

Dipeptidyl Peptidase-4 Inhibitors and Bone Fractures

A meta-analysis of randomized clinical trials

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OBJECTIVE—Thiazolidinediones and insulin are associated with a higher risk of fractures in type 2 diabetic patients. Incretin hormones increase bone density in experimental models, but the effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on bone fractures has not been reported so far.

RESEARCH DESIGN AND METHODS—A meta-analysis was performed including all randomized clinical trials with a duration of at least 24 weeks, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with placebo or active drugs.

RESULTS—Twenty-eight trials enrolling 11,880 and 9,175 patients for DPP-4 inhibitors and comparators, respectively, were included, reporting 63 fractures. DPP-4 inhibitors, compared with placebo or other treatments, were associated with a reduced risk of fractures (Mantel-Haenszel odds ratio [MH-OR] 0.60, 95% CI 0.37–0.99, $P = 0.045$), even after the exclusion of comparisons with thiazolidinediones or sulfonylureas (MH-OR 0.56, 0.33–0.93, $P = 0.026$).

CONCLUSIONS—The present meta-analysis suggests that treatment with DPP-4 inhibitors could be associated with a reduced risk of bone fractures.

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Type 2 diabetes is associated with an increased risk for bone fractures (1–3). The higher risk could be determined by several factors, including falls, diabetes complications, and comorbidities (2). Moreover, glucose-lowering agents such as thiazolidinediones have been reported to reduce bone density (4,5) and to increase the incidence of fractures in longer-term trials (6,7) and in epidemiologic studies (8). Insulin therapy is also associated with an increased fracture risk (9–11) despite its neutral effect on bone density (12). The increased risk of falls, due to hypoglycemia, could lead to higher fracture risk (10).

Glucagon-like peptide-1 (GLP-1) has been reported to induce osteoblast differentiation (13) and inhibit osteoclastic activity (14); GLP-1 receptor agonists

stimulate bone formation in rodents (15). Experimental data in animal models suggest that gastric intestinal polypeptide is also capable of increasing bone density (16,17). Drugs capable of increasing incretin levels, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, could therefore exert beneficial effects on the bone.

RESEARCH DESIGN AND METHODS

A MEDLINE and Embase search for “vildagliptin,” “sitagliptin,” “saxagliptin,” “alogliptin,” “linagliptin,” and “dutogliptin” was performed for randomized trials up to April 1, 2011. The selection of studies and the subsequent data extraction were performed independently by two of the authors (I.D. and M.M.), and conflicts were resolved by the third investigator (E.M.). Completed but

still unpublished trials were identified through a search of www.clinicaltrials.gov website. Food and Drug Administration (www.fda.gov) and European Medicines Agency (www.ema.europa.eu) reviews of approved drugs were also searched for retrieval of unpublished trials.

A meta-analysis was performed including all trials with a duration of ≥ 24 weeks, enrolling patients with type 2 diabetes, comparing DPP-4 inhibitors with placebo or other active drugs.

Results of unpublished trials were retrieved on www.clinicaltrials.gov, www.clinicalstudyresults.org, and Food and Drug Administration and European Medicines Agency websites.

The quality of trials was assessed using some of the parameters proposed by Jadad et al. (18), used only for descriptive purposes.

The principal outcome was the effect of DPP-4 inhibitors on the incidence of bone fractures reported as serious adverse events. Predefined separate analyses were performed for trials with different DPP-4 inhibitors.

Heterogeneity was assessed by using I^2 statistics. We report the results of the random-effects models because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication/disclosure bias, we used funnel plots (Supplementary Fig. A1) and the Begg adjusted rank correlation test (19,20), including published and unpublished, but disclosed, trials. However, because these tests have low statistical power when the number of trials is small (21), undetected bias may still be present. Mantel-Haenszel odds ratio (MH-OR) with 95% CI was calculated for all the adverse events defined above on an intention-to-treat basis, excluding trials with zero events. As a sensitivity analysis, MH-OR in all trials was also calculated with continuity correction.

The meta-analysis was reported following the PRISMA checklist (22) (Supplementary Table 1). All analyses were performed using Comprehensive Meta-analysis Version 2 (Biostat, Englewood, NJ) and SPSS 16.0 (SPSS Inc., Chicago, IL).

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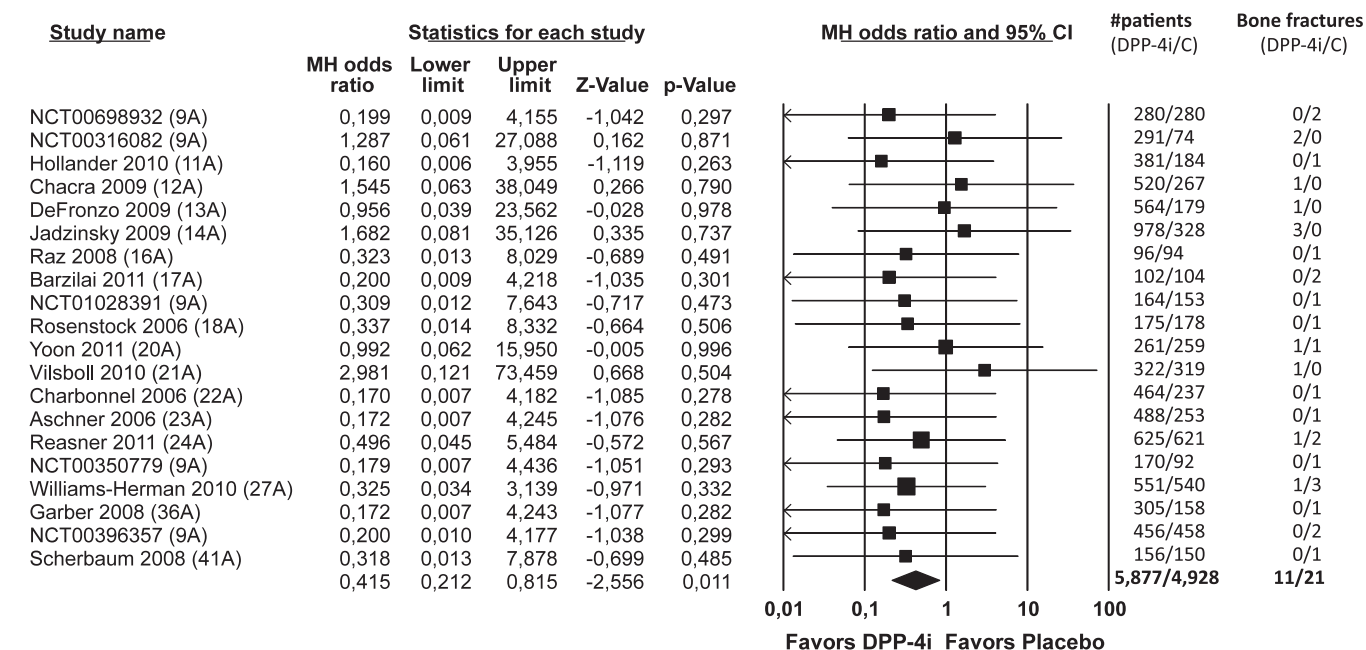


Figure 1—Subgroup analyses of MH-OR (95% CI) for bone fractures in placebo-controlled trials. DPP-4i, DPP-4 inhibitors.

This research was performed independently of any funding, as part of the institutional activity of the investigators.

RESULTS—The trial flow is summarized in Supplementary Figure A2. Of 54 available trials, 16 did not disclose bone fractures and 10 reported zero events. The meta-analysis was performed on 28 trials (11,880 and 9,175 patients for DPP-4 inhibitors and comparators, respectively; mean duration of treatment for both was 35 weeks). Of 28 trials, 20 and 7 were placebo- and active comparator-controlled, respectively, whereas one trial included both placebo and active comparator arms (Supplementary Tables 2 and 3). Of 12 unpublished trials, 5, with a planned enrollment of 4,377 patients, were undisclosed and therefore excluded from the analysis. Age, sex, BMI, duration of diabetes, and baseline HbA_{1c} were similar in DPP-4 inhibitor and comparator groups (data not shown).

The Begg adjusted rank correlation test (Kendall τ = 0.19; P = 0.16) suggested no major publication bias. I^2 test for heterogeneity suggested the use of a random-effects model.

The total number of bone fractures was 63 (26 and 37 with DPP-4 inhibitors and comparators, respectively). The MH-OR for DPP-4 inhibitors was 0.60 (95% CI 0.37–0.99, P = 0.045) (Supplementary Fig. A3); the corresponding figure with continuity correction was 0.60 (0.39–0.92,

P = 0.019). The MH-OR for DPP-4 inhibitors was 0.54 (0.28–1.03, P = 0.063) and 0.70 (0.32–1.52, P = 0.37) in trials with a duration <52 weeks or \geq 52 weeks, respectively; only 7 trials with events and duration \geq 52 weeks were available. Similar results (MH-OR 0.41, 0.21–0.81, P = 0.01) were obtained in placebo-controlled trials, with no difference across individual DPP-4 inhibitors (Fig. 1).

CONCLUSIONS—Bone fractures are not among the usual end points considered for choosing glucose-lowering therapies. However, therapeutic decisions can modulate the risk of bone fractures (4–9). The results of this meta-analysis should be considered with caution. The duration of the trials included is rather short, not allowing inferences on longer-term effects because of the small number of trials with longer duration. Furthermore, bone fractures were not the principal end points in any of the studies and were reported only as adverse events. This analysis is limited to cases classified as serious adverse events, which are only a fraction of all fractures. Nonserious adverse events were not considered because they are often not reported in detail. Furthermore, it was not possible to discriminate between sexes and between pre- and postmenopausal women; the small number of fractures also prevented separate analyses for different fracture sites. Finally, a reporting bias

in favor of DPP-4 inhibitors cannot be entirely ruled out.

Despite those limitations, available trials suggest that DPP-4 inhibitors could have a protective effect on the bone, even after the exclusion of comparisons with drugs associated with a reduction in bone density (thiazolidinediones) or an increase in hypoglycemic risk (sulfonylureas). This action could be due to the increase in circulating levels of GLP-1 and gastric intestinal polypeptide, which are both involved in the regulation of bone metabolism (13–17), whereas it is unlikely that such effect, which has never been reported with other drugs, could be due to the glucose-lowering action of DPP-4 inhibitors.

In view of the results of this meta-analysis, a more careful assessment of bone fractures in trials investigating cardiovascular outcomes with DPP-4 inhibitors is suggested.

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M.M. and E.M. designed the study, collected data, performed analysis, and wrote the manuscript. I.D. and A.A. collected data and performed analysis.

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