Glucagonlike Peptide 1–Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus

A Population-Based Matched Case-Control Study

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Importance: Acute pancreatitis has significant morbidity and mortality. Previous studies have raised the possibility that glucagonlike peptide 1 (GLP-1)–based therapies, including a GLP-1 mimetic (exenatide) and a dipeptidyl peptidase 4 inhibitor (sitagliptin phosphate), may increase the risk of acute pancreatitis.

Objective: To test whether GLP-1–based therapies such as exenatide and sitagliptin are associated with an increased risk of acute pancreatitis. We used conditional logistic regression to analyze the data.

Design: Population-based case-control study.

Setting: A large administrative database in the United States from February 1, 2005, through December 31, 2008.

Participants: Adults with type 2 diabetes mellitus aged 18 to 64 years. We identified 1269 hospitalized cases with acute pancreatitis using a validated algorithm and 1269 control subjects matched for age category, sex, enrollment pattern, and diabetes complications.

Main Outcome Measure: Hospitalization for acute pancreatitis.

Results: The mean age of included individuals was 52 years, and 57.45% were male. Cases were significantly more likely than controls to have hypertriglyceridemia (12.92% vs 8.35%), alcohol use (3.23% vs 0.24%), gallstones (9.06% vs 1.34), tobacco abuse (16.39% vs 5.52%), obesity (19.62% vs 9.77%), biliary and pancreatic cancer (2.84% vs 0%), cystic fibrosis (0.79% vs 0%), and any neoplasm (29.94% vs 18.05%). After adjusting for available confounders and metformin hydrochloride use, current use of GLP-1–based therapies within 30 days (adjusted odds ratio, 2.24 [95% CI, 1.36-3.68]) and recent use past 30 days and less than 2 years (2.01 [1.37-3.18]) were associated with significantly increased odds of acute pancreatitis relative to the odds in nonusers.

Conclusions and Relevance: In this administrative database study of US adults with type 2 diabetes mellitus, treatment with the GLP-1–based therapies sitagliptin and exenatide was associated with increased odds of hospitalization for acute pancreatitis.

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THE GLUCAGONLIKE PEPTIDE 1 (GLP-1)–based therapies include a GLP-1 mimetic, exenatide, and a dipeptidyl peptidase 4 inhibitor, sitagliptin phosphate. These therapies are used in patients with type 2 diabetes mellitus to lower blood glucose levels. Exenatide is a subcutaneous injectable GLP-1 agonist that enhances glucose-mediated insulin secretion. Sitagliptin is an oral dipeptidyl peptidase 4 inhibitor that prevents the proteolysis of endogenous GLP-1.[1]

Sitagliptin and exenatide have been shown to cause acute pancreatitis in rodent models via amplification of ductal replication and induction of acinar to ductal metaplasia.[2-5] Mouse models have also shown that GLP-1–based therapy may induce focal proliferation in the exocrine pancreas and accelerate formation of dysplastic lesions and pancreatitis.[6] Reports of spontaneous acute pancreatitis in humans have been published[7-9]; however, the strength of this association and causality cannot be inferred from these reports.

See Invited Commentary at end of article

Previous observational studies of this association have yielded inconsistent re-

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sults owing to limited statistical power, inadequate duration of follow-up, or inadequate adjustment for confounders such as obesity and diabetes disease severity.[10-14] The clinical trials of sitagliptin also had inconsistent findings owing to poor ascertainment and limited statistical power.[15,16] Acute pancreatitis is more prevalent among patients with type 2 diabetes mellitus compared with a nondiabetic cohort.[17] Thus, clinical uncertainty remains about whether the association between sitagliptin or exenatide and acute pancreatitis is causal. Given the significant risk of morbidity and mortality with acute pancreatitis, studies should determine whether the GLP-1–based therapies increase this risk.

Our objective was to determine the association of acute pancreatitis with the use of exenatide or sitagliptin in adults with type 2 diabetes mellitus. We aimed to test the hypothesis that 2 GLP-1–based therapies, one a GLP-1 mimetic (exenatide) and the other a dipeptidyl peptidase 4 inhibitor (sitagliptin), may increase the risk of acute pancreatitis.

METHODS

SETTING

We used administrative claims data from 7 Blue Cross Blue Shield Association (BCBS) plans. These are BCBS of Tennessee, Hawaii, Michigan, and North Carolina; Highmark, Inc, and Independence Blue Cross of Pennsylvania; and Wellmark, Inc, of Iowa and South Dakota.

STUDY DESIGN AND POPULATION

We assembled a population of BCBS beneficiaries with type 2 diabetes mellitus who filled at least 1 prescription for any drug used to treat type 2 diabetes from February 1, 2005, through December 31, 2008. We classified patients as having type 2 diabetes mellitus if they had 1 relevant inpatient code from the *International Classification of Disease, Ninth Revision* (*ICD-9*) or 2 outpatient *ICD-9* codes separated by at least 30 days (relevant codes included 250.xx, 648.0 [diabetes mellitus with pregnancy], 362.0 [diabetic retinopathy], and 266.41 [diabetic cataract]). Individuals were also classified as having diabetes mellitus if they filled a prescription for a medication to treat hyperglycemia (eTable 1; http://www.jamainternalmed.com). If the prescription was for metformin hydrochloride alone, the individual was also required to have an *ICD-9* code for diabetes for inclusion in this group. Individuals who had *ICD-9* codes for type 1 diabetes mellitus (250.x3) or gestational diabetes (648.83) only were excluded. To be eligible for inclusion, individuals had to be aged 18 to 64 years on the date of their first code for diabetes, contribute at least 6 months of medical or pharmacy coverage in the calendar year with a diabetes code, and of known sex. We excluded participants older than 64 years because their information concerning the use of health care resources was incomplete owing to insurance in addition to BCBS coverage (typically Medicare).

We determined eligibility for the study from computerized encounter data, including enrollment files for administrative data; benefits information to determine medical and pharmacy coverage; and inpatient, outpatient, and pharmacy claims records containing *Current Procedural Terminology* codes, *ICD-9* codes, and National Drug Codes, or diagnosis related group codes and costs and charges (submitted, allowed, and paid).

INCLUSION/EXCLUSION CRITERIA FOR CASES AND CONTROLS

Selection of Cases

Briefly, we identified presumptive cases by using a validated algorithm of *ICD-9* and *Current Procedural Terminology* codes for acute pancreatitis[18] (eTable 2). Cases were defined as individuals with an inpatient code for acute pancreatitis at any time after the first exposure to the drugs of interest. For patients with multiple episodes of acute pancreatitis, we included only the first episode. We excluded pancreatitis occurrences within 3 months of enrollment.

Selection of Controls

We randomly selected 1 control subject for each case from the eligible source population matched on age within 10 years, sex, insurance plan site, Diabetes Complication Severity Index (0, 1, 2, or ≥3),[19-21] and enrollment pattern or duration of follow-up (incidence density sampling). Acute pancreatitis cases were not eligible to undergo resampling as controls.

EXPOSURE WINDOWS

Prescription data were used as an indicator of drug exposure. We obtained information about drug use from a computerized pharmacy database containing the date the prescription was filled and the supply (measured as number of days). We used these data elements to determine the dates that a patient was exposed to the drug before the first observed diagnosis of acute pancreatitis. Drug exposure was defined as having filled a prescription for sitagliptin or exenatide before the first observed diagnosis of pancreatitis. An individual with exposure to sitagliptin or exenatide after the index diagnosis of acute pancreatitis was counted as unexposed. We defined 4 categories of exposure. *Any users* were exposed to sitagliptin or exenatide after the diagnosis of diabetes mellitus and before the index date of pancreatitis. *Current users* were exposed to sitagliptin or exenatide within 30 days before the index date of onset of pancreatitis. *Recent users* had a claim for sitagliptin or exenatide ranging from 30 days to 2 years before the index date of onset of pancreatitis. *Nonusers* had no sitagliptin or exenatide prescription more than 2 years before the index date of pancreatitis. Current users, recent users, and nonusers were mutually exclusive categories of exposure. However, any users included current and recent users.

STATISTICAL ANALYSIS

We calculated proportions for categorical variables and means or medians for continuous variables according to case or control status. We used conditional logistic regression to estimate the McNemar odds ratio (OR) for exposure to sitagliptin or exenatide to account for the matched design of the study. We conducted analyses for recent and current sitagliptin and exenatide users and for any users in a series of statistical models.

We adjusted statistical models for the matching variables, potential confounders specified a priori and identifiable in claims data, and metformin exposure during the same period. The confounders were hypertriglyceridemia, alcohol use, gallstones, tobacco abuse, obesity, biliary and pancreatic cancer, cystic fibrosis, and an indicator of general morbidity level (the resource utilization band from The Johns Hopkins adjusted clinical group case-mix system)[20] (eTable 3). In a sensitivity analysis, we excluded the cases and controls exposed to a combination of sitagliptin and metformin to test the robustness of our results.

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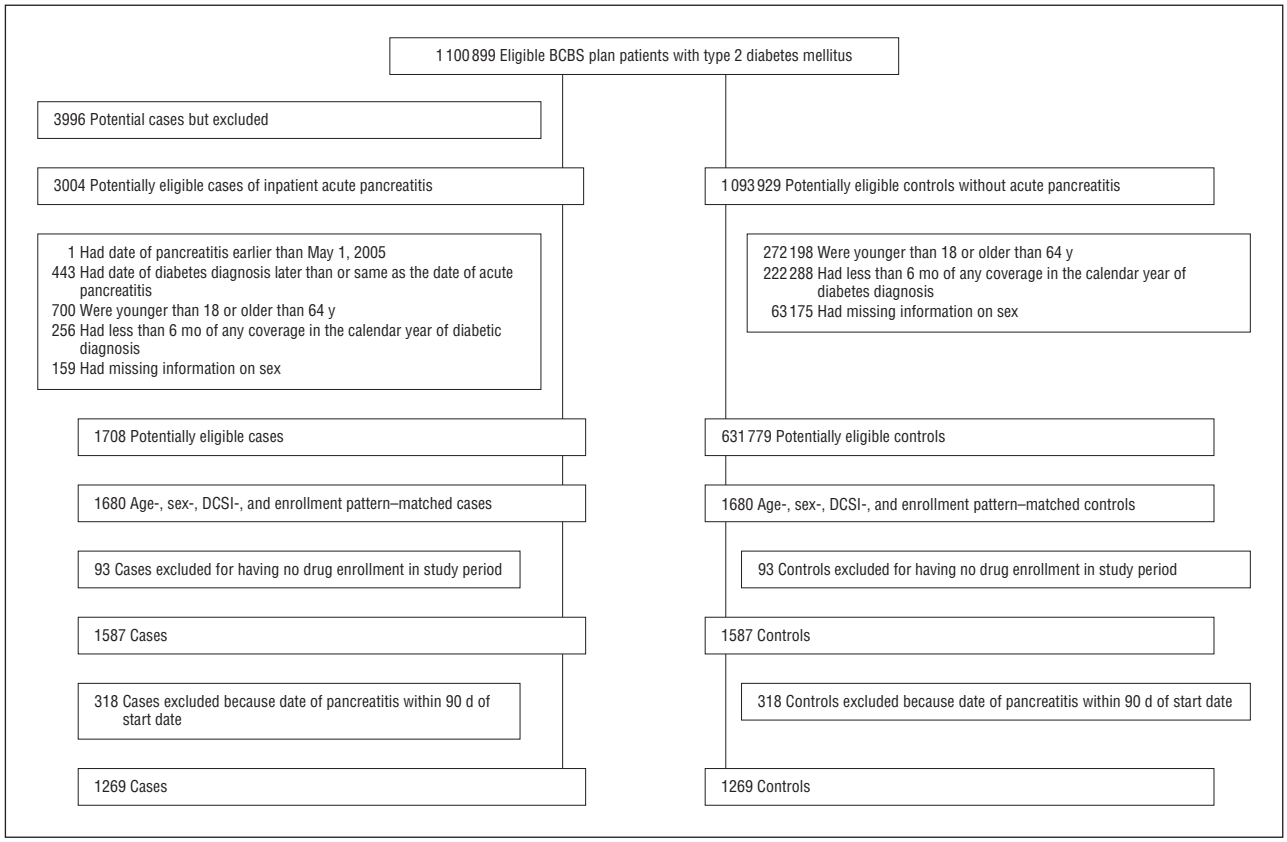

Figure. Selection of cases and control subjects. Some cases and controls met more than 1 exclusion criterion. BCBS indicates Blue Cross Blue Shield Association; DCSI, Diabetes Complication Severity Index.

We used commercially available statistical software (SAS, version 9.2; SAS Institute, Inc) for analysis. Statistical significance was set at 2-sided $P < .05$. We obtained ethical approval from the institutional review board at The Johns Hopkins University. This study was approved by the BCBS advisory board.

RESULTS

STUDY POPULATION

We identified 1 100 899 patients with type 2 diabetes mellitus who were potentially eligible during the study period. Within this group, 3004 participants experienced an episode of inpatient pancreatitis during the study period. We identified 1708 individuals with pancreatitis as our cases, after we excluded beneficiaries older than 64 years or younger than 18 years (n = 700), those who did not have 6 or more months of coverage in the calendar year of the starting date (n = 256), those with missing information on sex (n = 159), those with a diagnosis of diabetes after the date of the first pancreatitis diagnosis (n = 443), and those with onset of pancreatitis earlier than May 1, 2005 (n = 1) (some patients met more than 1 exclusion criterion). We matched 1680 controls selected from a pool of 631 779 potentially eligible controls. Ninety-three case-control pairs were excluded because they had no verifiable drug coverage during the study period, and 318 case-control pairs were excluded because the pancreatitis diagnosis was within 90 days of the index date (date of diabetes mellitus diagnosis or May 01, 2005, whichever was later). Thus, the analysis included 1269 each cases and controls (**Figure**). The mean age of included beneficiaries was approximately 52 years, and 57.45% were male (**Table 1**).

Cases with pancreatitis were statistically significantly more likely than controls to have hypertriglyceridemia (12.92% vs 8.35%), alcohol use (3.23% vs 0. 24%), gallstones (9.06% vs 1.34%), tobacco abuse (16.39% vs 5.52%), obesity (19.62% vs 9.77%), biliary and pancreatic cancer (2.84% vs 0%), cystic fibrosis (0.79% vs 0%), and neoplasms (29.94% vs 18.05%). Cases and controls also differed significantly in the use of health care resources.

The use of the studied GLP-1–based therapies associated with acute pancreatitis in cases and controls in various exposure windows is shown in **Table 2**.

ODDS OF HOSPITALIZATION FOR ACUTE PANCREATITIS

After adjusting for available confounders, including metformin use, current use within 30 days (adjusted OR [AOR], 2.24 [95% CI, 1.36-3.69]; $P = .01$) and recent use (2.01 [1.37-3.18]; $P = .01$) were associated with statistically significantly higher odds of acute pancreatitis. Any use was also associated with statistically significantly higher odds of acute pancreatitis (AOR, 2.07 [95% CI, 1.36-3.13]; $P = .01$).

SENSITIVITY ANALYSIS

The results of the sensitivity analysis with 1260 each cases and controls after exclusion of 9 pairs who were ex-

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Table 1. Characteristics of Acute Pancreatitis Cases and Control Subjects[a]

Characteristic	Cases (n = 1269)	Controls (n = 1269)
Age, mean (SD), y[b]	51.76 (9.19)	52.26 (9.21)
Age, y[b]		
18-30	2.52	2.52
31-44	17.89	17.89
45-65	79.59	79.59
Male sex[b]	57.45	57.45
DCSI, mean (SD)[b]	0.78 (1.35)	0.74 (1.24)
DCSI[b]		
0	65.09	65.09
1	13.79	13.79
2	10.56	10.56
≥3	10.56	10.56
Duration from date of pancreatitis to date of diabetes[b]		
1-6 mo	36.30	36.30
7-12 mo	20.90	20.90
13-18 mo	13.47	13.47
19-24 mo	10.66	10.66
3 y	13.23	13.23
≥4 y	5.44	5.44
Hypertriglyceridemia[c]	12.92	8.35
Alcohol use[c]	3.23	0.24
Gallstones[c]	9.06	1.34
Tobacco abuse[c]	16.39	5.52
Obesity[c]	19.62	9.77
Billiary/pancreatic cancer[c]	2.84	0.00
Cystic fibrosis[c]	0.79	0.00
Neoplasm[c]	29.94	18.05
Resource utilization band[c,d]		
0	3.70	5.04
1	0.06	1.02
2	4.73	8.43
3	32.47	48.23
4	22.46	20.88
5	36.64	16.39

Abbreviation: DCSI, Diabetes Complication Severity Index.
[a] Unless otherwise indicated, data are expressed as percentage of cases or controls.
[b] Indicates matching variable.
[c] Differences between cases and controls were statistically significant ($P < .05$).
[d] Described in Health Services Research and Development Center.[20]
Percentages have been rounded and might not total 100.

Table 2. Use of the Studied GLP-1–Based Therapies Based on Acute Pancreatitis Cases and Control Subjects in Prespecified Exposure Windows

Therapy[a]	No. of Cases (n = 1269)	No. of Controls (n = 1269)
Current exposure window		
Any GLP-1–based therapy	55	42
Exenatide	10	13
Sitagliptin	39	27
Combination of sitagliptin and metformin	6	2
None	1214	1227
Recent exposure window		
Any GLP-1–based therapy	72	48
Exenatide	29	16
Sitagliptin	38	29
Combination of sitagliptin and metformin	5	3
None	1197	1221
Any exposure window		
Any GLP-1–based therapy	87	58
Exenatide	34	24
Sitagliptin	47	31
Combination of sitagliptin and metformin	6	3
None	1182	1211

Abbreviation: GLP-1, glucagonlike peptide 1.
[a] Formulations used included sitagliptin phosphate and metformin hydrochloride. Exposure windows are described in the "Exposure Windows" subsection of the "Methods" section.

posed to metformin (along with sitagliptin) were consistent with the primary analysis. After adjusting for confounders and metformin use, current use within 30 days (AOR, 2.01 [95% CI, 1.19-3.38]; $P = .01$) and recent use (1.95 [1.21-3.14]; $P = .01$) were associated with a statistically significant odds of hospitalization for acute pancreatitis. Any use was also associated with statistically significantly higher odds of acute pancreatitis (AOR, 2.02 [95% CI, 1.31-3.01]; $P = .01$).

COMMENT

Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus. Our results support findings from mechanistic studies and spontaneous reports submitted to the US Food and Drug Association that such an association may be causal.[5]

Our findings need to be interpreted in the context of other studies. A cross-sectional analysis of spontaneous adverse events reported that the use of sitagliptin or exenatide increased the odds for reported pancreatitis 6-fold compared with the use of other antidiabetic drugs.[10] However, that study did not have data on confounders. An administrative claims–based study reported no difference in acute pancreatitis among exenatide users, sitagliptin users, and controls but could only adjust for a limited set of confounders.[11] Another administrative claims study reported no difference in acute pancreatitis among exenatide users, sitagliptin users, and controls owing to limited statistical power and limited duration of follow-up.[12] Another cohort study reported no significantly increased risk of acute pancreatitis with exposure to exenatide relative to other antihyperglycemics after propensity score adjustment but had limited statistical power and a limited exposure window.[13] In that study, the use of exenatide beyond 32 days was associated with a significantly increased risk of pancreatitis compared with the use of other antihyperglycemics. The study did not evaluate the role of sitagliptin. A descriptive database study reported no difference in the rates of acute pancreatitis among exenatide users (0.44%), sitagliptin users (0.28%), or controls (0.39%) after a follow-up of 540 days without any statistical tests or adjustment for confounders.[14] A meta-analysis of clinical trials reported no difference for sitagliptin use compared with placebo or other oral hypoglycemics in the incidence rates of pancreatitis (0.1% and 0%, respectively), acute pancreatitis (0% and 0.1%, respectively), and chronic pancreatitis (0.1% and 0%,

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respectively).[15] However, that study was limited by inadequate statistical power and incomplete ascertainment of adverse events in clinical trials.[16]

LIMITATIONS

Although we adjusted for diabetes severity, residual confounding is possible, and we recognize that tobacco abuse, obesity, and alcohol abuse are markedly undercoded in claims. Misclassification of case and control status is possible because we did not have access to the clinical records or diagnostic markers, such as serum amylase and serum lipase levels and/or radiological images. However, we used the best-performing algorithm with a positive predictive value of 60% to 80% and a negative predictive value of greater than 90% for acute pancreatitis.[18] Misclassification of exposure is possible because information on exposure was derived from pharmacy claims, and we cannot guarantee that the pills were ingested. The number of GLP-1–based therapy users was small, limiting our statistical power to detect an effect for specific drugs, resulting in imprecise estimates.

Our findings are not generalizable to patients older than 64 years, who were excluded from the analysis. We did not impute for missing data. We did not evaluate the risk of chronic pancreatitis because administrative databases are not suitable for outcomes detectable only by histological examination. We had limited duration of follow-up in our database, which was insufficient to evaluate the potential long-term risk of pancreatic cancer. Other GLP-1–based therapies, such as saxagliptin hydrochloride and liraglutide, were not available during the study period.

Our study also has several strengths. We minimized the possibility of type II error by selecting a large number of cases and focusing on the available class of GLP-1–based therapies during the study period rather than a single agent. We adjusted for a large number of available confounders, including metformin use. Our analytic plan allowed for adequate exposure windows because the timing of the risk of acute pancreatitis associated with GLP-1–based therapies was unknown.

UNANSWERED QUESTIONS AND FUTURE RESEARCH

We suggest that a self-controlled case series design that allows control for individual-level confounding by disease severity may offer additional insight. Further studies using new user designs should clarify the exact timing of these risks and determine whether susceptible subgroups, such as those with genetic mutations, or pancreatitis risks, such as obesity, may be at the highest risk. A recent study noted elevation of serum lipase and serum amylase levels in patients with GLP-1–based therapies.[22] Future studies should determine whether monitoring of serum enzyme levels can be used to predict the occurrence of acute pancreatitis among patients using GLP-1–based therapies. Long-term prospective studies should examine other outcomes, such as chronic pancreatitis and pancreatic cancer.

In summary, acute pancreatitis has significant morbidity and mortality. In this administrative database study of US adults with type 2 diabetes mellitus, treatment with the GLP-1–based therapies sitagliptin and exenatide was associated with an increased risk of hospitalization for acute pancreatitis.

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Online-Only Material: The eTables are available at http://www.jamainternalmed.com.
Additional Information: Information on NCRR is available at http://www.nih.gov/about/almanac/organization/NCRR.htm.

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INVITED COMMENTARY

Glucagonlike Peptide 1–Based Drugs and Pancreatitis

Clarity at Last, but What About Pancreatic Cancer?

The worldwide prevalence of type 2 diabetes mellitus (T2DM) is approaching 100 million.[1] Most affected individuals are treated for decades. Not surprisingly, the market for drug treatment of T2DM is worth more than $20 billion per year. The most lucrative drugs are those still protected by patent and deemed worthy of selection despite high expense because of clear advantages over cheaper drugs no longer covered by patent protection.

The glucagonlike peptide 1 (GLP-1)–based drugs are the most recently launched drug class for treatment of T2DM. Proponents of these drugs claim they are safe and offer advantages over existing drugs.[2] Glucagonlike peptide 1 is a hormone released by endocrine cells in the gut after meal ingestion, and one of its best characterized actions is amplification of glucose-mediated insulin secretion, a property that is of course desirable in T2DM. The first drug in this class approved in the United States was a peptide agonist of the GLP-1 receptor, exenatide (Byetta), followed by sitagliptin (Januvia), an inhibitor of the enzyme that degrades endogenously secreted GLP-1, dipeptidyl peptidase 4. Singh and colleagues[3] report that treatment with either of these GLP-1 mimetic drugs is associated with an increased risk of hospital admission for acute pancreatitis compared with other diabetes medications. The many strengths of this study include the large size of the sample, the ability to adjust for confounders, and the independence of the authors from the companies marketing the drugs. Because both drugs already carry US Food and Drug Administration (FDA) warnings for the risk of pancreatitis, why is this study important?

Pancreatitis associated with exenatide treatment was first described in case reports,[4] followed by adverse event reports by the FDA for sitagliptin and other drugs in this class. Vendors and supporters of GLP-1 treatment refuted the reported association of pancreatitis as being an artifact of the increased risk of pancreatitis in T2DM and pointed to a myriad of negative findings of animal and clinical studies, most performed by and/or sponsored by the marketing companies.[2] We appreciate why an increased risk of pancreatitis associated with drug treatment, even if rare, would be unwelcome. Antecedent pan-

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