ORIGINAL ARTICLE

The associations of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors as add-on to metformin with fracture risk in patients with type 2 diabetes mellitus

Veerle van Hulten MSc[1,2,3,4] | Johanna H. M. Driessen PhD[1,2,3,4] |
Jakob K. Starup-Linde PhD[5] | Zheer K. Al-Mashhadi MD[5,6,7] | Rikke Viggers MD[8,9] |
Olaf H. Klungel PhD[4] | Patrick C. Souverein PhD[4] | Peter Vestergaard MD[8,10] |
Coen D. A. Stehouwer MD[11] | Joop P. van den Bergh MD[2,12,13]

[1]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands

[2]School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands

[3]Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

[4]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands

[5]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

[6]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[8]Steno Diabetes Center North Denmark, Aalborg, Denmark

[9]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[10]Department of Endocrinology, Aalborg University Hospital, Aalborg, Denmark

[11]Department of Internal Medicine, Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre+ (MUMC+), Maastricht, Netherlands

[12]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands

[13]Department of Internal Medicine, Subdivision of Endocrinology, VieCuri Medical Center, Venlo, The Netherlands

Correspondence
Veerle van Hulten, Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+ (MUMC+), Maastricht, The Netherlands.
Email: veerle.van.hulten@mumc.nl

Funding information
Novo Nordisk Steno Collaborative Grant 2018

Abstract

Aim: To investigate whether sodium-glucose cotransporter-2 (SGLT2) inhibitor use as compared to dipeptidyl peptidase-4 (DPP-4) inhibitor use as add-on to metformin is associated with the risk of any fracture or major osteoporotic fractures (MOFs).

Methods: A cohort study using the Clinical Practice Research Datalink (CPRD) Aurum database was conducted. All patients aged 18 years and older with a first-ever prescription for a DPP-4 inhibitor or an SGLT2 inhibitor as add-on to metformin between January 1, 2013 and June 30, 2020 were selected. Patients starting with SGLT2 inhibitors were matched (up to 1:3) on propensity scores to patients starting with DPP-4 inhibitors. Propensity scores were calculated based on sex, age, body mass index, comorbidities, comedication and lifestyle factors. Cox proportional hazard models were used to estimate the risk of fracture with SGLT2 inhibitor use as compared to DPP-4 inhibitor use.

Results: A total of 13 807 SGLT2 inhibitor users (age 55.4 ± 10.6 years, 36.7% female) were included in this study, matched with 28 524 DPP-4 inhibitor users (age 55.4 ± 8.0 years, 36.4% female). The risk of any fracture with current SGLT2 inhibitor use was similar compared with current DPP-4 inhibitor use (adjusted hazard ratio [aHR] 1.09, 95% confidence interval [CI] 0.91-1.31), as was the risk of MOFs (aHR 0.89, 95% CI 0.64-1.22) and the risk of fractures at any of the individual MOF sites. Additionally, no association was found with duration of SGLT2 inhibitor use (longest duration >811 days) for any of the individual SGLT2 inhibitor agents, or after stratification by sex and age.

Conclusion: Use of SGLT2 inhibitors was not associated with the risk of any fracture, MOFs or fracture at the individual MOF sites when compared to DPP-4 inhibitor use.

KEYWORDS

cohort study, diabetes complications, DPP-4 inhibitor, pharmacoepidemiology, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Globally, the number of people with diabetes mellitus has quadrupled in the last 30 years.[1] Consequently, type 2 diabetes mellitus (T2D) is a major burden for public health and in terms of healthcare costs. Knowledge regarding current treatment options needs to be expanded.

Metformin is the first-line treatment for T2D and can be paired with an adjunct medication if metformin as a monotherapy does not adequately control blood sugar levels.[2,3] Currently, both dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors can be prescribed as an adjunct medication, according to the guidelines of the National Institute for Health and Clinical Excellence.[3]

The SGLT2 inhibitors are a relatively new drug class and have been approved by the European Medicines Agency (EMA) since 2012.[4] Therefore, more long-term putative side effects have only recently been brought forward, such as an increased risk of fractures.[5] DPP-4 inhibitors have been approved by the EMA for much longer, since 2007,[4] and could thus be considered a well-known comparator.

Some studies have been performed on the association between SGLT2 inhibitor use and fracture risk, and in the CANVAS study[6] it was reported that fracture risk was increased with canagliflozin treatment. Additionally, a propensity-score-matched cohort study (follow-up 31 weeks) and a randomized controlled trial (follow-up 52 weeks) also found an increased fracture risk when comparing SGLT2 inhibitor use to either DPP-4 inhibitor use, sulphonylurea (SU) use or placebo.[6,7] Conversely, an observational study, a propensity-score-matched cohort study and a meta-analysis plus post hoc analysis of randomized controlled trials did not find an increased fracture risk with SGLT2 inhibitor use.[8-11] In these studies, follow-up was limited to between 12 and 38 weeks.[8-11]

It is important to note, however, that, even though bone turnover is a continuous process, changes in bone turnover or osteoblast and osteoclast activity do not immediately translate into changes in fracture risk. Therefore, it is important to look at both a short-term association, whereby SGLT2 inhibitors could increase fall risk and subsequently fracture risk through hypovolaemia and orthostasis,[12] and also a long-term association, whereby SGLT2 inhibitors could affect bone turnover through increased calcium excretion[13] or other mechanisms. To summarize, current evidence is limited by short durations of follow-up. Therefore, our aim was to study a potential association between longer-term use of SGLT2 inhibitors as compared to DPP-4 inhibitors as add-on to metformin and the risk of fracture, separately looking at major osteoporotic fractures (MOFs).

2 | METHODS

2.1 | Data source

A cohort study using the Clinical Practice Research Datalink (CPRD; www.cprd.com) was conducted. The CPRD contains medical records of primary care practices in the United Kingdom. The data recorded in the CPRD include patient demographics, medical history, laboratory test results, prescription details, specialist referrals, hospital admissions and major outcomes since 1987, with on-going data collection. The study period for the present study was 2013 to 2020.

This study was performed separately in both the CPRD GOLD and CPRD Aurum databases. CPRD GOLD is considered a well-established database with contributing practices from across the United Kingdom. However, only general practices using Vision software contribute to CPRD GOLD,[14] and this number is declining, making the database less representative of the whole population. The general practices using EMIS Web software contribute to the relatively new CPRD Aurum database,[15] and in contrast to the GOLD database, this number is increasing. CPRD Aurum currently represents approximately 19.9% of the total population in the United Kingdom, including 1489 general practices.[16] CPRD GOLD includes approximately 4.6% of the total UK

population as active (alive, currently registered) patients, from 401 contributing practices.[17]

The independent scientific advisory committee of the CPRD approved the study protocol (number 22_002254). No further ethical approval was needed.

2.2 | Study population

All patients aged 18 years and older with a first-ever prescription for a DPP-4 inhibitor or an SGLT2 inhibitor between January 1, 2013, and June 30, 2020, were identified. This study period was chosen as SGLT2 inhibitors have been available since January 1, 2013, in the United Kingdom. The date of the first DPP-4 inhibitor prescription or SGLT2 inhibitor prescription defined the index date.

All patients were required to start with either a DPP-4 inhibitor or an SGLT2 inhibitor as a first intensification and as add-on to metformin and were thus required to have a prescription for metformin but no other glucose-lowering drug before the index date. The duration of the most recent metformin prescription was required to cover the index date, to ensure the DPP-4 inhibitor or SGLT2 inhibitor prescriptions were prescribed as add-on to metformin. The duration of the prescription was determined based on the prescribed quantity and the dosage instruction. If the duration could not be calculated due to missing data, the median of all calculated durations was assigned.

Furthermore, patients were excluded if they used glucose-lowering drugs other than metformin before the index date.

Patients with a history of polycystic ovary syndrome before the index date were excluded. Furthermore, all patients who had a prescription for glucocorticoids in the 6 months prior to the index date and all patients who had had a prescription for anti-osteoporotic drugs (defined as the use of bisphosphonates, strontium ranelate, bazedoxifene, raloxifene, vitamin D_3 [cholecalciferol], calcium or parathyroid hormone [PTH]/calcitonin) in the 12 months prior to the index date were excluded from the analysis.

2.3 | Exposure

Patients were followed from the index date until the end of data collection, discontinuation of drug of interest (DPP-4 inhibitor or SGLT2 inhibitor), start of comparator drug, start of other glucose-lowering drugs, or the event of interest, whichever came first. Patients needed to continue both metformin and the drug of interest (DPP-4 inhibitor or SGLT2 inhibitor). If patients discontinued treatment with either of these, the follow-up was censored. Furthermore, patients were censored in case of death or upon being transferred to another practice.

Discontinuation was determined based on the dosage instruction and prescribed quantity, from which the expected end date was calculated. If there was no new prescription in the 60 days after the expected end date, this was considered to be discontinuation.

2.4 | Outcomes

The primary outcome of interest was any fracture. Secondary outcomes included MOFs, defined according to the definition by the International Osteoporosis Foundation (IOF) as the first of a hip, radius/ulna, humerus or clinical symptomatic vertebral fracture,[18] or the occurrence of a fracture at any of the individual MOF sites. Fractures were classified according to Snomed concept ID's (Aurum) or to Read codes (GOLD).

2.5 | Characteristics

The presence of possible confounding variables was assessed by reviewing the computerized medical records. Sex, age, most recent body mass index (BMI), diabetes duration (defined as time since first metformin prescription), prior fractures, smoking status (never, past, current or missing) and alcohol use (yes, no or missing) status were established at baseline. Furthermore, the most recent glycated haemoglobin (HbA1c) value and estimated glomerular filtration rate (eGFR) were established in the year prior to the index date.

Furthermore, a history of the following comorbidities prior to the index date was considered to be a potential confounder: Alzheimer's disease/dementia, arrhythmia, osteoporosis, osteoarthritis, paralysis, chronic obstructive pulmonary disease (COPD), stroke, brain injury, heart failure, acute myocardial infarction, cancer (excluding non-melanoma skin cancers), hyper-/hypoparathyroidism, retinopathy, neuropathy, nephropathy, micro- or macroalbuminuria (1 year prior to index date), diabetic foot ulcer and previous fractures. Lastly, the use of any of the following drugs in the 6 months prior to the index date were additionally considered as potential confounders: anti-convulsants, diuretics, anxiolytics or sedatives, neuroleptics/anti-psychotics, antidepressants, statins, and non-statin cholesterol-lowering drugs, antihypertensives, skeletal muscle relaxants, proton pump inhibitors, H2 receptor antagonists, Parkinson's disease medication and antiarrhythmics.

2.6 | Statistical analysis plan

Propensity-score matching was used to control for confounding. The propensity score is defined as the predicted probability of a patient starting an SGLT2 inhibitor versus a DPP-4 inhibitor (both as add-on to metformin only) given the aforementioned baseline characteristics. Multivariable logistic regression was used to estimate the propensity score including all aforementioned potential confounders.

Patients starting SGLT2 inhibitors were matched (up to 1:3) to patients starting DPP-4 inhibitors using a nearest-neighbour matching algorithm without replacement, with a matching calliper of $0.2\times$ the

TABLE 1 Baseline characteristics of SGLT2 and DPP-4 inhibitor users, before and after propensity-score matching in the Clinical Practice Research Datalink Aurum and GOLD

| | Aurum | | | | | | GOLD | | | | | |
| | Before matching | | | After matching | | | Before matching | | | After matching | | |
	SGLT2 inhibitor users (N = 13 837)	DPP-4 inhibitor users (N = 37 292)	St. Diff.	SGLT2 inhibitor users (N = 13 807)	DPP-4 inhibitor users (N = 28 524)	St. Diff.	SGLT2 inhibitor users (N = 5641)	DPP-4 inhibitor users (N = 11 762)	St. Diff.	SGLT2 inhibitor users (N = 5517)	DPP-4 inhibitor users (N = 9543)	St. Diff.
Median follow-up time, years	0.8 (0.2–1.9)	1.0 (0.2–2.6)		0.8 (0.2–1.9)	1.0 (0.3–2.4)		0.7 (0.2–1.6)	0.8 (0.2–1.9)		0.7 (0.2–1.6)	0.8 (0.2–1.8)	
Mean follow-up time, years	1.3 (1.4)	1.7 (1.8)		1.3 (1.4)	1.6 (1.2)		1.1 (1.2)	1.4 (1.5)		1.1 (1.2)	1.3 (1.1)	
Mean diabetes duration, years	3.4 (3.0)	3.9 (3.4)		3.4 (3.0)	3.4 (2.1)		3.4 (3.2)	3.8 (3.3)		3.4 (3.2)	3.4 (2.3)	
Age, years	55.3 (10.6)	61.0 (12.8)	−0.5	55.4 (10.6)	55.4 (8.0)	0.0	56.5 (10.7)	62.2 (12.1)	−0.5	56.8 (10.4)	56.8 (8.4)	−0.0
Female, n (%)	5091 (36.8)	13 424 (36.0)	0.0	5071 (36.7)	5023 (36.4)	0.0	2188 (38.8)	4410 (37.5)	0.0	2122 (38.5)	2097 (38.0)	0.0
BMI category, n (%)			0.2			0.0			0.4			0.0
<25.0 kg/m²	503 (3.6)	3375 (9.1)		503 (3.6)	471 (3.4)		175 (3.1)	875 (7.4)		175 (3.2)	159 (2.9)	
25–29.9 kg/m²	2753 (19.9)	11 024 (29.6)		2753 (19.9)	2761 (20.0)		1001 (17.7)	3352 (28.5)		1001 (18.1)	1000 (18.1)	
30–34.9 kg/m²	4228 (30.6)	11 345 (30.4)		4226 (30.6)	4363 (31.6)		1727 (30.6)	3691 (31.4)		1722 (31.2)	1783 (32.3)	
≥35 kg/m²	6015 (43.5)	10 423 (27.9)		5987 (43.4)	5870 (42.5)		2685 (47.6)	3717 (31.6)		2566 (46.5)	2517 (45.6)	
Missing	338 (2.4)	1125 (3.0)		338 (2.4)	343 (2.5)		53 (0.9)	127 (1.1)		53 (1.0)	58 (1.1)	
Smoking status, n (%)			0.1			0.0			0.1			0.0
Never	3514 (25.4)	8688 (23.3)		3507 (25.4)	3492 (25.3)		1801 (31.9)	3625 (30.8)		1752 (31.8)	1755 (31.8)	
Past	3685 (26.6)	10 040 (26.9)		3676 (26.6)	3707 (26.8)		1038 (18.4)	1895 (16.1%)		1005 (18.2)	1017 (18.4)	
Current	6397 (46.2)	17 717 (47.5)		6383 (46.2)	6364 (46.1)		2794 (49.5)	6234 (53.0)		2754 (49.9)	2739 (49.6)	
Missing	241 (1.7)	847 (2.3)		241 (1.7)	244 (1.8)		8 (0.1)	8 (0.1)		6 (0.1)	7 (0.1)	
Alcohol use, n (%)			0.1			0.0			0.1			0.0
No	5783 (41.8)	16 251 (43.6)		5775 (41.8)	5766 (41.8)		1454 (25.8)	3275 (27.8)		1423 (25.8)	1406 (25.5)	
Yes	7400 (53.5)	19 047 (51.1)		7380 (53.5)	7386 (53.5)		3991 (70.7)	8132 (69.1)		3909 (70.9)	3932 (71.2)	
Missing	654 (4.7)	1994 (5.3)		652 (4.7)	655 (4.7)		196 (3.5)	355 (3.0)		185 (3.4)	180 (3.3)	
Most recent HbA1c[a], n (%)			0.2			0.0			0.2			0.0
HbA1c <7.0%	820 (5.9)	2606 (7.0)		816 (5.9)	804 (5.8)		248 (4.4)	726 (6.2)		246 (4.5)	240 (4.4)	
HbA1c 7.0–7.9%	3280 (23.7)	11 215 (30.1)		3280 (23.8)	3253 (23.6)		1280 (22.7)	3314 (28.2)		1270 (23.0)	1248 (22.6)	
HbA1c 8.0–8.9%	3892 (28.1)	10 908 (29.3)		3889 (28.2)	3953 (28.6)		1614 (28.6)	3703 (31.5)		1599 (29.0)	1629 (29.5)	
HbA1c ≥9.0%	5293 (38.3)	10 907 (29.2)		5272 (38.2)	5247 (38.0)		2339 (41.5)	3748 (31.9)		2247 (40.7)	2251 (40.8)	
Missing	552 (4.0)	1656 (4.4)		550 (4.0)	550 (4.0)		160 (2.8)	271 (2.3)		155 (2.8)	150 (2.7)	

TABLE 1 (Continued)

	Aurum						GOLD					
	Before matching			After matching			Before matching			After matching		
	SGLT2 inhibitor users (N = 13 837)	DPP-4 inhibitor users (N = 37 292)	St. Diff.	SGLT2 inhibitor users (N = 13 807)	DPP-4 inhibitor users (N = 28 524)	St. Diff.	SGLT2 inhibitor users (N = 5641)	DPP-4 inhibitor users (N = 11 762)	St. Diff.	SGLT2 inhibitor users (N = 5517)	DPP-4 inhibitor users (N = 9543)	St. Diff.
Kidney function, n (%)			0.5			0.0			0.4			0.0
CKD1	8589 (62.1)	17 508 (46.9)		8560 (62.0)	8527 (61.8)		2240 (39.7)	3834 (32.6)		2169 (39.3)	2201 (39.9)	
CKD2	4640 (33.5)	14 485 (38.8)		4639 (33.6)	4694 (34.0)		3172 (56.2)	6208 (52.8)		3120 (56.6)	3104 (56.3)	
CKD3	164 (1.2)	3852 (10.3)		164 (1.2)	146 (1.1)		119 (2.1)	1537 (13.1)		119 (2.2)	105 (1.9)	
Missing	444 (3.2)	1447 (3.9)		444 (3.2)	440 (3.2)		110 (2.0)	183 (1.6)		109 (2.0)	108 (2.0)	
Comorbidities (ever), n (%)												
Alzheimer's disease/dementia	22 (0.2)	460 (1.2)	−0.1	22 (0.2)	18 (0.1)	0.0	17 (0.3)	113 (1.0)	−0.1	17 (0.3)	17 (0.3)	−0.0
Arrhythmia	551 (4.0)	2347 (6.3)	−0.1	550 (4.0)	527 (3.8)	0.0	316 (5.6)	936 (8.0)	−0.1	311 (5.6)	305 (5.5)	0.0
Osteoporosis	33 (0.2)	241 (0.6)	−0.1	33 (0.2)	43 (0.3)	−0.0	20 (0.4)	102 (0.9)	−0.1	20 (0.4)	15 (0.3)	0.0
Osteoarthritis	2224 (16.1)	7714 (20.7)	−0.1	2224 (16.1)	2198 (15.9)	0.0	936 (16.6)	2501 (21.3)	−0.1	928 (16.8)	934 (16.9)	−0.0
Paralysis	47 (0.3)	239 (0.6)	−0.0	47 (0.3)	45 (0.3)	0.0	18 (0.3)	44 (0.4)	−0.0	18 (0.3)	17 (0.3)	0.0
COPD	461 (3.3)	1730 (4.6)	−0.1	461 (3.3)	466 (3.4)	−0.0	239 (4.2)	582 (4.9)	−0.0	236 (4.3)	243 (4.4)	−0.0
Stroke/brain injury	544 (3.9)	2313 (6.2)	−0.1	544 (3.9)	530 (3.8)	0.0	238 (4.2)	757 (6.4)	−0.1	236 (4.3)	239 (4.3)	−0.0
Heart failure	283 (2.0)	1183 (3.2)	−0.1	283 (2.0)	288 (2.1)	−0.0	20 (0.4)	102 (0.9)	−0.1	20 (0.4)	15 (0.3)	0.0
Acute myocardial infarction	628 (4.5)	1968 (5.3)	−0.0	627 (4.5)	634 (4.6)	−0.0	341 (6.0)	751 (6.4)	−0.0	337 (6.1)	326 (5.9)	0.0
Cancer	4394 (31.8)	12 186 (32.7)	−0.0	4384 (31.8)	4378 (31.7)	0.0	1288 (22.8)	3098 (26.3)	−0.1	1268 (23.0)	1274 (23.1)	−0.0
Hyper-/hypoparathyroidism	201 (1.5)	655 (1.8)	−0.0	201 (1.5)	201 (1.5)	−0.0	9 (0.2)	38 (0.3)	−0.0	9 (0.2)	9 (0.2)	0.0
Retinopathy	2607 (18.8)	8479 (22.7)	−0.1	2604 (18.9)	2611 (18.9)	−0.0	966 (17.1)	2380 (20.2)	−0.1	961 (17.4)	969 (17.6)	−0.0
Neuropathy	160 (1.2)	637 (1.7)	−0.0	160 (1.2)	158 (1.1)	0.0	25 (0.4)	90 (0.8)	−0.0	25 (0.5)	24 (0.4)	0.0
Nephropathy	261 (1.9)	1040 (9.8)	−0.1	261 (1.9)	261 (1.9)	0.0	59 (1.0)	213 (1.8)	−0.1	59 (1.1)	61 (1.1)	−0.0
Microalbuminuria (1 year prior)	1557 (11.3)	4644 (12.5)	−0.0	1557 (11.3)	1558 (11.3)	−0.0	799 (14.2)	1837 (15.6)	−0.0	778 (14.1)	779 (14.1)	−0.0
Macroalbuminuria (1 year prior)	174 (1.3)	582 (1.6)	−0.0	174 (1.3)	171 (1.2)	0.0	91 (1.6)	232 (2.0)	−0.0	88 (1.6)	87 (1.6)	0.0
Peripheral vascular disease	164 (1.2)	834 (2.2)	−0.1	164 (1.2)	159 (1.1)	0.0	67 (1.2)	199 (1.7)	−0.0	67 (1.2)	68 (1.2)	−0.0
Diabetic foot ulcer	89 (0.6)	396 (1.1)	−0.0	89 (0.6)	89 (0.5)	0.0	34 (0.6)	108 (0.9)	−0.0	34 (0.6)	32 (0.6)	0.0

(Continues)

TABLE 1 (Continued)

| | Aurum | | | | | | GOLD | | | | | |
| | Before matching | | | After matching | | | Before matching | | | After matching | | |
	SGLT2 inhibitor users (N = 13 837)	DPP-4 inhibitor users (N = 37 292)	St. Diff.	SGLT2 inhibitor users (N = 13 807)	DPP-4 inhibitor users (N = 28 524)	St. Diff.	SGLT2 inhibitor users (N = 5641)	DPP-4 inhibitor users (N = 11 762)	St. Diff.	SGLT2 inhibitor users (N = 5517)	DPP-4 inhibitor users (N = 9543)	St. Diff.
History of fractures	3395 (24.5)	8395 (22.5)	−0.1	3383 (24.5)	3364 (24.4)	0.0	1591 (28.2)	3115 (26.5)	0.0	1552 (28.1)	1551 (28.1)	0.0
Medication (6 months), n (%)												
Anti-Parkinson's disease drugs	96 (0.7)	339 (0.9)	−0.0	96 (0.7)	94 (0.7)	0.0	39 (0.7)	78 (0.7)	0.0	38 (0.7)	40 (0.7)	−0.0
Antihypertensives	8577 (62.0)	25 158 (67.5)	−0.1	8565 (62.0)	8570 (62.1)	−0.0	3642 (64.6)	8078 (68.7)	−0.1	3574 (64.8)	3576 (64.8)	−0.0
Anxiolytics/sedatives	551 (4.0)	1633 (4.4)	−0.0	550 (4.0)	552 (4.0)	−0.0	359 (6.4)	764 (6.5)	−0.1	353 (6.4)	346 (6.3)	0.0
Anti-depressants	3279 (23.7)	7810 (20.9)	0.1	3267 (23.7)	3230 (23.4)	0.0	1707 (30.3)	2956 (25.1)	0.1	1647 (29.9)	1609 (29.2)	0.0
Cholesterol-lowering drugs	9385 (67.8)	27 680 (74.2)	−0.1	9377 (67.9)	9466 (68.6)	−0.0	3829 (67.9)	8759 (74.5)	−0.1	3783 (68.6)	3803 (68.9)	−0.1
PPI/H2RA	4496 (32.5)	12 786 (34.3)	−0.0	4487 (32.5)	4476 (32.4)	0.0	2012 (35.7)	4233 (36.0)	−0.0	1965 (35.6)	1944 (35.2)	0.0
Anti-convulsants	931 (6.7)	2664 (7.1)	−0.0	929 (6.7)	936 (6.8)	−0.0	523 (9.3)	966 (8.2)	−0.0	507 (9.2)	505 (9.2)	0.0
Diuretics	1433 (10.4)	6219 (16.7)	−0.2	1433 (10.4)	1422 (10.3)	0.0	981 (17.4)	2796 (23.8)	−0.2	974 (17.7)	984 (17.8)	−0.0
Anti-psychotics	551 (4.0)	1601 (4.3)	−0.0	550 (4.0)	582 (4.2)	−0.0	198 (3.5)	386 (3.3)	0.0	194 (3.5)	198 (3.6)	−0.0
Muscle relaxants	814 (5.9)	2280 (6.1)	−0.0	811 (5.9)	799 (5.8)	0.0	319 (5.7)	594 (5.1)	0.0	307 (5.6)	295 (5.4)	0.0

Note: Continues variables are presented as mean (SD), unless stated otherwise. Categorical variables are presented as number of participants (%).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; PPI/H2RA, proton pump inhibitors/H2 receptor antagonist; St. Diff., standardized difference; SGLT2, sodium-glucose cotransporter-2.

[a]Year prior to index date.

TABLE 2 Risk of fractures in SGLT2 inhibitor versus DPP-4 inhibitor users, stratified by fracture type

	Number of patients	Number of fractures	IR/1000 PY	aHR (95% CI)
(A) Aurum				
Any fracture				
DPP-4 inhibitor use	28 524	201	9.1 (7.9–10.4)	Reference
SGLT2 inhibitor use	13 807	175	9.9 (8.6–11.5)	1.09 (0.91–1.31)
MOF fracture				
DPP-4 inhibitor use	28 524	73	3.2 (2.6–4.1)	Reference
SGLT2 inhibitor use	13 807	51	2.9 (2.1–3.8)	0.89 (0.64–1.22)
Hip fracture				
DPP-4 inhibitor use	28 524	10	0.4 (0.2–0.8)	Reference
SGLT2 inhibitor use	13 807	1	0.1 (0.0–0.4)	0.16 (0.02–1.19)
Vertebral fracture				
DPP-4 inhibitor use	28 524	12	0.5 (0.3–1.0)	Reference
SGLT2 inhibitor use	13 807	6	0.3 (0.2–0.7)	0.59 (0.24–1.47)
Humerus fracture				
DPP-4 inhibitor use	28 524	27	1.2 (0.8–1.7)	Reference
SGLT2 inhibitor use	13 807	21	1.2 (0.8–1.8)	1.00 (0.59–1.68)
Radius/ulna fracture				
DPP-4 inhibitor use	28 524	26	1.2 (0.8–1.7)	Reference
SGLT2 inhibitor use	13 807	25	1.4 (0.9–2.1)	1.15 (0.72–1.85)
(B) GOLD				
Any fracture				
DPP-4 inhibitor use	9543	64	8.8 (6.9–11.2)	Reference
SGLT2 inhibitor use	5517	55	8.9 (6.8–11.5)	1.01 (0.72–1.40)
MOF fracture				
DPP-4 inhibitor use	9543	24	3.2 (2.2–4.8)	Reference
SGLT2 inhibitor use	5517	17	2.7 (1.7–4.4)	0.84 (0.48–1.48)
Hip fracture				
DPP-4 inhibitor use	9543	6	0.8 (0.4–1.8)	Reference
SGLT2 inhibitor use	5517	3	0.5 (0.2–1.5)	0.58 (0.16–2.07)
Vertebral fracture				
DPP-4 inhibitor use	9543	3	0.4 (0.1–1.3)	Reference
SGLT2 inhibitor use	5517	2	0.3 (0.1–1.3)	0.71 (0.14–3.55)
Humerus fracture				
DPP-4 inhibitor use	9543	6	0.8 (0.4–1.8)	Reference
SGLT2 inhibitor use	5517	5	0.8 (0.3–1.9)	1.02 (0.37–2.83)
Radius/ulna fracture				
DPP-4 inhibitor use	9543	9	1.2 (0.6–2.3)	Reference
SGLT2 inhibitor use	5517	7	1.1 (0.5–2.3)	0.95 (0.38–2.38)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; MOF, major osteoporotic fractures PY, person-years; SGLT2, sodium-glucose cotransporter-2.

SD of the logit of the propensity score. Standardized mean differences were calculated to check the balance after matching. The missing indicator method was used to account for missing data.

Incidence rates (IRs) were calculated, and Cox proportional hazard models were used to estimate the risk of any fracture with SGLT2 inhibitor use as compared to DPP-4 inhibitor use. As secondary analyses, the risk of MOF and of fracture of the hip, radius/ulna, humerus, or a clinical symptomatic vertebral fracture was estimated. Furthermore, the analyses were stratified by sex and age categories. Moreover, the agent effect of the different agents of SGLT2 inhibitors, namely, canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, was studied. Lastly, duration of use was studied by dividing

follow-up time into intervals of 90 days. At the start of each interval, the duration of use was established. The groups were divided into duration-of-use categories, so that each category had approximately the same number of fractures.

As a sensitivity analysis, the number of extra days used to determine treatment discontinuation was shortened from 60 to 30. Furthermore, a sensitivity analysis was performed in which the reference group was changed to SU use, as this has been the main second-line treatment for many years and is still the most used second-line treatment after DPP-4 inhibitors.[19] Patients starting with SGLT2 inhibitors were matched (up to 1:3) on propensity scores to patients starting with SUs.

An additional sensitivity analysis was performed in which a less strict exposure definition was set. In this sensitivity analysis, patients who started antihyperglycaemic drugs other than SGLT2 inhibitors, DPP-4 inhibitors or metformin after the index date were not censored.

Lastly, the Cox regression analysis in the propensity-score-matched-population was repeated, with time-dependent correction for BMI and eGFR, since we expected the course of these covariates during follow-up to differ between exposure groups. For this analysis, the follow-up was divided into 90-day intervals and was corrected for the most recently recorded BMI and eGFR before the start of each interval.

Distributions of the propensity score per exposure group were compared before and after matching (Supplemental Figure S1).

TABLE 3 Risk of any or major osteoporotic fractures by duration of use in SGLT2 inhibitor versus DPP-4 inhibitor users

	Number of fractures	IR/1000 PY	aHR (95% CI)
(A) Aurum			
Any fracture			
DPP-4 inhibitor use (n = 28 524)	201	9.1 (7.9–10.4)	Reference
SGLT2 inhibitor use by duration of use (n = 13 807)	175		
0-89 days	37	12.3 (8.9–16.9)	1.37 (0.98–1.93)
90-180 days	38	9.1 (6.7–12.6)	1.01 (0.72–1.42)
181-450 days	38	9.1 (6.6–12.5)	1.03 (0.74–1.45)
451-810 days	35	11.0 (7.9–15.3)	1.26 (0.88–1.79)
≥811 days	27	8.7 (6.0–12.7)	1.00 (0.67–1.50)
MOF fracture			
DPP-4 inhibitor use (n = 28 524)	73	3.2 (2.6–4.1)	Reference
SGLT2 inhibitor use by duration of use (n = 13 807)	51		
0-89 days	12	4.0 (2.3–7.0)	1.23 (0.69–2.22)
90-449 days	15	2.1 (1.3–3.5)	0.65 (0.38–1.12)
450-719 days	12	3.9 (2.2–6.9)	1.30 (0.72–2.37)
≥720 days	12	2.6 (1.5–4.7)	0.89 (0.48–1.68)
(B) GOLD			
Any fracture			
DPP-4 inhibitor use (n = 9543)	64	8.8 (6.9–11.2)	Reference
SGLT2 inhibitor use by duration of use (n = 5517)	55		
0-180 days	22	10.6 (7.0–16.0)	1.17 (0.71–1.91)
181-730 days	20	7.8 (5.1–12.1)	0.85 (0.50–1.43)
>730 days	13	8.2 (4.8–14.1)	0.84 (0.45–1.57)
MOF fracture			
DPP-4 inhibitor use (n = 9543)	24	3.2 (2.2–4.8)	Reference
SGLT2 inhibitor use by duration of use (n = 5517)	17		
0-180 days	7	3.4 (1.6–7.0)	1.12 (0.49–2.55)
181-730 days	5	2.8 (1.2–6.6)	0.96 (0.36–2.54)
>730 days	5	2.1 (0.9–5.1)	0.73 (0.25–2.13)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; MOF, major osteoporotic fracture; PY, person-years; SGLT2, sodium-glucose cotransporter-2.

TABLE 4 Risk of any fracture in SGLT2 inhibitor versus DPP-4 inhibitor users, stratified by the different SGLT2 inhibitor agents available in the United Kingdom

	Number of fractures	IR/1000 PY	aHR (95% CI)
(A) Aurum			
Any fracture			
DPP-4 inhibitor use (n = 28 524)	201	9.1 (7.9-10.4)	Reference
SGLT2 inhibitor use by substance (n = 13 807)	175		
Ertugliflozin	0	N/A	N/A
Dapagliflozin	71	10.1 (8.0-12.7)	1.13 (0.87-1.45)
Canagliflozin	25	9.2 (6.2-13.6)	1.04 (0.69-1.57)
Empagliflozin	60	10.5 (8.2-13.6)	1.21 (0.91-1.60)
SGLT2 inhibitor past[a]	19	8.9 (5.7-14.0)	1.03 (0.65-1.65)
(B) GOLD			
Any fracture			
DPP-4 inhibitor use (n = 9543)	64	8.8 (6.9-11.2)	Reference
SGLT2 inhibitor use by substance (n = 5517)	55		
Ertugliflozin	0	N/A	N/A
Dapagliflozin	15	5.3 (3.2-8.8)	0.61 (0.35-1.06)
Canagliflozin	7	8.1 (3.9-16.9)	0.89 (0.41-1.93)
Empagliflozin	30	14.1 (9.9-20.1)	1.54 (0.97-2.46)
SGLT2 inhibitor past[a]	3	8.0 (2.6-24.8)	0.87 (0.27-2.83)

[a]Most recent SGLT2 inhibitor prescription more than 60 days ago.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; N/A, not applicable; PY, person years, SGLT2, sodium-glucose cotransporter-2.

Additionally, the proportional hazards assumption was tested. Lastly, Kaplan-Meier curves were created to visualize the results.

Data were analysed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Study population

The general characteristics of the study population are summarized in Table 1. In the Aurum cohort, a total of 13 837 SGLT2 inhibitor users and 37 292 DPP-4 inhibitor users were identified, of whom 13 807 SGLT2 inhibitor users were included in this study, matched with 28 524 DPP-4 inhibitor users (1 up to 3, weighted matching). The mean age after matching was 55.4 years in both groups, and 36.7% of the SGLT2 inhibitor users were female versus 36.4% of the DPP-4 inhibitor users. The mean duration of SGLT2 inhibitor and DPP-4 inhibitor use (time from first prescription until end of follow-up) was 1.4 years and 1.6 years, respectively. In the GOLD cohort, a total of 5641 SGLT2 inhibitor users and 11 762 DPP-4 inhibitor users were identified, of whom 5517 SGLT2 inhibitor users were included in this study, matched with 9543 DPP-4 inhibitor users (1 up to 3, weighted matching). After matching, the mean age was 56.8 years in both

groups, and 38.5% of the SGLT2 inhibitor users were female versus 38.0% of the DPP-4 inhibitor users. The mean duration of use was 2.2 years for SGLT2 inhibitors and 3.2 years for DPP-4 inhibitors.

Supplemental Figure S2 shows the selection from the original data extraction to the base cohort and the final study cohort for both Aurum (a) and GOLD (b).

3.2 | SGLT2 inhibitor use and risk of fractures

In the Aurum cohort, we observed 175 fractures (IR 9.9/1000 person-years) with current SGLT2 inhibitor use, and 201 fractures (IR 9.1/1000 person-years) with current DPP-4 inhibitor use. The risk of any fracture was similar with current SGLT2 inhibitor use compared to current DPP-4 inhibitor use, with an adjusted hazard ratio (aHR; using propensity-score matching to control for confounding) of 1.09 (95% confidence interval [CI] 0.91-1.31; Table 2A).

There was no significant difference in the risk of MOFs with SGLT2 inhibitor use compared to DPP-4 inhibitor use (aHR 0.89 [95% CI 0.64-1.22]; Table 2) nor in the risk of fractures at any of the individual MOF sites; aHR of 0.16 (95% CI 0.02-1.19) for hip fractures, 0.59 (95% CI 0.24-1.47) for vertebral fractures, 1.00 (95% CI 0.59-1.68) for humerus fractures and 1.15 (95% CI 0.72-1.85) for radius/ulna fractures (Table 2A).

TABLE 5 Risk of any fracture in SGLT2 inhibitor versus DPP-4 inhibitor users, stratified by sex and age group

	Number of patients	Number of fractures	IR/1000 PY	aHR (95% CI)
(A) Aurum				
Men, any fracture				
DPP-4 inhibitor use	8728	110	7.5 (6.3-9.1)	Reference
SGLT2 inhibitor use	8728	99	8.7 (7.1-10.6)	1.16 (0.91-1.48)
Women, any fracture				
DPP-4 inhibitor use	5053	95	12.6 (10.3-15.4)	Reference
SGLT2 inhibitor use	5053	76	12.3 (9.8-15.4)	0.96 (0.73-1.26)
Age 18-49 years, any fracture				
DPP-4 inhibitor use	3878	45	8.2 (6.1-10.9)	Reference
SGLT2 inhibitor use	3878	40	8.3 6.1-11.3)	1.00 (0.68-1.49)
Age 50-59 years, any fracture				
DPP-4 inhibitor use	5092	61	7.5 (5.9-9.6)	Reference
SGLT2 inhibitor use	5092	66	10.0 (7.8-12.7)	1.30 (0.94-1.80)
Age 60-69 years, any fracture				
DPP-4 inhibitor use	3520	59	9.4 (7.3-12.1)	Reference
SGLT2 inhibitor use	3520	40	8.7 (6.4-11.8)	0.93 (0.65-1.34)
Age > 70 years, any fracture				
DPP-4 inhibitor use	1258	41	19.0 (14.1-25.8)	Reference
SGLT2 inhibitor use	1258	26	17.6 (12.0-25.8)	0.93 (0.60-1.44)
(B) GOLD				
Men, any fracture				
DPP-4 inhibitor use	3393	31	6.8 (4.8-9.6)	Reference
SGLT2 inhibitor use	3393	30	7.8 (5.5-11.1)	1.12 (0.71-1.77)
Women, any fracture				
DPP-4 inhibitor use	2090	31	11.8 (8.3-16.8)	Reference
SGLT2 inhibitor use	2090	24	10.4 (7.0-15.5)	0.87 (0.53-1.42)
Age 18-49 years, any fracture				
DPP-4 inhibitor use	1261	10	6.3 (3.3-11.9)	Reference
SGLT2 inhibitor use	1261	14	10.5 (6.2-17.6)	1.49 (0.70-3.16)
Age 50-59 years, any fracture				
DPP-4 inhibitor use	1950	18	7.1 (4.5-11.3)	Reference
SGLT2 inhibitor use	1950	15	6.8 (4.1-11.3)	0.91 (0.48-1.73)
Age 60-69 years, any fracture				
DPP-4 inhibitor use	1562	21	9.1 (5.9-14.0)	Reference
SGLT2 inhibitor use	1562	20	10.8 (7.0-16.7)	1.23 (0.70-2.17)
Age > 70 years, any fracture				
DPP-4 inhibitor use	622	12	13.9 (8.0-24.2)	Reference
SGLT2 inhibitor use	622	4	6.0 (2.3-16.1)	0.49 (0.17-1.45)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; PY, person-years, SGLT2, sodium-glucose cotransporter-2.

In the GOLD cohort, no significantly increased risk was found for any fracture, MOFs, or fractures at any of the individual MOF sites (Table 2B).

Supplemental Figure S3 shows the results of the Kaplan-Meier analysis, visualizing risk of any fracture over several years.

3.3 | Duration-of-use analysis

In the Aurum cohort, after stratification into different duration periods, the risk of any fracture and MOFs was not different for SGLT2 inhibitor use compared to DPP-4 inhibitor use (Table 3A). Even

for the longest duration of use (≥811 days), the aHR was 1.00 (95% CI 0.67-1.50). The findings in the GOLD cohort were similar (Table 3B).

3.4 | Agent effect of SGLT2 inhibitors

The risk of any fracture in the Aurum cohort was not different for use of any of the SGLT2 inhibitors compared to DPP-4 inhibitor use: aHR 1.13 (95% CI 0.87-1.45) for dapagliflozin use, aHR 1.04 (95% CI 0.69-1.57) for canagliflozin use and aHR of 1.21 (95% CI 0.91-1.60) for empagliflozin use (Table 4A). No fractures were observed for ertugliflozin users; therefore, the aHR for this group could not be determined.

In the GOLD cohort, the risk of any fracture was not significantly altered for any of the individual agents of the SGLT2 inhibitor drug class (Table 4B).

3.5 | Stratification by sex and age

In the Aurum cohort, no substantial effect modification was demonstrated. After stratification by sex, the aHR for any fracture with SGLT2 inhibitor use compared to DPP-4 inhibitor use was 1.16 (95% CI 0.91-1.48) in men and 0.96 (95% CI 0.73-1.26) in women (Table 5A).

After stratification by age groups, the aHR of any fracture with SGLT2 inhibitor use compared to DPP-4 inhibitor use was 1.00 (95% CI 0.68-1.49) for individuals aged 18 to 49 years, 1.30 (95% CI 0.94-1.80) for those aged 50 to 59 years, 0.93 (95% CI 0.65-1.34) for those aged 60 to 69 years and 0.93 (95% CI 0.60-1.44) for those aged >70 years (Table 5A).

Findings in the GOLD cohort were similar. Neither men nor women showed a significantly increased aHR for SGLT2 inhibitor use versus DPP-4 inhibitor use, nor was fracture risk increased in any of the analysed age subgroups (Table 5B).

3.6 | Sensitivity analyses

We performed several sensitivity analyses. Firstly, the number of extra days to determine treatment discontinuation was shortened from 60 to 30. For the matched Aurum cohort, this resulted in an aHR for risk of any fracture of 1.03 (95% CI 0.85-1.25). In the matched GOLD cohort, we found a similar aHR of 1.05 (95% CI 0.73-1.51).

Secondly, in the sensitivity analysis comparing SGLT2 inhibitor use with SU use, the aHR of any fracture was 1.01 (95% CI 0.85-1.21) in the Aurum cohort and 0.86 (95% CI 0.63-1.19) in the GOLD cohort.

Additionally, in the sensitivity analysis without censoring patients who started antihyperglycaemic drugs other than SGLT2 inhibitors, DPP-4 inhibitors or metformin after the index date, the mean follow-up time was 2.19 (1.41) years for DPP-4 inhibitors and 1.49 (1.48) years for SGLT2 inhibitors and the aHR of any fracture was 1.15 (95% CI 0.98-1.35) in the Aurum cohort. In the GOLD cohort, the mean follow-up time was 1.62 (1.31) years for DPP-4 inhibitors and 1.24

(1.32) years for SGLT2 inhibitors and the aHR of any fracture was 0.97 (95% CI 0.71-1.32).

Lastly, when adjusting for BMI and eGFR in a time-dependent manner in the Cox regression analysis of the propensity-score-matched population, the aHR for any fracture was 1.09 (95% CI 0.90-1.32) and 0.97 (95% CI 0.68-1.40) in the Aurum and GOLD cohorts, respectively.

4 | DISCUSSION

In this study, we found that the use of SGLT2 inhibitors was not associated with an increased risk of any fracture or MOFs when compared to the use of DPP-4 inhibitors. This was confirmed in an agent-effect analysis, which showed that none of the individual agents of SGLT2 inhibitor use was associated with increased fracture risk. Additionally, a duration-of-use analysis showed that the results were independent of the duration of SGLT2 inhibitor use.

The results of the present study are contradictory to those of the CANVAS study.[6] The CANVAS study[6] concluded that fracture risk was increased with canagliflozin treatment, and these results were confirmed in a meta-analysis as well.[20] However, the results from the CANVAS study were driven by older subjects, with a history of cardiovascular disease, and with lower baseline eGFR and higher baseline diuretic use. Several possible explanations for the observed increased fracture risk have been discussed. Firstly, the previously observed increase in fracture incidence could have been mediated by falls. The CANVAS study found that more fractures occurred with canagliflozin use versus placebo, even early on in the follow-up, and this continued over 104 weeks of follow-up.[6] Furthermore, the mechanism through which SGLT2 inhibitors lower glucose levels is by inhibiting the exchange of glucose for sodium in the kidneys by the SGLT2 cotransporter, decreasing the reabsorption of dietary glucose back into the circulation.[21] However, this entails that the sodium gradient is preserved, which can be used for the reabsorption of phosphate by the sodium-dependent phosphate transport proteins, increasing blood phosphate levels.[22] Additionally, tubular flow in the kidneys is likely increased due to the osmotic diuresis, reducing calcium reabsorption and increasing calcium excretion levels.[13] Taken together, inhibiting SGLT2 may cause increased calcium excretion and increased phosphate uptake, resulting in increased PTH levels, which may negatively affect bone turnover.[13] Based on this hypothesis and the interim results of the CANVAS study, the US Food and Drug Administration included a warning concerning an increased risk of bone fracture for canagliflozin.[23] However, in our study, with a mean duration of follow-up for SGLT2 inhibitor use in the GOLD cohort of 1.4 years and in the Aurum cohort of 2.2 years, we did not observe such an increased risk of fractures. Even when focusing solely on patients with a duration of SGLT2 inhibitor use of >811 days, we did not find an increased fracture risk for SGLT2 inhibitor use when compared to DPP-4 inhibitor use as add-on to metformin.

Additionally, the results of our study are supported by several other studies, including randomized controlled trials, all pointing

towards a neutral effect of SGLT2 inhibitor use on fracture risk.[24-30] Our study used the CPRD database, which includes up to 19.9% (Aurum database) of the total population in the United Kingdom,[16] and did not find an increased fracture risk with SGLT2 inhibitor use versus DPP-4 inhibitor use in either Aurum or GOLD. This is also in line with a recent meta-analysis,[31] which included 11 large randomized clinical trials of this drug class in their meta-analysis on the association between SGLT2 inhibitor and fracture risk and concluded the CANVAS results were likely due to chance.

This study has several limitations. Firstly, the number of fractures in our study cohorts was relatively low, despite the respectable size of our study population. Therefore, subtle differences in fracture risk might not have been detected in our stratified analyses, such as the duration-of-use analysis and the agent-effect analyses. Indeed, the number of fractures within the group with the longest duration of SGLT2 inhibitor use was relatively low ($N = 27$ and > 811 days for Aurum and $N = 13$ and > 730 days for GOLD), and this should be kept in mind when interpreting these results. Furthermore, because this was an observational cohort study, we must consider the possibility of residual bias. For example, we only have data on prescriptions for SGLT2 inhibitors and DPP-4 inhibitors, the prescribed quantity and the dosage instructions from which we calculated the prescription duration. However, specific data on treatment adherence were unavailable. Additionally, we may have underestimated the prevalence of the comorbidities weighted in the propensity score, which may have led to insufficient correction for these factors. However, the propensity-score matching did allow us to adjust for a large number of subject characteristics, including concomitant medication use, comorbidities and lifestyle factors.

To conclude, the results of our study indicate that the use of SGLT2 inhibitors is not associated with an increased risk of any fracture, MOFs or fracture at an individual MOF site when compared to the use of DPP-4 inhibitors. These results were further supported by a duration-of-use analysis and an agent-effect analysis. Thus, our cohort study adds to previous studies and provides reassurance that SGLT2 inhibitors as add-on to metformin do not increase fracture risk compared to DPP-4 inhibitors.

ACKNOWLEDGEMENTS
None.

CONFLICT OF INTERESTS STATEMENT
VvH has nothing to disclose. JD has nothing to disclose. JS has nothing to disclose. ZA has nothing to disclose. RV has nothing to disclose. OK has nothing to disclose. PS has nothing to disclose. PV is head of research in the Steno Diabetes Center North Denmark funded by the Novo Nordisk Foundation. CS has nothing to disclose. JvdB has nothing to disclose.

PEER REVIEW
The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15220.

DATA AVAILABILITY STATEMENT
Data that was obtained from the Clinical Practice Research Datalink (CPRD) GOLD is available for on-site audit purposes to qualified auditors, subject to further discussion and contractual agreements with the licensor of CPRD GOLD data.

ORCID
Veerle van Hulten https://orcid.org/0000-0002-4233-7504
Coen D. A. Stehouwer https://orcid.org/0000-0001-8752-3223

REFERENCES
1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol.* 2018; 14(2):88-98.
2. Persson F, Bodegard J, Lahtela JT, et al. Different patterns of second-line treatment in type 2 diabetes after metformin monotherapy in Denmark, Finland, Norway and Sweden (D360 Nordic): a multinational observational study. *Endocrinol Diabetes Metab.* 2018;1(4): e00036.
3. NICE. Type 2 diabetes in adults: management. NICE guideline 28. Shared decision making tool. 2015.
4. EMA. https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga. Accessed 04-05-2023, 2023.
5. Simes BC, MacGregor GG. Sodium-glucose Cotransporter-2 (SGLT2) inhibitors: a Clinician's guide. *Diabetes Metab Syndr Obes.* 2019;12: 2125-2136.
6. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2016;101(1):157-166.
7. Adimadhyam S, Lee TA, Calip GS, Smith Marsh DE, Layden BT, Schumock GT. Sodium-glucose co-transporter 2 inhibitors and the risk of fractures: a propensity score-matched cohort study. *Pharmacoepidemiol Drug Saf.* 2019;28(12):1629-1639.
8. Fralick M, Kim SC, Schneeweiss S, Kim D, Redelmeier DA, Patorno E. Fracture risk after initiation of use of canagliflozin. *Ann Intern Med.* 2019;171(1):80.
9. Ueda P, Svanström H, Melbye M, et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study. *BMJ.* 2018;363:k4365.
10. Tang HL, Li D, Zhang J, et al. Lack of evidence for a harmful effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors on fracture risk among type 2 diabetes patients: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2016;18(12):1199-1206.
11. Kohler S, Kaspers S, Salsali A, Zeller C, Woerle HJ. Analysis of fractures in patients with type 2 diabetes treated with empagliflozin in pooled data from placebo-controlled trials and a head-to-head study versus glimepiride. *Diabetes Care.* 2018;41(8):1809-1816.
12. van Poelgeest EP, Handoko ML, Muller M, van der Velde N, On behalf of the ET, Finish group on Fall-risk-increasing drugs. Diuretics, SGLT2 inhibitors and falls in older heart failure patients: to prescribe or to deprescribe? A clinical review. *Eur Geriatr Med.* 2023:1-16
13. Vinke JSJ, Heerspink HJ, de Borst MH. Effects of sodium glucose cotransporter 2 inhibitors on mineral metabolism in type 2 diabetes mellitus. *Curr Opin Nephrol Hypertens.* 2019;28(4):321-327.
14. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol.* 2015;44(3): 827-836.
15. Wolf A, Dedman D, Campbell J, et al. Data resource profile: clinical practice research datalink (CPRD) aurum. *Int J Epidemiol.* 2019;48(6): 1740-1740g.

16. CPRD. Clinical Practice Research Datalink. *CPRD Aurum February 2022 (Version 2022.02.001)*. [Data set]. Clinical Practice Research Datalink; 2022.

17. CPRD. Clinical Practice Research Datalink. *CPRD GOLD May 2022 (Version 2022.05.001)* [Data set] Clinical Practice Research Datalink; 2022.

18. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19(4):385-397.

19. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000–2017. *BMJ Open*. 2018;8(7):e022768.

20. Lou Y, Yu Y, Duan J, et al. Sodium-glucose cotransporter 2 inhibitors and fracture risk in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Ther Adv Chronic Dis*. 2020; 11:2040622320961599.

21. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metabol*. 2010; 95(1):34-42.

22. Taylor SI, Blau JE, Rother KI. SGLT2-inhibitors trigger downstream mechanisms that may exert adverse effects upon bone. *Lancet Diabetes Endocrinol*. 2015;3(1):8-10.

23. Administration TUSFaD. FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. 2015. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-label-diabetes-drug-canagliflozin-invokana-invokamet.

24. Abrahami D, Douros A, Yin H, Yu OH, Azoulay L. Sodium–glucose cotransporter 2 inhibitors and the risk of fractures among patients with type 2 diabetes. *Diabetes Care*. 2019;42(9):e150-e152.

25. Al-Mashhadi Z, Viggers R, Fuglsang-Nielsen R, et al. Glucose-lowering drugs and fracture risk—a systematic review. *Curr Osteoporos Rep*. 2020;18(6):737-758.

26. Al-Mashhadi ZK, Viggers R, Starup-Linde J, Vestergaard P, Gregersen S. SGLT2 inhibitor treatment is not associated with an increased risk of osteoporotic fractures when compared to GLP-1 receptor agonists: a nationwide cohort study. *Front Endocrinol (Lausanne)*. 2022;13:861422.

27. Ha KH, Kim DJ, Choi YJ. Sodium–glucose cotransporter 2 inhibitors do not increase the risk of fractures in real-world clinical practice in Korea: a national observational cohort study. *J Diabetes Investig*. 2022;13:986-996.

28. Qian B, Chen Q, Li L, Yan C. Association between combined treatment with SGLT2 inhibitors and metformin for type 2 diabetes mellitus on fracture risk: a meta-analysis of randomized controlled trials. *Osteoporos Int*. 2020;31(12):2313-2320.

29. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019; 380(24):2295-2306.

30. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015; 373(22):2117-2128.

31. Arnott C, Fletcher RA, Neal B. Sodium glucose cotransporter 2 inhibitors, amputation risk, and fracture risk. *Heart Fail Clin*. 2022;18(4): 645-654.

SUPPORTING INFORMATION

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