Dipeptidyl peptidase-4 inhibitors and fracture risk: an updated meta-analysis of randomized clinical trials

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Data on the effects of dipeptidyl peptidase-4 (DPP-4) inhibitors on fracture risk are conflicting. Here, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the effects of DPP-4 inhibitors. Electronic databases were searched for relevant published articles, and unpublished studies presented at ClinicalTrials.gov were searched for relevant clinical data. Eligible studies included prospective randomized trials evaluating DPP-4 inhibitors versus placebo or other anti-diabetic medications in patients with type 2 diabetes. Study quality was determined using Jadad scores. Statistical analyses were performed to calculate the risk ratios (RRs) and 95% confidence intervals (CIs) using fixed-effects models. There were 62 eligible RCTs with 62,206 participants, including 33,452 patients treated with DPP-4 inhibitors. The number of fractures was 364 in the exposed group and 358 in the control group. The overall risk of fracture did not differ between patients exposed to DPP-4 inhibitors and controls (RR, 0.95; 95% CI, 0.83–1.10; P = 0.50). The results were consistent across subgroups defined by type of DPP-4 inhibitor, type of control, and length of follow-up. The study showed that DPP-4 inhibitor use does not modify the risk of bone fracture compared with placebo or other anti-diabetic medications in patients with type 2 diabetes.

Type 2 diabetes is a highly prevalent disease, especially in elderly and obese patients. Cumulative evidence shows that type 2 diabetes is associated with an increased risk of bone fracture1,2. Several anti-diabetes drugs have been reported to increase the incidence of fractures3,4.

Dipeptidyl peptidase-4 (DPP-4) inhibitors, a class of incretin based agents for the treatment of type 2 diabetes, have intermediate efficacy regarding glucose control with a satisfactory tolerability profile5–7. Data on the effects of DPP-4 inhibitors on fracture risk are conflicting. A meta-analysis of randomized controlled trials (RCTs) suggested that DPP-4 inhibitors reduced the risk of bone fracture8. However, a recent retrospective population-based cohort study concluded that DPP-4 inhibitors were not associated with fracture risk compared with controls and other non-insulin anti-diabetic drugs (NIADs)9.

The association between DPP-4 inhibitors and the risk of fracture in patients with type 2 diabetes has not been well established. We therefore performed a meta-analysis of randomized trials to provide a more robust answer regarding the risk of fracture in patients with type 2 diabetes treated with DPP-4 inhibitors.

Results

Search results. A total of 3092 unique titles and abstracts were identified in initial searches of the electronic database. After screening titles and abstracts, we retrieved 343 reports for full text screening. A total of 62 RCTs, including 13 from journals10–23 and 49 from the trial registry (available from https://clinicaltrials.gov) were included in the final analysis. The details of the study selection flow are described in Fig. 1.

Study characteristics. The baseline characteristics of trials are included in Table 1 and the quality assessment results are listed in Table S1. A total of 62,206 patients (33,452 in the experimental group and 28,754 in the

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control group) were included in this analysis, of which 722 had fractures (364 in the experimental group and 358 in the control group). The age of the included patients ranged from 49.7 to 74.9 years. The inhibitors tested in the trials were alogliptin in 7, linagliptin in 13, saxagliptin in 9, sitagliptin in 27, anagliptin in 1, and vildagliptin in 5. The duration of treatment ranged from 12 weeks to 40 months. Forty-three trials were placebo-controlled and 28 used an active comparator, while nine trials included both placebo and active comparator arms. Active comparators included albiglutide, canagliflozin, empagliflozin, gliptidone, voglibose, or thiazolidinediones. Of the 62 trials included in the meta-analysis, 61 were double blind trials.

Risk ratio of fracture. A meta-analysis was performed to calculate the overall risk ratio (RR) of fracture associated with DPP-4 inhibitors versus control. Analysis of 62 trials showed that DPP-4 inhibitors were not associated with a significantly increased risk of fracture. The RR of fracture for patients treated with DPP-4 inhibitors compared with that for controls was 0.95 [95% confidence interval (CI) 0.83–1.10, P = 0.50), with insignificant heterogeneity (I² = 0%) (Fig. 2). The evidence quality was moderate to high (Table S2).

Subgroup analysis according to drug type. Subgroup analysis was performed to determine whether drug type had an effect on the RR of fracture with DPP-4 inhibitors. The RR of fracture with individual DPP-4 inhibitors was 0.79 (95% CI: 0.55–1.13, P = 0.19) for alogliptin (seven trials with 12,085 individuals, enrolling 53 patients with fracture in the experimental group and 61 patients with fracture in the control group), 1.25 (0.66–2.38, P = 0.50) for linagliptin (13 trials with 7638 individuals, enrolling 23 patients with fracture in the experimental group and 10 patients with fracture in the control group), 1.03 (0.87–1.22, P = 0.73) for saxagliptin (nine trials with 21,877 individuals, enrolling 266 patients with fracture in the experimental group and 248 patients with fracture in the control group), 0.66 (0.41–1.06, P = 0.08) for sitagliptin (27 trials with 17,907 individuals, enrolling 17 patients with fracture in the experimental group and 35 patients with fracture in the control group), 4.16 (0.22–78.51, P = 0.34) for anagliptin (one trial with 108 individuals, enrolling three patients with fracture in the experimental group and 0 patients with fracture in the control group) and 0.47 (0.13–1.78, P = 0.27) for vildagliptin (five trials with 2591 individuals, enrolling two patients with fracture in the experimental group and four patients with fracture in the control group). There were no statistically significant differences in the risk of fracture between individual DPP-4 inhibitors (P = 0.22) (Table 2). The evidence quality was moderate to high (Table S2).

Subgroup analysis according to duration. Given the potential effect of duration of treatment on the association of DPP-4 inhibitors with risk of fracture, we performed a subgroup analysis stratified according to
| Study | NCT code | DPP-4 | Comparator(s) | N. of patients | Duration (weeks) | Age (years) | HbA1c (%) | Fracture |
|-------|----------|-------|---------------|----------------|-----------------|-------------|-----------|----------|
| Boissi | NCT00286468 | ALOG | Placebo | 401 | 99 | 26 | 57 | 8 | 1 |
| NCT01023581 | ALOG | Placebo/metformin | 450 | 334 | 26 | 53.5 | 8.5 | 0 | 1 |
| NCT00856284 | ALOG | Glipizide | 1765 | 874 | 24 | 57 | 8 | 2 | 0 |
| NCT00328627 | ALOG | Placebo/pioglitazone | 1037 | 517 | 24 | 54.4 | 8.6 | 0 | 1 |
| NCT00707993 | ALOG | Glipizide | 222 | 219 | 24 | 69.9 | NR | 2 | 1 |
| White || NCT00875080 | ALOG | Placebo | 2701 | 2679 | 24 | 60.9 | 8 | 3 | 50 |
| NCT01183013 | LINA | Placebo | 392 | 409 | 24 | 57.1 | 8.1 | 1 | 0 |
| NCT00286468 | ALOG | Placebo/metformin | 428 | 363 | 24 | 55.2 | 8 | 1 | 1 |
| NCT01438814 | ALOG | Placebo | 1765 | 874 | 24 | 57 | 8.5 | 0 | 1 |
| NCT00856284 | ALOG | Placebo/pioglitazone | 544 | 345 | 24 | 53 | NR | 0 | 1 |
| NCT00707993 | ALOG | Placebo | 523 | 177 | 24 | 56.5 | 8.0 | 1 | 0 |
| NCT01084005 | LINA | Placebo | 162 | 79 | 24 | 74.9 | 8 | 2 | 0 |
| NCT00954447 | LINA | Placebo | 631 | 630 | 24 | 60 | 8.3 | 5 | 1 |
| NCT00602472 | LINA | Placebo | 792 | 263 | 24 | 58.1 | 8.1 | 0 | 1 |
| NCT01183013 | LINA | Placebo | 205 | 100 | 24 | 55.5 | 8 | 1 | 0 |
| Barnett | NCT01084005 | LINA | Placebo | 162 | 79 | 24 | 74.9 | 8 | 2 | 0 |
| Barnett | NCT00757588 | SAXA | Placebo | 304 | 151 | 24 | 57.2 | 8.1 | 0 | 1 |
| Hollander | NCT00954447 | LINA | Placebo | 381 | 184 | 24 | 54 | 8 | 5 | 0 |
| Scirica | NCT00295633 | SAXA | Placebo | 8280 | 8212 | 2.9 years | 65 | NR | 241 | 240 |
| NCT01006603 | SAXA | Placebo | 359 | 359 | 24 | 72.6 | 8 | 4 | 1 |
| NCT00575588 | SAXA | Placebo/pioglitazone | 428 | 430 | 24 | 55.7 | 7.7 | 4 | 2 |
| NCT00614939 | SAXA | Placebo | 643 | 332 | 24 | 52 | 9.5 | 3 | 0 |
| NCT01076075 | SAXA | Placebo | 283 | 287 | 24 | 54 | 7.9 | 3 | 0 |
| NCT00509236 | SAXA | Placebo | 64 | 65 | 24 | 59.5 | 8 | 2 | 0 |
| NCT01076088 | SAXA | Placebo/metformin | 367 | 377 | 24 | 52.7 | 8 | 0 | 3 |
| NCT00509262 | SAXA | Placebo | 211 | 212 | 24 | 64.2 | 7.8 | 1 | 1 |
| NCT01076075 | SAXA | Placebo | 210 | 212 | 24 | 54.9 | 8.4 | 0 | 1 |
| NCT00885352 | SAXA | Placebo | 157 | 156 | 24 | 56.1 | 8.7 | 0 | 1 |
| NCT00395343 | SAXA | Placebo | 322 | 319 | 24 | 57.8 | 8.7 | 1 | 0 |
| NCT00722371 | SAXA | Placebo/pioglitazone | 691 | 693 | 24 | 57 | NR | 3 | 1 |
| NCT01462266 | SAXA | Placebo | 329 | 329 | 24 | 58.8 | NR | 0 | 1 |
| NCT00305064 | SAXA | Placebo | 102 | 104 | 24 | 71.9 | 7.8 | 2 | 0 |
| NCT00411554 | SAXA | Placebo | 163 | 156 | 12 | 60.7 | 7.8 | 0 | 1 |
| NCT01038577 | SAXA | Placebo | 372 | 540 | 104 | 53.4 | 9 | 1 | 3 |
| NCT01177813 | SAXA | Placebo | 223 | 448 | 31 | 55 | NR | 0 | 1 |
| NCT00449930 | SAXA | Metformin | 528 | 522 | 24 | 56 | 7.3 | 1 | 0 |
| NCT00701909 | SAXA | Placebo | 516 | 519 | 30 | 56.3 | 7.5 | 2 | 1 |
| NCT00865155 | SAXA | Glipizide | 464 | 237 | 24 | 54.5 | 8 | 0 | 1 |
| NCT01098539 | SAXA | Placebo | 246 | 249 | 24 | 63.3 | NR | 0 | 2 |
| NCT00885052 | SAXA | Placebo | 175 | 178 | 24 | 56.2 | 8 | 0 | 1 |
| NCT00949770 | SAXA | Glipizide | 588 | 584 | 104 | 56.7 | 7.7 | 3 | 3 |
| NCT01289990 | SAXA | Placebo | 223 | 223 | 76 | 55.6 | NR | 0 | 2 |
| NCT00482279 | SAXA | Placebo | 625 | 621 | 44 | 49.7 | 9.87 | 1 | 2 |
| NCT00397633 | SAXA | Placebo | 261 | 259 | 24 | 50.9 | 9.5 | 1 | 0 |
| NCT01106677 | SAXA | Placebo | 366 | 735 | 24 | 55.4 | NR | 0 | 1 |
| NCT01137812 | SAXA | Placebo | 378 | 377 | 24 | 56.5 | NR | 1 | 2 |
| NCT01106690 | SAXA | Placebo | 115 | 227 | 24 | 57.4 | NR | 0 | 2 |
| NCT00881530 | SAXA | Placebo | 56 | 56 | 78 | 58.6 | NR | 0 | 1 |
| Iwamoto | NCT00337610 | SITA | Placebo | 96 | 94 | 30 | 54.8 | 9.2 | 0 | 1 |

Continued
the length of follow-up. For a duration of ≥52 weeks with 41,641 participants, no statistically significant difference was observed between patients in the DPP4i and control groups (RR = 0.98, 95% CI, 0.84–1.13, P = 0.75), including 662 patients with fracture (332 in the experimental group and 330 in the control group). No significantly increased risk of fracture was observed for a duration of <52 weeks with 20,565 participants (RR = 0.78, 95% CI, 0.51–1.21, P = 0.28) including 60 patients with fracture (32 in the experimental group and 28 in the control group). There were no statistically significant differences in the risk of fracture according to the length of follow-up (P = 0.35) (Table 2). The evidence quality was moderate to high (Table S2).

**Subgroup analysis according to control regimen.** Investigation of the effect of inhibitors according to the type of control (active treatment vs. placebo) did not suggest apparent differences (P = 0.76). In trials using active drug for comparison with 16,773 participants, the RR was 0.88 (95% CI: 0.56–1.39, P = 0.58), including 59 patients with fracture (24 in the experimental group and 35 in the control group). In trials using placebo for comparison with 47,953 participants, the RR was 0.95 (95% CI: 0.82–1.10, P = 0.48), including 674 patients with fracture (340 in the experimental group and 334 in the control group) (Table 2). The evidence quality was moderate to high (Table S2).

**Risk of specific fractures.** Individual specific and non-specific fractures were listed in Table S3. There was no significant difference between the two groups in the incidence of specific fractures.

**Publication bias.** No evidence of publication bias was detected for the RR of fracture in this study (Figure S1).

**Discussion**

The effects of DPP-4 inhibitors on bone fractures in type 2 diabetes patients have not been well documented. Here, we performed an updated meta-analysis to provide a summary of current data. Analysis of 62 RCTs demonstrated that the use of DPP-4 inhibitors does not affect the risk of bone fracture compared with placebo or other antidiabetic medications in patients with type 2 diabetes. The results were consistent across subgroups defined by type of DPP-4 inhibitor, type of control, and length of follow-up.

Our results were in line with a recently published retrospective population-based cohort study that examined 216,816 patients and suggested that DPP-4 inhibitors were not associated with fracture risk compared with controls or other NIADs. Our study was inconsistent with that of Monami et al., which showed a 40% reduction of fracture risk in DPP4-I users compared with patients taking other anti-diabetic drugs or placebo. However, the positive effect observed in this study could be related to the limited number of trials included in the analysis. Compared with the study by Monami et al., our study has several strengths. First, we collected data from 62 randomized trials (N = 62,206), which together involved approximately three times as many patients as those included in the study by Monami et al. (N = 21,055). Second, we explored sources of heterogeneity with three priori subgroup hypotheses and the results remained robust.

Out results were largely influenced by a large RCT (N = 16,492) that compared saxagliptin with placebo and showed that the incidence of bone fracture was comparable between saxagliptin and placebo users. However, the results remained robust after omitting that trial.

Glucagon-like peptide-1 (GLP-1) has been suggested to have a beneficial effect on bone. However, the enzyme DPP-4 is involved in the degradation of GLP-1, and DPP-4 inhibitors are able to inhibit this process. However, a recent meta-analysis highlighted that the use of GLP-1 receptor agonists does not modify the risk of bone fracture in patients with type 2 diabetes compared with the use of other antidiabetic medications. Moreover, a recent in vivo study showed that MK-0626, a DPP-4 inhibitor, had neutral effects on cortical and trabecular bone in an animal model of type 2 diabetes, and MK-0626 did not alter osteoblast differentiation. Thus, bone quality may be more important than bone density in predicting the increased risk for fractures in patients with type 2 diabetes.

The present meta-analysis had several limitations. First, the duration of the trials included was not long enough to analyze the effects of DPP-4 inhibitors on the risk of bone fracture. We performed a subgroup analysis according to duration (≥52 weeks vs. <52 weeks) and found that the risk of fracture in different length of follow up were not significantly different. Second, fractures were not the primary endpoints in any of the included trials.
and were reported only as serious adverse events. Finally, no data could be obtained about gender and menopausal status. Therefore, trials with a longer follow-up duration and bone fracture as the primary endpoint are needed to further investigate the effects of DPP-4 inhibitors on fracture risk.

In summary, the current analysis suggested that the use of DPP-4 inhibitor does not decrease the risk of fracture in patients with type 2 diabetes. Given the negative effects of certain anti-diabetic drugs on bone, the results of the present study may be disappointing; however, a neutral effect on bone is still reassuring.

| Study or Subgroup | DPP-4 | Control | Risk Ratio M-H, Fixed | 95% CI |
|-------------------|-------|---------|----------------------|--------|
| Barnett 2012      | 2     | 3       | 0.33 [0.06, 1.96]    |        |
| Barnett 2013      | 2     | 26      | 0.25 [0.12, 0.52]    |        |
| Boise 2009        | 1     | 1       | 1.00 [0.58, 1.76]    |        |
| Boise 2011        | 6     | 409     | 1.48 [0.42, 5.21]    |        |
| Fonseca 2007      | 0     | 144     | 0.35 [0.01, 8.56]    |        |
| Hollander 2011    | 5     | 38      | 2.14 [0.28, 2.85]    |        |
| Inselsbo 2010     | 0     | 163     | 0.32 [0.01, 7.77]    |        |
| Inselsbo 2010V    | 0     | 188     | 0.20 [0.01, 4.23]    |        |
| NCT0086502       | 0     | 175     | 0.34 [0.01, 8.27]    |        |
| NCT0086515       | 0     | 464     | 0.17 [0.01, 4.17]    |        |
| NCT0094770       | 3     | 558     | 0.99 [0.20, 4.90]    |        |
| NCT0103857       | 1     | 551     | 0.22 [0.02, 2.11]    |        |
| NCT0121697       | 4     | 564     | 0.27 [0.16, 5.30]    |        |
| NCT0286648       | 1     | 401     | 0.75 [0.03, 18.18]   |        |
| NCT0305804       | 0     | 102     | 0.20 [0.01, 4.21]    |        |
| NCT0327015       | 3     | 978     | 2.35 [0.12, 45.42]   |        |
| NCT0328827       | 0     | 1037    | 0.17 [0.01, 4.08]    |        |
| NCT0335343       | 1     | 322     | 0.27 [0.12, 2.68]    |        |
| NCT0397631       | 1     | 261     | 0.28 [0.12, 2.74]    |        |
| NCT0411554       | 0     | 163     | 0.32 [0.01, 7.77]    |        |
| NCT0449930       | 1     | 528     | 0.27 [0.12, 6.64]    |        |
| NCT0648279       | 1     | 626     | 0.50 [0.05, 5.84]    |        |
| NCT0659236       | 2     | 64      | 5.08 [0.25, 103.72]  |        |
| NCT0659262       | 1     | 211     | 1.00 [0.06, 15.96]   |        |
| NCT0657568       | 4     | 428     | 2.51 [0.37, 10.91]   |        |
| NCT0661250       | 2     | 523     | 1.70 [0.08, 32.21]   |        |
| NCT0682272       | 3     | 792     | 2.33 [0.12, 44.92]   |        |
| NCT0681439       | 0     | 85      | 0.33 [0.01, 8.07]    |        |
| NCT06821140      | 1     | 336     | 0.25 [0.02, 2.72]    |        |
| NCT06961362      | 3     | 286     | 7.10 [0.37, 136.60]  |        |
| NCT0701909       | 2     | 516     | 2.01 [0.19, 22.12]   |        |
| NCT0707993       | 2     | 222     | 1.97 [0.19, 21.60]   |        |
| NCT0722371       | 3     | 922     | 2.25 [0.24, 21.62]   |        |
| NCT0798161       | 1     | 428     | 0.85 [0.05, 15.31]   |        |
| NCT08050863      | 2     | 68      | 4.78 [0.23, 97.76]   |        |
| NCT0806284       | 6     | 1765    | 0.74 [0.21, 263]     |        |
| NCT0881530       | 0     | 56      | 2.27 [0.09, 55.17]   |        |
| NCT0885352       | 0     | 157     | 0.33 [0.01, 8.07]    |        |
| NCT0915772       | 1     | 396     | 0.43 [0.03, 5.62]    |        |
| NCT0995447       | 6     | 631     | 1.20 [0.37, 3.91]    |        |
| NCT1009603       | 4     | 359     | 4.00 [0.45, 35.61]   |        |
| NCT1023581       | 0     | 442     | 0.25 [0.01, 6.02]    |        |
| NCT1076075       | 0     | 210     | 0.34 [0.01, 8.21]    |        |
| NCT1076088       | 0     | 367     | 0.15 [0.01, 2.83]    |        |
| NCT1104005       | 2     | 162     | 2.45 [0.12, 50.51]   |        |
| NCT1108539       | 0     | 246     | 0.20 [0.01, 4.20]    |        |
| NCT1106677       | 0     | 366     | 0.67 [0.03, 16.37]   |        |
| NCT1106990       | 0     | 115     | 0.39 [0.02, 8.12]    |        |
| NCT1137812       | 1     | 378     | 0.50 [0.05, 5.48]    |        |
| NCT1177813       | 0     | 223     | 1.01 [0.04, 24.84]   |        |
| NCT1183013       | 1     | 392     | 3.13 [0.13, 76.60]   |        |
| NCT1204294       | 1     | 228     | 1.84 [0.07, 39.90]   |        |
| NCT1215009       | 1     | 205     | 1.47 [0.06, 35.79]   |        |
| NCT1299999       | 0     | 223     | 0.60 [0.03, 12.54]   |        |
| NCT1438814       | 0     | 344     | 0.33 [0.01, 8.18]    |        |
| NCT1462266       | 0     | 329     | 0.33 [0.01, 8.18]    |        |
| Pan 2012          | 1     | 294     | 1.47 [0.06, 35.97]   |        |
| Raz 2008          | 0     | 96      | 0.33 [0.01, 7.91]    |        |
| Scherbaum 2008    | 0     | 156     | 0.32 [0.01, 8.16]    |        |
| Sorota 2013       | 241   | 829     | 1.00 [0.84, 1.18]    |        |
| White 2013        | 38    | 2701    | 0.75 [0.50, 1.15]    |        |
| Yang 2015         | 3     | 68      | 4.16 [0.22, 78.51]   |        |

Total (95% CI): 33452 [28754, 100.00] 0.95 [0.83, 1.10]

Total events: 358

Figure 2. Risk of fractures between patients with type 2 diabetes treated with DPP-4 inhibitors or control.
Methods

Data Sources and Searches. An extensive search of Medline, Embase, and Cochrane Central Register of Controlled Trials was performed by two of the investigators (J.F. and J.Z.). Data were collected on all randomized clinical trials in humans up to March 2016. Disparities in abstracted data between the reviewers were resolved by a third reviewer (Z.Z.). The search terms used were as follows: “DPP-4”, “dipeptidyl peptidase 4”, “alogliptin”, “linagliptin”, “saxagliptin”, “sitagliptin”, “vildagliptin”, “anagliptin”, and “dutogliptin”. The results of unpublished clinical trials in type 2 diabetes patients; (b) duration of at least 12 weeks; (c) patients assigned to treatment with DPP-4 inhibitors compared with placebo or active drugs; (d) data on bone fracture was available; and (f) trials with two zero events were excluded from the analysis.

Data Extraction and Quality Assessment. The following information was extracted independently from eligible RCTs by two of the investigators (Y.H. and C.G.): author’s name, year of publication, study design, sample size, number of treatment groups, length of follow-up, mean age, and registry number. In addition, for trials in which fracture data had not been published previously, the investigators abstracted the relevant numbers from their previously established databases of adverse events. The quality of included trials was assessed using the Jadad score32, which was only used for descriptive purposes. Any discrepancies in abstracted data between the reviewers were resolved by a third reviewer (Z.Z.).

Data analysis. The meta-analysis was performed following the PRISMA checklist33. The main outcome was bone fracture reported as a serious adverse event. Trials were pooled using the Mantel-Haenszel method to calculate RRs and their 95% CIs. P < 0.05 was considered significant. For studies reporting zero fracture events in a treatment or control arm, a classic half-integer continuity correction was used to calculate the RR and variance. Heterogeneity between studies was assessed by using the χ2 test and the I² statistic. Selection of the fixed- or random-effects model depended on the result of the Cochrane’s Q test. An I² value of 50% was considered to indicate significant heterogeneity between trials34. A fixed effects model was applied if there was no statistical heterogeneity among the studies; otherwise, the random effects model was used34. Pre-defined subgroup analyses were performed for trials that included different types of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, anagliptin, and vildagliptin), different types of control (active treatment vs. placebo), and different lengths of follow-up (≥ 52 weeks vs. < 52 weeks). Finally, publication bias was evaluated through funnel plots. Meta-analyses were performed using Review Manager 5.1 software. The criteria of the Grading of Recommendations Assessment, Development and Evaluation were used to evaluate the quality of evidence by outcome.35

Table 2. Risk ratio of fracture by subgroup analyses. NA, not applicable.

| Subgroup                | Studies n | No. of fracture | No. of participants | Risk ratio (95% CI) | P Value | RR | Group difference |
|-------------------------|-----------|-----------------|---------------------|---------------------|---------|----|------------------|
| Overall Individual DPP-4| 62        | 364             | 358                 | 33452               | 28754   | 0.95 | (0.82, 1.10)     | 0.50  | NA               |
| Alogliptin              | 7         | 53              | 61                  | 6972                | 5113    | 0.79 | (0.55, 1.14)     | 0.20  | 0.37             |
| Linagliptin             | 13        | 23              | 10                  | 4667                | 2971    | 1.19 | (0.60, 2.38)     | 0.62  |                  |
| Saxagliptin             | 9         | 266             | 248                 | 11662               | 10215   | 1.02 | (0.86, 1.21)     | 0.84  |                  |
| Sitagliptin             | 27        | 17              | 35                  | 8422                | 9485    | 0.67 | (0.39, 1.15)     | 0.15  |                  |
| Anagliptin              | 1         | 3               | 0                   | 68                  | 40      | 4.16 | (0.22, 78.51)    | 0.34  |                  |
| Vildagliptin            | 5         | 2               | 4                   | 1661                | 930     | 0.50 | (0.12, 2.05)     | 0.33  |                  |
| Duration                |           |                 |                     |                     |         |     |                  |
| ≥52 weeks               | 28        | 332             | 330                 | 21645               | 19996   | 0.97 | (0.83, 1.13)     | 0.69  | 0.37             |
| <52 weeks               | 34        | 32              | 28                  | 11807               | 8758    | 0.76 | (0.46, 1.27)     | 0.29  |                  |
| Comparators             |           |                 |                     |                     |         |     |                  |
| Active drug             | 28        | 24              | 35                  | 7594                | 9179    | 0.91 | (0.54, 1.52)     | 0.71  | 0.88             |
| Placebo                 | 43        | 340             | 334                 | 26235               | 21718   | 0.95 | (0.81, 1.10)     | 0.44  |                  |

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Author Contributions

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