Incretin-Based Therapy and Risk of Acute Pancreatitis: A Nationwide Population-Based Case-Control Study

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OBJECTIVE

To investigate whether the use of incretin-based drugs (GLP-1 receptor agonists and dipeptidyl peptidase 4 [DPP4] inhibitors) is associated with acute pancreatitis.

RESEARCH DESIGN AND METHODS

The study was a nationwide population-based case-control study using medical databases in Denmark. Participants were 12,868 patients with a first-time hospitalization for acute pancreatitis between 2005 and 2012 and a population of 128,680 matched control subjects. The main outcome measure was the odds ratio (OR) for acute pancreatitis associated with different antihyperglycemic drugs. We adjusted for history of gallstones, alcoholism, obesity, and other pancreatitis-associated comorbidities and medications.

RESULTS

A total of 89 pancreatitis patients (0.69%) and 684 control subjects (0.53%) were ever users of incretins. The crude OR for acute pancreatitis among incretin users was 1.36 (95% CI 1.08–1.69), while it was 1.44 (95% CI 1.34–1.54) among users of other antihyperglycemic drugs. After confounder adjustment, the risk of acute pancreatitis was not increased among incretin users (OR 0.95 [95% CI 0.75–1.21]), including DPP4 inhibitor users (OR 1.04 [95% CI 0.80–1.37]) or GLP-1 receptor agonist users (OR 0.82 [95% CI 0.54–1.23]), or among nonincretin antihyperglycemic drug users (OR 1.05 [95% CI 0.98–1.13]), compared with nonusers of any antihyperglycemic drugs. Findings were similar in current versus ever drug users and in patients with pancreatitis risk factors. The adjusted OR comparing incretin-based therapy with other antihyperglycemic therapy internally while also adjusting for diabetes duration and complications was 0.97 (95% CI 0.76–1.23).

CONCLUSIONS

Our findings suggest that the use of incretin-based drugs appears not to be associated with an increased risk of acute pancreatitis.

Incretin-based therapies represent a new and widely used class of oral antihyperglycemic drugs for the treatment of type 2 diabetes (1). These agents currently include three injectable incretin mimetic agents (GLP-1 receptor agonists: exenatide, liraglutide, and lixisenatide), five incretin enhancers (dipeptidyl peptidase 4 [DPP4] inhibitors: sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin [not currently licensed in Denmark]), and combinations of these DPP4 inhibitors with metformin or

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other antihyperglycemic drugs. Incretins exert their effect by augmenting glucose-stimulated insulin secretion from the pancreas through intestinally derived peptides released in the presence of nutrients in the gut (2,3). GLP-1 receptors are expressed in pancreatic islets and exocrine duct cells (4). Stimulation of these receptors may lead to overgrowth of the cells that cover the smaller ducts, resulting in hyperplasia (5) and chronic low-grade or acute inflammation (4).

Thus, there is a concern that incretins may cause pancreatitis and pancreatic cancer in humans (6,7), although the evidence is controversial (8). An increased risk of pancreatitis with incretin therapy was shown in some (4), but not all (8,9) experimental animal studies. In humans, a signal of pancreatitis associated with incretin use was detected by adverse event reports (10–12). However, spontaneous reports may be partially driven by professional and lay publications, while type 2 diabetes per se may increase the risk of acute pancreatitis 1.5-fold to 2-fold (13–18). Sitagliptin and exenatide increased the odds ratio (OR) for pancreatitis sixfold compared with that for other antidiabetic therapies, in a study from the U.S. Food and Drug Administration database (6). In contrast, as recently reviewed by Li et al. (19), most epidemiological observational studies to date have reported relative risks (RRs) of pancreatitis close to 1.0 among users of incretin-based versus other antihyperglycemic drugs. These studies include several cohort analyses from the U.S. (20–22) and U.K. (23). In contrast, a case-control study in the U.S. reported an adjusted OR of 2.24 (95% CI 1.36–3.68) for acute pancreatitis (24) associated with the use of exenatide or sitagliptin, while another Italian case-control study (25) reported an adjusted OR of 0.98 (95% CI 0.69–1.38). Thus, the issue of the relationship of incretins and acute pancreatitis remains under debate. In light of the limitations of many of the existing observational studies, including low statistical power, selected populations of insured individuals or specific age groups, incomplete prescription data, or limited confounder control, both the European Medicines Agency and the U.S. Food and Drug Administration have called for additional large high-quality studies of this issue (23). Since incretins have become widely used, any elevated risk of acute pancreatitis has important public health implications.

We therefore investigated the association between incretin use and the risk of acute pancreatitis using comprehensive data from Danish population-based nationwide medical databases. We hypothesized that the acute pancreatitis risk would be similarly increased with all antihyperglycemic therapies because of underlying diabetes and associated risk factors, and that the adjusted risks with incretin-based and other therapies would not differ materially.

RESEARCH DESIGN AND METHODS

Setting

We conducted this population-based case-control study using information from the following three nationwide databases: the Danish Civil Registration System (CRS) (26), the Danish National Database of Reimbursed Prescriptions (NDRP) (27), and the Danish National Patient Register (NPR) (28). Unambiguous data linkage was performed using the unique civil registration number assigned since 1968 to each Danish resident at birth or immigration. Denmark has 5.6 million inhabitants, who are mainly Caucasians (>90%). All Danish residents have equal tax-supported access to comprehensive health care, provided by the Danish National Health Service. Services include free access to hospitals and partial reimbursement of drug expenses, including those for antihyperglycemic medications (27).

Acute Pancreatitis Case Patients

We identified patients with acute pancreatitis from the NPR, which contains data on hospital inpatient discharges from all nonpsychiatric hospitals in Denmark since 1977 and on emergency department and hospital outpatient clinic visits since 1995 (28). Each hospital contact is associated with one primary diagnosis (the one listed first) and up to 20 secondary diagnoses, coded by physicians and classified according to the ICD-8 until the end of 1993 and the ICD-10 thereafter. We identified 12,868 eligible patients with a first-time acute inpatient hospital admission for pancreatitis (i.e., a primary or secondary diagnosis of acute pancreatitis; ICD-8 codes 577.00–577.09 and ICD-10 code K85) between 1 January 2005 and 31 December 2012. We excluded patients who were younger than 18 years old on the hospital admission date (the index date) and who had a hospital contact with acute pancreatitis between 1977 and 2004.

Population Control Subjects

We used the CRS to select 10 population control subjects for each case. Control subjects were individually matched on birth year, sex, index date, and Danish region of residence (26). The CRS has collected vital statistics, including date of birth, residence, migration, and exact date of death for the entire Danish population since 1968. We selected control subjects using risk-set sampling from persons alive and at risk for a first hospitalization with acute pancreatitis on the case patient's index date (29).

Use of Incretins and Other Antihyperglycemic Drugs

The Danish NDRP contains information on reimbursed prescriptions dispensed at all pharmacies in Denmark, including date of sale, active substance, route of administration, and amount dispensed (27). Incretins and all other antihyperglycemic drugs for the treatment of type 2 diabetes are reimbursed and available by prescription only at Danish pharmacies. We retrieved data from the NDRP from 2004 until the index date for both case patients and control subjects. Ever use of incretins was defined by one or more prescriptions for DPP4 inhibitors or GLP-1 receptor agonists as monotherapy or combination therapy, regardless of other comedication. Similarly, ever use of other antihyperglycemic drugs was defined by one or more prescriptions for metformin, sulfonylureas, thiazolidinediones, insulin, α-glucosidase inhibitors, combination products excluding incretins, or other oral antihyperglycemic drugs (see Supplementary Data for the relevant Anatomical Therapeutic Chemical classification system codes).

Current use of incretins or other antihyperglycemic drugs was defined by at least one relevant prescription within 100 days before the index date, since the typical package size of incretins and other antihyperglycemic drugs in Denmark is 100 daily doses. Former use was defined as redeeming no prescriptions within 100 days and at least one prescription >100 days before the index date. Nonuse was defined as no recorded prescription at any time

before the index date. New users (initiators) were defined as current users who redeemed their first recorded prescription for a given agent within 100 days before the index date. The intensity of each drug use was measured as the cumulative number of dispensed prescriptions, and was classified as no prescriptions, one to three prescriptions, or more than three prescriptions.

Potential Confounders

Data on potential confounding factors recorded before the index date were collected from the NPR and the NDRP. Potential confounders included history of the following hospital-diagnosed conditions recorded: gallstone disease; surgical procedures on the biliary tract including the gall bladder, pancreas, or endoscopy of the biliary tract (except procedures $\leq$10 days before the diagnosis of pancreatitis to avoid reverse causality); obesity; alcoholism-related diseases; any cancer (except first-time diagnoses $<$90 days before the diagnosis of pancreatitis to avoid misdiagnosis bias); and inflammatory bowel disease (see Supplementary Data for codes). We also computed three levels of a modified Charlson Comorbidity Index (CCI) score for each individual, excluding diseases already represented by other variables included in the analysis (see Supplementary Data). We categorized the CCI as low (score 0), medium (score 1–2), and high (score $\geq$3) as a measure of the overall comorbidity level. To supplement the information on the excessive use of alcohol, we categorized persons with ever use of disulfiram, identified through the NDRP, as having an alcohol-related disorder. Similarly, we retrieved information about the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, azathioprine, oral glucocorticoids, and lipid-lowering drugs, including statins, within 100 days before the index date. For patients exposed to antihyperglycemic drugs, we retrieved data on the presence of diabetic eye, renal, or neurological complications (classified as yes/no), and on the time between the first use of antihyperglycemic drugs and the index date (classified as $\leq$1 year, $>$1–5 years, and $>$5 years).

Statistical Analysis

We cross-tabulated the main study variables with the case and control status. Under risk-set sampling of the control subjects, the OR is an unbiased estimate of the incidence rate ratio. We computed the crude (i.e., age-, sex-, and residence-matched) ORs for acute pancreatitis according to ever, current, former, and new use of incretins (with separate estimates for GLP-1 receptor agonists and DPP4 inhibitors, and the two most frequently used individual incretins, liraglutide and sitagliptin) or other antihyperglycemic drugs (with separate estimates for metformin, sulfonylureas, and insulin). We used conditional logistic regression to compute the OR among users of incretins or other antihyperglycemic drugs, compared with nonusers of any antihyperglycemic drugs as the reference, adjusted for the potential confounders. Because we observed a strong correlation between gallstone diagnoses and surgical biliary tract procedures, the latter were omitted from the final regression model. We further computed ORs stratified by the presence of pancreatitis risk factors, using ordinary logistic regression adjusted for age, sex, and the potential confounders. We also estimated adjusted ORs associated with the cumulative number of antihyperglycemic drug prescriptions.

We conducted several sensitivity analyses. First, to account for possible low adherence and irregular prescription renewals, we repeated the analyses with the definition of current use extended to 200 days before the index date. Second, we used a stricter definition of acute pancreatitis based only on primary diagnoses, since these may have the highest validity. Third, since incretin-based therapy could theoretically cause gallstone disease or other pancreatitis-causing comorbidities in some patients, we repeated analyses excluding from the regression model all risk factors that had been diagnosed after the initiation of incretin therapy.

Finally, we conducted an internal comparison of acute pancreatitis risk among patients who all were treated with antihyperglycemic drugs, directly comparing the risk of pancreatitis in incretin-treated patients with that of patients treated with other antihyperglycemic regimens, adjusting for diabetes duration and complications (see Supplementary Data for codes).

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). This registry-based study was approved by the Danish Data Protection Agency (record no. 2012–41–0793) and did not require further ethics approval according to Danish law.

RESULTS

Study Population

A total of 12,868 patients with acute pancreatitis and 128,680 control subjects were included in the study. As expected, well-known risk factors for acute pancreatitis were more prevalent among the pancreatitis case patients than among the control subjects, including history of gallstone disease (17% vs. 4%) and alcoholism-related disease (15% vs. 4%). A medium or high CCI score was observed in 33% of case patients versus 21% of control subjects. Furthermore, more case patients than control subjects had filled prescriptions for potential pancreatitis-related medications, such as NSAIDs and antiepileptics (Table 1).

A total of 89 pancreatitis patients (0.69%) and 684 control subjects (0.53%) had used incretins at least once, whereas 54 case patients (0.42%) and 482 control subjects (0.37%) were current users of incretins (Table 2). Among the pancreatitis case patients, 68 (0.53%) were ever users of DPP4 inhibitors (including sitagliptin [53 users], vildagliptin [13 users], saxagliptin [4 users], and linagliptin [1 user]), and 30 (0.23%) were ever users of GLP-1 receptor agonists (including liraglutide [26 users] and exenatide [5 users]). Supplementary Table 1 shows clinical characteristics of case patients and control subjects with incretin-based therapy.

Crude ORs for Acute Pancreatitis

Patients with acute pancreatitis were more likely than matched control subjects to have been ever users of incretins (crude OR 1.36 [95% CI 1.08–1.69]), and also were more likely to have been ever users of nonincretin antihyperglycemic drugs (crude OR 1.44 [95% CI 1.34–1.54]). The crude ORs for ever use of individual antihyperglycemic agents ranged from 1.31 to 1.52 (Table 2). For current use, the crude OR was 1.17 for the incretins (0.98 for DPP4 inhibitors and 1.46 for GLP-1 receptor agonists), and ranged between 1.28 and 1.46 for the other antihyperglycemic drugs. Former incretin use was associated with a crude OR of 1.81 (95% CI 1.26–2.59) for acute pancreatitis, which was driven primarily by the former use of DPP4 inhibitors,

Table 1—Descriptive characteristics and potential risk factors among patients hospitalized with acute pancreatitis and age-, sex-, and resident-matched population control subjects

	Acute pancreatitis case patients, *N*	Acute pancreatitis case patients, %	Matched population control subjects, *N*	Matched population control subjects, %
Total	12,868	100.0	128,680	100.0
Sex				
Male	6,635	51.6	66,350	51.6
Female	6,233	48.4	62,330	48.4
Age				
18–39 years	2,293	17.8	22,914	17.8
40–59 years	4,413	34.3	44,202	34.4
60+ years	6,162	47.9	61,564	47.8
Previous hospital diagnoses				
Gallstone disease	2,163	16.8	5,130	4.0
Obesity	952	7.4	4,001	3.1
Alcoholism-related disease	1,980	15.4	5,625	4.4
Inflammatory bowel disease	282	2.2	909	0.7
Any cancer	1,189	9.2	9,734	7.6
Procedures on biliary tract or pancreas	1,146	8.9	4,579	3.6
CCI				
Low (0 points)	8,594	66.8	101,434	78.8
Medium (1–2 points)	3,614	28.1	24,300	18.9
High (≥3 points)	660	5.1	2,946	2.3
Pre–hospital admission drug use				
Statins				
Ever	2,881	22.4	23,438	18.2
≤100 days	1,898	14.8	16,579	12.9
Oral glucocorticoids				
Ever	1,640	12.7	9,883	7.7
≤100 days	539	4.2	2,393	1.9
Azathioprine				
Ever	156	1.2	453	0.4
≤100 days	88	0.7	155	0.1
NSAIDs				
Ever	8,500	66.1	66,095	51.4
≤100 days	2,856	22.2	12,996	10.1
Antiepileptics				
Ever	982	7.6	4,896	3.8
≤100 days	456	3.5	2,551	2.0

with an OR of 2.02 (95% CI 1.43–2.87). The OR for the former use of nonincretin antihyperglycemic drugs (1.93 [95% CI 1.67–2.22]) was also substantially higher than that for current use (Table 2). For most individual drugs, new users had higher ORs for pancreatitis than current users, although many estimates were imprecise.

Adjusted Odds of Acute Pancreatitis

After adjustment for potential confounding factors, the OR associated with ever use of incretin decreased from 1.36 to 0.95 (95% CI 0.75–1.21) (Table 2 and Fig. 1). The corresponding OR associated with current incretin use decreased from 1.17 to 0.81 (95% CI 0.60–1.10). The adjusted OR also was not increased for ever use of DPP4 inhibitors (1.04 [95% CI 0.80–1.37]), including sitagliptin (1.06 [95% CI 0.78–1.44]), or for ever use of GLP-1 receptor analogs (0.82 [95% CI 0.54–1.23]), including liraglutide (0.75 [95% CI 0.48–1.17]). The adjusted OR for acute pancreatitis associated with ever use of antihyperglycemic drugs other than incretins was 1.05 (95% CI 0.98–1.13), which was comparable (i.e., ranging between 0.96 and 1.13) with estimates associated with ever use of metformin, sulfonylurea, and insulin (Fig. 2). With the exception of GLP-1 receptor agonists, former use of antihyperglycemic drugs was associated with a higher adjusted risk of acute pancreatitis than current use (Table 2 and Figs. 1 and 2). The adjusted ORs for former use were 1.13–1.15 for metformin, sulfonylurea, and insulin, and 1.44 (95% CI 0.99–2.09) for DPP4 inhibitors. The adjusted OR was 1.51 (95% CI 1.02–2.24) for former sitagliptin use. The adjusted ORs for new use were 1.51 (95% CI 0.72–3.14) for DPP4 inhibitors and 0.17 (95% CI 0.02–1.27) for GLP-1 receptor agonists. These estimates were imprecise and not driven by new sitagliptin users, for whom the adjusted OR was 0.99 (95% CI 0.33–2.91). Adjusted ORs for new use were 1.98 (95% CI 1.15–3.41) for sulfonylureas and 3.62 (95% CI 2.22–5.91) for insulin.

Adjusted ORs for acute pancreatitis associated with ever use of incretins were close to 1, regardless of the presence or absence of obesity, gallstones, alcoholism, and most other pancreatitis risk factors (Supplementary Table 2).

For most antihyperglycemic drugs, ORs for pancreatitis decreased with a high cumulative number of prescriptions. For incretins, adjusted ORs for pancreatitis associated with ever filling one to three prescriptions and more than three prescriptions were 1.18 (95% CI 0.77–1.80) and 0.87 (95% CI

Table 2—Use of incretin-based therapies and other antihyperglycemic drugs among patients hospitalized with acute pancreatitis and age-, sex-, and residence-matched population control subjects

	Acute pancreatitis case patients		Matched population control subjects		Unadjusted age-/sex-matched OR (95% CI)	Adjusted* OR (95% CI)
	N	%	*N*	%		
Total	12,868	100.00	128,680	100.00	NA	NA
Never use of any antihyperglycemic drug	11,777	91.52	120,812	93.89	1.00 (ref.)	1.00 (ref.)
Ever use of any antihyperglycemic drug†	1,091	8.48	7,868	6.11	1.44 (1.35–1.54)	1.05 (0.98–1.13)
Use of any incretins‡						
Ever use	89	0.69	684	0.53	1.36 (1.08–1.69)	0.95 (0.75–1.21)
Current use (≤100 days)	54	0.42	482	0.37	1.17 (0.88–1.55)	0.81 (0.60–1.10)
Former use (past 100+ days)	35	0.27	202	0.16	1.81 (1.26–2.59)	1.27 (0.87–1.86)
New use (start ≤100 days)	10	0.08	89	0.07	1.17 (0.61–2.25)	0.88 (0.45–1.75)
Use of DPP4 inhibitors						
Ever use	68	0.53	516	0.40	1.38 (1.07–1.77)	1.04 (0.80–1.37)
Current use (≤100 days)	30	0.23	319	0.25	0.98 (0.67–1.43)	0.78 (0.53–1.16)
Former use (past 100+ days)	38	0.30	197	0.15	2.02 (1.43–2.87)	1.44 (0.99–2.09)
New use (start ≤100 days)	9	0.07	52	0.04	1.80 (0.89–3.65)	1.51 (0.72–3.14)
Use of sitagliptin						
Ever use	53	0.41	393	0.31	1.41 (1.05–1.88)	1.06 (0.78–1.44)
Current use (≤100 days)	19	0.15	218	0.17	0.91 (0.57–1.45)	0.69 (0.42–1.13)
Former use (past 100+ days)	34	0.26	175	0.14	2.04 (1.41–2.95)	1.51 (1.02–2.24)
New use (start ≤100 days)	4	0.03	31	0.02	1.33 (0.47–3.77)	0.99 (0.33–2.91)
Use of GLP-1 receptor agonists						
Ever use	30	0.23	230	0.18	1.35 (0.92–1.98)	0.82 (0.54–1.23)
Current use (≤100 days)	24	0.19	171	0.13	1.46 (0.95–2.24)	0.84 (0.53–1.34)
Former use (past 100+ days)	6	0.05	59	0.05	1.05 (0.45–2.43)	0.74 (0.31–1.77)
New use (start ≤100 days)	1	0.01	37	0.03	0.28 (0.04–2.05)	0.17 (0.02–1.27)
Use of liraglutide						
Ever use	26	0.20	206	0.16	1.31 (0.87–1.97)	0.75 (0.48–1.17)
Current use (≤100 days)	22	0.17	157	0.12	1.46 (0.93–2.28)	0.81 (0.50–1.33)
Former use (past 100+ days)	4	0.03	49	0.04	0.84 (0.30–2.33)	0.55 (0.19–1.57)
New use (start ≤100 days)	1	0.01	34	0.03	0.31 (0.04–2.25)	0.18 (0.02–1.42)
Use of any other antihyperglycemic drugs than incretins§						
Ever use	1,088	8.46	7,853	6.10	1.44 (1.34–1.54)	1.05 (0.98–1.13)
Current use (≤100 days)	860	6.68	6,629	5.15	1.35 (1.25–1.45)	0.99 (0.91–1.08)
Former use (past 100+ days)	228	1.77	1,224	0.95	1.93 (1.67–2.22)	1.35 (1.16–1.58)
New use (start ≤100 days)	85	0.66	400	0.31	2.20 (1.74–2.79)	1.64 (1.27–2.12)
Selected other antihyperglycemic drugs						
Use of metformin						
Ever use	732	5.69	5,475	4.25	1.39 (1.28–1.50)	1.01 (0.92–1.10)
Current use (≤100 days)	499	3.88	4,034	3.13	1.28 (1.17–1.41)	0.95 (0.86–1.06)
Former use (past 100+ days)	233	1.81	1,441	1.12	1.68 (1.46–1.93)	1.15 (0.99–1.34)
New use (start ≤100 days)	42	0.33	257	0.20	1.70 (1.22–2.35)	1.19 (0.84–1.70)
Use of sulfonylureas						
Ever use	546	4.24	3,748	2.91	1.52 (1.38–1.66)	1.13 (1.02–1.25)
Current use (≤100 days)	296	2.30	2,202	1.71	1.40 (1.23–1.58)	1.11 (0.97–1.26)
Former use (past 100+ days)	250	1.94	1,546	1.20	1.69 (1.47–1.93)	1.15 (1.00–1.34)
New use (start ≤100 days)	18	0.14	77	0.06	2.42 (1.45–4.05)	1.98 (1.15–3.41)
Use of insulin						
Ever use	355	2.76	2,473	1.92	1.49 (1.33–1.67)	0.96 (0.85–1.08)
Current use (≤100 days)	284	2.21	2,082	1.62	1.41 (1.25–1.60)	0.92 (0.80–1.06)
Former use (past 100+ days)	71	0.55	391	0.30	1.88 (1.46–2.42)	1.13 (0.86–1.49)
New use (start ≤100 days)	29	0.23	60	0.05	5.03 (3.22–7.85)	3.62 (2.22–5.91)

ref., reference value. *Adjusted for previous diagnoses of gallstone disease, alcoholism-related conditions, obesity, inflammatory bowel disease, or any cancer; for three levels of the CCI score; and for current use of oral glucocorticoids, azathioprine, lipid-lowering drugs, antiepileptics, or NSAIDs. †Use of any antihyperglycemic drugs refers to prescriptions for DPP4 inhibitors, GLP-1 receptor agonists, metformin, sulfonylureas, thiazolidinediones (glitazones), insulin, α-glucosidase inhibitors, combinations of any of the former drugs, or any other antihyperglycemic drugs. ‡Incretin-based therapies include DPP4 inhibitors or GLP-1 receptor agonists either alone or as a combination therapy with other antihyperglycemic drugs. Patients may have used more than one type of incretin-based therapy. §Most persons who used incretins also used other antihyperglycemic drugs.

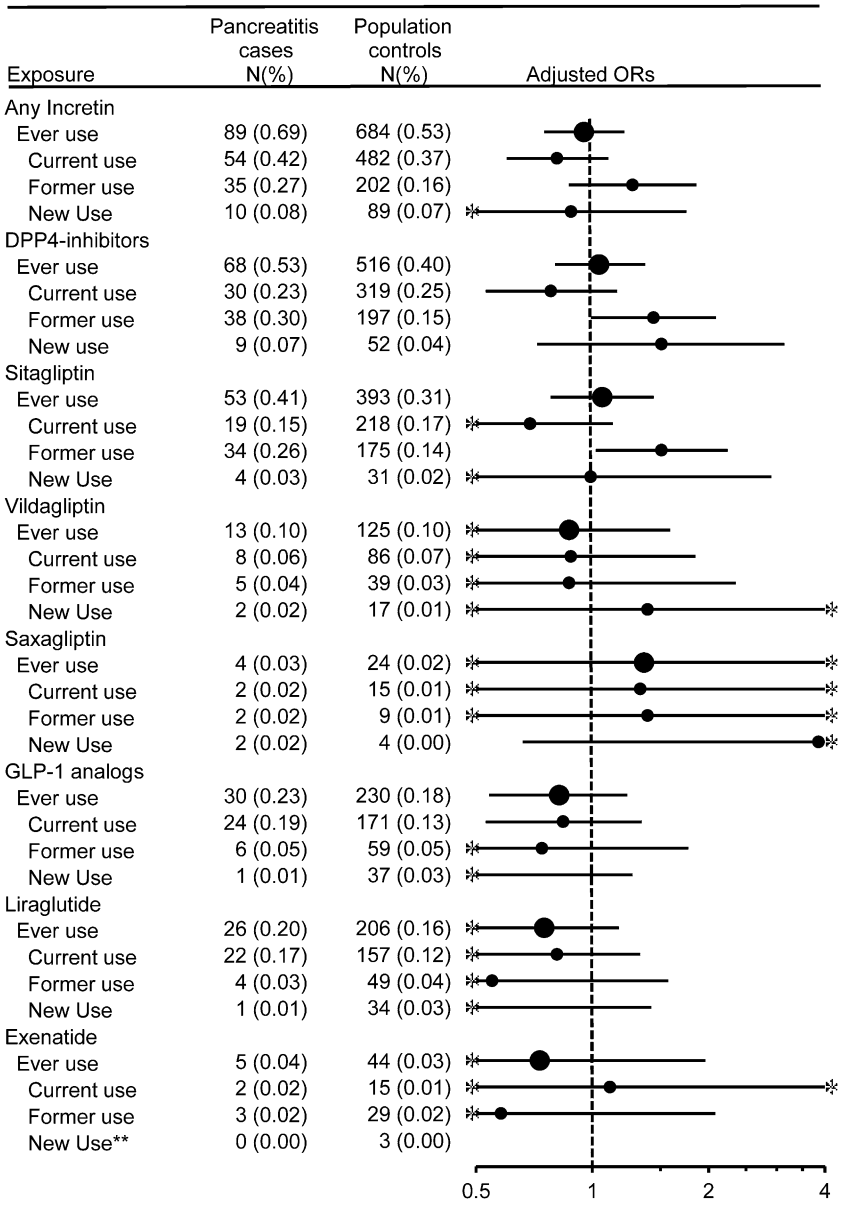

Figure 1—Adjusted ORs for hospitalization with acute pancreatitis according to use of incretin-based therapies. *Lower 95% confidence limit <0.5 or upper 95% confidence limit >4. **Data could not be modeled.

0.65–1.16), respectively. For DPP4 inhibitors, the adjusted ORs were 1.41 (95% CI 0.91–2.18) and 0.89 (95% CI 0.63–1.26), and for GLP-1 receptor agonists, 0.35 (95% CI 0.12–1.02) and 1.02 (95% CI 0.65–1.60), respectively.

Sensitivity Analyses

Table 3 shows the results of the sensitivity analyses and the effect of stepwise confounder adjustment for pancreatitis-associated risk factors. Judging by the decreasing ORs with successive adjustment, for most agents examined, pancreatitis-associated conditions were the strongest confounders (e.g., the adjustment caused the OR associated with ever use of incretins to decrease from 1.36 to 1.04). Extending the current use definition from 100 to 200 days before the index date produced results consistent with the primary analysis (Table 3). Restricting the case definition to primary diagnoses of acute pancreatitis (n = 10,644; 83% of all pancreatitis episodes) did not affect results for most drugs, except for ever use of DPP4 (crude OR 1.56 and fully adjusted OR 1.39 [95% CI 1.04–1.84]) (Table 3). When we excluded pancreatitis risk factors that were diagnosed later than incretin therapy initiation from the regression models, the risk estimates for ever-incretin use (OR 1.02) were comparable to those for the primary analyses (OR 0.95) (data not shown).

Analysis Directly Comparing Incretin-Based Therapy to Other Drugs

In a separate regression model that examined pancreatitis risk among antihyperglycemic drug users exclusively, the adjusted OR for incretin-based versus other therapy was 0.97 (95% CI 0.76–1.23).

CONCLUSIONS

Our large nationwide population-based study generally showed no association between adjusted risk of acute pancreatitis and treatment with incretins (DPP4 inhibitors or GLP-1 receptor agonists) or other antihyperglycemic drugs. The fact that crude ORs were increased to very similar levels for all antihyperglycemic drugs—given their different modes of action—points to a general underlying diabetes effect on pancreatitis risk, rather than a specific drug effect. For all therapies, our adjusted models showed that diabetes-related risk factors such as obesity, gallstones, and comorbidity may explain much of the apparent risk increase in crude analyses. Finally, a direct comparison of incretin-based and other drugs showed an adjusted acute pancreatitis OR close to 1.0.

We found an increased adjusted risk associated with recent initiation of therapy with DPP4 inhibitors that was also observed in individuals who had recently initiated therapy with several other antihyperglycemic drugs, including sulfonylureas and insulin. This lack of specificity suggests that either the increased pancreatitis risk is related to newly diagnosed and drug-treated type 2 diabetes per se, with a possibility of reverse causality due to pancreatogenic diabetes, or that the initiation of therapy with sulfonylureas and insulin also causes acute pancreatitis, which should be further investigated. Moreover, former use, but not current use, of DPP4 inhibitors was associated with increased risk for a primary diagnosis of pancreatitis. It is unclear whether this observation reflects therapy cessation secondary to emerging pancreatitis symptoms in some patients. A stronger association with former use than with current use was also observed for metformin, sulfonylureas,

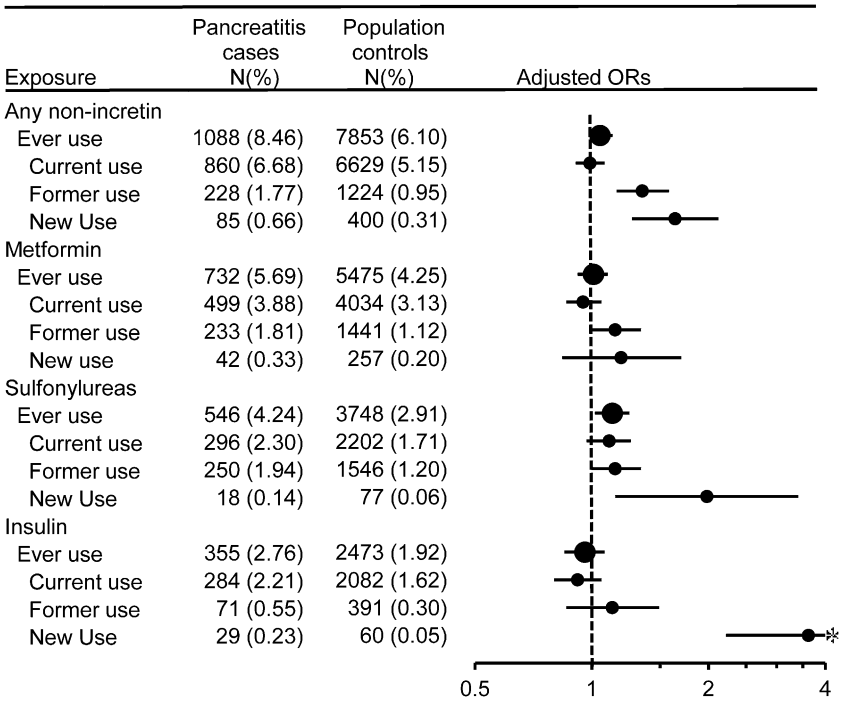

Figure 2—Adjusted ORs for hospitalization with acute pancreatitis according to use of non-incretin antihyperglycemic drugs. *Lower 95% confidence limit <0.5 or upper 95% confidence limit >4.

and insulin, arguing against a specific incretin effect.

Our results are consistent with a number of previous studies. In a U.S. cohort study by Garg et al. (20), the incidence of acute pancreatitis was three times higher in diabetic patients (5.64 episodes/1,000 person-years) than in control subjects (1.91 episodes/1,000 person-years), corresponding to an adjusted hazard ratio (HR) of 2.1 (95% CI 1.7–2.5). The incidence of pancreatitis was not increased among new users of exenatide (adjusted HR 0.9 [95% CI 0.6–1.5]) or sitagliptin (0.9 [95% CI 0.7–1.3]), compared with new users of other antidiabetic drugs (sulfonylurea, biguanide, or thiazolidinediones) (20). In another U.S. cohort study (21), the risk for hospitalization with acute pancreatitis was similar for individuals who had initiated therapy with exenatide (RR 1.0 [95% CI 0.6–1.7]) and sitagliptin (RR 1.0 [95% CI 0.5–2.0]), relative to those who had initiated metformin or glyburide therapy. In a third cohort study (22), the incidence of hospital admissions for acute pancreatitis was similar in exenatide users (1.32/1,000 person-years) and other antidiabetic drug users (1.33/1,000 person-years), corresponding to a propensity score–stratified RR of 1.07 (95% CI 0.79–1.45). In contrast, Singh et al. (24) reported, in a U.S. case-control study, that the use of GLP-1–based therapies (sitagliptin and exenatide) within 30 days of the index date (adjusted OR 2.24 [95% CI 1.36–3.68]) and use between 30 days and 2 years (adjusted OR 2.01 [95% CI 1.37–3.18]) were associated with an increased risk of acute pancreatitis relative to nonusers. That study was restricted to individuals younger than 65 years of age (~60% of our study population was in this age group), who had no data on liraglutide use but only sitagliptin and exenatide use (which were used by 65% of incretin users in our data set), and included no confounder data on other pancreatitis-related drugs. In another recent, population-based case-control analysis in Piedmont, Italy, Giorda et al. (25) found that current use of incretins versus other antihyperglycemic drugs was not associated with acute pancreatitis (adjusted OR 0.98 [95% CI 0.69–1.38]), which is consistent with our result. Compared with Singh et al. (24), Giorda et al. (25) examined all types of incretins, and used population-based data on unselected patients of all ages, similar to our study. Similar findings were recently reported by Faillie et al. (23), using the U.K. Clinical Practice Research Datalink and hospital episodes statistics databases to examine acute pancreatitis risk in those receiving incretin therapy versus those using sulfonylurea. After thorough confounding control, the adjusted HR for incretin use was 1.00 (95% CI 0.59–1.70).

The main strengths of our study include its population-based design and its setting in a comprehensive tax-supported health care system with universal population coverage, reducing the potential for selection and referral bias. We included patients of all ages and linked data from high-quality population-based registries with complete coverage of hospital encounters and prescribed drugs. The validity and coverage of the Danish prescription registries are excellent for reimbursed prescription drugs (27). The positive predictive value (PPV) of any hospital diagnosis (primary or secondary) of pancreatitis in the NPR is 82%, validated by clinical presentation with acute pancreatitis (abdominal pain) in the hospital record combined with either a twofold increase in serum amylase levels, or positive findings by ultrasound or CT scan, surgery, or autopsy (30). By comparison, the PPV of acute pancreatitis diagnosis was 60% for primary diagnoses in U.S. commercial health insurance inpatient claims, with similar PPVs noted for different antihyperglycemic drug users (31). Although we did not adjudicate individual pancreatitis cases, the accuracy of pancreatitis diagnoses is generally high and unlikely to differ by drug exposure status in our data.

This study also has limitations. First, when compared with people who have not received antihyperglycemic therapy, pancreatitis risk estimates associated with different antihyperglycemic drugs are expected to reflect both underlying diabetes and any possible drug effect. This was part of our analytic strategy, however, since a similar risk increase for all drugs examined would strongly propose a general diabetes effect on pancreatitis rather than a specific drug effect, and since this design allowed us to also examine the role of diabetes-associated risk factors. Moreover, our internal comparison analysis showed that the risk of acute pancreatitis associated with incretin use was not higher than that associated with other antihyperglycemic therapies, after

Table 3—Risk of pancreatitis according to use of individual antihyperglycemic drugs, compared with no use of any antihyperglycemic drug

	Incretins	DPP4	GLP-1	Metformin	Sulfonylurea	Insulin
Ever use of antihyperglycemic drug and risk of pancreatitis, restricted to only primary diagnosis of pancreatitis (n = 10,644)						
Unadjusted, age-/sex-matched	1.46 (1.15–1.84)	1.56 (1.19–2.03)	1.36 (0.90–2.05)	1.44 (1.32–1.58)	1.50 (1.36–1.67)	1.49 (1.32–1.69)
Adjusted						
Pancreatitis-associated conditions*	1.23 (0.96–1.57)	1.40 (1.06–1.85)	0.97 (0.63–1.49)	1.16 (1.06–1.28)	1.23 (1.10–1.37)	1.09 (0.95–1.24)
Plus pancreatitis-associated drug use†	1.17 (0.91–1.50)	1.37 (1.03–1.81)	0.88 (0.57–1.37)	1.12 (1.01–1.23)	1.19 (1.06–1.33)	1.07 (0.93–1.22)
Plus any comorbidity included in CCI‡	1.16 (0.90–1.50)	1.39 (1.04–1.84)	0.86 (0.55–1.33)	1.10 (0.99–1.21)	1.13 (1.01–1.27)	1.00 (0.87–1.14)
Ever use of antihyperglycemic drug and risk of pancreatitis (n = 12,868)						
Unadjusted, age-/sex-matched	1.36 (1.08–1.69)	1.38 (1.07–1.77)	1.35 (0.92–1.98)	1.39 (1.28–1.50)	1.52 (1.38–1.66)	1.49 (1.33–1.67)
Adjusted						
Pancreatitis-associated conditions*	1.04 (0.82–1.31)	1.11 (0.85–1.45)	0.95 (0.63–1.42)	1.08 (0.99–1.18)	1.23 (1.11–1.36)	1.07 (0.95–1.21)
Plus pancreatitis-associated drug use†	0.97 (0.77–1.23)	1.05 (0.80–1.37)	0.86 (0.57–1.30)	1.02 (0.93–1.12)	1.17 (1.06–1.29)	1.02 (0.90–1.15)
Plus any comorbidity included in CCI‡	0.95 (0.75–1.21)	1.04 (0.80–1.37)	0.82 (0.54–1.23)	1.01 (0.92–1.10)	1.13 (1.02–1.25)	0.96 (0.85–1.08)
Current use (≤100 days) of antihyperglycemic drug and risk of pancreatitis						
Unadjusted, age-/sex-matched	1.17 (0.88–1.55)	0.98 (0.67–1.43)	1.46 (0.95–2.24)	1.28 (1.17–1.41)	1.40 (1.23–1.58)	1.41 (1.25–1.60)
Adjusted						
Pancreatitis-associated conditions*	0.89 (0.66–1.20)	0.81 (0.55–1.20)	1.01 (0.64–1.59)	1.02 (0.92–1.13)	1.18 (1.04–1.35)	1.04 (0.91–1.19)
Plus pancreatitis-associated drug use†	0.82 (0.61–1.11)	0.77 (0.52–1.14)	0.88 (0.55–1.41)	0.95 (0.85–1.05)	1.13 (0.99–1.29)	0.98 (0.85–1.12)
Plus any comorbidity included in CCI‡	0.81 (0.60–1.10)	0.78 (0.53–1.16)	0.84 (0.53–1.34)	0.95 (0.86–1.06)	1.11 (0.97–1.26)	0.92 (0.80–1.06)
Current use (≤200 days) of antihyperglycemic drug and risk of pancreatitis						
Unadjusted, age-/sex-matched	1.25 (0.97–1.63)	1.19 (0.86–1.64)	1.40 (0.92–2.12)	1.32 (1.20–1.44)	1.48 (1.32–1.66)	1.43 (1.27–1.61)
Adjusted						
Pancreatitis-associated conditions*	0.95 (0.72–1.24)	0.96 (0.69–1.34)	0.95 (0.61–1.48)	1.04 (0.94–1.14)	1.25 (1.11–1.41)	1.06 (0.93–1.20)
Plus pancreatitis-associated drug use†	0.87 (0.66–1.15)	0.89 (0.64–1.25)	0.86 (0.55–1.36)	0.96 (0.87–1.06)	1.18 (1.05–1.34)	0.98 (0.86–1.12)
Plus any comorbidity included in CCI‡	0.86 (0.65–1.14)	0.90 (0.64–1.26)	0.84 (0.53–1.32)	0.97 (0.88–1.07)	1.16 (1.03–1.32)	0.93 (0.82–1.07)
Former use (past >100 days) of antihyperglycemic drug and risk of pancreatitis						
Unadjusted, age-/sex-matched	1.81 (1.26–2.59)	2.02 (1.43–2.87)	1.05 (0.45–2.43)	1.68 (1.46–1.93)	1.69 (1.47–1.93)	1.88 (1.46–2.42)
Adjusted						
Pancreatitis-associated conditions*	1.37 (0.94–2.00)	1.56 (1.08–2.26)	0.79 (0.33–1.87)	1.24 (1.07–1.44)	1.29 (1.12–1.49)	1.24 (0.94–1.63)
Plus pancreatitis-associated drug use†	1.32 (0.90–1.92)	1.47 (1.01–2.13)	0.78 (0.33–1.86)	1.22 (1.05–1.42)	1.22 (1.05–1.41)	1.23 (0.93–1.63)
Plus any comorbidity included in CCI‡	1.27 (0.87–1.86)	1.44 (0.99–2.09)	0.74 (0.31–1.77)	1.15 (0.99–1.34)	1.15 (1.00–1.34)	1.13 (0.86–1.49)
New use (use initiated ≤100 days) of antihyperglycemic drug and risk of pancreatitis						
Unadjusted, age-/sex-matched	1.17 (0.61–2.25)	1.80 (0.89–3.65)	0.28 (0.04–2.05)	1.70 (1.22–2.35)	2.42 (1.45–4.05)	5.03 (3.22–7.85)
Adjusted						
Pancreatitis-associated conditions*	0.96 (0.48–1.89)	1.55 (0.74–3.27)	0.21 (0.03–1.57)	1.34 (0.95–1.90)	2.02 (1.17–3.46)	3.96 (2.45–6.39)
Plus pancreatitis-associated drug use†	0.91 (0.46–1.81)	1.48 (0.71–3.08)	0.18 (0.02–1.40)	1.21 (0.85–1.72)	1.88 (1.09–3.22)	3.78 (2.32–6.15)
Plus any comorbidity included in CCI‡	0.88 (0.45–1.75)	1.51 (0.72–3.14)	0.17 (0.02–1.27)	1.19 (0.84–1.70)	1.98 (1.15–3.41)	3.62 (2.22–5.91)

Data are reported as OR (95% CI). This table shows the effect of stepwise adjustment for pancreatitis-associated conditions, pancreatitis-associated drug use, and any comorbidity, for different categories of acute pancreatitis diagnoses and drug exposure windows. *Previous hospital diagnosis (not including index hospital admission with pancreatitis) of gallstones, obesity, alcoholism-related disorders, irritable bowel disease, or any cancer (except new cancer diagnosis diagnosed within the past 90 days). †Previous prescription for lipid-lowering drugs, oral glucocorticoids, azathioprine, NSAIDs, or antiepileptics. ‡Modified CCI; see Supplementary Data.

further adjusting for diabetes duration and complications. Second, patients with medically treated diabetes are usually observed closely by health care providers, and it is possible that physicians are more likely to hospitalize a diabetic patient with pancreatitis than a nondiabetic patient. Such bias would lead to overestimation of the RR associated with diabetes in general. At the same time, acute pancreatitis is a painful, severe disease, which is likely to lead to a hospital contact regardless of diabetes status, especially in a universal health care setting. Third, some of the pancreatitis risk factors we adjusted for in our models may not fulfill confounder criteria, if they were direct effects of the drug exposure. For example, if incretin-based therapies caused gallstones or reduced obesity, gallstones and obesity may be intermediate factors (i.e., mechanisms by which incretin-based therapies may affect pancreatitis risk). Adjustment for possible intermediates may have led us to underestimate the associations between antihyperglycemic drug use and acute pancreatitis, and both crude and adjusted risk estimates should therefore be taken into account when interpreting our results. Of note, when we restricted the study only to risk factors diagnosed before the initiation therapy with the drugs, we found materially unchanged results. Moreover, we also examined the effect of incretin use separately in people with and without obesity, gallstones, and other important pancreatitis risk factors, finding no association. Fourth, we lacked data on lifestyle factors such as smoking habits and amount of alcohol intake. We therefore cannot rule out some uncontrolled confounding by lifestyle factors (e.g., in former users). Finally, redeemed prescriptions is an imperfect measure of the actual drug intake.

In conclusion, our data suggest that the use of DPP4 inhibitors or GLP-1 receptor agonists did not appear to be associated with increased risk for acute pancreatitis.

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Author Contributions. R.W.T. helped to review the literature and direct the analyses; organized the writing of and wrote the initial drafts of the manuscript; participated in the discussion and interpretation of the results; helped to critically revise the manuscript for intellectual content; and approved the final version of the manuscript. L.P. helped to conceive the study idea, design the study, collect the data, and direct the analyses; participated in the discussion and interpretation of the results; helped to critically revise the manuscript for intellectual content; and approved the final version of the manuscript. N.M. and H.B.-N. helped to conceive the study idea, design the study, and review the literature; participated in the discussion and interpretation of the results; helped to critically revise the manuscript for intellectual content; and approved the final version of the manuscript. J.K. helped to collect the data and direct and carry out the analyses; participated in the discussion and interpretation of the results; helped to critically revised the manuscript for intellectual content; and approved the final version of the manuscript. H.T.S. helped to conceive the study idea, design the study, review the literature, collect the data, and direct the analyses; participated in the discussion and interpretation of the results; helped to critically revised the manuscript for intellectual content; and approved the final version of the manuscript. H.T.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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