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The risk of fragility fractures in new users of dipeptidyl peptidase-4 inhibitors compared to sulfonylureas and other anti-diabetic drugs: A cohort study

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ABSTRACT

Aims: Mixed evidence exists for the effect of incretin-based therapies on osteoporosis in type-2 diabetes. Therefore, we conducted a cohort study to determine the association between dipeptidyl peptidase-4 (DPP-4) inhibitors and common osteoporotic “fragility fractures” (upper extremity, hip, spine).

Methods: The UK-based Clinical Practice Research Datalink was used to identify adults without prior fractures receiving a new anti-diabetic drug or a new type-2 diabetes diagnosis between 2007 and 2016. The primary aim was to compare new-users of DPP-4 inhibitors versus new-users of sulfonylureas (SU). The association between DPP-4 inhibitors and incident fractures was estimated using Cox proportional hazards models. Deciles of high-dimensional propensity scores and other anti-diabetic drugs were used as covariates.

Results: We identified 7993 and 26,636 new-users of DPP-4 inhibitors and SUs, respectively. At cohort entry, the mean age was 58.8, 40% were female, mean diabetes duration was 1.3 years, and 42% had A1c > 9%. Over 9 years (mean follow-up = 1.2 years), the incident rate of fragility fractures was lower among DPP-4 versus SU users (3.0/1000 vs. 5.2/1000 person-years; P-value = 0.007). After adjustment, there was no statistically significant difference in fracture risk (hazard ratio adjusted, aHR = 0.80, 95%CI 0.51–1.24; P-value = 0.3125). In a secondary analysis, DPP-4 inhibitors were not associated with a difference in fracture risk compared to insulin (aHR = 0.91, 95%CI 0.40–2.09); however were associated with a lower fracture risk versus thiazolidinediones (aHR = 0.47, 95%CI 0.26–0.83). Sensitivity analyses supported findings.

Conclusions: DPP-4 inhibitors are not associated with an increased risk of fragility fractures compared with SUs or insulin; however, are associated with a lower risk versus thiazolidinediones.

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1. Introduction

Patients with type 2 diabetes have increased bone mineral density and yet have a very high risk of osteoporotic fractures due to a clustering of risk factors such as postmenopausal status, smoking, advanced age, low physical activity, increased falls related to visual impairment and neuropathy, and increased frailty [1]. Studies have consistently demonstrated that having type 2 diabetes increases the risk of fragility fractures or major osteoporotic fractures (MOF), terms that collectively refer to low-trauma fractures of the hip, spine, distal radius, and proximal humerus [2–4]. The risk is estimated to be increased by 20–30% for all MOF together, with an increase as high as 70–80% for hip fractures specifically [5].

In 2006, the ADOPT trial [6] demonstrated that rosiglitazone had twice the risk of fractures compared to both metformin and glyburide in women with no difference observed in men. These results were duplicated with rosiglitazone with a re-analysis of the PROactive trial, showing the same two-fold increase in fracture risk among women [7]. Subsequent studies have uncovered possible mechanisms responsible for increasing the risk of fractures, and assessed fracture risk associated with other anti-diabetic drugs. The thiazolidinedione class effect is theorized to result from adipocyte differentiation resulting from PPAR- γ activation [8], and they induce bone marrow stromal cells toward adipocyte differentiation over osteoblastic differentiation. Observational studies have shown insulin increases fracture risks [9,10] despite known positive effects of insulin in bone matrix synthesis [11]. This increase may be the result of a higher risk of hypoglycemia leading to a greater number of falls and fractures. Other longstanding anti-diabetic drugs such as metformin, meglitinides, α -glucosidase inhibitors and sulfonylureas are believed to have neutral impacts on bone metabolism [12].

Clinical trials of newer agents, including the dipeptidyl-peptidase-4 (DPP-4) inhibitors, have reported on the risk of fracture, however long-term safety data is limited. An early meta-analysis of phase 2 and 3 DPP-4 inhibitor trials found a 40% reduction in fracture risk, purportedly attributed to the increased bone mineral density [13]. Only 63 fracture events were reported and long-term follow-up was limited. However, more recent meta-analyses have found no differences in fracture risk among DPP-4 inhibitor users compared to placebo or active comparators [14,15]. Similarly, observational data examining the association between DPP-4 inhibitors and fragility fractures does not support either an increased or decreased fracture risk [16–20]. Substantial variation exists in the study design, power, and analysis of previous observational studies.

Despite increased reporting of fracture as an outcome in diabetes therapy clinical trials, there still remains a paucity of evidence of the true long-term risk of DPP-4 inhibitor therapies on the occurrence of fragility fractures in the diabetes population compared to other classes of diabetes therapies. The aim of this study was to estimate the risk of fragility fractures after exposure to DPP-4 inhibitor initiators compared to sulfonylurea initiators and other anti-diabetic drugs.

2. Subjects, materials and methods

2.1. Study design and data sources

We used a cohort design to evaluate the comparative safety of DPP-4 inhibitors with respect to fragility fractures using the Clinical Practice Research Datalink (CPRD) database. The dataset includes longitudinal de-identified electronic medical data from primary care visits with general practitioners. It has records from more than 650 practices across the United Kingdom, representing approximately 7% of the UK population and is representative of the broader population [21]. The available information includes patient sociodemographic data (e.g., health behaviors, smoking status), physiological measures (e.g. blood pressure), laboratory data (e.g. glycated hemoglobin [HbA1c]), clinician-assigned diagnoses (via READ codes), and outpatient prescription records. Data from the CPRD include only patients acceptable for research based on numerous data quality checks [21].

Individuals were included in the source population if they met each of the following criteria between January 1st, 2001 and the end of the CPRD GOLD dataset for the study period (February 2016): (1) received a new prescription for any anti-diabetic agent or had a new diagnostic record for type 2 diabetes, with no previous anti-diabetic prescription or diagnostic record within the previous 365 days (The study entry date was defined as the first of a new anti-diabetic prescription or type 2 diabetes diagnosis); (2) had a minimum of 12 months of up-to-standard medical history prior to their study entry date; and (3) were at least 18 years of age at the time of their study entry date. In addition, we linked a subset of our source population (~58%) to hospitalization records, death certificate, and socioeconomic status information from the Hospital Episode Statistics (HES – data available up to March 31, 2014), the Office of National Statistics (ONS – data available up to April 30, 2014), and index of multiple deprivation (2010) databases, respectively. We excluded women with polycystic ovarian syndrome, pregnant women, and those with gestational diabetes. In addition, to minimize selection bias we excluded patients with a history of an osteoporotic or fragility fracture, osteoporosis, osteomalacia, neoplasms (non-skin), or who received a prescription for a bisphosphonate, calcitonin, denosumab, raloxifene or teriparatide within a year prior to their cohort entry date.

Our study protocol was approved by the Independent Scientific Advisory Committee (ISAC 15_016RARA, August 2017) and the Health Research Ethics Board at Memorial University.

2.2. Exposure

Exposure status was defined as new use of one of the following medication classes: (1) DPP-4 inhibitors, (2) Glucagon-like peptide-1 (GLP-1) receptor agonists, (3) Metformin, (4) Sulfonylureas, (5) Thiazolidinediones, (6) Sodium glucose co-transporter-2 (SGLT2) inhibitors, (7) Meglinides, (8) Acarbose, (9) Insulin. Periods of no anti-diabetic medication exposure were defined as diet/lifestyle management (no therapy). Individuals contributed person-time into the exposure categories

of interest beginning on the first day a patient was prescribed a new anti-diabetic drug or newly diagnosed with diabetes after January 1, 2007, which was set as the index date. Individuals were censored once they discontinued the medication, began therapy with a comparator medication, left the CPRD participating practice, died or on the last day of documented follow-up, whichever occurred first. To account for potential non-adherence, whenever a no treatment gap of less than 1.5 times of the average day supply (45 days) was observed, we replaced this gap with the previous therapy. Similarly, whenever a therapy gap of less than the average day supply (30 days) was observed, we replaced this therapy gap with the previous therapy. Where there were overlaps of less than 30 days between anti-diabetic medications, we censored the discontinued medication at the time of the medication start for the medication being initiated. Where medication duration was unable to be calculated, a 30-day duration was assumed.

2.3. Outcomes

Our primary endpoint was time to the first diagnosis of fragility fracture recorded during the study follow-up period in the CPRD GOLD database or HES database. Fragility fracture was defined based on READ codes contained in the GOLD data and ICD-10 codes in the HES data (see [Supplementary Appendix Table S1](#) for list of codes). Our secondary outcomes were based on fracture location including the hip, spine, distal radius, and proximal humerus.

2.4. Covariates

We used high-dimensional propensity scores (hdPS) to adjust for potential confounding whereby we selected 40 covariates from hundreds of potential confounders through an empirical, multi-step process [22]. Logistic regression was used to estimate the propensity score or predicted probability of exposure to DPP-4 inhibitors compared to sulfonylureas (or other comparators in sensitivity analyses), conditional on the 40 empirical variables identified from the hdPS procedure and several pre-defined covariates measured within the 365 days prior to the index date. Pre-defined covariates ([Supplementary Appendix Table S2](#)) included age, sex, smoking status, socioeconomic status, year of cohort entry, alcohol abuse, body mass index, duration of diabetes, history of cirrhosis, heart failure, hypertension, hyperlipidemia, ischemic heart disease, peripheral vascular disease, number of hospitalizations, number of distinct prescription drugs, most recent HbA1c value, prescription for a bisphosphonate, estrogen, oral contraceptive, oral corticosteroid, thiazide diuretics, and anti-diabetic agents prior to initiating a DPP-4 inhibitor or comparator agent. Patients without overlapping propensity scores were trimmed from analyses.

2.5. Statistical analysis

Standard descriptive statistics were used to compare the characteristics of DPP-4 inhibitor users with sulfonylurea users. Although no ideal active comparator exists, our pri-

mary analysis pre-specified sulfonylurea users as an active comparator referent group because sulfonylureas represents the largest comparison group and they are used in a similar clinical framework (i.e., often used as second and third line agents following metformin monotherapy) as DPP-4 inhibitors. Patients contributed time at risk for either a DPP-4 inhibitor or a sulfonylurea until the first gap in therapy, or a switch from a DPP-4 inhibitor to a sulfonylurea, or switch from a sulfonylurea to a DPP-4 inhibitor. Therefore, once a patient has initiated a DPP-4 inhibitor or sulfonylurea, they were continuously exposed until experiencing an event or censored. Multivariable Cox Proportional Hazards regression analysis was used to estimate the independent association between DPP-4 inhibitor use and the risk of fragility fractures after controlling for multiple potential confounders. Covariates included deciles of the high-dimensional propensity scores, as well as an ordinal time-dependent variable indicating the number of anti-diabetic agents an individual was exposed to during follow-up (1, 2, or 3+). We used standard Cox proportional hazards regression methods to estimate an unadjusted and adjusted hazard ratio and 95% confidence interval (2-sided p-values) and to check for model assumptions. Assuming 25% of the cohort is exposed to a DPP-4 inhibitor and a fracture rate of 2% [16,19], approximately 33,628 patients are required to detect a 20% relative risk reduction (i.e. hazard ratio of 0.80).

For the secondary analysis, the reference group was varied to examine the difference between DPP-4 inhibitors and other anti-diabetic medication classes. For each exposure contrast (e.g. DPP-4 inhibitors vs. thiazolidinediones and DPP-4 inhibitors vs. insulin) a new analytic cohort was identified whereby the high-dimensional propensity score procedure was rerun and trimming was applied to form new analytic cohorts for each comparison of interest.

In addition to our primary and secondary analyses, we also conducted a number of sensitivity analyses, including:

1. Repeating the main analysis using a matched propensity score to control for confounding. Patients were matched 1:1 using a greedy nearest neighbor approach with treated patients selected in random order.
2. Repeating the main analysis restricting the cohort to patients eligible for HES linkage.
3. Repeating our main analysis using alternative methods to define our drug exposure over time. First, we restricted the population to monotherapy users. Second, we restricted the population to patients initiating metformin monotherapy who added-on a DPP-4 inhibitor or sulfonylurea. Third, we used time-dependent variables to classify person-time over a patient's entire follow-up period based to further explore DPP-4 inhibitor monotherapy vs. sulfonylurea monotherapy, DPP-4 inhibitor monotherapy vs. metformin monotherapy, and DPP-4 inhibitor combination therapy (DPP-4 inhibitor/metformin, DPP-4 inhibitor/SU, and DPP-4 inhibitor/insulin, vs. metformin/SU [referent category]).
4. Conducting an additional analysis whereby patients exposed to a DPP-4 inhibitor were grouped with patients exposed to a sulfonylurea who had identical ordering of exposure to other anti-diabetic medication classes. In

other words, when comparing DPP-4 inhibitor and sulfonylurea users, we grouped patients who were exposed to identical anti-diabetic regimens with the exception of DPP-4 inhibitors and sulfonylureas. For example, when comparing initiators of DPP-4 inhibitors vs. sulfonylurea, patients who started with metformin as the first line therapy and then added DPP-4 inhibitor are in the same group as the subjects who started with metformin and added sulfonylurea. We removed from the analysis patients who are in groups with less than 25 people. This approach reduces the power of the analysis (compared to our primary analysis); however, patients using the most frequent and clinically relevant anti-diabetic regimens are included in the analysis. We adjusted for groups by using a categorical variable with K groups within our multivariable cox proportional hazards model, whereby K is the total number of groups. Deciles of the propensity score were also included as covariates in our model to be consistent with the main analysis.

5. Repeating the primary analysis on our secondary outcomes (i.e. location of fracture: hip, spine, distal radius, and proximal humerus).

All analyses were conducted with R version 3.3.3.

3. Results

A total of 130,236 patients from within the CPRD dataset met our inclusion criteria (Fig. 1). There were 7993 and 26,636 new users of DPP-4 inhibitors and sulfonylureas respectively; of these 4273 (53%) and 15,510 (58%) were linked to HES and ONS data. Mean duration of follow-up was 1.2 years, with a maximum follow-up of 9 years. Patients initiating DPP-4 inhibitors were on average younger, had a longer history with type 2 diabetes, less likely to have prior hospitalizations, had a lower HbA1c, and less likely to have impaired renal function (Table 1). However, a comparison of groups after matching with the high-density propensity score showed similarities across patient characteristics including prior antidiabetic use (Supplementary Appendix Table S3).

After 40,203 years of person-time follow-up there were a total of 189 fractures among new users of DPP-4 inhibitors ($n = 27$, incidence rate = 3.0 per 1000 person-years) and sulfonylureas ($n = 162$, incidence rate = 5.2 per 1000 person-years) (Table 2A). Though the crude hazard ratio (HR 0.57, 95% CI 0.38–0.86) suggested a significant lower risk of fractures among DPP-4 initiators compared to sulfonylurea initiators, the association dissipated after adjustment for confounding (adjusted HR (aHR) 0.80, 95% CI 0.51–1.24). Similarly, we did not observe an association between DPP-4 inhibitor initiation and fractures when compared to insulin (aHR = 0.91, 95% CI 0.40–2.09) (Table 2B). Of note, however, DPP-4 inhibitors were associated with a significantly lower fracture risk when compared with thiazolidinediones (aHR = 0.47, 95% CI 0.26–0.83) (Table 2C).

Fig. 2 presents the summary of the sensitivity analysis comparing DPP-4 inhibitors against SU (detailed results are reported in supplementary Tables S4–S9) based on: (1) matched propensity scores (HR 0.90, 95% CI 0.53–1.53)

(Table S4); (2) restriction to HES linked data only (HR 0.88, 95% CI 0.49–1.56) (Table S5); (3) adjusted for anti-diabetic therapy pattern (HR 0.72, 95% CI 0.42–1.23) (Table S6); (4) restriction to individuals on monotherapy (HR 0.28, 95% CI 0.04–2.20) (Table S7); (5) restriction to patients who combined metformin with a DPP-4 inhibitor or sulfonylurea as a second-line add on therapy (HR 0.82, 95% CI 0.34–1.99) (Table S8); (6) time-dependent DPP-4 inhibitor monotherapy vs. sulfonylurea monotherapy (HR 0.73, 95% CI 0.42–1.27), DPP-4 inhibitor monotherapy vs. metformin monotherapy (HR 0.88, 95% CI 0.52–1.50), and DPP-4 inhibitor combination therapy use (DPP4i/metformin vs. SU/metformin: HR 0.67, 95% CI 0.41–1.10; DPP4i/SU vs. SU/metformin: HR 0.98, 95% CI 0.48–2.03) (Tables S9a, S9b, Sdc) and (7) a break down based on fracture location (wrist, humerus, vertebral and hip) (Tables S10–S13). The results from the sensitivity analysis were consistent with the primary analysis, showing no statistically significant differences.

4. Discussion

In this large representative cohort of type 2 diabetes patients in the UK, we found that the incidence of fragility fracture was 4.7 per 1000 patient years. Following adjustment for potential confounding, there was no statistically significant association between DPP-4 inhibitor use and the risk of fractures compared to sulfonylurea use. Numerous sensitivity analyses demonstrated consistent findings, with the exception of thiazolidinediones which were associated with an increased risk of fragility fractures compared to DPP-4 inhibitors.

Our study provides some important clinical and statistical insights into the risk profile of DPP-4 inhibitors that helps better explain both previous meta-analyses of RCTs [14,15] and observational studies [16–20]. Previous meta-analyses identified RCTs that compared DPP-4 inhibitors to either placebo or an active anti-diabetic therapy. Mamza et al. (2016) included 51 eligible studies ($N = 36,402$) and found no significant difference in fracture risk between DPP-4 and placebo (37 studies, OR; 0.82, 95% CI 0.57–1.16, $P = 0.9$) or active comparator (14 studies, OR; 1.59, 95% CI 0.91–2.80, $P = 0.9$). Fu et al. (2016) included 62 eligible RCTs ($N = 62,206$) and also found no significant difference in fracture risk over controls (RR, 0.95; 95% CI, 0.83–1.10; $P = 0.50$). Of these two meta-analyses the majority of studies were less than or equal to 52 weeks in duration.

Our findings are consistent with prior observational studies including Majumdar et al. [20] and Josse et al. [19] who both found no increased risk of fractures associated with sitagliptin use, the latter including sitagliptin users and placebo controls from the TECOS randomized clinical trial. Driessen et al. conducted several observational studies [16–18], including two cohort studies using the CPRD database comparing DPP-4 inhibitor users to non-insulin anti-diabetic users [16,18] neither of which observed an increased fracture risk among DPP-4 users.

Our study contributes to the growing body of evidence regarding the fracture risk of DPP-4 inhibitors. Specifically, we include follow-up data until early 2016 and measure the

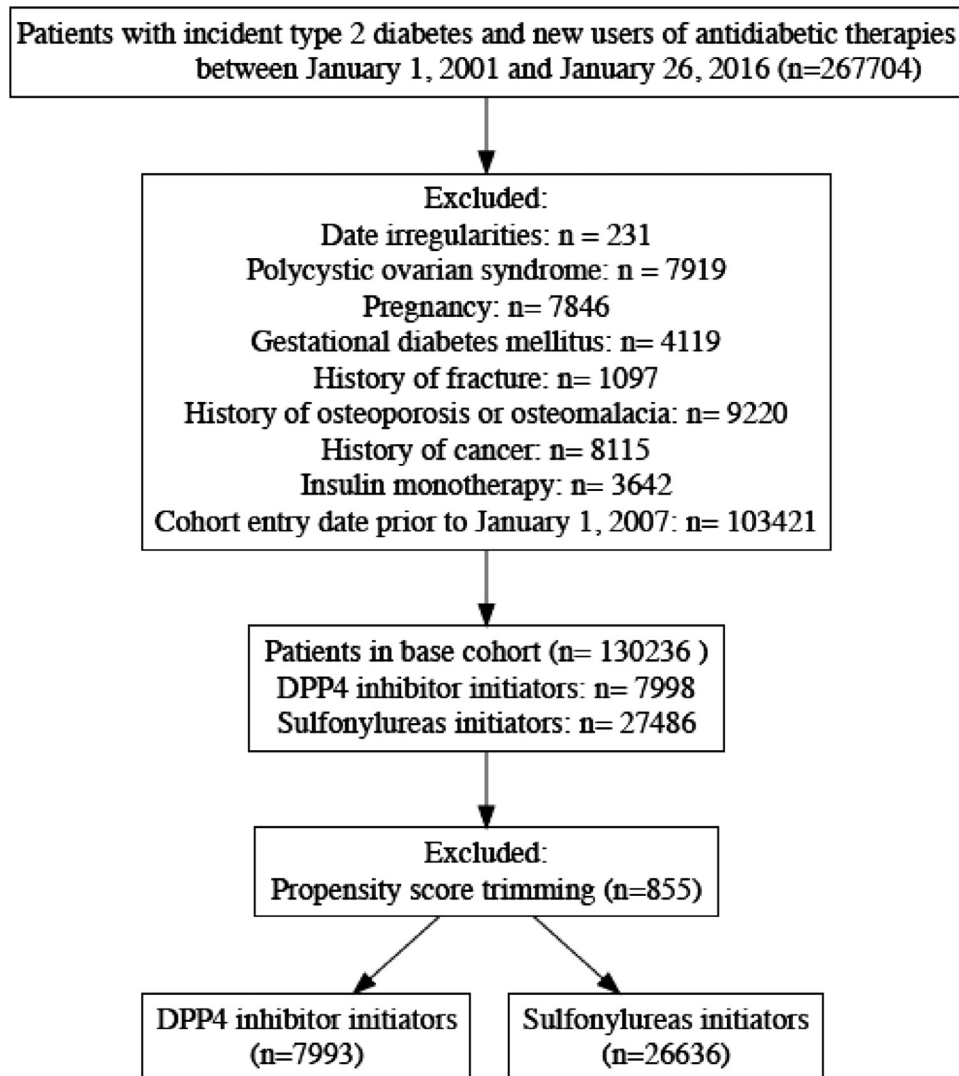


Fig. 1 – Flow diagram to identify new users of DPP-4 Inhibitors and Sulfonylureas.

fracture risk of DPP-4 inhibitors compared to sulfonylureas, insulin, and thiazolidinediones. Previous observational studies primarily used a mixed antidiabetic comparator group; where as we used a single class for each active comparator to enhance the clarity of interpretation of our findings. It is important to note that our comparator group also included patients using other antidiabetic agents; however, all patients in the reference group were continuously exposed to the comparator of interest. Specifically, we used sulfonylureas as the referent group in the primary analysis, with other active comparators in secondary analyses. There has been speculation that sulfonylureas may increase the risk of fragility fractures due to the increased risk of hypoglycemia, although to our knowledge this has not been previously demonstrated in the literature [23–25]. We believe this makes sulfonylureas an appropriate comparison group as they (as well as DPP-4 inhibitors) are commonly used as second line therapies. Moreover, our study corroborates prior evidence demonstrating that thiazolidinediones increase fracture risk [6,7]. Specifically, when we used thiazolidinediones as a comparator group, we found a 53% lower fracture risk among DPP-4 users

(i.e., an 113% increase risk of fracture among those who use thiazolidinediones).

It is important to note that although we did not find an association between DPP-4 inhibitor use and osteoporotic fractures, there exists convincing mechanistic evidence supporting the potential beneficial effects of incretin-based therapies such as DPP-4 inhibitors on bone tissue. Indeed, the incretin hormones GLP-1, GLP-2, and glucose-dependent insulinotropic polypeptide (GIP) have multiple actions on bone. GLP-1 receptors are present on both osteoblasts and osteocytes. In rodents, activation of GLP-1 receptors may induce osteoblast differentiation leading to increased bone formation [26], and decrease bone resorption via inhibition of osteoclast activity [27]. GLP-2 receptor activation may also have a role in decreasing bone resorption and has been shown to increase BMD in a dose-dependent manner [28]. GIP receptors are also present on osteoblasts, osteocytes, and osteoclasts [29]. Notably, GIP receptor polymorphism may result in differential fracture risk as was recently demonstrated in a study of perimenopausal women with a functional variant of the GIP receptor whom had a lower bone

Table 1 – Patient characteristics of new users of DPP-4 inhibitors and sulfonylureas.

	DPP-4i	SU
N	7993	26,636
<i>Sociodemographic variables</i>		
Age (years)	57.1 (12.1)	59.3 (13.5)
<i>Sex</i>		
Male	4767 (59.6%)	16,059 (60.3%)
<i>Measure of deprivation</i>		
Least deprived	765 (9.6%)	2796 (10.5%)
<i>Clinical variables</i>		
Diabetes duration (yrs)	2 (1.8)	1.1 (1.5)
<i>Number of hospitalizations</i>		
0	7204 (90.1%)	22,398 (84.1%)
1	534 (6.7%)	2568 (9.6%)
2	147 (1.8%)	911 (3.4%)
3+	108 (1.4%)	759 (2.8%)
<i>Number of drugs</i>		
0–4	752 (9.4%)	3094 (11.6%)
5–10	3721 (46.6%)	11,610 (43.6%)
11+	3520 (44%)	11,932 (44.8%)
<i>HbA1c</i>		
<6.5% (<48 mmol/mol)	317 (4%)	1597 (6%)
6.5–7.5% (48–58 mmol/mol)	1439 (18%)	4039 (15.2%)
7.5–9% (58–75 mmol/mol)	3592 (44.9%)	8702 (32.7%)
9%+ (75 + mmol/mol)	2606 (32.6%)	11,913 (44.8%)
Unknown	39 (<1%)	385 (1.4%)
Heart Failure	78 (1%)	412 (1.5%)
Hypertension	1430 (17.9%)	5278 (19.8%)
Cirrhosis	12 (<1%)	93 (<1%)
Osteoporosis	48 (<1%)	256 (1%)
Dyslipidemia	291 (3.6%)	1301 (4.9%)
Ischemic heart disease	232 (2.9%)	1182 (4.4%)
Peripheral vascular disease	29 (<1%)	180 (<1%)
<i>eGFR</i>		
<60	1072 (13.4%)	5027 (18.9%)
<i>Anti-diabetic drug use</i>		
Metformin	7471 (93.5%)	20,723 (77.8%)
Acarbose	3 (<1%)	12 (<1%)
SGLT2 inhibitors	57 (<1%)	132 (<1%)
Meglitinide	64 (<1%)	50 (<1%)
Thiazolidinedione	349 (4.4%)	511 (1.9%)
Insulin	119 (1.5%)	386 (1.4%)
<i>Other medication use</i>		
Oral contraceptions	170 (2.1%)	603 (2.3%)
Oral corticosteroids	2343 (29.3%)	8183 (30.7%)
Thiazide diuretics	1337 (16.7%)	4476 (16.8%)

mineral density and increased fracture risk after 10 years of follow-up [29].

It is also plausible that a significant period of exposure is required before any beneficial effects of DPP-4 inhibitors would occur. Although there is some debate among experts on the role that duration of diabetes plays on the overall risk of fracture, with some claiming no association with duration and some that short duration diabetes increases risk, the majority of evidence appears to suggest that a long duration of illness is a significant determinant of fracture risk [30–33]. Majumdar et al. (2016) conducted a large cohort study of women (49,098 with and 8840 without diabetes) to assess the impact of duration of type 2 diabetes on incident fractures

over 7 years [30]. They found that the risk for MOF only increased after a long duration (>10 years), though the risk of hip fracture was increased regardless of duration of illness. Similarly, Swartz et al. reported an increase in hip fracture rates after 14 years of diabetes duration compared to women without diabetes [34]. This evidence highlights the fact that the true impact of diabetes medications on MOF risk may not be evident until longer term data is available.

4.1. Limitations

Despite the major strengths in this research, there are several limitations. First, there is the potential for unmeasured con-

Table 2 – Incidence and Hazard ratios for fragility fracture in new users of DPP-4 inhibitors (DPP-4i) versus Sulfonylureas (A), Insulin (B), and Thiazolidinediones (C).

(A) Primary analysis: comparison with new users of sulfonylureas (SU)			
	DPP-4i	SU	Total
N	7993	26,636	34,629
Person Year	9134	31,069	40,203
Events	27	162	189
Incidence rate per 1000 person years	3.0 (2–4.3)	5.2 (4.5–6.1)	4.7 (4.1–5.4)
Crude HR	0.57 (0.38–0.86)	-ref-	-
Adjusted HR	0.80 (0.51–1.24)	-ref-	-
(B) Secondary analysis: comparison with new users of insulin			
	DPP-4i	Insulin	Total
N	13,155	4559	17,714
Person Year	15,834	3078	18,912
Events	52	16	68
Incidence rate per 1000 person-years	3.3 (2.5–4.3)	5.2 (3.2–8.4)	3.6 (2.8–4.6)
Crude HR	0.71 (0.40–1.26)	-ref-	-
Adjusted HR	0.91 (0.40–2.09)	-ref-	-
(C) Secondary analysis: comparison with new users of thiazolidinediones (TZD)			
	DPP-4i	TZD	Total
N	12,694	3205	15,899
Person Year	15,014	4640	19,554
Events	51	26	77
Incidence per 1000 person-years	3.4 (2.6–4.5)	5.7 (3.9–8.4)	3.9 (3.2–4.9)
Crude HR	0.61 (0.38–0.99)	-ref-	-
Adjusted HR	0.47 (0.26–0.83)	-ref-	-

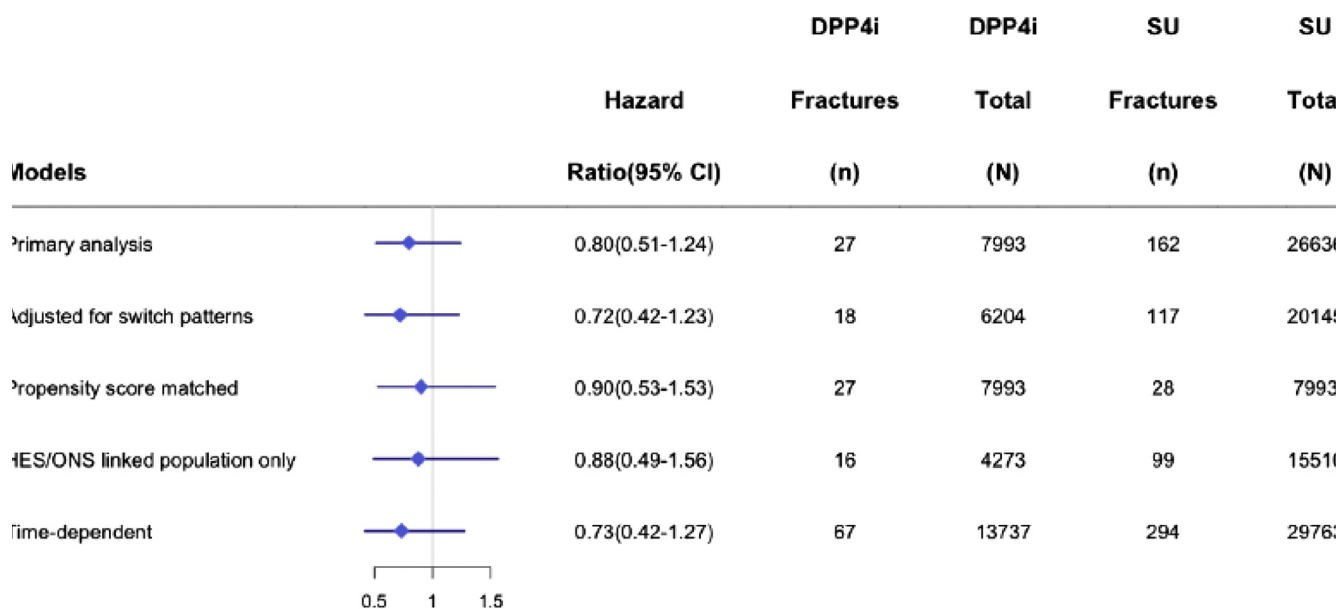


Fig. 2 – Hazard ratios and number of events within DPP4i and SU users across sensitivity analysis.

foundings; however, we were able to account for numerous potential confounders in a clinically rich dataset using advanced methods such as high-dimensional propensity scores.

Second, though we were able to capture a mean follow-up time 1.2 years and longer follow-up for a portion of patients (11% of cohort had 3 or more years of follow-up and 3% of cohort had 5 or more years follow-up), the impact of anti-

diabetic agents on fracture risk may take much longer. As previously discussed, previous studies suggest that duration of diabetes is a risk factor for increased fracture risk [30,32]. Therefore, further studies with longer follow-up periods are required to rule out a protective effect of DPP-4 inhibitors on fractures.

Third relates to potential outcome ascertainment bias. There is a possibility that fractures were misclassified within

the CPRD and HES datasets; however, previous studies have demonstrated that the CPRD data set to be highly valid (>90%) for confirmed fractures, especially hip fracture diagnosis [35,36].

Fourth is the completeness of the data of risk factors for fractures and markers of osteoporosis. There was limited data on bone mineral density (only captured in <1% of our study cohort) or bone turn over and no information on parental history of hip fracture or previous injurious falls. The impact of the particular limitation is thought to be minimal given there is no reason to anticipate that risk factors would be distributed differently across groups based on their prescriptions for anti-diabetic drug treatments.

Finally, we have used prescription data as a proxy for exposure to anti-diabetic agents. There is a risk that we may have overestimated the exposure due to the occurrence of primary and secondary non-adherence. It is possible that some individuals may never fill a prescription written by their provider (primary non-adherence), while others may fill a prescription but never consume, or only partially consume the medication (secondary non-adherence).

In conclusion, new DPP-4 inhibitors use was not associated with an increased risk of fractures among individuals with type 2 diabetes when compared to sulfonylureas or insulin; however these patients appeared to have a lower fracture risk when compared to thiazolidinediones. Larger studies with longer follow-up are needed to further characterize the fracture risk among individual DPP-4 inhibitors and longer term risks.

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Conflicts of Interest

None.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabres.2017.12.008>.

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