

RESEARCH

Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: cohort study

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Abstract

Objectives To determine whether the use of incretin based drugs, compared with sulfonylureas, is associated with an increased risk of acute pancreatitis.

Design Population based cohort study.

Setting 680 general practices in the United Kingdom contributing to the Clinical Practice Research Datalink.

Participants From 1 January 2007 to 31 March 2012, 20 748 new users of incretin based drugs were compared with 51 712 users of sulfonylureas and followed up until 31 March 2013.

Main outcome measures Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for acute pancreatitis in users of incretin based drugs compared with users of sulfonylureas. Models were adjusted for tenths of high dimensional propensity score (hdPS).

Results The crude incidence rate for acute pancreatitis was 1.45 per 1000 patients per year (95% confidence interval 0.99 to 2.11) for incretin based drug users and 1.47 (1.23 to 1.76) for sulfonylurea users. The rate of acute pancreatitis associated with the use of incretin based drugs was not increased (hdPS adjusted hazard ratio: 1.00, 95% confidence interval 0.59 to 1.70) relative to sulfonylurea use.

Conclusions Compared with use of sulfonylureas, the use of incretin based drugs is not associated with an increased risk of acute pancreatitis. While this study is reassuring, it does not preclude a modest increased risk, and thus additional studies are needed to confirm these findings.

Introduction

Glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors are new classes of antidiabetes drugs. These drugs stimulate insulin secretion according to glucose concentration and inhibit glucagon secretion by either direct binding to the GLP-1 receptor or by inhibiting the degradation of endogenous GLP-1.¹ While these drugs have been shown to have a modest effect on haemoglobin A1c (HbA1c), with favourable effects on weight and a reduced risk of hypoglycaemia,² there have been safety concerns regarding their effects on the pancreas. Specifically, analyses of adverse event databases have associated incretin based drugs with acute pancreatitis,³⁻⁶ resulting in pharmacovigilance alerts⁷⁻⁹ and the addition of this possible adverse event on product monographs.¹⁰⁻¹⁴ Currently, there are continued concerns, partly due to the conflicting results of the observational studies conducted to date.¹⁵⁻²³ As a result, the European Medicines Agency and the US Food and Drug Administration have called for additional studies to assess this potential risk.^{24 25}

Given the increasing number of patients being prescribed incretin based drugs and concerns regarding their safety, we conducted a large population based study to determine whether the use of GLP-1 analogues and DPP-4 inhibitors, when compared with sulfonylureas, a second line treatment for type 2 diabetes, is associated with an increased risk of acute pancreatitis.

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Appendix: Supplementary tables A-G

Methods

Data sources

This study was conducted with the UK Clinical Practice Research Datalink (CPRD) and hospital episodes statistics (HES) database. The CPRD has medical information on more than 13 million individuals across 680 general practices, with similar age and sex distributions to those reported by the UK National Population Census.²⁶ Information collected includes demographic characteristics, diagnoses, and drug prescriptions issued by the general practitioners. Diagnoses and procedures are coded with the Read classification and prescriptions are coded according to the UK Prescription Pricing Authority Dictionary. Data collected in the CPRD have been validated and deemed to be of high quality.²⁷ Since 1997, the HES database collects information on dates of hospital admissions, discharge diagnoses (coded with ICD-10 (international classification of diseases, 10th revision)), and procedures (coded using the Office of Population Censuses and Surveys classification of interventions and procedures, 4th version).

Study population

Base cohort

From the CPRD population, we identified a base cohort consisting of all patients aged at least 18 newly treated with a non-insulin antidiabetes drug (metformin, sulfonylureas, prandial glucose regulators, thiazolidinediones, acarbose, DPP-4 inhibitors, and GLP-1 analogues) from 1 January 1988 to 31 March 2013. All patients were required to have at least six months of “up to standard” medical history in the CPRD before their first non-insulin prescription.

Subcohorts of patients treated with incretin based drugs and sulfonylureas

Within the base cohort defined above, we identified all patients who were newly prescribed incretin based drugs (GLP-1 analogues: exenatide and liraglutide; DPP-4 inhibitors: sitagliptin, saxagliptin, vildagliptin, linagliptin), either in monotherapy or combination, during the study period. These patients were compared with patients prescribed sulfonylureas, either in monotherapy or combination, as of 2007—that is, after the first DPP-4 inhibitor was licensed in the UK. Thus, cohort entry for both exposure groups was defined as the first prescription received as of 2007. We excluded patients previously diagnosed with pancreatic cancer, those who had undergone a pancreatectomy, those with a history of pancreatic injury or congenital defects of the pancreas, as well as those with cystic fibrosis, lupus, polycystic ovarian syndrome, and those who had undergone bariatric (bypass) surgery (as these surgeries have been associated with increased levels of endogenous GLP-1)²⁸ at any time before cohort entry. All patients meeting the study inclusion criteria were followed until a diagnosis of acute pancreatitis (recorded in either the CPRD (on the basis of Read codes) or HES database (ICD-10 codes: K85.0, K85.1, K85.2, K85.3, K85.8, K85.9 in primary or secondary position)), death from any cause, end of registration with the general practice, or the end of the study period (31 March 2013), whichever came first.

Exposure definition

We used an “as treated” definition of exposure for patients in the incretin based drug and sulfonylurea groups. For this definition, we considered patients as continuously exposed if the duration of one prescription overlapped with the prescribing

of the subsequent prescription. In the event of non-overlap, we allowed for a 30 day grace period between two successive prescriptions. Termination of treatment was therefore defined by either the absence of a new prescription by the end of a 30 day grace period or a switch to insulin, whichever came first.

Statistical analysis

We used descriptive statistics to summarise the characteristics of users of incretin based drugs and sulfonylureas. Person time at risk was measured from cohort entry (that is, first prescription of an incretin based drug or sulfonylurea on or after 2007) to time of event or end of exposure for the as treated analysis. We calculated crude incidence rates, with confidence intervals based on the Poisson distribution, by dividing the number of patients with acute pancreatitis over the person time at risk for each exposure group.

We constructed Kaplan-Meier curves for each exposure group to compare the cumulative incidence of acute pancreatitis. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals for acute pancreatitis associated with the use of incretin based drugs compared with the use of sulfonylureas based on the as treated exposure definition. We also conducted two secondary analyses. In the first, we evaluated whether the risk varied with duration of use. For this analysis, we calculated hazard ratios for three time intervals of use (0–1 year, 1–2 years, >2 years). In the second, we assessed whether the risk varied between men and women. We could not conduct separate analyses for patients who used DPP-4 inhibitors compared with GLP-1 analogues as the latter group was too small.

All models were adjusted for tenths of high dimensional propensity score (hdPS), which is a method that empirically selects covariates based on their prevalence and potential for confounding.²⁹ For each patient we used multivariate logistic regression to calculate a propensity score, which was the probability of being exposed to incretin based drugs compared with sulfonylureas, conditional on 500 empirically identified and 13 predefined covariates measured at cohort entry. We estimated the empirical covariates from five data dimensions (drug prescriptions, procedures, diagnoses, disease history, and administrative information), while the predefined covariates consisted of age, sex, duration of treated diabetes (defined as the time between a first ever non-insulin prescription and cohort entry), HbA1c, excessive alcohol use (based on diagnoses for alcohol related disorders, such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), body mass index (BMI), smoking status, history of gallstones, and use of antidiabetes drugs in the year before cohort entry (metformin, sulfonylureas, thiazolidinediones, insulins, and other agents). In addition to the tenths of hdPS, we adjusted the models for calendar year of cohort entry. Variables with missing data were coded with an “unknown” category.³⁰ Overall, there was good overlap in the propensity score distributions between the exposure groups, and the hdPS model had excellent discrimination (C statistic 0.89).³¹

Sensitivity analyses

We also performed four sensitivity analyses to assess the robustness of the results. Firstly, we repeated the analyses using an “intention to treat” exposure definition, which was defined by considering patients continuously exposed from cohort entry until the end of follow-up, regardless of treatment terminations or switches to other antidiabetes drugs. Secondly, we repeated the primary analysis by matching each user of an incretin based

drug with up to two users of a sulfonylurea on the nearest hdPS score using a greedy matching algorithm.³² Thirdly, as some people in both the incretin based drug and sulfonylurea groups had a history of sulfonylurea use, we conducted a sensitivity analysis by stratifying patients on this history of use. Finally, to deal with uncertainties related to the choice of our sulfonylurea reference group, we repeated the primary analyses in an identical fashion comparing users of incretin based drugs with users of insulins and with users of metformin. All analyses described above were conducted with SAS, version 9.3 (SAS Institute, Cary, NC).

Results

We identified 153 983 users of antidiabetes drugs after 2007, which included 20 748 users of incretin based drugs and 51 712 users of sulfonylureas (fig 1). The mean time the patients were receiving treatment was 1.4 years, corresponding to 99 497 person years of follow-up. We identified 146 cases of acute pancreatitis, generating an overall incidence rate of 1.47 per 1000 person years.

Table 1 shows the characteristics of the incretin based drug and sulfonylurea users. Compared with sulfonylurea users, incretin based drug users were younger, more likely to be obese, had longer durations of treated diabetes, higher concentrations of HbA1c, and were more likely to use antidiabetes drugs in the year before cohort entry.

Table 2 presents the results of the primary as treated analysis. The mean (SD) time patients were taking treatment was 0.9 (0.9) and 1.6 (1.6) years for incretin based drug users and sulfonylurea users, respectively. Overall, 13.5% in the incretin based drug group and 28.7% in the sulfonylurea group were prescribed these drugs as monotherapy during follow-up, while 75.6% and 67.3% were prescribed them concurrently with combinations containing metformin, respectively.

The crude incidence rate of acute pancreatitis (per 1000 person years) in incretin based drug users was similar to the rate in sulfonylurea users (1.45, 95% confidence interval 0.99 to 2.11, and 1.47, 1.23 to 1.76, respectively). Kaplan-Meier curves for incretins and sulfonylureas were not significantly different from each other (log rank $P=0.36$; fig 2). In the hdPS adjusted model, the use of incretin based drugs was not associated with an increased risk of acute pancreatitis (hazard ratio 1.00, 95% confidence interval 0.59 to 1.70).

Table 3 presents the results of secondary analyses. The risk of acute pancreatitis did not vary with duration of use of incretin based drugs. When stratified by sex, the hazard ratio was higher in men than in women but did not reach significance.

Sensitivity analyses

When we used an intention to treat definition of exposure, results were similar to those generated with the as treated definition (table A in appendix). Likewise, the results were similar after we matched on hdPS scores (table B in appendix). Overall, stratification on history of sulfonylurea use before cohort entry did not result in significant associations, although the hazard ratio was higher among patients with such a history (table C in appendix). Finally, in the analyses comparing incretin based drug users with users of insulin and metformin, we noted important yet expected differences. Specifically, duration of treated diabetes was longer in insulin users, while the opposite was the case for metformin users (mean durations 6.1 and 1.7 years, respectively; tables D and E in appendix). In the hdPS adjusted models, when compared with insulins, the use of

incretin based drugs was not associated with a significant risk of acute pancreatitis, with the hazard ratio under the null value (0.79, 95% confidence interval 0.19 to 3.35; table F in appendix). A similar non-significant association was observed when we compared incretins with metformin, although the hazard ratio was numerically increased (1.52, 0.83 to 2.81; table G in appendix).

Discussion

The results of our cohort study do not support the hypothesis of an increased risk of acute pancreatitis associated with the use of incretin based drugs compared with sulfonylureas in people with type 2 diabetes. We did not observe any variation with duration of use or after stratification by sex, with all point estimates close to the null value. Moreover, the results remained consistent after we performed several sensitivity analyses. Nonetheless, given the rarity of the outcome, this study does not preclude a possible modest increased risk of acute pancreatitis associated with incretin based drugs.

Comparison with other studies

The potential risk for acute pancreatitis associated with incretin based drugs was raised after signals issued from pharmacovigilance systems.³⁻⁹ A hypothesis for this possible association relates to pancreatic enlargement and duct occlusion by proliferation of duct cells,³³⁻³⁴ although this has been disputed.³⁵ Our null results are consistent with the conclusions of two recent meta-analyses of randomised controlled trials on the effects of DPP-4 inhibitors (odds ratio 0.89, 95% confidence interval 0.32 to 2.49)³⁶ and GLP-1 analogues (1.01, 0.37 to 2.76)³⁷ on acute pancreatitis, as well as with eight¹⁵⁻²² of the nine²³ observational studies conducted to date. In two studies, the use of exenatide and sitagliptin for up to one year was not associated with increased risks of acute pancreatitis (rate ratio 1.0 (95% confidence interval 0.6 to 1.7) and 1.0 (0.5 to 2.0), respectively).¹⁵⁻¹⁶ For past users of exenatide, however, a significant increased risk was observed (2.8, 1.6 to 4.7).¹⁵ Subsequently, five other observational studies did not observe any significant increased risk of acute pancreatitis associated with the use of incretin based drugs.¹⁷⁻²² These results are also consistent with those of recent randomised controlled trials, in which no increased risk of acute pancreatitis was noted with saxagliptin and alogliptin.³⁸⁻³⁹ Our results, however, contrast with those of a recent case-control study,²³ in which current and recent use (between 30 days and two years before the event) of incretin based drugs was significantly associated with an increased risk of acute pancreatitis (odds ratio 2.24 (95% confidence interval 1.36 to 3.68) and 2.01 (1.37 to 3.18), respectively). The fact that the risk remained in recent users, however, potentially signals bias related to confounding by indication. Indeed, the comparator group in that study consisted of any antidiabetes drug, which included a mix of preferred treatments such as metformin, second line treatments, and third and fourth line treatments such as insulin. As incretin based drugs are typically second to third line drugs² and the risk of acute pancreatitis increases with type 2 diabetes and possibly with duration of disease,⁴⁰⁻⁴² it is imperative that they are compared with drugs used at the same or a similar stage of diabetes, otherwise this would introduce a time lag bias.⁴³ It is for this reason that our primary comparator group consisted of sulfonylurea users, which we believe is the clinically most appropriate comparator. In sensitivity analyses, we compared users of incretin based drugs with alternate comparators—namely, insulin and metformin. While both

analyses yielded non-significant results, interestingly, the hazard ratios for insulin and metformin were 0.79 and 1.52, respectively. The difference in the magnitude of these hazard ratios is consistent with the hypothesis that insulin users are at a higher risk of acute pancreatitis than metformin users, and thus the use of these drugs likely reflects the underlying severity of the disease. These analyses underline the importance of choosing an appropriate comparator, which future studies will need to consider.

Strengths and limitations of this study

The strengths of our study include the use of a large population based cohort of patients with type 2 diabetes followed for up to 25 years in CPRD, a database that has been shown to be representative of the UK general population. Moreover, the CPRD allowed us to consider important potential confounders (such as BMI, excessive alcohol use, and HbA1c), which were included along with over 500 variables in the hdPS model.⁴⁴ In contrast with standard propensity score methods, the hdPS method empirically selects variables based on their prevalence and potential for confounding.²⁹ This particularity allows for the inclusion of potential confounders that might not been considered a priori. Finally, using a primary cohort of patients newly treated with non-insulin drugs allowed us to accurately calculate the duration of treated diabetes before cohort entry, a potentially major confounder.

This study does have some limitations. Drug exposures recorded in the CPRD are from prescriptions written by general practitioners, and the database does not record prescriptions written by specialists. We do not believe, however, that such missing information was differential between patients exposed to incretin based drugs and the active comparator group. Moreover, we do not know if patients complied with the treatment, although renewal of prescriptions is probably a good indicator of drug use. To our knowledge, the validity of the recording of acute pancreatitis in the CPRD has not been formerly validated, although it has been used previously in another unrelated study.⁴² For this reason, we used the HES database as an additional data source to capture this outcome, which probably maximised the validity of the case ascertainment. Another limitation relates to the rarity of acute pancreatitis, which probably limited some of the secondary analyses by duration of use and sex. It is important to note, however, that our study had 98% power to detect a large effect, such as a hazard ratio of 2.0, one similar in magnitude as in the study reporting an association.²³ A potentially important confounder is hypertriglyceridaemia, a known risk factor for pancreatitis. Use of results of laboratory tests to adjust for this variable was not possible as they were missing for a large proportion of patients. The use of fibrates (a proxy for treated hypertriglyceridaemia), however, was included in the hdPS score estimation. Although our results remained consistent after the models were adjusted for tenths of hdPS, residual confounding is always possible, as it is with any observational study. Furthermore, the results remained somewhat consistent when we compared incretin based drugs with other classes of antidiabetes drugs. This is especially relevant as past use of sulfonylureas has been suspected to increase the risk of acute pancreatitis compared with other antidiabetes drugs.⁴⁰ In a sensitivity analysis, we obtained consistent results after excluding patients who used sulfonylureas before cohort entry. Finally, given the limited number of events, we could not investigate the effect of dose of incretin based drugs on the outcome.

Conclusions and implications

In summary, the results of our population based study suggest that, compared with use of sulfonylureas, the use of incretin based drugs is not associated with an increased risk of acute pancreatitis among patients with type 2 diabetes. While our study provides some reassurance to physicians and patients using these drugs, the upper bound of the confidence interval for the hazard ratio suggests that we cannot preclude a modest increase in risk. Additional large well conducted observational studies are needed to confirm our findings.

Contributors: All authors participated in the study design. SS acquired the data. JLF, LA, and VP did the statistical analyses. JLF wrote the initial draft, and all authors critically revised the manuscript. SS is guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: database acquisitions were funded by the Canadian Institute of Health Research (CIHR) and the Canada Foundation for Innovation; SS has received research grants, participated in advisory board meetings and/or as a speaker at conferences for AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Merck, and Novartis, all of which except Bayer are manufacturers of incretin based drugs, though none of these activities were related to diabetes or incretins, with the exception of a single participation in a mock advisory panel for Bristol-Myers-Squibb. **Ethical approval:** The study protocol was approved by the independent scientific advisory committee of the Clinical Practice Research Datalink and by the research ethics board of the Jewish General Hospital, Montreal, Canada.

Data sharing: No additional data available.

Transparency declaration: SS affirms that this 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 (and, if relevant, registered) have been explained.

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What is already known on this topic

The occurrence of acute pancreatitis associated with the use of glucagon-like peptide 1 analogues and dipeptidyl peptidase-4 inhibitors is controversial, with conflicting data from preclinical animal studies, randomised controlled trials, adverse event databases, and observational studies

Additional observational studies are needed to assess whether these drugs are associated with acute pancreatitis

What this study adds

Compared with sulfonylureas, the use incretin based drugs was not associated with an increased risk of acute pancreatitis in a population based cohort study from the Clinical Practice Research Datalink

While these null results are reassuring, large well conducted population based studies are needed to rule out a modest increased risk of acute pancreatitis associated with these drugs

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Tables

Table 1 | Baseline characteristics of users of incretin based drugs and sulfonylureas. Figures are numbers (percentage) of users unless specified otherwise

Baseline characteristics	Incretin based drug users (n=20 748)	Sulfonylurea users (n=51 712)
Mean (SD) age (years)	56.0 (11.3)	62.9 (12.9)
Men	11 897 (57.3)	30 091 (58.2)
Year of cohort entry:		
2007	273 (1.3)	25 466 (49.2)
2008	1427 (6.9)	5295 (10.2)
2009	3459 (16.7)	5620 (10.9)
2010	5449 (26.3)	5360 (10.4)
2011	5121 (24.7)	5130 (9.9)
2012	4647 (22.4)	4412 (8.5)
2013	372 (1.8)	429 (0.8)
Mean (SD) duration of treated diabetes (years)	5.2 (3.7)	3.4 (3.2)
Excessive alcohol use	3711 (17.9)	7627 (14.7)
Smoking status:		
Ever	13 331 (64.3)	32 624 (63.1)
Never	7408 (35.7)	18 926 (36.6)
Unknown	9 (0.04)	162 (0.3)
BMI categories:		
≤25	1326 (6.4)	9167 (17.7)
25-30	4631 (22.3)	18 214 (35.2)
>30	14 728 (71.0)	23 500 (45.4)
Unknown	63 (0.3)	831 (1.6)
HbA1c categories:		
≤7%	1710 (8.2)	12,610 (24.4)
7-8%	5925 (28.6)	14 837 (28.7)
>8%	12 950 (62.4)	21 152 (40.9)
Unknown	163 (0.8)	3113 (6.0)
Previous pancreatitis*	283 (1.4)	864 (1.7)
History of gallstones	1272 (6.1)	2818 (5.4)
Antidiabetes drugs before cohort entry†:		
Metformin	18 688 (90.1)	35 865 (69.4)
Sulfonylureas	11 931 (57.5)	21 165 (40.9)
Mean (SD) duration of use (years)	1.2 (2.0)	0.9 (1.7)
Insulins	1372 (6.6)	1233 (2.4)
Thiazolidinediones	4986 (24.0)	6305 (12.2)
Other antidiabetes drugs	353 (1.7)	349 (0.7)

BMI=body mass index; HbA1c=haemoglobin A1c.

*Either acute or chronic pancreatitis.

†Measured in year before cohort entry.

Table 2| Crude and adjusted hazard ratios for acute pancreatitis associated with use of incretin based drugs compared with sulfonylureas*

Exposure group	No of patients	Events	Person years	Incidence rate (per 1000 person years)	HR (95% CI)	
					Crude	Adjusted†
Sulfonylureas	51 712	119	80 815	1.47 (1.23 to 1.76)	1.00 (reference)	1.00 (reference)
Incretin based drugs	20 748	27	18 682	1.45 (0.99 to 2.11)	0.82 (0.54 to 1.25)	1.00 (0.59 to 1.70)

*Analysis based on as treated exposure definition.

†Adjusted for tenths of high dimensional propensity score and year of cohort entry.

Table 3| Crude and adjusted hazard ratios for acute pancreatitis associated with use of incretin based drugs compared with sulfonylureas according to duration of use and sex*

Exposure group	No of patients	Events	Person years	Incidence rate (per 1000 person years)	HR (95% CI)	
					Crude	Adjusted†
Time interval of duration of use						
0-1 years:						
Sulfonylureas	51 712	74	35 502	2.08 (1.66 to 2.62)	1.00 (reference)	1.00 (reference)
Incretin based drugs	20 748	21	11 955	1.76 (1.15 to 2.69)	0.84 (0.52 to 1.37)	1.08 (0.57 to 2.03)
1-2 years:						
Sulfonylureas	24 412	24	18 894	1.27 (0.85 to 1.90)	1.00 (reference)	1.00 (reference)
Incretin based drugs	6814	4	4517	0.89 (0.33 to 2.36)	0.68 (0.24 to 1.96)	1.06 (0.31 to 3.60)
>2 years:						
Sulfonylureas	14 659	21	26 312	0.80 (0.52 to 1.22)	1.00 (reference)	1.00 (reference)
Incretin based drugs	2824	2	2183	0.92 (0.23 to 3.66)	0.97 (0.22 to 4.27)	0.51 (0.09 to 2.86)
Sex						
Women:						
Sulfonylureas	21 621	43	33 526	1.28 (0.95 to 1.73)	1.00 (reference)	1.00 (reference)
Incretin based drugs	8851	5	7629	0.66 (0.27 to 1.57)	0.42 (0.17 to 1.07)	0.45 (0.15 to 1.31)
Men:						
Sulfonylureas	30 091	76	47 289	1.61 (1.28 to 2.01)	1.00 (reference)	1.00 (reference)
Incretin based drugs	11 897	22	11 053	1.99 (1.31 to 3.02)	1.04 (0.65 to 1.69)	1.41 (0.75 to 2.63)

*Analysis based on as treated exposure definition.

†Adjusted for tenths of high dimensional propensity score and year of cohort entry.

Figures

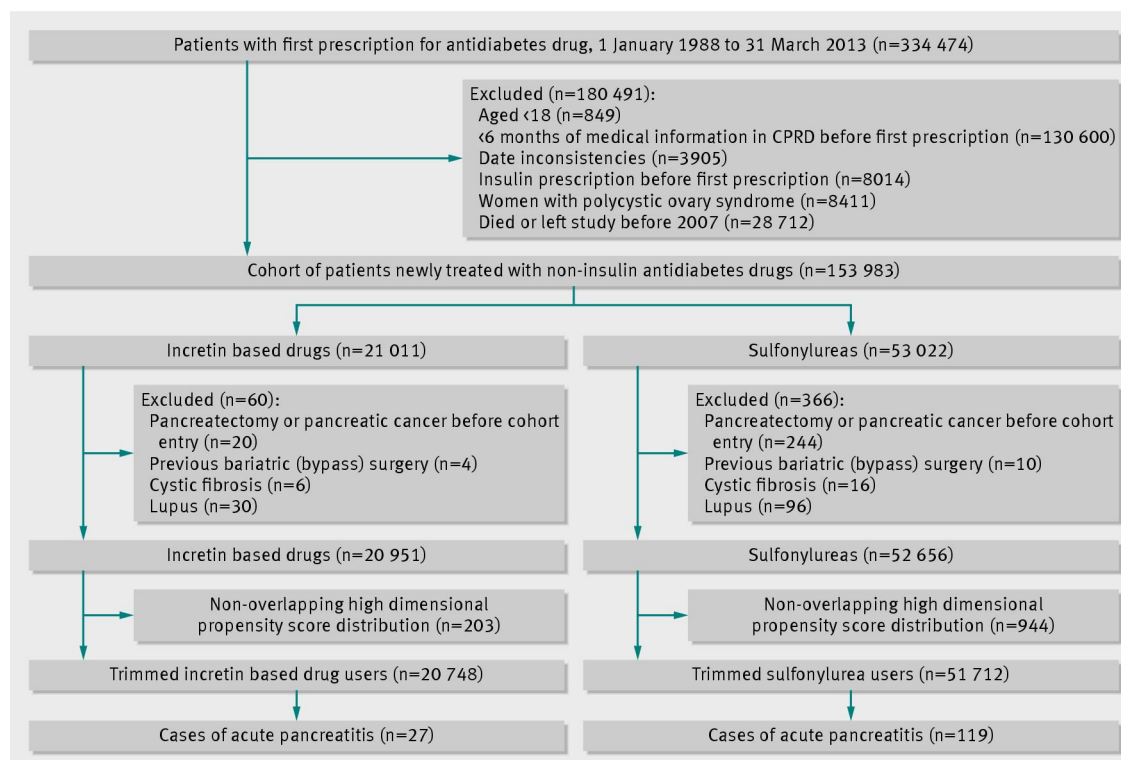


Fig 1 Flow of participants in cohort study of effect of incretin based drugs in patients with type 2 diabetes

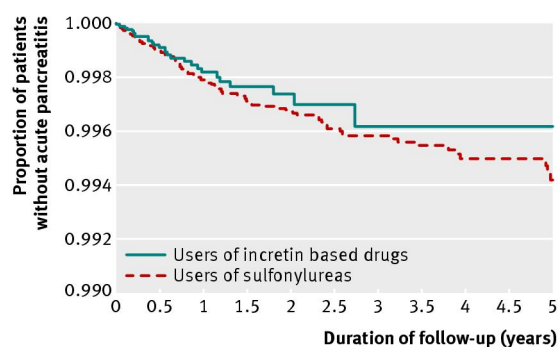


Fig 2 Kaplan-Meier curves for acute pancreatitis in users of incretins compared with users of sulfonylurea (log rank $P=0.36$)