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Sodium-glucose cotransporter-2 inhibitors and the risk of gout in patients with type 2 diabetes mellitus: A propensity-score-matched, new-user design study with an active comparator using the IQVIA Medical Research Data UK database

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Abstract

Aim: To conduct a pharmacoepidemiological study to explore the association between sodium-glucose cotransporter-2 (SGLT2) inhibitors and gout in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: A retrospective open cohort study using the IQVIA Medical Research Data UK database was performed between November 1, 2012 and December 31, 2018, estimating the risk of gout in patients with T2DM who were new users of SGLT2 inhibitors, compared to propensity-score-matched new users of dipeptidyl peptidase-4 (DPP-4) inhibitors.

Results: A total of 85 incident cases of gout were recorded over 30 389 person-years of observation in 13 617 new users of SGLT2 inhibitors and 29 426 new users of DPP-4 inhibitors. Crude incidence rates (IRs) per 1000 person-years were 2.90 and 2.47 for new users of SGLT2 inhibitors and DPP-4 inhibitors, respectively. The unadjusted hazard ratio (HR) was 1.18 (95% confidence interval [CI] 0.76-1.83). The adjusted HR was 1.20 (95% CI 0.77-1.86). In the at-treatment analysis, crude IRs per 1000 person-years were found to be 2.68 and 2.53 for SGLT2 inhibitor and DPP-4 inhibitor users, respectively. In the adjusted model, the adjusted HR was 1.3 (95% CI 0.90-2.29). Sensitivity analyses did not change the findings.

Conclusions: In this nationwide study, no difference in the incidence of gout was documented in patients treated with SGLT2 inhibitors compared to DPP-4 inhibitor users. This neutral finding remained consistent in sensitivity analyses.

KEYWORDS
canagliflozin, cohort study, dapagliflozin, database research, diabetes complications, type 2 diabetes

1 | INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (namely, canagliflozin, dapagliflozin empagliflozin and ertugliflozin) constitute an established class of antidiabetic medications, which exerts their hypoglycaemic effects through induction of glycosuria.[1] Their main site of action is a high-capacity, low-affinity glucose transporter, SGLT2, located in the proximal convoluted renal tubule.[2] Inhibition of tubular glucose reuptake results in a consistent increase in urinary glucose and, thus, calorie excretion, leading to a relatively modest decrease (in the order of 0.3%-0.7%) in glycated haemoglobin (HbA1c) level.[3] The mechanism is insulin-independent, that is, it does not rely on ß-cell function or insulin sensitivity. The SGLT2 inhibitor class has been shown to have a range of pleiotropic effects beyond the urinary spillover of sodium and glucose.[4] These effects start with a dynamic realignment of energy metabolism, renal filtration and plasma volume, followed, in the medium term, by a beneficial resetting of energy/salt/water physiology, and are associated with a salutary impact on cardiovascular function, renal function, blood pressure, body weight and, importantly, the survival of patients.[5]

Sodium-glucose cotransporter-2 inhibitor-induced glycosuria and the ensuing resetting of energy/salt/water physiology seems to be a multifaceted process with several secondary effects. This is particularly exemplified by changes in the renal handling of urate. In light of the prevalence of hyperuricaemia and gout in patients with type 2 diabetes mellitus (T2DM) and the association between uric acid levels and cardiovascular disease, these changes in renal urate handling could be considered clinically relevant.[6] Increased concentration of glucose within the renal tubular lumen, diminished extracellular glucose on the basolateral membrane of the proximal convoluted renal tubule and increased delivery of glucose to the collecting ducts collectively set the scene for increased secretion of urate into the tubular lumen and a decreased reabsorption of urate. These actions are putatively mediated by competition at the level of the antiporter GLUT9b,[7] which exchanges glucose for urate on the apical and basolateral membrane of the proximal convoluted renal tubule.[8] From a clinical perspective, they are associated with a decrease in uric acid levels in patients with T2DM treated with SGLT2 inhibitors.[9]

Prompted by the observation of uric acid-lowering properties, it was plausible to assume that treatment with an SGLT2 inhibitor would result in a decrease in the incidence of inflammatory episodes related to gout. Given that gout is an independent predictor of cardiovascular disease,[10,11] highly prevalent in patients with T2DM,[12-14] and that medications for gout may be associated with cardiovascular death,[15] such evidence would be relevant in the care of individuals with T2DM. Evidence to date is conflicting. Some preliminary studies have documented a significant decrease in the incidence of gout with SGLT2 inhibitor treatment compared to placebo[16] or glucagon-like peptide-1 receptor agonists (GLP-1RAs),[17] whereas this finding was not confirmed in other studies.[18] Several potentially important effect modifiers, such as body mass index (BMI) and glycaemic control, are currently missing in the previous real-world study estimates, which should ideally be addressed in future research to establish the relationship under question.

To address this discrepancy, we undertook a retrospective, open-cohort study using the IQVIA Medical Research Data (IMRD) UK database. This study used dipeptidyl peptidase-4 (DPP-4) inhibitors as the main active comparator. The DPP-4 inhibitors that are licensed in the United Kingdom include sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin and their combinations with metformin. The selection of DPP-4 inhibitors was made on the basis that (i) they are known to have a neutral effect on uric acid levels in patients with T2DM[19] and (ii) they are recommended at the first intensification step beyond metformin treatment (National Institute for Health and Care Excellence [NICE] guideline NG28), and thus are commonly used as second-choice treatment (similar to SGLT2 inhibitor) in the treatment of diabetes.

The aim of this study was to explore the incidence of gout in patients with T2DM who were new users of SGLT2 inhibitors in comparison to propensity-score (PS)-matched new users of DPP-4 inhibitors.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This was a retrospective open cohort study using the IMRD-UK. The study period, when index events (drug initiation) and outcomes of interest were observed, extended from November 1, 2012 (market authorization date for SGLT2 inhibitors in the United Kingdom) to December 31, 2018 (end of data availability). Data were derived from a large database of anonymized electronic medical records from UK general practices, VISION Electronic Medical Records. This database includes records for more than 5% of the UK population, and holds data on demographic characteristics, clinical diagnosis, physical measurement, laboratory results and drug prescriptions. To maximize data and recording quality, general practices were included in the study from the latest of the following dates: 12 months after reporting acceptable mortality rates (to define the start of follow-up period with acceptable data quality wherein mortality reporting seemed complete and acceptable),[20] 12 months after starting to use electronic medical records, and study start date (November 1, 2012). Adults aged >18 years, registered with an eligible general practice for a minimum of 12 months, and with a record of T2DM were eligible for inclusion. Patients registered in IMRD-UK have similar age and sex distributions to those in the general UK population, and it is therefore well suited for epidemiological studies.[21,22] Data were extracted automatically using the software programme DExtER (Data Extraction for Epidemiological Research).[23]

After meeting patient eligibility criteria, new users of SGLT2 inhibitors and DPP-4 inhibitors were included in the exposed and the comparator cohorts, respectively, and were followed up from the date of their first prescription date (index date). For the intention-to-treat (ITT) analysis, they were followed up until the earliest of the following endpoints: date of outcome recording, study end date (December 31, 2018), patient death date, patient transfer out of practice date, and date of termination of data contributed by the practice to IMRD-UK.

TABLE 1 Baseline characteristics of the study population (demographics, lifestyle factors, diabetes complications and other comorbidities)

	Pre-matched			Matched		
Number of patients	SGLT2 inhibitor cohort 13 617	DPP-4 inhibitor cohort 29 426	SMD	SGLT2 inhibitor cohort 8650	DPP-4 inhibitor cohort 8650	SMD
Age at index, mean (SD) years	57.71 (10.64)	65.97 (12.83)	0.701	58.97 (10.65)	58.97 (11.56)	0.000
Age group, n (%)						
18-54 years	5401 (39.66)	6151 (20.90)		3087 (35.69)	3210 (37.11)	
55-64 years	4675 (34.33)	7011 (23.83)		2965 (34.28)	2748 (31.77)	
65-74 years	2964 (21.77)	8511 (28.92)		2103 (24.31)	1969 (22.76)	
75+ years	577 (4.24)	7753 (26.35)		495 (5.72)	723 (8.36)	
Male, n (%)	7626 (56.00)	16 438 (55.86)	0.003	4942 (57.13)	4945 (57.17)	0.001
Ethnicity, n (%)			0.092			0.028
White	6650 (48.84)	14 220 (48.32)		4208 (48.65)	4140 (47.86)	
Black	159 (1.17)	563 (1.91)		117 (1.35)	111 (1.28)	
South Asian	521 (3.83)	1481 (5.03)		374 (4.32)	370 (4.28)	
Mixed race	92 (0.68)	267 (0.91)		73 (0.84)	65 (0.75)	
Other ethnic minorities	42 (0.31)	111 (0.38)		31 (0.36)	41 (0.47)	
Missing	6153 (45.19)	12 784 (43.44)		3847 (44.47)	3923 (45.35)	
Townsend deprivation quintile, n (%)			0.082			0.009
1 (least deprived)	1827 (13.42)	4484 (15.24)		1196 (13.83)	1206 (13.94)	
2	1943 (14.27)	4539 (15.43)		1248 (14.43)	1262 (14.59)	
3	2359 (17.32)	5300 (18.01)		1495 (17.28)	1489 (17.21)	
4	2381 (17.49)	5066 (17.22)		1465 (16.94)	1451 (16.77)	
5 (Most deprived)	1973 (14.49)	3882 (13.19)		1233 (14.25)	1246 (14.40)	
Missing	3134 (23.02)	6155 (20.92)		2013 (23.27)	1996 (23.08)	
Calendar year at index, n (%)			0.666			0.026
2012	0 (0)	994 (3.38)		0 (0)	0 (0)	
2013	491 (3.61)	5703 (19.38)		352 (4.07)	359 (4.15)	
2014	1727 (12.68)	5166 (17.56)		975 (11.27)	997 (11.53)	
2015	2551 (18.73)	5151 (17.50)		1494 (17.27)	1561 (18.05)	
2016	2991 (21.97)	4552 (15.47)		1900 (21.97)	1900 (21.97)	
2017	3043 (22.35)	4139 (14.07)		1994 (23.05)	1939 (22.42)	
2018	2814 (20.67)	3721 (12.65)		1935 (22.37)	1894 (21.90)	
Lifestyle variables, n (%)						
Obesity	10 741 (78.88)	16 581 (56.35)	0.496	6304 (72.88)	6329 (73.17)	0.007
Overweight	2661 (19.54)	9670 (32.86)	0.306	2047 (23.66)	2035 (23.53)	0.003
Smoking status	7832 (57.52)	16 031 (54.48)	0.061	4910 (56.76)	4918 (56.86)	0.002
Alcohol abuse	9038 (66.37)	18 235 (61.97)	0.092	5735 (66.30)	5726 (66.20)	0.002
Drug abuse	182 (1.34)	262 (0.89)	0.043	110 (1.27)	116 (1.34)	0.006
Diabetes complications, n (%)						
Diabetic retinopathy	7752 (56.93)	16 057 (54.57)	0.048	4363 (50.44)	4462 (51.58)	0.023
Diabetes with other ophthalmic manifestations	325 (2.39)	1367 (4.65)	0.123	217 (2.51)	220 (2.54)	0.002
Retinal detachment, vitreous haemorrhage, vitrectomy	106 (0.78)	306 (1.04)	0.028	61 (0.71)	58 (0.67)	0.004
Retinal laser coagulation therapy	75 (0.55)	119 (0.40)	0.021	23 (0.27)	28 (0.32)	0.011
Diabetic neuropathy	2535 (18.62)	5926 (20.14)	0.039	1369 (15.83)	1404 (16.23)	0.011
Diabetic nephropathy	65 (0.48)	586 (1.99)	0.137	31 (0.36)	33 (0.38)	0.004

(Continues)

TABLE 1 (Continued)

	Pre-matched			Matched		
Number of patients	SGLT2 inhibitor cohort 13 617	DPP-4 inhibitor cohort 29 426	SMD	SGLT2 inhibitor cohort 8650	DPP-4 inhibitor cohort 8650	SMD
Hypoglycaemia	463 (3.40)	1118 (3.80)	0.021	237 (2.74)	241 (2.79)	0.003
Hyperglycaemia	490 (3.60)	1010 (3.43)	0.009	243 (2.81)	238 (2.75)	0.004
Disorders of fluid electrolyte and acid-base balance	5 (0.04)	56 (0.19)	0.046	4 (0.05)	2 (0.02)	0.012
Diabetic ketoacidosis	30 (0.22)	44 (0.15)	0.016	10 (0.12)	17 (0.20)	0.021
Hyperosmolar hyperglycaemic nonketotic syndrome	5 (0.04)	21 (0.07)	0.015	2 (0.02)	3 (0.03)	0.007
Diabetes with peripheral circulatory disorders	5 (0.04)	64 (0.22)	0.051	4 (0.05)	5 (0.06)	0.005
Diabetic foot	13 203 (96.96)	28 184 (95.78)	0.063	8298 (95.93)	8304 (96.00)	0.004
Gangrene	6 (0.04)	38 (0.13)	0.029	5 (0.06)	2 (0.02)	0.017
Lower extremity amputation	77 (0.57)	233 (0.79)	0.028	50 (0.58)	47 (0.54)	0.005
Osteomyelitis	70 (0.51)	183 (0.62)	0.014	40 (0.46)	42 (0.49)	0.003
Skin infections	508 (3.73)	939 (3.19)	0.030	319 (3.69)	288 (3.33)	0.019
Erectile dysfunction	2154 (15.82)	4245 (14.43)	0.039	1269 (14.67)	1275 (14.74)	0.002
Diabetes with unspecified complication	108 (0.79)	258 (0.88)	0.009	43 (0.50)	49 (0.57)	0.01
Diabetes mellitus without mention of complications	24 (0.18)	35 (0.12)	0.015	13 (0.15)	15 (0.17)	0.006
Other comorbidities, n (%)						
Hypertension	7744 (56.87)	18 044 (61.32)	0.091	4772 (55.17)	4783 (55.29)	0.003
Ischaemic heart disease	1757 (12.90)	5548 (18.85)	0.163	1111 (12.84)	1091 (12.61)	0.007
Acute myocardial infarction	763 (5.60)	2242 (7.62)	0.081	489 (5.65)	487 (5.63)	0.001
Stable angina	821 (6.03)	2838 (9.64)	0.135	496 (5.73)	481 (5.56)	0.008
Previous cardiac procedure	476 (3.50)	1444 (4.91)	0.070	300 (3.47)	297 (3.43)	0.002
History of CABG or PTCA	209 (1.53)	890 (3.02)	0.100	137 (1.58)	137 (1.58)	0
Any stroke	350 (2.57)	1492 (5.07)	0.131	249 (2.88)	236 (2.73)	0.009
Haemorrhagic stroke	26 (0.19)	122 (0.41)	0.041	23 (0.27)	19 (0.22)	0.009
Cerebrovascular procedure	2 (0.01)	3 (0.01)	0.004	0 (0)	1 (0.01)	0.015
CHF	313 (2.30)	1546 (5.25)	0.155	213 (2.46)	201 (2.32)	0.009
Peripheral vascular disease or surgery	185 (1.36)	627 (2.13)	0.059	119 (1.38)	108 (1.25)	0.011
Atrial fibrillation	503 (3.69)	2401 (8.16)	0.190	353 (4.08)	352 (4.07)	0.001
Other cardiac dysrhythmia	26 (0.19)	52 (0.18)	0.003	13 (0.15)	18 (0.21)	0.014
Oedema	2135 (15.68)	5739 (19.50)	0.101	1269 (14.67)	1296 (14.98)	0.009
COPD	757 (5.56)	2345 (7.97)	0.096	512 (5.92)	514 (5.94)	0.001
Asthma	2279 (16.74)	4205 (14.29)	0.068	1352 (15.63)	1348 (15.58)	0.001
Pneumonia	740 (5.43)	1814 (6.16)	0.031	455 (5.26)	452 (5.23)	0.002
Chronic kidney disease	550 (4.04)	6099 (20.73)	0.524	404 (4.67)	421 (4.87)	0.009
Chronic renal insufficiency	54 (0.40)	540 (1.84)	0.137	40 (0.46)	42 (0.49)	0.003
Chronic kidney disease stage 1-2	420 (3.08)	1188 (4.04)	0.051	231 (2.67)	236 (2.73)	0.004
Chronic kidney disease stage 3-4	166 (1.22)	1855 (6.30)	0.270	127 (1.47)	126 (1.46)	0.001
Hypertensive nephropathy	1 (0.01)	4 (0.01)	0.006	0 (0)	0 (0)	
Liver disease	165 (1.21)	343 (1.17)	0.004	104 (1.20)	116 (1.34)	0.012
Osteoarthritis	2416 (17.74)	6918 (23.51)	0.143	1543 (17.84)	1554 (17.97)	0.003

TABLE 1 (Continued)

Number of patients	Pre-matched			Matched		
	SGLT2 inhibitor cohort 13 617	DPP-4 inhibitor cohort 29 426	SMD	SGLT2 inhibitor cohort 8650	DPP-4 inhibitor cohort 8650	SMD
Other arthritis, arthropathies and musculoskeletal pain	201 (1.48)	545 (1.85)	0.029	142 (1.64)	149 (1.72)	0.006
Bone fractures	1510 (11.09)	3391 (11.52)	0.014	933 (10.79)	937 (10.83)	0.001
Falls	321 (2.36)	1270 (4.32)	0.109	219 (2.53)	217 (2.51)	0.001
Osteoporosis	288 (2.12)	1405 (4.77)	0.146	200 (2.31)	197 (2.28)	0.002
Hyperthyroidism	114 (0.84)	281 (0.95)	0.012	62 (0.72)	59 (0.68)	0.004
Hypothyroidism	1372 (10.08)	2988 (10.15)	0.003	800 (9.25)	803 (9.28)	0.001
Other disorders of the thyroid gland	10 (0.07)	17 (0.06)	0.006	5 (0.06)	6 (0.07)	0.005
Depression	5147 (37.80)	8801 (29.91)	0.167	2996 (34.64)	3040 (35.14)	0.011
Anxiety	2239 (16.44)	4492 (15.27)	0.032	1408 (16.28)	1450 (16.76)	0.013
Sleep disorder	926 (6.80)	920 (3.13)	0.170	426 (4.92)	409 (4.73)	0.009
Dementia	85 (0.62)	806 (2.74)	0.165	69 (0.80)	71 (0.82)	0.003
Delirium	10 (0.07)	51 (0.17)	0.028	8 (0.09)	8 (0.09)	0
Psychosis	94 (0.69)	234 (0.80)	0.012	69 (0.80)	76 (0.88)	0.009
Foot ulcer	47 (0.35)	91 (0.31)	0.006	24 (0.28)	26 (0.30)	0.004
Cellulitis or abscess of toe	2 (0.01)	4 (0.01)	0.001	0 (0)	0 (0)	
Imaging	4079 (29.96)	8883 (30.19)	0.005	2511 (29.03)	2509 (29.01)	0.001
Glaucoma or cataracts	497 (3.65)	1725 (5.86)	0.104	307 (3.55)	324 (3.75)	0.01

Abbreviations: CABG, coronary artery bypass grafting; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference.

For the at-treatment analysis, date of discontinuation of the exposed drug and switch to the comparator drug or vice versa were also considered points at which to censor follow-up. Patients were excluded if: (i) they had a prescription for SGLT2 inhibitors or DPP-4 inhibitors in the 12-month period prior to the index date; (ii) they coinitiated SGLT2 inhibitor and DPP-4 inhibitor treatment; (iii) they had a diagnosis of type 1 diabetes, secondary diabetes, end-stage renal disease, or outcome (gout) recorded at any time prior to index date; or (iv) they had a diagnosis of gestational diabetes in the 12-month period prior to index date.

2.2 | Study variables

Data were collected for each patient on the basis of diagnoses and procedures recorded during health consultations, including demographic factors (such as age, sex, ethnicity, Townsend deprivation index score [a marker of socioeconomic deprivation]), calendar year at index drug initiation, lifestyle variables (BMI, smoking status, alcohol consumption and drug abuse), diabetes complications, other comorbidities including risk factors for gout, use of other antidiabetic medications, other medications for concomitant health conditions and physical and biochemical measurements (high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, total cholesterol [TC], triglycerides, estimated glomerular filtration rate [eGFR], serum creatinine and uric acid; detailed description in Table S1). The primary outcome was incident gout identified through Read codes (listed in TableS2 and validated in a previous study[20]). A sensitivity analysis using both incident gout and commencement of uric acid-lowering medications (prescription claim for a medication used to treat gout) as the outcome definition was also conducted. Patients with a previous prescription of medications to treat gout (allopurinol, febuxostat, colchicine, probenecid and benzbromarone) before index date were excluded from the sensitivity analysis.

2.3 | Statistical analysis

Missing values for HbA1c, LDL cholesterol, HDL cholesterol, TC, triglycerides and eGFR were imputed using multiple imputation by chained equations; 12 imputed datasets were obtained (due to maximum missingness of 12.02% for the variable LDL cholesterol) and combined using Rubin's rule. Because there was a high level of missingness for uric acid, we considered this covariate as a categorical variable, categorized as low, normal, high and missing. Among women, uric acid levels <89.22 μmol/l (1.5 mg/dL), 89.22-356.91 μmol/l (1.5 to 6.0 mg/dL) and ≥356.91 μmol/l (6.0 mg/dL) were considered as low, normal and high. Among men, uric acid levels <148.71 μmol/l

TABLE 2 Baseline characteristics of the study population (biochemical measures and other drug use at baseline)

	Pre-matched			Matched		
	SGLT2 inhibitor cohort	DPP-4 inhibitor cohort	SMD	SGLT2 inhibitor cohort	DPP-4 inhibitor cohort	SMD
Biochemical measures, mean (SD)						
HbA1c, mmol/mol or %	78.7 (15.2) or 9.35 (1.61)	73 (14.7) or 8.83 (1.56)	0.326	76.3 (14.8) or 9.13 (1.57)	76.5 (15) or 9.15 (1.59)	0.009
LDL cholesterol, mmol/L	95.63 (41.13)	89.74 (38.30)	0.149	96.45 (40.71)	96.14 (41.45)	0.007
HDL cholesterol, mmol/L	43.22 (11.38)	45.69 (12.79)	0.204	43.79 (11.29)	43.86 (11.58)	0.006
TC, mmol/L	171.55 (43.76)	166.68 (42.36)	0.114	172.38 (43.27)	172.10 (44.01)	0.006
Triglycerides, mmol/L	209.70 (126.76)	186.02 (109.12)	0.200	203.34 (120.36)	204.11 (121.09)	0.006
Creatinine, µmol/L	73.29 (17.05)	88.45 (35.74)	0.542	74.12 (17.90)	74.39 (16.92)	0.015
eGFR, mL/min/1.73 m^2	90.66 (16.55)	76.03 (24.09)	0.708	89.35 (16.84)	89.16 (16.82)	0.012
Uric acid level categories, n (%)			0.031			0.01
Low (<148.71 µmol/l or 2.5 mg/dL for men; <89.22 µmol/l or 1.5 mg/dL for women)	6 (0.04)	7 (0.02)		4 (0.05)	2 (0.02)	
Normal (148.71-413.39 µmol/l or 2.5-7.0 mg/dL for men; 89.22-356.91 µmol/l or 1.5-6.0 mg/dL for women)	1618 (11.88)	3066 (10.42)		943 (10.90)	991 (11.46)	
High (≥416.39 µmol/l or 7.0 mg/dL for men; ≥ 356.91 µmol/l or 6.0 mg/dL for women)	380 (2.79)	1111 (3.78)		245 (2.83)	213 (2.46)	
Missing	11 613 (85.28)	25 242 (85.78)		7458 (86.22)	7444 (86.06)	
Use of other antidiabetic drugs						
Number of antidiabetic substances at index, mean (SD)	2.64	2.30	0.436	2.34 (0.70)	2.37 (0.71)	0.052
Naïve new use of antidiabetic drugs, n (%)	224 (1.65)	1177 (4.00)	0.143	212 (2.45)	205 (2.37)	0.005
Initiation of the study drug as monotherapy, n (%)	163 (1.20)	960 (3.26)	0.140	155 (1.79)	149 (1.72)	0.005
Dual therapy with metformin, n (%)	3918 (28.77)	11 347 (38.56)	0.208	3761 (43.50)	3568 (41.27)	0.045
Concomitant initiation or current use of other antidiabetic drugs, n (%)						
Any other antidiabetic medications	11 309 (83.05)	23 088 (78.46)	0.117	7302 (84.46)	7302 (84.46)	0
Metformin	11 309 (83.05)	23 088 (78.46)	0.117	7302 (84.46)	7302 (84.46)	0
Sulphonylureas, 2nd generation	4902 (36.00)	11 567 (39.31)	0.068	3065 (35.45)	3101 (35.87)	0.009
GLP-1RAs	2398 (17.61)	184 (0.63)	0.618	65 (0.75)	165 (1.91)	0.101
Thiazolidinediones	1730 (12.70)	4112 (13.97)	0.037	1058 (12.24)	1080 (12.49)	0.008
Meglitinides	38 (0.28)	76 (0.26)	0.004	20 (0.23)	19 (0.22)	0.002
Insulin	2703 (19.85)	1534 (5.21)	0.453	525 (6.07)	708 (8.19)	0.082
Alpha-glucosidase inhibitors	25 (0.18)	37 (0.13)	0.015	8 (0.09)	10 (0.12)	0.007
Prior use of other antidiabetic drugs, n (%)						
Any other antidiabetic medications	2143 (15.74)	5332 (18.12)	0.064	1187 (13.73)	1188 (13.74)	0
Metformin	1299 (9.54)	2891 (9.82)	0.010	802 (9.28)	793 (9.17)	0.004
Sulphonylureas, 2nd generation	877 (6.44)	2026 (6.89)	0.018	489 (5.66)	487 (5.63)	0.001
GLP-1RAs	736 (5.41)	193 (0.66)	0.280	68 (0.79)	135 (1.56)	0.072
Thiazolidinediones	1061 (7.79)	1874 (6.37)	0.056	613 (7.09)	603 (6.97)	0.005
Meglitinides	16 (0.12)	24 (0.08)	0.011	7 (0.08)	10 (0.12)	0.011
Insulin	316 (2.32)	354 (1.20)	0.085	100 (1.16)	120 (1.39)	0.021
Alpha-glucosidase inhibitors	4 (0.03)	20 (0.07)	0.017	1 (0.01)	1 (0.01)	0

TABLE 2 (Continued)

	Pre-matched			Matched		
	SGLT2 inhibitor cohort	DPP-4 inhibitor cohort	SMD	SGLT2 inhibitor cohort	DPP-4 inhibitor cohort	SMD
Current use of other drugs, n (%)						
Angiotensin-converting-enzyme inhibitors	6409 (47.07)	13 888 (47.20)	0.003	3857 (44.61)	3883 (44.91)	0.006
Angiotensin II receptor blockers	2318 (17.02)	5468 (18.58)	0.041	1374 (15.89)	1397 (16.16)	0.007
Calcium channel blockers	3919 (28.78)	9630 (32.73)	0.086	2460 (28.45)	2427 (28.07)	0.008
Thiazides	2037 (14.96)	4905 (16.67)	0.047	1240 (14.34)	1262 (14.60)	0.007
Loop diuretics	984 (7.23)	4390 (14.92)	0.247	598 (6.92)	598 (6.92)	0
Nitrates	1002 (7.36)	2865 (9.74)	0.085	618 (7.15)	611 (7.07)	0.003
Other hypertension drugs	9862 (72.42)	22 627 (76.89)	0.103	6049 (69.96)	6090 (70.44)	0.01
Digoxin	141 (1.04)	951 (3.23)	0.152	99 (1.15)	113 (1.31)	0.015
Antiarrhythmic drugs	72 (0.53)	245 (0.83)	0.037	48 (0.56)	46 (0.53)	0.003
COPD or asthma medications	2736 (20.09)	5993 (20.37)	0.007	1683 (19.47)	1683 (19.47)	0
Statin	10 516 (77.23)	23 082 (78.44)	0.029	6493 (75.10)	6538 (75.62)	0.012
Other lipid-lowering drugs, excluding statins	703 (5.16)	1365 (4.64)	0.024	347 (4.01)	368 (4.26)	0.012
Antiplatelet	3898 (28.63)	10 765 (36.58)	0.170	2319 (26.82)	2343 (27.10)	0.006
Anticoagulants	608 (4.47)	2487 (8.45)	0.163	410 (4.74)	417 (4.82)	0.004
Nonsteroidal anti-inflammatory drugs	2522 (18.52)	4128 (14.03)	0.122	1524 (17.63)	1543 (17.85)	0.006
Oral corticosteroids	1072 (7.87)	2854 (9.70)	0.065	687 (7.95)	674 (7.80)	0.006
Bisphosphonates	188 (1.38)	1202 (4.08)	0.166	139 (1.61)	128 (1.48)	0.01
Opioids	2214 (16.26)	4329 (14.71)	0.043	1260 (14.57)	1255 (14.52)	0.002
Antidepressants	4566 (33.53)	7676 (26.09)	0.163	2556 (29.56)	2538 (29.35)	0.005
Antipsychotics	853 (6.26)	1899 (6.45)	0.008	520 (6.01)	515 (5.96)	0.002
Anticonvulsants	1613 (11.85)	2782 (9.45)	0.078	880 (10.18)	887 (10.26)	0.003
Lithium	35 (0.26)	86 (0.29)	0.007	23 (0.27)	18 (0.21)	0.012
Other anxiolytics/hypnotics	709 (5.21)	1518 (5.16)	0.002	461 (5.33)	439 (5.08)	0.011
Agents for dementia	21 (0.15)	278 (0.94)	0.107	19 (0.22)	14 (0.16)	0.013

Abbreviations: COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter-2; SMD, standardized mean difference; TC, total cholesterol.

(2.5 mg/dL), 148.71-416.39 μmol/l (2.5 to 7.0 mg/dL) and ≥416.39 μmol/l (7.0 mg/dL) were considered as low, normal and high, respectively. Propensity scores were estimated from a logistic regression model, using all the covariates in Table S1, to indicate the predicted treatment probability of being in the SGLT2 inhibitor cohort. A standardized morbidity ratio weighting method was used to assign patients in the SGLT2 inhibitor cohort with a weight of 1 and patients in the DPP-4 inhibitor cohort with a weight of [PS]/[1 − PS]. In addition to weighting, a caliper of 0.20 of the standard deviation of the logit of the PS was used for nearest-neighbour matching of SGLT2 inhibitor and DPP-4 inhibitor users. Covariate balance between the matched cohorts was assessed by using standardized differences, with a value below 0.1 indicating negligible differences between groups. After PS matching, proportional hazards were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the outcome. After PS weighting, standardized morbidity ratio-weighted Cox proportional hazard models were estimated. To obtain adjusted HRs, the models were adjusted for covariates that were imbalanced after matching (standardized mean difference > 0.1).

3 | RESULTS

A total of 362 937 eligible patients aged 18 years or older had a diagnosis of T2DM. Of these patients, 25 507 and 33 553 were new users of SGLT2 inhibitors and DPP-4 inhibitors, respectively. After implementation of the exclusion criteria, 13 617 new users of SGLT2 inhibitors and 29 426 new users of DPP-4 inhibitors were included in the study, and were followed up over a median (interquartile range) period of 1.68 (0.76-2.87) and 1.76 (0.78-3.21) person-years, respectively (Figure S1). The baseline characteristics of the study population are shown in Tables 1 and 2. Overall, biochemical measurements such as

TABLE 3 Risk of gout among new users of sodium-glucose cotransporter-2 inhibitors compared to new users of dipeptidyl peptidase-4 inhibitors in the intention-to-treat and at-treatment analyses in propensity-score-weighted and matched cohorts

	SGLT2 inhibitor cohort Weighted analysis	DPP-4 inhibitor cohort[a]	SGLT2 inhibitor cohort Matched analysis	DPP-4 inhibitor cohort
Intention-to-treat analysis				
Gout, n (%)	79 (0.58)	50 (0.33)	46 (0.53)	39 (0.45)
Number of patients	13 617	15 424	8646	8646
Total person-years of follow-up	26 066	25 177	15 836	14 553
Crude incidence rate/1000 person-years	3.03	2.00	2.90	2.68
Unadjusted HR (95% CI)	1.53 (0.93-2.51) $P = 0.091$		1.09 (0.71-1.67) $P = 0.693$	
Adjusted HR (95% CI)[b]	1.53 (0.95-2.45) $P = 0.080$		1.10 (0.71-1.68) $P = 0.676$	
At-treatment analysis				
Gout, n (%)	46 (0.34)	35 (0.23)	28 (0.32)	32 (0.37)
Number of patients	13 617	15 424	8646	8646
Total person-years of follow-up	18 359	19 021	10 807	11 419
Crude incidence rate/1000 person years	2.51	1.86	2.59	2.80
Unadjusted HR (95% CI)	1.35 (0.85-2.14) $P = 0.198$		0.92 (0.55-1.53) $P = 0.751$	
Adjusted HR (95% CI)[b]	1.33 (0.85-2.09) $P = 0.215$		0.92 (0.55-1.53) $P = 0.752$	

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; IQR, interquartile range; PS, propensity score; SGLT2, sodium-glucose cotransporter-2.

[a]Pseudo-cohort of DPP-4 inhibitor new users weighted using PS (weight = PS/[1 – PS]).

[b]Adjusted for covariates that were imbalanced between the SGLT2 inhibitor and DPP-4 inhibitor cohorts after PS matching (current use of glucagon-like peptide-1 agonists).

HbA1c, LDL cholesterol, HDL cholesterol, TC, triglycerides and eGFR were missing for 3.04%, 12.04%, 2.67%, 0.76%, 4.99% and 0.44% of the patients, respectively, and were imputed. In general, patients who initiated SGLT2 inhibitors were more likely to be younger, to be obese and to have worse glycaemic and cholesterol control compared to patients who initiated DPP-4 inhibitors. SGLT2 inhibitor initiators were also more likely to have initiated the drug during the later years of the study period compared to DPP-4 inhibitor initiators. SGLT2 inhibitor initiators were less likely to have diabetes complications and other comorbidities compared to DPP-4 inhibitor initiators (with the exception of asthma, and mental health and sleep disorders), and they were more likely to be current or past users of other antidiabetic medications, especially GLP-1RAs and insulin.

After PS matching, a total of 8650 matched pairs of SGLT2 inhibitor and DPP-4 inhibitor new users remained. PS distribution overlap was sufficient (Figure S2) and balance between the groups was found to be satisfactory for the covariates; a standardized mean difference > 0.1 was observed for only one of the covariates, current use of GLP-1RAs (Table 2).

In the PS-matched ITT analysis, a total of 85 incident cases of gout were recorded over 30 389 person-years of observation. Crude incidence rates (IRs) per 1000 person-years were found to be 2.90 and 2.47 for SGLT2 inhibitor and DPP-4 inhibitor new users, respectively. The unadjusted HR was 1.18 (95% CI 0.76-1.83). After adjustment for the covariate with standardized mean difference > 0.1 after matching (current use of GLP-1RA), the HR was similar (adjusted HR 1.20 [95% CI 0.77-1.86]). In the at-treatment analysis, in which patients were censored at the time of discontinuation of the index drug (2199 [25.42%] and 2236 patients [25.85%] in the SGLT2 inhibitor and DPP-4 inhibitor cohorts, respectively) or at time of switch to the comparator drug [1157 (13.38%) and 3 (0.03%) in the SGLT2 and DPP-4 inhibitor cohorts, respectively), a total of 58 incident cases of gout were recorded over 22 315 person-years of observation. The crude IRs per 1000 person-years were found to be 2.68 and 2.53 for SGLT2 and DPP-4 inhibitor users, respectively. In the adjusted model, the adjusted HR was 1.07 (95% CI 0.64-1.79). In a sensitivity analysis, in which commencement of a uric acid-lowering medication was also included in the outcome definition, the findings remained unchanged (adjusted HR 1.43 [95% CI 0.90-2.29] and 1.15 [95% CI 0.67-1.99]) in the ITT and at-treatment analysis, respectively (Table 3).

After PS weighting, a cohort of 13 617 SGLT2 inhibitor new users and a pseudo-cohort of 15 422 DPP-4 inhibitor new users were obtained. A total of 130 incident gout cases were recorded over a feigned follow-up period of 29 039 person-years in the ITT analysis. Crude IRs of 3.03 and 2.03 per 1000 person-years were estimated for gout in the SGLT2 inhibitor and DPP-4 inhibitor cohorts, respectively. The unadjusted HR was 1.51 (95% CI 0.91-2.51). After adjustment for current use of GLP-1RAs, the adjusted HR was 1.51 (95% CI 0.93-2.44). In the at-treatment analysis, the unadjusted and adjusted HRs were 1.35 (95% CI 0.85-2.13) and 1.33 (95% CI 0.84-2.08), respectively.

In a post hoc analysis exploring the characteristics of patients with incident gout in the SGLT2 inhibitor and DPP-4 inhibitor cohorts, descriptive characteristics of patients who developed gout were summarized stratified by the exposure drug and are presented in Tables S3 and S4. Of those who developed gout, compared to

patients in the DPP-4 inhibitor cohort, patients in the SGLT2 inhibitor cohort were likely to be younger (mean [SD] 61.08 (9.12) vs. 63.14 [11.01] years) and obese (25 [86.21%] vs. 20 patients [68.97%]). Of those who developed gout, patients in the SGLT2 inhibitor cohort were more likely to have cardiovascular comorbidities at baseline compared to patients in the DPP-4 inhibitor cohort.

4 | DISCUSSION

In this nationwide study, we calculated the risk of incident gout in patients with diabetes treated with SGLT2 inhibitors compared to that in DPP-4 inhibitor users. No significant difference was observed between treatment cohorts after PS matching. This neutral finding was consistent in both ITT and at-treatment analyses.

Despite the fact that the incidence rate estimates of the present study were comparable with previous literature, our main finding lies in contrast to several previous publications, detailed below. In a post hoc analysis of the prospectively collected data within the CANVAS program, which involved a total of 10 142 participants and was designed for exploring cardiovascular events in patients receiving canagliflozin or placebo,[16] the incidence of gout flare was explored as a composite outcome consisting of occurrence of gout flare and/or commencement of a medication for gout (allopurinol, febuxostat, benzbromarone, colchicine or probenecid) and/or recording of hyperuricaemia. A total of 80 events of gout and 147 events of drug commencement were recorded during the observation period. The risk of gout flare or the commencement of a drug for gout was found to be lower in participants using canagliflozin than in those using placebo (4.1 vs. 6.6 per 1000 person-years; HR 0.53, 95% CI 0.40-0.71). Similarly, in a real-world study (insurance database claims), involving a total population of 295 907 adults with T2DM who were newly prescribed a SGLT2 inhibitor or a GLP-1RA,[17] the risk of gout in individuals receiving SGLT2 inhibitors was found to be lower compared to those receiving GLP-1RAs (4.9 vs.7.8 events per 1000 person-years) during the observation period, with a mean follow-up of less than 1 year. This study was complementary to the post hoc analysis by Li et al,[16] in which the effect of SGLT2 inhibitors on gout incidence was compared to an active comparator (GLP-1RA), as opposed to placebo. However, the external validity of this study might be limited by the following methodological considerations: (i) the list of covariates available for use in the PS matching did not include HbA1c, creatinine levels or BMI, all of which are strongly correlated with both exposure and outcome and (ii) short duration of the study. Notably, in a subanalysis of the EMPA-REG OUTCOME trial, the use of empagliflozin was not associated with a significant decrease in the risk of gout in accordance with our findings, although this specific outcome was underpowered because the absolute number of events did not permit an interpretable analysis.[18] In a later post hoc analysis of the EMPA-REG trial, the authors reported a modest decrease in uric acid levels in those patients who were taking empagliflozin compared to placebo and a significant decrease in the composite outcome of gout flare and/or commencement of an anti-gout medication among approximately 6600 patients not taking antigout medications at baseline.[24] However, it should be noted that the difference in gout flares among groups was not found to be significant.

The main strength of the present study was the covariate list included in the PS matching; specifically, it included BMI, renal function, glycaemic control as assessed by HbA1c, concomitant medications and underlying diseases and comorbidities, which may significantly impact clinical decisions regarding treatment intensification, while also affecting gout risk. Thus, the incorporation of these variables in the PS matching procedure might provide a more pragmatic and balanced estimate of the independent treatment effects. The choice of comparator should be also considered in the interpretation of the results; DPP-4 inhibitors' effect on urate levels is considered to be neutral, whereas GLP-1RAs might increase urate levels (in the short term), an observation reported in a post hoc analysis of clinical trials.[25] Another main strength of the study is the large sample and power calculated post hoc as 80%.

The findings of the present study should be interpreted within the context of its limitations. Ideally, the exploration of a potential relationship between a drug exposure and an outcome would require an observation period sufficiently long to permit the full documentation of events and account for late-onset actions. However, this was not the case in the present study or in the previous literature. Moreover, the possibility of information bias resulting from incorrect documentation of outcomes or covariates is inherent in database studies and cannot be precluded in the present study. Additionally, the issue of non-adherence and non-compliance to treatment may result in misclassification of exposure. However, there is no reason to assume that this would result in differential misclassification since drop-out rates in the SGLT2 inhibitor and DPP-4 inhibitor cohorts were similar. Finally, some of the medications associated with gout flares in the literature, such as antituberculosis agents, have not been included as covariates in the analyses. However, considering tuberculosis incidence and its continuing downtrend, it is unlikely that this would have distorted the findings of the present study.

In conclusion, the use of SGLT2 inhibitors was not found to be associated with a significantly reduced risk of gout and there is no firm evidence to suggest that the SGLT2 inhibitor class may be more useful compared to DPP-4 inhibitors in terms of addressing risk of gout in patients with T2DM.

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CONFLICT OF INTEREST

None declared.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

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

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