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RESEARCH

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=353 639), consisting of 55 randomised controlled trials (n=33 350) and five observational studies (three retrospective cohort studies, and two case-control studies; n=320 289) were included. Pooled estimates of 55 randomised controlled trials (at low or moderate

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Appendix 1: Search strategies
Appendix 2: Characteristics, exposures, outcomes, results, and risk of bias of three excluded cohort studies
Appendix 3: Risk of bias of randomised controlled trials
Appendix 4: Supplementary forest plots

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 *v* control; 1.06 (0.46 to 2.45) for DPP-4 inhibitors *v* 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%) also 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.[1] Exposure to certain drugs is also associated with acute pancreatitis.[1] 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%,[2] reduce body weight, and rarely cause hypoglycaemia when used as monotherapy[3 4]; DDP-4 inhibitors have intermediate efficacy regarding glucose control[5] with no impact on body weight and a low risk of hypoglycaemia.[3 6] 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.[6 7]

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.[8] 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 88 post-marketing cases of acute pancreatitis.[9] In 2012, one consumer group in the United States called for the withdrawal of liraglutide[10] and cautioned that liraglutide 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 liraglutide 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.[11 12] The *BMJ* has published several commentaries discussing the potential risk of pancreatitis and implications of using incretin based drugs.[13-17] The FDA also has announced ongoing efforts to assess the risk of pancreatic associated with incretins.[18] 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[19] and formation of pancreatic intraepithelial neoplasia[20]; sitagliptin increased pancreatic ductal turnover and ductal metaplasia.[21] Others suggested that exenatide improved chemically induced pancreatitis in normal and diabetic rodents[22] and that liraglutide induced cytokines with anti-inflammatory effects.[23] Another study found that liraglutide 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.[24]

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),[8 9 25] 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 DDP-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)[26] and typically includes extensive lists of adverse events.[27] 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[28] 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.[29]

We used a modified version of the Newcastle-Ottawa quality assessment scale[30] 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.[31] 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 χ^2 test and the I^2 statistic. We pooled trials using Peto's methods[32 33] 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)[34] and preferred reporting items for systematic reviews and meta-analyses (PRISMA).[35]

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[36-90] (40 from journals and 15 from the trial registry) reported in 61 reports, three cohort studies,[91-93] and one case-control study[94] were eligible for inclusion (fig 1⇓). Eight months after our formal search (November 2013), however, an additional large case-control study[95] was published. We therefore also included this study, resulting in inclusion of two case-control studies. These studies recruited 353 639 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[96-98]; 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 1⇓). None of the studies explicitly mentioned their criteria for diagnosis of pancreatitis.

Twenty seven randomised controlled trials tested GLP-1 receptor agonists, 26 tested DDP-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 test 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/combination treatment) also did not suggest significant difference (0.84 monotherapy *v* 1.22 add-on/combination 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,[91-93] and two case-control studies specifically assessed the risk of admission to hospital for acute pancreatitis in patients with type 2 diabetes taking incretins [94 95] (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.[91] Patients aged 18-63 were identified with ICD-9 code for drugs for type 2 diabetes and were followed up for a mean of 0.7 year (0.6 exenatide, 0.8 sitagliptin, 0.7 control). Exposure to incretins was probably identified from pharmacy claims. Study investigators computed a chronic disease score based on pharmacy claims data and identified risk factors for pancreatitis, including drugs and medical conditions by using pharmacy claims and ICD-9 codes. Acute pancreatitis was identified with ICD-9 codes; 154 pancreatitis events (0.4%) occurred (22 in the exenatide group (0.3%), 67 in the sitagliptin group (0.4%), 65 in the control group (0.4%)), with a corresponding incidence of 563.9 cases per 100 000 patient years (569.9 in the exenatide group, 554.4 in the sitagliptin group, and 571.9 in the control group). After adjustment for the influence of age, sex, history of pancreatic disease, alcohol intake, biliary stone disease, hypertriglyceridaemia, and chronic disease score, the risk of acute pancreatitis was similar between exenatide and control (adjusted hazard ratio 0.9, 95% confidence interval 0.6 to 1.5) and sitagliptin and control (1.0, 0.7 to 1.3).

The second study included 268 561 patients (530 574 patient years, 13 791 patient years in exenatide group, 516 783 non-exenatide) with type 2 diabetes from an employer-provided health insurance covering about 6.6 million employees in the US.[92] Patients were aged 63.1 on average, with mean duration of diabetes of 3.1 years. Study investigators used ICD-9 codes to identify patients with type 2 diabetes and their pancreatic outcome (admission for acute pancreatitis, code 577.0). The information regarding exposure to exenatide was identified by National Drug Codes. They also used ICD-9 codes to identify information regarding a set of 19 co-morbid conditions (such as congestive heart failure, chronic obstructive pulmonary disease, and stroke) and traditional risk factors for pancreatitis. They identified 1312 (0.5%) admissions for acute pancreatitis events (27 in those taking exenatide, 1285 in those not taking exenatide), with corresponding incidence of 247.3 cases per 100 000 patient years (195.8 for exenatide, 248.7 for non-exenatide). The risk of admission for acute pancreatitis in patients who have used exenatide was not statistically different (0.20% *v* 0.25%; adjusted odds ratio 0.93, 95% confidence interval 0.63 to 1.36) after adjustment for age, sex, years since diagnosis of diabetes, year of observation, 19 co-morbid conditions, and traditional risk factors for pancreatitis.

The third study recruited 5560 patients from a diabetes specialty care centre in India.[93] Of these patients, 2817 received sitagliptin and 2743 self injected insulin glargine. Information regarding ascertainment of other variables (confounders), however, was not reported. This study found no patient with either symptoms or signs of acute pancreatitis in the sitagliptin or insulin glargine group.

The first case-control study identified 1269 cases (admissions for acute pancreatitis) and 1269 controls from administrative claims of Blue Cross Blue Shield plan.[94] All of these patients, aged 52 on average, had type 2 diabetes, as confirmed by ICD-9 codes or drug history for hyperglycaemia. 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

during the same period, we found that use of sitagliptin or exenatide within 30 days before pancreatitis versus non-use (that is, no use for more than two years before the index date of pancreatitis event; adjusted odds ratio 2.24, 95% confidence interval 1.36 to 3.68), recent use (30 days to two years before admission; 2.01, 1.37 to 3.18), and any use within two years (2.07, 1.36 to 3.13) were associated with significantly increased odds of acute pancreatitis.

The second case-control study, conducted in Italy, assessed the use of incretins (exenatide, liraglutide, sitagliptin, saxagliptin, and vildagliptin).[95] This study identified 1003 cases (admission for acute pancreatitis) and 4012 controls matched for year of birth, sex, and year of first exposure to antidiabetic drugs from regional administrative data of the Italian national health system that allowed the linkage of drugs dispensed with hospital discharges. All the patients with type 2 diabetes, dispensed at least one dose of antidiabetic drugs and aged 72 on average, were identified according to the ICD-9 system. Patients coded for type 1 diabetes (250.x1, 250.x3) were excluded. Cases were identified through the ICD-9 code (577.0) at discharge. The exposure to incretins and other antidiabetic drugs (metformin or glibenclamide) was measured according to the anatomical therapeutic classification system. Potential confounders—history of chronic or acute pancreatitis, gallstones, alcohol misuses, biliary tract or pancreatic cancers, and admission for cardiovascular diseases and diabetic retinopathy—were measured with ICD-9 codes. After adjustment for those confounders and the use of other antidiabetic drugs, the adjusted analyses did not show a significant association between the exposure to incretins and the risk of admission for acute pancreatitis (adjusted odds ratio 0.98, 95% confidence interval 0.69 to 1.38).

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.[91 92 95] 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 37 cases of pancreatitis among 33 227 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,[27] 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

study and the other studies are not clear: the selection of different study populations (that is, different age groups, thus differing baseline risk) and different choices of exposures and non-exposures are possible explanations. Varying risk of bias and inadequate control of confounders are other explanations.

In addition to those five eligible observational studies, three retrospective cohort studies (appendix 2), at moderate risk of bias and that failed to limit patients to those with type 2 diabetes (and were therefore excluded), reported the risk of acute pancreatitis associated with exenatide.[96-98] These studies consistently suggested that exenatide was not associated with an increased risk of acute pancreatitis.

The FDA adverse drug event system has 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.[12] 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.

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 ClincialTrials.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.[99] The FDA adverse drug event system documented 258 cases of pancreatic cancer in patients taking exenatide, 63 cases in those taking liraglutide, 81 cases in those taking sitagliptin, and 18 cases in those taking saxagliptin.[12] The number of cancer cases did not seem larger in patients taking incretins (except exenatide) than other drugs for diabetes. We also did not specifically assess the risk of chronic pancreatitis associated with the use of incretins; few data on this issue are available.

Comparison with other studies

Two other meta-analyses have assessed the risk of pancreatitis among patients using incretins, one examining GLP-1 agonists[100] and another DPP-4 inhibitors.[101] 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.[100] 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 to1.22) 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, investigated risk of pancreatitis in DDP-4 inhibitors.[101] 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).[101] 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.

Conclusion

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. Trialists 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 thiazolidinedones (TZDs), incretins, and amylin analogues in people with type 2 diabetes.[102] The resulting findings might provide more definitive evidence.

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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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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 age (years)	Mean BMI	Mean HbA1c (%)	Mean FPG (mmol/L)	Mean diabetes duration (years)
Araki (2013)[36]	No	1	47	III	561	4	12	395 (70.4)	60	25	8	9.1	286 (51.0)*
Barnett (2012)[37]	Yes	7	53	III	227	2	18	88 (38.8)	56.5	29.5	8.1	10.1	165 (75.0)*
Bergenstal (2010)[38]	Yes	3	72	III	514	3	26	254 (51.7)	52.3	32	8.5	9.1	5.7
Bunck (2009)[39]	Yes	3	3	III	69	2	52	45 (65.2)	58.4	30.5	7.5	9.2	4.9
Buse (2011)[40]	Yes	5	59	III	261	2	30	148 (57.1)	59	33.5	8.4	8.1	12
Chacra (2011)[41]	Yes	NR	NR	III	768	3	76	346 (45.1)	55.1	29	8.4	9.6	6.9
Diamant (2010)[42]	Yes	16	72	III	467	2	26	243 (53.3)	58	32	8.3	9.8	7.9
Fonseca (2012)[43]	Yes	12	61	III	361	2	12	186 (51.5)	53.7	31.9	8	9	1.3‡
Gallwitz (2012)a[44]	Yes	16	209	III	1551	2	104	933 (60.2)	56.6	30.2	7.7	9.1	715 (47.1)*
Gallwitz (2012)b[45]	Yes	14	128	III	1029	2	234†	524 (53.6)	56	32.5	7.5	8.8	5.7
Garber (2009)[46]	Yes	2	138	III	746	3	52	371 (49.7)	53	33.1	8.3	9.4	5.4
Grunberger (2012)[47]	Yes	7	44	II	164	5	12	74 (45.1)	56.6	32.1	7.3	NR	3.9
Haak (2012)[48]	Yes	14	133	III	791	6	24	426 (53.9)	55.3	29.1	8.7	10.9	562 (74.3)*
Henry (2012)[49]	Yes	8	113	III	326	3	24	170 (54.3)	54.1	32.6	8.1	9.4	7.7
Hollander (2011)[50]	Yes	8	133	III	565	3	76	280 (49.6)	54	30	8.3	9.0	5.2
Hollander (2012)[51]	Yes	8	63	III	305	2	24	119 (40.8)	53.5	36.7	7.5	8.9	5.1
Inagaki (2012)[52]	No	1	NR	III	427	2	26	290 (67.9)	56.8	26.1	8.5	NR	9
Kadowaki (2009)[53]	No	1	20	II	153	4	12	104 (68.9)	60.3	25.3	8	9.2	11.9
Kaku (2010)[54]	No	1	49	NR	264	3	24	169 (64)	59.7	24.9	8.4	9.5	10.3
Kikuchi (2010)[55]	No	1	29	III	202	2	12	144 (71.3)	59.7	24.5	7.9	9.1	9.2
Kothny (2012)[56]	Yes	13	108	NR	369	2	52	207 (56.1)	66.5	30.3	7.8	8.8	16.6
Marre (2009)[57]	Yes	21	116	III	1041	5	26	516 (49.6)	56.1	29.9	8.4	9.8	6.6‡
Nauck (2009)[58]	Yes	49	NR	II	306	6	12	143 (48.1)	55.7	32.7	7.9	NR	5.3
Nauck (2013) a[59]	Yes	25	187	III	1049	3	24	549 (53.4)	57.7	32.4	8.3	11.1	9.3
Nauck (2013)b[60]	Yes	21	170	III	1091	5	104	635 (58.2)	56.7	31	8.4	10	7.6
NCT00082381 (2009)[61]	Yes	13	82	III	551	2	26	306 (55.7)	58.9	31.4	8.2	10.2	9.6
NCT00094770 (2009)[62]	Yes	NR	173	III	1172	2	104	694 (59.2)	56.7	31.2	7.7	9.2	6.4
NCT00103857 (2009)[63]	Yes	NR	140	III	915	5	104	539 (49.4)	53.5	NR	8.8	11.1	NR
NCT00327015 (2009)[64]	Yes	13	211	III	1306	4	24	643 (49.2)	52	30.2	9.5	11.1	1.7
NCT00328172 (2011)[65]	Yes	6	71	II	302	5	12	175 (57.9)	57.3	31.1	8.3	10.5	NR
NCT00395512 (2013)[66]	Yes	23	268	III	655	4	26	320 (48.9)	52.6	31.1	8.8	10.6	3.2
NCT00482729 (2009)[67]	Yes	2	229	III	1250	2	44	708 (56.8)	49.7	NR	9.9	NR	NR
NCT00575588 (2010)[68]	Yes	11	130	III	858	2	104	444 (51.7)	57.5	31.4	7.7	9	5.4
NCT00614939 (2011)[69]	Yes	14	75	III	170	2	52	73 (42.9)	66.5	30.7	8.3	9.9	16.7

Table 1 (continued)

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 age (years)	Mean BMI	Mean HbA1c (%)	Mean FPG (mmol/L)	Mean diabetes duration (years)
NCT00722371 (2011)[70]	NR	NR	NR	III	1615	7	54	912 (56.5)	NR	NR	NR	NR	NR
NCT00757588 (2011)[71]	Yes	10	72	III	455	2	52	188 (41.3)	57.2	32.3	8.7	9.6	11.9
NCT00954447 (2012)[72]	Yes	19	167	III	1261	2	52	658 (52.2)	60	31	8.3	8.3	NR
NCT01137812 (2013)[73]	Yes	17	140	III	755	2	52	422 (55.9)	56.5	NR	NR	NR	NR
NCT01204294 (2012)[74]	No	1	43	III	352	4	52	246 (69.9)	61.3	NR	8	NR	NR
NCT01289119 (2013)[75]	No	1	30	III	506	6	16	275 (54.3)	52.6	25.7	NR	NR	4.1
Pan (2012)[76]	Yes	4	40	III	568	2	24	315 (55.5)	51.4	25.9	8.2	9.1	1
Pratley (2013)[77]	Yes	17	130	III	760	3	24	362 (48.9)	56.4	32.7	8.3	10	8.8
Ratner (2010)[78]	Yes	7	133	NR	542	9	13	270 (49.8)	56.2	31.9	7.5	8.8	6.6
Raz (2012)[79]	Yes	NR	53	III	373	3	24	130 (36.7)	54.8	32.3	7.6	8.8	2.4
Rosenstock (2009) a[80]	Yes	4	118	II	361	10	16	170 (47.8)	53.5	32.1	8	9.8	4.9
Rosenstock (2009) b[81]	Yes	13	110	III	390	3	26	161 (41.3)	55.4	32.5	9.3	10.6	12.6
Ross (2012)[82]	Yes	9	81	II	491	3	12	280 (57.0)	58.6	29.6	8	9.2	227 (47.5)*
Russell-Jones (2009)[83]	Yes	17	107	III	581	3	26	326 (56.6)	57.5	30.5	8.3	NR	9.4
Russell-Jones (2012)[84]	Yes	22	124	III	820	4	26	484 (59.0)	53.8	31.2	8.5	NR	2.7
Seino (2010)[85]	No	1	75	III	411	2	24	268 (67)	58.3	24.5	8.9	11.3	8.2
Seino (2012)a[86]	No	1	30	III	288	3	12	198 (68.8)	52.6	25.9	8	NR	6.3
Seino (2012)b[87]	Yes	4	57	III	311	2	24	149 (47.9)	58.4	25.3	8.5	7.7	13.9
Umpierrez (2011)[88]	Yes	2	39	II	262	2	16	129 (36.4)	56.5	33.9	8.2	NR	8.3
Yang (2011)[89]	Yes	3	51	NR	929	4	16	514 (55.3)	53.3	25.6	8.6	9.7	7.5
Zinman (2009)[90]	Yes	2	96	III	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**

		Incretin		Control		Follow-up from start of treatment
Author (year)	**Drugs used across groups**	**Type**	**Events**	**Type**	**Events**	**(weeks)**
Araki (2013)[36]	None	Linagliptin	0/319	Placebo	0/80	12
		Linagliptin	0/319	Voglibose	0/162	
Barnett (2012)[37]	None	Linagliptin	0/151	Placebo	0/76	18
Bergenstal (2010)[38]	Metformin	Exenatide	0/160	Pioglitazone	2/165	26
		Sitagliptin	0/166	Pioglitazone	2/165	
Bunck (2009)[39]	Metformin	Exenatide	1/36	Insulin glargine	0/33	52
Buse (2011)[40]	Insulin glargine ± metformin/pioglitazone (or both agents)	Exenatide	0/137	Placebo	0/122	30
Chacra (2011)[41]	Glyburide	Saxagliptin	0/501	Placebo	0/267	76
Diamant (2010)[42]	Metformin ± SU	Exenatide	1/233	Insulin glargine	0/223	26
Fonseca (2012)[43]	None	Lixisenatide	0/239	Placebo	0/122	12
Gallwitz (2012)a[44]	Metformin	Linagliptin	1/776	Glimepiride	0/775	104
Gallwitz (2012)b[45]	Metformin	Exenatide	1/511	Glimepiride	1/508	107*
Garber (2009)[46]	None	Liraglutide	2/497	Glimepiride	0/248	52
Grunberger (2012)[47]	None	Dulaglutide	0/132	Placebo	1/32	12
Haak (2012)[48]	None	Linagliptin	0/428	Placebo	0/72	24
Henry (2012)[49]	Metformin	Taspoglutide	0/223	Placebo	0/101	24
Hollander (2011)[50]	TZD	Saxagliptin	1/381	Placebo	0/184	76
Hollander (2012)[51]	Metformin	Taspoglutide	0/154	Placebo	0/150	24
Inagaki (2012)[52]	BG or BG + TZD	Exenatide	0/215	Insulin glargine	0/212	26
Kadowaki (2009)[53]	SU ± BG/TZD	Exenatide	0/111	Placebo	0/40	12
Kaku (2010)[54]	SU (glibenclamide, glicazide or glimeprimide)	liraglutide	0/176	Placebo	0/88	24
Kikuchi (2010)[55]	Glimepiride	Vildagliptin	0/102	Placebo	0/100	12
Kothny (2012)[56]	Untreated, insulin, OADs or any combination	Vildagliptin	0/216	Placebo	0/153	52
Marre (2009)[57]	Glimepiride	Liraglutide	1/695	Placebo	0/114	26
		Liraglutide	1/695	Rosiglitazone	0/231	
Nauck (2009)[58]	Metformin	Taspoglutide	0/248	Placebo	0/49	12
Nauck (2013)a[59]	Metformin	Taspoglutide	0/715	Insulin glargine	0/322	24
Nauck (2013) b[60]	Metformin	Liraglutide	1/724	Placebo	0/121	104
		Liraglutide	1/724	Glimepiride	1/242	
NCT00082381 (2009)[61]	Metformin + SU	Exenatide	0/282	Insulin glargine	1/267	26
NCT00094770 (2009)[62]	Metformin	Sitagliptin	1/588	Glipizide	0/584	104
NCT00103857 (2009)[63]	None	Sitagliptin	1/551	Metformin	0/364	104
NCT00327015 (2009)[64]	None	Saxagliptin	0/978	Metformin	1/328	24
NCT00328172 (2011)[65]	None	Linagliptin	1/170	Placebo	0/67	12
		Linagliptin	1/170	Metformin	0/65	
NCT00395512 (2013)[66]	None	Alogliptin	1/491	Pioglitazone	0/163	26
NCT00482729 (2009)[67]	Metformin	Sitagliptin	1/625	No additional drug	0/621	44
NCT00575588 (2010)[68]	Metformin	Saxagliptin	0/428	Glipizide	1/430	104
NCT00614939 (2011)[69]	OADs and/or insulin	Saxagliptin	0/85	Placebo	1/85	52
NCT00722371 (2011)[70]	None	Sitagliptin	0/922	Pioglitazone	1/693	54
NCT00757588 (2011)[71]	Insulin ± metformin	Saxagliptin	0/304	Placebo	0/151	52
NCT00954447 (2012)[72]	Insulin and/or metformin and/or pioglitazone	Linagliptin	3†/631	Placebo	1/630	52
NCT01137812 (2013)[73]	Metformin + SU	Sitagliptin	0/378	Canagliflozin	1/377	52
NCT01204294 (2012)[74]	SU or A-GI	Linagliptin	0/228	Metformin	0/124	52
NCT01289119 (2013)[75]	None	Alogliptin	0/252	Placebo	1/92	16
		Alogliptin	0/252	Metformin	0/98	

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) [76]	None	Saxagliptin	0/284	Placebo	0/284	24
Pratley (2013) [77]	SU ± metformin	Taspoglutide	1/494	Pioglitazone	0/257	24
Ratner (2010) [78]	Metformin	Lixisenatide	0/433	Placebo	0/109	13
Raz (2012) [79]	None	Taspoglutide	0/245	Placebo	0/123	24
Rosenstock (2009) a[80]	None	Exenatide	0/35	Placebo	0/51	16
		Albiglutide	0/270	Placebo	0/51	
Rosenstock (2009)b[81]	Insulin ± metformin	Alogliptin	2/260	Placebo	0/129	26
Ross (2012) [82]	metformin	Linagliptin	0/447	Placebo	0/44	12
Russell-Jones (2009) [83]	Metformin + glimepiride	Liraglutide	0/230	Placebo	0/114	
		Liraglutide	0/230	Insulin glargine	0/232	26
Russell-Jones (2012) [84]	None	Exenatide	0/248	Metformin	0/246	26
		Exenatide	0/248	Pioglitazone	0/163	
		Sitagliptin	1/163	Metformin	0/246	
		Sitagliptin	1/163	Pioglitazone	0/163	
Seino (2010) [85]	None	Liraglutide	0/268	Glibenclamide	0/132	24
Seino (2012)a [86]	Metformin	Alogliptin	0/188	Placebo	0/100	12
Seino (2012)b [87]	Insulin ± SU	Lixisenatide	0/154	Placebo	0/157	24
Umpierrez (2011)[88]	Each of the two different classes (SU, biguanide, TZD or DPP-4)	Dulaglutide	2/196	Placebo	0/66	16
Yang (2011)[89]	Metformin	Liraglutide	0/697	Glimepiride	0/231	16
Zinman (2009) [90]	Metformin + rosiglitazone	Liraglutide	0/356	Placebo	0/177	26

SU=sulfonylurea; TZD=thiazolidinedione; BG=biguanide; OADs=oral antidiabetic 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 (%) male	Mean age (years)	Mean BMI	Mean HbA1c (%)	Mean FPG (mmol/L)	Mean diabetes duration (years)
Garg (2010)[91]	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 (54.3)	52.7	NR	NR	NR	NR
Romley (2012)[92]	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 (54.2)	63.1	NR	NR	NR	3.1
Sudhakaran (2011) [93]	Retrospective cohort study	Case records/India	No financial support	Asian Indian patients with type 2 diabetes in Indian tertiary diabetes care centre	NR	3512 (63.2)	55.1	30.0	9.2	10.0	15.1
Singh (2013)[94]	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 2008; 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 (57.5)	52	NR	NR	NR	NR
Giorda (2013) [95]	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 (54.8)	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)[91]	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)[92]	Exenatide	Non-exenatide	Admission for acute pancreatitis	1 312	268 561	Exenatide *v* control: OR 0.93 (0.63 to 1.36)
Sudhakaran (2011)[93]	Sitagliptin	Insulin glargine	Acute pancreatitis	0	5 560	No events reported
Singh (2013)[94]	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)[95]	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)[91]	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)[92]	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)[93]	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	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)	Ascertainment of type 2 diabetes conditions	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	Completeness of data within database
Singh (2013)[94]	Type 2 diabetes mellitus identified as 1 relevant inpatient code of ICD-9 or 2 outpatient ICD-9 codes separated by at least 30 days (250.xx, 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 complication severity index (0, 1, 2, 3, or more), and enrolment 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	Ascertainment of risk factors 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)[95]	Patients with type 2 diabetes 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, cardio vascular 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, hypertrigly ceridaemia, 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

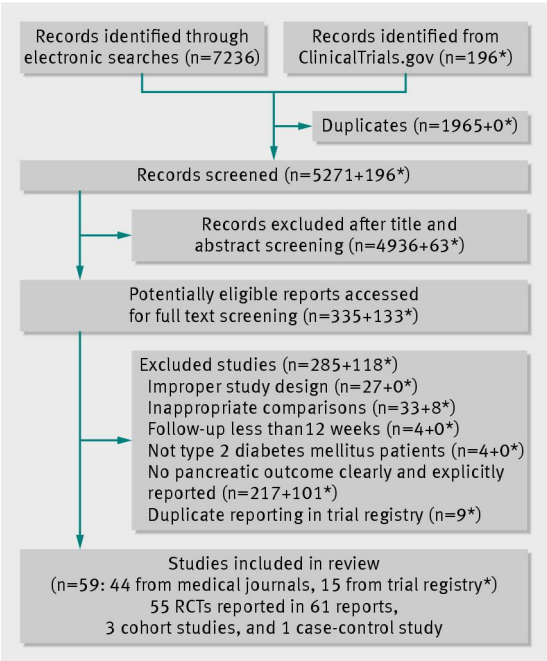

Fig 1 Flow chart of article selection. *Data from ClinicalTrials.gov

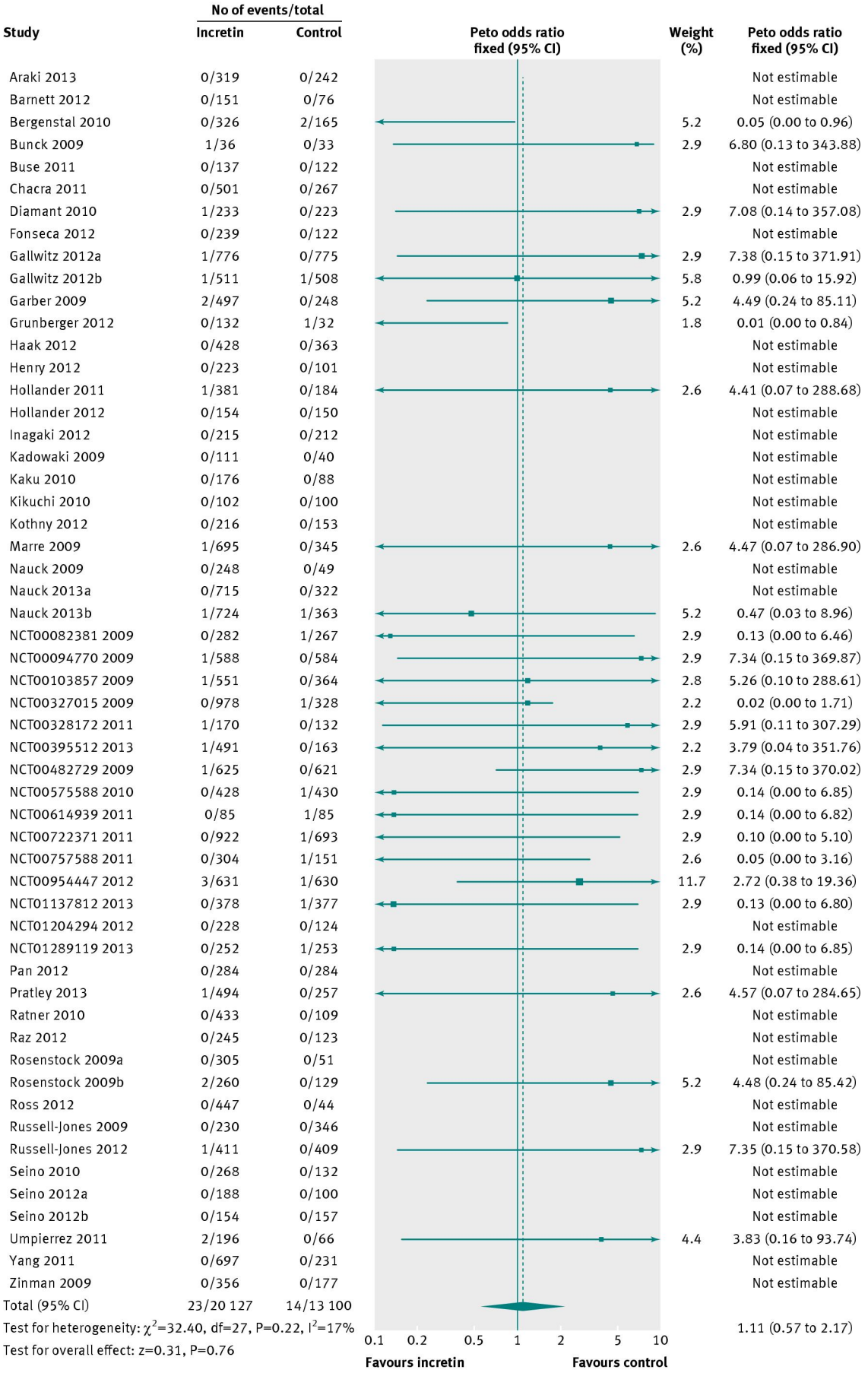

Fig 2 Risk of pancreatitis events between patients with type 2 diabetes mellitus treated with incretin or control