WILEY

ORIGINAL ARTICLE

Long-term use of dipeptidyl peptidase-4 inhibitors and risk of fracture: A retrospective population-based cohort study

Johanna H. M. Driessen MSc[1,2,3] | Joop P. W. van den Bergh MD PhD[4,5,6] |
Hein A. W. van Onzenoort PharmD, PhD[3,7] | Ronald M. A. Henry MD PhD[8,9] |
Hubert G. M. Leufkens PharmD PhD[1] | Frank de Vries PharmD PhD[1,2,3,10]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, The Netherlands

[2]Care and Public Health Research Institute (CAPHRI), Maastricht, The Netherlands

[3]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre+, Maastricht, The Netherlands

[4]Department of Internal Medicine, Viecuri Medical Centre, Venlo, The Netherlands

[5]Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

[6]Biomedical Research Institute, University Hasselt, Hasselt, Belgium

[7]Department of Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

[8]Department of Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

[9]Cardiovascular Research Institute Maastricht, Maastricht University Medical Centre, Maastricht, The Netherlands

[10]MRC Epidemiology Lifecourse Unit, Southampton General Hospital, Southampton, UK

Correspondence
Frank de Vries, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.
Email: f.devries@uu.nl

Funding information
No funding was received for this study.

Aims: To investigate the association between long-term dipeptidyl peptidase-4 (DPP-4) inhibitor use and risk of fracture among people with type 2 diabetes mellitus (T2DM).

Methods: A retrospective population-based cohort study, using data from the Clinical Practice Research Datalink database (2007-2015), was conducted. All those (N = 328 254) with at least one prescription for a non-insulin antidiabetic drug (NIAD), aged ≥18 years at the time of data collection, were included. Cox proportional hazards models were used to estimate the hazard ratios of any fracture, osteoporotic fracture and hip fracture in DPP-4 inhibitor users compared with those using other NIADs. Analyses were stratified by continuous duration of DPP-4 inhibitor use. Time-dependent adjustments were made for age, sex, lifestyle, comorbidity and concomitant drug use.

Results: Current use of DPP-4 inhibitors was not associated with risk of any fracture (adjusted hazard ratio [HR] 0.99 [95% confidence interval {CI} 0.93-1.06]) as compared with current other NIAD use. Current use of DPP-4 inhibitors was also not associated with risk of osteoporotic or hip fracture. After stratification by continuous duration of DPP-4 inhibitor use the highest category was not associated with any (>4.0-8.5 years of use, adjusted HR 0.99 [95% CI 0.70-1.41]), osteoporotic (>3.0-8.5 years of use, adjusted HR 0.75 [95% CI 0.52-1.09]) or hip (>2.0-8.5 years of use; adjusted HR 1.24 [95% CI 0.85-1.79]) fracture.

Conclusion: Continuous long-term DPP-4 inhibitor use (defined as >4.0-8.5 years of DPP-4 inhibitor use for any fracture, >3.0-8.5 years for osteoporotic fracture and >2.0-8.5 years for hip fracture was not associated with risk of any, osteoporotic or hip fracture. These findings may be of value for clinical decisions regarding treatment of patients with T2DM, especially those at high risk of fracture.

KEYWORDS

cohort-study, CPRD, DPP-4 inhibitor, fracture, type 2 diabetes mellitus

1 | INTRODUCTION

Worldwide, ~422 million people have type 2 diabetes mellitus (T2DM).[1] In addition to other complications, people with T2DM have a greater risk of fracture compared with those without T2DM.[2]

Explanations for this elevated fracture risk include a higher risk of falling,[3] the effect of the pathophysiology of diabetes itself on bone quality[4] as well as the effect of antihyperglycaemic drugs used in T2DM.[5]

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new type of antihyperglycaemic drug which have been marketed since

2006.[6] It has been suggested that DPP-4 inhibitors might influence bone metabolism and thereby potentially reduce fracture risk.[5] A first meta-analysis of randomized controlled trials (RCTs) indeed showed a reduced risk of fracture with the use of DPP-4 inhibitors.[7] Recently, we performed the first observational studies investigating the association between use of DPP-4 inhibitors and risk of fracture.[8,9] In contrast to the results of the previous meta-analysis, we found no association between use of DPP-4 inhibitors and fracture risk. One of the explanations might be the fact that the meta-analysis was based on a small number of fractures, which were reported as severe adverse outcomes. By contrast, the observational studies used routinely collected data on fractures. Recently, another observational study was published that compared current use of metformin and DPP-4 inhibitors with non-use. Non-use was defined as insufficient exposure to diabetes medication (ie, a medication possession ratio <20%).[10] This study showed no association with fracture risk when a DPP-4 inhibitor was added to metformin.

A major limitation of both these observational studies as well as the meta-analysis was the median actual duration of DPP-4 inhibitor use. For the observational studies it ranged between 47 weeks[9] and 1.04 years[8] and for the meta-analysis the median duration of the included trials was 24 weeks.[7]

Based on these findings, the limited duration of DPP-4 inhibitor use might have been too short to show an association between use of DPP-4 inhibitors and fracture risk; therefore, in the present study we aimed to investigate the association between long-term use of DPP-4 inhibitors and risk of fracture.

2 | MATERIALS AND METHODS

Data for the present study were obtained from the Clinical Practice Research Datalink (CPRD) in the UK, previously known as the General Practice Research Database (http://www.CPRD.com). The CPRD contains computerized medical records of 674 primary care practices in the UK, representing 6.9% of the population.[11] The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes since 1987. Previous studies using CPRD data have been shown to be highly valid, with, for example, >90% confirmed diagnoses for hip fractures.[12]

We conducted a retrospective population-based cohort study. The study population consisted of all patients with at least one prescription for a non-insulin antidiabetic drug (NIAD), who were aged ≥18 years during the period of valid CPRD data collection. For this study, data collection started on June 13, 2007, the date of the first-ever prescription of a DPP-4 inhibitor in the CPRD, and ended on December 31, 2015. The index date was defined as the date of the first NIAD prescription since the start of the study period (ie, the study population was a mix of incident and prevalent NIAD users). Approval for this study was obtained from the independent scientific advisory committee of the CPRD (protocol number: 12_161R).

2.1 | Exposure

The follow-up time for the NIAD users was divided into fixed intervals of 30 days. When there was a prescription of a NIAD in the 90 days before the start of an interval, the interval was classified as "current NIAD use," otherwise the interval was classified as "past NIAD use." Patients were allowed to move between current and past NIAD use. All DPP-4 inhibitor exposure intervals were classified, according to the time since the most recent prescription, as current (1-90 days), recent (91-180 days) or past (over 180 days) use.

Continuous duration of use was determined at the start of every interval. The prescribed quantity and the written dosage instruction were used to estimate the duration of each DPP-4 inhibitor prescription. Continuous duration was defined as the time from the first continuous prescription until the start of an interval, allowing a gap of 30 days[13] between the estimated end date of a prescription and the start of the next prescription.

2.2 | Outcome

Patients were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, the patient's death, or the fracture type of interest, whichever came first. Fractures were classified by use of read codes.[14] We used the following categories to classify fractures: any, hip and osteoporotic fracture. An osteoporotic fracture was defined as a fracture of the hip, vertebrae, radius/ulna or humerus according to the World Health Organisation (WHO) definition.[15]

2.3 | Potential confounders

The presence of risk factors was assessed by reviewing the computerized medical records for any record of a risk factor prior to the start of an interval. The following potential confounders were determined at baseline: sex; body mass index (BMI); smoking status; and alcohol use. All other risk factors that were considered in this study were determined time-dependently (ie, at the start of each interval). We considered the following potential confounders: age; most recent glycated haemoglobin (HbA1c) measurement in the year prior to the start of an interval; occurrence of falls in the 7 to 12 months before the start of an interval; a history of chronic obstructive pulmonary disease; previous fracture; rheumatoid arthritis; hypothyroidism; hyperthyroidism; cancer; retinopathy; neuropathy; congestive heart failure; and secondary osteoporosis (hypogonadism or premature menopause). In addition, the following drug prescriptions in the 6 months prior to the start of an interval were considered as potential confounders: oral glucocorticoids; cholesterol-modifying drugs; antidepressants; anxiolytics or hypnotics; antipsychotics; anti-Parkinson's drugs; antihypertensives (β blockers, thiazide diuretics, renin angiotensin aldosterone system inhibitors, calcium channel blockers, loop diuretics); antiarrhythmics; opposed hormone replacement therapy; calcium; bisphosphonates; vitamin D; raloxifene; strontium ranelate; calcitonin; parathyroid hormone.

2.4 | Statistical analyses

Regression analysis with Cox proportional hazards models (SAS 9.4, PHREG procedure) was used to estimate the fracture rate of current DPP-4 inhibitor users compared with other NIAD users, excluding glucagon-like peptide 1 (GLP-1) receptor agonist (RA) users. GLP-1-RA use was taken into account as a separate exposure group as this has been associated with a decreased risk of fracture.[16] In further analyses we stratified current DPP-4 inhibitor use by categories of continuous duration. In all analyses potential confounders were included if they independently changed the β-coefficient for current DPP-4 inhibitor exposure by at least 5%, or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature. For confounder data with missing values (BMI, HbA1c, alcohol use and smoking status) a missing indicator variable was added.

2.5 | Sensitivity analyses

As a sensitivity analysis the gap used to determine continuous duration was changed to 60 and 90 days. In a second sensitivity analyses we performed a new-user design in which all NIAD users with a NIAD prescription before the start of the study were excluded from the analyses. Additionally, we performed a sensitivity analysis in which all patients with a history of a fracture before the index date were excluded. A fourth sensitivity analysis was performed in which we adjusted the main analyses for current use of thiazolidinediones and current use of sulphonylurea derivatives, as they have both been associated with fracture risk.[17,18]

3 | RESULTS

In total 328 254 NIAD users were included, of whom 46 355 were DPP-4 inhibitor users. The baseline characteristics are shown in Table 1. The median actual duration of DPP-4 inhibitor use was 1.6 years and the mean duration of follow-up was 6.3 and 5.6 years for the DPP-4 inhibitor users and the NIAD users, respectively. DPP-4 inhibitor users were less often women, were slightly younger, and had a higher HbA1c concentration (8.8% vs 8.0%) and BMI (32.6 vs 31.4 kg/m^2) at index date as compared with other NIAD users. History of retinopathy, use of statins and use of antihypertensives was higher in DPP-4 inhibitor users at baseline than in other NIAD users.

Table 2 shows that any DPP-4 inhibitor use was associated with a decreased risk of any fracture (adjusted hazard ratio [HR] 0.93 [95% confidence interval {CI} 0.88-0.94]). Current use of DPP-4 inhibitors was not associated with risk of any fracture (adjusted HR 0.99 [95% CI 0.93-1.06]) as compared with current other NIAD use. Recent DPP-4 inhibitor use was not associated with risk of fracture either, whereas past DPP-4 inhibitor use was associated with a decreased risk of fracture (adjusted HR 0.83 [95% CI 0.75-0.91]). Past NIAD use was associated with a 60% reduced risk of any fracture (adjusted HR 0.40 [95% CI 0.38-0.43]). The fully adjusted model including all potential confounders showed an HR of 0.95 (95% CI 0.89-1.01) with current use of DPP-4 inhibitor and risk of any fracture. Stratification by continuous duration of use resulted in an increased risk of fracture for patients who continuously used DPP-4 inhibitors for 2.0-2.9 years (adjusted HR 1.23 [95% CI 1.03-1.48]). Other categories showed no association with continuous duration of DPP-4 inhibitor use (Table 2).

Any DPP-4 inhibitor use was associated with a decreased risk of osteoporotic fracture but not with hip fracture (adjusted HR for osteoporotic fracture 0.91 [95% CI 0.84-0.98] and for hip fracture 0.92 [95% CI 0.79-1.06]). Current use of DPP-4 inhibitors was not associated with risk of osteoporotic (adjusted HR 0.96 [95% CI 0.87-1.05]) or hip fracture (adjusted HR 0.96 [95% CI 0.81-1.15]; Table 3). Both recent and past DPP-4 inhibitor use showed a decreased risk of osteoporotic fracture (adjusted HR for recent DPP-4 inhibitor use 0.72 [95% CI 0.52-0.99], past DPP-4 inhibitor use 0.84 [95% CI 0.73–0.96]). Recent and past DPP-4 inhibitor use were not associated with risk of hip fracture. Past NIAD use was associated with a reduced risk of major osteoporotic fracture and hip fracture. Current use of DPP-4 inhibitors stratified by continuous duration of use was not associated with risk of osteoporotic fracture nor with risk of hip fracture.

In the first sensitivity analysis we extended the gap between the expected end date of a prescription and the start of the next prescription to 60 and 90 days, respectively. When the gap was set to 60 days the results for risk of any, osteoporotic or hip fracture did not substantially change except for continuous duration of DPP-4 inhibitor use of 2.0 to 2.9 years and risk of any fracture, which was no longer significant (adjusted HR 1.04 [95% CI 0.87-1.24]). When the gap was set to 90 days, similar results were seen: no materially altered results for risk of any, osteoporotic or hip fracture except with 2.0 to 2.9 years of DPP-4 inhibitor use and risk of any fracture, which was no longer significant (adjusted HR 1.04 [95% CI 0.88-1.24]).

In a second sensitivity analysis the study population was restricted to new users of NIADs. Current DPP-4 inhibitor use stratified by continuous duration of use categories was not associated with risk of any fracture. Additional adjustment for diabetes duration did not materially alter the results. In a third sensitivity analysis we excluded all patients with a history of a fracture. Current use of DPP-4 inhibitors stratified by continuous duration of use was not associated with risk of any fracture. Additional adjustments for current use of thiazolidinediones and sulphonylurea derivatives resulted in a significantly decreased risk of any fracture with current DPP-4 inhibitor use (adjusted HR 0.94 [95% CI 0.88-1.00]).

4 | DISCUSSION

The present study showed that current use of DPP-4 inhibitors was not associated with risk of any, osteoporotic or hip fracture. After stratification by continuous duration of use we showed no association between the highest continuous duration of DPP-4 inhibitor use category and any (>4.0-8.5 years of use), osteoporotic (>3.0-8.5 years of use) or hip (>2.0-8.5 years of use) fracture. Different sensitivity analyses confirmed the results of no association between current use of DPP-4 inhibitors and risk of any fracture.

TABLE 1 Baseline characteristics of current DPP-4 inhibitor users and other NIAD users

Characteristic	DPP-4 inhibitor users (N = 46 355)	Other NIAD users (N = 281 899)
Mean (s.d.) follow-up time, years	6.3 (2.5)	5.6 (2.8)
Median (IQR) actual duration of DPP-4 inhibitor use	1.6 (0.7-3.1)	n/a
Women	19 428 (41.9)	114 467 (48.6)
Mean (s.d.) age at index date, years	59.7 (12.4)	61.5 (16.1)
Age		
18-49 years	9883 (21.3)	53 131 (22.6)
50-59 years	12 550 (27.1)	44 660 (19.0)
60-69 years	13 448 (29.0)	56 812 (24.1)
70-79 years	8065 (17.4)	50 561 (21.5)
≥80 years	2409 (5.2)	30 380 (12.9)
Mean (s.d.) BMI at index date, kg/m^2	32.6 (6.7)	31.4 (6.8)
BMI		
<20.0 kg/m^2	273 (0.6)	3646 (1.5)
20.0-24.9 kg/m^2	4044 (8.7)	30 956 (13.1)
25.0-29.9 kg/m^2	13 270 (28.6)	71 599 (30.4)
30.0-34.9 kg/m^2	14 059 (30.3)	63 347 (26.9)
≥35.0 kg/m^2	14 023 (30.3)	57 971 (24.6)
Missing	686 (1.5)	8025 (3.4)
Mean (s.d.) HbA1c	8.8 (1.5)	8 (1.8)
HbA1c		
<6%	394 (0.8)	8550 (3.6)
6.0%-6.9%	2807 (6.1)	35 868 (15.2)
7.0%-7.9%	10 418 (22.5)	42 017 (17.8)
8.0%-8.9%	12 217 (26.4)	22 598 (9.6)
≥9.0%	15 720 (33.9)	31 355 (13.3)
Missing	4799 (10.4)	95 156 (40.4)
Smoking status		
Never smoker	14 839 (32.0)	77 335 (32.8)
Current smoker	8015 (17.3)	40 256 (17.1)
Ex-smoker	23 334 (50.3)	116 180 (49.3)
Missing	167 (0.4)	1773 (0.8)
Alcohol use		
No	14 349 (31.0)	74 826 (31.8)
Yes	30 416 (65.6)	145 609 (61.8)
Missing	1590 (3.4)	15 109 (6.4)
Falls (in 6-12 months before index date)	477 (1.0)	2427 (1.0)
History of diseases		
Fracture	9575 (20.7)	49 438 (21.0)
Hyperthyroidism	535 (1.2)	2315 (1.0)
Hypothyroidism	4180 (9.0)	18 997 (8.1)
COPD	2765 (6.0)	12 559 (5.3)
Congestive heart failure	1929 (4.2)	9119 (3.9)
Cancer	11 491 (24.8)	51 587 (21.9)
Rheumatoid arthritis	726 (1.6)	3621 (1.5)
Retinopathy	12 976 (28.0)	31 532 (13.4)

TABLE 1 Continued

Characteristic	DPP-4 inhibitor users (N = 46 355)	Other NIAD users (N = 281 899)
Secondary osteoporosis	3774 (8.1)	19 655 (8.3)
Neuropathy	3090 (6.7)	10 506 (4.5)
Drug use within 6 months prior to index date		
Glucocorticoids	9160 (19.8)	40 683 (17.3)
Statins	34 574 (74.6)	118 488 (50.3)
Antiarrhythmics	641 (1.4)	3464 (1.5)
Antidepressants	9688 (20.9)	38 909 (16.5)
Anti-Parkinson's drugs	259 (0.6)	1235 (0.5)
Antipsychotics	997 (2.2)	5794 (2.5)
Anxiolytics/hypnotics	3133 (6.8)	16 402 (7.0)
Antihypertensives	32 411 (69.9)	129 584 (55.0)
Bisphosphonates	1032 (2.2)	6399 (2.7)
Raloxifene	14 (0.0)	282 (0.1)
Calcium/vitamin D	2393 (5.2)	10 574 (4.5)
Strontium	16 (0.0)	126 (0.1)
Parathyroid hormone/calcitonin	<6 (0.0)	<6 (0.0)
Hormone replacement therapy	178 (0.4)	820 (0.3)

Data are presented as *n* (%), unless stated otherwise.

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range; n/a, not applicable; s.d., standard deviation.

The present results are in line with the results of 2 recently performed meta-analyses, which included 51 and 62 RCTs, respectively, comparing DPP-4 inhibitors with placebo or an active comparator.[19,20] Both meta-analyses showed no association between use of DPP-4 inhibitors and risk of fracture. The adverse events fracture data of a large clinical trial (n = 16 492) comparing saxagliptin, a DPP-4 inhibitor, with placebo have been analysed in more depth[21] and showed a relative risk of 1. The present results are also supported by the results of an analysis of the fracture data of a cardio-vascular trial comparing sitagliptin, a DPP-4 inhibitor, with placebo in patients with T2DM (N = 14 671), which showed no association with risk of fracture.[22]

The present results are also consistent with our previous observational studies comparing current use of DPP-4 inhibitors with use of other NIADs,[8,9] with a meta-analysis of the observational studies[23] and with an observational study comparing use of metformin and DPP-4 inhibitor with non-use.[10] The present results are not consistent with a meta-analysis including 28 RCTs comparing DPP-4 inhibitors with placebo or active treatment, which showed a 40% reduced risk[7]; however, the 2 updated meta-analyses showed no reduced risk of fracture with use of DPP-4 inhibitors,[19,20] suggesting that the large reduction in fracture risk found in the first meta-analysis might have been a consequence of the small number of included trials and the small number of reported fractures.

It has been shown that DPP-4 inhibitors increase the concentration of incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP).[5] *In vitro* research has shown that GIP stimulates osteoblast

TABLE 2 Use of DPP-4 inhibitors and risk of any fracture stratified by continuous duration of use

Exposure	Number of fractures N = 16 572[1]	Incidence rate/1000 person-years	Age/gender-adjusted HR (95% CI)	Adjusted HR (95% CI)[2]
Current NIAD use[3] excluding incretins	12 575	14.3	Reference	Reference
Past NIAD use[4]	1923	3.3	0.23 (0.22-0.24)[8]	0.40 (0.38-0.43)[8]
Any DPP-4 inhibitor use	1700	10.3	0.88 (0.83-0.92)[8]	0.93 (0.88-0.94)[8]
By recency				
Past DPP-4 inhibitor use[5]	479	7.6	0.65 (0.59-0.72)[8]	0.83 (0.75-0.91)[8]
Recent DPP-4 inhibitor use[6]	93	9.9	0.84 (0.68-1.03)	0.83 (0.67-1.02)
Current DPP-4 inhibitor use[7]	1128	12.2	1.02 (0.96-1.08)	0.99 (0.93-1.06)
By continuous duration of use				
No continuous duration of use	275	12.0	1.00 (0.89-1.13)	0.97 (0.86-1.09)
≤0.5 year	311	12.2	1.01 (0.90-1.13)	1.00 (0.89-1.12)
0.6-0.9 year	162	11.6	0.96 (0.82-1.12)	0.93 (0.80-1.09)
1.0-1.9 years	192	12.4	1.02 (0.88-1.18)	1.00 (0.87-1.16)
2.0-2.9 years	117	14.9	1.25 (1.04-1.50)[8,9]	1.23 (1.03-1.48)[8,9]
3.0-3.9 years	40	9.9	0.86 (0.63-1.17)	0.84 (0.62-1.15)
4.0-8.5 years	31	11.0	1.02 (0.72-1.45)	0.99 (0.70-1.41)

[1] GLP-1-RA use not shown, therefore the total numbers of fractures do not add up to the total number of fractures.

[2] Adjusted for: age, gender, BMI, smoking status, HbA1c, use of antipsychotics, glucocorticoids, statins, antidepressants, antihypertensives, anxiolytics/hypnotics, calcium/vitamin D, anti-osteoporotic drugs (use of bisphosphonates, raloxifene, strontium ranelate or parathyroid hormone/calcitonin), history of fracture, falls, secondary osteoporosis, retinopathy and neuropathy.

[3] Current NIAD use: most recent NIAD prescription within 90 days before start of an interval.

[4] Past NIAD use: most recent prescription over 90 days before start of an interval.

[5] Past DPP-4 inhibitor use: most recent prescription over 180 days before start of an interval.

[6] Recent DPP-4 inhibitor use: most recent prescription within 91 to 180 days before start of an interval.

[7] Current DPP-4 inhibitor use: most recent prescription within 90 days before start of an interval.

[8] Statistically significant (P < 0.05).

[9] Statistically significant difference compared with no continuous duration of use, 0.5 to 1 year of continuous duration of use and 3 to 4 years of continuous duration of use, using Wald test (P < 0.05).

differentiation.[24] Treatment with GLP-1 has been associated with an increase in bone density in rodent models with osteopenia.[25,26] It was therefore hypothesized that DPP-4 inhibitors may reduce fracture risk; however, in the present study, we did not show a decreased risk of fracture with use of DPP-4 inhibitors. One of the explanations for this might be that DPP-4 inhibitors have still not been used long enough to establish this reduced risk of fracture; however, a small group of patients used DPP-4 inhibitors continuously for >4 years, in our analysis of risk of any fracture. Antihyperglycaemic drugs that have been associated with an unintended effect on bone, such as thiazolidinediones, showed this already after 2 years of use.[27,28] In addition, bisphosphonates, used to prevent fractures, have shown a reduction in fracture risk after 18 months of use.[29,30] GIP and GLP-1 have been shown to be reduced in patients with T2DM.[31] It might be that, because of the use of DPP-4 inhibitors, the levels of GIP and GLP-1 increase to the normal level, but not to the higher levels required to have an effect on bone metabolism and, in the end, on fracture risk.

Current use of DPP-4 inhibitors was associated with an increased risk of any fracture when patients used them continuously for 2.0 to 2.9 years. Longer use was not associated with an increased fracture risk, which would be expected if DPP-4 inhibitor use increased fracture risk. In addition, in all sensitivity analyses this increased risk

disappeared, suggesting that this increased risk was a chance finding. Unexpectedly, past NIAD use was associated with a 60% reduced risk of any fracture, which is hard to explain and should be interpreted with caution. Past NIAD use includes use in patients who are switched to insulin; however, this has been associated with an increased not a decreased risk of fracture.[32]

The strengths of the present study include its large sample size as well as the representativeness of the used CPRD data for the general population of the UK. In addition, we were able to adjust for many potential important confounders in a time-dependent manner. We also had data on important lifestyle factors, such as BMI, and data on HbA1c concentrations. Moreover, we were able to investigate the association between current use of DPP-4 inhibitors for >4.0 to 8.5 years and risk of any fracture. Additionally, it has been shown that the CPRD fracture data has a high validity.[12]

The present study also has some limitations. For osteoporotic and hip fracture we had to combine the highest categories of continuous duration of use into >3.0 to 8.5 years and >2.0 to 8.5 years, respectively. Another limitation is that, despite the fact that the follow-up period was extended by almost 3.5 years as compared with the previous observational studies,[8,9] the median duration of actual DPP-4 inhibitor use only increased by 0.6 years. Future work is

TABLE 3 Use of DPP-4 inhibitors and risk of osteoporotic and hip fracture, stratified by continuous duration of use

Exposure	Osteoporotic fracture				Hip fracture			
	Number of fractures N = 8046[1]	Incidence rate/1000 person-years	Age-/gender-adjusted HR (95% CI)	Adjusted HR (95% CI)[2]	Number of fractures N = 2737[1]	Incidence rate/1000 person-years	Age-/gender-adjusted HR (95% CI)	Adjusted HR (95% CI)[2]
Current NIAD[3] excluding incretins	6952	6.9	Reference	Reference	392	2.3	Reference	Reference
Past NIAD[4]	952	1.6	0.20 (0.19-0.22)[10]	0.37 (0.34-0.41)[10]	2110	0.6	0.19 (0.17-0.22)[10]	0.38 (0.34-0.44)[10]
Any DPP-4 inhibitor	755	4.4	0.83 (0.77-0.90)[10]	0.91 (0.84-0.98)[10]	223	1.3	0.82 (0.71-0.94)[10]	0.92 (0.79-1.06)
By recency								
Past DPP-4 inhibitor use[5]	220	3.4	0.64 (0.55-0.73)[10]	0.84 (0.73-0.96)[10]	68	1.0	0.64 (0.50-0.83)[10]	0.91 (0.71-1.17)
Recent DPP-4 inhibitor use[6]	37	3.8	0.72 (0.52-1.00)[10]	0.72 (0.52-0.99)[10]	8	0.8	0.52 (0.25-1.05)	0.51 (0.25-1.02)
Current DPP-4 inhibitor use[7]	498	5.2	0.97 (0.89-1.07)	0.96 (0.87-1.05)	147	1.5	0.96 (0.81-1.14)	0.96 (0.81-1.15)
By continuous duration of use								
No continuous duration of use	113	4.8	0.88 (0.73-1.06)	0.86 (0.71-1.04)[8]	37	1.5	0.95 (0.68-1.31)	0.94 (0.68-1.30)
≤0.5 year	155	5.9	1.11 (0.95-1.31)	1.11 (0.94-1.30)	40	1.5	0.98 (0.72-1.35)	1.00 (0.73-1.37)
0.6-0.9 year	67	4.7	0.86 (0.68-1.10)	0.85 (0.67-1.08)	19	1.3	0.83 (0.52-1.30)	0.82 (0.52-1.29)
1.0-1.9 years	80	5.0	0.91 (0.73-1.14)	0.90 (0.72-1.13)	22	1.4	0.84 (0.55-1.29)	0.85 (0.56-1.29)
2.0-2.9 years	55	6.7	1.26 (0.96-1.64)[9]	1.24 (0.95-1.62)[9]	29	1.9	1.23 (0.85-1.77)	1.24 (0.85-1.79)
3.0-8.5 years	28	3.9	0.77 (0.53-1.12)	0.75 (0.52-1.09)	-	-	-	-

[1] GLP1-RA use not shown, therefore the total numbers of fractures do not add up to the total number of fractures.

[2] Adjusted for age, gender, BMI, smoking status, HbA1c, use of antipsychotics, glucocorticoids, statins, antidepressants, antihypertensives, history of congestive heart failure, fracture, falls, secondary osteoporosis, retinopathy and neuropathy.

[3] Current NIAD use: most recent NIAD prescription <90 days before start of an interval.

[4] Past NIAD use: most recent prescription >90 days before start of an interval.

[5] Past DPP-4 inhibitor use: most recent prescription >180 days before start of an interval.

[6] Recent DPP-4 inhibitor use: most recent prescription within 91 to 180 days before start of an interval.

[7] Current DPP-4 inhibitor use: most recent prescription <90 days before start of an interval.

[8] Statistically significant difference compared with ≤0.5 years of continuous duration of use, using Wald test (P < 0.05).

[9] Statistically significant difference compared with no continuous duration of use, 0.5 to 1 years of continuous duration of use and 3 to 8.5 years of continuous duration of use, using Wald test (P < 0.05).

[10] Statistically significant (P < 0.05).

required to evaluate properly the association between long duration of DPP-4 inhibitor use and the effects on fracture risk, once the duration data have had sufficient time to mature. Moreover, although we were able to adjust for many confounders, residual confounding may be present.

We showed that current use of DPP-4 inhibitors was not associated with risk of any, osteoporotic or hip fracture. Moreover, we showed that, when stratified by continuous duration of use, current use of DPP-4 inhibitors was not associated with a decreased risk of any (>4.0-8.5 years of DPP-4 inhibitor use), osteoporotic (>3.0-8.5 years of DPP-4 inhibitor use) or hip (>2.0-8.5 years of DPP-4 inhibitor use) fracture. These findings may be of value for clinical decisions regarding treatment of people with T2DM, especially those at high fracture risk.

Conflict of interest

Author contributions

REFERENCES

1. WHO. *Global Report on Diabetes*. Geneva: World Health Organization; 2016.
2. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes–a meta-analysis. *Osteoporos Int*. 2007;18(4):427-444.
3. de Waard EA, van Geel TA, Savelberg HH, Koster A, Geusens PP, van den Bergh JP. Increased fracture risk in patients with type 2 diabetes mellitus: an overview of the underlying mechanisms and the usefulness of imaging modalities and fracture risk assessment tools. *Maturitas*. 2014;79(3):265-274.
4. Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. *Diabetes Metab Res Rev*. 2004;20:196-204.
5. Mannucci E, Dicembrini I. Drugs for type 2 diabetes: role in the regulation of bone metabolism. *Clin Cases Miner Bone Metab*. 2015;12(2):130-134.
6. Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. *Diabetes Care*. 2011;34:S276-S278.
7. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care*. 2011;34(11):2474-2476.
8. Driessen JH, van Onzenoort HA, Henry RM, et al. Use of dipeptidyl peptidase-4 inhibitors for type 2 diabetes mellitus and risk of fracture. *Bone*. 2014;68:124-130.
9. Driessen JH, van Onzenoort HA, Starup-Linde J, et al. Use of dipeptidyl peptidase 4 inhibitors and fracture risk compared to use of other anti-hyperglycemic drugs. *Pharmacoepidemiol Drug Saf*. 2015;24(10):1017-1025.
10. Choi HJ, Park C, Lee YK, Ha YC, Jang S, Shin CS. Risk of fractures and diabetes medications: a nationwide cohort study. *Osteoporos Int*. 2016;27(9):2709-2715.
11. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.
12. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf*. 2000;9(5):359-366.
13. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. The association between compliance with antihypertensive drugs and modification of antihypertensive drug regimen. *J Hypertens*. 2004;22(9):1831-1837.
14. Health and Social Care Information Centre. UK terminology centre-read codes. http://systems.hscic.gov.uk/data/uktc/readcodes/index_html. Accessed July 20, 2016.
15. FRAX. WHO fracture risk assessment tool. 2001. www.shef.ac.uk/FRAX/index.aspx. Accessed July 20, 2016.
16. Su B, Sheng H, Zhang M, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. *Endocrine*. 2015;48(1):107-115.
17. Bazelier MT, Gallagher AM, van Staa TP, et al. Use of Thiazolidinediones and risk of osteoporotic fracture: disease or drugs? *Pharmacoepidemiol Drug Saf*. 2012;21(5):507-514.
18. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia*. 2005;48(7):1292-1299.
19. Mamza J, Marlin C, Wang C, Chokkalingam K, Idris I. DPP-4 inhibitor therapy and bone fractures in people with type 2 diabetes – a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2016;116:288-298.
20. Fu J, Zhu J, Hao Y, Guo C, Zhou Z. Dipeptidyl peptidase-4 inhibitors and fracture risk: an updated meta-analysis of randomized clinical trials. *Sci Rep*. 2016;6:29104.
21. Mosenzon O, Wei C, Davidson J, et al. Incidence of fractures in patients with type 2 diabetes in the SAVOR-TIMI 53 trial. *Diabetes Care*. 2015;38(11):2142-2150.
22. Josse RG, Majumdar SR, Zheng Y, et al. Sitagliptin and risk of fractures in type 2 diabetes: results from the TECOS trial. *Diabetes Obes Metab*. 2016; doi:10.1111/dom.12786. [Epub ahead of print].

23. Driessen JH, de Vries F, van Onzenoort HA, et al. The use of incretins and fractures - a meta-analysis on population-based real life data. *Br J Clin Pharmacol*. 2016; doi:10.1111/bcp.13167. [Epub ahead of print].

24. Bollag RJ, Zhong Q, Phillips P, et al. Osteoblast-derived cells express functional glucose-dependent insulinotropic peptide receptors. *Endocrinology*. 2000;141:1228-1235.

25. Nuche-Berenguer B, Moreno P, Portal-Nuñez S, et al. Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. *Regul Pept*. 2010;159:61-66.

26. Nuche-Berenguer B, Lozano D, Gutiérrez-Rojas I, et al. GLP-1 and exendin-4 can reverse hyperlipidic-related osteopenia. *J Endocrinol*. 2011;209:203-210.

27. Bazelier MT, Vestergaard P, Gallagher AM, et al. Risk of fracture with thiazolidinediones: disease or drugs? *Calcif Tissue Int*. 2012;26(9):2271-2279.

28. Kahn S, Zinman B, Lachin JM, et al., Diabetes Outcome Progression Trial (ADOPT) Study Group. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from a diabetes outcome progression trial (ADOPT). *Diabetes Care*. 2008;31(5):845-851.

29. Black DM, Delmas PD, Eastell R, et al. Once-year ly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822.

30. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med*. 2001;344(5):333-340.

31. Vilsboll T, Holst JJ. Incretins, insulin secretion and type-2 diabetes mellitus. *Diabetologia*. 2004;47:357-366.

32. Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. *Diabetes Metab Res Rev*. 2004;20(3):196-204.