Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies

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Abstract

Objective To investigate the risk of pancreatitis associated with the use of incretin-based treatments in patients with type 2 diabetes mellitus.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov.

Eligibility criteria Randomised and non-randomised controlled clinical trials, prospective or retrospective cohort studies, and case-control studies of treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors in adults with type 2 diabetes mellitus compared with placebo, lifestyle modification, or active anti-diabetic drugs.

Data collection and analysis Pairs of trained reviewers independently screened for eligible studies, assessed risk of bias, and extracted data. A modified Cochrane tool for randomised controlled trials and a modified version of the Newcastle-Ottawa scale for observational studies were used to assess bias. We pooled data from randomised controlled trials using Peto odds ratios, and conducted four prespecified subgroup analyses and a post hoc subgroup analysis. Because of variation in outcome measures and forms of data, we describe the results of observational studies without a pooled analysis.

Results 60 studies (n=353639), consisting of 55 randomised controlled trials (n=33350) and five observational studies (three retrospective cohort studies, and two case-control studies; n=320289) were included. Pooled estimates of 55 randomised controlled trials (at low or moderate...
risk of bias involving 37 pancreatitis events, raw event rate 0.11%) did not suggest an increased risk of pancreatitis with incretins versus control (odds ratio 1.11, 95% confidence interval 0.57 to 2.17). Estimates by type of incretin suggested similar results (1.05 (0.37 to 2.94) for GLP-1 agonists vs control; 1.06 (0.46 to 2.45) for DPP-4 inhibitors vs control).

Analyses according to the type of control, mode, duration of treatment, and individual incretin agents suggested no differential effect by subgroups, and sensitivity analyses by alternative statistical modelling and effect measures did not show important differences in effect estimates. Three retrospective cohort studies (moderate to high risk of bias, involving 1466 pancreatitis events, raw event rate 0.47%) did not suggest an increased risk of pancreatitis associated with either exenatide (adjusted odds ratios 0.93 (0.63 to 1.36) in one study and 0.9 (0.6 to 1.5) in another) or sitagliptin (adjusted hazard ratio 1.0, 0.7 to 1.3); a case-control study at moderate risk of bias (1003 cases, 4012 controls) also suggested no significant association (adjusted odds ratio 0.98, 0.69 to 1.38). Another case-control study (1269 cases, 1269 controls) at moderate risk of bias, however, suggested that the use of either exenatide or sitagliptin was associated with significantly increased odds of acute pancreatitis (use within two years v no use, adjusted odds ratio 2.07, 1.36 to 3.13).

Conclusions The available evidence suggests that the incidence of pancreatitis among patients using incretins is low and that the drugs do not increase the risk of pancreatitis. Current evidence, however, is not definitive, and more carefully designed and conducted observational studies are warranted to definitively establish the extent, if any, of increased risk.

Introduction

Acute pancreatitis is a serious condition that often leads to hospital admission and even death. Important risk factors for acute pancreatitis include gallstones, alcohol use, older age, black race, smoking, obesity, and type 2 diabetes. Exposure to certain drugs is also associated with acute pancreatitis. Glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are two classes of incretin based treatments for type 2 diabetes mellitus. Evidence from randomised controlled trials has shown that GLP-1 agonists effectively lower glycated haemoglobin (HbA1c) by about 1%, reduce body weight, and rarely cause hypoglycaemia when used as monotherapy; DPP-4 inhibitors have intermediate efficacy regarding glucose control with no impact on body weight and a low risk of hypoglycaemia. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends the consideration of DPP-4 inhibitors and GLP agonists as second line treatment options.

In 2008, the US Food and Drug Administration (FDA) warned of a strong temporal association between exenatide and pancreatitis on the basis of 30 case reports of acute pancreatitis. In 2009, the FDA notified healthcare professionals and patients of revisions to the prescribing information for Januvia (sitagliptin) and Janumet (sitagliptin/metformin) after announcing the observation of 58 post-marketing cases of acute pancreatitis. In 2012, one consumer group in the United States called for the withdrawal of lixisenatide and cautioned that lixisenatide is associated with higher than expected rates of pancreatitis, thyroid cancer, and kidney failure based on the following statement from FDA reviewers: “in clinical trials patients taking lixisenatide had a risk of pancreatitis that was 3.7 fold higher than the risk in patients taking other antidiabetes drugs.” In 2013, the concerns regarding the risk of pancreatitis and pancreatic cancer continued to grow, resulting in international debate.

The BMJ has published several commentaries discussing the potential risk of pancreatitis and implications of using incretin based drugs. The BMJ also has announced ongoing efforts to assess the risk of pancreatic associated with incretins. Yet the definitive recommendations regarding the risk are not available.

Findings from animal studies have been inconsistent. Some showed that exenatide seemed to increase inflammation of pancreatic acinar cells and formation of pancreatic intraepithelial neoplasia; sitagliptin increased pancreatic ductal turnover and ductal metaplasia. Others suggested that exenatide improved chemically induced pancreatitis in normal and diabetic rodents, and that lixisenatide induced cytokines with anti-inflammatory effects. Another study found that lixisenatide did not induce pancreatitis in mice, rats, or monkeys when it was given for up to two years and at exposure concentrations up to 60 times higher than in used in humans.

Results from drug safety surveillance systems have been more concerning. The evidence to support a causal relation between incretin based drugs and pancreatitis is weak. Most safety data have been acquired through the FDA adverse event reporting system (AERS), by which an appropriate selection of control and collection of information regarding the exposure and confounding factors is challenging. Because of ongoing safety concerns, there is a clear need for a rigorous evaluation of the safety of GLP-1 agonists and DPP-4 inhibitors. We conducted a systematic review of randomised and non-randomised studies to provide a comprehensive assessment regarding the risk of pancreatitis associated with GLP-1 agonists and DPP-4 inhibitors relative to placebo or active drugs.

Methods

Eligibility criteria

We included randomised and non-randomised controlled trials, prospective and retrospective cohort studies, and case-control studies that enrolled adult patients with type 2 diabetes mellitus; included an unconfounded comparison of GLP-1 agonists or DPP-4 inhibitors against placebo, lifestyle modification, or active antidiabetic drugs; followed up patients for at least 12 weeks (not applicable for case-control studies); and explicitly reported event data on pancreatitis.

To be classified as an unconfounded comparison, we required that planned interventions were identical between treatment and control groups except the GLP-1 agonists or DPP-4 inhibitors under consideration. We also required that authors clearly and explicitly reported numbers of pancreatitis events in all treatment groups under consideration.

Literature search

We searched Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to March 2013 for published studies without language restrictions. We used both MeSH and free text terms to identify relevant articles. An information expert (DP) developed the search strategy (appendix 1). At the time of searching, we planned to investigate the effect of incretin treatments on people with and without on diabetes. We thus included search terms defining incretin drugs and study designs only.

We also searched ClinicalTrials.gov to identify additional eligible clinical trials. This trial registry documents all drug trials other than phase I studies as required by Section 801 of the US Food and Drug Administration Amendments Act (FDAAA 801) and typically includes extensive lists of adverse events. This provides important information regarding data on pancreatitis. We searched generic names of each individual drug to ensure high sensitivity. We undertook the search of
ClinicalTrials.gov in August 2013 to ensure that data from previously published trials were updated on the registry. We limited our search to those trials labelled as “completed” and for which results were available.

**Study process**

We developed standardised pilot-tested forms together with detailed instructions for screening of abstracts and full text, risk of bias assessment, and data collection. Pairs of reviewers with training in research methods, independently and in duplicate, screened study reports for eligibility, assessed risk of bias, and collected data from each eligible study. Reviewers dealt with discrepancies through discussion or, if required, adjudication by a third reviewer (XS).

**Risk of bias assessment**

We used a modified version of Cochrane Collaboration’s tool to assess the risk of bias of randomised controlled trials. We considered random sequence generation; allocation concealment; blinding of participants, caregivers, and outcome (that is, pancreatitis) assessors; adjudication of pancreatitis events; prognostic balance between treatment groups; and selective outcome reporting. In assessing the risk of bias with blinding, our modified instrument removed the “unclear” option for the assessment of blinding, an approach we have previously validated. We used a modified version of the Newcastle-Ottawa quality assessment scale to assess the risk of bias in cohort and case-control studies. For cohort studies, we removed the item regarding representativeness of sample and the item “was the follow-up long enough?” as these items relate to applicability of results. For case-control studies, we also removed the item “representativeness of the cases.” For both types of studies, we added two items, one dealing with ascertainment of type 2 diabetes and another with ascertaining confounding variables. We did not assess publication bias because of the low power associated with studies of rare events.

**Data collection**

From eligible randomised controlled trials we collected information on study characteristics (study design, sample size, number of treatment groups, length and design (such as variable or fixed) of follow-up, funding source, registry number, whether trials were international and, if so, countries involved, number of study sites, and study phase); patient characteristics (sex, age, duration of type 2 diabetes, baseline HbA1c concentrations, body mass index (BMI), and fasting plasma glucose); interventions (drugs commonly used across all groups (baseline treatment), incretin treatment, control group, dose, intensity, and duration of treatment); pancreatitis events in each of the treatment groups; and number of patients included for analyses in each of the treatment groups (that is, considered as a safety set).

For extension randomised controlled trials, in which treatment assignments were switched (for example, patients in placebo group started receiving incretins), we documented only the outcome data before that point. For multiple reports of the same trial, we collated all data into a single study. If outcome data for pancreatitis were reported at multiple follow-up points, we used data from the longest follow-up.

For observational studies, we documented information as for randomised controlled trials, when applicable. Additionally, we collected information regarding study design (such as retrospective cohort study), sources of data (such as claims data), method of ascertaining type 2 diabetes status (such as ICD (international classification of diseases) code), exposures (such as incretins, and such exposure variables as age), method of adjustment for confounding (such as adjustment or matching, and variables used for these techniques), and follow-up. We also documented unadjusted and adjusted results, in addition to raw event data and exposure time.

**Data analysis**

We analysed randomised controlled trials and observational studies separately. For randomised trials, we assessed heterogeneity between studies using a χ² test and the I² statistic. We pooled trials using Peto’s methods and reported pooled Peto odds ratios and their associated 95% confidence intervals. P<0.05 was considered significant. We explored sources of heterogeneity with four a priori subgroup hypotheses: type of incretin (GLP-1 agonists v control; DPP-4 inhibitors v control); type of control (incretin v placebo, incretin v active treatment); length of follow-up (incretin v control by subgroup of ≤26 weeks, 26-52 weeks, >52 weeks); and mode of treatment (incretin monotherapy v control, incretin add-on combination treatment v control), and a post hoc subgroup analysis of different incretins. We undertook sensitivity analyses by using alternative effect measures (odds ratio v relative risk), pooling methods (Peto methods v Mantel-Haenszel method), and consideration on heterogeneity (random v fixed effect).

We qualitatively analysed the data from observational studies because of differences in outcome measures, exposures (that is, drug under consideration), and forms of outcome data (that is, adjusted v unadjusted data; hazard ratio v incidence rate ratio). We reported the results according to meta-analysis of observational studies in epidemiology (MOOSE) and preferred reporting items for systematic reviews and meta-analyses (PRISMA).

**Results**

Our search yielded 7432 potentially relevant reports. After screening titles and abstracts, we retrieved 468 reports for full text screening. Fifty nine studies, including 55 randomised controlled trials (40 from journals and 15 from the trial registry) reported in 61 reports, three cohort studies, and one case-control study were eligible for inclusion (fig 1). Eight months after our formal search (November 2013), however, an additional large case-control study was published. We therefore also included this study, resulting in inclusion of two more trials. This study recruited 353 699 patients, including 33 350 from randomised controlled trials and 320 289 from observational studies. Three other retrospective cohort studies also examined risk of pancreatitis with incretin drugs, but they did not explicitly limit patients to those with type 2 diabetes mellitus and were therefore excluded (appendix 2).

**Evidence from randomised controlled trials**

The 55 randomised controlled trials—all industry funded—were conducted in 2-49 (median 11) countries and 3-268 (median 110) study sites; 45 (82%) were international and 44 (80%) were phase III studies. The length of follow-up ranged from 12 to 234 weeks. The trials enrolled 69 to 1615 patients (total 33 350), with a mean age range of 49.7-66.5, mean BMI range of 24.5-36.7, mean baseline HbA1c range of 7.3-9.8%, mean fasting plasma glucose range of 7.7-11.3 mmol/L, and mean duration of diabetes range of 1-16.7 years (table I). None of the studies explicitly mentioned their criteria for diagnosis of pancreatitis.
Twenty-seven randomised controlled trials tested GLP-1 receptor agonists, 26 tested DPP-4 inhibitors, and two tested both agents; 17 tested incretin monotherapy, and 38 used incretin agents as add-on or combination treatment (table 2). Duration of treatment ranged from 12-107 weeks (median 26; 22 trials longer than 26 weeks).

Thirty-six randomised controlled trials (66%) adequately generated random sequence, 33 (60%) adequately concealed allocation (appendix 3); 47 (86%) blinded patients, caregivers, and outcome assessors. None of the trials adjudicated pancreatitis events.

**Risk of pancreatitis in randomised trials**

Of the 55 randomised controlled trials reporting pancreatitis, 27 explicitly stated that no events of pancreatitis occurred during the course of study. Eight studies mentioned pancreatic enzymes; none, however, reported usable data. Overall, 37 pancreatitis events occurred in 33,227 patients who used at least one drug (raw event rate 0.11%). Results did not show a significant difference between incretins versus control (odds ratio 1.11, 95% confidence interval 0.57 to 2.17; fig 2).

When we explored the sources of heterogeneity, the risk did not differ by the type of incretin (GLP-1 agonists v DPP-4 inhibitors; interaction P=0.99); 29 trials, involving 14,562 patients and 16 pancreatitis events (0.11%) compared GLP-1 agonists versus control (odds ratio 1.05, 95% confidence interval 0.37 to 2.94); 28 trials, involving 19,241 patients and 23 events (0.12%) compared DPP-4 inhibitors versus control (1.06, 0.46 to 2.45). Neither analysis suggested an increased risk of pancreatitis (fig A in appendix 4).

The subgroup analysis by type of control (that is, placebo v active drug) did not suggest apparent difference (odds ratio 1.27 in trials comparing with placebo, 1.00 in those comparing with active drug treatments; interaction P=0.72) (fig B in appendix 4). Exploration of the effect by the mode of treatment (monotherapy v add-on/comboination treatment) also did not suggest significant difference (0.84 monotherapy v 1.22 add-on/comboination treatment; interaction P=0.63) (fig C in appendix 4). Nor was there a difference by length of follow-up (interaction P=0.84; odds ratio 0.90 at 26 weeks or shorter v 1.44 at 26-52 weeks v 1.14 over 52 weeks) (fig D in appendix 4). The post hoc analysis of individual incretins did not show difference among those agents (fig E in appendix 4).

The sensitivity analysis using alternative effect measures (relative risk v odds ratio), statistical models (Mantel-Haenszel v Peto) and considerations on heterogeneity (random effect v fixed effect) did not show important change in the pooled effects (figs F-H in appendix 4).

**Evidence from observational studies**

Of the five observational studies, three retrospective cohort studies examined the risk of acute pancreatitis associated with the use of exenatide, sitagliptin, or both, and two case-control studies specifically assessed the risk of admission to hospital for acute pancreatitis in patients with type 2 diabetes taking incretins.39 40 (tables 3 and 4).

Of the three cohort studies, the first included 38,615 patients with diabetes (6545 exenatide, 15,826 sitagliptin, and 16,244 control) recruited in the US Medco National Integrated Database.39 Patients aged 18-63 were identified with ICD-9 codesordrughistoryforhyperglycaemia. Patients with type 1 diabetes or gestational diabetes were excluded. Cases were identified with a validated algorithm based on ICD-9 and current procedural terminology codes for acute pancreatitis, and occurrences of pancreatitis within three months of enrolment were excluded. Controls were selected, on a 1:1 ratio, for each case; they were matched for age within 10 years, sex, insurance plan site, diabetes complication severity index, and enrolment pattern or duration of follow-up. Information on drug exposure (exenatide or sitagliptin) was identified from the pharmacy database. No information was available regarding the ascertainment of risk factors for acute pancreatitis and use of other drugs. After we controlled for the influence of hypertriglyceridaemia, alcohol use, gallstones, tobacco abuse, obesity, biliary and pancreatic cancer, cystic fibrosis, an indicator of general morbidity level, and metformin exposure.
Risk of bias in observational studies

All observational studies used either claims data or patients’ medical records for their analyses. Studies using claims data or medical records confirmed diagnosis of type 2 diabetes, drug exposures, confounding factors, and occurrence of pancreatitis based on ICD-9 codes and pharmacy claims data (tables 5 and 6). The approaches for ascertaining type 2 diabetes differed across those studies (the ICD-9 codes they used varied), and the accuracy of ascertaining type 2 diabetes remains unclear. Three studies described the method for ascertaining confounding factors and the use of drugs other than incretins. Though the four studies that used claims data adjusted for the association, they chose different variables, leaving the adequacy of adjustment questionable. All studies failed to report the extent to which the claims data were complete in the overall database. Because of these limitations the risk of bias associated with eligible observational data was moderate to high.

Discussion

Main findings

In this systematic review and analysis of 55 randomised trials (low to moderate risk of bias involving 57 cases of pancreatitis among 43 277 patients), three retrospective cohort studies (moderate to high risk of bias involving 1466 pancreatitis events among 312 736 patients), and one case-control study (moderate risk of bias involving 1003 patients admitted to hospital for acute pancreatitis) we found no evidence to suggest an increased risk of pancreatitis associated with the use of incretins in patients with type 2 diabetes. The other case-control study (1269 patients admitted for acute pancreatitis) at moderate risk of bias, reported increased risk of admission for pancreatitis associated with the use of sitagliptin or exenatide.

The incidence of pancreatitis was low. In randomised trials, pancreatitis occurred in 0.11% of patients (0.11% in those taking incretins; 0.11% in control patients). In cohort studies, the risk of acute pancreatitis and admission for pancreatitis was higher (0.47%) than the risk in randomised trials, potentially because of a higher incidence of risk factors such as gallstones and longer follow-up.

Our findings should be interpreted cautiously. Although we included a large number of randomised trials, those trials were typically designed for testing efficacy. Many had relatively small sample sizes and relatively short follow-up. Because pancreatitis is rare and the event rates low, the confidence intervals around relative effects are wide, leaving the possibility of an undetected increase in risk. Furthermore, these trials—mostly phase III studies—often recruited patients with less co-morbidity than patients seen in clinical practice. The risk in the non-exposed patient group is therefore lower than usual (as above 0.11% in trials v 0.47% in observational studies). This in part explains the wide confidence intervals and also limits generalisability of the results.

There are further potential limitations of the randomised trials. Trials could have failed to document pancreatitis events or, if documented, failed to report these events (that is, selective reporting bias). Pancreatitis, however, is usually considered a serious adverse event in trials of type 2 diabetes, and, according to FDA’s policy, the reporting of serious adverse event data is mandatory to ClinicalTrials.gov, limiting the risk of lack of monitoring and selective reporting. Even if pancreatitis events were monitored, however, they might not have been independently adjudicated, raising the possibility of inaccurate data.

A final issue is the possibility of failure to identify patients with subclinical minimally symptomatic pancreatitis. The increase of pancreatic enzyme activity (lipase and amylase), a surrogate measure, could represent supporting evidence in the assessment of the risk of pancreatitis; these data, however, were not readily usable.

The five observational studies, involving patients in real practice, had large sample sizes, but had limitations related to use of claims data or patients’ medical records. Because most studies relied on the ICD-9 coding system to identify study populations and outcomes, the ascertainment of type 2 diabetes, and particularly pancreatitis, was probably inadequate because of the variation of diagnosis criteria and lack of outcome adjudication. Similar to the situation with trials, subclinical and minimally symptomatic cases of pancreatitis were less likely to be identified in those studies. Additionally, the exposure to incretins and control drugs and the exposure to other confounding factors might not have been accurately documented. The completeness of data within each of those databases is also unclear; investigators might have excluded those without complete exposure and outcome data from analyses. Finally, the accurate measurement and adjustment for other prognostic factors was limited. Overall, the risk of bias was moderate to high in all observational studies.

Among those five observational studies, a single case-control study suggested an increased risk of admissions for acute pancreatitis; the four others, including three cohort studies and one case-control study, did not. Of the four studies suggesting no increased risk, three consistently reported the point estimates close to 1 and the confidence intervals were similar (0.6 to 1.5). The reasons for discrepancy between the single case-control
In summary, the available evidence suggests that the incidence of pancreatitis in patients taking incretins is low and that these drugs do not increase the risk of pancreatitis. The current body evidence, however, is not definitive, and more carefully designed and conducted observational studies are warranted to definitively establish the extent, if any, of increased risk. In addition, incretins, which are expensive, are no superior to widely used antidiabetic drugs (such as metformin) for glucose control. Given the uncertainty about the effect of incretins on important outcomes, including pancreatitis, the lack of apparent benefits in glucose control over other drugs, and the relatively high costs, the use of incretins might not be preferable to other available antidiabetic drugs.

Future demonstration of consistency of the putative association across studies is warranted. Trials exploring the effect of incretins should report all adverse events affecting the pancreas. Presentation of associations both in class of agents (such as GLP-1 agonists) and individual incretins is important and informative to assess the potential risk. Reporting of results for the gradient of pancreatic outcomes—pancreatic enzymes, asymptomatic pancreatitis, symptomatic pancreatitis, and admission for acute pancreatitis—will also be helpful for informing risks associated with incretin treatment. Future randomised trials that specifically examine this issue, however, are unlikely. We need more carefully designed and conducted observational studies that clearly define study population, accurately collect information regarding length to follow exposure and confounding factors, completely collect outcome data, and adequately adjust for the influence of confounders. Currently, a European study is applying surveillance and observational study methods to assess vascular and pancreatic safety of diabetes drugs, including thiazolidinediones (TZDs), incretins, and amylin analogues in people with type 2 diabetes. The resulting findings might provide more definitive evidence.

We thank Daphne Plaut for developing the search strategy and conducting literature search and Stephen D Walter for useful advice in data analysis.

**Conclusion**

**Strengths and limitations**

Our study has several strengths. Firstly, we systematically identified and included both randomised and non-randomised studies to examine the risk of pancreatitis associated with incretin treatment. Secondly, in addition to published reports, we searched ClinicalTrials.gov, which provided additional outcome information and eligible trials. Thirdly, we instituted a rigorous approach to ensure the data were accurate, in particular using the data on pancreatitis reported in ClinicalTrials.gov and journal publications for consistency.

We did not assess the risk of pancreatic cancer associated with the use of incretins. Although studies have suggested a potentially increased risk, they have many limitations. The FDA adverse drug event system documented 2327 spontaneously reported cases of pancreatitis in patients taking exenatide, 888 case in those taking liraglutide, 718 cases in those taking sitagliptin, and 125 cases in those taking saxagliptin. The number of cases of pancreatitis seemed larger in those taking incretins than other active antidiabetic drugs, suggesting a potentially increased risk. The absence of data on number of patients exposed to those antidiabetic drugs, and the possibility of a lower threshold of reporting with new drugs, however, severely limits the usefulness of these data for making causal inferences.

**Comparison with other studies**

Two other meta-analyses have assessed the risk of pancreatitis among patients using incretins, one examining GLP-1 agonists and another DPP-4 inhibitors. The first meta-analysis, involving 22 randomised controlled trials and three retrospective cohort studies, reported no significant association between pancreatitis events and the exposure to exenatide or liraglutide. This analysis pooled results of randomised trials and large observational studies, making the interpretation of estimates challenging: in 10 randomised controlled trials and three retrospective cohort studies the odds ratio for exenatide was 0.84 (95% confidence interval 0.58 to 1.22) and in the combined results of 10 randomised controlled trials the odds ratio for liraglutide was 0.97 (0.21 to 4.39). Furthermore, this study included two cohort studies, in which patients might not be strictly limited to those with type 2 diabetes mellitus and were thus excluded from our review. The second study was a meta-analysis of exclusively randomised controlled trials, investigating risk of pancreatitis in DDP-4 inhibitors. It found that DPP-4 inhibitors were not associated with an increased risk of pancreatitis (odds ratio 0.93, 95% confidence interval 0.51 to 1.69). Both meta-analyses included trials that had no explicit information regarding pancreatitis; they might have assumed that no pancreatitis occurred in such trials. It is probably reasonable to assume no event in the absence of reporting in such situation. This approach, however, could artificially reduce the incidence of pancreatitis as more patients are added to the population whereas no events are added. In either of the approaches (ours and those of the two other published meta-analyses), however, the statistical model did not include zero event trials in meta-analyses, as they are statistically omitted in pooling relative effects. Compared with these two meta-analyses, our study included five observational studies that carry more important information regarding the risk of pancreatitis.
What is already known on this topic
A number of cases of acute pancreatitis have been reported in patients with type 2 diabetes who were taking incretins
Concerns have arisen regarding the risk of pancreatitis associated with these agents, though findings from various studies are conflicting

What this study adds
Data from randomised controlled trials are not adequate to assess the risk of pancreatitis, but several large observational studies, with methodological limitations, provide relatively precise estimates

The available evidence suggests that the incidence of pancreatitis in patients with type 2 diabetes taking incretins is low and that incretins do not increase risk of pancreatitis

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Transparency: The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been shared.

Data sharing: No additional data available.

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## Tables

### Table 1 | Characteristics of randomised controlled trials of incretin treatment in patients with type 2 diabetes mellitus

| Author (year) | International study | No of countries involved | No of study sites | Study phase | Total No of patients | No of groups | Follow up (weeks) | No (%) male | Mean diabetes duration (years) | Mean BMI | Mean FPG (mmol/L) | Mean HbA1c (%) |
|---------------|---------------------|--------------------------|-------------------|-------------|----------------------|--------------|------------------|-------------|---------------------------|----------|----------------|-----------------|
| Araki (2013)  | No                  | 1                        | 47                | III         | 561                  | 4            | 12               | 395 (70.4) | 60                        | 25       | 9.1            | 5.0*            |
| Barnett (2012)| Yes                 | 7                        | 53                | III         | 227                  | 2            | 18               | 88 (38.8)  | 56.5                      | 29.5     | 8.1            | 10.1*           |
| Bergenstal (2010)| Yes             | 3                        | 72                | III         | 514                  | 3            | 26               | 254 (51.7) | 52.3                      | 32       | 8.5            | 9.1            |
| Bunck (2009)  | Yes                 | 3                        | 3                 | III         | 69                   | 2            | 52               | 45 (65.2)  | 58.4                      | 30.5     | 7.5            | 9.2            |
| Buse (2011)   | Yes                 | 5                        | 59                | III         | 261                  | 2            | 30               | 148 (57.1) | 59                        | 33.5     | 8.4            | 8.1            |
| Chacra (2011) | Yes                 | NR                       | NR                | III         | 768                  | 3            | 76               | 346 (45.1) | 55.1                      | 29       | 8.4            | 9.6            |
| Diamant (2010)| Yes                 | 16                       | 72                | III         | 467                  | 2            | 26               | 243 (53.3) | 58                        | 32       | 8.3            | 9.8            |
| Forseca (2012)| Yes                 | 12                       | 61                | III         | 361                  | 2            | 12               | 186 (51.5) | 53.7                      | 31.9     | 8               | 9.3            |
| Gallwitz (2012)| Yes                | 16                       | 209               | III         | 1551                 | 2            | 104              | 933 (60.2) | 56.6                      | 30.2     | 7.7            | 9.1            |
| Gallwitz (2012)| Yes                | 14                       | 128               | III         | 1029                 | 2            | 234              | 524 (53.6) | 56                        | 32.5     | 7.5            | 8.8            |
| Garber (2009) | Yes                 | 2                        | 138               | III         | 746                  | 3            | 52               | 371 (49.7) | 53                        | 33.1     | 8.3            | 9.4            |
| Grunberger (2012)| Yes           | 7                        | 44                | II          | 164                  | 5            | 12               | 74 (45.1)  | 56.6                      | 32.1     | 7.3            | 9.3            |
| Haak (2012)   | Yes                 | 14                       | 133               | III         | 791                  | 6            | 24               | 426 (53.9) | 55.3                      | 29.1     | 8.7            | 10.9*           |
| Henry (2012)  | Yes                 | 8                        | 113               | III         | 326                  | 3            | 24               | 170 (54.3) | 54.1                      | 32.6     | 8.1            | 9.4            |
| Hollander (2011)| Yes             | 8                        | 133               | III         | 565                  | 3            | 76               | 280 (49.6) | 54                        | 30       | 8.3            | 9.0           |
| Hollander (2012)| Yes             | 8                        | 63                | III         | 305                  | 2            | 24               | 119 (40.8) | 53.5                      | 36.7     | 7.5            | 8.9            |
| Inagaki (2012)| No                  | 1                        | NR                | III         | 427                  | 2            | 26               | 290 (67.9) | 56.6                      | 26.1     | 8.5            | NR             |
| Kadowaki (2009)| No                 | 1                        | 20                | II          | 153                  | 4            | 12               | 104 (68.9) | 60.3                      | 25.3     | 8              | 9.2            |
| Kaku (2010)   | No                  | 1                        | 49                | NR          | 264                  | 3            | 24               | 169 (64)   | 59.7                      | 24.9     | 8.4            | 9.5            |
| Kikuchi (2010)| No                  | 1                        | 29                | III         | 202                  | 2            | 12               | 144 (71.3) | 59.7                      | 24.5     | 7.9            | 9.1            |
| Kohny (2012)  | Yes                 | 13                       | 108               | NR          | 369                  | 2            | 52               | 207 (56.1) | 66.5                      | 30.3     | 7.8            | 8.8            |
| Marre (2009)  | Yes                 | 21                       | 116               | III         | 1041                 | 5            | 26               | 516 (49.6) | 56.1                      | 29.9     | 8.4            | 9.8            |
| Nauck (2009)  | Yes                 | 49                       | NR                | II          | 306                  | 6            | 12               | 143 (48.1) | 55.7                      | 32.7     | 7.9            | NR             |
| Nauck (2013)  | Yes                 | 25                       | 187               | III         | 1049                 | 3            | 24               | 549 (53.4) | 57.7                      | 32.4     | 8.3            | 11.1           |
| Nauck (2013)  | Yes                 | 21                       | 170               | III         | 1091                 | 5            | 104              | 635 (58.2) | 56.7                      | 31       | 8.4            | 10              |
| NCT00082381  | Yes                 | 13                       | 82                | III         | 551                  | 2            | 26               | 306 (55.7) | 58.9                      | 31.4     | 8.2            | 10.2*          |
| NCT00094770  | Yes                 | NR                       | 173               | III         | 1172                 | 2            | 104              | 694 (59.2) | 56.7                      | 31.2     | 7.7            | 9.2            |
| NCT0103857   | Yes                 | NR                       | 140               | III         | 915                  | 5            | 104              | 539 (49.4) | 53.5                      | 8.8      | 11.1           | NR             |
| NCT00327015  | Yes                 | 13                       | 211               | III         | 1306                 | 4            | 24               | 643 (49.2) | 52                        | 30.2     | 9.5            | 11.1           |
| NCT00382172  | Yes                 | 6                        | 71                | II          | 302                  | 5            | 12               | 175 (57.9) | 57.3                      | 31.1     | 8.3            | 10.5           |
| NCT00395512  | Yes                 | 23                       | 268               | III         | 655                  | 4            | 26               | 320 (48.9) | 52.6                      | 31.1     | 8.8            | 10.6           |
| NCT00482729  | Yes                 | 2                        | 229               | III         | 1250                 | 2            | 44               | 708 (56.8) | 49.7                      | NR       | 9.9            | NR             |
| NCT00575588  | Yes                 | 11                       | 130               | III         | 858                  | 2            | 104              | 444 (51.7) | 57.5                      | 31.4     | 7.7            | 9              |
| NCT00614939  | Yes                 | 14                       | 75                | III         | 170                  | 2            | 52               | 73 (42.9)  | 66.5                      | 30.7     | 8.3            | 9.9            |

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Table 1 (continued)

| Author (year) | International study | International study | No of countries involved | No of countries involved | Study phase | Study phase | Total No of patients | Study sites | Total No of patients | Study sites | No of groups | No of groups | Follow up (weeks) | Follow up (weeks) | No (%) of patients with no more than 5 years' diabetes duration | No (%) of patients with no more than 5 years' diabetes duration |
|---------------|---------------------|---------------------|-------------------------|-------------------------|-------------|-------------|---------------------|------------|---------------------|------------|--------------|--------------|----------------|----------------|------------------------------------------------|------------------------------------------------|
| NCT00722371 (2011)' | NR | NR | NR | NR | III | 1615 | 7 | 54 | 912 (56.5) | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| NCT00757588 (2011)' | Yes | 10 | 72 | NR | NR | 455 | 2 | 52 | 188 (41.3) | 57.2 | 32.3 | 8.7 | 9.6 | 11.9 |
| NCT00954447 (2012)' | Yes | 19 | 167 | NR | NR | 1261 | 2 | 52 | 658 (52.2) | 60 | 31 | 8.3 | 8.3 | NR |
| NCT01137812 (2013)' | Yes | 17 | 140 | NR | NR | 755 | 2 | 52 | 422 (55.9) | 56.5 | NR | NR | NR | NR |
| NCT01204294 (2012)' | No | 1 | 43 | NR | NR | 352 | 4 | 52 | 246 (69.9) | 61.3 | NR | NR | NR | NR |
| NCT01289119 (2013)' | No | 1 | 30 | NR | NR | 506 | 6 | 16 | 275 (54.3) | 52.6 | 35.7 | NR | NR | 4.1 |
| Pan (2012)' | Yes | 4 | 40 | NR | NR | 568 | 2 | 24 | 315 (55.5) | 51.4 | 25.9 | 8.2 | 9.1 | 1 |
| Pratley (2013)' | Yes | 17 | 130 | NR | NR | 760 | 3 | 24 | 362 (48.9) | 56.4 | 32.7 | 8.3 | 10 | 8.8 |
| Ratiner (2010)' | Yes | 7 | 133 | NR | NR | 542 | 9 | 13 | 270 (49.8) | 56.2 | 31.9 | 7.5 | 8.8 | 6.6 |
| Raz (2012)' | Yes | NR | 53 | NR | NR | 373 | 3 | 24 | 130 (36.7) | 54.8 | 32.3 | 7.6 | 8.8 | 2.4 |
| Rosenstock (2009) | Yes | 4 | 118 | NR | NR | 361 | 10 | 16 | 170 (47.8) | 53.5 | 32.1 | 8 | 9.8 | 4.9 |
| Rosenstock (2009) | Yes | 13 | 110 | NR | NR | 390 | 3 | 26 | 161 (41.3) | 55.4 | 32.5 | 9.3 | 10.6 | 12.6 |
| Ross (2012)' | Yes | 9 | 81 | NR | NR | 491 | 3 | 12 | 280 (57.0) | 58.6 | 29.6 | 8 | 9.2 | 227 (47.5)* |
| Russell-Jones (2009)' | Yes | 17 | 107 | NR | NR | 581 | 3 | 26 | 326 (56.6) | 57.5 | 30.5 | 8.3 | NR | 9.4 |
| Russell-Jones (2012)' | Yes | 22 | 124 | NR | NR | 820 | 4 | 26 | 484 (59.0) | 53.8 | 31.2 | 8.5 | NR | 2.7 |
| Seino (2010)' | No | 1 | 75 | NR | NR | 411 | 2 | 24 | 268 (67) | 58.3 | 24.5 | 8.9 | 11.3 | 8.2 |
| Seino (2012) | No | 1 | 30 | NR | NR | 288 | 3 | 12 | 198 (68.8) | 52.6 | 25.9 | 8 | NR | 6.3 |
| Seino (2012)' | Yes | 4 | 57 | NR | NR | 311 | 2 | 24 | 149 (47.9) | 58.4 | 25.3 | 8.5 | 7.7 | 13.9 |
| Umpierrez (2011)' | Yes | 2 | 39 | NR | NR | 262 | 2 | 16 | 129 (36.4) | 56.5 | 33.9 | 8.2 | NR | 8.3 |
| Yang (2011)' | Yes | 3 | 51 | NR | NR | 929 | 4 | 16 | 514 (55.3) | 53.3 | 25.6 | 8.6 | 9.7 | 7.5 |
| Zinman (2009)' | Yes | 2 | 96 | NR | NR | 533 | 3 | 26 | 302 (56.7) | 55 | 33.5 | 8.5 | 10.1 | 9 |

BMI=body mass index; FPG=fasting plasma glucose; NR=not reported.

*No (%) of patients with no more than 5 years' diabetes duration.
†Longest follow-up time (weeks).
‡Median duration of diabetes (years).
## Table 2: Intervention characteristics of randomised controlled trials of incretin treatment in patients with type 2 diabetes mellitus

| Author (year) | Drugs used across groups | Incretin Type | Events | Control Type | Events | Follow-up from start of treatment (weeks) |
|---------------|--------------------------|---------------|--------|--------------|--------|------------------------------------------|
| Araki (2013)⁹⁹ | None                     | Linagliptin 0/319 | Placebo 0/80 | 12 |
| Barnett (2012)⁷⁷ | None                     | Linagliptin 0/151 | Placebo 0/76 | 18 |
| Bergenstal (2010)⁴⁴ | Metformin               | Exenatide 0/160 | Pioglitazone 2/165 | 26 |
| Bunck (2009)⁵⁶ | Metformin                | Exenatide 1/36 | Insulin glargine 0/33 | 52 |
| Buse (2011)⁸⁰ | Insulin glargine ± metformin/pioglitazone (or both agents) | Exenatide 0/137 | Placebo 0/122 | 30 |
| Chacra (2011)⁹⁹ | Glyburide                | Saxagliptin 0/501 | Placebo 0/267 | 76 |
| Diamant (2010)⁹⁹ | Metformin ± SU           | Exenatide 1/233 | Placebo 0/223 | 26 |
| Fonseca (2012)⁴⁴ | None                     | Lixisenatide 0/239 | Placebo 0/122 | 12 |
| Gallwitz (2012)⁴⁴ | Metformin                | Linagliptin 1/776 | Glimepiride 0/775 | 104 |
| Gallwitz (2012)⁴⁴ | Metformin                | Exenatide 1/511 | Glimepiride 1/508 | 107* |
| Garber (2009)⁹⁹ | None                     | Liraglutide 2/497 | Glimepiride 0/248 | 52 |
| Grunberger (2012)⁷⁷ | None                     | Dulaglutide 0/132 | Placebo 1/32 | 12 |
| Haak (2012)⁹⁹ | None                     | Linagliptin 0/428 | Placebo 0/72 | 24 |
| Henry (2012)⁹⁹ | Metformin                | Taspoglutide 0/223 | Placebo 0/101 | 24 |
| Hollander (2011)⁹⁹ | TZD                      | Saxagliptin 1/381 | Placebo 0/184 | 76 |
| Hollander (2012)⁹⁹ | Metformin                | Taspoglutide 0/154 | Placebo 0/150 | 26 |
| Inagaki (2012)⁷⁹ | BG or BG + TZD           | Exenatide 0/215 | Insulin glargine 0/212 | 26 |
| Kadowitz (2011)⁹⁹ | SU ± BG/TZD              | Exenatide 0/111 | Placebo 0/40 | 12 |
| Kaku (2010)⁵⁶ | SU (glibenclamide, glycazide or glimepiride) | Liraglutide 0/176 | Placebo 0/88 | 24 |
| Kikuchi (2010)⁵⁶ | Glimepiride              | Vildagliptin 0/102 | Placebo 0/100 | 12 |
| Kohry (2012)⁵⁶ | Untreated, insulin, OADs or any combination | Vildagliptin 0/216 | Placebo 0/153 | 52 |
| Marre (2009)⁵⁶ | Glimepiride              | Liraglutide 1/695 | Placebo 0/114 | 26 |
| Nauck (2009)⁹⁹ | Metformin                | Taspoglutide 0/248 | Placebo 0/49 | 12 |
| Nauck (2013)⁹⁹ | Metformin                | Taspoglutide 0/715 | Placebo 0/322 | 24 |
| Nauck (2013)⁹⁹ | Metformin                | Taspoglutide 0/248 | Placebo 0/121 | 104 |
| NCT00082381 (2009)⁹⁹ | Metformin + SU          | Exenatide 0/282 | Insulin glargine 1/267 | 26 |
| NCT00094770 (2009)⁹⁹ | Metformin               | Sitagliptin 1/588 | Glipizide 0/584 | 104 |
| NCT00103857 (2009)⁹⁹ | None                    | Sitagliptin 1/551 | Metformin 0/364 | 104 |
| NCT00327015 (2009)⁹⁹ | None                    | Saxagliptin 0/978 | Metformin 1/328 | 24 |
| NCT00328172 (2011)⁹⁹ | None                    | Linagliptin 1/170 | Placebo 0/67 | 12 |
| NCT00395512 (2013)⁹⁹ | None                    | Alogliptin 1/491 | Pioglitazone 0/163 | 26 |
| NCT00482729 (2009)⁹⁹ | Metformin               | Sitagliptin 1/625 | No additional drug 0/621 | 44 |
| NCT00575588 (2010)⁹⁹ | Metformin               | Saxagliptin 0/428 | Glipizide 1/430 | 104 |
| NCT00614909 (2011)⁹⁹ | OADs and/or insulin      | Saxagliptin 0/85 | Placebo 1/85 | 52 |
| NCT00722371 (2011)⁹⁹ | None                    | Sitagliptin 0/922 | Pioglitazone 1/693 | 54 |
| NCT00757588 (2011)⁹⁹ | Insulin ± metformin      | Saxagliptin 0/304 | Placebo 0/151 | 52 |
| NCT00954447 (2012)⁹⁹ | Insulin and/or metformin and/or pioglitazone | Linagliptin 31/631 | Placebo 1/630 | 52 |
| NCT01137812 (2013)⁹⁹ | Metformin + SU          | Sitagliptin 0/378 | Canagliflozin 1/377 | 52 |
| NCT01204294 (2012)⁹⁹ | SU or A-GI               | Linagliptin 0/228 | Metformin 0/124 | 52 |
| NCT01289119 (2013)⁹⁹ | None                    | Alogliptin 0/252 | Placebo 1/92 | 16 |
Table 2 (continued)

| Author (year) | Drugs used across groups | Incretin | Control | Follow-up from start of treatment (weeks) |
|---------------|--------------------------|----------|---------|------------------------------------------|
|               |                          | Type     | Events  | Type     | Events  |                          |
|               |                          | Alogliptin | 0/252  | Pioglitazone | 0/63  |                          |
| Pan (2012)    | None                     | Saxagliptin | 0/284  | Placebo | 0/284  | 24                         |
| Pratley (2013)| SU + metformin           | Taspoglutide | 1/494  | Pioglitazone | 0/257  | 24                         |
| Ratner (2010) | Metformin                | Lixisenatide | 0/433  | Placebo | 0/109  | 13                         |
| Raz (2012)    | None                     | Taspoglutide | 0/245  | Placebo | 0/123  | 24                         |
| Rosenstock (2009) | None                     | Exenatide | 0/35   | Placebo | 0/51   | 16                         |
| Rosenstock (2009) | Insulin + metformin   | Alogliptin | 2/260  | Placebo | 0/129  | 26                         |
| Ross (2012)   | Metformin                | Linagliptin | 0/447  | Placebo | 0/44   | 12                         |
| Russell-Jones (2009) | Metformin + glimepiride | Liraglutide | 0/230  | Placebo | 0/114  |                          |
| Russell-Jones (2012) | None                     | Exenatide | 0/248  | Metformin | 0/246  | 26                         |
| Seino (2010)  | None                     | Liraglutide | 0/268  | Glibenclamide | 0/132  | 24                         |
| Seino (2012)  | Metformin                | Alogliptin | 0/188  | Placebo | 0/100  | 12                         |
| Seino (2012)  | Insulin + SU             | Lixisenatide | 0/154  | Placebo | 0/157  | 24                         |
| Umpierrez (2011)| Each of the two different classes (SU, biguanide, TZD or DPP-4)| Dulaglutide | 2/196  | Placebo | 0/66   | 16                         |
| Yang (2011)   | Metformin                | Liraglutide | 0/697  | Glimipide | 0/231  | 16                         |
| Zinman (2009) | Metformin + rosiglitazone | Liraglutide | 0/356  | Placebo | 0/177  | 26                         |

SU=sulfonylurea; TZD=thiazolidinedione; BG=biguanide; OADs=oral anti-diabetic drugs.

*Average treatment time (weeks); A-GI, alpha-glucosidase inhibitor.
†Pancreatitis events data extracted from additional information reported in ClinicalTrials.gov.
Table 3 | Characteristics of observational studies of incretin treatment and pancreatitis in patients with type 2 diabetes mellitus

| Author (year) | Study design | Data source/country | Funding | Inclusion criteria | Exclusion criteria | No (%) | Mean age (years) | Mean HbA1c (%) | Mean BMI | Mean FPG (mmol/L) | Mean diabetes duration (years) |
|---------------|--------------|---------------------|---------|-------------------|-------------------|---------|-----------------|--------------|----------|-----------------|-------------------------------|
| Garg (2010)** | Retrospective cohort study | Claims data/US | NR | Diabetic patients aged 18-63 years with pharmacy and medical claims data for continuous period of at least 12 months between 1 January 2007 and 30 June 2009 | Patients aged >63 because of possibility of incomplete medical data; patients with acute pancreatitis 6 months before or on index date; treatment with repaglinide, nateglinide, acarbose, or miglitol and treatment with both exenatide and sitagliptin | 26953 | 52.7 | NR | NR | NR | NR |
| Romley (2012)** | Retrospective cohort study | Claims data/US | Public funding | Patients having two or more medical claims with ICD-9 code of 250.xx within calendar year and fewer than two claims with ICD-9 code of 250.x1 within each year, using oral antidiabetes drugs at any point during study period, and enrolled for at least 1 year during 2007-09 with continuously enrolled throughout each year, with no gaps between years | Users of sitagliptin were patients aged <18; patients with pancreatic cancer subsequent to incident cancer diagnosis; patients with occurrence of first event before 2007 or before first use of exenatide | 145560 | 63.1 | NR | NR | NR | 3.1 |
| Sudhakaran (2011)** | Retrospective cohort study | Case records/India | No financial support | Asian Indian patients with type 2 diabetes in Indian tertiary diabetes care centre | | 3512 | 55.1 | 30.0 | 9.2 | 10.0 | 15.1 |
| Singh (2013)** | Case-control study | Claims data/US | Public funding | Type 2 diabetes mellitus patients who filled at least 1 prescription for any drug used to treat type 2 diabetes from 1 February 2005 to 31 December 2006; patients aged 18-64 on date of first code for diabetes, and contributed at least 6 months of medical or pharmacy coverage in calendar year with diabetes code, and of known sex | Participants aged >64 because of incomplete healthcare information; pancreatitis occurrences within 3 months of enrollment | 1458 | 52 | NR | NR | NR | NR |
| Giorda (2013)** | Case-control study | Claims data/Italy | Non-profit funding | Type 2 diabetes patients aged ≥41 who were dispensed at least one dose of any drug to treat diabetes between 1 Jan 2008 and 31 Dec 2012 | Individuals who had ICD-9-CM code for type 1 diabetes mellitus (250.x1 or 250.x3) | 2750 | 72.2 | NR | NR | NR | NR |

NR=not reported.
### Table 4 | Exposures, outcomes, and results of observational studies of incretin treatment and pancreatitis in patients with type 2 diabetes mellitus

| Author (year) | Exposure of interest | Control group | Outcome measures | No of events | Total No of patients | Adjusted estimates (95% CI) |
|---------------|----------------------|---------------|-----------------|--------------|----------------------|-----------------------------|
| Garg (2010)   | Exenatide, sitagliptin| Diabetic control group (new sulfonylurea, biguanide, or thiazolidinedione and no sitagliptin or exenatide prescription) | Acute pancreatitis | 154 | 38 615 | Exenatide v control: HR 0.9 (0.6 to 1.5); sitagliptin v control: HR 1.0 (0.7 to 1.3) |
| Romley (2012) | Exenatide             | Non-exenatide | Admission for acute pancreatitis | 1 312 | 268 561 | Exenatide v control: OR 0.93 (0.63 to 1.36) |
| Sudhakaran (2011) | Sitagliptin       | Insulin glargine | Acute pancreatitis | 0 | 5 560 | No events reported |
| Singh (2013)  | Exenatide, sitagliptin| No sitagliptin or exenatide prescription | Admission for acute pancreatitis | 1 269 | 2 538 | Current use of sitagliptin or exenatide within 30 days before pancreatitis v no use: OR 2.24 (1.36 to 3.68); recent use past 30 days and <2 years v no use: OR 2.01 (1.37 to 3.18); any use within 2 years v no use: OR 2.07 (1.36 to 3.13) |
| Giorda (2013) | Exenatide, liraglutide, sitagliptin, saxagliptin, vildagliptin | Not clearly reported | Admission for acute pancreatitis | 1 003 | 5 015 | All incretin agents v control: OR 0.98 (0.69 to 1.38) |

HR=hazard ratio; OR=odds ratio.
## Table 5 | Risk of bias of cohort studies of incretin treatment and pancreatitis in patients with type 2 diabetes mellitus

| Author (year) | Ascertainment of type 2 diabetes conditions | Ascertainment of exposure to incretin agents | Selection of non-exposed cohort | Ascertainment of other confounding variables | Demonstration that outcome of interest not present at start of study | Comparability of study controls for important factors | Assessment of outcome | Completeness of outcome and exposure variables |
|---------------|---------------------------------------------|---------------------------------------------|---------------------------------|---------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|------------------------|-----------------------------------------------|
| Garg (2010)   | Patients with diabetes identified by presence of at least 1 ICD-9 code of 250.XX and claim for new antidiabetes drugs | Statement not explicit; likely from new antidiabetes drug of pharmacy claims | Drawn from same population as exposed cohort | Risk factors for acute pancreatitis determined from ICD-9 claims data | Yes, patients with acute pancreatitis 6 months before or on index date were excluded | Cox proportional hazard model built to control for age, sex, hypertriglyceridaemia, alcohol abuse, biliary stone disease, cholestatic liver disease, and drug therapy | Acute pancreatitis determined by claim for ICD-9 code 577.0 | Completeness of outcome and exposure variable data in database not mentioned |
| Romley (2012) | Patients with type 2 diabetes identified with ICD code (250.XX and 250.X1) and with use of antidiabetes drugs identified by National Drug Code within pharmacy claims | Exenatide use identified by National Drug Code within pharmacy claims | Drawn from same population as exposed cohort | Co-morbid conditions and traditional pancreatitis risk factors, such as history of gallstones or alcohol abuse, identified from ICD-9 codes | Yes, patients excluded if pancreatitis occurred before enrolment and use of exenatide | Logistic analyses used to control for influence of age, sex, years since diabetes diagnosis, 19 co-morbid conditions, and traditional risk factors for pancreatitis (such as gallstones or alcohol abuse) | Admission for pancreatitis identified by inpatient claims with ICD-9 code 577.0 | Completeness of outcome and exposure variable data in database not mentioned |
| Sudhakaran (2011) | Patients with type 2 diabetes prescribed sitagliptin or insulin glargine identified from medical records | Statement not explicit; likely from medical records | Drawn from same population as exposed cohort | Not reported | No, patients had significant difference in age, sex, BMI, duration of diabetes between sitagliptin and insulin glargine, and no adjusted analysis conducted | Medical records | All patients with complete follow up | |
Table 6 | Risk of bias in case-control studies of incretin treatment and pancreatitis in patients with type 2 diabetes mellitus

| Author (year) | Type of diabetes conditions | Ascertainment of controls | Is case definition adequate | Selection of controls | Definition of controls | Ascertainment of exposure to incretin agents | Ascertainment of other confounding variables | Same method of ascertainment for exposure to incretin agents | Comparability of study controls for important factors | Comprehensiveness of data within database |
|--------------|-----------------------------|---------------------------|-----------------------------|-----------------------|-----------------------|-------------------------------------------|------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|
| Singh (2013) | Type 2 diabetes mellitus identified as 1 relevant outpatient code of ICD-9 or 2 outpatient ICD-9 codes separated by at least 30 days (250.x, 648.0, 362.0, and 266.41) | Yes, presumptive cases identified with validated algorithm of ICD-9 and Current Procedural Terminology codes for acute pancreatitis | Each case randomly selected 1 control subject from same population matched on age within 10 years, sex, insurance plan site, diabetes complicating severity index (0, 1, 2, 3, or more), and enrollment pattern or duration of follow-up | Patients with no acute pancreatitis | Drug exposure defined as having filled prescription for sitagliptin or exenatide before first observed diagnosis of pancreatitis, and prescription data used as indicator of drug exposure | Ascertained for acute pancreatitis not mentioned | Yes, both groups used drug use information from computerised pharmacy database containing date of prescription filled and supplied to determine exposure to sitagliptin or exenatide, and patient with exposure after index diagnosis of acute pancreatitis counted as unexposed | Logistic regression model used control for matching variables, potential confounders specified a priori and identifiable in claims data, and metformin exposure during same period | Both groups had same rate of missing information on sex |
| Giorda (2013) | Patients with type 2 diabetes mellitus identified as at least 1 dose of any drug to treat diabetes and patients with type 1 diabetes excluded by ICD-9 code (250.x1 or 250.x3) | Yes, cases identified by having at least one discharge for acute pancreatitis (ICD-9 code 577.0) discharge diagnosis at any time after first exposure to antidiabetic drugs | Each case randomly selected four controls from same population source, matched for year of birth, sex, and year of first exposure to antidiabetic drugs | Patients with no acute pancreatitis | Incretins selected by anatomical therapeutic chemical (ATC) classification system (ATC codes A10BH01 and A10BD07 (sitagliptin), A10BH02 and A10BD08 (vildagliptin), A10BH03 (saxagliptin), A10BX04 (exenatide), and A10BX07 (liraglutide)) | Potential confounders identified from ICD-9 codes, such as chronic or acute pancreatitis (excluding episode of index case (ICD-9 code 577.0)), gallstones, alcohol misuse, hypertriglyceridaemia, obesity, biliary tract or pancreatic cancers, cardiovascular diseases, and diabetic retinopathy | Yes, both cases and controls who had been prescribed incretins identified with regional drug database | Logistic regression model built to control for confounders, including past history of pancreatitis, gallstones, alcohol use, hypertriglyceridaemia, obesity, biliary tract or pancreatic cancer, cardiovascular disease, and metformin or glibenclamide use | Authors did not mention completeness of outcome and exposure variable data in database |
Figures

Fig 1 Flow chart of article selection. *Data from ClinicalTrials.gov
| Study            | No of events/total | Peto odds ratio fixed (95% CI) | Weight (%) | Peto odds ratio fixed (95% CI) |
|------------------|--------------------|-------------------------------|------------|-------------------------------|
| Araki 2013       | 0/319              | Not estimable                 | 0/342      |                               |
| Barnett 2012     | 0/151              | Not estimable                 | 0/76       |                               |
| Bergenstal 2010  | 0/326              | Not estimable                 | 2/165      |                               |
| Bunck 2009       | 1/36               | Not estimable                 | 0/33       |                               |
| Buse 2011        | 0/137              | Not estimable                 | 0/122      |                               |
| Charca 2011      | 0/501              | Not estimable                 | 0/267      |                               |
| Diamant 2010     | 1/233              | Not estimable                 | 0/223      |                               |
| Fonseca 2012     | 0/239              | Not estimable                 | 0/122      |                               |
| Gallwitz 2012a   | 1/776              | 2.9 (0.00 to 6.80)            | 7.08 (0.14 to 35.70) |
| Gallwitz 2012b   | 1/511              | 5.8 (0.06 to 15.92)           | 7.38 (0.15 to 37.19) |
| Garber 2009      | 2/497              | 5.2 (0.24 to 85.11)           | 4.49 (0.26 to 85.11) |
| Grunberger 2012  | 0/132              | 1.8 (0.01 to 0.84)            | Not estimable |
| Haak 2012        | 0/428              | Not estimable                 | 0/363      |                               |
| Henry 2012       | 0/223              | Not estimable                 | 0/101      |                               |
| Hollander 2011   | 1/381              | 2.6 (0.07 to 288.68)          | 4.41 (0.07 to 288.68) |
| Hollander 2012   | 0/154              | Not estimable                 | 0/150      |                               |
| Inagaki 2012     | 0/215              | Not estimable                 | 0/212      |                               |
| Kadowaki 2009    | 0/111              | Not estimable                 | 0/40       |                               |
| Kaku 2010        | 0/176              | Not estimable                 | 0/88       |                               |
| Kikuchi 2010     | 0/102              | Not estimable                 | 0/100      |                               |
| Kohy 2012        | 0/216              | Not estimable                 | 0/153      |                               |
| Marre 2009       | 1/695              | 2.6 (0.07 to 286.90)          | 4.47 (0.07 to 286.90) |
| Nauck 2009       | 0/248              | Not estimable                 | 0/49       |                               |
| Nauck 2013a      | 0/713              | Not estimable                 | 0/322      |                               |
| Nauck 2013b      | 1/724              | Not estimable                 | 1/363      |                               |
| NCT00082381 2009 | 0/282              | Not estimable                 | 0/267      |                               |
| NCT00142770 2009 | 1/588              | 2.9 (0.00 to 6.46)            | 7.34 (0.15 to 369.87) |
| NCT00193587 2009 | 1/551              | 2.9 (0.00 to 6.46)            | 5.26 (0.10 to 288.61) |
| NCT00327015 2009 | 0/978              | 2.2 (0.02 to 1.71)            | 7.12 (0.14 to 370.02) |
| NCT00328172 2011 | 1/170              | 2.2 (0.02 to 1.71)            | 7.12 (0.14 to 370.02) |
| NCT00395512 2013 | 1/491              | 2.2 (0.02 to 1.71)            | 7.12 (0.14 to 370.02) |
| NCT00482729 2009 | 1/625              | 2.2 (0.02 to 1.71)            | 7.12 (0.14 to 370.02) |
| NCT00575588 2010 | 0/428              | 2.9 (0.14 to 6.85)            | 7.12 (0.14 to 370.02) |
| NCT00614939 2011 | 0/85               | 2.9 (0.14 to 6.85)            | 7.12 (0.14 to 370.02) |
| NCT00722371 2011 | 0/922              | 2.9 (0.14 to 6.85)            | 7.12 (0.14 to 370.02) |
| NCT00755588 2011 | 0/304              | 2.9 (0.14 to 6.85)            | 7.12 (0.14 to 370.02) |
| NCT00954447 2012 | 3/516              | 2.9 (0.10 to 5.10)            | 7.12 (0.14 to 370.02) |
| NCT01137812 2013 | 0/378              | 2.9 (0.10 to 5.10)            | 7.12 (0.14 to 370.02) |
| NCT01204294 2012 | 0/228              | 2.9 (0.10 to 5.10)            | 7.12 (0.14 to 370.02) |
| NCT01289119 2013 | 0/252              | 2.9 (0.10 to 5.10)            | 7.12 (0.14 to 370.02) |
| Pan 2012         | 0/284              | 2.9 (0.10 to 5.10)            | 7.12 (0.14 to 370.02) |
| Pratiley 2013    | 1/494              | 2.6 (0.07 to 284.65)          | 7.12 (0.14 to 370.02) |
| Ratner 2010      | 0/433              | Not estimable                 | 0/109      |                               |
| Raz 2012         | 0/245              | Not estimable                 | 0/133      |                               |
| Rosenstock 2009a | 0/305              | Not estimable                 | 0/51       |                               |
| Rosenstock 2009b | 2/260              | Not estimable                 | 0/129      |                               |
| Ross 2012        | 0/447              | Not estimable                 | 0/44       |                               |
| Russell-Jones 2009 | 0/730           | Not estimable                 | 0/346      |                               |
| Russell-Jones 2012 | 1/411            | Not estimable                 | 0/409      |                               |
| Selino 2010      | 0/268              | Not estimable                 | 0/132      |                               |
| Selino 2012a     | 0/188              | Not estimable                 | 0/100      |                               |
| Selino 2012b     | 0/154              | Not estimable                 | 0/157      |                               |
| Umpierrez 2011   | 2/196              | Not estimable                 | 0/66       |                               |
| Yang 2011        | 0/697              | Not estimable                 | 0/231      |                               |
| Zinman 2009      | 0/356              | Not estimable                 | 0/177      |                               |

Test for heterogeneity: $\chi^2 = 32.40, df = 27, P=0.22, I^2 = 17\%$

Test for overall effect: $z=0.31, P=0.76$

Fig 2 Risk of pancreatitis events between patients with type 2 diabetes mellitus treated with incretin or control