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Use of incretin agents and risk of acute and chronic pancreatitis: A population-based cohort study

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Aim: To determine the association between the use of incretin agents (dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists) for the treatment of type 2 diabetes mellitus (T2DM) and the risk of any, acute and chronic pancreatitis.

Research design and methods: A population-based cohort study was conducted using data from the UK Clinical Practice Research Datalink (CPRD 2007–2012). A total of 182 428 adult patients with ≥1 non-insulin antidiabetic drug (NIAD) prescription were matched to control subjects without diabetes. Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of pancreatitis in incretin-users (N = 28 370) compared with controls and with other NIAD users. Adjustments were made for lifestyle, disease and drug history. In a sensitivity analysis, a new-user design was used.

Results: Current incretin users had a 1.5-fold increased risk of any pancreatitis compared with NIAD users (adjusted HR 1.47, 95% CI 1.06–2.04). In incident current incretin users the risk of any and acute pancreatitis was increased 2.1- and 2.0-fold compared with NIAD users (adjusted HR 2.12, 95% CI 1.31–3.43 and adjusted HR 1.96, 95% CI 1.13–3.41), whereas there was no increased risk found for chronic pancreatitis.

Conclusions: Incretin use was associated with an increased risk of any pancreatitis. Moreover, risk of any and acute pancreatitis was higher when applying a new-user design. We were not able to detect an association with chronic pancreatitis, but the number in this subgroup was small.

KEYWORDS

acute pancreatitis, chronic pancreatitis, cohort studies, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, incretin-based therapy, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a major threat to human health. Almost 90% of patients with T2DM fail to achieve target values for glucose, lipids and blood pressure while treated with non-insulin antidiabetic drugs (NIADs) or insulin.[1] Incretin agents or incretin-based therapies (glucagon-like peptide-1 receptor agonists [GLP-1RAs], such as exenatide or liraglutide, and dipeptidyl peptidase-4 [DPP-4] inhibitors, such as saxagliptin, linagliptin, vildagliptin or sitagliptin) are new therapeutic agents for the treatment of T2DM. Incretin-based therapies have an antihyperglycaemic effect, while promoting weight loss with a minimal risk of hypoglycaemia.[2] Yet, in recent years, evidence has become available that pancreatitis might be an important side effect.[3]

The glucagon-like peptide 1 (GLP-1) receptors are expressed in pancreatic islet β-cells as well as other cell types. They are directly stimulated by GLP-1RAs and indirectly stimulated by DPP-4 inhibitors through the increase in the body's GLP-1 concentration by inhibition of DPP-4.[4] GLP-1 receptor stimulation may lead to overgrowth of the cells that cover the smaller ducts, resulting in hyperplasia, an increase in pancreatic weight, duct occlusion, back pressure and ultimately acute or chronic pancreatic inflammation.[5–7] Pancreatitis is a serious condition, often leading to hospitalization, diminished quality of life and even death.[8] Furthermore, there is a spectrum of pancreatitis, often starting with one attack of pancreatitis, which leads to recurrent pancreatitis in some patients (±20%-30%) and progresses to chronic pancreatitis in others (±10%).[8,9]

Recent literature shows limited and conflicting evidence for an association between incretin-based therapy and risk of acute pancreatitis.[10] Spontaneous adverse event reporting systems have detected cases of pancreatitis in incretin users.[11] One observational study found that current use of sitagliptin or exenatide was significantly associated with risk of hospitalization for acute pancreatitis[12]; however, a systematic review and meta-analysis, including 9 studies, with >1.3 million individuals and an average follow-up of 0.7 to 1.4 years, found that incretin-based therapy did not increase the risk of pancreatitis.[13] Multiple observational studies have assessed the association between incretin-based therapy and pancreatitis.[14–17] Given the controversy, the European Medicines Agency and the US Food and Drug Administration have called for additional studies.[18–20]

Furthermore, in contrast to the risk of acute pancreatitis, the risk of chronic pancreatitis with incretin use has not been investigated in an observational setting. The aim of the present study, therefore, was to evaluate the association between incretin use and the risk of any, acute and chronic pancreatitis in a population-based cohort study.

2 | RESEARCH DESIGN AND METHODS

Data for this study were obtained from the UK Clinical Practice Research Datalink (CPRD; www.CPRD.com), previously known as the General Practice Research Database. The CPRD contains computerized medical records of 625 primary care practices in the UK, representing 6.9% of the population.[21] The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes since 1987. Previous studies using CPRD data have shown a high validity concerning wide ranges of diseases, including acute and chronic pancreatitis.[15,22,23]

We conducted a population-based cohort study, largely according to methods that have been described previously.[24] All patients aged ≥18 years at start of follow-up, with ≥1 NIAD prescription during the period of valid data collection, were included in the study population. The study period started on June 13, 2007 (date of first recorded prescription of an incretin in CPRD) and ended on August 31, 2012. The index date was defined as the date of first NIAD prescription after the practice had started to contribute data delivery to CPRD.

Each NIAD user was matched by sex, year of birth (within 5 years) and practice to one control patient who had never received prescriptions of NIADs or insulin during follow-up. The index date of each control patient was set to the index date of his/her matched NIAD user.

For NIAD users, follow-up time was divided into intervals based on their NIAD (and incretin) prescriptions; that is, for every prescription, a new interval was created. Exposure to an NIAD was defined as follows: after a washout period of 90 days, an interval was classified as "past NIAD use," until the end of follow-up or a new prescription of an antidiabetic drug, whichever came first. Otherwise an interval was classified as "current NIAD use." For control patients, the follow-up was divided into 90-day intervals. Each patient was followed from the index date up to the end of data collection, the date of transfer out of the practice area, the patient's death, or the earliest record of any, acute or chronic pancreatitis; that is, the outcome of interest, whichever came first.

NIAD users could move between current and past exposure over time. Current NIAD use was further stratified by the exposure status to incretin-based therapy and other non-incretin NIADs. Incretin use was further stratified by current GLP-1RA use and DPP-4 inhibitor use. Current, recent and past incretin use were defined as GLP-1RA/DPP-4 inhibitor use 0 to 90, 91 to 180 and >180 days prior to start of an interval, respectively. Patients could move between current, recent and past use. To evaluate the effect of cumulative exposure to incretin-based therapy, a duration of incretin use analysis was performed. Current use was stratified by the number of incretin prescriptions ever before (in the UK, a single incretin prescription is generally issued every 28 days in case of chronic use). The following incretin-based therapy was recorded in the CPRD and included in this study: exenatide and liraglutide (GLP-1RAs) and sitagliptin, vildagliptin, saxagliptin and linagliptin (DPP-4 inhibitors).

Any, acute and chronic pancreatitis were classified by the use of read codes that were reviewed by a gastroenterologist (Y.K.). The group "any pancreatitis" included read codes for acute and chronic pancreatitis, as well as read codes for pancreatitis not otherwise specified. For the outcome "any pancreatitis," all patients with a history of pancreatitis, either acute or chronic, were excluded. For acute pancreatitis, all patients with a history of acute pancreatitis were excluded, and for chronic pancreatitis, all patients with a history of chronic pancreatitis were excluded (Figure 1). For all studied outcomes, patients with polycystic ovaries or polycystic ovarian syndrome prior to start of follow-up were excluded because metformin may be used as a treatment for these conditions (Figure 1).

The presence of potential confounders was assessed by reviewing the computerized medical records for any evidence of these risk factors before the start of an interval. The following potential confounders were considered to be general risk factors and were determined at baseline: sex, body mass index (BMI), smoking status and alcohol use. Other confounders considered in the present study were determined time-dependently (ie, at the start of each new interval): age, gallstones/endoscopic retrograde cholangiopancreatography procedure or alcoholism.[25–28] Alcoholism was defined as history of specific drugs used to treat alcoholism or a diagnosis of alcoholism. In

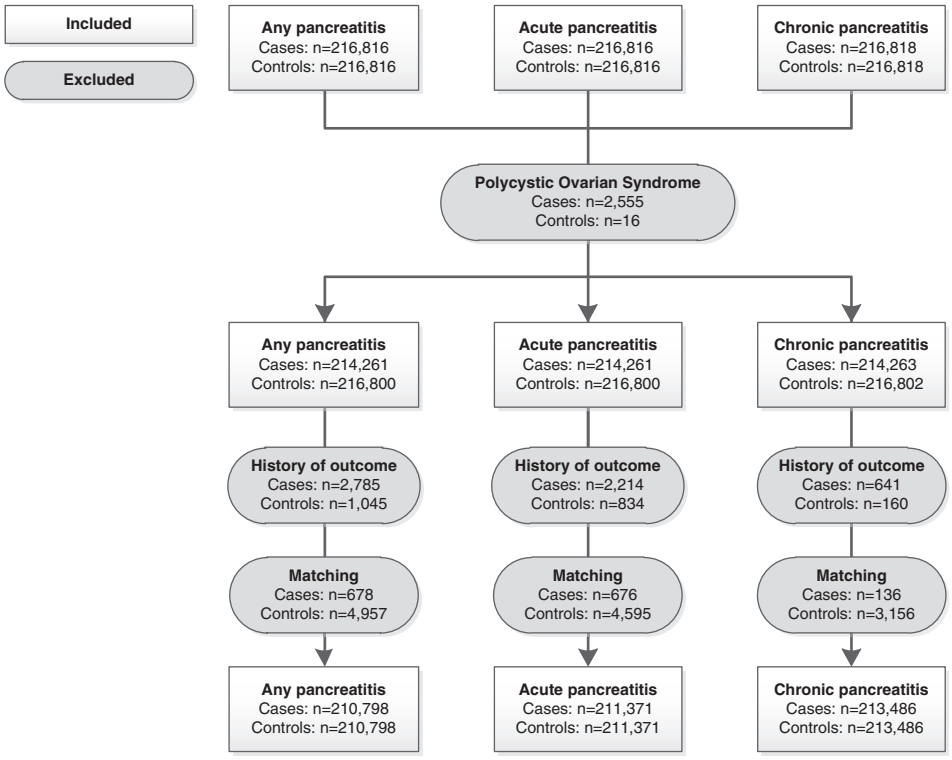

FIGURE 1 Study flow chart, stratified by study outcome.

addition, the following drug prescriptions 6 months prior to the start of an interval were considered to be potential confounders: paracetamol; antibiotics (co-trimoxazole/macrolides/tetracyclines); angiotensin-converting enzyme (ACE) inhibitors; loop diuretics; statins; proton pump inhibitors; and systemic glucocorticoids.[29–31] The following potential confounders for disease severity were considered time-dependently: a history of retinopathy; neuropathy; and the most recent glycated haemoglobin (HbA1c) value in the year preceding the start of an interval.[30–32]

We estimated the adjusted hazard ratio (HR) of any, acute and chronic pancreatitis among current NIAD users vs controls and among current incretin users vs other NIAD users using time-varying Cox proportional hazards regression (SAS 9.2, PHREG procedure). Potential confounders and indicators of disease severity were included in the final model if they independently changed the β coefficient for the exposure of interest by at least 5%, or when a consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature. A sensitivity analysis repeated the main analysis in a "new-user" design, in which only patients who had started NIADs after June 13, 2007 were included.[33] To be more detailed, we excluded every patient with a NIAD prescription before June 13, 2007, therefore, patients were only included in the new user design if their record was available in the database for ≥1 year and patients who were not receiving any NIADs in the period from 1987 to June 13, 2007. An additional sensitivity analysis was performed to exclude all controls with an HbA1c measurement >7% at baseline, because the HbA1c level might indicate that these controls are actually T2DM patients. Furthermore, an extra sensitivity analysis was performed to compare current incretin use with current thiazolidinedione (TZD) use because TZD users might also be an appropriate comparison group. We also performed an extra sensitivity analysis to investigate the association between current incretin use and chronic pancreatitis when all patients with a history of both acute and chronic pancreatitis were excluded.

This study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency database research by protocol number 14_036R5.

3 | RESULTS

3.1 | Study population

The study population for any pancreatitis consisted of 28 370 incretin users and 182 428 NIAD users, who were matched with 210 798 controls without diabetes (Figure 1). For acute pancreatitis we included 211 371 controls without diabetes and for chronic pancreatitis 213 486 controls (Figure 1). The mean duration of follow-up was 4.1 years for incretin users, 3.3 years for other NIAD users and 3.3 years for controls without diabetes. The mean duration of actual incretin use was 1.2 years. Among incretin users, 43.7% of all patients were women, and the mean age at index was 58.1 years. At baseline, the average age of incretin users was 4 years younger than users of other NIADs, and incretin users had a higher body mass index (BMI). The severity of the underlying diabetes mellitus was higher among incretin users compared with other NIAD users, as their most recently recorded mean HbA1c measurement in the past 12 months was 8.7% higher. Besides exposure to ACE inhibitors, statins or various antidiabetic drug classes, there were no remarkable

TABLE 1 Baseline characteristics of incretin users, other NIAD users and non-diabetic controls for the outcome any pancreatitis

Characteristic	Incretin users (N = 28 370)		Other NIAD users (N = 182 428)		Controls (N = 210 798)	
	n	%	n	%	n	%
Women	12 410	(43.7)	86 000	(47.1)	98 410	(46.7)
Mean (s.d.) duration of follow-up, years	4.05	(1.5)	3.3	(1.8)	3.3	(1.8)
Age						
Mean (s.d.) at index date, years	58.1	(11.8)	62.4	(14.9)	61.8	(14.6)
18–49 years	6746	(23.8)	35 585	(19.5)	42 331	(20.1)
50–59 years	8319	(29.3)	34 764	(19.1)	43 083	(20.4)
60–69 years	8359	(29.5)	47 650	(26.1)	56 009	(26.6)
>70 years	4946	(17.4)	64 429	(35.3)	69 375	(32.9)
BMI at index date						
Mean (s.d.) BMI at index date, kg/m^2	33.6	(7.1)	31.1	(6.5)	26.8	(5.1)
<25.0 kg/m^2	2180	(7.7)	26 648	(14.6)	72 236	(34.3)
25.0–29.9 kg/m^2	7243	(25.5)	59 489	(32.6)	74 047	(35.1)
30.0–34.9 kg/m^2	8462	(29.8)	50 309	(27.6)	29 927	(14.2)
≥35.0 kg/m^2	10 293	(36.3)	41 014	(22.5)	12 095	(5.7)
Missing	192	(0.7)	4968	(2.7)	22 493	(10.7)
Smoking status						
Never	13 897	(49.0)	90 786	(49.8)	110 907	(52.6)
Current	5935	(20.9)	35 823	(19.6)	43 821	(20.8)
Ex	8505	(30.0)	54 780	(30.0)	50 490	(24.0)
Missing	33	(0.1)	1039	(0.6)	5580	(2.6)
Alcohol use						
Yes	19 297	(28.6)	118 957	(29.0)	38 090	(18.1)
No	8107	(68.0)	52 935	(65.2)	148 979	(70.7)
Missing	966	(3.4)	10 536	(5.8)	23 729	(11.3)
Alcoholism	533	(1.9)	3961	(2.2)	4105	(1.9)
History of comorbidities						
Gallstones	1465	(5.2)	9031	(5.0)	6455	(3.1)
ERCP	162	(0.6)	1302	(0.7)	897	(0.4)
Retinopathy	3768	(13.3)	22 184	(12.2)	758	(0.4)
Neuropathy	2128	(7.5)	14 047	(7.7)	2492	(1.2)
Drug use within 6 months						
Metformin	15 099	(53.2)	67 087	(36.8)	n/a	
Sulphonylurea derivatives	8156	(28.7)	31 812	(17.4)	n/a	
Thiazolidinediones	5481	(19.3)	13 899	(7.6)	n/a	
Insulin	2219	(7.8)	19 283	(10.6)	n/a	
Paracetamol	7170	(25.3)	47 502	(26.0)	38 093	(18.1)
ACE inhibitors	10 826	(38.2)	64 848	(35.5)	30 733	(14.6)
Loop diuretics	2588	(9.1)	20 809	(11.4)	10 330	(4.9)
Statins	17 114	(60.3)	98 909	(54.2)	44 297	(21.0)
Proton pump inhibitors	5891	(20.8)	37 850	(20.7)	31 998	(15.2)
Systemic glucocorticoids	1086	(3.8)	9387	(5.1)	6791	(3.2)
HbA1c						
<6%	435	(1.5)	6490	(3.5)	2381	(1.1)
6%-6.9%	3345	(11.7)	26 968	(14.7)	2122	(1.0)
7%-7.9%	5623	(19.7)	32 869	(17.9)	438	(0.2)
8%-8.9%	3403	(11.9)	16 986	(9.3)	222	(0.1)
≥9%	5135	(18.0)	22 084	(12.0)	238	(0.1)
Missing	10 598	(37.1)	78 213	(42.6)	206 748	(97.5)

Values are n, (%) unless otherwise stated.

Abbreviations: ACE, angiotensin-converting-enzyme; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; HbA1c, glycosylated hemoglobin type A1C; NIAD, non-insulin antidiabetic drug; s.d., standard deviation.

differences in history of comorbidities with incretin users vs other NIAD users at baseline (Table 1).

3.2 | Incretin use and risk of pancreatitis compared with controls

Table 2 shows that as compared with control subjects without diabetes, current incretin users had a doubled risk of any pancreatitis (adjusted HR 2.01, 95% CI 1.42-2.83). The risk of developing acute pancreatitis was increased 1.6-fold (adjusted HR 1.60, 95% CI 1.09-2.35), while the risk of developing chronic pancreatitis was increased almost 6-fold (adjusted HR 5.82, 95% CI 2.77-12.23). DPP-4 inhibitor users had a higher risk of any pancreatitis than GLP-1RA users (adjusted HR 2.21, 95% CI 1.53-3.20 vs adjusted HR 1.23, 95% CI 0.62-2.43). Furthermore, we observed a 4.6-fold increased risk of any pancreatitis in the youngest age group (18-59 years). The elevated risks were partly explained by the underlying disease: patients with T2DM had a 1.4-fold increased risk of any pancreatitis as compared with controls without diabetes (adjusted HR 1.41, 95% CI 1.18-1.68).

3.3 | Incretin use and risk of pancreatitis compared with other NIAD use

To reduce confounding by indication, incretin users were compared with users of other NIADs (Table 3). Results showed a statistically significant 1.5-fold increased risk of any pancreatitis among current incretin users (HR 1.47, 95% CI 1.06-2.04), while no statistically significant association was found for the acute and chronic pancreatitis group (HR 1.42, 95% CI 0.98-2.06 and HR 0.87, 95% CI 0.45-1.69, respectively). The statistical adjustment for proxy indicators of disease severity and general risk factors did not substantially change the associations (Table S2). Similar to the results in Table 2, the risk of pancreatitis was higher among younger patients (age 18-59 years), those with a BMI <25 kg/m^2, or DPP-4 inhibitor users compared with other NIAD users. No trend was observed in the duration-of-use analysis regarding the risk of pancreatitis.

3.4 | Sensitivity analysis

Table 4 shows a sensitivity analysis with a new-user design, in which the cohort was restricted to starters of NIADs (including patients using incretin-based therapy). A statistically significant 2-fold risk of any pancreatitis was found in current incretin users vs other NIAD users (adjusted HR 2.12, 95% CI 1.31-3.43). This was mainly explained by the risk of acute pancreatitis (adjusted HR 1.96, 95% CI 1.13-3.41). The risk of acute and any pancreatitis was highest in patients who had been prescribed up to 150 to 270 days of incretin-based therapy (5-9 prescriptions), whereas there was no significant elevated risk with short (<5 prescriptions) and long-term use (≥10 prescriptions). In the extra sensitivity analysis in which controls with an HbA1c >7% at baseline were excluded, we found that current incretin use was still associated with any pancreatitis (adjusted HR 2.01, 95% CI 1.42-2.83). In the extra sensitivity analysis in which TZD users were used as a comparison group for the incretin users, we found that current incretin use was still associated with any pancreatitis (adjusted HR 1.59, 95% CI 1.05-2.41). In the sensitivity analysis in which all patients with a history of both acute and chronic pancreatitis were excluded, we found that current incretin use was still associated with chronic pancreatitis (adjusted HR 4.73, 95% CI 2.97-7.54).

4 | DISCUSSION

The present study found a 1.5-fold statistically significant increased risk of any pancreatitis with current use of incretin-based therapy vs other NIAD use. The risk of acute pancreatitis was 1.4-fold greater in current incretin users vs other NIAD users, but this did not reach statistical significance. Furthermore, we were not able to detect an association between chronic pancreatitis and incretin use, but numbers in this subgroup were small. Interestingly, the increased risk of acute pancreatitis remained statistically significant in current users of DDP-4 inhibitors only, suggesting that differences in the pharmacodynamic properties of these agents are important for the incretin–pancreatitis link.

The present results are not consistent with the results of the studies by Elashoff et al.[3], Singh et al.[12] and Roshanov and Dennis[34] regarding the risk of acute pancreatitis with incretin use. In a case–control study, Singh et al.[12] found that current use of sitagliptin or exenatide 30 days before the study outcome vs non-use was significantly associated with hospitalization for acute pancreatitis (odds ratio 2.24, 95% CI 1.36-3.68). Elashoff et al.[3] showed that pancreatitis was significantly more often reported among patients treated with sitagliptin or exenatide as compared with users of other antidiabetic therapies; however, that study only provided hypothesis-generating evidence as it was based on data from the US Food and Drug Administration's spontaneous adverse event reporting system. The meta-analysis of large randomized clinical trials by Roshanov and Dennis[34] found an 82% increase in the odds ratio of acute pancreatitis with the use of incretin-based therapy as compared with usual care (95% CI 1.17-2.82).

Several previous studies have shown results consistent with the present findings regarding the risk of acute pancreatitis with incretin use, identifying no statistically significant increased risk of acute pancreatitis for incretin use.[13–15] A meta-analysis of 6 cohort and 2 case–control studies found no effect on the occurrence of acute pancreatitis (odds ratio 1.03, 95% CI 0.87-1.20).[13] That meta-analysis included a previous CPRD cohort study by Faillie et al., finding no effect on acute pancreatitis occurrence.[15] Furthermore, a large cohort study (n = 1 532 513, mean follow-up 2.3 years) which included data from the CPRD did not find an association between current use of incretin-based drugs and acute pancreatitis.[35] A large systematic review and meta-analysis of randomized and non-randomized studies did not suggest an increased risk of acute pancreatitis with the use of incretin-based therapy.[14] In both the SAVOR (n = 16 492, median follow-up 2.1 years) and EXAMINE (n = 5380, median follow-up 18 months) cardiovascular outcome trials the cases of acute and chronic pancreatitis were similar in the saxagliptin and alogliptin arms as compared with the comparator agent arm.[36,37] The results of observational studies regarding the risk of pancreatitis remain

TABLE 2 Risk of pancreatitis in incretin users compared with controls, stratified by age, sex and type of NIAD

	Any pancreatitis			Acute pancreatitis			Chronic pancreatitis		
	Events (n = 797)	IR, per 1000 person-years	Fully adjusted HR[1] (95% CI)	Events (n = 640)	IR, per 1000 person-years	Fully adjusted HR[1] (95% CI)	Events (n = 196)	IR, per 1000 person-years	Fully adjusted HR[1] (95% CI)
NIAD exposure									
No NIAD use	287	0.40	Reference	246	0.34	Reference	36	0.05	Reference
Past NIAD use	37	0.35	0.88 (0.62-1.25)	25	0.23	0.64 (0.42-0.97)	17	0.16	4.59 (2.55-8.28)
Current NIAD use	473	0.78	1.44 (1.21-1.72)	369	0.61	1.21 (1.00-1.47)	143	0.23	5.06 (3.37-7.61)
Type of NIAD									
Non-incretin	422	0.76	1.41 (1.18-1.68)	329	0.59	1.19 (0.98-1.45)	130	0.23	5.00 (3.32-7.54)
Any incretin	51	1.02	1.88 (1.36-2.61)	40	0.80	1.52 (1.06-2.19)	13	0.26	5.94 (3.01-11.73)
Incretin recency									
Past	-[2]	0.58	0.99 (0.37-2.69)	-[2]	0.29	0.51 (0.13-2.08)	-[2]	0.43	6.39 (1.92-21.32)
Recent	-[2]	1.49	2.59 (0.83-8.15)	-[2]	1.98	3.56 (1.31-9.67)	-[3]	-[3]	-[3]
Current	44	1.07	2.01 (1.42-2.83)	34	0.83	1.60 (1.09-2.35)	10	0.24	5.82 (2.77-12.23)
Type of incretin									
Current GLP-1RA	9	0.81	1.23 (0.62-2.43)	8	0.72	1.25 (0.60-2.58)	-[2]	0.09	2.56 (0.34-19.20)
Current DPP-4 inhibitor	35	1.19	2.21 (1.53-3.20)	26	0.88	1.78 (1.16-2.72)	9	0.30	6.96 (3.24-14.95)
Sex[4]									
Men	26	1.11	2.06 (1.31-3.22)	19	0.81	1.49 (0.89-2.50)	6	0.25	6.14 (2.36-15.97)
Women	18	1.03	1.96 (1.15-3.33)	15	0.85	1.76 (0.98-3.15)	-[2]	0.22	5.26 (1.62-17.11)
Age[5]									
18-49 years	10	1.49	4.58 (1.95-10.75)	7	1.04	2.84 (1.07-7.59)	-[2]	0.44	14.34 (3.08-66.74)
50-59 years	14	1.26	5.55 (2.70-11.42)	13	1.17	5.34 (2.45-11.65)	-[2]	0.09	2.28 (0.26-20.02)
60-69 years	11	0.83	1.07 (0.55-2.11)	8	0.59	0.89 (0.41-1.94)	-[2]	0.22	2.60 (0.67-10.14)
≥70 years	9	0.93	1.37 (0.68-2.75)	6	0.62	0.92 (0.40-2.13)	-[2]	0.31	9.41 (2.51-35.20)

Abbreviations: adj. adjusted; CI, confidence interval; DPP-4I, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; NIAD, non-insulin antidiabetic drug.

[1] Adjusted for age, gender, BMI, smoking status, alcohol use, history of alcoholism, neuropathy, retinopathy, gallstones/endoscopic retrograde cholangiopancreatography procedure and the use of ACE inhibitors, loop diuretics or proton pump inhibitors in the previous 6 months.

[2] Number of events in the group was <5.

[3] No estimation of IR or HR possible because there were zero events in group

[4] Compared with controls of the same gender.

[5] Compared with controls in the same age category.

TABLE 3 Risk of pancreatitis in incretin users compared with other NIAD users

	Any pancreatitis			Acute pancreatitis			Chronic pancreatitis		
	Events (n = 510)	IR, per 1000 person-years	Fully adjusted HR[1] (95% CI)	Events (n = 394)	IR, per 1000 person-years	Fully adjusted HR[2] (95% CI)	Events (n = 160)	IR, per 1000 person-years	Fully adjusted HR[3] (95% CI)
NIAD exposure									
Current NIAD use	422	0.76	Reference	329	0.59	Reference	130	0.23	Reference
Past NIAD use	37	0.35	0.50 (0.34-0.73)	25	0.26	0.44 (0.29-0.50)	17	0.16	0.65 (0.37-1.13)
Any incretin	51	1.02	1.35 (0.99-1.85)	40	0.26	1.36 (0.96-1.93)	13	0.26	0.90 (0.50-1.64)
Incretin recency									
Past	-[4]	0.58	0.67 (0.25-1.80)	-[4]	0.29	0.47 (0.12-1.89)	-[4]	0.43	1.04 (0.33-3.33)
Recent	-[4]	1.49	1.74 (0.55-5.47)	-[4]	1.98	3.23 (1.19-8.73)	-[5]	-[5]	-[5]
Current	44	1.07	1.47 (1.06-2.04)	34	0.83	1.42 (0.98-2.06)	10	0.24	0.87 (0.45-1.69)
Type of incretin									
Current GLP-1RA	9	0.81	1.08 (0.56-2.10)	8	0.72	1.11 (0.54-2.26)	-[4]	0.09	0.29 (0.04-2.12)
Current DPP-4 inhibitor	35	1.19	1.68 (1.18-2.39)	26	0.88	1.59 (1.05-2.40)	9	0.30	1.14 (0.57-2.28)
Sex[6]									
Men	26	1.11	1.42 (0.93-2.19)	19	0.81	1.32 (0.81-2.17)	6	0.25	0.81 (0.35-1.91)
Women	18	1.02	1.56 (0.93-2.60)	15	0.85	1.56 (0.89-2.74)	-[4]	0.22	0.97 (0.34-2.78)
Age[7]									
18-49 years	10	1.49	2.86 (1.36-6.02)	7	1.04	2.53 (1.07-5.99)	-[4]	0.44	1.69 (0.49-5.88)
50-59 years	14	1.26	2.12 (1.13-3.97)	13	1.17	2.41 (1.25-4.65)	-[4]	0.09	0.22 (0.03-1.65)
60-69 years	11	0.81	1.03 (0.54-1.97)	8	0.59	0.95 (0.45-2.01)	-[4]	0.22	0.92 (0.27-3.17)
≥70 years	9	0.93	1.05 (0.52-2.09)	6	0.62	0.92 (0.40-2.12)	-[4]	0.31	1.36 (0.41-4.53)
BMI									
<25 kg/m^2	7	2.58	3.65 (1.71-7.77)	-[4]	1.46	2.71 (0.97-7.58)	5	1.82	6.08 (2.45-15.08)
25-30 kg/m^2	5	0.5	0.72 (0.29-1.74)	-[4]	0.30	0.63 (0.20-1.98)	-[4]	0.20	0.63 (0.16-2.59)
30-35 kg/m^2	12	0.96	1.32 (0.73-2.36)	11	0.88	1.55 (0.82-2.91)	-[4]	0.11	0.32 (0.19-0.52)
≥35.0 kg/m^2	20	1.27	1.70 (1.07-2.69)	16	1.02	1.53 (0.89-2.63)	-[5]	-[5]	-[5]
Number of prescriptions									
0-6	21	1.30	1.75 (1.12-2.74)	17	1.05	1.84 (1.11-3.03)	-[4]	0.25	0.84 (0.31-2.29)
7-12	7	0.67	0.92 (0.43-1.95)	6	0.57	0.99 (0.44-2.23)	-[4]	0.19	0.71 (0.17-2.88)
≥13	16	1.11	1.50 (0.90-2.50)	11	0.76	1.27 (0.69-2.36)	-[4]	0.27	1.03 (0.37-2.83)

Abbreviations: adj. adjusted; CI, confidence interval; DPP-4I: dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HR, hazard ratio; IR, incidence rate; NIAD, non-insulin antidiabetic drug.

[1] Adjusted for age, gender, HbA1c, BMI, smoking status, alcohol use, history of alcoholism, neuropathy, retinopathy, gallstones/endoscopic retrograde cholangiopancreatography procedure and the use of ACE inhibitors, loop diuretics or proton pump inhibitors in the previous 6 months.

[2] Adjusted for age, gender, HbA1c, BMI, smoking status, alcohol use, history of alcoholism, retinopathy, neuropathy, gallstones/endoscopic retrograde cholangiopancreatography procedure, and the use of proton pump inhibitors in the previous 6 months.

[3] Adjusted for age, gender, HbA1c, alcohol use, history of alcoholism and the use of ACE inhibitors or loop diuretics in the previous 6 months.

[4] Number of events in the group was <5.

[5] No estimation of IR or HR possible because there were zero events in group.

[6] Compared with controls of the same gender.

[7] Compared with controls in the same age category.

TABLE 4 Risk of pancreatitis in incretin users compared with other NIAD users, by type of pancreatitis, new user design (sensitivity analysis)

	Any pancreatitis			Acute pancreatitis			Chronic pancreatitis		
	Events (n = 186)	IR, per 1000 person-years	Fully adjusted HR[1] (95% CI)	Events (n = 143)	IR, per 1000 person-years	Fully adjusted HR[2] (95% CI)	Events (n = 60)	IR	Fully adjusted HR[3] (95% CI)
NIAD exposure									
Current NIAD use	151	0.73	Reference	118	0.57	Reference	47	0.23	Reference
Past NIAD use	13	0.43	0.73 (0.41-1.30)	8	0.26	0.58 (0.28-1.20)	8	0.26	1.13 (0.52-2.43)
Any incretin	22	1.26	1.96 (1.23-3.13)	17	0.97	1.87 (1.11-3.17)	5	0.28	1.32 (0.52-3.37)
Incretin recency									
Past	-[4]	0.51	0.75 (0.10-5.37)	-[4]	0.51	0.93 (0.13-6.70)	-[4]	0.38	1.75 (0.24-12.82)
Recent	-[4]	1.53	2.25 (0.31-16.16)	-[4]	1.52	2.75 (0.38-19.78)	-[5]	-[5]	-[5]
Current	20	1.34	2.12 (1.31-3.43)	15	1.00	1.96 (1.13-3.41)	-[4]	0.27	1.24 (0.44-3.50)
Number of prescriptions									
<5	6	1.25	2.15 (0.94-4.93)	-[4]	0.83	1.96 (0.71-5.39)	-[5]	-[5]	-[5]
5-9	7	1.71	3.06 (1.41-6.61)	6	1.46	3.44 (1.49-7.93)	-[5]	-[5]	-[5]
≥10	7	1.17	2.11 (0.97-4.58)	5	0.83	1.97 (0.79-4.92)	-[5]	-[5]	-[5]

Abbreviations: adj. adjusted; CI, confidence interval; HR, hazard ratio; IR, incidence rate; NIAD, non-insulin antidiabetic drug.

[1] Adjusted for age, gender, alcohol use, history of alcoholism, neuropathy, retinopathy, smoking status, gallstones/endoscopic retrograde cholangiopancreatography procedure, and the use of ACE-inhibitors, loop diuretics, paracetamol, systemic glucocorticoids or proton pump inhibitors in the previous 6 months.

[2] Adjusted for age, gender, alcohol use, history of alcoholism, smoking status, gallstones/endoscopic retrograde cholangiopancreatography procedure, and the use of ACE-inhibitors and loop diuretics or proton pump inhibitors in the previous 6 months.

[3] Adjusted for age, gender, alcohol use and history of alcoholism.

[4] Number of events in the group was <5.

[5] No estimation of IR or HR possible because there were zero events in group.

conflicting. We therefore advise regulatory agencies to consider using observational studies to learn about the methodological factors that influence the aetiology of pancreatitis risk in people with T2DM using incretin-based therapy, rather than confirming whether an association is truly present.[38]

The evidence regarding chronic pancreatitis is scarce and mainly based on *in vitro* and animal studies.[39–41] Other studies that did find cases of chronic pancreatitis in users of incretin-based therapy were most often post-marketing reports or reports in patients with T2DM aged ≥40 years with a history of a cardiovascular disease.[42] We are the first to report on the risk of chronic pancreatitis in an observational setting, finding no indication that patients with T2DM using incretin-based therapy were more prone to develop chronic pancreatitis. The results should be interpreted with caution, because the number of cases was small and follow-up time might have been too short; most acute pancreatitis events in randomized controlled trials occurred between 6 and 24 months after treatment initiation.[10] Furthermore, we were not able to confirm data from the literature showing a higher risk of chronic pancreatitis among men.[9] It is important to note that chronic pancreatitis is a serious disease, causing significant morbidity and mortality. Two to three decades after diagnosis of chronic pancreatitis, there is a mortality rate of 50%, and thus such patients have shorter survival times than the average population.[8] We have only started to learn about the association between incretin use and chronic pancreatitis, and hope future studies will investigate this in more detail.

In contrast to the study by Li et al., but consistent with the study by Roshanov and Dennis, we found that DPP-4 inhibitor users had a higher risk of any pancreatitis compared with GLP-1RA users.[14,34] There are key pharmacological differences between DPP-4 inhibitors and GLP-1RAs, such as the effect on HbA1c reduction (−0.6% to −1.9% for GLP-1RAs vs −0.5% to −0.8% for DPP-4 inhibitors) and body weight (reduced for GLP-1RA but neutral for DPP-4 inhibitors).[43] Clinical data suggest that GLP-1RAs improve β-cell function, whereas the effects of DPP-4 inhibitors are less clear.[43] The different effects on β-cell function might contribute to the difference in risk of pancreatitis, but this is very speculative and more studies are needed to investigate this further.

The potential biological mechanisms of incretin agents promoting or enhancing pancreatitis are supported by limited indirect evidence. In animal models, three GLP-1-induced pathways have been proposed; proliferation in b-cells, inhibition of b-cells, and enhanced differentiation of adult stem cells in the ductal pancreatic epithelium. This could lead to chronic pancreatic damage, inflammation of pancreatic acinar and ductal cells, increased formation of dysplastic pancreatic intraepithelial neoplasia (PanIN) lesions and an increase in pancreatic weight.[3,5–7,12,15,19,20,44,45] Furthermore, duct cell proliferation and PanIN lesions might lead to duct occlusion, which could cause back pressure in the pancreas, stressing the acinar cells to release digestive enzymes with the resulting chronic pancreatitis fostering further development of PanINs and duct cell proliferation.[7,41] By activating both above-mentioned pathways, incretin agents could promote acute pancreatitis and chronic pancreatitis.[7,41] Additionally, it was hypothesized that an incretin-based therapy-induced pancreatitis would mostly occur soon after initiating treatment with these agents (<5 prescriptions); however, based on the duration-of-use analysis it is also possible that a delayed onset of pancreatitis is induced by incretin-based therapy through underlying (cumulative) pathophysiological mechanisms, such as duct cell proliferation leading to inflammation. In the duration-of-use analysis of the prevalent cohort, pancreatitis risk was highest in patients who had been prescribed <7 prescriptions, while in the incident analysis pancreatitis risk was highest in patients who had been prescribed up to 5 to 9 months of incretin-based therapy.[46] The information provided from the duration-of-use analysis should be interpreted with caution because of the small number of events.

It is important to note several limitations of this observational study. True causality cannot be provided. Furthermore, it is likely that our observed associations are not without residual confounding and there might also be residual confounding as a result of adjustment for imperfect variables, such as the missing variables. Residual confounding might also be present because incretin-based therapy is less likely to be prescribed to patients with T2DM who consume alcohol, smoke or have a lower socio-economic status. This could have led to an underestimation in the results; however, it can also be proposed that incretin-based therapy is more likely to be prescribed to alcoholics with T2DM. It is known that alcoholics are more likely to experience hypoglycaemia, causing physicians to be more likely, in turn, to prescribe incretin agents rather than sulphonylurea derivatives. This could have led to overestimation in the results. Moreover, we were not able to correct for the amount of physical exercise. Hypertriglyceridemia, which is indirectly related to a lack of physical exercise, appears to increase the risk of pancreatitis, especially among overweight people.[47] Incretin users might be less physically active than non-incretin users, which could lead to an overestimation of our effect. Also, incretin-based therapy may be prescribed earlier to people with a higher BMI because of the promotion of weight loss and to people with a history of a cardiovascular disease because of the cardiovascular benefits of such therapy.[2] Furthermore, diagnostic bias may have influenced the results. As a result of early warnings of the possible side effects of incretin-based therapy by regulatory agencies, diabetes specialists are likely to have been vigilant for the occurrence of pancreatitis when first prescribing incretin-based therapy. This could have led to overestimation in the results. Lastly, the read codes used in this study for acute, chronic and any pancreatitis have not been validated, therefore, there might be some misclassification. We expect the misclassification to be non-differential, resulting in an underestimation of the relationship between incretin-based therapy and pancreatitis, which might have led to restricted statistical power.

The present study also has a number of strengths. We were able to adjust statistically for several potentially important confounders, including age, HbA1c, alcoholism and drug use. Also, we were able to show the effect of confounding by indication on the risk of pancreatitis. Furthermore, CPRD data are collected prospectively, eliminating the risk of recall bias. In addition, this study gives the first insights into the risk of chronic pancreatitis in users of incretin-based therapy.

In conclusion, in this first study to report on all types of pancreatitis, it was found that incretin use was associated with an increased risk of any type of pancreatitis, but not with acute or chronic pancreatitis in patients with T2DM; however, the risk of any and acute

pancreatitis was higher among users of DPP-4 inhibitors and incident incretin users. Observational studies that assessed the risk of pancreatitis in incretin-based therapy had conflicting results. The complex relationship, methodological challenges and relatively small numbers of exposed patients in published research suggest that we should probably learn more about the methodological factors that influence the aetiology of incretin-induced pancreatitis, rather than to confirm whether an association is truly present.[38]

Conflict of interest

The Division of Pharmacoepidemiology and Clinical Pharmacology, of which F. V., M. B., J. D. and R. J. are employees, has received unrestricted funding from the Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), and the private–public funded Top Institute Pharma (www.tipharma.nl), and co-funding from universities, government and industry, the European Union Innovative Medicines Initiative (IMI), the European Union 7th Framework Program (FP7), and the Dutch Ministry of Health and Industry (including GlaxoSmithKline, Pfizer, and others).

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Author contributions

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

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