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The use of incretins and fractures – a meta-analysis on population-based real life data

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The aim of the present study was to estimate the effect of incretins on fracture risk in the real-world situation by meta-analysis of the available population-based cohort data. Pubmed and Embase were searched for original articles investigating use of incretin agents, and fracture risk up to December 2015. Adjusted results were extracted and pooled by use of generic inverse variance methods, assuming a random-effects model. Neither current dipeptidyl peptidase 4-inhibitor use nor current glucagon-like peptide 1 receptor agonist use was associated with a decreased risk of fracture: pooled relative risk (pooled RR [95% confidence interval]: 1.02 [0.91–1.13] and 1.03 [0.87–1.22]), respectively. This meta-analysis demonstrated that current use of incretin agents, was not associated with decreased fracture risk. Our findings show the value of representative real-world populations, and the risks associated with suggesting benefits for medications on the basis of safety reporting in randomized controlled trials.

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Table of Links

LIGANDS
DPP4
GLP-1

This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

Fractures are associated with increased morbidity and mortality, and place a considerable economic burden upon health care systems [2]. Patients with type 2 diabetes (T2D) are at increased fracture risk, both from the disease itself and potentially from associated medications [3]. Since 2007, incretin agents, such as dipeptidyl peptidase 4-inhibitors (DPP4-Is) and glucagon-like peptide 1 receptor agonists (GLP1-ras), have been available for the treatment of T2D. Interestingly, a meta-analysis, solely based upon randomized controlled trial (RCT) data, showed that the use of DPP4-Is was associated with a 40% reduction in fracture risk [4]. In contrast, meta-analyses showed that GLP1-ra use was not associated with fracture risk [5, 6], although stratification by type of GLP1-ra resulted in a 62% risk with a specific GLP1-ra, while another type showed a two-fold increased risk [6]. We have recently investigated the association between incretin use and fracture risk, using real-life data from large population-based cohorts [7–10]. In contrast to the RCT meta-analyses [4, 6] we did not observe a reduced fracture risk with use of either incretin.

The aim of the present study was to obtain the highest quality estimate of the effect of incretins on fracture risk in the real-world situation by meta-analysis of the available population-based cohort data.

Methods

Extensive supplemental information on the methods (search strategy and statistical analysis) is electronically available. In brief, we searched for studies investigating either DPP4-I or GLP1-ra agents and fracture risk up to 2015. To be included, a study had to meet the following criteria: use of an observational study design; compare the use of at least one of the incretin agents (DPP4-I or GLP1-ra) to the use of other oral glucose-lowering drugs; report fractures as outcome variable; report relative risks (RR), odds ratios or hazard ratios including 95% confidence intervals (CIs); the studies had to be written in English. Adjusted results were pooled using generic inverse variance methods, assuming a random effects model. Analyses were performed using RevMan Version 5.3 (Cochrane Collaboration, Oxford, UK).

Results

In total, four studies were included in the present meta-analysis and they contained 22 961 current DPP4-I users (568 fractures) and 8505 current GLP1-ra users (202 fractures) [7–10] (supplemental Table S1, Figure S1).

We found that neither current DPP4-I use, nor current GLP1-ra use was associated with a decreased risk of fracture (corresponding forest plots Figures S2 and Figures S3): pooled relative risk (pooled RR [95% CI]: 1.02 [0.91–1.13] and 1.03 [0.87–1.22]) respectively, except for GLP1-ra use which was associated with an increased risk of vertebral fracture risk (pooled RR [95%CI] 1.86 [1.19–2.91]) (data not shown). The results were similar if DPP4-I use was stratified according to cumulative exposure or average daily dose. When GLP1-ra use was stratified according to cumulative exposure or average daily dose there was no consistent increased or decreased fracture risk with cumulative dose, whereas fracture risk was increased if the average daily GLP1-ra dose exceeded 22.5 μg day^{-1} (pooled RR [95% CI] 1.63 [1.11–2.41]; all Table S2).

Discussion

The results of this meta-analysis on real-life population-based data demonstrate that, contrary to pooled RCT-data [4, 6], the current use of incretins (either DPP4-Is or GLP1-ras) was not associated with a decreased fracture risk. Moreover, GLP1-ra use was associated with an increased risk of any fracture if the average daily dosage exceeded 22.5 μg day^{-1}. The present results were in line with a previous meta-analysis, showing no association between use of GLP1-ra and risk of fracture [5]. It is possible that the discrepancies between the pooled RCT-data and our real-life population-based data may be a result of selection bias due to the use of strict inclusion and exclusion criteria with RCTs and the fact that data on fractures in the RCT studies were not predefined outcomes and therefore not routinely systematically collected. Importantly, the notion that incretins may have skeletal effects stems from *in vitro* and experimental animal studies, possibly acting via osteoclast inhibition and modulation of thyroid C-cells, which express incretin receptors [11, 12]; the translation of such observations to the human clinical situation must be viewed with caution.

A particular strength of this short report is, next to its analyses of real-life population-based data, its use of the same cumulative and average daily dose categories which allowed us to use the same definitions across the studies. The number of fractures with current GLP1-ra use was relatively small, which limited the statistical power to detect associations, particularly when stratified by cumulative exposure, average daily dose and fracture type. In addition, only a small number of observational studies, all performed by us, could be

included in the present meta-analysis. Another limitation is the relative short duration of incretin use (37 weeks to 1.7 years) [7–10]. We nevertheless have tested the hypothesis that incretin use was associated with a decreased risk of fracture in multiple ways, and none of the analyses showed a decreased risk of fracture. Moreover, we used data representative for the UK (2007–2012) and data on all fractures in Denmark between 2007 and 2011.

In short, this meta-analysis demonstrated that the current use of incretin agents, either DPP4-I or GLP1-ra, was not associated with decreased fracture risk. Moreover, current GLP1-ra use was associated with an increased risk of any fracture when the average daily dosage exceeded 22.5 μg day^{-1}. Our findings show the value of representative real-world populations, and the risks associated with suggesting benefits for medications on the basis of safety reporting in RCTs. An adequately powered trial with fracture as the primary endpoint will be required to properly demonstrate the skeletal efficacy or otherwise of incretins.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: J.D. and F.V. are employed by the Division of Pharmacoepidemiology & Clinical Pharmacology, which has received unrestricted funding from the Netherlands Organisation for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (www.tipharma.nl), includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), the EU 7th Framework Program (FP7), the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer, and others). J.B. reports grants from MSD, grants from Eli Lilly, grants from Amgen, grants from Will Pharma, outside the submitted work. N.H. reports grants, personal fees and other from Consultancy/ lecture fees/ honoraria, outside the submitted work. P.V. reports other from Eli Lilly, grants from MSD, other from Astra Zeica, outside the submitted work. H.O., C.N. and R.H. declare no conflicts of interest.

Contributors

All authors drafted the manuscript, revised it critically for important intellectual content, and approved the final version to be published. All authors were responsible for the study concept and design and participated and interpretation of data. J.D. and F.V. participated in the analysis. J.D. led the statistical analysis. J.D., F.V. and P.V. were responsible for the data acquisition. F.V. is the study guarantor.

Ethical approval

The Clinical Practice Research Datalink group obtained ethical approval from a multicentre research ethics committee for a purely observational research using data from the database, such as ours. This study obtained approval for the independent scientific advisory committee of the Clinical Practice Research Datalink, which is responsible for reviewing protocols for scientific quality. For the Danish data no ethical approval was needed as the study was not a clinical trial.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13167/suppinfo

Table S1 Characteristics of included studies
Table S2 Risk of fracture in dipeptidyl peptidase 4-inhibitors and glucagon-like peptide 1-receptor agonists users compared with noninsulin antidiabetic drug users, by age, sex, cumulative exposure and average daily dose
Figure S1 Flowchart of included studies
Figure S2 Forest plots of current dipeptidyl peptidase 4-inhibitors use compared to current other noninsulin antidiabetic drug use
Figure S3 Forest plots of current glucagon-like peptide 1-receptor agonists use compared to current other noninsulin antidiabetic drug use