JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Effect of sodium–glucose cotransporter 2 inhibitor medication on new prescriptions of antihypertensives, antigout/antihyperuricemics and antidyslipidemics in Japan: Analysis using the JMDC Claims Database

Maki Gouda[1]*, Kenji Arakawa[2], Masaya Inagaki[1], Yoshiteru Ushirogawa[1]

[1]Data Science Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan, and [2]Medical Intelligence Department, Ikuyaku. Integrated Value Development Division, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan

Keywords
Claims database, Concomitant medication, sodium–glucose cotransporter 2 inhibitor

***Correspondence**
Maki Gouda
Tel.: +81-3-6748-7737
Fax: +81-3-3663-6779
E-mail address:
gouda.maki@mm.mt-pharma.co.jp

J Diabetes Investig 2022; 13: 1842–1851

doi: 10.1111/jdi.13887

ABSTRACT

Aims/Introduction: This study aimed to investigate the effects of sodium–glucose cotransporter 2 inhibitors (SGLT2i) on new prescriptions of drugs, including antihypertensives, antigout/antihyperuricemics and antidyslipidemics, for the treatment of lifestyle-related diseases in Japanese patients with diabetes mellitus using the JMDC Claims Database.

Materials and Methods: Patients with type 2 diabetes mellitus who were newly treated with SGLT2i or other oral antidiabetic drugs and had not been prescribed any antihypertensives, antigout/antihyperuricemics or antidyslipidemics for at least 1 year were extracted from the database. Using propensity score calibration matching (1:1), we assessed the proportion of patients who started the aforementioned concomitant medications within 2 years, and the risk ratio of SGLT2i to other antidiabetic medication groups was calculated.

Results: In 856,796 patients with diabetes mellitus, 734, 1,197 and 703 propensity score calibration-matched patients in each group were analyzed for the prescription of antihypertensives, antigout/antihyperuricemics and antidyslipidemics, respectively. The new prescriptions of antihypertensives and antigout/antihyperuricemics were lower in the SGLT2i group than those in the other oral antidiabetic drug group (risk ratio 0.66 and 0.37, respectively), whereas those of antidyslipidemics were more common in the SGLT2i group (risk ratio 1.43).

Conclusions: New prescriptions of antihypertensives or antigout/antihyperuricemics were lower for patients taking SGLT2i than those taking other oral antidiabetic drugs, probably due to a reduction of blood pressure and uric acid levels by SGLT2i. The more frequent prescriptions of antidyslipidemics might partially reflect a moderate increase in low-density lipoprotein cholesterol levels as a result of sodium–glucose cotransporter 2 inhibition.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) primarily reduce plasma glucose levels by inhibiting glucose reabsorption in the kidney and enhancing urinary glucose excretion. Clinical studies showed the efficacy of SGLT2i not only in reducing hyperglycemia, but also in decreasing bodyweight, blood pressure, blood triglyceride (TG) and uric acid levels[1,2]. Lifestyle-related diseases, including hypertension, hyperuricemia and dyslipidemia, are risk factors for the development of

Received 25 March 2022; revised 13 July 2022; accepted 15 July 2022

arteriosclerosis and chronic kidney diseases, and are often comorbid in patients with type 2 diabetes mellitus[3–7]. Recent large-scale clinical outcome studies, including CANagliflozin cardioVascular Assessment Study (CANVAS)[8], Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)[9], EMPAgliflozin-Remove Excess Glucose (EMPA-REG) OUTCOME[10] and Dapagliflozin Effect on ardiovascuLAR Events-Thrombolysis in Myocardial Infarction 58 (DECLARE TIMI58)[11], showed that SGLT2i suppress the incidence of cardiac and renal events. Despite these refined clinical study results, the impact of reducing the aforementioned risk factors by SGLT2i on the medications of lifestyle-related diseases has not been proven in studies using real-world data in Japan. The JMDC Claims Database[12] collects claims from multiple health insurance unions, and their anonymized data are available from this database to show real-world medical practices for research.

The present study aimed to substantiate the preventive effects of SGLT2i on lifestyle-related diseases in the real-world data in Japan. We assumed that any beneficial effects on lifestyle-related diseases are realized by the reduced number of drug prescriptions for relevant diseases. In this study, we compared the effects of SGLT2i and other oral antidiabetic drugs (OAD) on the number of newly prescribed antihypertensives, antigout/antihyperuricemics or antidyslipidemics in patients with type 2 diabetes mellitus by using the data from the JMDC Claims Database.

MATERIALS AND METHODS

This is an exploratory cross-sectional study using the JMDC Claims Database[12]. Anonymized data from the database for the period from September 2010 to August 2020 were used for this study. This database collects the claims data from company employees and their families in Japan, but does not include data from older adults aged >75 years who are covered by the Latter-Stage Elderly Healthcare System. The dataset available in this database includes patient information, such as sex, year of birth, disease data, prescriptions, medical practices and medical checkups. Furthermore, using the database, it is possible to track the treatment history of patients, even if they visit multiple hospitals.

Study population

In the present study, the assessment drugs included antihypertensives, antigout/hyperuricemics and antidyslipidemics. The number of prescriptions of these assessment drugs was compared between the users of SGLT2i and OADs. OAD included the following class of oral drugs: sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, glinides and dipeptidyl peptidase-4 inhibitors. The patients with prescription records of SGLT2i or combination drugs containing SGLT2 inhibitors during any periods were excluded from the OAD group. Among patients with diabetes mellitus defined by International Classification of Diseases 10th revision Code E 11–E 14, new users of SGLT2i and OAD were extracted from 1 April 2014, when the first-in-class SGLT2i was launched, to 31 August 2018. In both SGLT2i and OAD groups, only the patients taking two or more antidiabetic drugs were selected for analysis, as patients received SGLT2i in most cases in combination with other antidiabetic drugs. The index date was defined as the date when the patient started SGLT2i or the earliest date when the patients started new combination of OADs, which means that the same combination of antidiabetic drugs has not been prescribed in the previous year. Combination antidiabetic drugs containing multiple active ingredients were counted as each class of drugs for each ingredient included. The following population sets were assessed for concomitant medication: population I for antihypertensives, population II for antigout/antihyperuricemics and population III for antidyslipidemics.

Patients were considered eligible if they meet the following inclusion criteria: (i) patients whose any medical records are available in the database for ≥1 year before the index date; (ii) patients who have medical checkup data, including body mass index (BMI), glycated hemoglobin and serum creatinine within 1 year before the index date, and blood pressure, uric acid and lipid parameters in the medical checkup for populations I, II and III, respectively; (iii) patients with a treatment period between the index date and the last prescription date of >730 days as described below; (iv) patients with a proportion of days covered with SGLT2i or OAD prescription ≥0.8; and (v) patients who have no antihypertensive, antigout/antihyperuricemic or antidyslipidemic medication for populations I, II or III, respectively, ≥1 year before the index date. The lookback period of the medical record was set at 1 year before the index date.

When a gap between the last dose of the previous prescription to the next prescription was ≥61 days in SGLT2i or OAD treatment, the treatment was considered discontinued, and the last prescription date before discontinuation was considered the end of the treatment period. Proportion of days covered was expressed as the ratio of the number of days covered by SGLT2i or OAD prescriptions to the days of the treatment period. The proportion of days covered inclusion criterion was set, because the patients with poor drug adherence would have infrequently visited clinics or hospitals and, therefore, might have fewer opportunities to be treated with other lifestyle-related diseases. Exclusion criteria included patients with type 1 diabetes or records of dialysis, and those for whom adherence could not be ensured were excluded from the study.

For the classification of assessment drugs, antihypertensives included beta-blockers, calcium channel blockers, renin–angiotensin system inhibitors, diuretic and other oral agents that were indicated for hypertension; antigout/antihyperuricemics included uricosuric drugs, uric acid synthesis inhibitors and colchicine; and antidyslipidemics included statins, fibrates, ion exchange resins, proprotein convertase subtilisin/kexin type 9 inhibitors and other cholesterol-/TG-regulating agents. The combination product containing amlodipine and atorvastatin, Caduet, was classified into both statin and calcium channel

blocker prescription classes. For patient demographics, laboratory data and the presence of comorbidities, defined by the Charlson Comorbidity Index[13], were obtained from the medical checkup and disease data, respectively, within the lookback period. Disease or drug definitions were based on International Classification of Diseases 10th revision or ATC codes, respectively (Table S1).

End-points

Primary end-point

Propensity score calibration (PSC) matching was carried out in a 1:1 ratio between the SGLT2i and OAD groups. Patients who were newly prescribed an antihypertensive, antigout/antihyperuricemic or antidyslipidemic drug were defined as a new user (event of outcome) in populations I, II or III, respectively. New users who were prescribed each assessment drug ≥7 days during the treatment period of 730 days from the index date were identified. The risk ratio (RR) of the SGLT2i group to the OAD group was calculated on the basis of the proportion of new users in each group.

Other end-points

With a prescription of each assessment drug as an event within 730 days from the index date, the number of patients with the events and the incidence rate per 1,000 patient-years were calculated for the SGLT2i and OAD groups. The number of patients with new prescriptions of assessment drugs was also summarized on the basis of major pharmacological classes in populations I, II and III. Changes in laboratory values from baseline to the last medical checkup (days 366–730 from the index date) were calculated by stratification according to the presence or absence of new prescriptions. In these patients, the number and percentage of patients exceeding the standard reference range or treatment-recommended criteria[14–17] in the laboratory values were summarized at the baseline and the last medical checkup: in population I, systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg (exceeding the standard reference range), or SBP ≥140 mmHg or DBP ≥90 mmHg (exceeding the treatment-recommended criteria); in population II, uric acid ≥7.0 mg/dL (exceeding the treatment-recommended criteria); and in population III, TG ≥150 mg/dL or low-density lipoprotein (LDL) cholesterol ≥120 mg/dL (exceeding the standard reference range). If patients had two or more medical checkup data, the laboratory data closest to day 730 were adopted.

Statistical analysis

The PSC-matched populations were used to compare the proportion of the patients who were prescribed the assessment drugs. From a clinical perspective, covariates in each population that might affect exposure (SGLT2i or OAD) or outcomes were included in the PSC. Common covariates for all three populations included age, sex, index year, class of concomitant antidiabetics at the index date, comorbidity defined by Charlson Comorbidity Index, BMI, glycated hemoglobin and estimated glomerular filtration rate categories by chronic kidney disease stage. Additional covariates were SBP and DBP, uric acid, and LDL cholesterol and TG for populations I, II and III, respectively. A caliper of 0.2 on the propensity scale was used, and standardized difference was used to assess the covariate balance[18].

For patient background characteristics, categorical variables were expressed as the number of patients and percentage, and continuous variables were expressed as mean and standard deviation. The proportion of patients who were prescribed the assessment drugs within 730 days and its 95% confidence interval (CI) were calculated by group in each population. The RR and 95% CI for the SGLT2i group to the OAD group were also calculated and analyzed using Pearson's χ^2-test. The Kaplan–Meier curve was prepared for the time to the events by group, and the *P*-value was calculated using the log-rank test. Statistical analyses were carried out using SAS Ver. 9.4 (SAS Institute, Inc., Cary, NC, USA) and conducted by ATLEAF Corporation (Tokyo, Japan).

RESULTS

Study population

A total of 856,796 patients with a diagnosis code of diabetes mellitus were identified; of whom, 3,387 patients (SGLT2i: n = 1,751, OAD: n = 1,636), 5,374 patients (SGLT2i: n = 2,892, OAD: n = 2,482) and 3,203 patients (SGLT2i: n = 1,562, OAD: n = 1,641) were prescription-free of antihypertensives (population I), antigout/antihyperuricemics (population II) and antidyslipidemics (population III), respectively, for 1 year before the index date (Figure 1).

Patient background characteristics

In the patient background data before PSC matching (Table S2), the mean age was younger in the SGLT2i group than that in the OAD group in all three populations. The proportion of patients with diabetic complications and mild hepatic impairment was higher in the SGLT2i groups. Additionally, mean BMI and estimated glomerular filtration rate were higher in the SGLT2i groups. The PSC matching ratio (before/after) in the SGLT2i and OAD groups was 0.419 (734/1,751) and 0.449 (734/1,636), respectively, for antihypertensives; 0.414 (1,197/2,892) and 0.482(1,197/2,482), respectively, for antigout/antihyperuricemics; and 0.450 (703/1,562) and 0.428 (703/1,641), respectively, for antidyslipidemics; and approximately 40% of patients were matched in all three populations (Figure 1).

In all three populations, the absolute standardized differences were <0.1 for all covariates (Table 1). In the OAD group of all populations, the patients initiated metformin most commonly followed by dipeptidyl peptidase-4 inhibitors (Table S3). In population I, which assesses antihypertensive drug prescriptions, the mean SBP and DBP were approximately 126 and 79 mmHg, respectively. The mean uric acid level in

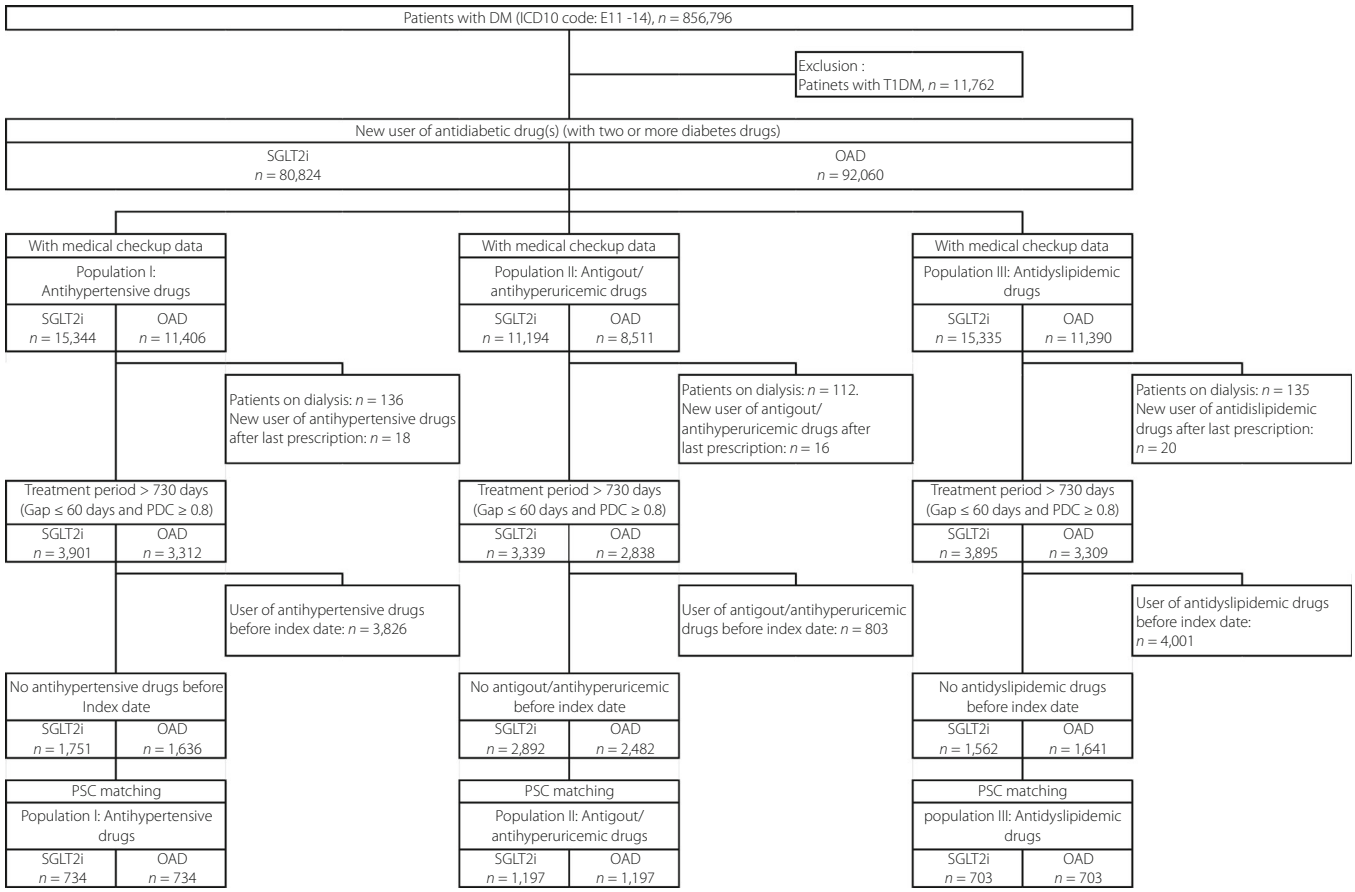

Figure 1 | Patient disposition and flow chart. DM, diabetes mellitus; OAD, other oral antidiabetic drugs except SGLT2i; PSC, propensity score calibration; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

population II, which assesses antigout/antihyperuricemic drug prescriptions, was approximately 5.5 mg/dL. In population III, which assesses antidyslipidemic drugs, the mean LDL cholesterol and TG levels were approximately 126 and 155 mg/dL, respectively.

Outcomes

In population I, the number (percentage) of patients who were newly prescribed antihypertensive drugs within 730 days from the index date was 50 (6.8%) in the SGLT2i group and 76 (10.4%) in the OAD group, and the RR of onset in the SGLT2i group relative to the OAD group was 0.66 (95% CI 0.47–0.93; $P = 0.015$, Table 2). As shown in the Kaplan–Meier curves (Figure 2a), the incidence of the initiation of medication was significantly different between the two groups (log-rank test; $P = 0.017$), and the incidence rates for 730 days from the index date were 25.95 and 40.28 per 1,000 person-years in the SGLT2i and OAD groups, respectively. For the prescription of antihypertensives by drug class, no differences between the SGLT2i and OAD groups were noted; angiotensin II antagonists were prescribed most frequently, followed by calcium channel blockers in both groups (Table S4).

In population II, 14 (1.2%) and 38 (3.2%) patients in the SGLT2i and OAD groups, respectively, newly received antigout/antihyperuricemic prescriptions. The RR in the SGLT2i group relative to the OAD group was 0.37 (95% CI 0.20–0.68; $P < 0.001$, Table 2). The incidence rates for 730 days from the index date were 4.24 and 11.72 per 1,000 person-years in the SGLT2i and OAD groups, respectively, and a significant difference between the groups was observed (log-rank test, $P < 0.001$; Figure 2b). No difference in the class of the antigout/antihyperuricemics between both groups was noted (Table S4).

In population III, the numbers of patients newly prescribed antidyslipidemic drugs were 134 (19.1%) and 94 (13.4%) in the SGLT2i and OAD groups, respectively. The RR of SGLT2i relative to the OAD group was 1.43 (95% CI 1.12–1.82; $P = 0.004$, Table 2). The incidence of the initiation of medication was significantly different between the groups (log-rank test, $P = 0.005$), and the incidence rates in the SGLT2i and OAD groups were 78.48 and 53.36 per 1,000 person-years, respectively, in 730 days from the index date (Figure 2c). Statins were the most frequently prescribed drugs in both groups, followed by fibrates; the prescription rates were similar in these two

Table 1 | Background data after propensity score calibration matching

Groups	Population I			Population II			Population III		
	SGLT2i *n* = 734	OAD *n* = 734	Standardized difference	SGLT2i *n* = 1197	OAD *n* = 1197	Standardized difference	SGLT2i *n* = 703	OAD *n* = 703	Standardized difference
Sex, *n* (%)									
Male	607 (82.7)	608 (82.8)	0.004	978 (81.7)	957 (79.9)	−0.045	591 (84.1)	606 (86.2)	0.060
Female	127 (17.3)	126 (17.2)		219 (18.3)	240 (20.1)		112 (15.9)	97 (13.8)	
Age (years), mean (SD)	51.8 (7.4)	52.0 (7.8)	−0.035	53.1 (7.2)	53.3 (7.5)	−0.034	51.9 (7.4)	52.4 (7.6)	−0.061
Index, *n* (%)									
April 2014–March 2015	99 (13.5)	98 (13.4)	−0.004	148 (12.4)	162 (13.5)	0.032	80 (11.4)	75 (10.7)	−0.020
April 2015–March 2016	134 (18.3)	132 (18.0)	−0.007	236 (19.7)	213 (17.8)	−0.047	119 (16.9)	125 (17.8)	0.022
April 2016–March 2017	156 (21.3)	156 (21.3)	0.000	280 (23.4)	284 (23.7)	0.008	164 (23.3)	175 (24.9)	0.038
April 2017–August 2018	345 (47.0)	348 (47.4)	0.008	533 (44.5)	538 (44.9)	0.009	340 (48.4)	328 (46.7)	−0.035
Antidiabetic drugs, *n* (%)									
Insulin	52 (7.1)	45 (6.1)	−0.035	85 (7.1)	86 (7.2)	0.003	48 (6.8)	39 (5.5)	−0.046
Sulfonylurea	125 (17.0)	118 (16.1)	−0.023	220 (18.4)	197 (16.5)	−0.047	114 (16.2)	107 (15.2)	−0.025
Biguanide	278 (37.9)	256 (34.9)	−0.067	463 (38.7)	422 (35.3)	−0.076	258 (36.7)	232 (33.0)	−0.081
Thiazolidinedione	75 (10.2)	61 (8.3)	−0.062	105 (8.8)	97 (8.1)	−0.021	49 (7.0)	46 (6.5)	−0.015
α-Glucosidase inhibitor	86 (11.7)	78 (10.6)	−0.031	136 (11.4)	125 (10.4)	−0.026	64 (9.1)	58 (8.3)	−0.027
Glinide	23 (3.1)	22 (3.0)	−0.006	45 (3.8)	34 (2.8)	−0.043	22 (3.1)	21 (3.0)	−0.007
DPP-4 inhibitors	445 (60.6)	421 (57.4)	−0.070	719 (60.1)	701 (58.6)	−0.032	418 (59.5)	413 (58.7)	−0.015
GLP-1 R agonists	8 (1.1)	8 (1.1)	0.000	15 (1.3)	12 (1.0)	−0.018	5 (0.7)	5 (0.7)	0.000
None	58 (7.9)	65 (8.9)	0.035	77 (6.4)	101 (8.4)	0.079	60 (8.5)	62 (8.8)	0.010
Comorbidity, *n* (%)									
Myocardial infarction	5 (0.7)	4 (0.5)	−0.018	27 (2.3)	28 (2.3)	0.005	2 (0.3)	2 (0.3)	0.000
Congestive heart failure	20 (2.7)	19 (2.6)	−0.008	71 (5.9)	74 (6.2)	0.010	31 (4.4)	33 (4.7)	0.013
Peripheral vascular disease	51 (6.9)	41 (5.6)	−0.053	89 (7.4)	99 (8.3)	0.030	43 (6.1)	41 (5.8)	−0.011
Cerebrovascular disease	46 (6.3)	47 (6.4)	0.006	101 (8.4)	111 (9.3)	0.030	41 (5.8)	39 (5.5)	−0.012
Dementia	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	–	0 (0.0)	0 (0.0)	0.000
Chronic pulmonary disease	112 (15.3)	106 (14.4)	−0.023	190 (15.9)	186 (15.5)	−0.009	104 (14.8)	112 (15.9)	0.031
Rheumatic disease	12 (1.6)	10 (1.4)	−0.025	16 (1.3)	12 (1.0)	−0.031	9 (1.3)	9 (1.3)	0.000
Peptic ulcer disease	65 (8.9)	71 (9.7)	0.028	134 (11.2)	134 (11.2)	0.000	65 (9.2)	67 (9.5)	0.009
Mild liver disease	204 (27.8)	202 (27.5)	−0.006	331 (27.7)	323 (27.0)	−0.015	181 (25.7)	188 (26.7)	0.023
Diabetes (uncomplicated)	31 (4.2)	28 (3.8)	−0.019	53 (4.4)	61 (5.1)	0.030	32 (4.6)	36 (5.1)	0.025
Diabetes (complicated)	265 (36.1)	256 (34.9)	−0.025	418 (34.9)	412 (34.4)	−0.010	231 (32.9)	237 (33.7)	0.018
Hemiplegia or paraplegia	0 (0.0)	0 (0.0)	–	1 (0.1)	2 (0.2)	0.016	1 (0.1)	1 (0.1)	0.000
Renal disease	6 (0.8)	4 (0.5)	−0.038	18 (1.5)	11 (0.9)	−0.055	4 (0.6)	5 (0.7)	0.016
Any malignancy	26 (3.5)	30 (4.1)	0.027	41 (3.4)	48 (4.0)	0.029	21 (3.0)	23 (3.3)	0.014
Moderate or severe liver disease	1 (0.1)	2 (0.3)	0.030	2 (0.2)	1 (0.1)	−0.020	3 (0.4)	3 (0.4)	0.000
Metastatic solid tumor	1 (0.1)	1 (0.1)	0.000	2 (0.2)	2 (0.2)	0.000	2 (0.3)	1 (0.1)	−0.022
AIDS/HIV	0 (0.0)	0 (0.0)	0.000	1 (0.1)	1 (0.1)	0.000	0 (0.0)	0 (0.0)	0.000
BMI (kg/m^2)									
<25, *n* (%)	267 (36.4)	304 (41.4)		358 (29.9)	442 (35.3)		196 (27.9)	238 (33.9)	

Table 1. (*Continued*)

Groups	Population I			Population II			Population III		
	SGLT2i *n* = 734	OAD *n* = 734	Standardized difference	SGLT2i *n* = 1197	OAD *n* = 1197	Standardized difference	SGLT2i *n* = 703	OAD *n* = 703	Standardized difference
≥25, <30, *n* (%)	350 (47.7)	305 (41.6)		582 (48.6)	523 (43.7)		335 (47.7)	302 (43.0)	
≥30, *n* (%)	117 (15.9)	125 (17.0)		257 (21.5)	252 (21.1)		172 (24.5)	163 (23.2)	
Mean (SD)	26.50 (3.60)	26.36 (4.29)	0.034	27.19 (3.94)	26.93 (4.33)	0.058	27.51 (4.02)	27.26 (4.69)	0.053
HbA1c (%)									
<7.0, *n* (%)	168 (22.9)	178 (24.3)		313 (26.1)	318 (26.6)		168 (23.9)	182 (25.9)	
≥7.0, <8.0, *n* (%)	293 (39.9)	291 (39.6)		464 (38.8)	490 (40.9)		272 (38.7)	285 (40.5)	
≥8.0, *n* (%)	273 (37.2)	265 (36.1)		420 (35.1)	389 (32.5)		263 (37.4)	236 (33.6)	
Mean (SD)	8.01 (1.52)	8.01 (1.66)	−0.001	7.86 (1.40)	7.86 (1.53)	−0.001	7.95 (1.43)	7.99 (1.64)	−0.026
eGFR (mL/min/1.73 m^2)									
≥90, *n* (%)	214 (29.2)	202 (27.5)	−0.036	310 (25.9)	304 (25.4)	−0.011	190 (27.0)	194 (27.6)	0.013
≥60, <90, *n* (%)	484 (65.9)	496 (67.6)	0.035	790 (66.0)	790 (66.0)	0.000	471 (67.0)	455 (64.7)	−0.048
≥45, <60, *n* (%)	34 (4.6)	34 (4.6)	0.000	82 (6.9)	91 (7.6)	0.029	37 (5.3)	48 (6.8)	0.064
≥30, <45, *n* (%)	2 (0.3)	2 (0.3)	0.000	14 (1.2)	10 (0.8)	−0.037	5 (0.7)	6 (0.9)	0.016
<30, *n* (%)	0 (0.0)	0 (0.0)	–	1 (0.1)	2 (0.2)	0.027	0 (0.0)	0 (0.0)	0.000
Mean (SD)	83.26 (17.60)	82.62 (16.05)		81.22 (17.26)	80.28 (16.39)		81.82 (16.34)	81.67 (16.22)	
SBP (mmHg), mean (SD)	126.4 (14.7)	126.5 (14.6)	−0.001	ND	ND		ND	ND	
DBP (mmHg), mean (SD)	79.1 (9.9)	79.2 (10.5)	−0.009	ND	ND		ND	ND	
Uric acid (mg/dL), mean (SD)	ND	ND		5.47 (1.20)	5.45 (1.20)	0.022	ND	ND	
LDL cholesterol (mg/dL), mean (SD)	ND	ND		ND	ND		126.3 (28.7)	126.9 (28.8)	−0.020
Triglyceride (mg/dL), mean (SD)	ND	ND		ND	ND		155.2 (105.2)	159.5 (124.6)	−0.037

BMI, body mass index; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; ND, not determined; OAD, other oral antidiabetic drugs except SGLT2i; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

Table 2 | Primary outcomes

Group	SGLT2i	OAD
Population I		
No. patients (*n*)	734	734
No. patients prescribed antihypertensive drugs (%)	50 (6.8)	76 (10.4)
95% CI	5.1–8.9	8.2–12.8
RR (vs OAD group)	0.66	
RR 95% CI	0.47–0.93	
P-value	0.015	
Population II		
No. patients (*n*)	1197	1197
No. patients prescribed antigout/antihyperuricemic drugs (%)	14 (1.2)	38 (3.2)
95% CI	0.6–2.0	2.3–4.3
RR (vs OAD group)	0.37	
RR 95% CI	0.20–0.68	
P-value	<0.001	
Population III		
Group	SGLT2i	OAD
No. patients (*n*)	703	703
No. patients prescribed antidyslipidemic drugs (%)	134 (19.1)	94 (13.4)
95% CI	16.2–22.2	10.9–16.1
RR (vs OAD group)	1.43	
RR 95% CI	1.12–1.82	
P-value	0.004	

CI, confidence interval; OAD, other oral antidiabetic drugs except sodium–glucose cotransporter 2 inhibitors; RR, risk ratio; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

groups (Table S4). The prescriptions of statins and fibrates were numerically higher in the SGLT2i group than in the OAD group.

Change from the baseline in each parameter

The change from baseline in blood pressure and clinical laboratory tests by their values and the percentage of the patients outside the reference range in medical checkups are shown in Tables S5–S7. In population I, both SBP and DBP were numerically reduced from baseline for patients who were not prescribed antihypertensives in the SGLT2i group. In contrast, no obvious change from baseline for both SBP and DBP in the OAD group was observed. Similarly, in population II, uric acid levels at the last medical checkup were also numerically lower than those at baseline for patients who were not newly prescribed antigout/antihyperuricemics in the SGLT2i group, but did not change in the OAD group. The percentage of patients with high blood pressure or high uric acid levels tended to be lower at the last physical examination than that at baseline in the SGLT2i group (Tables S5 and S6). In population III, the LDL cholesterol level and the percentage of patients with higher LDL cholesterol levels at the last medical checkup were comparable with those at baseline in patients who did not receive new prescriptions of antidyslipidemics in the SGLT2i group; however, these parameters were numerically decreased in the OAD group. The TG level and the percentage of patients with higher TG levels decreased from baseline to the last medical checkup in both treatment groups in patients who were not newly prescribed antidyslipidemics (Table S7).

DISCUSSION

In the present study, we compared the frequency of new prescriptions for concomitant diseases between the SGLT2i and OAD groups in patients with diabetes by using the JMDC Claims Database. A lower frequency of new prescriptions was shown for antihypertensives and antigout/antihyperuricemics in patients taking SGLT2i than those taking OADs. In contrast, the number of new prescriptions for antidyslipidemic drugs was higher in the SGLT2i group than that in the OAD group.

Most OADs have mild or neutral effects on blood pressure[19]. In contrast, SGLT2i reduce SBP and DBP without affecting heart rate[19]; for example, in clinical trials in Japanese patients with type 2 diabetes mellitus, SGLT2i showed a blood pressure-lowering effect over the treatment period[20]. In the EMPA-REG BP trial, empagliflozin decreased the 24-h mean SBP and DBP in patients with type 2 diabetes mellitus with hypertension, irrespective of antihypertensive medication use[21]. Furthermore, weight loss and high blood pressure are often associated with a high BMI[22,23]. In antihypertensive medication-free patients, the percentage of patients with high blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg, and SBP ≥140 mmHg or DBP ≥90 mmHg) did not change from baseline to the last medical checkup in the OAD group; however, the percentage numerically decreased in the SGLT2i group due to SGLT2 inhibition, which might have partially contributed to the decrease in blood pressure. It is suggested that the treatment with SGLT2i decreased the blood pressure in patients with diabetes mellitus and resulted in the less frequent prescriptions of antihypertensive medications.

The proportion of patients prescribed antigout/antihyperuricemics was also lower in the SGLT2i group than that in the OAD group. In the last medical checkup, the mean uric acid level was reduced, and the percentage of patients with higher uric acid levels decreased from baseline in the SGLT2i group. In a cohort study using a commercial claims database (IBM MarketScan) in the United States, the gout incidence rate was lower in patients with diabetes treated with SGLT2i than those treated with GLP-1 receptor agonist[24]. In subanalyses of CANVAS, EMPA-REG and DAPA-HF studies, not only were the serum uric acid levels decreased more in the SGLT2i group than those in the placebo group[25–28], but also the incidences of gout flare, antigout drugs initiation and adverse events related to hyperuricemia were lower in the SGLT2i group[25,26]. Therefore, our result in the real-world data is consistent with the previous large-scale clinical studies reporting lower onset of antigout/antihyperuricemic medication in the SGLT2i group.

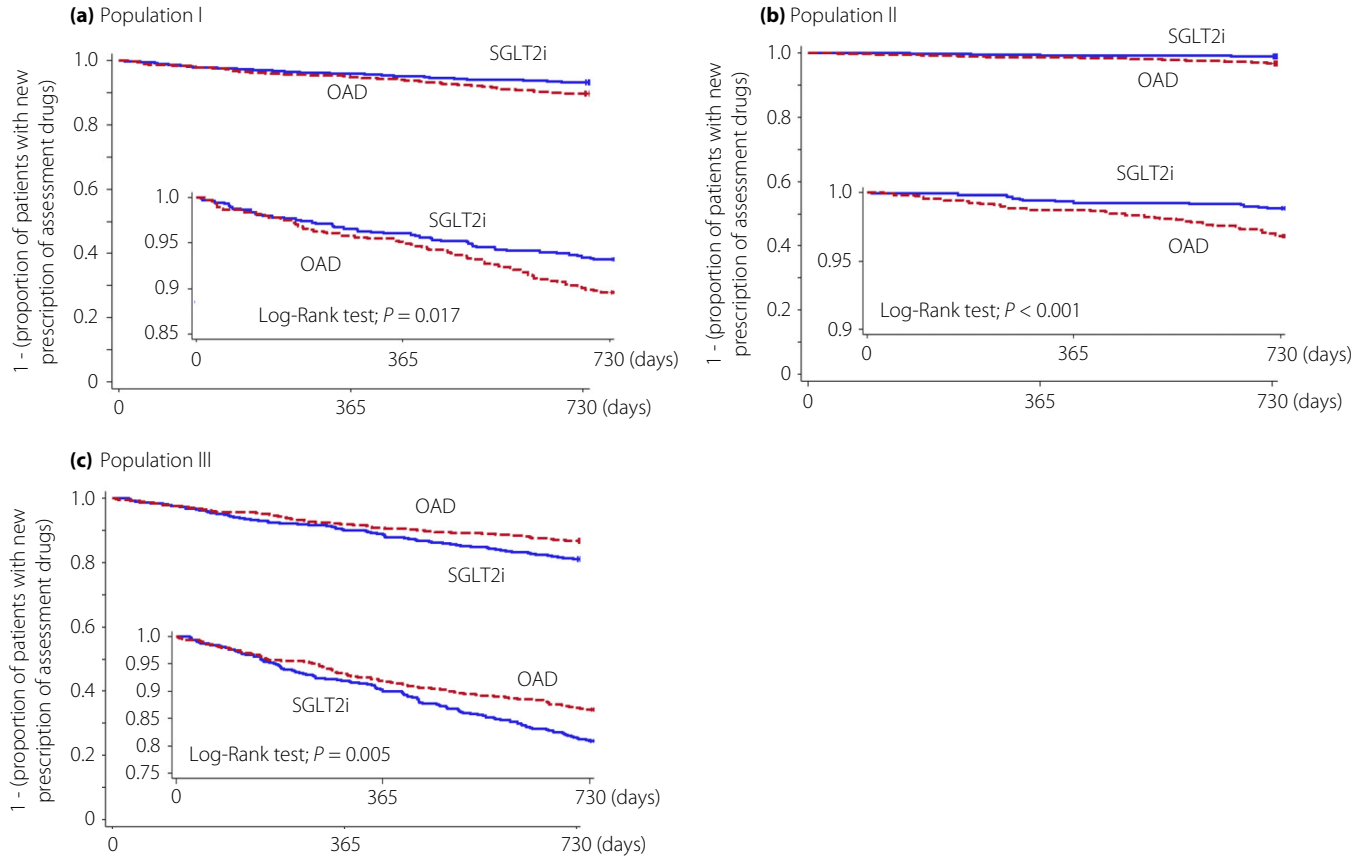

Figure 2 | Time to the first prescription of antihypertensive, antigout/antihyperuricemic or antidyslipidemic medications. The Kaplan–Meier curve is prepared for the propensity score calibration-matched rate of each population. (a) Population I, antihypertensive drugs. The incidence rates at day 730 from the index date are 25.95 and 40.28 per 1,000 person-years in the sodium–glucose cotransporter 2 inhibitor (SGLT2i) and oral antidiabetic drugs (OAD) groups, respectively. (b) Population II, antigout/antihyperuricemic drugs. The incidence rates at day 730 are 4.24 and 11.72 per 1,000 person-years in the SGLT2i and OAD groups, respectively. (c) Population III, antidyslipidemic drugs. The incidence rates at day 730 are 78.48 and 53.36 per 1,000 person-years in the SGLT2i and OAD groups, respectively.

As the mechanism of SGLT2i in reducing serum uric acid levels, it has been postulated that increased glucose levels in the proximal tubules by SGLT2i enhance urate excretion into the lumen through GLUT9 as an antiporter that mediates exchange of urate for glucose or fructose[29]. Additionally, the persistent inhibition of SGLT2 might downregulate xanthine oxidase through enhancing the sirtuin-1 signaling pathway[26]. Therefore, the low number of new prescriptions of antihyperuricemics in the SGLT2i group is likely to reflect the reduced serum uric acid level mediated by the aforementioned indirect uric acid-lowering effect of SGLT2i.

A higher percentage of patients were prescribed antidyslipidemic drugs in the SGLT2i group than those in the OAD group. SGLT2i have been reported to decrease TG, and mildly increase HDL and LDL cholesterol levels[30]. LDL cholesterol levels were elevated in patients on a low-carbohydrate diet or under fasting conditions[31–33], suggesting that the changes in lipid metabolism brought about by SGLT2i are based on calorie loss through increased urinary glucose excretion. It has also been proposed that SGLT2i switch energy metabolism from carbohydrates to fat oxidation to stimulate ketone body and hepatic cholesterol productions, resulting in a decrease in LDL receptors[34]. Furthermore, enhanced lipolysis of TG-rich lipoproteins through an increase in lipoprotein lipase activity mediates the TG-lowering effect of SGLT2i[35]. In diabetic animal models, empagliflozin promotes lipolysis of TG-rich lipoproteins and decreases LDL clearance[35]. Thus, it can be explained that LDL cholesterol levels were elevated owing to enhanced fat oxidation by SGLT2i in some patients, and that these patients were newly prescribed antidyslipidemic drugs.

The present study had some limitations. First, the JMDC Claims Database used in this study enables tracking of medical prescription records from multiple hospitals; however, the majority of our study population were workers in the database, withdrawal from health insurers due to retirement resulted in a small population of patients aged in their 60s and no patients aged ≥75 years. Second, the database consists of medical information of company employees and their families; the percentage of male patients is higher than that of patients with diabetes in general. Therefore, the present findings might not

be generalized especially to older or female patients with diabetes. Third, the impact of prescription changes in antidiabetic drugs was not analyzed, which might be a potential bias affecting prescription trends. Finally, the influence of the patient's lifestyle was not analyzed, because lifestyle assessments data, such as smoking, eating and exercise habits, are self-reports, and the data might include recall and report biases.

Under treatment with SGLT2i, new prescriptions for antihypertensives or antigout/antihyperuricemics were less frequent than those for OADs, probably due to a reduction of blood pressure and uric acid levels by SGLT2i. In contrast, the number of patients who were newly prescribed antidyslipidemics was slightly higher in the SGLT2i group than that in the OAD group. This might partly reflect the mild increase in the LDL cholesterol level associated with changes in energy metabolism caused by SGLT2i.

ACKNOWLEDGMENTS

The authors express their gratitude to the following co-workers: Hiroaki Fujii (Mitsubishi Tanabe Pharma Corporation) for analytical support and Akira Saito PhD (International Medical Translation Service, Inc.) for providing medical writing support funded by Mitsubishi Tanabe Pharma Corporation. This study was funded by Mitsubishi Tanabe Pharma Corporation.

DISCLOSURE

All the authors are employees of Mitsubishi Tanabe Pharma Corporation.

Approval of the research protocol: This study protocol has been reviewed and approved by the Mitsubishi Tanabe Pharma Corporation Ethics Committee on 28 July 2021 (Review No.: KENRIN H-21-015), and it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

REFERENCES

1. Bonora BM, Avogaro A, Fadini GP. Extraglycemic effects of SGLT2 inhibitors: a review of the evidence. *Diabetes Metab Syndr Obes* 2020; 13: 161–174.
2. Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. *Nat Rev Cardiol* 2020; 17: 761–772.
3. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007; 116: 894–900.
4. He J, Whelton PK. Elevated systolic blood pressure and risk of cardiovascular and renal disease: overview of evidence from observational epidemiologic studies and randomized controlled trials. *Am Heart J* 1999; 138: 211–219.
5. Appel LJ, Wright JT Jr, Greene T, *et al*. Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. *Arch Intern Med* 2008; 168: 832–839.
6. Klag MJ, Whelton PK, Randall BL, *et al*. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; 334: 13–18.
7. Crews DC, Plantinga LC, Miller ER 3rd, *et al*. Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension* 2010; 55: 1102–1109.
8. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 2099.
9. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
10. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
11. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
12. JMDC Claims Database. Available from: https://www.jmdc.co.jp/en/jmdc-claims-database/ Accessed March 2, 2022.
13. Quan H, Sundararajan V, Halfon P, *et al*. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43: 1130–1139.
14. Yamada S, Inoue G, Ooyane H, *et al*. Changes in body weight, dysglycemia, and dyslipidemia after moderately low-carbohydrate diet education (LOCABO Challenge Program) among workers in Japan. *Diabetes Metab Syndr Obes* 2021; 14: 2863–2870.
15. Tsushita K, SH A, Miura K, *et al*. Rationale and descriptive analysis of specific health guidance: the nationwide lifestyle intervention program targeting metabolic syndrome in Japan. *J Atheroscler Thromb* 2018; 25: 308–322.
16. Yamanaka H, Metabolism TG. Essence of the revised guideline for the management of hyperuricemia and gout. *Japan Med Assoc J* 2012; 55: 324–329.
17. Araki E, Goto A, Kondo T, *et al*. Japanese clinical practice guideline for diabetes 2019. *Diabetol Int* 2020; 11: 165–223.
18. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; 46: 399–424.
19. Ilias I, Thomopoulos C, Michalopoulou H, *et al*. Antidiabetic drugs and blood pressure changes. *Pharmacol Res* 2020; 161: 105108.
20. Inagaki N, Goda M, Yokota S, *et al*. Effects of baseline blood pressure and low-density lipoprotein cholesterol on safety and efficacy of canagliflozin in japanese patients with type 2 diabetes mellitus. *Adv Ther* 2015; 32: 1085–1103.

21. Mancia G, Cannon CP, Tikkanen I, *et al*. Impact of empagliflozin on blood pressure in patients with type 2 diabetes mellitus and hypertension by background antihypertensive medication. *Hypertension* 2016; 68: 1355–1364.
22. Neter JE, Stam BE, Kok FJ, *et al*. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension* 2003; 42: 878–884.
23. Reed JW. Impact of sodium-glucose cotransporter 2 inhibitors on blood pressure. *Vasc Health Risk Manag* 2016; 12: 393–405.
24. Fralick M, Chen SK, Patorno E, *et al*. Assessing the risk for gout with sodium-glucose cotransporter-2 inhibitors in patients with type 2 diabetes: a population-based cohort study. *Ann Intern Med* 2020; 172: 186–194.
25. Li J, Badve SV, Zhou Z, *et al*. The effects of canagliflozin on gout in type 2 diabetes: a post-hoc analysis of the CANVAS program. *Lancet Rheumatol* 2019; 1: e220–e228.
26. Ferreira JP, Inzucchi SE, Mattheus M, *et al*. Empagliflozin and uric acid metabolism in diabetes: a post hoc analysis of the EMPA-REG OUTCOME trial. *Diabetes Obes Metab* 2022; 24: 135–141.
27. Zhao Y, Xu L, Tian D, *et al*. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2018; 20: 458–462.
28. McDowell K, Welsh P, Docherty KF, *et al*. Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. *Eur J Heart Fail* 2022; 24: 1066–1076.
29. Chino Y, Samukawa Y, Sakai S, *et al*. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. *Biopharm Drug Dispos* 2014; 35: 391–404.
30. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, *et al*. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: a systematic review and meta-analysis of 48 randomized controlled trials. *Pharmacol Res* 2020; 160: 105068.
31. Mansoor N, Vinknes KJ, Veierød MB, *et al*. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. *Br J Nutr* 2016; 115: 466–479.
32. Sävendahl L, Underwood LE. Fasting increases serum total cholesterol, LDL cholesterol and apolipoprotein B in healthy, nonobese humans. *J Nutr* 1999; 129: 2005–2008.
33. Radhakishun N, Blokhuis C, van Vliet M, *et al*. Intermittent fasting during Ramadan causes a transient increase in total, LDL, and HDL cholesterols and hs-CRP in ethnic obese adolescents. *Eur J Pediatr* 2014; 173: 1103–1106.
34. Briand F, Mayoux E, Brousseau E, *et al*. Empagliflozin, via switching metabolism toward lipid utilization, moderately increases LDL cholesterol levels through reduced LDL catabolism. *Diabetes* 2016; 65: 2032–2038.
35. Basu D, Huggins LA, Scerbo D, *et al*. Mechanism of increased LDL (low-density lipoprotein) and decreased triglycerides with SGLT2 (sodium-glucose cotransporter 2) inhibition. *Arterioscler Thromb Vasc Biol* 2018; 38: 2207–2216.

SUPPORTING INFORMATION

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

Table S1 | Definitions of diseases, drugs, and procedures.

Table S2 | Background data of each population before matching.

Table S3 | Classification of initiation drugs at index date.

Table S4 | Medication class in each population.

Table S5 | Change from baseline in blood pressure and percentage of patients exceeding standard reference range at the last medical checkup in population I.

Table S6 | Change from baseline in uric acid and percentage of patients with treatment recommendation at the last medical checkup in population II.

Table S7 | Change from baseline in lipid parameters and percentage of patients exceeding standard reference range at the last medical checkup in population III.