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Lower risk of gout in sodium glucose cotransporter 2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP4) inhibitors in type-2 diabetes

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Abstract

Objectives: The effects of sodium-glucose cotransporter 2 inhibitors (SGLT2I) *vs* dipeptidyl peptidase-4 inhibitors (DPP4I) on the risk of new-onset gout remains unknown. This study aims to compare the effects of SGLT2I against DPP4I on gout risks.

Methods: This was a retrospective population-based cohort study of patients with type-2 diabetes mellitus treated with SGLT2I or DPP4I between 1 January 2015 and 31 December 2020 in Hong Kong. The study outcomes are new-onset gout and all-cause mortality. Propensity score matching (1:1 ratio) between SGLT2I and DPP4I was performed. Univariable and multivariable Cox regression models were conducted. Competing risks models and multiple approaches based on the propensity score were applied.

Results: This study included 43 201 patients [median age: 63.23 years old (Interquartile range, IQR): 55.21–71.95, 53.74% males; SGLT2I group: $n = 16\,144$; DPP4I group: $n = 27\,057$] with a median follow-up of 5.59 years (IQR: 5.27–5.81 years) since initial drug exposure. The incidence rate of developing gout [Incidence rate (IR): 2.5; 95% CI: 2.2, 2.9] among SGLT2I users was significantly lower than DPP4I users (IR: 5.2; 95% CI: 4.8, 5.8). SGLT2I was associated with 51% lower risks of gout (HR: 0.49; 95% CI: 0.42, 0.58; P-value < 0.0001) and 51% lower risks of all-cause mortality (HR: 0.49; 95% CI: 0.42, 0.58; P-value < 0.0001) after adjusting for significant demographics, past comorbidities, medications and laboratory results. The results remained consistent on competing risk and other propensity score approaches.

Conclusions: SGLT2I use was associated with lower risks of new gout diagnosis compared with DPP4I use.

Keywords: SGLT2, DPP4, anti-diabetic drugs, diabetes mellitus, metabolic syndrome, gout, crystalline arthropathy, mortality, retrospective study, cohort study

Introduction

Type 2 diabetes mellitus (T2DM) is a complex multi-systemic disorder that predisposes to adverse events involving different organs, such as chronic renal disease, retinopathy and stroke. It was estimated that 462 million people of the global population were affected by T2DM in 2017 [1]. Gout is a condition known to be associated with T2DM under the umbrella of metabolic syndrome [2, 3]. Given the lifestyle and dietary changes in the 21st century, the prevalence of gout continued to increase [4, 5]. Gout was also suggested to be associated with higher risks of hypertension, obesity and

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Rheumatology key messages

- SGLT2I was associated with a 51% lower risk of gout and all-cause mortality compared to DPP4I among type 2 diabetes patients after adjustments.
- Patients are recommended to use SGLT2I instead of DPP4I in terms of gout prevention.

cardiovascular diseases [6, 7]. Gout and T2DM were linked to hyperuricaemia, as hyperuricaemia is involved in the development of insulin resistance [8]. Besides, both conditions express pathological activation of interleukin-1β [9].

Previous studies suggested the use of anti-diabetic medications may reduce the risks of gout. Sodium-glucose cotransporter 2 inhibitors (SGLT2I) and dipeptidyl peptidase-4 inhibitors (DPP4I) are novel second-line anti-diabetic agents. Both of the newer drug classes have reduced risks of hypoglycaemia compared with the older generation of second-line anti-diabetic medications. DPP4I helps blood glucose control by inhibiting the degradation of incretins and increasing the level of glucagon-like peptide-1 (GLP-1) [10, 11]. It was suggested that some DPP4I, such as linagliptin and teneligliptin, may reduce uric acid levels among T2DM patients and provide extra benefits against gout [12, 13]. Meanwhile, SGLT2I reduces the blood glucose level by blocking the glucose reabsorption at the S1 segment of the proximal convoluted tubules of the kidney [14]. Therefore, it attains blood glucose control by an insulin-independent method [15]. SGLT2I was reported to help lower the serum uric acid level by increasing the urinary uric acid excretion [16, 17]. This works via the SGLT2I induced glycosuria, which changes the uric acid transportation involving channels such as the glucose transporter 9 (GLUT9) [18, 19].

It was previously suggested that SGLT2I reduce the risks of gout by 40% compared with the GLP-1 agonist [20]. It was also suggested that SGLT2I had a lower risk of gout compared with DPP4I after 2.5 years of follow-up [21]. Meanwhile, in the post-hoc analysis of the EMPA-REG study analysis regarding empagliflozin, empagliflozin was demonstrated to reduce the episodes of gout or the use of antigout medications [22]. Furthermore, in a recent meta-analysis, it was demonstrated that the anti-gout effect of SGLT2I is a class effect among T2DM patients [23]. As SGLT2I and DPP4I as hypoglycaemic agents are now more frequently prescribed with similar efficacy in controlling glucose variability, it is important to investigate and compare their effects on gout. Therefore, the present study aimed to compare the incidence of gout between SGLT2I and DPP4I patients among T2DM patients in Hong Kong 5.6 years follow-up.

Methods

Study design and population

This was a retrospective, territory-wide cohort study on patients with T2DM treated with SGLT2I or DPP4I between 1 January 2015 and 31 December 2020 in Hong Kong. This study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee and complied with the Declaration of Helsinki. The retrospective study was based on deidentified data and thus the written informed consent was waived by the committee. Patients during the aforementioned period were enrolled and followed up until 31 December 2020 or until death. Patients were excluded once by the following criteria (Fig. 1): with both DPP4I and SGLT2I use, without complete demographics data, without mortality data, with HIV infection/AIDS, with pregnancy during follow-up, <18 years old, with a prior diagnosis of gout, and patients died within 30 days at initial drug exposure. This cohort has been used to study cardiovascular outcomes [24]. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS), a city-wide database that centralizes patient information from individual local hospitals to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results and drug treatment details. The system has been previously used by both our team and other teams in Hong Kong to conduct epidemiological studies on diabetes [25–28] and gout [29]. Clinical and biochemical data were extracted for the present study. Patients' demographics included gender and age of initial drug use (baseline). Prior comorbidities were extracted based on standard *International Classification of Diseases Ninth Edition* (ICD-9) codes (Supplementary Table S1, available at *Rheumatology* online). Charlson's standard comorbidity index was also calculated.

In addition, we also calculated biomarkers, including the estimated glomerular filtration rate based on the abbreviated modification of diet in renal disease (aMDRD) formula [30]. Mortality was recorded using the *International Classification of Diseases Tenth Edition* (ICD-10) coding. Medication histories and baseline laboratory examinations results were extracted. The variability measures of the laboratory examination were also calculated (Supplementary Table S2, available at *Rheumatology* online).

Study outcomes and statistical analysis

The study outcomes were new onset gout and all-cause mortality. The all-cause mortality was assessed to ensure that any decrease in the risk of gout was not associated with increased mortality.

The end point date of interest is the date when patients developed gout, died, or until 31 December 2020. Mortality data were obtained from the Hong Kong Death Registry, a population-based official government registry with the registered death records of all Hong Kong citizens linked to CDARS.

Descriptive statistics were used to summarize baseline clinical and biochemical characteristics of patients with SGLT2I and DPP4I use. For baseline clinical characteristics, the continuous variables were presented as mean (95% CI/S.D.) and the categorical variables were presented as total numbers (percentage). Continuous variables were compared using the two-tailed Mann–Whitney *U* test, *t* test or Wilcoxon rank-sum test, while the two-tailed χ^2 test with Yates' correction or Fisher's exact test was used to test 2×2 contingency data. Propensity score matching with 1:1 ratio for SGLT2I use *vs* DPP4I use based on demographics, Charlson comorbidity index, prior comorbidities, non-SGLT2I/DPP4I medications (including other anti-diabetic drugs) were performed using the nearest neighbour search strategy. We used Stata software (Version

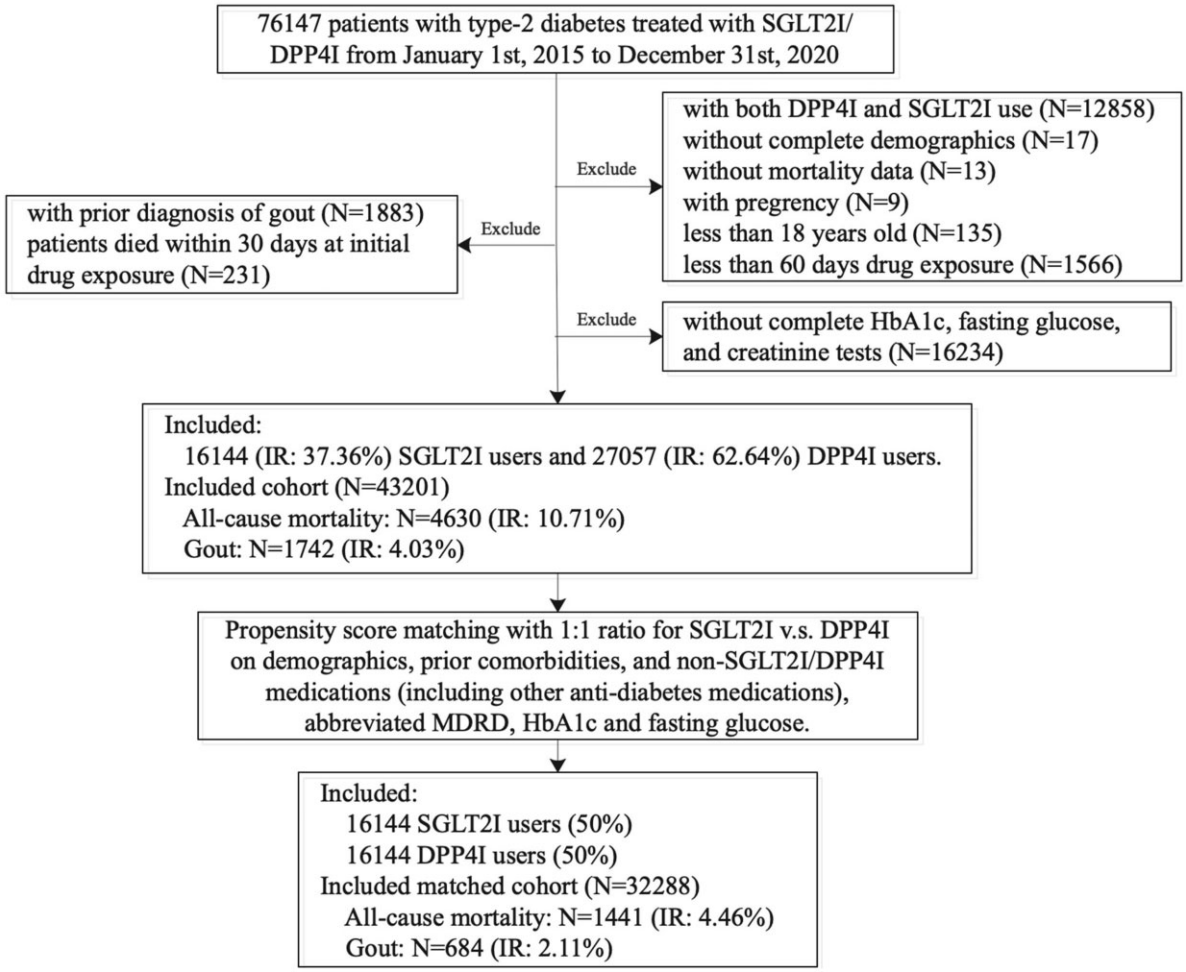

Figure 1. Procedures of data processing for the study cohort. DPP4I: dipeptidyl peptidase-4 inhibitors; IR: incidence rate; SGLT2I: sodium-glucose cotransporter-2 inhibitors

16.0) to conduct the propensity score matching procedures. The propensity score matching comparisons and checking of proportional hazards assumption are shown in Supplementary Fig. S1, available at *Rheumatology* online. The nearest neighbour search strategy with calliper of 0.1 was used.

Baseline characteristics between patients with SGLT2I and DPP4I use before and after matching were compared with standardized mean difference (SMD). SMD < 0.20 was regarded as well-balanced. Cox regression was used to identify significant risk predictors of new onset gout and all-cause mortality. Multiple propensity score approaches were used, including propensity score stratification [31], inverse probability of treatment weighting [32], and stable inverse probability weighting [33]. The hazard ratio (HR), 95% CI and *P*-value were reported. Statistical significance is defined as *P*-value <0.05. All statistical analyses were performed with RStudio software v1.1.456 and Python v3.6.

Results

Basic characteristics

This retrospective cohort was composed of 76 147 patients with T2DM treated with SGLT2I or DPP4I between 1 January 2015 and 31 December 2020 in Hong Kong. Patients during the aforementioned period were enrolled and followed up until 31 December 2020 or until death. Patients were excluded once by the following criteria (Fig. 1): with both DPP4I and SGLT2I use ($n = 12\,858$), without complete demographics ($n = 17$), without mortality data ($n = 13$), with pregnancy ($n = 9$), <18 years old ($n = 135$), with a prior diagnosis of gout ($n = 1883$), patients died within 30 days at initial drug exposure ($n = 231$), and patients without complete HbA1c, fasting glucose and creatinine tests ($n = 16\,234$) were excluded.

The study cohort composed of a total of 43 201 patients with T2DM {median age: 63.23 years old [interquartile range (IQR): 55.21–71.95]; 53.74% males}, of which 16 144 patients (35.55%) used SGLT2I and 27 057 patients (64.45%) used DPP4I. After a median follow-up of 5.6 (IQR: 5.3–5.8) years after initial drug exposure, 2343 patients (3.84%) developed gout, and 6622 patients (10.85%) passed away. After 1:1 propensity score matching, 684 (2.11%) patients developed new-onset gout and 1441 (2.21%) patients passed away. The characteristics of patients with SGLT2I or DPP4I users, new-onset gout and all cause-mortality before and after propensity score matching (1:1) are shown in Table 1, Supplementary Tables S3 and S4 (available at *Rheumatology* online). Among 43 201 patients, 7020 patients

Table 1. Baseline and clinical characteristics of patients with SGLT2I users *vs* DPP4I users before and after propensity score matching (1:1)

Characteristics	Before matching All ($n = 43\,201$) mean(S.D.); n or count(%)	SGLT2I ($n = 16\,144$) mean(S.D.); n or count(%)	DPP4I ($n = 27\,057$) mean(S.D.); n or count(%)	SMD	After matching All ($n = 32\,288$) mean(S.D.); n or count(%)	SGLT2I ($n = 16\,144$) mean(S.D.); n or count(%)	DPP4I ($n = 16\,144$) mean(S.D.); n or count(%)	SMD
Demographics								
Male gender	23 220(53.74%)	9295(57.57%)	13 925(51.46%)	0.12	17 571(54.41%)	9295(57.57%)	8276(51.26%)	0.13
Female gender	19 981(46.25%)	6849(42.42%)	13 132(48.53%)	0.12	14 717(45.58%)	6849(42.42%)	7868(48.73%)	0.13
Baseline age, years	63.4(12.3); $n = 43\,201$	58.2(10.9); $n = 16\,144$	66.5(12.1); $n = 27\,057$	0.72[a]	59.1(10.9); $n = 32\,288$	58.2(10.9); $n = 16\,144$	60.0(10.9); $n = 16\,144$	0.16
18–50	5460(12.63%)	3212(19.89%)	2248(8.30%)	0.34[a]	5965(18.47%)	3212(19.89%)	2753(17.05%)	0.07
50–60	11 764(27.23%)	5800(35.92%)	5964(22.04%)	0.31[a]	11 373(35.22%)	5800(35.92%)	5573(34.52%)	0.03
60–70	13 223(30.60%)	5032(31.16%)	8191(30.27%)	0.02	10 258(31.77%)	5032(31.16%)	5226(32.37%)	0.03
70–80	8281(19.16%)	1749(10.83%)	6532(24.14%)	0.36[a]	3781(11.71%)	1749(10.83%)	2032(12.58%)	0.05
>80	4477(10.36%)	353(2.18%)	4124(15.24%)	0.48[a]	913(2.82%)	353(2.18%)	560(3.46%)	0.08
Past comorbidities								
Charlson standard comorbidity index	2.2(1.5); $n = 43\,201$	1.6(1.3); $n = 16\,144$	2.5(1.6); $n = 27\,057$	0.61[a]	1.7(1.3); $n = 32\,288$	1.6(1.3); $n = 16\,144$	1.7(1.3); $n = 16\,144$	0.08
Diabetes with chronic complication	609(1.40%)	224(1.38%)	385(1.42%)	<0.01	446(1.38%)	224(1.38%)	222(1.37%)	<0.01
Diabetes without chronic complication	943(2.18%)	410(2.53%)	533(1.96%)	0.04	809(2.50%)	410(2.53%)	399(2.47%)	<0.01
Heart failure	1502(3.47%)	416(2.57%)	1086(4.01%)	0.08	821(2.54%)	416(2.57%)	405(2.50%)	<0.01
Hyperlipidaemia	1428(3.30%)	685(4.24%)	743(2.74%)	0.08	1316(4.07%)	685(4.24%)	631(3.90%)	0.02
Hypertension	11 841(27.40%)	4327(26.80%)	7514(27.77%)	0.02	8623(26.70%)	4327(26.80%)	4296(26.61%)	<0.01
Hypoglycaemia	423(0.97%)	57(0.35%)	366(1.35%)	0.11	113(0.34%)	57(0.35%)	56(0.34%)	<0.01
Ischaemic heart disease	4959(11.47%)	2269(14.05%)	2690(9.94%)	0.13	4277(13.24%)	2269(14.05%)	2008(12.43%)	0.05
Liver diseases	1146(2.65%)	573(3.54%)	573(2.11%)	0.09	1123(3.47%)	573(3.54%)	550(3.40%)	0.01
Acute myocardial infarction	1352(3.12%)	603(3.73%)	749(2.76%)	0.05	1181(3.65%)	603(3.73%)	578(3.58%)	0.01
Peripheral vascular disease	394(0.91%)	103(0.63%)	291(1.07%)	0.05	206(0.63%)	103(0.63%)	103(0.63%)	<0.01
Chronic kidney diseases	8649(20.02%)	826(5.11%)	7823(28.91%)	0.67[a]	1681(5.20%)	826(5.11%)	855(5.29%)	0.01
Stroke/transient ischemic attack	1567(3.62%)	470(2.91%)	1097(4.05%)	0.06	931(2.88%)	470(2.91%)	461(2.85%)	<0.01
Atrial fibrillation	1211(2.80%)	367(2.27%)	844(3.11%)	0.05	727(2.25%)	367(2.27%)	360(2.22%)	<0.01
Anaemia	2049(4.74%)	434(2.68%)	1615(5.96%)	0.16	856(2.65%)	434(2.68%)	422(2.61%)	<0.01
Overweight, obesity and hyperalimentation	363(0.84%)	293(1.81%)	70(0.25%)	0.15	570(1.76%)	293(1.81%)	277(1.71%)	0.01
Alcohol dependence	98(0.22%)	25(0.15%)	73(0.26%)	0.02	50(0.15%)	25(0.15%)	25(0.15%)	<0.01
Smoking	673(1.55%)	96(0.59%)	577(2.13%)	0.13	192(0.59%)	96(0.59%)	96(0.59%)	<0.01
Cancer	1340(3.10%)	376(2.32%)	964(3.56%)	0.07	746(2.31%)	376(2.32%)	370(2.29%)	<0.01
Medications								
SGLT2I frequency	8.3(10.4); $n = 16\,144$	8.3(10.4); $n = 16\,144$	—	—	8.3(10.4); $n = 16\,144$	8.3(10.4); $n = 16\,144$	—	—
DPP4I frequency	5.3(7.5); $n = 27\,057$	—	5.3(7.5); $n = 27\,057$	—	7.1(6.8); $n = 16\,144$	—	7.1(6.8); $n = 16\,144$	—
SGLT2I duration, days	621.1(696.8); $n = 16\,144$	621.1(696.8); $n = 16\,144$	—	—	621.1(696.8); $n = 16\,144$	621.1(696.8); $n = 16\,144$	—	—
DPP4I duration, days	516.8(284.9); $n = 27\,057$	—	516.8(284.9); $n = 27\,057$	—	564.1(283.3); $n = 16\,144$	—	564.1(283.3); $n = 16\,144$	—

(continued)

Table 1. (continued)

Characteristics	Before matching All ($n = 43\,201$) mean(S.D.); n or count(%)	SGLT2I ($n = 16\,144$) mean(S.D.); n or count(%)	DPP4I ($n = 27\,057$) mean(S.D.); n or count(%)	SMD	After matching All ($n = 32\,288$) mean(S.D.); n or count(%)	SGLT2I ($n = 16\,144$) mean(S.D.); n or count(%)	DPP4I ($n = 16\,144$) mean(S.D.); n or count(%)	SMD
Metformin	39 091(90.48%)	15 157(93.88%)	23 934(88.45%)	0.19	30 392(94.12%)	15 157(93.88%)	15 235(94.36%)	0.02
Sulphonylurea	34 011(78.72%)	11 775(72.93%)	22 236(82.18%)	0.22[a]	24 074(74.56%)	11 775(72.93%)	12 299(76.18%)	0.07
Insulin	23 053(53.36%)	8948(55.42%)	14 105(52.13%)	0.07	17 704(54.83%)	8948(55.42%)	8756(54.23%)	0.02
Acarbose	1301(3.01%)	788(4.88%)	513(1.89%)	0.17	1510(4.67%)	788(4.88%)	722(4.47%)	0.02
Thiozolidinedone	8989(20.80%)	4906(30.38%)	4083(15.09%)	0.37[a]	9041(28.00%)	4906(30.38%)	4135(25.61%)	0.11
Glucagon-like peptide-1 receptor agonists	1461(3.38%)	1328(8.22%)	133(0.49%)	0.39[a]	2242(6.94%)	1328(8.22%)	914(5.66%)	0.1
Statins and fibrates	21 888(50.66%)	13 461(83.38%)	8427(31.14%)	1.24[a]	25 795(79.89%)	13 461(83.38%)	12 334(76.39%)	0.17
Calculated biomarkers								
Abbreviated MDRD, ml/min/1.73m^2	80.1(28.6); $n = 43\,201$	90.6(23.8); $n = 16\,144$	73.9(29.4); $n = 27\,057$	0.63[a]	90.1(23.2); $n = 32\,288$	90.6(23.8); $n = 16\,144$	89.7(22.7); $n = 16\,144$	0.04
<15	507(1.17%)	15(0.09%)	492(1.81%)	0.18	30(0.09%)	15(0.09%)	15(0.09%)	<0.01
(15–30)	1225(2.83%)	42(0.26%)	1183(4.37%)	0.28[a]	84(0.26%)	42(0.26%)	42(0.26%)	<0.01
(30–45)	3383(7.83%)	274(1.69%)	3109(11.49%)	0.40[a]	549(1.70%)	274(1.69%)	275(1.70%)	<0.01
(45–60)	5169(11.96%)	986(6.10%)	4183(15.45%)	0.31[a]	1956(6.05%)	986(6.10%)	970(6.00%)	<0.01
(60–90]	17 059(39.48%)	6963(43.13%)	10 096(37.31%)	0.12	13 927(43.13%)	6963(43.13%)	6964(43.13%)	<0.01
>90	15 858(36.70%)	7864(48.71%)	7994(29.54%)	0.40[a]	15 742(48.75%)	7864(48.71%)	7878(48.79%)	<0.01
Neutrophil-to-lymphocyte ratio	3.5(4.7); $n = 21\,883$	2.9(3.7); $n = 8769$	4.0(5.2); $n = 13\,114$	0.23[a]	3.0(3.7); $n = 15\,450$	2.9(3.7); $n = 8769$	3.2(3.7); $n = 6681$	0.07
Laboratory examinations								
Urate, mmol/L	0.4(0.1); $n = 7020$	0.37(0.1); $n = 3170$	0.41(0.12); $n = 3850$	0.4[a]	0.4(0.1); $n = 4949$	0.4(0.1); $n = 3170$	0.3(0.1); $n = 1779$	0.18
Urate Q1	1683.0(3.89%)	930.0(5.76%)	753.0(2.78%)	0.15	1153.0(3.57%)	665.0(4.11%)	488.0(3.02%)	0.06
Urate Q1–Q3	3623.0(8.38%)	1731.0(10.72%)	1892.0(6.99%)	0.13	2580.0(7.99%)	1677.0(10.38%)	903.0(5.59%)	0.18
Urate Q3	1714.0(3.96%)	509.0(3.15%)	1205.0(4.45%)	0.07	1216.0(3.76%)	828.0(5.12%)	388.0(2.40%)	0.14
Albumin, g/L	41.6(4.0); $n = 33\,827$	42.5(3.3); $n = 13\,962$	41.0(4.3); $n = 19\,865$	0.38[a]	42.3(3.5); $n = 25\,404$	42.5(3.3); $n = 13\,962$	42.1(3.7); $n = 11\,442$	0.12
Urea, mmol/L	6.6(3.6); $n = 43\,097$	5.7(2.0); $n = 16\,110$	7.1(4.2); $n = 26\,987$	0.44[a]	5.6(2.0); $n = 32\,195$	5.7(2.0); $n = 16\,110$	5.6(2.0); $n = 16\,085$	0.05
Creatinine, umol/L	95.2(78.6); $n = 43\,201$	78.1(27.6); $n = 16\,144$	105.5(95.6); $n = 27\,057$	0.39[a]	77.6(29.0); $n = 32\,288$	78.1(27.6); $n = 16\,144$	77.1(30.3); $n = 16\,144$	0.04
Triglyceride, mmol/L	1.7(1.5); $n = 41\,581$	1.8(1.8); $n = 15\,692$	1.6(1.3); $n = 25\,889$	0.1	1.7(1.6); $n = 31\,327$	1.8(1.8); $n = 15\,692$	1.7(1.3); $n = 15\,635$	0.07
Low-density lipoprotein, mmol/L	2.4(0.8); $n = 40\,890$	2.39(0.8); $n = 15\,427$	2.38(0.81); $n = 25\,463$	0.02	2.4(0.8); $n = 30\,742$	2.39(0.8); $n = 15\,427$	2.45(0.78); $n = 15\,315$	0.07
High-density lipoprotein, mmol/L	1.2(0.3); $n = 41\,532$	1.17(0.31); $n = 15\,671$	1.22(0.34); $n = 25\,861$	0.16	1.2(0.3); $n = 31\,305$	1.17(0.31); $n = 15\,671$	1.22(0.33); $n = 15\,634$	0.15
Total cholesterol, mmol/L	4.3(1.0); $n = 41\,612$	4.34(1.01); $n = 15\,703$	4.32(0.98); $n = 25\,909$	0.01	4.4(1.0); $n = 31\,347$	4.3(1.0); $n = 15\,703$	4.4(0.9); $n = 15\,644$	0.06
Haemoglobin A1C, %	8.1(1.6); $n = 43\,201$	8.3(1.6); $n = 16\,144$	7.9(1.5); $n = 27\,057$	0.25*	8.2(1.5); $n = 32\,288$	8.3(1.6); $n = 16\,144$	8.2(1.5); $n = 16\,144$	0.1
Fasting glucose, mmol/L	8.9(3.9); $n = 43\,201$	9.2(3.6); $n = 16\,144$	8.7(4.0); $n = 27\,057$	0.13	9.1(3.5); $n = 32\,288$	9.2(3.6); $n = 16\,144$	9.0(3.3); $n = 16\,144$	0.07

[a] for SMD $\geq$0.2. CV: coefficient of variation; DPP4I: dipeptidyl peptidase-4 inhibitor; SGLT2I: sodium glucose cotransporter-2 inhibitor.

had the urate level. After matching, patients on SGLT2I had a mean urate level of 0.4 mmol/l, and patients on DPP4I had a mean urate level of 0.3 mmol/l. The characteristics of the patients stratified by the demographics and the urate levels are also shown in Supplementary Tables S5 and S6 (available at *Rheumatology* online). In the matched cohort, the incidence of gout among the SGLT2I users was 2.5 (95% CI: 2.2, 2.9), and the incidence among the DPP4I user was 5.2 (95% CI: 4.8, 5.8) (Table 2).

Cox regression analyses

Univariable Cox analysis identified the significant risk factors for gout and all-cause mortality before and after propensity score matching (Supplementary Table S7, available at *Rheumatology* online). The cumulative incidence curves for gout and all-cause mortality stratified by SGLT2I and DPP4I demonstrated that SGLT2I had significantly lower cumulative hazards for both gout and all-cause mortality than DPP4I (Fig. 2). In the multivariable Cox analysis, SGLT2I was associated with lower risks for gout (HR: 0.49; 95% CI: 0.42, 0.58; *P*-value < 0.0001) and lower risks of all-cause mortality (HR: 0.49; 95% CI: 0.43, 0.55; *P*-value < 0.0001) after adjusting for significant demographics, past comorbidities, medications, MDRD, HbA1c and fasting glucose in the matched cohort (Table 3). The risks of gout were also compared among the individual SGLT2I drugs in the matched cohort. Among the SGLT2I, dapagliflozin was the most commonly prescribed drug (58.98%), followed by canagliflozin (22.86%), empagliflozin (20.03%) and ertugliflozin (10.85%) (Supplementary Table S8, available at *Rheumatology* online). In particular, dapagliflozin (HR: 0.49; 95% CI: 0.40, 0.60; *P*-value < 0.0001), canagliflozin (HR: 0.70; 95% CI: 0.53, 0.91; *P*-value = 0.0080) and ertugliflozin (HR: 0.60; 95% CI: 0.40, 0.90; *P*-value = 0.0141) were associated with lower risks of gout.

Sensitivity analysis

The sensitivity analyses were conducted to confirm the outcome of our study. SGLT2I was associated with a significantly lower risks of gout after adjusting for urate level (HR: 0.29, 95% CI: 0.22, 0.39; *P*-value < 0.0001) (Supplementary Table S9, available at *Rheumatology* online). SGLT2I use was associated with lower risks for gout (HR: 0.45, 95% CI: 0.37, 0.55; *P*-value < 0.0001) and mortality (HR: 0.52; 95% CI: 0.46, 0.60; *P*-value < 0.0001) in the matched cohort with one-year lag time. Cause-specific and subdistribution hazard models were conducted to further examine the effects of SGLT2I and DPP4I on gout and all-cause mortality (Supplementary Table S10, available at *Rheumatology* online). The models validated the same observation that SGLT2I was associated with a lower risk of gout and all-cause mortality than DPP4I for the T2DM patients after 1:1 propensity score matching. Furthermore, the comparison between SGLT2I/DPP4I was also validated using different propensity score approaches (Supplementary Table S11, available at *Rheumatology* online). The effects of the SGLT2I *vs* DPP4I were further investigated in different subgroups. SGLT2I users have a consistently lower risk for both new-onset gout and all-cause mortality regardless of age and sex (Supplementary Figs S2 and S3, available at *Rheumatology* online). At 2.5 years of follow up, SGLT2I was associated with lower risks of new-onset gout compared with DPP4I after adjusting for the significant demographics, past comorbidities, medications, urate, MDRD, HbA1c and fasting glucose (HR: 0.59, 95% CI: 0.32, 0.79; *P*-value < 0.0001) (Supplementary Tables S12 and S13, available at *Rheumatology* online).

Discussion

In this population-based cohort study, we demonstrated that SGLT2I was associated with lower risks of gout compared with DPP4I after adjustments. SGLT2I was also associated with lower all-cause mortality compared with DPP4I while lowering the risks of gout. The association was consistent among different sex and age group. This study confirms the effects of SGLT2I and DPP4I on gout after 5.6 years of follow-up [21].

SGLT2I is a commonly prescribed second-line antidiabetic drug that controls the blood glucose level by increasing urine glucose elimination [34, 35]. Our team has previously reported that SGLT2I use was associated with lower risks of

Table 2. Person-year statistics of adverse outcomes in the matched cohort

Gout				All-cause mortality			
DPP4I users	**Person-year**	**Number of events**	**IR[95% CI]**	**DPP4I users**	**Person-year**	**Number of events**	**IR[95% CI]**
Total	86 990.4	457	5.2[4.8–5.8]	Total	88 098.8	1002	11.4[10.7–12.1]
Year 1	16 104.8	71	4.4[3.5–5.6]	Year 1	16 137	22	1.4[0.9–2.1]
Year 2	15 961.5	88	5.5[4.5–6.8]	Year 2	16 073.7	104	6.5[5.3–7.8]
Year 3	15 752.6	33	2.1[1.5–2.9]	Year 3	15 920.9	210	13.2[11.5–15.1]
Year 4	15 472.1	92	5.9[4.8–7.3]	Year 4	15 675	261	16.7[14.7–18.8]
Year 5 or above	23 699.4	173	7.3[6.3–8.5]	Year 5 or above	24 292.2	405	16.7[15.1–18.4]
SGLT2I users	**Person-year**	**Number of events**	**IR[95% CI]**	**SGLT2I users**	**Person-year**	**Number of events**	**IR[95% CI]**
Total	89 375.8	227	2.5[2.2-2.9]	Total	90 025.9	439	4.9[4.4–5.4]
Year 1	16 115.9	45	2.8[2.1-3.7]	Year 1	16 144	0	—
Year 2	16 073.2	36	2.2[1.6-3.1]	Year 2	16 136.8	22	1.4[0.9–2.1]
Year 3	16 002.1	36	2.2[1.6-3.1]	Year 3	16 098.3	57	3.5[2.7–4.6]
Year 4	15 878.5	58	3.7[2.8-4.7]	Year 4	16 021.4	101	6.3[5.2–7.7]
Year 5 or above	25 306.1	52	2.1[1.5-2.7]	Year 5 or above	25 625.4	259	10.1[8.9–11.4]
Overall	176 366.2	684	3.9[3.6-4.2]	Overall	178 124.7	1441	8.1[7.7–8.5]

IR: Incidence rate.

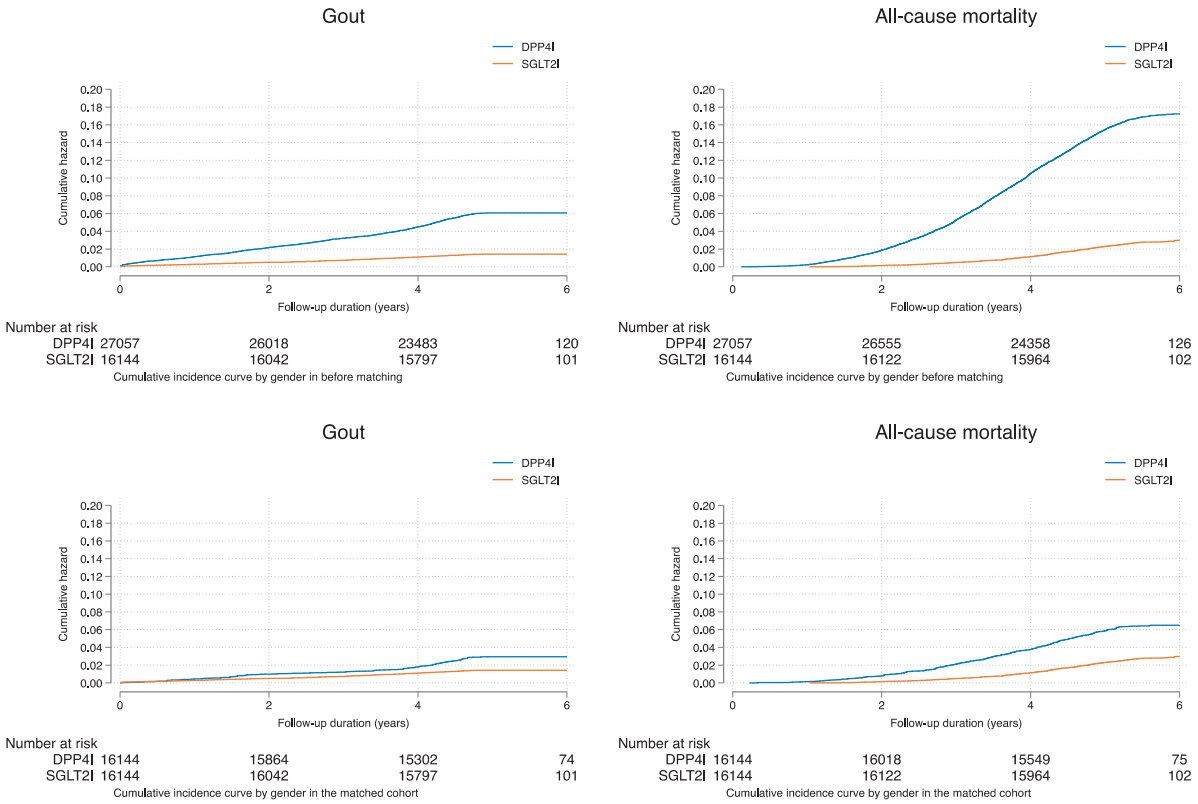

Figure 2. Cumulative incidence of gout and all-cause mortality between SGLT2I and DPP4I before and after matching

stroke, myocardial infarction, heart failure, atrial fibrillation, stroke and dementia [36]. This study extends these findings to new diagnoses of gout. Gout has an intimal relationship with diabetes mellitus. Most of the urate was reabsorbed by the urate transporter 1 (URAT1) protein and ATP-binding cassette subfamily G member 2 (ABCG2), both of which are upregulated during hyperinsulinaemia [37, 38]. Urate is also reabsorbed through GLUT9, a glucose and urate transporter expressed in the apical and basolateral membranes of the renal tubules. SGLT2I was shown to reduce the serum uric acid level previously, which is an important link to gout [17, 39]. SGLT2I reduces the uric acid by inhibiting uric acid reabsorption in the proximal renal tubule via channels such as GLUT9 and, thus, lowering the serum urate concentration.[34] For instance, in the URAT1 knockout mice model, it was demonstrated that URAT1 is important in mediating the uricosuric effects of canagliflozin [40]. SGLT2I also enhances the excretion of glucose into the urine and increases uric acid release from blood [18, 40]. Besides, SGLT2I was also shown to reduce the serum uric acid level independent of the urine uric acid secretion [41]. SGLT2I reduces uric acid synthesis by inhibiting the xanthine oxidase by activating the nutrient deprivation sensor sirtuin-1 around the body [42]. Furthermore, sirtuin-1 also promotes the intestinal excretion of uric acid [43]. This reduces uric acid production in the body. Our results showed that patients on SGLT2I had higher aMDRD, which patients with the lowest MDRD had the highest risks of gout. The glomerular filtration rate was shown to be associated with gout [44]. SGLT2I was suggested to exert its beneficial renal effects by inhibition of the epithelial-mesenchymal transition and aberrant glycolysis induction [45]. Indeed, it was previously suggested that SGLT2I had lower risks of adverse kidney outcomes compared with DPP4I [46, 47]. Therefore, we hypothesized SGLT2I might reduce the risks of gout via its renal effects. Furthermore, SGLT2I would also exert other pleiotropic effects in gout [48], including metabolic benefits by reducing body weight, cardiovascular benefits by reducing inflammation and enhancing endothelial function, and renal benefits by reducing the rate of glomerular filtration rate decline and enhancing the vascular function [49]. In addition to reducing the risk of gout, the use of SGLT2I might therefore also benefit cardiometabolic-renal comorbidities.

Our results demonstrated that the patients on SGLT2I had lower risks of a new diagnosis of gout compared with DPP4I among T2DM patients after 5.6 years of follow-up. This was in accord with the result previously published, which also suggested that patients on SGLT2I have a lower risk of gout compared with DPP4I after 2.5 years of follow-up [21]. Our study demonstrated a 51% risk reduction in the risk of gout, compared with the reported 13% reduction at the study end point. Meanwhile, at the same time point (2.5 years follow-up) (Supplementary Tables S11 and S12, available at *Rheumatology* online), SGLT2I was associated with a 41% reduction in the risks of gout compared with a 13% reduction reported in Chung *et al.* after adjustments [21]. One of the explanations could be the difference in the timing of DPP4I and SGLT2I initiation between different localities. In Chung *et al.* 12.67% of patients were using insulin; meanwhile, in our study 53.36% of patients were on insulin. This could be due to the timing of DPP4I and SGLT2I initiation, which may be later owing to the more stringent drug initiation criteria. However, further studies are needed to compare the effects on gout between mild and severe diabetes patients. Another study demonstrated that patients on SGLT2I had lower risks of gout compared with the GLP-1 agonist [20]. Meanwhile, in the post-hoc analysis of the EMPA-REG and the CANVAS

Table 3. Multivariate Cox analysis for new onset gout and all-cause mortality in the matched cohort

Model 1: Adjusted for significant demographics		
Characteristics	**All-cause mortality HR [95% CI]; *P*-value**	**Gout HR [95% CI]; *P*-value**
SGLT2I *vs* DPP4I	0.48[0.43, 0.54];<0.0001***	0.50[0.43, 0.59];<0.0001***
Dapagliflozin *vs* DPP4I	0.60[0.52, 0.68];<0.0001***	0.48[0.39, 0.59];<0.0001***
Empagliflozin *vs* DPP4I	0.47[0.37, 0.60];<0.0001***	0.84[0.64, 1.10]; 0.2015
Canagliflozin *vs* DPP4I	0.56[0.46, 0.69];<0.0001***	0.72[0.55, 0.94]; 0.0141*
Ertugliflozin *vs* DPP4I	0.65[0.50, 0.86]; 0.0022**	0.60[0.40, 0.90]; 0.0145*
Model 2: Adjusted for significant demographics and past comorbidities		
Characteristics	**All-cause mortality HR [95% CI]; *P*-value**	**Gout HR [95% CI]; *P*-value**
SGLT2I *vs* DPP4I	0.47[0.42, 0.52];<0.0001***	0.50[0.42, 0.58];<0.0001***
Dapagliflozin *vs* DPP4I	0.58[0.51, 0.67];<0.0001***	0.48[0.39, 0.58];<0.0001***
Empagliflozin *vs* DPP4I	0.48[0.37, 0.60];<0.0001***	0.83[0.64, 1.08]; 0.1722
Canagliflozin *vs* DPP4I	0.56[0.46, 0.69];<0.0001***	0.72[0.55, 0.94]; 0.0164*
Ertugliflozin *vs* DPP4I	0.64[0.49, 0.84]; 0.0015**	0.60[0.40, 0.90]; 0.0134*
Model 3: Adjusted for significant demographics, past comorbidities, and medications		
Characteristics	**All-cause mortality HR [95% CI]; *P*-value**	**Gout HR [95% CI]; *P*-value**
SGLT2I *vs* DPP4I	0.49[0.44, 0.55];<0.0001***	0.50[0.43, 0.59];<0.0001***
Dapagliflozin *vs* DPP4I	0.61[0.53, 0.70];<0.0001***	0.48[0.39, 0.59];<0.0001***
Empagliflozin *vs* DPP4I	0.48[0.38, 0.61];<0.0001***	0.84[0.64, 1.09]; 0.1921
Canagliflozin *vs* DPP4I	0.59[0.48, 0.72];<0.0001***	0.73[0.56, 0.95]; 0.0189*
Ertugliflozin *vs* DPP4I	0.70[0.53, 0.92]; 0.0111*	0.61[0.40, 0.91]; 0.0165*
Model 4: Adjusted for significant demographics, past comorbidities, medications and MDRD		
Characteristics	**All-cause mortality HR [95% CI]; *P*-value**	**Gout HR [95% CI]; *P*-value**
SGLT2I *vs* DPP4I	0.49[0.44, 0.55];<0.0001***	0.49[0.42, 0.58];<0.0001***
Dapagliflozin *vs* DPP4I	0.61[0.53, 0.69];<0.0001***	0.48[0.39, 0.60];<0.0001***
Empagliflozin *vs* DPP4I	0.48[0.38, 0.61];<0.0001***	0.80[0.61, 1.04]; 0.0939
Canagliflozin *vs* DPP4I	0.59[0.48, 0.72];<0.0001***	0.70[0.54, 0.92]; 0.0096**
Ertugliflozin *vs* DPP4I	0.70[0.53, 0.92]; 0.0108*	0.60[0.40, 0.90]; 0.0136*
Model 5: Adjusted for significant demographics, past comorbidities, medications, MDRD, HbA1c and fasting glucose		
Characteristics	**All-cause mortality HR [95% CI]; *P*-value**	**Gout HR [95% CI]; *P*-value**
SGLT2I *vs* DPP4I	0.49[0.43, 0.55];<0.0001***	0.49[0.42, 0.58];<0.0001***
Dapagliflozin *vs* DPP4I	0.60[0.53, 0.69];<0.0001***	0.49[0.40, 0.60];<0.0001***
Empagliflozin *vs* DPP4I	0.48[0.38, 0.61];<0.0001***	0.79[0.61, 1.04]; 0.0892
Canagliflozin *vs* DPP4I	0.59[0.48, 0.72];<0.0001***	0.70[0.53, 0.91]; 0.0080**
Ertugliflozin *vs* DPP4I	0.70[0.53, 0.92]; 0.0098**	0.60[0.40, 0.90]; 0.0141*

* $P \leq 0.05$,
** $P \leq 0.01$,
*** $P \leq 0.001$.
DPP4I: dipeptidyl peptidase-4 inhibitor; HR: hazard ratio; IR: incidence rate; SGLT2I: sodium glucose cotransporter-2 inhibitor.

study, empagliflozin and canagliflozin not only lowered the urate level, they also reduced the risks of gout [22]. Furthermore, a meta-analysis found that the anti-gout effect of SGLT2I was not only a relative effect between different drugs, but rather a class effect among T2DM patients [23, 50]. Thus, SGLT2I may have a lower risk of gout compared with other second-line anti-diabetic drugs. Our study demonstrates the potential SGLT2I long-term benefit in protecting T2DM patients from gout.

Limitations

Several limitations should be noted for the present study. Firstly, given its observational nature, there is inherent information bias due to under-coding, coding errors and missing

data. Besides, the drug exposure duration was not controlled, affecting their risk against the study outcomes. The patients' medication adherence was also not coded into the system. Secondly, confounding factors may still be present despite propensity-matching. Other important lifestyle risk factors and laboratory results for gout, such as body mass index, were not available. Given that uric acid level was not routinely measured in all gout patients and measurement during or immediately after an acute gouty attack does not reflect the usual uric acid level, the parameter during follow-up was not included in the present study. Additionally, the occurrence of gout out of the public hospitals was not considered. However, given the severe pain from acute gouty attacks, patients were likely to present to public hospitals at their initial attack. Lastly, the retrospective design of our study necessitates the presentation of associations but not causal links between SGLT2I *vs* DPP4I use and the risk of new-onset gout risk. Further studies are required to demonstrate the causation and uncover the underlying mechanisms.

Conclusions

SGLT2I use was associated with lower risks of gout and all-cause mortality compared with DPP4I after propensity score matching with multiple adjustments.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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References

1. Khan MAB, Hashim MJ, King JK, Govender RD *et al.* Epidemiology of type 2 diabetes – global burden of disease and forecasted trends. J Epidemiol Glob Health 2020;10:107–11.
2. Xiong Q, Liu J, Xu Y. Effects of uric acid on diabetes mellitus and its chronic complications. Int J Endocrinol 2019;2019:9691345.
3. Fang YJ, Chung YL, Lin CL, Lim YP. Association between gout, urate-lowering therapy, and risk of developing type 2 diabetes mellitus: a nationwide population-based retrospective cohort study. Biomed Res Int 2020;2020:6358954.
4. Tsoi MF, Chung MH, Cheung BMY, Lau CS, Cheung TT. Epidemiology of gout in Hong Kong: a population-based study from 2006 to 2016. Arthritis Res Ther 2020;22:204.
5. Cea Soriano L, Rothenbacher D, Choi HK, García Rodríguez LA. Contemporary epidemiology of gout in the UK general population. Arthritis Res Ther 2011;13:R39.
6. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. Circulation 2007;116:894–900.
7. Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 2009;202:11–7.
8. Vuorinen-Markkola H, Yki-Järvinen H. Hyperuricemia and insulin resistance. J Clin Endocrinol Metab 1994;78:25–9.
9. Böni-Schnetzler M, Meier DT. Islet inflammation in type 2 diabetes. Semin Immunopathol 2019;41:501–13.
10. Thornberry NA, Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4). Best Pract Res Clin Endocrinol Metab 2009;23:479–86.
11. Dalla Man C, Bock G, Giesler PD *et al.* Dipeptidyl peptidase-4 inhibition by vildagliptin and the effect on insulin secretion and action in response to meal ingestion in type 2 diabetes. Diabetes Care 2009;32:14–8.
12. Yamagishi S, Ishibashi Y, Ojima A, Sugiura T, Matsui T. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor, decreases serum uric acid levels in type 2 diabetic patients partly by suppressing xanthine oxidase activity. Int J Cardiol 2014;176:550–2.
13. Moriya C, Satoh H. Teneligliptin decreases uric acid levels by reducing xanthine dehydrogenase expression in white adipose tissue of male wistar rats. J Diabetes Res 2016;2016:3201534.
14. Wu JH, Foote C, Blomster J *et al.* Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2016;4:411–9.
15. Desai M, Yavin Y, Balis D *et al.* Renal safety of canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus. Diabetes Obes Metabol 2017;19:897–900.
16. Xin Y, Guo Y, Li Y *et al.* Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: a systematic review with an indirect comparison meta-analysis. Saudi J Biol Sci 2019;26:421–6.
17. Suijk DLS, van Baar MJB, van Bommel EJM *et al.* SGLT2 inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. Clin J Am Soc Nephrol 2022;17:663–71.
18. 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.
19. McGill JB. The SGLT2 inhibitor empagliflozin for the treatment of type 2 diabetes mellitus: a bench to bedside review. Diabetes Ther 2014;5:43–63.
20. Fralick M, Chen SK, Patorno E, Kim SC. 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;172:186–94.
21. Chung M-C, Hung P-H, Hsiao P-J *et al.* Association of sodium-glucose transport protein 2 inhibitor use for type 2 diabetes and incidence of gout in Taiwan. JAMA Network Open 2021;4:e2135353.
22. 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;24:135–41.
23. Banerjee M, Pal R, Mukhopadhyay S. Can SGLT2 inhibitors prevent incident gout? A systematic review and meta-analysis. Acta Diabetol 2022;59:783–91.
24. Zhou J, Lee S, Leung KSK *et al.* Incident heart failure and myocardial infarction in sodium-glucose cotransporter-2 vs. dipeptidyl peptidase-4 inhibitor users. ESC Heart Fail 2022;9:1388–99.
25. Lee S, Liu T, Zhou J *et al.* Predictions of diabetes complications and mortality using hba1c variability: a 10-year observational cohort study. Acta Diabetol 2021;58:171–80.
26. Lee S, Zhou J, Guo CL *et al.* Predictive scores for identifying patients with type 2 diabetes mellitus at risk of acute myocardial infarction and sudden cardiac death. Endocrinol Diabetes Metab 2021;4:e00240.
27. Lee S, Zhou J, Wong WT *et al.* Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. BMC Endocr Disord 2021;21:94.

28. Chou OHI, Zhou J, Lee TTL *et al.* Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study. Clin Res Cardiol 2022;1–6. doi:10.1007/s00392-022-02007-0.
29. Ju C, Lai RWC, Li KHC *et al.* Comparative cardiovascular risk in users versus non-users of xanthine oxidase inhibitors and febuxostat versus allopurinol users. Rheumatology 2020; 59:2340–9.
30. Soliman AR, Fathy A, Khashab S, Shaheen N. Comparison of abbreviated modification of diet in renal disease formula (aMDRD) and the Cockroft-Gault adjusted for body surface (aCG) equations in stable renal transplant patients and living kidney donors. Ren Fail 2013;35:94–7.
31. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.
32. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–79.
33. Avagyan V, Vansteelandt S. Stable inverse probability weighting estimation for longitudinal studies. Scand J Stat 2021;48: 1046–67.
34. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. Diabetes Obes Metab 2019;21:1291–8.
35. Hussain M, Elahi A, Hussain A *et al.* Sodium-Glucose Cotransporter-2 (SGLT-2) attenuates Serum Uric Acid (SUA) level in patients with type 2 diabetes. J Diabetes Res 2021;2021:9973862.
36. Mui JV, Zhou J, Lee S *et al.* Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors vs. Dipeptidyl Peptidase-4 (DPP4) inhibitors for new-onset dementia: a propensity score-matched population-based study with competing risk analysis. Front Cardiovasc Med 2021;8:747620.
37. Song D, Zhao X, Wang F, Wang G. A brief review of urate transporter 1 (URAT1) inhibitors for the treatment of hyperuricemia and gout: current therapeutic options and potential applications. Eur J Pharmacol 2021;907:174291.
38. Choi HK, Mount DB, Reginato AM; American Physiological Society. Pathogenesis of gout. Ann Intern Med 2005;143: 499–516.
39. Hainer BL, Matheson E, Wilkes RT. Diagnosis, treatment, and prevention of gout. Am Fam Physician 2014;90:831–6.
40. Novikov A, Fu Y, Huang W *et al.* SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. Am J Physiol Renal Physiol 2019;316:F173–85.
41. Stack AG, Han D, Goldwater R *et al.* Dapagliflozin added to verinurad plus febuxostat further reduces serum uric acid in hyperuricemia: the QUARTZ study. J Clin Endocrinol Metabol 2021;106: e2347–56.
42. Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. J Card Fail 2020;26:977–84.
43. Wang J, Zhu XX, Liu L *et al.* SIRT1 prevents hyperuricemia via the PGC-1α/PPARγ-ABCG2 pathway. Endocrine 2016;53: 443–52.
44. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS One 2012;7:e50046.
45. Li J, Liu H, Takagi S *et al.* Renal protective effects of empagliflozin via inhibition of EMT and aberrant glycolysis in proximal tubules. JCI Insight 2020;5:e129034.
46. Bae JH, Park EG, Kim S *et al.* Comparative renal effects of dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter 2 inhibitors on individual outcomes in patients with type 2 diabetes: a systematic review and network meta-analysis. Endocrinol Metab 2021;36:388–400.
47. Heerspink HJL, Karasik A, Thuresson M *et al.* Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. Lancet Diabetes Endocrinol 2020;8: 27–35.
48. Choi HK, McCormick N, Yokose C. Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care. Nat Rev Rheumatol 2022;18:97–111.
49. Heerspink HJL, Stefánsson BV, Correa-Rotter R *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020;383:1436–46.
50. 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 Rheumatology 2019;1:e220–8.