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Association Between Incretin-Based Drugs and the Risk of Acute Pancreatitis

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IMPORTANCE The association between incretin-based drugs, such as dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, and acute pancreatitis is controversial.

OBJECTIVE To determine whether the use of incretin-based drugs, compared with the use of 2 or more other oral antidiabetic drugs, is associated with an increased risk of acute pancreatitis.

DESIGN, SETTING, AND PARTICIPANTS A large, international, multicenter, population-based cohort study was conducted using combined health records from 7 participating sites in Canada, the United States, and the United Kingdom. An overall cohort of 1 532 513 patients with type 2 diabetes initiating the use of antidiabetic drugs between January 1, 2007, and June 30, 2013, was included, with follow-up until June 30, 2014.

EXPOSURES Current use of incretin-based drugs compared with current use of at least 2 oral antidiabetic drugs.

MAIN OUTCOMES AND MEASURES Nested case-control analyses were conducted including hospitalized patients with acute pancreatitis matched with up to 20 controls on sex, age, cohort entry date, duration of treated diabetes, and follow-up duration. Hazard ratios (HRs) and 95% CIs for hospitalized acute pancreatitis were estimated and compared current use of incretin-based drugs with current use of 2 or more oral antidiabetic drugs. Secondary analyses were performed to assess whether the risk varied by class of drug (DPP-4 inhibitors and GLP-1 agonists) or by duration of use. Site-specific HRs were pooled using random-effects models.

RESULTS Of 1 532 513 patients included in the analysis, 781 567 (51.0%) were male; mean age was 56.6 years. During 3 464 659 person-years of follow-up, 5165 patients were hospitalized for acute pancreatitis (incidence rate, 1.49 per 1000 person-years). Compared with current use of 2 or more oral antidiabetic drugs, current use of incretin-based drugs was not associated with an increased risk of acute pancreatitis (pooled adjusted HR, 1.03; 95% CI, 0.87-1.22). Similarly, the risk did not vary by drug class (DPP-4 inhibitors: pooled adjusted HR, 1.09; 95% CI, 0.86-1.22; GLP-1 agonists: pooled adjusted HR, 1.04; 95% CI, 0.81-1.35) and there was no evidence of a duration-response association.

CONCLUSIONS AND RELEVANCE In this large population-based study, use of incretin-based drugs was not associated with an increased risk of acute pancreatitis compared with other oral antidiabetic drugs.

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D ipeptidylpeptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists are incretin-based drugs that are widely used in the treatment of type 2 diabetes. Despite lowering the risk of hypoglycemia and having favorable effects on body weight compared with other antidiabetic drugs,[1] there have been concerns that the use of incretin-based drugs may increase the risk of pancreatic-related events. Indeed, analyses[2-4] of adverse events databases have associated the use of incretin-based drugs with an increased risk of acute pancreatitis, although such analyses have well-known limitations. In addition, in a meta-analysis[5] of randomized clinical trials (RCTs), incretin-based drugs were associated with an increased risk of pancreatic enzyme level elevation, but the association with acute pancreatitis was inconclusive because of sparse data. This association was also assessed in several observational studies, but these have generated conflicting findings.[6-23] Such discrepancies may be the result of important methodologic limitations, such as confounding by indication, and none were adequately powered to detect a modest increased risk of this rare outcome.[24]

Thus, given the continued concerns regarding the safety of incretin-based drugs,[25] the Canadian Network for Observational Drug Effect Studies (CNODES)[26] assessed their association with 3 clinically important adverse events, including pancreatic cancer[27] and heart failure,[28] and acute pancreatitis. We describe a large, multicenter study using health records from 3 countries to determine whether the use of incretin-based drugs is associated with an increased risk of acute pancreatitis in patients with type 2 diabetes.

Methods

Data Sources

This cohort study used the administrative and electronic medical record databases from 7 participating sites across 3 countries. The data sources included 5 Canadian provinces (Alberta, Manitoba, Ontario, Quebec, and Saskatchewan), the United States (MarketScan), and the United Kingdom (Clinical Practice Research Datalink [CPRD]).[29] The Canadian databases include patient-level information on prescription drug claims, hospitalization data, and physician billings; the Ontario data were restricted to patients 65 years or older; the US MarketScan database includes medical information from individuals and their dependents insured by private health insurance plans; and the UK CPRD database contains complete primary care medical records for more than 13 million individuals enrolled in more than 680 general practices and has been shown to be representative of the UK population.

This was a large, international, multicenter, population-based cohort study (clinicaltrials.gov identifier: NCT02476760). All participating sites followed a common analytical protocol that was approved by the institutional review boards at all participating sites (Conjoint Health Research Ethics Board, University of Saskatchewan Research Ethics Office, University of Manitoba Health Research Ethics Board, University of British Columbia Office of Research Ethics, Sunnybrook Health Sciences Centre, Jewish General Hospital Research Ethics Office, and the Independent Scientific Advisory Committee of the CPRD [protocol number 14_119R]). All data were deidentified for research purposes; thus, patient informed consent was not necessary.

Study Population

At each participating site, a base cohort was assembled consisting of all patients who initiated treatment with a first-ever prescription for a noninsulin antidiabetic drug. These agents included metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, GLP-1 agonists, α-glucosidase inhibitors, and meglitinides, from the earliest date of data availability in each participating site up to June 30, 2013, or the most recent date of data availability at each participating site. Patients with the following characteristics were then sequentially excluded at the time of the first prescription for a noninsulin antidiabetic drug: age younger than 18 years (or the minimum age for which prescription data are available plus 365 days), less than 365 days of medical history in the database before the first prescription for a noninsulin antidiabetic drug, a previous insulin prescription (as this may indicate more advanced disease), and women with a history of polycystic ovarian syndrome or a diagnosis of gestational diabetes in the 365 days before the first prescription for a noninsulin antidiabetic drug since these conditions are other possible indications for use of metformin.

Within the base cohort, a cohort consisting of all patients who initiated use of a new antidiabetic drug class any time after incretin-based drugs entered the market in each participating site until June 30, 2013 (or the most recent date of data availability at each participating site) was identified. These cohort members included individuals who initiated treatment with an antidiabetic drug (ie, first-ever prescription of a noninsulin antidiabetic drug) as well as those who added or switched to an antidiabetic drug class not previously identified in their medication history. The date of this new prescription defined cohort entry. Patients were then sequentially excluded if they met the following criteria at any time before cohort entry: previous diagnosis of pancreatic cancer, history of pancreatectomy or pancreatic injury, presence of congenital defects of the pancreas, diagnosis of cystic fibrosis or lupus erythematosus, bariatric surgery, or diagnosis of human immunodeficiency virus or treatment with highly active antiretroviral therapy (a known

Key Points

Question Is the use of the incretin-based drugs (glucagon-like peptide 1 agonist and dipeptidyl peptidase 4 inhibitors) associated with an increased risk of acute pancreatitis?

Findings In this international population-based study of 1.5 million patients with type 2 diabetes, compared with other antidiabetic drugs, the use of incretin-based agents was not associated with an overall increased risk of acute pancreatitis. Similarly, there was no association by duration of use and by type of incretin-based drug.

Meaning The findings of this real-world study provide some reassurance that the use of incretin-based drugs is not associated with an increased risk of acute pancreatitis.

risk factor for acute pancreatitis[30]). Finally, patients hospitalized for acute pancreatitis (defined below) in the 30 days before cohort entry were excluded.

All patients meeting the study inclusion criteria were monitored from cohort entry until a hospitalization for acute pancreatitis (defined below) or censored on a new diagnosis of human immunodeficiency virus or prescription for highly active antiretroviral therapy, death from any cause, end of coverage in the database, or end of the study period (June 30, 2014, or the most recent date of data availability at each participating site), whichever occurred first.

Case-Control Selection

Nested case-control analyses were conducted within the cohort in each participating site. This approach was chosen because of the size of the cohorts and the time-varying nature of exposure.[31] Risk-set sampling was used for the matching of controls to cases, which produces odds ratios that are unbiased estimators of hazard ratios (HRs).[31-33]

Cases consisted of all patients with a hospital admission for acute pancreatitis during follow-up (*International Classification of Diseases, Ninth Revision*, code 577.0, and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, codes K85.0, K85.1, K85.2, K85.3, K85.8, and K85.9 in either the primary [or most responsible] or secondary position). For each case, the index date was defined by the date of the hospital admission. The recording of hospitalized acute pancreatitis events was shown to have good positive and negative predictive values.[34]

Up to 20 controls were randomly selected for each case, matched on age (±365 days), date of cohort entry (±180 days), sex, duration of pharmacologically treated diabetes before cohort entry (defined as the time between base-cohort entry and cohort entry, ±90 days), and duration of follow-up. Matched controls were assigned the index date of their respective cases.

Exposure Assessment

Cases and matched controls were classified into 1 of 5 mutually exclusive exposure groups at index date, with patients sequentially categorized by (1) current use of incretin-based drugs (DPP-4 inhibitors [linagliptin, sitagliptin phosphate, vildagliptin, and saxagliptin] or GLP-1 agonists [exenatide and liraglutide], alone or in combination with other antidiabetic drugs); (2) current use of insulin (alone or in combination with other nonincretin-based antidiabetic drugs); (3) current use of 2 or more oral antidiabetic drugs; (4) current use of 1 oral antidiabetic drug; and (5) noncurrent use of any antidiabetic drug. Current use was defined by prescription duration, plus a 30-day grace period overlapping the index date. Since incretin-based drugs are considered second- to third-line antidiabetic agents,[35] the reference group consisted of current use of at least 2 oral antidiabetic drugs, which is a common second-to third-line treatment strategy.[35]

Potential Confounders

In addition to age, calendar year of cohort entry, sex, duration of treated diabetes, and duration of follow-up on which the models were conditioned, the following potential baseline confounders were considered: alcohol-related disorders (based on diagnoses for alcohol-related disorders, such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic failure), history of gallstones, history of cancer (other than nonmelanoma skin cancer), and history of acute or chronic pancreatitis, all measured at any time before cohort entry. The models were also adjusted for prescription drugs previously associated with acute pancreatitis, including use of angiotensin-converting enzyme inhibitors, loop or thiazide diuretics, oral contraceptives and hormone replacement therapy, statins, fibrates, and valproic acid; all were measured in the year before cohort entry. Microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy) were also adjusted for, as well as the number of different antidiabetic drug classes received in the patient's history before cohort entry, with both factors as proxies of diabetes severity. In addition, the models were adjusted for 2 general measures of comorbidity: total number of hospitalizations and total number of unique nondiabetic drugs prescribed, with both measured in the year before cohort entry.[36] In the CPRD, the models were additionally adjusted for body mass index (<25, 25-29, and ≥30 [calculated as weight in kilograms divided by height in meters squared]; last measure prior to cohort entry), hemoglobin A_{1c} level (≤7.0%, 7.1%-8.0%, and >8.0% [to convert to proportion of total hemoglobin, multiply by 0.01]; last measure before cohort entry), and smoking status (ever or never). These variables were modeled by including a category for missing values, given that information was missing in relatively few patients.
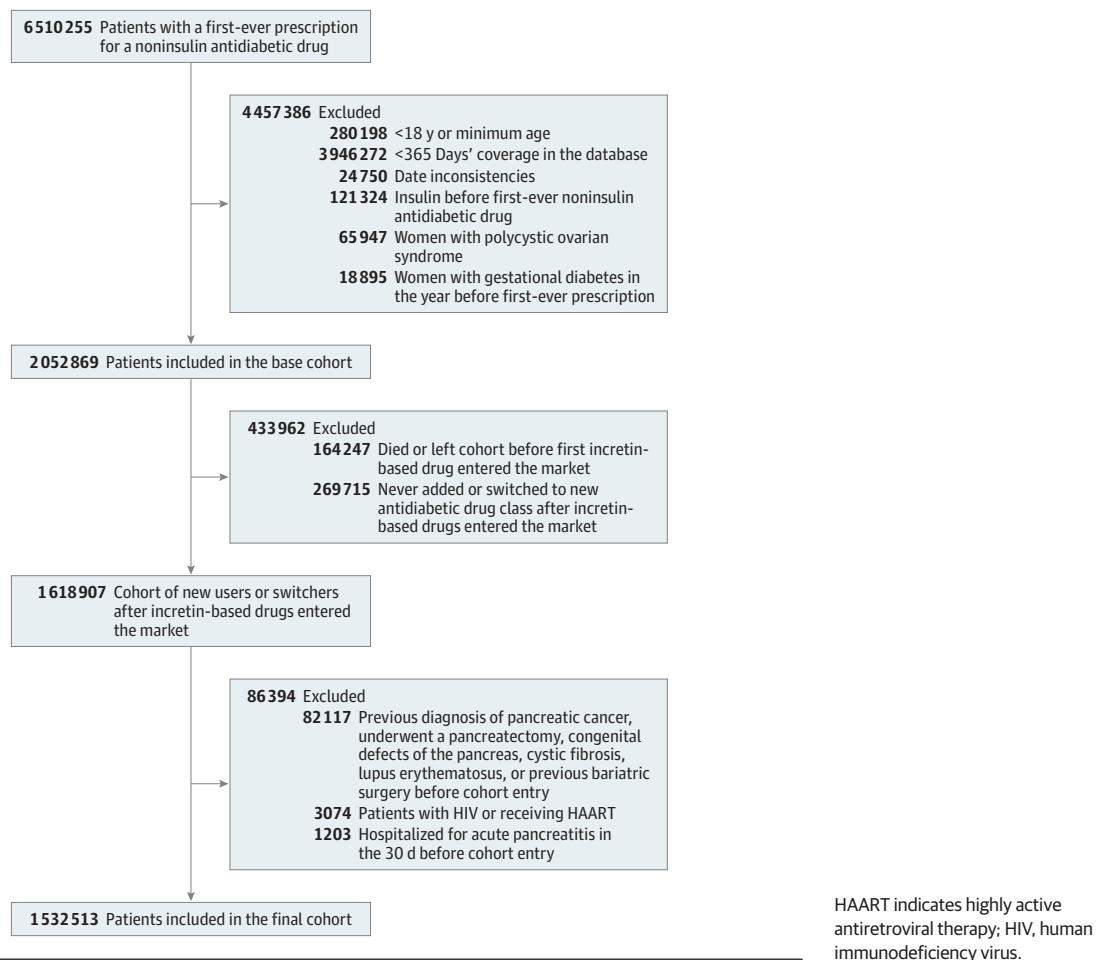
Statistical Analysis

The crude incidence rate of acute pancreatitis was calculated with 95% CIs based on the Poisson distribution. Conditional logistic regression was used to estimate HRs and corresponding 95% CIs of hospitalized acute pancreatitis, comparing current use of incretin-based drugs with current use of 2 or more oral antidiabetic drugs. All models were adjusted for the potential confounders listed above. Statistical analysis was conducted using SAS, version 9.4 (SAS Institute).

Secondary Analyses

We conducted 3 secondary analyses. First, we assessed whether there was a duration-response association between the use of incretin-based drugs and the risk of acute pancreatitis. Thus, patients deemed to be current users of incretin-based drugs in the primary analysis were further categorized according to duration of continuous use (<1.0, 1.0-1.9, and ≥2 years). Continuous drug use was defined as receiving consecutive overlapping prescriptions for incretin-based drugs, allowing for 30-day grace periods in the event of no overlap. Second, individuals with current use of incretin-based drugs were further categorized according to current use of DPP-4 inhibitors and GLP-1 agonists. Finally, we determined whether a history of acute or chronic pancreatitis is an effect modifier of the association between incretin-based drugs and acute pancreatitis. Effect modification was assessed by including an interaction term between the exposure and history of pancreatitis variables.

Figure 1. Construction of the Base and Study Cohorts

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┌─────────────────────────────────────────────┐
│ 6510255  Patients with a first-ever          │
│          prescription for a noninsulin       │
│          antidiabetic drug                   │
└─────────────────────────────────────────────┘
        │
        │     ┌──────────────────────────────────────────────────────┐
        │     │ 4457386 Excluded                                       │
        │     │   280198  <18 y or minimum age                         │
        │     │  3946272  <365 Days' coverage in the database          │
        ├────▶│    24750  Date inconsistencies                         │
        │     │   121324  Insulin before first-ever noninsulin         │
        │     │           antidiabetic drug                            │
        │     │    65947  Women with polycystic ovarian syndrome       │
        │     │    18895  Women with gestational diabetes in the       │
        │     │           year before first-ever prescription          │
        │     └──────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────────┐
│ 2052869  Patients included in the base cohort│
└─────────────────────────────────────────────┘
        │
        │     ┌──────────────────────────────────────────────────────┐
        │     │ 433962 Excluded                                        │
        │     │   164247  Died or left cohort before first incretin-   │
        ├────▶│           based drug entered the market                │
        │     │   269715  Never added or switched to new antidiabetic  │
        │     │           drug class after incretin-based drugs        │
        │     │           entered the market                           │
        │     └──────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────────┐
│ 1618907  Cohort of new users or switchers    │
│          after incretin-based drugs entered  │
│          the market                          │
└─────────────────────────────────────────────┘
        │
        │     ┌──────────────────────────────────────────────────────┐
        │     │ 86394 Excluded                                         │
        │     │    82117  Previous diagnosis of pancreatic cancer,     │
        │     │           underwent a pancreatectomy, congenital       │
        │     │           defects of the pancreas, cystic fibrosis,    │
        ├────▶│           lupus erythematosus, or previous bariatric   │
        │     │           surgery before cohort entry                  │
        │     │     3074  Patients with HIV or receiving HAART         │
        │     │     1203  Hospitalized for acute pancreatitis in       │
        │     │           the 30 d before cohort entry                 │
        │     └──────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────────┐
│ 1532513  Patients included in the final cohort│
└─────────────────────────────────────────────┘
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HAART indicates highly active antiretroviral therapy; HIV, human immunodeficiency virus.

Sensitivity Analyses

Eight prespecified sensitivity analyses were conducted to assess the robustness of the results. First, given the unknown validity of the acute pancreatitis diagnosis in the different CNODES participating sites, the primary analysis was repeated with restriction to cases with the diagnosis in primary position (ie, most responsible). Second, because there are no clear comparators for incretin-based drugs, the primary analysis was repeated using alternative comparators, consisting of current use of the metformin-sulfonylurea combination therapy and current use of insulin (with or without oral antidiabetic drugs). Third, the primary analysis was repeated by varying the grace period between prescriptions to 0 and 90 days. Fourth, the primary analysis was repeated by additionally adjusting for the antidiabetic drugs used in the year before cohort entry. Fifth, the primary analysis was repeated after excluding patients with a history of insulin use prior to the index date. Sixth, the primary analysis was repeated with the study period restricted to the period before the first alert regarding the potential association between incretin-based drugs and acute pancreatitis (October 2007). The latter analysis was restricted to the participating sites where incretin-based drugs entered their market prior to October 2007.[37] Seventh, to account for changes in health status that occurred during follow-up, the primary analysis was repeated with adjustment of covariates at the index date rather than baseline. Eighth, the primary analysis was repeated with a reduced set of covariates to ensure model convergence at all participating sites, with variables included in their continuous form where possible in one reduced model and using the Deyo version of the Charlson comorbidity index in a second reduced model.[38] Finally, in a post hoc sensitivity analysis, current use of incretin-based drugs was restricted to patients using these agents in combination with at least 1 other antidiabetic drug.

Meta-analysis

DerSimonian and Laird[39] random-effects models were used with inverse variance weighting to pool site-specific estimates. The estimates were also pooled using fixed-effects modeling in sensitivity analyses. Between-site heterogeneity was estimated using the I^2 statistic.

Results

A total of 1 532 513 patients met the study inclusion criteria (**Figure 1**). The mean age at cohort entry was 56.6 years, and

781 567 were male (51.0%) ; additional baseline characteristics of the cohort can be found in eTable 1 and site-specific baseline characteristics are presented in eTables 2-8 in the Supplement. Overall, the cohort was followed for a mean of 2.3 years, generating 3 464 659 person-years of follow-up; site-specific durations of follow-up are reported in eTable 9 in the Supplement. During this time, 5165 patients were hospitalized for acute pancreatitis, generating a crude incidence rate of 1.49 (95% CI, 1.45-1.53) per 1000 person-years. The site-specific incidence rates ranged between 1.09 and 2.00 per 1000 person-years (eTable 10 in the Supplement).

Table 1 presents the baseline characteristics of the 5165 cases and 96 654 matched controls. As expected, cases were more likely to have a history of alcohol-related disorders, gallstones, cancer (other than nonmelanoma skin cancer), and acute or chronic pancreatitis. Compared with controls, cases were also more likely to have used prescription drugs previously associated with acute pancreatitis, including fibrates, angiotensin-converting enzyme inhibitors, loop or thiazide diuretics, and valproic acid.

Overall, compared with current users of 2 or more oral antidiabetic drugs, current users of incretin-based drugs were less likely to be male, but had longer durations of treated diabetes, were more likely to be obese, and were more likely to have a history of gallstones and cancer. Both exposure groups had similar histories of acute or chronic pancreatitis (eTable 11 in the Supplement).

Table 2 presents the results of the primary and secondary analyses. Compared with current use of 2 or more oral antidiabetic drugs, current use of incretin-based drugs was not associated with an increased risk of hospitalization for acute pancreatitis (pooled adjusted HR, 1.03; 95% CI, 0.87-1.22) (Figure 2). Similarly, there was no association in the secondary analysis that categorized the use of incretin-based drugs by class (DPP-4 inhibitors: pooled adjusted HR, 1.09; 95% CI, 0.86-1.22; GLP-1 agonists: pooled adjusted HR, 1.04; 95% CI, 0.81-1.35) or by duration of use (Table 2 and eFigures 1-5 in the Supplement). Finally, there was no evidence of effect modification by history of acute or chronic pancreatitis (no history: pooled adjusted HR, 1.05; 95% CI, 0.86-1.27; history: pooled adjusted HR, 0.70; 95% CI, 0.42-1.17; P = .20 for interaction); (eFigures 6 and 7 in the Supplement).

The results of the sensitivity analyses are summarized in Figure 3; site-specific estimates are presented in eFigures 8-19 in the Supplement. Overall, these analyses yielded findings that were consistent with those of the primary analysis. The HR in the fixed-effects model (pooled adjusted HR, 1.00; 95% CI, 0.87-1.13) was similar to the one generated with the random-effects model for the primary analysis (pooled adjusted HR, 1.03; 95% CI, 0.87-1.22).

Discussion

To our knowledge, this is the largest population-based study to have investigated the association between the use of incretin-based drugs and the risk of acute pancreatitis. With a combined cohort of more than 1.5 million patients with type 2

Table 1. Characteristics of Acute Pancreatitis Cases and Matched Controls Among Patients With Type 2 Diabetes[a]

Baseline Characteristics	No. (%)	
	Cases	Controls[b]
No. of patients	5165	96 654
CNODES site		
US MarketScan	3458 (67.0)	69 160 (71.6)
Quebec	704 (13.6)	11 338 (11.7)
UK Clinical Practice Research Datalink	268 (5.2)	4083 (4.2)
Ontario	215 (4.2)	3901 (4.0)
Alberta	274 (5.3)	5429 (5.6)
Manitoba	209 (4.0)	2391 (2.5)
Saskatchewan	37 (0.7)	352 (0.4)
Age, mean, y[c]	57.9	57.9
18-25	46 (0.9)	881 (0.9)
26-35	280 (5.4)	5203 (5.2)
36-45	717 (13.9)	13 419 (13.8)
46-55	1345 (26.0)	25 953 (26.3)
56-65	1214 (23.5)	22 829 (23.4)
66-75	897 (17.4)	16 838 (17.6)
≥76	665 (12.9)	11 531 (12.7)
Male sex[c]	2943 (57.0)	55 189 (57.0)
Calendar year of cohort entry[c]		
2007	776 (15.0)	15 027 (14.9)
2008	995 (19.3)	17 906 (19.4)
2009	1159 (22.4)	22 058 (22.6)
2010	922 (17.9)	17 380 (17.9)
2011	741 (14.3)	14 031 (14.3)
2012	408 (7.9)	7488 (7.9)
2013	160 (3.1)	2733 (3.1)
2014	5 (0.1)	30 (0.0)
Duration of treated diabetes, mean,[c] y	0.7	0.7
BMI[d]		
<25	S	402 (10.8)
25-29	73 (27.2)	1262 (31.6)
≥30	146 (54.5)	2313 (55.5)
Missing	S	106 (2.1)
Hemoglobin A_{1c}, % [d]		
≤7.0	42 (15.7)	581 (13.3)
7.1-8.0	54 (20.1)	1091 (26.6)
>8.0	113 (42.2)	1630 (45.4)
Missing	59 (22.0)	781 (14.8)
Smoking status[d]		
Ever	195 (72.8)	2505 (61.9)
Never	73 (27.2)	1554 (37.6)
Missing	0	24 (0.5)
Alcohol-related disorders	246 (4.8)	680 (0.8)
Gallstones	438 (8.5)	2694 (3.2)
Cancer, excluding nonmelanoma skin cancer	704 (13.6)	8165 (8.9)
Acute or chronic pancreatitis	726 (14.1)	782 (0.9)
Microvascular complications of diabetes		
Neuropathy	107 (2.1)	1031 (1.5)
Renal disease	525 (10.2)	4966 (5.9)
Retinopathy	420 (8.1)	7293 (8.4)
Peripheral arteriopathy	331 (6.4)	4088 (4.4)

(continued)

Table 1. Characteristics of Acute Pancreatitis Cases and Matched Controls Among Patients With Type 2 Diabetes[a] (continued)

Baseline Characteristics	No. (%) Cases	Controls[b]
Prescription drugs		
Statins	2354 (45.6)	44 977 (48.1)
Fibrates	505 (9.8)	4583 (4.8)
ACE inhibitors	2028 (39.3)	31 907 (33.9)
Loop or thiazide diuretics	1985 (38.4)	33 383 (35.0)
Oral contraceptives or hormone replacement therapy	276 (5.3)	5543 (5.5)
Valproic acid	58 (1.1)	529 (0.6)
No. of hospitalizations, mean	0.5	0.2
0	3790 (73.4)	84 929 (87.3)
1	917 (17.8)	9225 (9.8)
2	274 (5.3)	1851 (2.1)
3	98 (1.9)	409 (0.5)
≥4	89 (1.7)	237 (0.3)
No. of unique nonantidiabetic drugs, mean	9.5	7.6
0	483 (9.4)	12 086 (11.9)
1	233 (4.5)	6000 (6.0)
2	273 (5.3)	6687 (6.7)
3	264 (5.1)	6994 (7.2)
≥4	3911 (75.7)	64 887 (68.3)
Precohort entry antidiabetic drugs, mean	0.2	0.2
0	4566 (88.4)	91 151 (88.5)
1	260 (5.0)	2926 (5.8)
2	190 (3.7)	1501 (3.2)
3	100 (1.9)	724 (1.6)
≥4	49 (0.9)	352 (0.9)
Cohort entry drugs[e]		
Metformin	3618 (70.0)	76 498 (75.1)
Sulfonylureas	1172 (22.7)	16 396 (18.3)
Thiazolidinediones	349 (6.8)	6377 (6.9)
DPP-4 inhibitors	378 (7.3)	5907 (6.9)
GLP-1 agonists	46 (0.9)	1069 (1.2)
α-Glucosidase inhibitors	18 (0.3)	285 (0.5)
Meglitinides	84 (1.6)	765 (1.0)
Insulins	143 (2.8)	688 (1.8)
Other	70 (0.1)	216 (0.2)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CNODES, Canadian Network for Observational Drug Effect Studies; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; S, suppressed.

SI conversion factor: To convert hemoglobin A[1c] to proportion of total hemoglobin, multiply by 0.01.

[a] When summing data across sites, we assigned a value of 3 to small cells (≤5). As such, the sum of count data may differ from the presented total. Cells with fewer than 5 observations were suppressed (denoted by an S) owing to privacy restrictions.

[b] The means and proportions among controls were weighted by the number of controls per case and then weighted by the number of cases per site.

[c] Matching variable.

[d] Data from the UK Clinical Practice Research Datalink; percentages based on 268 cases and 4083 matched controls.

[e] Nonmutually exclusive categories.

Table 2. Association Between Use of Incretin-Based Drugs and the Incidence of Acute Pancreatitis[a]

Current Use[b]	Cases (n = 5165)	Controls (n = 96 654)	Adjusted HR (95% CI)[c]	I^2, %
Primary analysis				
≥2 Oral antidiabetic drugs	679 (13.2)	10 809 (11.2)	1.00 [Reference]	13.6
Incretin-based drugs	562 (10.9)	9043 (9.4)	1.03 (0.87-1.22)	
Class of incretin-based drug				
DPP-4 inhibitors	488 (9.5)	7824 (8.1)	1.09 (0.86-1.38)	39.4
GLP-1 agonists[d]	74 (1.4)	1219 (1.3)	1.04 (0.81-1.35)	0.0
Duration of use, y				
<1.0	470 (9.1)	7191 (7.4)	1.15 (0.87-1.51)	34.7
1.0-1.9	62 (1.2)	1289 (1.3)	0.73 (0.54-0.99)	0.5
≥2.0	36 (0.7)	563 (0.6)	0.84 (0.51-1.37)	11.8

Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HR, hazard ratio.

[a] Cases and controls were matched on sex, age, year of cohort entry, duration of treated diabetes, and duration of follow-up.

[b] Users of other antidiabetic drugs and treatment combinations (corresponding to 3924 cases and 76 802 controls) are not included but were considered in the regression model for proper estimation of treatment effects.

[c] Adjusted for alcohol-related disorders; history of gallstones; history of cancer (other than nonmelanoma skin cancer); history of acute or chronic pancreatitis; microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy); use of statins, fibrates, angiotensin-converting enzyme inhibitors, oral contraceptives or hormone replacement therapy, or valproic acid; number of hospitalizations (0, 1, 2, 3, and ≥4); number of unique nondiabetic drugs (0, 1, 2, 3, and ≥4); and number of antidiabetic drugs received prior to cohort entry (0, 1, 2,3, ≥4). In the Clinical Practice Research Datalink, the models were further adjusted for body mass index, smoking status, and hemoglobin A[1c] level (≤7.0%, 7.1%-8.0%, >8.0% (to convert to proportion of total hemoglobin, multiply by 0.01).
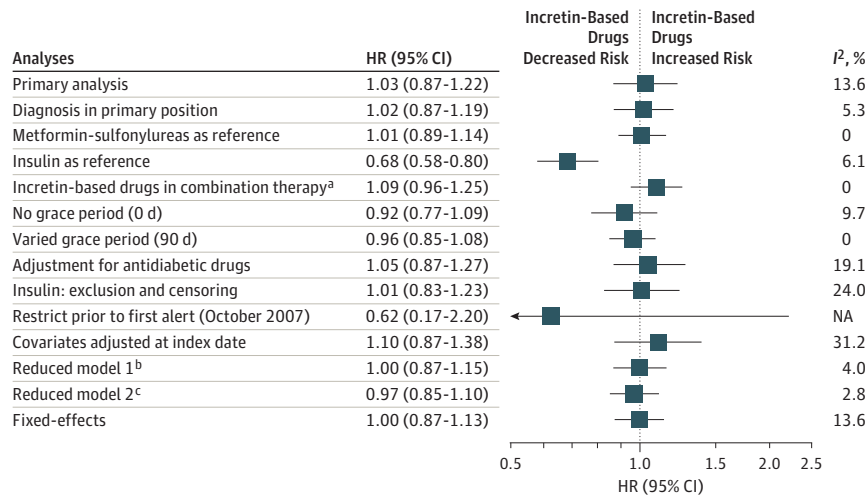
[d] This analysis was limited to the Alberta site, the UK Clinical Practice Research Datalink, and the US MarketScan, the 3 of the 4 sites where GLP-1 agonists were available. The Manitoba site was not included owing to few events preventing model convergence.

Figure 2. Association Between the Use of Incretin-Based Drugs and the Risk of Acute Pancreatitis Among Patients With Type 2 Diabetes

Site	HR (95% CI)
Alberta	1.49 (0.72-3.08)
UK CPRD	1.13 (0.67-1.91)
Manitoba	2.17 (0.92-5.14)
US MarketScan	0.93 (0.79-1.09)
Ontario	0.83 (0.49-1.42)
Saskatchewan	4.32 (0.23-79.92)
Quebec	1.09 (0.79-1.51)
Overall	1.03 (0.87-1.22)
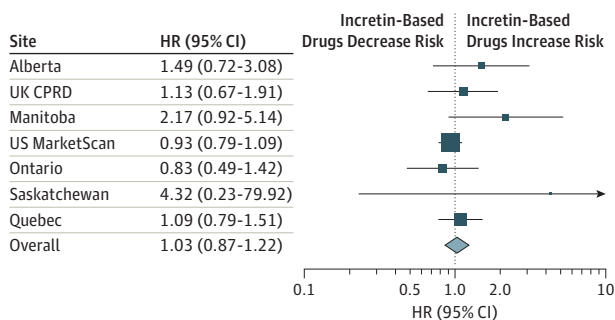
The reference category was current use of 2 or more oral antidiabetic drugs. The size of the boxes is proportional to the weight of a given participating site in the random-effects meta-analysis. The I^2 (percentage of the total variance due to between-study heterogeneity) was 13.6% (P = .33 for heterogeneity). CPRD indicates Clinical Practice Research Datalink; HR, hazard ratio.

Figure 3. Sensitivity Analyses for the Association Between the Use of Incretin-Based Drugs and the Incidence of Acute Pancreatitis

Analyses	HR (95% CI)	Incretin-Based Drugs Decreased Risk	Incretin-Based Drugs Increased Risk	I^2, %
Primary analysis	1.03 (0.87-1.22)			13.6
Diagnosis in primary position	1.02 (0.87-1.19)			5.3
Metformin-sulfonylureas as reference	1.01 (0.89-1.14)			0
Insulin as reference	0.68 (0.58-0.80)			6.1
Incretin-based drugs in combination therapy[a]	1.09 (0.96-1.25)			0
No grace period (0 d)	0.92 (0.77-1.09)			9.7
Varied grace period (90 d)	0.96 (0.85-1.08)			0
Adjustment for antidiabetic drugs	1.05 (0.87-1.27)			19.1
Insulin: exclusion and censoring	1.01 (0.83-1.23)			24.0
Restrict prior to first alert (October 2007)	0.62 (0.17-2.20)			NA
Covariates adjusted at index date	1.10 (0.87-1.38)			31.2
Reduced model 1[b]	1.00 (0.87-1.15)			4.0
Reduced model 2[c]	0.97 (0.85-1.10)			2.8
Fixed-effects	1.00 (0.87-1.13)			13.6

0.5   1.0   1.5   2.0   2.5
HR (95% CI)

HR indicates hazard ratio; NA, not applicable.

[a] Defined as current use of incretin-based drugs in combination with at least 1 other antidiabetic drug.

[b] The models were adjusted for a composite variable of microvascular complications variable, categorical variables were converted to their continuous counterparts where possible, and insulin, oral antidiabetic drug

monotherapy, and not currently exposed were collapsed to a single "other exposure" category.

[c] The models included only exposure (current use of incretin-based drugs, current use of oral antidiabetic combinations, and other exposure) and the Deyo version of the Charlson comorbidity index.

diabetes, our findings suggest that use of incretin-based drugs is not associated with an overall increased risk of acute pancreatitis compared with use of 2 or more oral antidiabetic drugs. We observed similar results in secondary analyses that assessed the risk with DPP-4 inhibitors and GLP-1 agonists separately and by duration of use. Finally, our findings remained consistent in several sensitivity analyses that considered different potential sources of bias.

To date, several observational studies[6-23] have investigated the association between incretin-based drugs and acute pancreatitis. Overall, most of these studies[6-11,14-18,20,21,23] have reported null associations, with the exception of 4 investigations[12,13,19,22] in which positive associations were reported. The heterogeneity between these studies is likely the result of several methodologic shortcomings, including the use of inappropriate comparator groups, confounding by indication, time-lag bias,[40] prevalent user bias, small sample sizes, and short durations of follow-up.

In addition to the aforementioned observational studies, 4 large RCTs of DPP-4 inhibitors and GLP-1 agonists have been published.[41-44] In the RCTs of DPP-4 inhibitors, there were imbalances in the number of acute pancreatitis events between the experimental and placebo groups. Specifically, in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53) trial,[41] there were 24 events in the saxagliptin group and 21 in the placebo group; in the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care) trial,[42] there were 12 events in the alogliptin benzoate group and 4 in the placebo group; and in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) trial,[43] 23 events occurred in the sitagliptin

group compared with 12 in the placebo group. However, the imbalance was in the other direction in the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial,[44] with 5 events documented in the lixisenatide group and 8 events in the placebo group. These RCTs recruited patients with long-standing disease as well as a history of cardiovascular complications, which contrasts with the population using incretin-based drugs in a real-world setting. In our study, patients receiving incretin-based drugs had a relatively short duration of treated diabetes, and relatively few had microvascular complications of diabetes. However, it is unclear whether the apparent differences between our findings and the imbalance observed in these RCTs[41-44] is a reflection of the populations being evaluated. As such, future studies including patients with longer durations of diabetes will need to be conducted to reassess this association.

The present study has several strengths. First, with a combined cohort of more than 1.5 million patients, our study was well powered to detect modest but clinically important associations. Second, the use of population-based cohorts from 7 participating sites across 3 countries strengthens the generalizability of our findings. Finally, prevalent user bias[45] was avoided by requiring patients entering the base and study cohorts to be new users of antidiabetic drugs.

The study also has some limitations. Because of its observational design, residual confounding should be considered. However, we believe that residual confounding was mitigated through 3 different approaches. The first of these involved matching cases and controls on important variables, such as duration of treated diabetes, a proxy for disease severity.[46] In the second approach, we adjusted the models for a wide variety of potential confounders, including proxies of

diabetes severity (eg, microvascular complications of type 2 diabetes and number of antidiabetic drugs) and variables previously associated with acute pancreatitis. In the third approach, we compared incretin-based drugs with the use of oral antidiabetic drug combinations, the latter representing a second- to third-line treatment approach used at a similar stage of the disease as incretin-based drugs.[35] It was not possible to ascertain treatment adherence, possibly resulting in some exposure misclassification. Finally, although none of the sites generated statistically significant results, we observed some heterogeneity in the direction of their point estimates. Specifically, the HRs were above the null in the databases of the CPRD and Canadian sites (with the exception of the Ontario site), whereas the HR was under the null in the US MarketScan database. This heterogeneity may be the result of formulary restrictions in certain jurisdictions, differences in population, and the availability of certain potential confounders (eg, the CPRD was the only site where it was possible to additionally adjust for smoking, body mass index, and hemoglobin A_{1c}). The heterogeneity observed between the different data sets highlights the importance of replication in many databases, which is a key strength of the present study.

Conclusions

The findings of this large, population-based study indicate that the use of incretin-based drugs is not associated with an overall increased risk of acute pancreatitis compared with the use of oral antidiabetic drug combinations. Although it remains possible that these drugs may be associated with acute pancreatitis, the upper limit of our 95% CI suggests that this risk is likely to be small. Thus, the findings of this study should provide some reassurance to patients treated with incretin-based drugs.

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IMAGES FROM OUR READERS

A Chance of Showers

Courtesy of: Sagar S. Patel, MD, Cleveland Clinic, Department of Hematology and Medical Oncology, Cleveland, Ohio.

On a recent hiking trip through Iceland, we came across this infamous outdoor shower in Krafla that once was accompanied by an equally open toilet.