SU: 55.0%; TZD: 28.3%; glinide: 36.7%; SGLT2i: 33.3%; insulin: 38.2%) (table 4).

In PT patients whose index treatment was a DPP-4i, the most frequent treatment switch was to insulin (JMDC: 35.0%; MDV: 30.1%) or SU (JMDC: 18.5%; MDV: 25.8%). In PT patients who had received any other antidiabetic drug class as the index prescription, treatment switches varied by database. In the JMDC database, the most common treatment switch was to a DPP-4i from index therapy with a TZD (43.5%), glinide (36.8%), SGLT2i (32.0%) or insulin (31.3%), and to insulin from index therapy with a BG (40.2%), SU (32.1%), α-GI (52.9%), or GLP-1 receptor agonist (25.9%). In the MDV database, the most common treatment switch was to a DPP-4i from index therapy with a BG (37.0%), SU (49.6%), TZD (41.7%), glinide (36.1%), SGLT2i (44.1%), or insulin (34.2%); and to insulin from index therapy with a GLP-1 receptor agonist (34.7%). For PT patients treated initially with α-GI, switch rates were similar between DPP-41 (37.0%) and insulin (37.8%) (table 5).

Persistence and adherence with index monotherapy

In both patient subgroups across both databases, the probability of remaining on treatment with index monotherapy at 12 months (not including insulin and GLP-1 receptor agonists) was highest with DPP-4i schedules (JMDC: 67.4%; MDV: 77.2%) and lowest with glinide schedules (JMDC: 38.8%; MDV: 53.8%) (table 6). This is illustrated schematically by Kaplan-Meier survival curves showing the distribution of median time to treatment discontinuation during 12 months' observation by index antidiabetic drug class for UT and PT patients in each database. Among UT patients, persistence with all antidiabetic drug classes was considerably lower in the JMDC database, particularly with glinide schedules (fig 3a), compared with the MDV database (fig 3b). Among PT patients, persistence with all antidiabetic drug classes tended to be slightly lower in the JMDC database for all antidiabetic drug classes except TZD and especially for glinide schedules (fig 3c) compared with the MDV database (fig 3d). 12-month persistence rates of approximately 50% or less were recorded in one or both patient subgroups from one or both databases for SU, α-GI, TZD, and glinides (table 6).

Adherence to index antidiabetic drug classes (not including insulin and GLP-1 receptor agonists) was high in both patient subgroups across both databases, with rates ranging from 75.0% to 98.9%. In UT patients (fig 4a) and in PT patients (fig 4b), adherence rates with index antidiabetic drug classes were consistently lower in the JMDC database than in the MDV database. The lowest adherence rates were recorded with SGLT2i in UT patients (75.0%) and PT patients (77.0%) in the JDMC database.

Persistence and adherence with index combination therapy

Among the five most common antidiabetic drug combinations prescribed to PT patients on the index date (i.e. a DPP-4i plus: BG, SU, BG + SU, α-GI, or SU + α-GI), 12-month

persistence rates were highest for DPP-4i plus BG (JMDC: 53.7%; MDV: 72.0%) and lowest with DPP-4i plus SU + α-GI (JMDC: 30.8%; MDV: 64.2%) (fig 5). Overall, 12-month persistence rates were considerably lower in the JMDC database compared with the MDV database (fig 5).

Adherence rates were ≥80% across all antidiabetic drug combinations in both database populations, although were slightly lower in the JMDC database (86.4–91.8%) than in the MDV database (96.6–98.8%).

Discussion

Principal findings

This real-world evaluation of data from two administrative claims databases in Japan reveals that the most common index antidiabetic drug class was DPP-4i in UT patients (44–55%) and combination therapy in PT patients (~75–80%), with the latter most frequently comprising dual therapy with a DPP-4i plus BG or SU.

Among patients with a change to their index antidiabetic drug therapy during follow-up: the most common add-on to index DPP-4i therapy was a BG or SU; the most common add-on to index BG or SU therapy was a DPP-4i; the most common switch from index DPP-4i therapy was to a BG or SU; the most common switch from index drug classes other than DPP-4i (except GLP-1 receptor agonists) was to a DPP-4i. Overall patterns for add-on or switch therapy were similar between JMDC and MDV databases and between UT and PT patients.

Across all four patients subgroups, 12-month persistence rates were highest with index DPP-4i monotherapy compared with all other index antidiabetic drug classes, although did not exceed 78.8% (with DPP-4i in PT patients in the MDV database) and were around 50% or less with several index antidiabetic drug classes especially in the JMDC database. Mean adherence to antidiabetic monotherapy was high overall, and the proportion of adherent

patients (PDC ≥0.80) was higher with index DPP-4i than with all other antidiabetic drug classes. Among drug combinations, 12-month persistence rates were higher for DPP-4i plus BG than for other combinations, although did not exceed 72.0%. Adherence rates were ≥80% for commonly prescribed antidiabetic drug combinations.

We also analysed persistence (≥12 months, <12 months) and drug adherence (<80%, ≥80%) in UT patients according to other patient- and treatment-related factors. Persistence tended to increase with age (supplementary table 1). In the JMDC database, the adjusted odds ratio for non-persistence was 3.31 (P<0.05) in the 65–74-year age group compared with the reference group (18–34 years). In addition, persistence with multiple medications tended to be good in patients receiving ≤5 medications, but poorer in patients receiving ≥6 medications. In the MDV database, 29.1% of patients with 4–5 medications were non-persistent, whereas 47.6% of patients with >8 medications were non-persistent. Persistence was good in patients with comorbid hypertension (JMDC: 66.0%; MDV: 71.4%) or hyperlipidaemia (JMDC: 62.3%; MDV: 73.6%). However, persistence was poor in patients treated with multiple antidiabetic drug classes: in both the JMDC and MDV databases, approximately 60–70% of patients receiving ≥3 index antidiabetic drug classes were non-persistent. Similar findings were evident for adherence (supplementary table 2). In the MDV database, only 2.0% of patients receiving antidiabetic monotherapy were non-adherent, whereas 6.6–9.5% of those with ≥3 antidiabetic drugs were non-adherent. All these findings are interesting and suggest that higher rates of persistence and adherence observed in elderly patients treated with multiple medications may reflect greater insight into their disease among this group. Conversely, the relatively low rates of persistence and adherence evident in patients treated with more index antidiabetic drug classes may have resulted from patient or caregiver difficulties regarding drug management. Therefore, FDC therapy, with its potential to enhance persistence and adherence, may be especially appropriate for patients treated with several index oral antidiabetic drug classes.

Strengths and limitations of the study

The main strengths of the present study are that it provides robust real-world evidence from two large administrative claims databases for patterns of antidiabetic drug use in T2DM patients in Japan, clearly highlighting the widespread use of DPP-4i schedules (as monotherapy, add-on therapy, switch therapy, or in combination regimens) and marked persistence and adherence with DPP-4i therapy.

The study was limited by the observational design, which can introduce selection bias, and by the strict inclusion criteria, which restricted the proportion of patients eligible for analysis. The analyses did not factor in HbA1c levels at the start of treatment, or the level of HbA1c control achieved during treatment, which may have influenced the various treatment decisions. Another limitation was the use of prescription events, rather than patient-derived data (e.g. patient diaries), to estimate outcomes. A limitation specific to the JMDC database was the relative scarcity of data for patients aged ≥65 years. A limitation specific to the MDV database was the absence of information about whether patients received care in other medical facilities. For example, receipt of a prescription at another medical facility could result in a missing medication history and misclassification of the patient in our analysis. The inability to examine reasons for treatment discontinuation as these are not collected in administrative claims databases, and any potential health benefits (e.g. reduced symptom severity or improved health-related quality of life) resulting from increased persistence were limitations that applied to both databases. Lastly, the study may not have accurately captured the uptake of SGLT2i use given the timing of their introduction in Japan. Between May and October 2015, prescribing of SGLT2i was restricted to 14–28 days' therapy, which may have impacted on usage rates. Further analysis based on updated databases is required to reflect current trends in prescribing practices.

Comparison with other studies

A recent update to a position statement from the American Diabetes Association and European Association for the Study of Diabetes regarding management of hyperglycaemia in T2DM stipulates clearly that metformin is the best therapeutic option for monotherapy.[21–23] If target HbA1c is not attained after approximately 3 months, progression to double therapy is advocated. If, after a further 3 months, target HbA1c remains unattained, progression to triple therapy is recommended. After a 3-month trial of triple therapy, the introduction of combination injectable therapy with insulin plus a GLP-1 receptor agonist may be indicated.

Conversely, JDS guidelines stipulate that the '… choice of glucose-lowering agent should be made based on the disease condition of each particular patient with consideration given to the pharmacological and safety profile of each glucose-lowering agent'.[6] In accordance with these recommendations, and in conjunction with appropriate patient education about diet, exercise and lifestyle, treatment of T2DM in Japan may be started with any oral hypoglycaemic agent. As illustrated in the current study, DPP-4i are widely used in Japan, and this concurs with findings from other studies. For example, the ATTAK-J study reported real-world evidence of significant hypoglycaemic activity and favourable safety for DPP-4i therapy in Japanese patients with T2DM.[24] The PREFERENCE 4 study documented that treatment-naive Japanese patients preferred (in terms of treatment satisfaction) a DPP-4i to a BG, SU, or α-GI.[25] Use of a weekly DPP-4i also improved treatment satisfaction.[26,27] However, these are preliminary findings, and additional real-world data from other DPP-4i studies are awaited.

A systematic review and meta-analysis of studies which compared persistence and adherence associated with two or more antidiabetic medications in patients with T2DM found considerable variation among studies in the methods used to define these terms but, nonetheless, was able to ascertain major differences between drug classes.[28] Adherence was better with DPP-4i than with TZD, SU, and metformin, possibly reflecting the superior tolerability and convenient dosing schedules of these incretin-based agents.

Data about T2DM management in Asian patients indicate that DPP-4i are a viable first-line intervention, in a manner similar to that of metformin in Caucasian patients with T2DM.[1] There is broad recognition that DPP-4i are more effective in Asian than non-Asian patients[1,17,18,29] and, in Japan, >70% of patients treated with antidiabetic drugs receive incretin-based therapies. As approximately 60% of such patients are treatment-naïve, DPP-4i are establishing a definitive role in the first-line treatment of T2DM in Japan.[1,30] While it is important to remain vigilant for potential safety signals,[31] it is worth remembering that no significant association between DPP-4i and possible pancreatic disorder was observed in several large-scale studies.[24,32–34]

Conclusions and implications

DPP-4i have a prevalent and pivotal role (as monotherapy, add-on therapy, switch therapy, and in combination regimens) in the management of T2DM in Japan. High persistence and adherence to DPP-4i-containing treatment schedules demonstrated in the current study were a positive finding given the multitude of factors contributing to poor adherence,[9] but also suggest that enhanced diabetes awareness and patient education programmes are needed to improve persistence and adherence rates overall in Japan. For antidiabetic drug therapy in general, research is warranted to quantify the extent to which augmenting persistence and adherence is likely to improve glycaemic control. In the case of DPP-4i, strategies to improve adherence might be through the use of novel once-weekly administration schedules or FDCs.[13,35] Overall, consistent findings from these two large administration claims databases confirm the key central role of DPP-4i in the management of Japanese patients with T2DM and indicate high persistence and adherence with DPP-4i-containing schedules, implying patient satisfaction with treatment.

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Contributors and sources:

RN, HK, SH, YO, FG and YS are responsible for the work described in this paper.

RN, HK, SH, YO, FG and YS were involved in the conception, design, or planning of the study.

YO and FG were involved in the analysis of data.

RN, HK, KK, AO, SH and YS were involved in the interpretation of results.

RN, HK, KK, AO and YO contributed substantially to drafting of the manuscript.

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HK, KK, AO, and YS are employees of Takeda Pharmaceutical Co. Ltd.

SH was an employee of Takeda Pharmaceutical Co. Ltd. at the time the study was conducted.

FG and YO are employees of Creativ-Ceutical K.K.

Data sharing:

Given the administrative nature of the data, patients did not provide informed consent for data sharing; however, all data are fully anonymised and the risk of patient identification is low.

Disclaimer:

The study made use of de-identified data from the JMDC and MDV databases. The opinions, results and conclusions reported are those of the authors. No endorsement by JMDC or MDV or any of its funders or partners is intended or should be inferred.

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Tables

Table 1 Patient demographics and clinical characteristics

Characteristics	UT patients		PT patients	
	JMDC database n=19 428	MDV database n=24 820	JMDC database n=21 480	MDV database n=65 601
Follow-up, days, mean (SD):	1027.1 (473.5)	1053.7 (468.9)	1103.8 (514.9)	1143.9 (518.0)
Age at index date, years, mean (SD):	51.7 (9.9)	67.6 (11.8)	54.4 (9.2)	65.9 (12.0)
Gender: male, n (%):	14 042 (72.3)	15 093 (60.8)	15 779 (73.5)	40 160 (61.2)
Multiple medications*, mean (SD):	2.0 (4.0)	3.0 (2.2)	2.3 (3.1)	3.3 (2.0)
Charlson Comorbidity Index, mean (SD):	2.2 (1.5)	2.5 (2.3)	2.5 (1.6)	2.6 (2.2)
Comorbidities				
Hypertension (% pts)	47.8	70.1	58.3	71.3
Hyperlipidaemia (% pts)	39.8	70.0	50.0	67.2
Dementia (% pts)	0.2	1.9	0.2	2.0
Diabetic nephropathy (% pts)	3.7	18.1	6.1	15.7

* Number of drugs prescribed (by 3-digit Anatomical Therapeutic Chemical Classification System)
JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; pts, patients; UT, untreated.

Table 2 Changes to index therapy: add-on treatment according to index antidiabetic drug class in UT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=2839**	**n=1102**	**n=364**	**n=316**	**n=102**	**n=50**	**n=76**	**n=7**	**n=8**
+ DPP-4i	NA	748 (67.9)	208 (57.1)	146 (46.2)	57 (55.9)	21 (42.0)	34 (44.7)	4 (57.1)	1 (12.5)
+ BG	1324 (46.6)	NA	80 (22.0)	85 (26.9)	21 (20.6)	9 (18.0)	28 (36.8)	2 (28.6)	1 (12.5)
+ SU	537 (18.9)	66 (6.0)	NA	30 (9.5)	8 (7.8)	1 (2.0)	5 (6.6)	0 (0.0)	2 (25.0)
+ α-GI	255 (9.0)	40 (3.6)	25 (6.9)	NA	4 (3.9)	15 (30.0)	5 (6.6)	0 (0.0)	0 (0.0)
+ TZD	293 (10.3)	58 (5.3)	20 (5.5)	16 (5.1)	NA	1 (2.0)	1 (1.3)	0 (0.0)	2 (25.0)
+ Glinide	79 (2.8)	16 (1.5)	0 (0.0)	17 (5.4)	0 (0.0)	NA	0 (0.0)	1 (14.3)	0 (0.0)
+ SGLT2i	256 (9.0)	128 (11.6)	11 (3.0)	2 (0.6)	7 (6.9)	2 (4.0)	NA	0 (0.0)	2 (25.0)
+ Insulin	5 (0.2)	2 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
+ GLP-1	0 (0.0)	16 (1.5)	2 (0.5)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=3179**	**n=878**	**n=342**	**n=344**	**n=81**	**n=74**	**n=35**	**n=24**	**n=12**
+ DPP-4i	NA	602 (68.6)	215 (62.9)	208 (60.5)	43 (53.1)	42 (56.8)	12 (34.3)	113 (50.4)	0 (0.0)
+ BG	1168 (36.7)	NA	51 (14.9)	36 (10.5)	14 (17.3)	7 (9.5)	12 (34.3)	26 (11.6)	4 (33.3)
+ SU	736 (23.2)	44 (5.0)	NA	36 (10.5)	3 (3.7)	1 (1.4)	4 (11.4)	10 (4.5)	4 (33.3)
+ α-GI	414 (13.0)	38 (4.3)	29 (8.5)	NA	6 (7.4)	15 (20.3)	0 (0.0)	28 (12.5)	1 (8.3)
+ TZD	168 (5.3)	29 (3.3)	13 (3.8)	4 (1.2)	NA	4 (5.4)	0 (0.0)	1 (0.4)	0 (0.0)
+ Glinide	189 (5.9)	9 (1.0)	0 (0.0)	26 (7.6)	2 (2.5)	NA	0 (0.0)	12 (5.4)	0 (0.0)
+ SGLT2i	190 (6.0)	94 (10.7)	7 (2.0)	5 (1.5)	8 (9.9)	0 (0.0)	NA	2 (0.9)	3 (25.0)

+ Insulin	239 (7.5)	35 (4.0)	14 (4.1)	19 (5.5)	1 (1.2)	3 (4.1)	1 (2.9)	NA	0 (0.0)
+ GLP-1	2 (0.1)	10 (1.1)	4 (1.2)	1 (0.3)	0 (0.0)	1 (1.4)	4 (11.4)	0 (0.0)	NA

'+' indicates add-on therapy with new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Table 3 Changes to index therapy: switch treatment according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=440**	**n=267**	**n=224**	**n=221**	**n=76**	**n=44**	**n=50**	**n=336**	**n=6**
→ DPP-4i	NA	157 (58.8)	106 (47.3)	126 (57.0)	43 (56.6)	22 (50.0)	26 (52.0)	115 (34.2)	1 (16.7)
→ BG	144 (32.7)	NA	47 (21.0)	40 (18.1)	15 (19.7)	8 (18.2)	13 (26.0)	107 (31.8)	1 (16.7)
→ SU	52 (11.8)	12 (4.5)	NA	4 (1.8)	0 (0.0)	3 (6.8)	1 (2.0)	11 (3.3)	1 (16.7)
→ α-GI	20 (4.5)	12 (4.5)	4 (1.8)	NA	2 (2.6)	2 (4.5)	2 (4.0)	19 (5.7)	0 (0.0)
→ TZD	26 (5.9)	19 (7.1)	8 (3.6)	11 (5.0)	NA	0 (0.0)	0 (0.0)	5 (1.5)	0 (0.0)
→ Glinide	22 (5.0)	3 (1.1)	5 (2.2)	11 (5.0)	0 (0.0)	NA	0 (0.0)	11 (3.3)	0 (0.0)
→ SGLT2i	82 (18.6)	26 (9.7)	3 (1.3)	10 (4.5)	7 (9.2)	3 (6.8)	NA	2 (0.6)	1 (16.7)
→ Insulin	63 (14.3)	17 (6.4)	36 (16.1)	8 (3.6)	5 (6.6)	4 (9.1)	2 (4.0)	NA	2 (33.3)
→ GLP-1	7 (1.6)	3 (1.1)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	6 (1.8)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=446**	**n=271**	**n=199**	**n=224**	**n=69**	**n=47**	**n=20**	**n=417**	**n=11**
→ DPP-4i	NA	206 (76.0)	144 (72.4)	155 (69.2)	41 (59.4)	24 (51.1)	6 (30.0)	224 (53.7)	5 (45.5)
→ BG	117 (26.2)	NA	15 (7.5)	21 (9.4)	14 (20.3)	4 (8.5)	6 (30.0)	34 (8.2)	2 (18.2)
→ SU	51 (11.4)	12 (4.4)	NA	15 (6.7)	4 (5.8)	4 (8.5)	2 (10.0)	25 (6.0)	0 (0.0)
→ α-GI	38 (8.5)	7 (2.6)	1 (0.5)	NA	1 (1.4)	7 (14.9)	0 (0.0)	26 (6.2)	0 (0.0)
→ TZD	18 (4.0)	9 (3.3)	0 (0.0)	4 (1.8)	NA	0 (0.0)	0 (0.0)	7 (1.7)	0 (0.0)
→ Glinide	14 (3.1)	4 (1.5)	5 (2.5)	10 (4.5)	0 (0.0)	NA	0 (0.0)	30 (7.2)	0 (0.0)
→ SGLT2i	52 (11.7)	14 (5.2)	2 (1.0)	1 (0.4)	3 (4.3)	0 (0.0)	NA	2 (0.5)	2 (18.2)

→ Insulin	136 (30.5)	10 (3.7)	21 (10.6)	15 (6.7)	4 (5.8)	6 (12.8)	0 (0.0)	NA	1 (9.1)
→ GLP-1 agonist	11 (2.5)	4 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	9 (2.2)	NA

'→' indicates treatment switch to new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Table 4 Changes to index therapy: add-on treatment according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=1141**	**n=370**	**n=163**	**n=119**	**n=68**	**n=71**	**n=129**	**n=9**	**n=53**
+ DPP-4i	NA	186 (50.3)	77 (47.2)	52 (43.7)	18 (26.5)	30 (42.3)	39 (30.2)	5 (55.6)	0 (0.0)
+ BG	347 (30.4)	NA	23 (14.1)	14 (11.8)	11 (16.2)	12 (16.9)	19 (14.7)	0 (0.0)	12 (22.6)
+ SU	279 (24.5)	27 (7.3)	NA	12 (10.1)	9 (13.2)	1 (1.4)	5 (3.9)	2 (22.2)	15 (28.3)
+ α-GI	172 (15.1)	21 (5.7)	13 (8.0)	NA	2 (2.9)	10 (14.1)	2 (1.6)	1 (11.1)	3 (5.7)
+ TZD	120 (10.5)	13 (3.5)	12 (7.4)	1 (0.8)	NA	0 (0.0)	4 (3.1)	0 (0.0)	1 (1.9)
+ Glinide	43 (3.8)	8 (2.2)	1 (0.6)	6 (5.0)	1 (1.5)	NA	0 (0.0)	1 (11.1)	0 (0.0)
+ SGLT2i	46 (4.0)	24 (6.5)	3 (1.8)	2 (1.7)	0 (0.0)	2 (2.8)	NA	0 (0.0)	2 (3.8)
+ Insulin	8 (0.7)	3 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
+ GLP-1 agonist	3 (0.3)	16 (4.3)	7 (4.3)	3 (2.5)	2 (2.9)	0 (0.0)	3 (2.3)	0 (0.0)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=3362**	**n=616**	**n=322**	**n=211**	**n=53**	**n=180**	**n=114**	**n=335**	**n=140**
+ DPP-4i	NA	249 (40.4)	177 (55.0)	63 (29.9)	15 (28.3)	66 (36.7)	38 (33.3)	128 (38.2)	1 (0.7)
+ BG	727 (21.6)	NA	31 (9.6)	8 (3.8)	7 (13.2)	16 (8.9)	23 (20.2)	35 (10.4)	18 (12.9)
+ SU	768 (22.8)	38 (6.2)	NA	11 (5.2)	6 (11.3)	1 (0.6)	4 (3.5)	12 (3.6)	61 (43.6)
+ α-GI	444 (13.2)	28 (4.5)	20 (6.2)	NA	1 (1.9)	25 (13.9)	3 (2.6)	28 (8.4)	11 (7.9)
+ TZD	131 (3.9)	15 (2.4)	9 (2.8)	3 (1.4)	NA	3 (1.7)	1 (0.9)	5 (1.5)	1 (0.7)
+ Glinide	216 (6.4)	10 (1.6)	1 (0.3)	9 (4.3)	0 (0.0)	NA	0 (0.0)	10 (3.0)	5 (3.6)
+ SGLT2i	59 (1.8)	29 (4.7)	4 (1.2)	2 (0.9)	3 (5.7)	2 (1.1)	NA	6 (1.8)	3 (2.1)

+ Insulin	828 (24.6)	163 (26.5)	37 (11.5)	80 (37.9)	14 (26.4)	45 (25.0)	7 (6.1)	NA	22 (15.7)
+ GLP-1 agonist	1 (0.0)	24 (3.9)	16 (5.0)	3 (1.4)	2 (3.8)	2 (1.1)	6 (5.3)	12 (3.6)	NA

'+' indicates add-on therapy with new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

Table 5 Changes to index therapy: switch treatment according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=303**	**n=92**	**n=56**	**n=70**	**n=46**	**n=38**	**n=50**	**n=268**	**n=27**
→ DPP-4i	NA	27 (29.3)	15 (26.8)	14 (20.0)	20 (43.5)	14 (36.8)	16 (32.0)	84 (31.3)	4 (14.8)
→ BG	44 (14.5)	NA	8 (14.3)	8 (11.4)	8 (17.4)	2 (5.3)	6 (12.0)	48 (17.9)	6 (22.2)
→ SU	56 (18.5)	8 (8.7)	NA	3 (4.3)	5 (10.9)	5 (13.2)	2 (4.0)	27 (10.1)	5 (18.5)
→ α-GI	15 (5.0)	2 (2.2)	1 (1.8)	NA	1 (2.2)	3 (7.9)	1 (2.0)	17 (6.3)	2 (7.4)
→ TZD	14 (4.6)	8 (8.7)	1 (1.8)	1 (1.4)	NA	2 (5.3)	4 (8.0)	6 (2.2)	1 (3.7)
→ Glinide	12 (4.0)	2 (2.2)	4 (7.1)	1 (1.4)	0 (0.0)	NA	1 (2.0)	7 (2.6)	0 (0.0)
→ SGLT2i	17 (5.6)	2 (2.2)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.4)	1 (3.7)
→ Insulin	106 (35.0)	37 (40.2)	18 (32.1)	37 (52.9)	6 (13.0)	6 (15.8)	9 (18.0)	NA	7 (25.9)
→ GLP-1	8 (2.6)	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	2 (4.0)	9 (3.4)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=651**	**n=154**	**n=135**	**n=119**	**n=36**	**n=119**	**n=34**	**n=480**	**n=75**
→ DPP-4i	NA	57 (37.0)	67 (49.6)	44 (37.0)	15 (41.7)	43 (36.1)	15 (44.1)	164 (34.2)	19 (25.3)
→ BG	66 (10.1)	NA	7 (5.2)	6 (5.0)	4 (11.1)	3 (2.5)	6 (17.6)	19 (4.0)	5 (6.7)
→ SU	168 (25.8)	13 (8.4)	NA	6 (5.0)	4 (11.1)	22 (18.5)	1 (2.9)	48 (10.0)	4 (5.3)
→ α-GI	66 (10.1)	7 (4.5)	3 (2.2)	NA	1 (2.8)	9 (7.6)	0 (0.0)	18 (3.8)	2 (2.7)
→ TZD	26 (4.0)	11 (7.1)	2 (1.5)	3 (2.5)	NA	0 (0.0)	1 (2.9)	10 (2.1)	2 (2.7)
→ Glinide	48 (7.4)	3 (1.9)	8 (5.9)	2 (1.7)	0 (0.0)	NA	0 (0.0)	32 (6.7)	2 (2.7)
→ SGLT2i	16 (2.5)	3 (1.9)	2 (1.5)	2 (1.7)	1 (2.8)	0 (0.0)	NA	2 (0.4)	0 (0.0)

→ Insulin	196 (30.1)	48 (31.2)	32 (23.7)	45 (37.8)	10 (27.8)	27 (22.7)	1 (2.9)	NA	26 (34.7)
→ GLP-1 agonist	18 (2.8)	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	3 (8.8)	3 (0.6)	NA

'→' indicates treatment switch to new antidiabetic drug.

DPP-4i, dipeptidyl peptidase-4 inhibitor; α-GI, α-glucosidase inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

Table 6 Persistence with monotherapy schedules of index antidiabetic drug classes

UT patients

Index therapy	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**
JMDC database	**n=8545**	**n=3354**	**n=979**	**n=1346**	**n=504**	**n=165**	**n=430**
Median time to discontinuation (days)	1138.0	582.0	384.0	280.0	400.0	161.0	471.0
12-month persistence rate (% pts)	67.4	57.3	50.4	45.5	51.2	38.8	53.5
MDV database	**n=13 598**	**n=2777**	**n=1174**	**n=1666**	**n=449**	**n=292**	**n=224**
Median time to discontinuation (days)	707.0	672.0	474.5	458.0	491.0	438.5	537.5
12-month persistence rate (% pts)	77.2	73.8	56.0	54.9	57.2	53.8	63.4

PT patients

Index therapy	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**
JMDC database	**n=2354**	**n=680**	**n=284**	**n=256**	**n=158**	**n=135**	**n=285**
Median time to discontinuation (days)	1583.0	917.0	599.0	304.5	370.0	266.0	691.0
12-month persistence rate (% pts)	73.5	69.3	58.1	46.9	50.0	43.0	62.8
MDV database	**n=7658**	**n=1100**	**n=633**	**n=495**	**n=133**	**n=446**	**n=229**
Median time to discontinuation (days)	764.0	666.5	532.0	422.0	333.0	396.0	553.0
12-month persistence rate (% pts)	78.8	73.6	62.2	52.7	48.1	52.2	66.4

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV,

Medical Data Vision; PT, previously treated; pts, patients; SGLT2i , sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Figure legends

Fig 1 Patient disposition.

JMDC, Japan Medical Data Center; MDV, Medical Data Vision; T2DM, type 2 diabetes mellitus.

Fig 2 Antidiabetic drug classes prescribed at the index date in (a) UT patients; and (b) PT patients in the JMDC and MDV databases.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione; UT, untreated.

Fig 3 Kaplan-Meier survival distribution of median time to treatment discontinuation according to index antidiabetic drug class; (a) UT patients; JMDC database; (b) UT patients, MDV database; (c) PT patients, JMDC database; (d) PT patients, MDV database.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; UT, untreated.

Fig 4 12-month adherence to index antidiabetic drug classes in (a) untreated (UT) patients and (b) previously treated (PT) patients in the JMDC and MDV databases.

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2; TZD, thiazolidinedione; UT, untreated.

Fig 5 12-month persistence rates with the five most frequent antidiabetic drug combinations in PT patients in the JMDC and MDV databases.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SU, sulfonylurea.

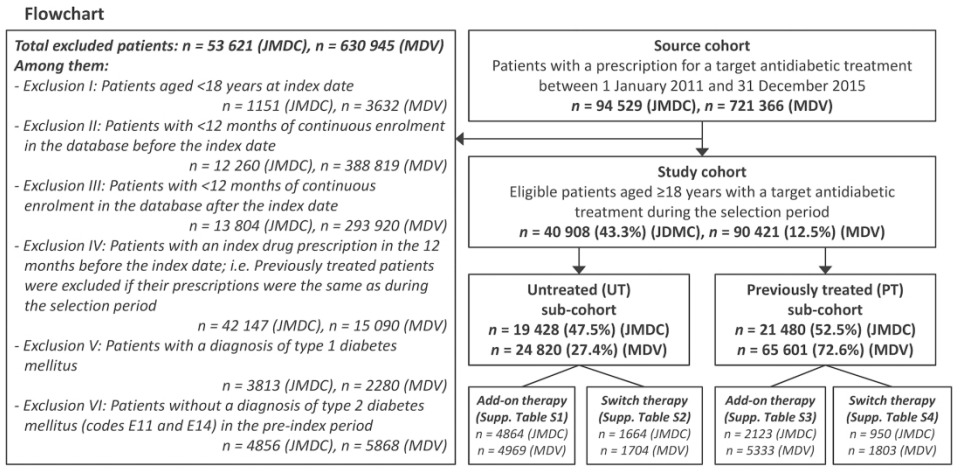

Figure 1

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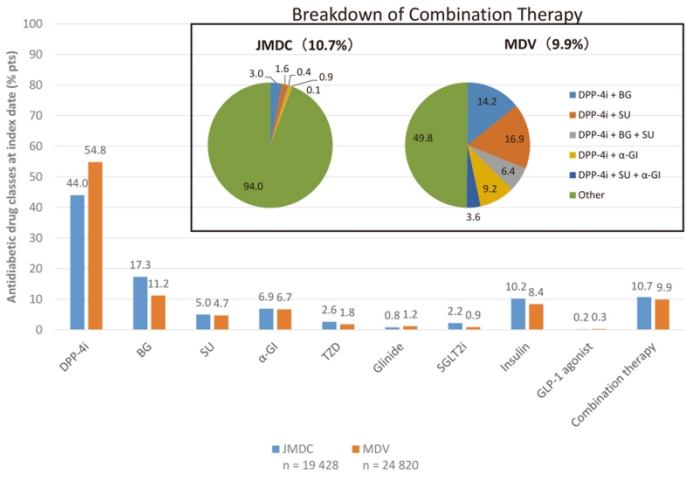

Figure 2A Index prescription UT pts

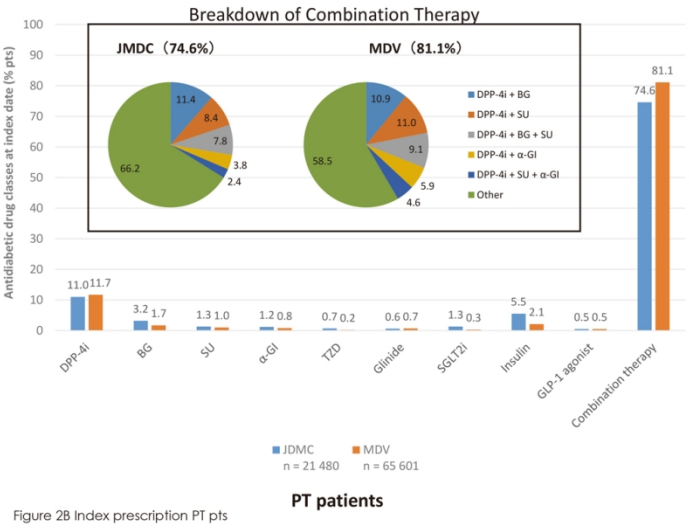

Figure 2B Index prescription PT pts

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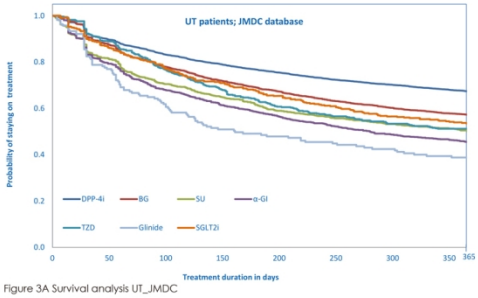

Figure 3A Survival analysis UT_JMDC

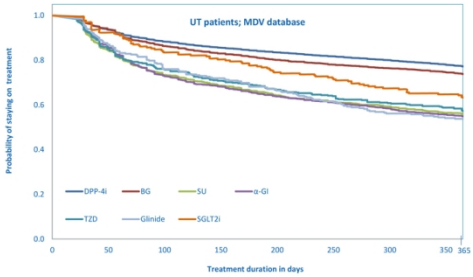

Figure 3B Survival analysis UT_MDV

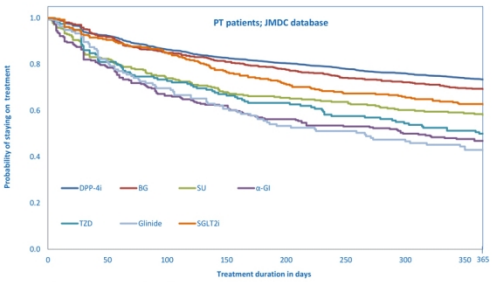

Figure 3C Survival analysis PT_JMDC

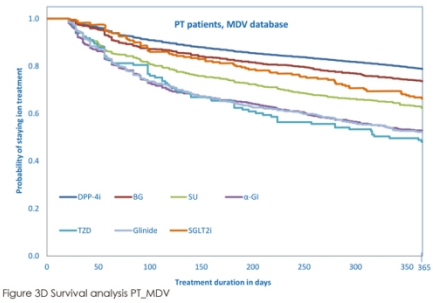

Figure 3D Survival analysis PT_MDV

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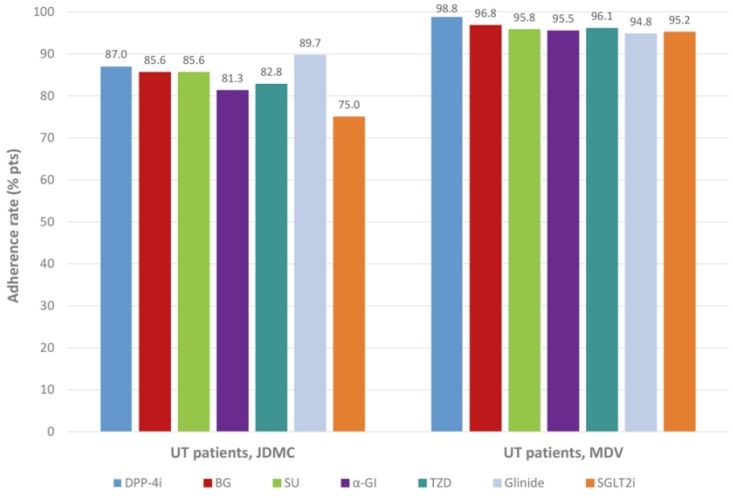

Figure 4A Adherence UT pts

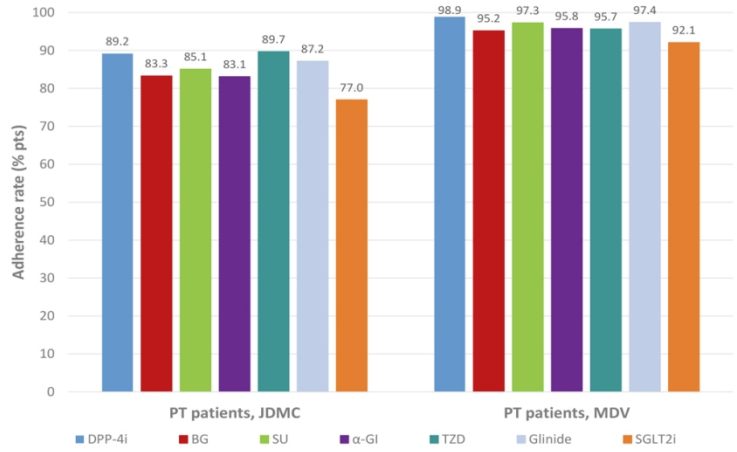

Figure 4B Adherence PT pts

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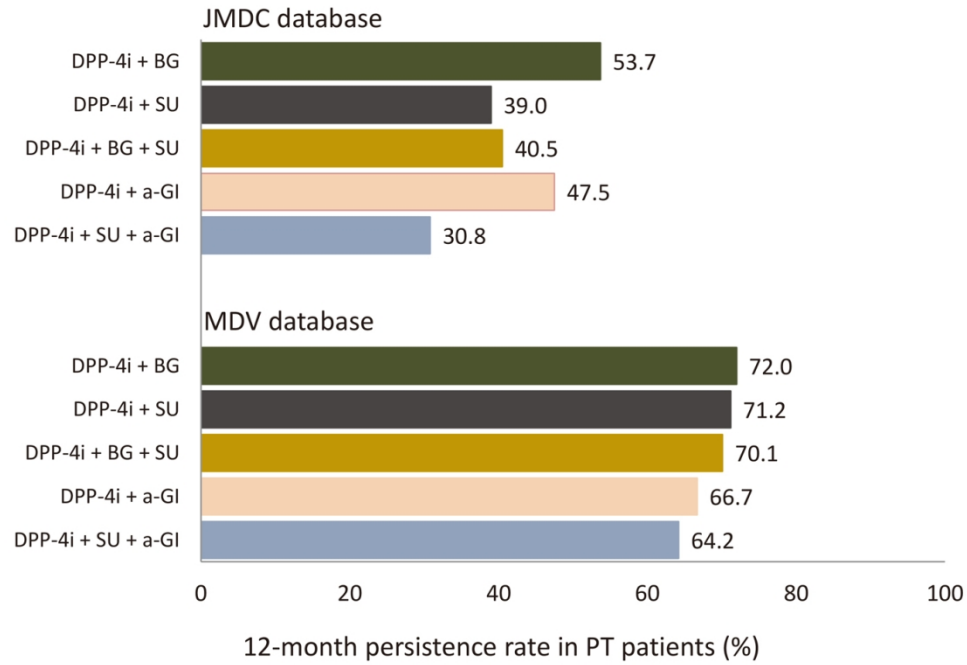

Figure 5

121x90mm (300 x 300 DPI)

Supplementary table 1 Factors associated with non-persistence with the index antidiabetic drug class in untreated patients

Characteristics	*JMDC database*			*MDV database*		
	N	Not persistent (% pts)	Adjusted odds ratio (95% CI)[a]	N	Not persistent (% pts)	Adjusted odds ratio (95% CI)[a]
Age at index date (years):						
18–34	659	66.9	1.00	205	38.0	1.00
35–44	2734	53.1	1.64 (1.37, 1.97)*	791	29.5	1.34 (0.96, 1.86)
45–54	6356	41.3	2.45 (2.06, 2.92)*	2016	26.7	1.48 (1.09, 2.02)*
55–64	5891	34.8	3.04 (2.55, 3.62)*	4872	26.3	1.55 (1.15, 2.09)*
65–74	1777	31.5	3.31 (2.72, 4.03)*	7880	29.3	1.39 (1.03, 1.87)*
≥ 75	34	35.3	2.52 (1.21, 5.25)*	6602	33.8	1.22 (0.90, 1.64)
Number of medications:						
0	7585	46.1	1.00	2957	34.2	1.00
1–3	6980	37.9	1.21 (1.13, 1.30)*	10,907	26.7	1.38 (1.26, 1.51)*
4–5	1594	33.4	1.30 (1.15, 1.46)*	5707	29.1	1.31 (1.18, 1.45)*
6–8	883	35.2	1.23 (1.05, 1.43)*	2528	37.9	1.04 (0.92, 1.17)
> 8	409	38.4	1.11 (0.89, 1.37)*	267	47.6	0.73 (0.56, 0.95)*
Hypertension:						
No	9053	47.3	1.00	6534	32.8	1.00
Yes	8398	34.0	1.43 (1.33, 1.52)*	15,832	28.6	1.17 (1.09, 1.25)*
Hyperlipidaemia:						
No	10,335	43.2	1.00	8535	35.3	1.00
Yes	7116	37.7	1.12 (1.05, 1.20)*	13,831	26.4	1.40 (1.31, 1.49)*
Number of antidiabetic drug classes at index date:						
1	15,368	39.1	1.00	20,180	27.2	1.00
2	1707	52.7	0.62 (0.56, 0.69)*	1594	51.8	0.37 (0.33, 0.41)*

3	299	60.2	0.44 (0.35, 0.56)*	489	59.5	0.27 (0.22, 0.32)*
≥ 4	77	68.8	0.31 (0.19, 0.50)*	103	59.2	0.25 (0.16, 0.37)*

[a] Adjusted for age, gender, multiple medications at index date, comorbidities at baseline, and number of antidiabetic drug classes at index date.

* $p < 0.05$.

CI, confidence interval; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; pts, patients.

Supplementary table 2 Factors associated with non-adherence with the index antidiabetic drug class in untreated patients

Characteristics	*JMDC database*			*MDV database*		
	N	**Not adherent (% pts)**	**Adjusted odds ratio (95% CI)[a]**	**N**	**Not adherent (% pts)**	**Adjusted odds ratio (95% CI)[a]**
Age at index date (years):						
18–34	599	16.7	1.00	190	7.4	1.00
35–44	2571	14.0	1.23 (0.97, 1.57)	727	4.8	1.40 (0.73, 2.69)
45–54	6056	11.4	1.54 (1.22, 1.94)*	1893	2.1	3.06 (1.61, 5.81)*
55–64	5638	8.8	2.05 (1.61, 2.61)*	4555	2.0	3.18 (1.75, 5.80)*
65–74	1694	4.6	3.83 (2.78, 5.27)*	7341	2.0	3.30 (1.83, 5.95)*
≥ 75	32	6.3	2.39 (0.63, 9.02)	6225	2.7	2.67 (1.47, 4.86)*
Number of medications:						
0	7186	10.0	1.00	2713	2.3	1.00
1–3	6661	10.9	0.86 (0.77, 0.97)*	10,178	1.9	1.03 (0.78, 1.39)
4–5	1515	10.4	0.82 (0.68, 0.99)*	5373	2.4	0.80 (0.58, 1.12)
6–8	840	10.1	0.83 (0.65, 1.06)	2410	3.8	0.61 (0.43, 0.87)
> 8	388	10.8	0.72 (0.51, 1.00)	257	6.2	0.38 (0.21, 0.70)
Hypertension:						
No	8528	11.0	1.00	6060	2.9	1.00
Yes	8062	9.8	1.05 (0.95, 1.18)	14,871	2.2	1.26 (1.03, 1.54)*
Hyperlipidaemia:						
No	9800	10.5	1.00	7959	3.1	1.00
Yes	6790	10.3	1.01 (0.91, 1.12)	12,972	1.9	1.52 (1.26, 1.84)*
Number of antidiabetic drug classes at index date:						
1	14,507	10.5	1.00	18,892	2.0	1.00
2	1707	9.8	1.14 (0.96, 1.35)	1492	4.6	0.50 (0.38, 0.65)*
3	299	8.7	1.36 (0.91, 2.05)	452	6.6	0.33 (0.22, 0.49)*

≥ 4	77	11.7	0.92 (0.46, 1.87)	95	9.5	0.21 (0.10, 0.42)*

[a] Adjusted for age, gender, multiple medications at index date, comorbidities at baseline, and number of antidiabetic drug classes at index date.

* $p < 0.05$.

CI, confidence interval; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; pts, patients.

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study

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Treatment patterns, persistence and adherence rates in patients with type 2 diabetes mellitus in Japan: a claims-based cohort study

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Abstract

Objective To determine real-world trends in antidiabetic drug use, and persistence and adherence, in Japanese patients with type 2 diabetes mellitus (T2DM).

Design Retrospective evaluation of administrative claims data (2011–2015) using the Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases.

Setting Analysis of two administrative claims databases for Japanese patients with T2DM.

Participants Adults (aged ≥18 years) with an ICD-10 code of T2DM, and at least one antidiabetic drug prescription.

Interventions Not applicable.

Main outcome measures Treatment patterns in untreated (UT) or previously treated (PT) patients receiving antidiabetic therapy; persistence with treatment at 12 months; adherence with treatment as 12 months.

Results 40,908 and 90,421 patients were included from the JMDC and MDV databases, respectively. The most frequently prescribed therapy at the index (first prescription) date was dipeptidyl peptidase-4 inhibitor (DPP-4i) in UT patients (JMDC: 44.0%, MDV: 54.8%) and combination therapy in PT patients (74.6%, 81.1%). Most common combinations were DPP-4i plus: biguanide (BG; 11.4%, 10.9%), sulfonylurea (SU; 8.4%, 11.0%), or BG + SU (7.8%, 9.1%). In UT or PT patients from either database whose index prescription was for any antidiabetic drug class(es) other than DPP-4i, the most frequent add-on or switch was to DPP-4i. 12-month persistence with index monotherapy was highest with DPP-4i and BG. Adherence was high (≥80%) for all monotherapy schedules, except insulin and glucagon-like peptide-1 agonist, and for the five most frequent 2- and 3-drug combinations. Persistence was greater in elderly UT patients and in those receiving ≤5 medications, but comparatively worse in UT patients with ≥3 index antidiabetic drug classes.

Conclusions The findings indicate that DPP-4i is the most commonly used antidiabetic drug class in Japanese patients with T2DM, and persistence and adherence to this antidiabetic drug class is high.

Trial registration Not applicable.

Strengths and limitations of this study

- This retrospective evaluation of administrative claims data (2011–2015) using the Japan Medical Data Center (JMDC) and Medical Data Vision (MDV) databases was conducted to determine real-world trends in antidiabetic drug use, and persistence and adherence, in Japanese patients with type 2 diabetes mellitus (T2DM); 40,908 and 90,421 patients were included from the JMDC and MDV databases, respectively.
- The main strengths of the study are that it provides robust real-world evidence from two large administrative claims databases for patterns of antidiabetic drug use in Japanese patients with T2DM, highlighting widespread use of DPP-4i schedules (as monotherapy, add-on therapy, switch therapy, or in combination regimens) and marked persistence and adherence with DPP-4i therapy.
- The study was limited to some extent by the strict inclusion criteria which restricted the number of patients eligible for analysis, and by the use of prescription events rather than patient-derived data to estimate outcomes.
- Database-specific limitations were the relative scarcity of data for patients aged ≥65 years (JMDC), the absence of information as to whether patients received care in other medical facilities (MDV), and the inability to examine reasons for treatment discontinuation and potential health benefits resulting from increased persistence (JMDC and MDV).
- Uptake of SGLT2i use may not have been accurately captured given the timing of their introduction in Japan.

Introduction

The prevalence of diabetes mellitus continues to increase globally. In 2015, approximately 415 million people worldwide had diabetes, and this figure is projected to reach almost 650 million by 2040.[1] As about 20% of men and 10% of women in Japan are considered to have, or are highly likely to have, diabetes, the public health implications are enormous.[2]

Disease characteristics in Asian individuals with type 2 diabetes mellitus (T2DM) differ from those in Caucasian patients; Japanese patients with T2DM principally have pancreatic β-cell dysfunction, with less insulin resistance and adiposity than Caucasians.[1] Nevertheless, even in patients with mild metabolic dysfunction, T2DM has serious long-term consequences (i.e. nephropathy, neuropathy, and retinopathy) and is an important risk factor for atherosclerotic cardiovascular diseases.[3,4]

The benefits of early and effective intervention in T2DM are extensively acknowledged. Enhanced glycaemic control can markedly reduce micro- and macroangiopathic development and progression.[4] An intensified intervention to achieve lower treatment targets was shown to be significantly superior to conventional therapy for prevention of cerebrovascular events in patients with T2DM.[5] The Japan Diabetes Society (JDS) has developed evidence-based guidelines for management of diabetes.[6] In patients who fail to achieve adequate glycemic control with diet, exercise and lifestyle improvement alone, treatment options include biguanides (BG), thiazolidinediones (TZD), sulfonylureas (SU), glinides, dipeptidyl peptidase-4 inhibitor (DPP-4i), α-glucosidase inhibitors (α-GI), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), with treatment selection to be based on the underlying causes of T2DM.[6]

Despite widespread availability of the JDS guidelines and highly favourable conditions for access to health care in Japan, a 2-year longitudinal study using claims data identified that the quality of care for T2DM patients is often suboptimal.[7] Notably, screening for diabetic renal and ocular disease was less frequent than recommended in the guidelines and less than half of

diabetic patients were achieving the glycaemic goal (glycosylated haemoglobin [HbA1c] <7%) recommended by JDS for their circumstances.

Allied to these factors is the potential for suboptimal adherence to, and poor persistence with, treatment. Adherence is typically lower among patients with chronic conditions compared to those with acute conditions, and treatment persistence for chronic conditions is particularly low, tending to decline most dramatically within the first 6 months of treatment.[8] The reasons for poor adherence and persistence are complex and multifactorial, involving patient- and physician-related factors as well as treatment regimen factors such as pill burden, regimen complexity, and dosing schedule.[9]

In Japan, it has been estimated that approximately 60% of patients with diabetes forget to take their medication at some stage.[10] Non-adherence to antidiabetic medications is associated with increased healthcare expenditure and higher rates of hospitalisation and death.[11,12] It has been suggested that use of a once-weekly DPP-4i, or a fixed-dose combination (FDC) therapy, may improve adherence in patients with T2DM.[13] A 10% increase in adherence has been linked with a 0.1% decrease in HbA1c.[11,14] Recent studies suggest that dual-therapy schedules containing a DPP-4i may improve persistence relative to DPP-4i monotherapy,[15] or sulfonylurea (SU)-containing schedules.[16]

Contemporary meta-analyses of studies involving incretin-based treatments (i.e. DPP-4i or glucagon-like peptide-1 [GLP-1] receptor agonists) in patients with T2DM have shown that these agents are more effective in Asian than in non-Asian populations, possibly due to greater attenuation of β-cell dysfunction.[1,17–19] Moreover, the HbA1c-reducing activity of DPP-4i has been linked with fish intake, suggesting that dietary factors may also contribute to their greater efficacy in Asian patients with T2DM.[1,20,21]

Despite widespread recognition of the deleterious long-term consequences of poorly managed T2DM, and the proven efficacy of incretin-based therapies in Asian populations with diabetes, surprisingly little is known about actual antidiabetic drug utilisation trends and persistence and adherence patterns with antidiabetic drug therapy in patients with T2DM in

Japan. Under Japan's compulsory insurance system, all residents are legally obligated to be covered by a form of public health insurance, and claims-related data are captured and stored in propriety databases. In the current study, data from two large administrative claims databases were used to determine real-world trends in antidiabetic drug use, and treatment persistence and adherence rates, in patients with T2DM in Japan.

Methods

Overview

This was a real-world, retrospective evaluation of data from two administrative claims databases in Japan: the Japan Medical Data Center (JMDC) database (Japan Medical Data Center Co., Ltd; Tokyo, Japan); and the Medical Data Vision (MDV) database (Medical Data Vision Co., Ltd; Tokyo, Japan). The JMDC database contains monthly claims submitted to health insurance societies from medical institutions since January 2005 and, as at July 2017, covered approximately 4 million beneficiaries (employees and their dependants). MDV is a nationwide hospital-based claims database covering nearly 19 million cumulative patients since April 2008 who, as at July 2017, had been treated as inpatients or outpatients at the approximately 300 hospitals in Japan (20% of total number of hospitals) that participate in the Diagnostic Procedure Combination (DPC)/Per-Diem payment system. Both databases hold anonymised information about diagnoses, patient characteristics, drug prescriptions, medical procedures, features of medical facilities, and reimbursement costs. All patient data are encrypted before entry.

Based on Ethical Guidelines for Epidemiological Research issued by the Japanese Ministry of Health, Labour and Welfare, ethics approval and informed consent were not applicable for this study.

Study population

Eligible patients were adults (≥18 years) with a diagnosis of T2DM (International Classification of Diseases [ICD]-10 code: E11 or E14) who had been issued at least one prescription for an antidiabetic drug during the target selection period of January 2011 to December 2015. All patients were starting a new antidiabetic drug therapy.

The first prescription date for an antidiabetic drug class initiated during the selection period was the index date, and the antidiabetic drug class prescribed was designated as the index antidiabetic drug class. Only patients with a new prescription during the selection period were included for analysis. The minimum 12-month pre-index ('look-back') period allowed time to observe patients' baseline characteristics and ascertain that the first prescription of a given antidiabetic drug class corresponded to initiation of that drug class. The minimum 12-month post-index observational period allowed time to evaluate treatment-related outcomes of interest.

Patients were excluded for the following reasons: age <18 years at the index date; <12 months of continuous enrolment in the database before or after the index date; index prescription received in the 12 months before the index date; no T2DM diagnosis (ICD code E11 or E14) in the pre-index period (fig 1).

The patient population was divided into two subgroups: 1) untreated (UT) patients, i.e. patients without a prescription for any antidiabetic drug class of interest during the pre-index period; and 2) previously treated (PT) patients, i.e. patients with a prescription for at least one non-index antidiabetic drug class during the pre-index period.

Antidiabetic drug classes of interest

Target antidiabetic drug classes of interest were DPP-4i, BG, SU, α-GI, TZD, glinides, SGLT2i, insulin and GLP-1 receptor agonists and, in PT patients, the five most common

combinations of these same drug classes. Data for insulin and GLP-1 receptor agonists were excluded from the persistence and adherence analyses mainly because of inconsistent database information regarding the duration of therapy for these injectable drug classes.

Objectives

The primary objectives of the study were to describe patterns of antidiabetic drug use and persistence and adherence with antidiabetic drug classes in T2DM patients, overall and by patient subgroup (UT and PT), in the JMDC and MDV database populations.

Outcomes

A treatment line was defined as the period during which a patient took a specific antidiabetic drug class or a combination of antidiabetic drug classes continuously, i.e. without addition of new class(es) or withdrawal/discontinuation of existing drug class(es). A treatment line-related event was defined as: an 'add-on' when a new antidiabetic drug class was prescribed in addition to an existing drug class(es) for more than 21 days (e.g. DPP-4i <<add-on event>> DPP-4i + metformin); as a 'switch' when at least one new antidiabetic drug class was prescribed in place of an existing drug class(es) within the grace period which was 1.5 times the median prescription duration for a given drug class (e.g. DPP-4i <<switch event>> metformin).

Treatment persistence was defined as the time from the index date until discontinuation of at least one index antidiabetic drug class. The median time to discontinuation and the proportion of patients persistent with treatment at 12 months were reported. The date of discontinuation was defined as the date of the last prescription of the first discontinued drug in an antidiabetic drug combination, plus the days of supply of that prescription.

Adherence analyses were performed for patients who received at least two prescriptions of the index antidiabetic drug class(es) during the 12-month post-index follow-up period. Adherence to an antidiabetic drug class of interest was defined as the proportion of days covered (PDC) or the period in which patients had the treatment in their possession (i.e. from the index date to first discontinuation of index treatment), and was calculated according to the formula:

Total number of prescription days covered for defined drug class of interest /
Total number of days in the follow-up period.

As the JMDC and MDV databases each contain a field corresponding to the number of days' supply of a medication, these data were used to calculate the number of prescription days.

Patients were considered adherent if a PDC of ≥0.8 (also expressed as an adherence rate of ≥80%) was achieved. The PDC was calculated from the index date to first discontinuation of index treatment.

Adherence/persistence were calculated according to the number of antidiabetic drug prescription days, without differentiating between inpatient/outpatient prescribing. No information was available about possible pill dumping or stockpiling.

Statistical analyses

Analyses were performed using SAS® version 9.3 (SAS Institute; Cary, NC, USA) and were conducted on all patients who met the inclusion criteria and were stratified into the two pre-specified patient subgroups (UT and PT) on the index date. Patient demographics, clinical characteristics, treatment-related events affecting index therapy (add-on, switch) and adherence were reported descriptively. The median time to discontinuation was calculated by antidiabetic drug class using Kaplan–Meier survival analysis, with differences between patient subgroups (UT and PT) assessed by log-rank test. The first discontinuation of the

index antidiabetic drug class was the survival event and patients were censored if they reached the end of follow-up without discontinuation.

The log-rank test was used to compare the Kaplan–Meier estimates between groups. Cox regression analysis was used to estimate the hazard ratio of each event, adjusting for baseline characteristics. For all analyses, a p-value of less than α=0.05 was considered as statistically significant. For the selection of patient characteristics to be included in regression models, a threshold level of α=0.10 was used.

Patient involvement

No patients were involved in setting the research question or outcome measures, and no patients were involved in developing plans for study implementation. Furthermore, no patients were asked for advice about interpretation or writing up of results. There are no plans to distribute the research findings to study participants or the specific patient community. Individual patient consent was not required for this study, as the trial was based on anonymised administrative claims data.

Results

Patient disposition

Between January 2011 and December 2015, 94,529 patients in the JMDC database and 721,366 patients in the MDV database with at least one prescription for an antidiabetic drug class of interest were identified. Of these, 40,908 patients (43.3%) in the JMDC database and 90,421 patients (8.0%) in the MDV database met the inclusion criteria and were included in the analyses (fig 1). The ratio of UT to PT patients was approximately 1:1 in the JMDC database and 1:3 in the MDV database.

Patient characteristics

Patient demographics and clinical characteristics are presented in table 1.

Median duration of follow-up in UT patients was 929 days in the JDMC database and 942 days in the MDV database. Mean age was 51.7 years and 67.6 years, respectively. There was a higher proportion of males (72.3% *vs* 60.8%), a lower mean number of concurrent medications (2.0 *vs* 3.0), and lower incidences of comorbid hypertension (47.8% *vs* 70.1%), hyperlipidaemia (39.8% *vs* 70.0%), dementia (0.2% *vs* 1.9%), and diabetic nephropathy (3.7% *vs* 18.1%) among UT patients in the JMDC versus MDV database.

Among PT patients, median duration of follow-up was 980 days in the JDMC database and 1027 days in the MDV database. Mean age was 54.4 years and 66.9 years, respectively. There was a higher proportion of males (73.5% *vs* 61.2%), a lower mean number of concurrent medications (2.3 *vs* 3.3), and lower incidences of comorbid hypertension (58.3% *vs* 71.3%), hyperlipidaemia (50.0% *vs* 67.2%), dementia (0.2% *vs*2.0%), and diabetic nephropathy (6.1% *vs* 15.7%) among PT patients in the JMDC versus MDV database.

Index date therapy

Treatment patterns for index antidiabetic drug classes were broadly similar for UT patients and PT patients irrespective of dataset (JMDC or MDV).

In UT patients (fig 2a), the most common index prescription was for DPP-4i monotherapy (JMDC: 44.0%; MDV: 54.8%), followed by BG, insulin and combination therapy. The composition of combination therapy (i.e. combinations of antidiabetic drug classes) was highly varied.

In PT patients (fig 2b), the most common index prescription was for combination therapy (JMDC: 74.6%; MDV: 81.1%), and the most frequent combinations were a DPP-4i plus a BG or/and a SU. Combinations could consist of single agents in combination, FDC, or FDC + single agents in combination. The next most common index therapy in PT patients was DPP-4i monotherapy (JMDC: 11.0%; MDV: 11.7%). Use of other antidiabetic drug classes as monotherapy was low.

Changes to index therapy

In UT patients who had received a DPP-4i as the index prescription, the most frequent add-on was a BG (JMDC: 46.6%; MDV: 36.7%). In UT patients whose index prescription was for any other antidiabetic drug class, the most frequent add-on in all cases (apart from GLP-1 receptor agonists) was a DPP-4i (table 2).

In UT patients who had received a DPP-4i as the index prescription, the most frequent treatment switch to another antidiabetic drug class was to a BG (JMDC: 32.7%; MDV: 26.2%) or insulin (JMDC: 14.3%; MDV: 30.5%). In UT patients whose index prescription was for any other antidiabetic drug class, the most frequent treatment switch was to a DPP-4i (table 3).

In PT patients who had received a DPP-4i as the index prescription, the most frequent add-on was a BG (JMDC: 30.4%; MDV: 21.6%), SU (JMDC: 24.5%; MDV: 22.8%), or insulin, but only in the MDV population (JMDC: 0.7%; MDV: 24.6%). In PT patients whose index prescription was for any other antidiabetic drug class, the most frequent add-on was a DPP-4i to all drug classes except GLP-1 receptor agonists in the JMDC database, and was a DPP-4i to all drug classes except α-GI and GLP-1 receptor agonists in the MDV database (table 4).

In PT patients whose index treatment was a DPP-4i, the most frequent treatment switch was to insulin (JMDC: 35.0%; MDV: 30.1%). In PT patients whose index prescription was for

any other antidiabetic drug class, the most common treatment switch for either dataset was to a DPP-4i or to insulin (table 5).

Persistence and adherence with index monotherapy

In both patient subgroups across both databases, the probability of remaining on treatment with index monotherapy at 12 months (not including insulin and GLP-1 receptor agonists) was highest with DPP-4i schedules and lowest with glinide schedules (table 6). This is illustrated schematically by Kaplan-Meier survival curves showing the distribution of median time to treatment discontinuation during 12 months' observation by index antidiabetic drug class for UT and PT patients in each database. Among UT patients, persistence with all antidiabetic drug classes was considerably lower in the JMDC database especially with glinide schedules (fig 3a), than in the MDV database (fig 3b). Among PT patients, persistence with all antidiabetic drug classes tended to be slightly lower in the JMDC database for all antidiabetic drug classes except TZD and especially for glinide schedules (fig 3c) than in the MDV database (fig 3d). 12-month persistence rates of approximately 50% or less were recorded for SU, α-GI, TZD, and glinides in one or both patient subgroups from one or both datasets (table 6).

Adherence to index antidiabetic drug classes (not including insulin and GLP-1 receptor agonists) was high in both patient subgroups across both databases, with rates ranging from 75.0% to 98.9%. In UT patients (fig 4a) and in PT patients (fig 4b), adherence rates with index antidiabetic drug classes were consistently lower in the JMDC database than in the MDV database. The lowest adherence rates were recorded with SGLT2i in UT patients (75.0%) and PT patients (77.0%) in the JDMC database.

Persistence and adherence with index combination therapy

For the five most common antidiabetic drug combinations prescribed to PT patients on the index date (i.e. a DPP-4i plus BG, SU, BG + SU, α-GI, or SU + α-GI), 12-month persistence rates were highest for DPP-4i plus BG (JMDC: 53.7%; MDV: 72.0%) and lowest with DPP-4i plus SU + α-GI (JMDC: 30.8%; MDV: 64.2%) (fig 5). Overall, 12-month persistence rates were considerably lower in the JMDC versus MDV database (fig 5).

For the five most common antidiabetic drug combinations prescribed to PT patients on the index date (i.e. a DPP-4i plus BG, SU, BG + SU, α-GI, or SU + α-GI), adherence rates were ≥80% in both database populations although were slightly lower in the JMDC versus MDV database (fig 6).

Discussion

Principal findings

This real-world evaluation of data from two administrative claims databases in Japan reveals that the most common index antidiabetic drug class was DPP-4i in UT patients (44–55%) and combination therapy in PT patients (~75–80%), with the latter most frequently comprising dual therapy with a DPP-4i plus a BG or SU.

Among patients with a change to their index antidiabetic drug therapy during follow-up: the most common add-on to DPP-4i index therapy was a BG or SU; the most common add-on to BG or SU index therapy was a DPP-4i; the most common switch from DPP-4i index therapy was to a BG or SU; the most common switch from index drug classes other than DPP-4i (except GLP-1 receptor agonists) was to a DPP-4i. Overall patterns for add-on or switch therapy were similar between the JMDC and MDV datasets and between UT and PT patients.

Across all four patient subgroups, 12-month persistence rates were highest with index DPP-4i monotherapy compared with all other index antidiabetic drug classes, although did not

exceed 78.8% (with DPP-4i in PT patients in the MDV database) and were around 50% or less with several index antidiabetic drug classes especially in the JMDC database. Mean adherence to antidiabetic monotherapy was high overall, and the proportion of patients with high adherence (≥80%) was higher with index DPP-4i than with all other antidiabetic drug classes. Among drug combinations, 12-month persistence rates were higher for DPP-4i plus BG than for other combinations, although did not exceed 72.0%. Adherence rates were ≥80% for commonly prescribed antidiabetic drug combinations.

We also analysed persistence (≥12 months, <12 months) and drug adherence (<80%, ≥80%) in UT patients according to other patient- and treatment-related factors. Persistence tended to increase with age (supplementary table 1). In the JMDC database, the adjusted odds ratio for non-persistence was 3.31 ($P<0.05$) in the 65–74-year age group compared with the reference group (18–34 years). In addition, persistence with multiple medications tended to be good in patients receiving ≤5 medications, but poorer in patients receiving ≥6 medications. In the MDV database, 29.1% of patients with 4–5 medications were non-persistent, whereas 47.6% of patients with >8 medications were non-persistent. Persistence was good in patients with comorbid hypertension (JMDC: 66.0%; MDV: 71.4%) or hyperlipidaemia (JMDC: 62.3%; MDV: 73.6%). However, persistence was poor in patients treated with multiple antidiabetic drug classes: in both the JMDC and MDV databases, approximately 60–70% of patients receiving ≥3 index antidiabetic drug classes were non-persistent. Similar findings were evident for adherence (supplementary table 2). In the MDV database, only 2.0% of patients receiving antidiabetic monotherapy were non-adherent, whereas 6.6–9.5% of those with ≥3 antidiabetic drugs were non-adherent. All these findings are interesting and suggest that higher rates of persistence and adherence observed in elderly patients treated with multiple medications may reflect greater insight by this group into their disease. Conversely, the relatively low rates of persistence and adherence evident in patients treated with more index antidiabetic drug classes may have resulted from patient or caregiver difficulties regarding drug management. Therefore, FDC therapy, with its potential to enhance persistence and

adherence, may be especially appropriate for patients treated with several index oral antidiabetic drug classes.

Strengths and limitations of the study

The main strengths of the present study are that it provides robust real-world evidence from two large administrative claims databases for patterns of antidiabetic drug use in T2DM patients in Japan, clearly highlighting the widespread use of DPP-4i schedules (as monotherapy, add-on therapy, switch therapy, or in combination regimens), and shows marked persistence and adherence with DPP-4i therapy.

The study was limited to some extent by the strict inclusion criteria, which restricted the proportion of patients from each database eligible for analysis. The analyses did not factor in HbA1c levels at the start of treatment, or the level of HbA1c control achieved during treatment, which may have influenced the various treatment decisions. Another limitation was the use of prescription events, rather than patient-derived data (e.g. patient diaries), to estimate outcomes. A limitation specific to the JMDC database was the relative scarcity of data for patients aged ≥65 years. A limitation specific to the MDV database was the absence of information about whether patients received care in other medical facilities. For example, receipt of a prescription at another medical facility could result in a missing medication history and misclassification of the patient in our analysis. The inability to examine reasons for treatment discontinuation or to analyse any potential health benefits (e.g. reduced symptom severity or improved health-related quality of life) resulting from increased persistence, as such data are not collected in administrative claims databases, were limitations that applied to both databases. Lastly, the study may not have accurately captured the uptake of SGLT2i use given the timing of their introduction in Japan. In the first 6 months of their use (May–October 2015), prescribing of SGLT2i was restricted to 14 days' therapy for safety reasons, which may have had an impact on usage rates. The restriction applied to this new class of drugs was routine, as directed by the Japanese Pharmaceuticals and Medical Devices

Agency. Further analysis of prescribing practices based on updated databases is required to reflect current trends.

Comparison with other studies

A recent update to a position statement from the American Diabetes Association and European Association for the Study of Diabetes regarding management of hyperglycaemia in T2DM stipulates clearly that metformin is the best therapeutic option for monotherapy.[22–24] If target HbA1c is not attained after approximately 3 months, progression to double therapy is advocated. If, after a further 3 months, target HbA1c remains unattained, progression to triple therapy is recommended. After a 3-month trial of triple therapy, the introduction of combination injectable therapy with insulin plus a GLP-1 receptor agonist may be indicated.

Conversely, JDS guidelines stipulate that the '… choice of glucose-lowering agent should be made based on the disease condition of each particular patient with consideration given to the pharmacological and safety profile of each glucose-lowering agent'.[6] In accordance with these recommendations, and in conjunction with appropriate patient education about diet, exercise and lifestyle, treatment of T2DM in Japan may be started with any oral hypoglycaemic agent. As illustrated in the current study, DPP-4i are widely used in Japan, and this concurs with findings from other studies. For example, the ATTAK-J study reported real-world evidence of significant hypoglycaemic activity and favourable safety for DPP-4i therapy in Japanese patients with T2DM.[25] The PREFERENCE 4 study documented that treatment-naive Japanese patients preferred (in terms of treatment satisfaction) a DPP-4i to a BG, SU, or α-GI.[26] Use of a weekly DPP-4i also improved treatment satisfaction.[27,28] However, these are preliminary findings, and additional real-world data from other DPP-4i studies are awaited.

A systematic review and meta-analysis of studies which compared persistence and adherence associated with two or more antidiabetic medications in patients with T2DM found

considerable variation among studies in the methods used to define these terms but, nonetheless, was able to ascertain major differences between drug classes.[29] Adherence rates were higher with DPP-4i than with TZD, SU, and metformin, possibly reflecting the superior tolerability and convenient dosing schedules of these incretin-based agents.

Data about T2DM management in Asian patients indicate that DPP-4i are a viable first-line intervention, in a manner similar to that of metformin in Caucasian patients with T2DM.[1] Based on numerous studies involving mainly Japanese or Chinese patients, there is broad recognition that DPP-4i are more effective in East Asian than non-Asian patients[1,17–19,30] and, in Japan, >70% of patients treated with antidiabetic drugs receive incretin-based therapies. As approximately 60% of such patients are treatment-naïve, DPP-4i are establishing a definitive role in the first-line treatment of T2DM in Japan.[1,31] Although no significant association between DPP-4i and possible pancreatic disorder was observed in several large-scale studies,[25,32–34], it is important to remain vigilant for potential safety signals[35] since DPP-4i-related pancreatitis is a low but established risk.[36]

Conclusions and implications

The study indicated that DPP-4i have a prevalent role (as monotherapy, add-on therapy, switch therapy, and in combination regimens) in the management of T2DM in Japan. The high persistence and adherence we observed to DPP-4i-containing treatment schedules was a positive finding given the myriad factors contributing to poor adherence,[9] but also suggested to us that enhanced diabetes awareness and patient education programmes are needed to improve persistence and adherence rates overall in Japan. For antidiabetic drug therapy in general, research is warranted to quantify the extent to which augmenting persistence and adherence is likely to improve glycaemic control. In the case of DPP-4i, strategies to improve adherence might involve use of novel once-weekly administration schedules or FDCs.[13,37] Frequent prescribing of DPP-4i by Japanese physicians and high patient persistence and adherence with DPP-4i-containing schedules imply satisfaction with treatment. Although

there is no current evidence to indicate that DPP-4i provide better glycemic, microvascular or macrovascular outcomes compared with metformin or other oral antidiabetic agents in Japanese patients, they may be a good treatment option where adherence is an issue.

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Contributors and sources:

RN, HK, SH, YO, FG and YS are responsible for the work described in this paper.

RN, HK, SH, YO, FG and YS were involved in the conception, design, or planning of the study.

YO and FG were involved in the analysis of data.

RN, HK, KK, AO, SH and YS were involved in the interpretation of results.

RN, HK, KK, AO and YO contributed substantially to drafting of the manuscript.

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RN has received speaker honoraria from Astellas Pharma Inc, Nippon Boehringer Ingelheim Co. Ltd, Eli Lilly Japan K.K., Kissei Pharmaceutical Co. Ltd, Medtronic Japan Co. Ltd, MSD, Novartis Pharma K.K., Novo Nordisk Pharma Ltd, Sanofi K.K., and Takeda Pharmaceutical

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HK, KK, AO, and YS are employees of Takeda Pharmaceutical Co. Ltd.

SH was an employee of Takeda Pharmaceutical Co. Ltd. at the time the study was conducted.

FG and YO are employees of Creativ-Ceutical K.K.

Data sharing:

Given the administrative nature of the data, patients did not provide informed consent for data sharing; however, all data are fully anonymised and the risk of patient identification is low.

Disclaimer:

The study made use of de-identified data from the JMDC and MDV databases. The opinions, results and conclusions reported are those of the authors. No endorsement by JMDC or MDV or any of its funders or partners is intended or should be inferred.

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Tables

Table 1 Patient demographics and clinical characteristics

Characteristics	UT patients		PT patients	
	JMDC database n=19 428	MDV database n=24 820	JMDC database n=21 480	MDV database n=65 601
Follow-up, days, median (IQR):	929 (635; 1345)	942 (675; 1356)	980 (671; 1446)	1027 (715; 1521)
Age at index date, years, mean (SD):	51.7 (9.9)	67.6 (11.8)	54.4 (9.2)	65.9 (12.0)
Gender: male, n (%):	14 042 (72.3)	15 093 (60.8)	15 779 (73.5)	40 160 (61.2)
Multiple medications*, mean (SD):	2.0 (4.0)	3.0 (2.2)	2.3 (3.1)	3.3 (2.0)
Charlson Comorbidity Index, mean (SD):	2.2 (1.5)	2.5 (2.3)	2.5 (1.6)	2.6 (2.2)
Comorbidities				
Hypertension (% pts)	47.8	70.1	58.3	71.3
Hyperlipidaemia (% pts)	39.8	70.0	50.0	67.2
Dementia (% pts)	0.2	1.9	0.2	2.0
Diabetic nephropathy (% pts)	3.7	18.1	6.1	15.7

* Number of drugs prescribed (by 3-digit Anatomical Therapeutic Chemical Classification System)

JMDC, Japan Medical Data Center; MDV, Medical Data Vision; IQR, interquartile range; PT, previously treated; pts, patients; SD, standard deviation; UT, untreated.

Table 2 Changes to index therapy: add-on treatment over 12 months according to index antidiabetic drug class in UT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=2839**	**n=1102**	**n=364**	**n=316**	**n=102**	**n=50**	**n=76**	**n=7**	**n=8**
+ DPP-4i	NA	748 (67.9)	208 (57.1)	146 (46.2)	57 (55.9)	21 (42.0)	34 (44.7)	4 (57.1)	1 (12.5)
+ BG	1324 (46.6)	NA	80 (22.0)	85 (26.9)	21 (20.6)	9 (18.0)	28 (36.8)	2 (28.6)	1 (12.5)
+ SU	537 (18.9)	66 (6.0)	NA	30 (9.5)	8 (7.8)	1 (2.0)	5 (6.6)	0 (0.0)	2 (25.0)
+ α-GI	255 (9.0)	40 (3.6)	25 (6.9)	NA	4 (3.9)	15 (30.0)	5 (6.6)	0 (0.0)	0 (0.0)
+ TZD	293 (10.3)	58 (5.3)	20 (5.5)	16 (5.1)	NA	1 (2.0)	1 (1.3)	0 (0.0)	2 (25.0)
+ Glinide	79 (2.8)	16 (1.5)	0 (0.0)	17 (5.4)	0 (0.0)	NA	0 (0.0)	1 (14.3)	0 (0.0)
+ SGLT2i	256 (9.0)	128 (11.6)	11 (3.0)	2 (0.6)	7 (6.9)	2 (4.0)	NA	0 (0.0)	2 (25.0)
+ Insulin	5 (0.2)	2 (0.2)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
+ GLP-1	0 (0.0)	16 (1.5)	2 (0.5)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=3179**	**n=878**	**n=342**	**n=344**	**n=81**	**n=74**	**n=35**	**n=24**	**n=12**
+ DPP-4i	NA	602 (68.6)	215 (62.9)	208 (60.5)	43 (53.1)	42 (56.8)	12 (34.3)	113 (50.4)	0 (0.0)
+ BG	1168 (36.7)	NA	51 (14.9)	36 (10.5)	14 (17.3)	7 (9.5)	12 (34.3)	26 (11.6)	4 (33.3)
+ SU	736 (23.2)	44 (5.0)	NA	36 (10.5)	3 (3.7)	1 (1.4)	4 (11.4)	10 (4.5)	4 (33.3)
+ α-GI	414 (13.0)	38 (4.3)	29 (8.5)	NA	6 (7.4)	15 (20.3)	0 (0.0)	28 (12.5)	1 (8.3)
+ TZD	168 (5.3)	29 (3.3)	13 (3.8)	4 (1.2)	NA	4 (5.4)	0 (0.0)	1 (0.4)	0 (0.0)
+ Glinide	189 (5.9)	9 (1.0)	0 (0.0)	26 (7.6)	2 (2.5)	NA	0 (0.0)	12 (5.4)	0 (0.0)
+ SGLT2i	190 (6.0)	94 (10.7)	7 (2.0)	5 (1.5)	8 (9.9)	0 (0.0)	NA	2 (0.9)	3 (25.0)

+ Insulin	239 (7.5)	35 (4.0)	14 (4.1)	19 (5.5)	1 (1.2)	3 (4.1)	1 (2.9)	NA	0 (0.0)
+ GLP-1	2 (0.1)	10 (1.1)	4 (1.2)	1 (0.3)	0 (0.0)	1 (1.4)	4 (11.4)	0 (0.0)	NA

'+' indicates add-on therapy with new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Table 3 Changes to index therapy: switch treatment over 12 months according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=440**	**n=267**	**n=224**	**n=221**	**n=76**	**n=44**	**n=50**	**n=336**	**n=6**
→ DPP-4i	NA	157 (58.8)	106 (47.3)	126 (57.0)	43 (56.6)	22 (50.0)	26 (52.0)	115 (34.2)	1 (16.7)
→ BG	144 (32.7)	NA	47 (21.0)	40 (18.1)	15 (19.7)	8 (18.2)	13 (26.0)	107 (31.8)	1 (16.7)
→ SU	52 (11.8)	12 (4.5)	NA	4 (1.8)	0 (0.0)	3 (6.8)	1 (2.0)	11 (3.3)	1 (16.7)
→ α-GI	20 (4.5)	12 (4.5)	4 (1.8)	NA	2 (2.6)	2 (4.5)	2 (4.0)	19 (5.7)	0 (0.0)
→ TZD	26 (5.9)	19 (7.1)	8 (3.6)	11 (5.0)	NA	0 (0.0)	0 (0.0)	5 (1.5)	0 (0.0)
→ Glinide	22 (5.0)	3 (1.1)	5 (2.2)	11 (5.0)	0 (0.0)	NA	0 (0.0)	11 (3.3)	0 (0.0)
→ SGLT2i	82 (18.6)	26 (9.7)	3 (1.3)	10 (4.5)	7 (9.2)	3 (6.8)	NA	2 (0.6)	1 (16.7)
→ Insulin	63 (14.3)	17 (6.4)	36 (16.1)	8 (3.6)	5 (6.6)	4 (9.1)	2 (4.0)	NA	2 (33.3)
→ GLP-1	7 (1.6)	3 (1.1)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	6 (1.8)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=446**	**n=271**	**n=199**	**n=224**	**n=69**	**n=47**	**n=20**	**n=417**	**n=11**
→ DPP-4i	NA	206 (76.0)	144 (72.4)	155 (69.2)	41 (59.4)	24 (51.1)	6 (30.0)	224 (53.7)	5 (45.5)
→ BG	117 (26.2)	NA	15 (7.5)	21 (9.4)	14 (20.3)	4 (8.5)	6 (30.0)	34 (8.2)	2 (18.2)
→ SU	51 (11.4)	12 (4.4)	NA	15 (6.7)	4 (5.8)	4 (8.5)	2 (10.0)	25 (6.0)	0 (0.0)
→ α-GI	38 (8.5)	7 (2.6)	1 (0.5)	NA	1 (1.4)	7 (14.9)	0 (0.0)	26 (6.2)	0 (0.0)
→ TZD	18 (4.0)	9 (3.3)	0 (0.0)	4 (1.8)	NA	0 (0.0)	0 (0.0)	7 (1.7)	0 (0.0)
→ Glinide	14 (3.1)	4 (1.5)	5 (2.5)	10 (4.5)	0 (0.0)	NA	0 (0.0)	30 (7.2)	0 (0.0)
→ SGLT2i	52 (11.7)	14 (5.2)	2 (1.0)	1 (0.4)	3 (4.3)	0 (0.0)	NA	2 (0.5)	2 (18.2)

→ Insulin	136 (30.5)	10 (3.7)	21 (10.6)	15 (6.7)	4 (5.8)	6 (12.8)	0 (0.0)	NA	1 (9.1)
→ GLP-1 agonist	11 (2.5)	4 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	9 (2.2)	NA

'→' indicates treatment switch to new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Table 4 Changes to index therapy: add-on treatment over 12 months according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=1141**	**n=370**	**n=163**	**n=119**	**n=68**	**n=71**	**n=129**	**n=9**	**n=53**
+ DPP-4i	NA	186 (50.3)	77 (47.2)	52 (43.7)	18 (26.5)	30 (42.3)	39 (30.2)	5 (55.6)	0 (0.0)
+ BG	347 (30.4)	NA	23 (14.1)	14 (11.8)	11 (16.2)	12 (16.9)	19 (14.7)	0 (0.0)	12 (22.6)
+ SU	279 (24.5)	27 (7.3)	NA	12 (10.1)	9 (13.2)	1 (1.4)	5 (3.9)	2 (22.2)	15 (28.3)
+ α-GI	172 (15.1)	21 (5.7)	13 (8.0)	NA	2 (2.9)	10 (14.1)	2 (1.6)	1 (11.1)	3 (5.7)
+ TZD	120 (10.5)	13 (3.5)	12 (7.4)	1 (0.8)	NA	0 (0.0)	4 (3.1)	0 (0.0)	1 (1.9)
+ Glinide	43 (3.8)	8 (2.2)	1 (0.6)	6 (5.0)	1 (1.5)	NA	0 (0.0)	1 (11.1)	0 (0.0)
+ SGLT2i	46 (4.0)	24 (6.5)	3 (1.8)	2 (1.7)	0 (0.0)	2 (2.8)	NA	0 (0.0)	2 (3.8)
+ Insulin	8 (0.7)	3 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)
+ GLP-1 agonist	3 (0.3)	16 (4.3)	7 (4.3)	3 (2.5)	2 (2.9)	0 (0.0)	3 (2.3)	0 (0.0)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with add-on therapy	**n=3362**	**n=616**	**n=322**	**n=211**	**n=53**	**n=180**	**n=114**	**n=335**	**n=140**
+ DPP-4i	NA	249 (40.4)	177 (55.0)	63 (29.9)	15 (28.3)	66 (36.7)	38 (33.3)	128 (38.2)	1 (0.7)
+ BG	727 (21.6)	NA	31 (9.6)	8 (3.8)	7 (13.2)	16 (8.9)	23 (20.2)	35 (10.4)	18 (12.9)
+ SU	768 (22.8)	38 (6.2)	NA	11 (5.2)	6 (11.3)	1 (0.6)	4 (3.5)	12 (3.6)	61 (43.6)
+ α-GI	444 (13.2)	28 (4.5)	20 (6.2)	NA	1 (1.9)	25 (13.9)	3 (2.6)	28 (8.4)	11 (7.9)
+ TZD	131 (3.9)	15 (2.4)	9 (2.8)	3 (1.4)	NA	3 (1.7)	1 (0.9)	5 (1.5)	1 (0.7)
+ Glinide	216 (6.4)	10 (1.6)	1 (0.3)	9 (4.3)	0 (0.0)	NA	0 (0.0)	10 (3.0)	5 (3.6)
+ SGLT2i	59 (1.8)	29 (4.7)	4 (1.2)	2 (0.9)	3 (5.7)	2 (1.1)	NA	6 (1.8)	3 (2.1)

+ Insulin	828 (24.6)	163 (26.5)	37 (11.5)	80 (37.9)	14 (26.4)	45 (25.0)	7 (6.1)	NA	22 (15.7)
+ GLP-1 agonist	1 (0.0)	24 (3.9)	16 (5.0)	3 (1.4)	2 (3.8)	2 (1.1)	6 (5.3)	12 (3.6)	NA

'+' indicates add-on therapy with new antidiabetic drug class.

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

Table 5 Changes to index therapy: switch treatment over 12 months according to index antidiabetic drug class in PT patients, n (%)

JMDC database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=303**	**n=92**	**n=56**	**n=70**	**n=46**	**n=38**	**n=50**	**n=268**	**n=27**
→ DPP-4i	NA	27 (29.3)	15 (26.8)	14 (20.0)	20 (43.5)	14 (36.8)	16 (32.0)	84 (31.3)	4 (14.8)
→ BG	44 (14.5)	NA	8 (14.3)	8 (11.4)	8 (17.4)	2 (5.3)	6 (12.0)	48 (17.9)	6 (22.2)
→ SU	56 (18.5)	8 (8.7)	NA	3 (4.3)	5 (10.9)	5 (13.2)	2 (4.0)	27 (10.1)	5 (18.5)
→ α-GI	15 (5.0)	2 (2.2)	1 (1.8)	NA	1 (2.2)	3 (7.9)	1 (2.0)	17 (6.3)	2 (7.4)
→ TZD	14 (4.6)	8 (8.7)	1 (1.8)	1 (1.4)	NA	2 (5.3)	4 (8.0)	6 (2.2)	1 (3.7)
→ Glinide	12 (4.0)	2 (2.2)	4 (7.1)	1 (1.4)	0 (0.0)	NA	1 (2.0)	7 (2.6)	0 (0.0)
→ SGLT2i	17 (5.6)	2 (2.2)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.4)	1 (3.7)
→ Insulin	106 (35.0)	37 (40.2)	18 (32.1)	37 (52.9)	6 (13.0)	6 (15.8)	9 (18.0)	NA	7 (25.9)
→ GLP-1	8 (2.6)	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)	2 (4.0)	9 (3.4)	NA
MDV database									
Index treatment	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**	**Insulin**	**GLP-1**
Pts with switch therapy	**n=651**	**n=154**	**n=135**	**n=119**	**n=36**	**n=119**	**n=34**	**n=480**	**n=75**
→ DPP-4i	NA	57 (37.0)	67 (49.6)	44 (37.0)	15 (41.7)	43 (36.1)	15 (44.1)	164 (34.2)	19 (25.3)
→ BG	66 (10.1)	NA	7 (5.2)	6 (5.0)	4 (11.1)	3 (2.5)	6 (17.6)	19 (4.0)	5 (6.7)
→ SU	168 (25.8)	13 (8.4)	NA	6 (5.0)	4 (11.1)	22 (18.5)	1 (2.9)	48 (10.0)	4 (5.3)
→ α-GI	66 (10.1)	7 (4.5)	3 (2.2)	NA	1 (2.8)	9 (7.6)	0 (0.0)	18 (3.8)	2 (2.7)
→ TZD	26 (4.0)	11 (7.1)	2 (1.5)	3 (2.5)	NA	0 (0.0)	1 (2.9)	10 (2.1)	2 (2.7)
→ Glinide	48 (7.4)	3 (1.9)	8 (5.9)	2 (1.7)	0 (0.0)	NA	0 (0.0)	32 (6.7)	2 (2.7)
→ SGLT2i	16 (2.5)	3 (1.9)	2 (1.5)	2 (1.7)	1 (2.8)	0 (0.0)	NA	2 (0.4)	0 (0.0)

→ Insulin	196 (30.1)	48 (31.2)	32 (23.7)	45 (37.8)	10 (27.8)	27 (22.7)	1 (2.9)	NA	26 (34.7)
→ GLP-1 agonist	18 (2.8)	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)	3 (8.8)	3 (0.6)	NA

'→' indicates treatment switch to new antidiabetic drug.

DPP-4i, dipeptidyl peptidase-4 inhibitor; α-GI, α-glucosidase inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; NA, not applicable; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione.

Table 6 Persistence with monotherapy schedules of index antidiabetic drug classes

UT patients

Index therapy	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**
JMDC database	**n=8545**	**n=3354**	**n=979**	**n=1346**	**n=504**	**n=165**	**n=430**
Median time to discontinuation (days)	1138.0	582.0	384.0	280.0	400.0	161.0	471.0
12-month persistence rate (% pts)	67.4	57.3	50.4	45.5	51.2	38.8	53.5
MDV database	**n=13 598**	**n=2777**	**n=1174**	**n=1666**	**n=449**	**n=292**	**n=224**
Median time to discontinuation (days)	707.0	672.0	474.5	458.0	491.0	438.5	537.5
12-month persistence rate (% pts)	77.2	73.8	56.0	54.9	57.2	53.8	63.4

PT patients

Index therapy	**DPP-4i**	**BG**	**SU**	**α-GI**	**TZD**	**Glinide**	**SGLT2i**
JMDC database	**n=2354**	**n=680**	**n=284**	**n=256**	**n=158**	**n=135**	**n=285**
Median time to discontinuation (days)	1583.0	917.0	599.0	304.5	370.0	266.0	691.0
12-month persistence rate (% pts)	73.5	69.3	58.1	46.9	50.0	43.0	62.8
MDV database	**n=7658**	**n=1100**	**n=633**	**n=495**	**n=133**	**n=446**	**n=229**
Median time to discontinuation (days)	764.0	666.5	532.0	422.0	333.0	396.0	553.0
12-month persistence rate (% pts)	78.8	73.6	62.2	52.7	48.1	52.2	66.4

α-GI, α-glucosidase inhibitor; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV,

Medical Data Vision; PT, previously treated; pts, patients; SGLT2i , sodium-glucose cotransporter-2 inhibitor; TZD, thiazolidinedione; UT, untreated.

Figure legends

Fig 1 Patient disposition.

JMDC, Japan Medical Data Center; MDV, Medical Data Vision; T2DM, type 2 diabetes mellitus.

Fig 2 Antidiabetic drug classes prescribed at the index date in (a) UT patients; and (b) PT patients in the JMDC and MDV databases.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2; SU, sulfonylurea; TZD, thiazolidinedione; UT, untreated.

Fig 3 Kaplan-Meier survival distribution of median time to treatment discontinuation according to index antidiabetic drug class; (a) UT patients; JMDC database; (b) UT patients, MDV database; (c) PT patients, JMDC database; (d) PT patients, MDV database.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; UT, untreated.

Fig 4 12-month adherence to index antidiabetic drug classes in (a) untreated (UT) patients and (b) previously treated (PT) patients in the JMDC and MDV databases.

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; pts, patients; SGLT2i, sodium-glucose cotransporter-2; TZD, thiazolidinedione; UT, untreated.

Fig 5 12-month persistence rates with the five most frequent index antidiabetic drug combinations in PT patients in the JMDC and MDV databases.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SU, sulfonylurea.

Fig 6 Adherence rates for the five most frequent index antidiabetic drug combinations in PT patients in the JMDC and MDV databases.

α-GI, α-glucosidase inhibitor; BG, biguanide; DPP-4i, dipeptidyl peptidase-4 inhibitor; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SU, sulfonylurea.

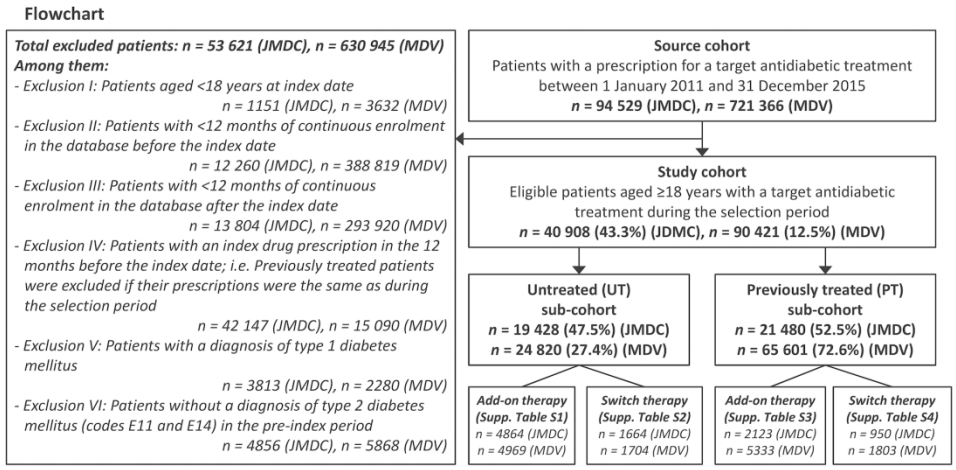

Figure 1

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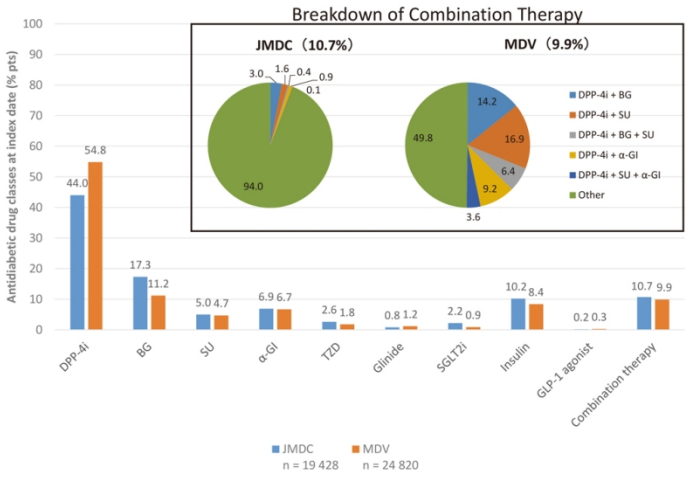

Figure 2A Index prescription UT pts

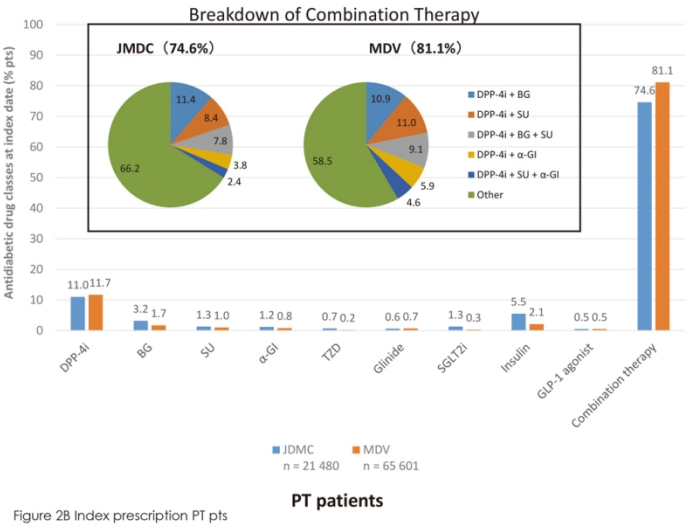

Figure 2B Index prescription PT pts

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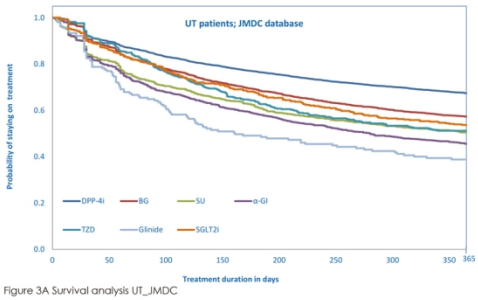

Figure 3A Survival analysis UT_JMDC

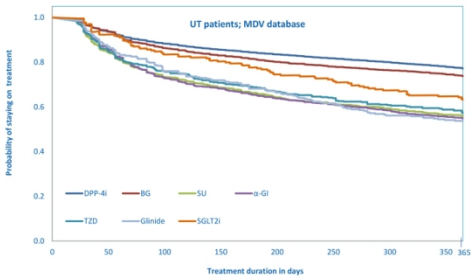

Figure 3B Survival analysis UT_MDV

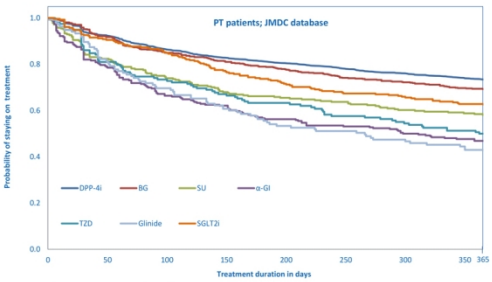

Figure 3C Survival analysis PT_JMDC

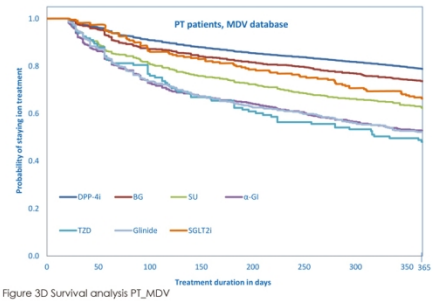

Figure 3D Survival analysis PT_MDV

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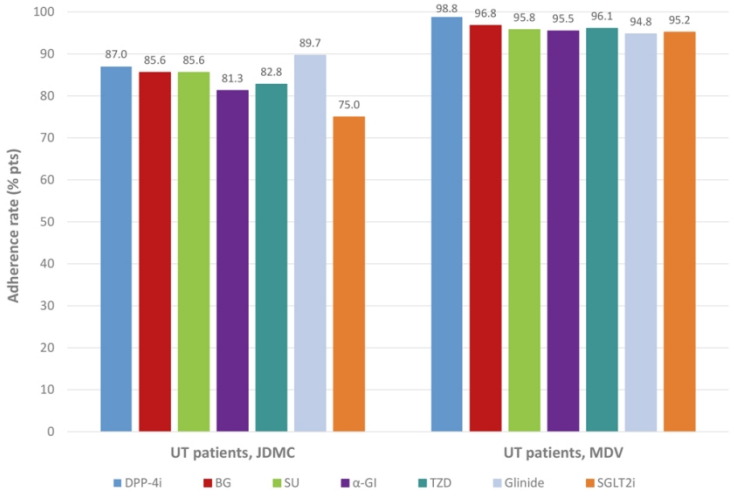

Figure 4A Adherence UT pts

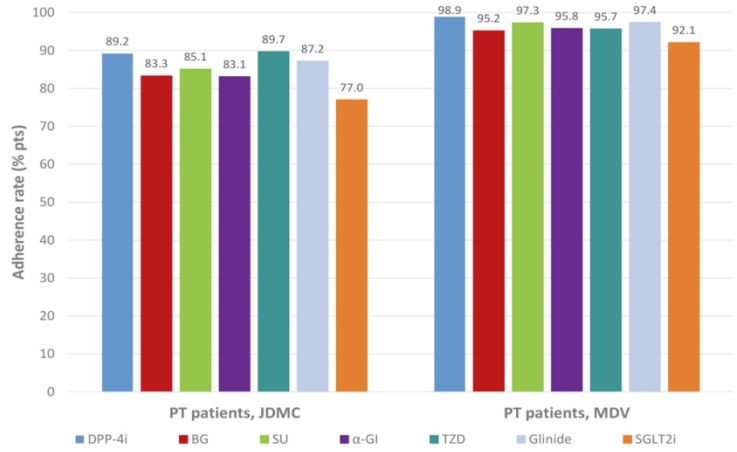

Figure 4B Adherence PT pts

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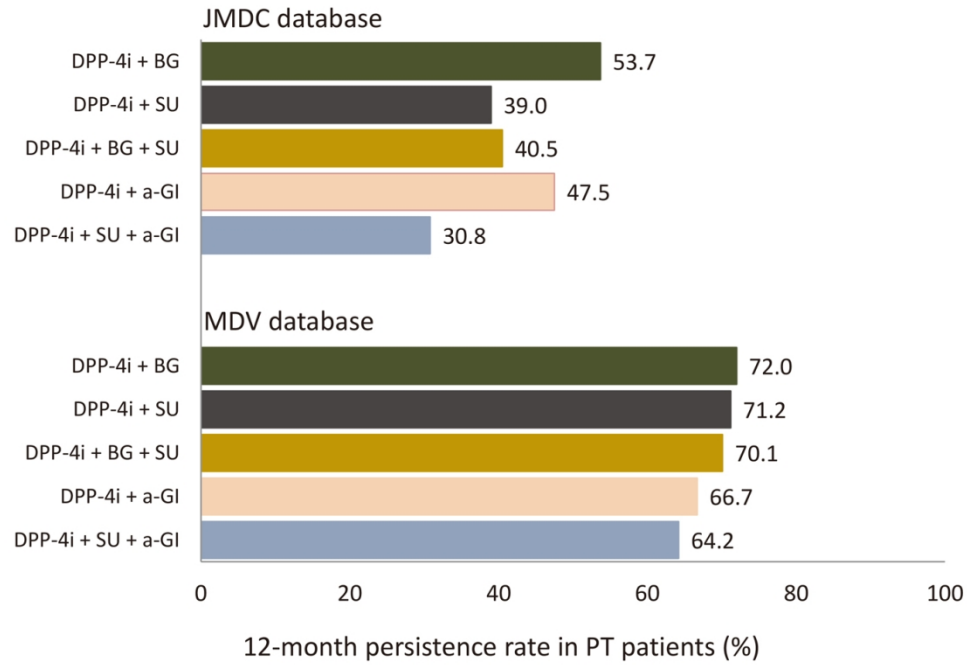

Figure 5

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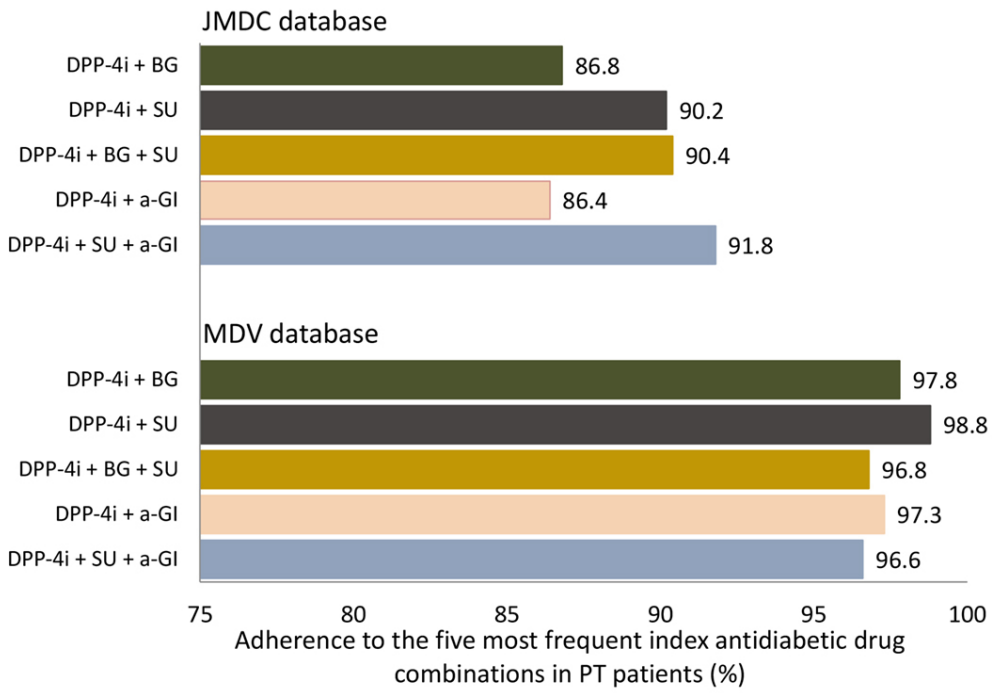

90x90mm (300 x 300 DPI)

Supplementary table 1 Factors associated with non-persistence with the index antidiabetic drug class in untreated patients

Characteristics	*JMDC database*			*MDV database*		
	N	**Not persistent (% pts)**	**Adjusted odds ratio (95% CI)[a]**	**N**	**Not persistent (% pts)**	**Adjusted odds ratio (95% CI)[a]**
Age at index date (years):						
18–34	659	66.9	1.00	205	38.0	1.00
35–44	2734	53.1	1.64 (1.37, 1.97)*	791	29.5	1.34 (0.96, 1.86)
45–54	6356	41.3	2.45 (2.06, 2.92)*	2016	26.7	1.48 (1.09, 2.02)*
55–64	5891	34.8	3.04 (2.55, 3.62)*	4872	26.3	1.55 (1.15, 2.09)*
65–74	1777	31.5	3.31 (2.72, 4.03)*	7880	29.3	1.39 (1.03, 1.87)*
≥ 75	34	35.3	2.52 (1.21, 5.25)*	6602	33.8	1.22 (0.90, 1.64)
Number of medications:						
0	7585	46.1	1.00	2957	34.2	1.00
1–3	6980	37.9	1.21 (1.13, 1.30)*	10,907	26.7	1.38 (1.26, 1.51)*
4–5	1594	33.4	1.30 (1.15, 1.46)*	5707	29.1	1.31 (1.18, 1.45)*
6–8	883	35.2	1.23 (1.05, 1.43)*	2528	37.9	1.04 (0.92, 1.17)
> 8	409	38.4	1.11 (0.89, 1.37)*	267	47.6	0.73 (0.56, 0.95)*
Hypertension:						
No	9053	47.3	1.00	6534	32.8	1.00
Yes	8398	34.0	1.43 (1.33, 1.52)*	15,832	28.6	1.17 (1.09, 1.25)*
Hyperlipidaemia:						
No	10,335	43.2	1.00	8535	35.3	1.00
Yes	7116	37.7	1.12 (1.05, 1.20)*	13,831	26.4	1.40 (1.31, 1.49)*
Number of antidiabetic drug classes at index date:						
1	15,368	39.1	1.00	20,180	27.2	1.00
2	1707	52.7	0.62 (0.56, 0.69)*	1594	51.8	0.37 (0.33, 0.41)*

3	299	60.2	0.44 (0.35, 0.56)*	489	59.5	0.27 (0.22, 0.32)*
≥ 4	77	68.8	0.31 (0.19, 0.50)*	103	59.2	0.25 (0.16, 0.37)*

[a] Adjusted for age, gender, multiple medications at index date, comorbidities at baseline, and number of antidiabetic drug classes at index date.

* $p < 0.05$.

CI, confidence interval; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; pts, patients.

Supplementary table 2 Factors associated with non-adherence with the index antidiabetic drug class in untreated patients

Characteristics	*JMDC database*			*MDV database*		
	N	**Not adherent (% pts)**	**Adjusted odds ratio (95% CI)[a]**	**N**	**Not adherent (% pts)**	**Adjusted odds ratio (95% CI)[a]**
Age at index date (years):						
18–34	599	16.7	1.00	190	7.4	1.00
35–44	2571	14.0	1.23 (0.97, 1.57)	727	4.8	1.40 (0.73, 2.69)
45–54	6056	11.4	1.54 (1.22, 1.94)*	1893	2.1	3.06 (1.61, 5.81)*
55–64	5638	8.8	2.05 (1.61, 2.61)*	4555	2.0	3.18 (1.75, 5.80)*
65–74	1694	4.6	3.83 (2.78, 5.27)*	7341	2.0	3.30 (1.83, 5.95)*
≥ 75	32	6.3	2.39 (0.63, 9.02)	6225	2.7	2.67 (1.47, 4.86)*
Number of medications:						
0	7186	10.0	1.00	2713	2.3	1.00
1–3	6661	10.9	0.86 (0.77, 0.97)*	10,178	1.9	1.03 (0.78, 1.39)
4–5	1515	10.4	0.82 (0.68, 0.99)*	5373	2.4	0.80 (0.58, 1.12)
6–8	840	10.1	0.83 (0.65, 1.06)	2410	3.8	0.61 (0.43, 0.87)
> 8	388	10.8	0.72 (0.51, 1.00)	257	6.2	0.38 (0.21, 0.70)
Hypertension:						
No	8528	11.0	1.00	6060	2.9	1.00
Yes	8062	9.8	1.05 (0.95, 1.18)	14,871	2.2	1.26 (1.03, 1.54)*
Hyperlipidaemia:						
No	9800	10.5	1.00	7959	3.1	1.00
Yes	6790	10.3	1.01 (0.91, 1.12)	12,972	1.9	1.52 (1.26, 1.84)*
Number of antidiabetic drug classes at index date:						
1	14,507	10.5	1.00	18,892	2.0	1.00
2	1707	9.8	1.14 (0.96, 1.35)	1492	4.6	0.50 (0.38, 0.65)*
3	299	8.7	1.36 (0.91, 2.05)	452	6.6	0.33 (0.22, 0.49)*

≥ 4	77	11.7	0.92 (0.46, 1.87)	95	9.5	0.21 (0.10, 0.42)*

[a] Adjusted for age, gender, multiple medications at index date, comorbidities at baseline, and number of antidiabetic drug classes at index date.

* $p < 0.05$.

CI, confidence interval; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; pts, patients.

STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.