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ORIGINAL ARTICLE

Use of incretin agents and risk of pancreatic cancer: a population-based cohort study

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Aim: To investigate the association between the use of incretin agents and the risk of pancreatic cancer.
Methods: A retrospective population-based cohort study, using data from the Clinical Practice Research Datalink, 2007–2012, was conducted. Patients (n = 182 428) with at least one non-insulin antidiabetic drug (NIAD) prescription and aged ≥18 years during data collection, were matched one-to-one to control patients without diabetes. Multivariable Cox proportional hazards models and a new user design were used to estimate the hazard ratio (HR) of pancreatic cancer in incretin users (n = 28 370) compared with control subjects without diabetes and other NIAD-treated patients. Time-dependent adjustments were made for age, sex, lifestyle, comorbidities and drug use.
Results: The mean duration of follow-up was 4.1 years for incretin users. Current NIAD use was associated with a fourfold increased risk of pancreatic cancer [HR 4.28, 95% confidence interval (CI) 3.49–5.24]. This risk was almost doubled among current incretin users as compared with control subjects. Incretin use was not associated with pancreatic cancer when compared with control subjects with diabetes (HR 1.36, 95% CI 0.94–1.96); however, the 'new user' design did show an association between incretin use and pancreatic cancer when compared with control subjects with diabetes. In both cohorts with prevalent and incident users of antidiabetic drugs, the risk of pancreatic cancer almost doubled in those who had recently initiated incretin therapy (up to seven prescriptions), whereas this elevated risk dropped to baseline levels with prolonged use.
Conclusions: We found that incretin use was not associated with pancreatic cancer after adjustment for the severity of the underlying Type 2 Diabetes Mellitus (T2DM). The elevated risk of pancreatic cancer in those recently initiating incretin agents is likely to be caused by protopathic bias or other types of unknown distortion. The presence of considerable confounding by disease severity and the lack of a duration-of-use relationship do not support a causal explanation for the association between incretin agents and pancreatic cancer.
Keywords: cohort studies, dipeptidyl-peptidase-4 inhibitors, glucagon-like peptide 1, incretins, pancreatic cancer, type 2 diabetes mellitus

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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 a non-insulin antidiabetic drug (NIAD) or insulin [1]. Incretin agents [glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as exenatide or liraglutide, and dipeptidyl peptidase-4 (DPP-4) inhibitors, such as saxagliptin or sitagliptin] are new therapeutic agents for the treatment of T2DM. Incretin agents have a sustained antihyperglycaemic effect, while promoting weight loss with a minimal risk of hypoglycaemia [2]; however, evidence has arisen that pancreatic cancer is an important potential side effect of incretin agents [2]. Spontaneous Adverse Event Reporting systems have detected cases of pancreatitis in users of incretin agents [3]. Moreover, animal models showed that incretin agents can lead to alterations associated with pancreatic cancer, such as inflammation, chronic pancreatic damage, inhibition of apoptosis and proliferation in β-cells, proliferation of pancreatic acinar and ductal cells and increased pancreatic mass [2,4–10]. A post mortem clinical study showed an average 40% increase in pancreas mass in American organ donors who had been treated with incretins versus other antidiabetic drugs [10]; however, randomized controlled trials (RCT) and a meta-analysis of RCTs (n = 29 598, follow-up 0.23–2.1 years) did not show an increased risk of pancreatic cancer [11–13]. Furthermore, no association between the use of incretin agents and pancreatic cancer was found in a large observational cohort study [DPP-4 inhibitor and thiazolidinedione treatment cohort, n = 29 366; DPP-4 inhibitor and sulphonylurea derivative treatment cohort, n = 18 179; follow-up period 5–18 months] [14]. These RCTs were restricted, however, to patients with cardiovascular disease or the elderly, whereas incretins are also used by other groups of patients [15].

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Most studies did not evaluate the association between pancreatic cancer and GLP-1RAs or the widely prescribed DPP-4 inhibitors vildagliptin and linagliptin. Moreover, the results were not stratified according to the duration of drug use which could shed more light on the plausibility of the underlying aetiology [11–13]. The aim of the present study, therefore, was to assess the risk of pancreatic cancer in patients with T2DM who were using incretin agents (GLP-1RAs and DPP-4 inhibitors) compared with patients with T2DM using other NIADs and with population-based control subjects without diabetes mellitus.

Materials and Methods

Data for this study were obtained from the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), previously known as the General Practice Research Database (http://www.CPRD.com). The CPRD contains computerized medical records of 625 primary care practices in the UK, representing 8% of the population. 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 with regard to a wide range of diseases. Moreover, CPRD data have previously been used to study a wide range of malignancies, including pancreatic cancer [16–18].

We conducted a retrospective population-based cohort study largely according to methods that have been described previously [15]. All patients aged ≥18 years at start of follow-up, with at least one NIAD prescription during the period of valid CPRD data collection were included in the study population. The study period started on 13 June 2007 (the date of the first recorded prescription of an incretin agent in the CPRD) and ended on 31 August 2012. The index date was defined as the date of the first NIAD prescription after the practice 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 subject who never received a NIAD or insulin prescription during follow-up. The index date of each control subject was set to the index date of his or her matched NIAD user. Their period of follow-up was divided into 90-day intervals. Each subject was then followed from his or her index date up to the end of data collection, the date of transfer out of the practice area, or the subject's death, or the earliest record of pancreatic cancer, i.e. the outcome of interest, whichever came first.

Follow-up time was divided into intervals based on the NIAD and incretin prescriptions, i.e. for every prescription a new interval was created. Exposure of NIAD users 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'.

The NIAD users could move between current and previous exposure over time. Current NIAD users were further stratified by their exposure status to incretin agents 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 0–90, 91–180 and >180 days before the start of an interval, respectively. Recent and past users became current users again with a new GLP-1RA/DPP-4 inhibitor prescription. To evaluate duration of incretin use, current users were 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).

Each patient was followed until the first event of pancreatic cancer, which was classified by the use of read codes that were reviewed by a gastroenterologist (Y.K.). Operational definitions are shown in Table 1. All patients with a history of pancreatic cancer were excluded as well as patients with polycystic ovaries or polycystic ovarian syndrome before the start of follow-up because metformin may be used as a treatment for these conditions.

Table 1. Identification of pancreatic cancer by read codes.

Medcode	Clinical events	Readcode	Readterm
8166	12 138	B170.00	Malignant neoplasm of pancreas
16931	1821	B80Z000	Carcinoma *in situ* of pancreas
8771	853	B170.00	Malignant neoplasm of head of pancreas
34388	884	B17Z.00	Malignant neoplasm of pancreas NOS
35535	95	B173.00	Malignant neoplasm of pancreatic duct
35795	6	B174.00	Malignant neoplasm of Islets of Langerhans
39870	90	B172.00	Malignant neoplasm of tail of pancreas
40810	97	B171.00	Malignant neoplasm of body of pancreas
48537	6	B17Y.00	Malignant neoplasm of other specific sites of pancreas
49629	7	BB5C100	[M] Gastrinoma, malignant
61764	6	BB5Y100	[M] Vipoma
63102	6	BB5B100	[M] Islet cell carcinoma
95783	9	B17YZ00	Malignant neoplasm of specified site of pancreas NOS
96635	2	B17Y000	Malignant neoplasm of ectopic pancreatic tissue
97875	1	B175.00	Malignant neoplasm, overlapping lesion of pancreas
98825	2	BB5B600	[M] Mixed islet cell and exocrine adenocarcinoma

NOS, not otherwise specified.

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 as general risk factors and were determined at baseline: sex, body mass index (BMI), smoking status and alcohol use. Other confounders considered in this study were determined time-dependently (i.e. at the start of each new interval): age [19], gallstones/endoscopic retrograde cholangiopancreatography procedure (ERCP) [20,21] or alcoholism [19,22]. Alcoholism was defined as history of specific drugs used to treat alcoholism or a diagnosis of alcoholism. In addition, the following drug prescriptions 6 months before the start of an interval were considered to be potential confounders: paracetamol [23]; antibiotics (co-trimoxazole/macrolides/tetracyclines) [24,25]; angiotensin-converting enzyme (ACE) inhibitors [24,25]; loop diuretics [24,25]; statins [24,25]; proton pump inhibitors [24,25]; or systemic glucocorticoids [23,25]. The following potential confounders for disease severity were considered time-dependently: a history of retinopathy and neuropathy [23,25,26] and the most recent glycated haemoglobin (HbA1c) value in the year preceding the start of an interval.

We estimated the adjusted hazard ratio (HR) of pancreatic cancer among current NIAD users versus controls and among current incretin users versus 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 literature. A sensitivity analysis repeated the main analysis in a 'new user' design [27]. Only patients who had started NIADs after 13 June 2007 were included. An extra sensitivity analysis was performed in order to exclude all women with a record of gestational diabetes during follow-up, as metformin may be used as a treatment for this condition. Furthermore, an extra sensitivity analysis was performed adjusting the main analysis for insulin use as well as a sensitivity analysis for history of pancreatitis, and use of calcium channnel blockers and angiotensin receptor blockers in the previous 6 months.

Results

The study population consisted of 28 370 incretin users and 182 428 NIAD users, who were matched with 210 798 control subjects without diabetes. 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 control subjects. The mean duration of incretin use was 1.18 years. Of the incretin users, 43.7% were female and their mean age at index date was 58.1 years. At baseline, the mean age of incretin users was 4 years younger than users of other NIADs, and they had a higher mean 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 preceding 12 months was 8.7% higher. With the exception of exposure to ACE inhibitors, statins or various antidiabetic drugs classes, there were no notable differences in history of comorbidities with incretin users versus other NIAD users at baseline (Table 2).

Table 3 shows that current NIAD users had a fourfold higher risk of pancreatic cancer as compared with control subjects without diabetes (fully adjusted HR 4.28; 95% CI 3.49–5.24). This association almost doubled when the subgroup of current incretin users was compared with control subjects without diabetes (fully adjusted HR 7.52; 95% CI 5.09–11.12). There was no difference between current use of GLP-1RAs or DPP-4 inhibitors and the risk of pancreatic cancer.

To adjust for confounding by indication, current incretin users were compared with other NIAD users. Results show a 1.7-fold increased risk of pancreatic cancer among current incretin users. This association decreased after adjustment for disease severity, yielding a fully adjusted HR of 1.27 (95% CI 0.88–1.83). Additional statistical adjustment for general risk factors did not substantially change this result (adjusted HR 1.36; 95% CI 0.94–1.96). The prolonged use of incretin agents did not further increase the risk of pancreatic cancer. Incretin users who had recently started taking the drugs (4–7 prescriptions) had an almost twofold higher risk (adjusted HR 1.86; 95% CI 1.01–3.42), whereas this elevated risk dropped to baseline levels with prolonged use [adjusted HR 0.95; 95% CI 0.53–1.72] (Table 4).

Table 5 shows the sensitivity analysis with a 'new user' design, in which the cohort was restricted to starters of NIADs (including incretins). A statistically significant 1.7-fold increased risk for pancreatic cancer was found in current incretin users (HR 1.67; 95% CI 1.01–2.77) versus other NIAD users. Similar to the results in Table 4, this risk was more than twice as high among patients who had been prescribed up to 60 days of incretins (two prescriptions), whereas the risk dropped to baseline levels with long-term use (8 months, measured as prescriptions, exposure or more). In the extra sensitivity analysis in which women with gestational diabetes were excluded, we found that current incretin use was not associated with pancreatic cancer (adjusted HR 1.36; 95% CI 0.94–1.96). Furthermore, the main results of the extra sensitivity analysis showed that incretin use (adjusted HR 1.44; 95% CI 0.99–2.09) as well as use of calcium channel blockers and angiotensin receptor blockers in the previous 6 months (adjusted HR 1.37; 95% CI 0.95–1.98) were not associated with pancreatic cancer.

Discussion

The present study found an 1.7-fold increased risk of pancreatic cancer with incretin use which disappeared after statistical adjustments for the severity of the underlying T2DM. In recent starters of incretin agents, the risk of pancreatic cancer was almost doubled and dropped to baseline levels with prolonged use. The presence of considerable confounding by disease severity and the lack of a duration of use relationship in our results do not support a causal relationship between incretin use and pancreatic cancer.

Our results are not consistent with the study by Elashoff et al. [28,29]. This study showed that pancreatic cancer was

Table 2. Baseline characteristics of incretin users, other non-insulin antidiabetic drug users and control subjects.

Characteristic	Incretin users (n = 28 370)		Other NIAD users (n = 182 428)		Control subjects (n = 210 798)	
	n	%	n	%	n	%
Females	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
Median (IQR) duration of follow-up, years	5.1	2.1	3.7	3.4	4.0	3.1
Age						
Mean (s.d.) age 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

ACE, angiotensin-converting-enzyme; BMI, body mass index; ERCP, endoscopic retrograde cholangiopancreatography; HbA1c, glycated haemoglobin; IQR, interquartile range; n/a, not applicable; NIAD, non-insulin antidiabetic drug; s.d., standard deviation.
Values are n, (%) unless otherwise stated.

significantly more reported in patients treated with sitagliptin or exenatide as compared with users of other antidiabetic therapies [28]; however, that study provided hypothesis-generating evidence only, as it was based on data from the United States (US) Food and Drug Administration's Spontaneous Adverse Event Reporting System [29].

Several previous studies have reported results in line with our results, identifying no statistically significant risk of pancreatic cancer [11–14]. A meta-analysis of 25 RCTs (sitagliptin arm, n = 7726; comparator agent, n = 6885), with a follow-up period of 12–104 weeks, found no effect on pancreatic cancer occurrence (0.05 and 0.06 events per 100 patient-years in the sitagliptin and non-exposed group, respectively) [11]. In

Table 3. Risk of pancreatic cancer in incretin users compared with control subjects without diabetes, by age, sex and type of non-insulin antidiabetic drug.

NIAD exposure	Number of pancreatic cancer events (n = 576)	Total person-years (person-years)	Incidence rate (per 1000 person-years)	Age-, sex-adjusted HR (95% CI)	Severity-adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
Never	154	718 505	0.21	Reference	Reference	Reference
Past (>180 days before)	9	107 499	0.08	0.41 (0.21–0.80)	0.45 (0.23–0.88)	0.51 (0.26–0.99)
Current (≤90 days before)	413	616 621	0.67	3.23 (2.69–3.89)	3.78 (3.12–4.58)	4.28 (3.49–5.24)
By incretin exposure						
Never‡	367	566 015	0.65	3.06 (2.53–3.70)	3.58 (2.94–4.35)	4.06 (3.31–4.98)
Past (>180 days before)	6	7010	0.86	5.02 (2.21–11.40)	6.26 (2.75–14.24)	7.36 (3.22–16.81)
Recent (91–180 days before)	6	2044	2.94	17.83 (7.87–40.40)	21.87 (9.63–49.69)	26.06 (11.43–59.41)
Current (≤90 days before)	34	41 552	0.82	5.17 (3.55–7.55)	6.23 (4.25–9.13)	7.52 (5.09–11.12)
By type of incretin						
GLP-1-RAs	6	11 206	0.54	4.33 (1.90–9.83)	5.38 (2.36–12.25)	7.28 (3.16–16.79)
DPP-4 inhibitors	28	29 704	0.94	5.48 (3.64–8.24)	6.55 (4.34–9.88)	7.67 (5.05–11.65)
By sex§						
Men	15	23 756	0.63	4.47 (2.55–7.85)	5.37 (3.04–9.48)	5.77 (3.23–10.31)
Women	19	17 796	1.07	5.98 (3.59–9.95)	7.23 (4.32–12.12)	9.85 (5.80–16.71)
By age¶						
18–49 years	2	6771	0.30	27.44 (2.43–309.90)	29.98 (2.55–351.81)	20.57 (1.54–274.34)
50–59 years	2	11 196	0.18	2.40 (0.52–11.02)	2.69 (0.58–12.52)	2.64 (0.54–13.06)
60–69 years	16	13 755	1.16	5.93 (3.29–10.69)	7.09 (3.90–12.88)	9.24 (4.92–17.35)
≥70 years	14	9830	1.42	4.16 (2.37–7.30)	5.09 (2.88–8.98)	6.36 (3.58–11.31)

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; NIAD, non-insulin antidiabetic drug.
*Pancreatic cancer: adjusted for retinopathy, neuropathy.
†Pancreatic cancer: adjusted for alcoholism, alcohol use, body mass index, smoking, neuropathy, retinopathy.
‡Current NIAD use excluding current incretin use.
§Compared with controls of the same gender.
¶Compared with controls in the same age category.

the SAVOR cardiovascular outcome trial (n = 16 492, median follow-up 2.1 years) there were five cases of pancreatic cancer in the saxagliptin arm and 12 in the comparator agent arm, while no events of pancreatic cancer were reported in the alogliptin or placebo arm of the EXAMINE cardiovascular outcome trial (n = 5380, median follow-up 18 months) [12,13]. Furthermore, an observational cohort study using a US claims database did not show an association between risk of pancreatic cancer with DPP-4 inhibitor use versus use of sulphonylurea derivatives or thiazolidinediones [14].

The potential biological mechanisms of incretin agents promoting or enhancing pancreatic cancer are supported by limited indirect evidence. In animal models three GLP-1-induced pathways have been proposed; proliferation in β-cells, inhibition of β-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 lesions and an increase in pancreatic weight [2,4,5,8,30–34]. GLP-1RA-dependent effects on β-cell proliferation include activation of phosphatidylinositol-3 (PI3) kinase, protein kinase B (AKT), mitogen-activated protein kinase (MAPK), protein kinase C, the *src* kinase, and the epidermal growth factor receptor (EGFR) [6,35,36]; however, the exact mechanism by which GLP-1RA activates the PI3 kinase signalling pathway remains unknown [6]. Both EGFR and *src* have been implicated in the pathogenesis and progression of numerous malignant tumours, including pancreatic cancer [35]. Furthermore, duct cell proliferation and pancreatic intraepithelial neoplasia lesions might lead to duct occlusion, which could cause back pressure in the pancreas, stressing the acinar cells to release the digestive enzymes, with the resulting chronic pancreatitis fostering futher development of pancreatic intraepithelial neoplasia lesions and duct cell proliferation [5,34]. By activating both above-mentioned pathways, incretin agents could promote acute pancreatitis, chronic pancreatitis and eventually development of pancreatic cancer [34,35]. Instead of inducing pancreatic cancer, it was hypothesized that incretin agents may enhance tumour growth, which could lead to earlier detection. This underlying mechanism was also not confirmed by our data, including the duration of use analysis.

It is important to note that the duration of follow-up of the present study was relatively short (up to 5 years) in order to detect a causal effect of incretins on pancreatic cancer. The mean duration of incretin use was only 1.2 years. The time span from an initiated pancreatic intraepithelial neoplasia lesion to a parental clone, which will initiate an infiltrating pancreatic carcinoma, is ~12 years [37].

Although a limited duration of follow-up and continuous use of incretins may not be supportive for an observational study to evaluate a causal relationship, it can give valuable information about the alternative hypothesis that the results may be flawed by unmeasured distortion. Other well-known examples include CPRD studies that have evaluated the association between hip fracture and the use of statins [38] or proton pump inhibitors [39]. Similarly to the present study, the associations were

Table 4. Risk of pancreatic cancer in incretin users compared with other non-insulin antidiabetic drug users, by age, sex and body mass index.

NIAD exposure	Number of pancreatic cancer events (n = 422)	Total person-years	Incidence rate (per 1000 person-years)	Age-, sex-adjusted HR (95% CI)	Severity-adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
Past (>180 days before)	9	107 499	0.08	0.14 (0.07–0.26)	0.15 (0.08–0.30)	0.15 (0.08–0.30)
Current (≤90 days before)‡	367	566 015	0.65	Reference	Reference	Reference
By incretin exposure						
Past (>180 days before)	6	7010	0.86	1.70 (0.75–3.83)	1.17 (0.52–2.65)	1.22 (0.54–2.77)
Recent (91–180 days before)	6	2044	2.94	6.01 (2.67–13.52)	3.50 (1.55–7.90)	3.70 (1.64–8.36)
Current (≤90 days before)	34	41 552	0.82	1.74 (1.21–2.50)	1.27 (0.88–1.83)	1.36 (0.94–1.96)
By type of incretin						
GLP1-RAs	6	11 206	0.54	1.45 (0.64–3.27)	0.99 (0.44–2.24)	1.18 (0.52–2.69)
DPP-4 inhibitors	28	29 704	0.94	1.84 (1.24–2.73)	1.38 (0.93–2.05)	1.43 (0.96–2.13)
By sex§						
Males	15	23 756	0.63	1.42 (0.83–2.44)	1.11 (0.64–1.91)	1.15 (0.67–1.99)
Females	19	17 796	1.07	2.12 (1.30–3.47)	1.44 (0.88–2.36)	1.59 (0.97–2.62)
By age (years)¶						
18–59	4	17 967	0.22	0.70 (0.16–3.01)	1.29 (0.44–3.83)	1.46 (0.49–4.38)
60–69	16	13 755	1.16	2.03 (1.17–3.53)	1.50 (0.86–2.62)	1.64 (0.93–2.88)
≥70	14	9830	1.42	1.44 (0.83–2.49)	0.98 (0.57–1.71)	1.05 (0.60–1.83)
By BMI**						
<25 kg/m^2	5	2780	1.80	2.74 (1.13–6.64)	2.09 (0.86–5.08)	2.09 (0.86–5.07)
25–29.9 kg/m^2	14	10 151	1.38	2.49 (1.45–4.28)	1.90 (1.10–3.26)	1.89 (1.10–3.25)
30–34.9 kg/m^2	7	12 586	0.56	1.18 (0.55–2.50)	0.85 (0.40–1.81)	0.85 (0.40–1.80)
≥35 kg/m^2	8	15 878	0.50	1.31 (0.64–2.66)	0.92 (0.45–1.87)	0.93 (0.45–1.89)
By number of prescriptions						
Low (1–3)	11	8892	1.24	2.62 (1.43–4.80)	1.58 (0.86–2.90)	1.67 (0.91–3.07)
Middle (4–7)	11	9528	1.15	2.46 (1.34–4.50)	1.75 (0.95–3.21)	1.86 (1.01–3.42)
High (≥8)	12	23 132	0.52	1.09 (0.61–1.96)	0.88 (0.49–1.58)	0.95 (0.53–1.72)

BMI, body mass index; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1RAs, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; NIAD, non-insulin antidiabetic drug.

*Pancreatic cancer: adjusted for retinopathy, neuropathy, HbA1c (glycated haemoglobin).

†Pancreatic cancer: adjusted for alcoholism, alcohol use, body mass index (BMI), smoking, neuropathy, retinopathy, HbA1c (glycated haemoglobin).

‡Current NIAD use excluding current incretin use.

§Compared with controls of the same gender.

¶Compared with controls in the same age category.

**As the number of events in the BMI missing group was zero the person time of this group was not taken into account in the analysis.

strongest briefly after the initation of statins or proton pump inhibitors, and then attenuated with prolonged use (the opposite of a causal hypothesis). The lack of an association between statin use and fracture risk was confirmed in various large randomized clinical trials [38,39]. Protopathic bias is a potential explanation for the rapidly increased risk of pancreatic cancer that we observed in the present study. Protopathic bias occurs when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected [40,41]. It is well known that pancreatic cancer is a powerful diabetogenic state, as illustrated by prevalence of pancreatic cancer-associated T2DM varying from 4 to 64% [39,42,43]. T2DM was found to be more prevalent (47 vs 7%; $p < 0.001$) and at onset (<2 years; 74 vs 53%; $p = 0.002$) among patients with pancreatic cancer compared with patients without pancreatic cancer [43,44]. Lifestyle interventions and use of antihyperglycaemic drugs are usually inadequate in treating this pancreatic cancer-associated T2DM, leading to rapid prescribing of antihyperglycaemic treatment, such as incretin agents. This may be indirectly supported by the previously reported 1.7-fold increased risk of pancreatic cancer with sulphonylurea derivative use [45], and the fourfold increased risk of pancreatic cancer with NIAD treatment observed in the present study.

In addition to the presence of protopathic bias and confounding by disease severity, it is likely that our observed associations are not without residual confounding. For instance, we were not able to correct for the amount of exercise. Physical activity appears to decrease the risk of pancreatic cancer, especially among overweight people [46]. Incretin users might perform less exercise compared with non-incretin users, which could lead to an overestimation of our effect.

The present study has several strengths. We were able to adjust statistically in a time-dependent way for several potentially important confounders, including age, the most recently recorded HbA1c value in the preceding year, and different comorbidities, such as retinopathy, neuropathy, alcoholism and drug use. Additionally, we had information at baseline on sex, smoking status, BMI and alcohol use for almost all patients. Furthermore, CPRD data are collected prospectively, eliminating the risk of recall bias. Finally, a substantial amount of data representing the general population of the UK was

Table 5. Risk of pancreatic cancer in incretin users compared with other non-insulin antidiabetic drug users, new user design (sensitivity analysis).

NIAD exposure	Number of pancreatic cancer events (n = 221)	Total person-years	Incidence rate (per 1000 person-years)	Age-, sex-adjusted HR (95% CI)	Severity-adjusted HR (95% CI)*	Fully adjusted HR (95% CI)†
Past (>180 days prior)	5	30 456	0.16	0.22 (0.09–0.53)	0.22 (0.09–0.54)	0.22 (0.09–0.53)
Current‡	195	208 561	0.93	Reference	Reference	Reference
By incretin exposure						
Past (>180 days before)	2	1997	1.00	1.79 (0.44–7.24)	1.24 (0.31–5.05)	1.31 (0.32–5.31)
Recent (91–180 days before)	1	662	1.51	2.64 (0.37–18.91)	1.47 (0.21–10.57)	1.56 (0.22–11.20)
Current (≤90 days before)	18	15 059	1.20	2.15 (1.31–3.54)	1.51 (0.92–2.50)	1.67 (1.01–2.77)
By number of prescriptions						
Low (1–2)	6	2625	2.29	3.92 (1.73–8.88)	2.20 (0.97–5.01)	2.37 (1.04–5.40)
Middle (3–7)	6	4932	1.22	2.15 (0.95–4.87)	1.42 (0.62–3.24)	1.56 (0.69–3.56)
High (≥8)	6	7501	0.80	1.48 (0.65–3.37)	1.21 (0.53–2.77)	1.37 (0.60–3.13)

CI, confidence interval; HR, hazard ratio; NIAD, non-insulin antidiabetic drug.
*Pancreatic cancer; adjusted for retinopathy, neuropathy, HbA1c (glycated haemoglobin).
†Pancreatic cancer; adjusted for alcoholism, alcohol use, body mass index (BMI), smoking, neuropathy, retinopathy, HbA1c (glycated haemoglobin).
‡Current NIAD use excluding current incretin use.

available. It is important to note, however, that the incidence rates of pancreatic cancer in the present study were slightly higher compared with known rates in the UK population [47]. We observed a rate of 21 per 100 000 person years for patients without T2DM and 67 per 100 000 person years for patients with T2DM. This is possibly attributable to the characteristics of the study cohort, which included only patients aged ≥18 years (i.e. it excluded children, who represent ~20% of the UK population), and also to the fact that the control cohort had the same age and gender distribution as the T2DM cohort as a result of matching. Given that age is an important risk factor for pancreatic cancer, the average incidence rates would be expected to be higher.

In conclusion, we found that incretin use was not associated with pancreatic cancer after adjustment for indicators of the severity of the underlying T2DM. The elevated risk of pancreatic cancer found in recent starters of incretin agents may be the result of protopathic bias or other types of unknown distortion. The presence of considerable confounding by disease severity and the lack of duration of use relationship do not support a causal explanation for the observed association between incretin agents and pancreatic cancer. A longer duration of follow-up and exposure to incretin agents is required to investigate the association between exposure time to incretin agents and pancreatic cancer.

Conflict of Interest

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

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

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