Acute Pancreatitis in Type 2 Diabetes Treated With Exenatide or Sitagliptin

A retrospective observational pharmacy claims analysis

RAJESH GARG, MD[1]
WILLIAM CHEN, PHD, MPH[2]
MERRI PENDERGRASS, MD, PHD[2,3]

OBJECTIVE — Cases of acute pancreatitis have been reported in association with exenatide, sitagliptin, and type 2 diabetes without use of these medications. It remains unknown whether exenatide or sitagliptin increase the risk of acute pancreatitis.

RESEARCH DESIGN AND METHODS — A retrospective cohort study of a large medical and pharmacy claims database was performed. Data for 786,656 patients were analyzed. Cox proportional hazard models were built to compare the risk of acute pancreatitis between diabetic and nondiabetic subjects and between exenatide, sitagliptin, and control diabetes medication use.

RESULTS — Incidence of acute pancreatitis in the nondiabetic control group, diabetic control group, exenatide group, and sitagliptin group was 1.9, 5.6, 5.7, and 5.6 cases per 1,000 patient years, respectively. The risk of acute pancreatitis was significantly higher in the combined diabetic groups than in the nondiabetic control group (adjusted hazard ratio 2.1 [95% CI 1.7–2.5]). Risk of acute pancreatitis was similar in the exenatide versus diabetic control group (0.9 [0.6–1.5]) and sitagliptin versus diabetic control group (1.0 [0.7–1.3]).

CONCLUSIONS — Our study demonstrated increased incidence of acute pancreatitis in diabetic versus nondiabetic patients but did not find an association between the use of exenatide or sitagliptin and acute pancreatitis. The limitations of this observational claims-based analysis cannot exclude the possibility of an increased risk.

Diabetes Care 33:2349–2354, 2010

The most recently approved classes of agents for treatment of type 2 diabetes are the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors. Postmarketing surveillance of exenatide, the first GLP-1 receptor agonist, and sitagliptin, the first dipeptidyl peptidase-4 inhibitors, has raised the possibility of acute pancreatitis in association with their use (1–4). Based on case reports, the U.S. Food and Drug Administration (FDA) has added warnings about acute pancreatitis to the labeling information of exenatide and sitagliptin (5,6). More recently, acute pancreatitis has been reported to occur more often in clinical trials of patients who took liraglutide, a GLP-1 agonist approved by the FDA in January 2010 (7). The FDA is requiring a risk evaluation and mitigation strategy to help patients and health care providers understand the potential risk of acute pancreatitis with liraglutide.

As the use of incretin-based therapies increases, it is critical that potential adverse effects be fully characterized so clinicians and patients can balance potential benefits and harms of these agents. Clinical trials are unlikely to provide definitive answers about whether incretin-based therapies increase acute pancreatitis because this condition occurs at a very low frequency and because type 2 diabetes is associated with increased incidence of acute pancreatitis (8). Although epidemiological analyses have numerous limitations and cannot provide definitive conclusions, they may be helpful in exploring relationships between medication use and very low frequency adverse events. We performed an analysis of a large medical and pharmacy claims database to evaluate the relationship between exenatide, sitagliptin, and acute pancreatitis.

RESEARCH DESIGN AND METHODS

The source of data was the Medco National Integrated Database, which stores medical and pharmacy claims data. Medco's data repository contains >36 months of pharmacy claims for >60 million lives. More than 450 insurance plans provide medical claims data for ~13 million patients. Medical and pharmacy data are linked by a Medco-assigned identification number. The medical claims contain all inpatient, outpatient, nursing home, and laboratory and diagnostic testing claims the insurance plan has received. Laboratory values and medical care paid out of pocket or through Medicare are not included in the database.

Patients aged 18–63 years with pharmacy and medical claims data for a continuous period of at least 12 months between 1 January 2007 and 30 June 2009 were included in this study. This allowed a 6-month period for baseline observations and at least 6 months of observation after initiation of the index medication. Patients >63 years were excluded from the analysis because of the possibility of incomplete medical data due to dual Medicare coverage.

Diabetic patients were identified by the presence of at least one ICD-9 code of 250.XX during the study. The index date was defined as the fill date of the first claim for a new antidiabetes drug during the target period 1 July 2007 through 31 December 2008. An antidiabetes drug was considered new if there were no

From the [1]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Medco Health Solutions, Franklin Lakes, New Jersey; and the [3]University of Texas Southwestern Medical Center, Dallas, Texas.
Corresponding author: Merri Pendergrass, merri_pendergrass@medco.com.
Received 12 March 2010 and accepted 24 July 2010. Published ahead of print at http://care.diabetesjournals.org on 3 August 2010. DOI: 10.2337/dc10-0482.

claims for the medication during the prior 6 months. Based on the new antidiabetes drug (index drug), patients were divided into three groups: *1*) exenatide group (new exenatide start); *2*) sitagliptin group (new sitagliptin start); and *3*) diabetic control group (a new sulfonylurea, biguanide, or thiazolidinedione and no sitagliptin or exenatide prescription during the entire study period).

Patients with acute pancreatitis 6 months before or on the index date were excluded. Patients with other pancreatic diseases, e.g., chronic pancreatitis, were included. The following additional exclusions applied: treatment with repaglinide, nateglinide, acarbose, or miglitol (n = 4,153) and treatment with both exenatide and sitagliptin (n = 6,399). Nondiabetic patients were included as a second control group. Patients in the nondiabetic control group had at least one prescription claim for any medication other than antidiabetes medications (exenatide, sitagliptin, metformin, sulfonylureas, thiazolidinediones, insulin, acarbose, miglitol, repaglinide, or nateglinide) during the target period, at least one medical claim during the wash-in period or target period, and no ICD9 code of 250.XX or antidiabetes medication during the entire study period. The index date for the nondiabetic control group was a randomly generated date during the target period.

The observation period started on the index date and ended at the occurrence of one of the following events, whichever was the earliest: *1*) acute pancreatitis; *2*) 30 days after the index drug supply was predicted to run out (diabetic patients), based on the supply of drug that was dispensed; *3*) 18 months of follow-up; or *4*) end of eligibility. A secondary analysis was performed when exclusion *2* did not apply.

Acute pancreatitis was determined by a claim for ICD-9 code 577.0. The following risk factors for acute pancreatitis were determined from ICD-9 code claims data: hypertriglyceridemia (272.1), alcoholism (291.xx, 303.xx), biliary stone disease (574.xx, 575.xx), cholestatic liver disease (573.8), and pancreatic disease (577.1, 577.2, 577.8, 577.9, 157.xx). In addition, information on lipid-lowering drugs, glucocorticoids, azathioprine, mercaptopurine, sulfonamides, tetracyclines, nonsteroidal anti-inflammatory agents, and α-methyldopa was collected because of their common association with acute pancreatitis. Chronic disease score was calculated from pharmacy claims data by a method proposed by Von Korff et al. (9).

Statistical analysis

The primary outcome was the first occurrence of acute pancreatitis after the index date. All data were summarized as mean ± SD or number and percentage. The overall diabetic group (combined exenatide, sitagliptin, and diabetic control) was compared with the nondiabetic control group. Exenatide and sitagliptin groups were compared separately with the diabetic control group. Continuous variables were compared using an unpaired t test. Categorical variables were compared using the χ^2 test. Kaplan-Meier survival curves were constructed for each group to show the time to acute pancreatitis. Cox proportional hazard models were built to compare the adjusted risk of acute pancreatitis in diabetic (versus nondiabetic control) patients and in patients treated with exenatide and sitagliptin (versus other antidiabetic medications). Independent variables included age, sex, hypertriglyceridemia, alcohol abuse, biliary stone disease, cholestatic liver disease, and drug therapy. All analyses were performed with SAS software (version 9.1).

RESULTS — Baseline characteristics are shown in Table 1. Diabetic patients were slightly older than nondiabetic patients. The exenatide group was slightly younger and included more women than the other diabetic groups. Chronic disease score was higher in the exenatide and sitagliptin groups. Both the exenatide and sitagliptin groups received more antidiabetes drugs from multiple classes before starting the index drug. Lipid-lowering drugs were also used more often in the exenatide and sitagliptin groups. Sulfonamides were used more often in the exenatide group, whereas there were no differences in use of other drugs associated with pancreatitis. Other acute pancreatitis risk factors were equally distributed except that hypertriglyceridemia was more common in the exenatide and sitagliptin groups. Incidence of acute pancreatitis is also shown in Table 1. Acute pancreatitis was more frequent in the overall diabetic group compared with that in the nondiabetic control group, but there were no differences among the three diabetic groups.

Figure 1 shows the Kaplan-Meier curve of time to acute pancreatitis in patients with diabetes compared with that in nondiabetic control patients. In the Cox proportional hazard model that controlled for diabetes, age, preexisting pancreatic disease, alcohol intake, biliary stone disease, and chronic disease score, patients with diabetes were 2.1 times more likely to have a claim for acute pancreatitis than patients without diabetes (Table 2). Figure 2 shows the Kaplan-Meier curve of time to acute pancreatitis in the diabetic subgroups. In the Cox proportional hazards model for the diabetic subgroups, acute pancreatitis was not significantly higher in the exenatide and sitagliptin groups compared with that in the diabetic control group (Table 3). The sensitivity analysis indicated that extending follow-up beyond 30 days of running out of the index medication did not significantly affect the results.

CONCLUSIONS — This study confirms prior findings that the incidence of acute pancreatitis is approximately two times higher in patients with type 2 diabetes. However, we did not find an increased risk for acute pancreatitis with exenatide or sitagliptin.

Our negative findings are consistent with those of Dore et al. (10). However, these studies need to be interpreted with caution in view of the inherent limitations with retrospective observational insurance and pharmacy claims–based studies that may have incomplete data and unknown confounders. The study of Dore et al., funded by Amylin Pharmaceuticals, analyzed an insurance claims database to investigate the risk of acute pancreatitis in patients treated with exenatide and sitagliptin compared with that in patients taking metformin or glyburide. The incidence of acute pancreatitis was extremely low with exenatide (0.13%) and sitagliptin (0.12%), and the risk of acute pancreatitis was comparable for patients initiating exenatide or sitagliptin compared with glyburide and metformin. Dore et al. used propensity scoring methodology, excluded patients with evidence of pancreatic disease and did not adjust for known pancreatitis risk factors. In contrast, our study included patients with evidence of chronic pancreatic disease and estimated risk of acute pancreatitis using Cox models adjusted for numerous medical conditions and medications associated with an increased risk of acute pancreatitis. Our study identified a total of 154 cases of acute pancreatitis whereas their study identified 92 cases, which gave our study greater power to detect potential effects of these medications.

Table 1—*Baseline characteristics and incidence of acute pancreatitis*

	Nondiabetic	Diabetic	*P* value Nondiabetic vs. diabetic	Exenatide	Sitagliptin	Diabetes control	*P* value Exenatide vs. diabetes control	*P* value Sitagliptin vs. diabetes control
Patient characteristics								
No. of subjects	748,041	38,615		6,545	15,826	16,244		
Age (years)	51.4 ± 8.3	52.7 ± 7.5	<0.0001	51.4 ± 8.0	53.1 ± 7.3	52.9 ± 7.4	<0.0001	NS
Female sex	346,427 (46.3)	17,662 (45.7)	<0.05	3,699 (56.5)	7,011 (44.3)	6,952 (42.8)	<0.0001	<0.01
Chronic disease score (1 year)	16.8 ± 13.3	31.4 ± 16.8	<0.0001	35.7 ± 17.8	31.2 ± 16.8	30.0 ± 16.0	<0.0001	<0.0001
Medications (diabetes and lipid: ≥1 claims during wash-in)								
No. of classes of diabetes medications	0	1.5 ± 0.7		1.7 ± 0.7	1.7 ± 0.7	1.3 ± 0.4	<0.0001	<0.0001
Sulfonylureas	0	16,621 (43.0)		3,220 (49.2)	7,693 (48.6)	5,708 (35.1)	<0.0001	<0.0001
Metformin	0	27,581 (71.4)		5,335 (81.5)	12,543 (79.3)	9,703 (59.7)	<0.0001	<0.0001
Thiazolidinediones	0	14,627 (37.9)		2,878 (44.0)	6,751 (42.7)	4,998 (30.8)	<0.0001	<0.0001
Fibrates	33,680 (4.5)	4,032 (10.4)	<0.0001	719 (11.0)	1,757 (11.1)	1,556 (9.6)	0.0014	<0.0001
Statins	329,394 (44.0)	21,746 (56.3)	<0.0001	3,791 (57.9)	9,256 (58.5)	8,699 (53.5)	<0.0001	<0.0001
Nicotinic acid	16,694 (2.2)	1,171 (3.0)	<0.0001	236 (3.6)	524 (3.3)	411 (2.5)	<0.0001	<0.0001
Bile acid sequestrant	5,685 (0.8)	289 (0.7)	NS	58 (0.9)	125 (0.8)	106 (0.6)	NS	NS
Ezetimibe	25,967 (3.5)	1,838 (4.8)	<0.0001	329 (5.0)	844 (5.3)	665 (4.1)	<0.005	<0.0001
Risk factors (medications): ≥1 claim during wash-in								
Azathioprine	1,077 (0.1)	57 (0.1)	NS	9 (0.1)	27 (0.2)	21 (0.1)	NS	NS
Glucocorticoids	51,353 (6.9)	2,373 (6.1)	<0.0001	410 (6.3)	969 (6.1)	994 (6.1)	NS	NS
Sulfonamides	18,970 (2.5)	1,482 (3.8)	<0.0001	295 (4.5)	597 (3.8)	590 (3.6)	<0.005	NS
Nonsteroidal anti-inflammatory drugs	61,387 (8.2)	3,765 (9.7)	<0.0001	678 (10.4)	1,498 (9.5)	1,589 (9.8)	NS	NS
Mercaptopurine	44 (0.01)	16 (0.04)	<0.0001	2 (0.03)	7 (0.04)	7 (0.04)	NS	NS
Methyldopa	689 (0.09)	27 (0.07)	NS	7 (0.11)	8 (0.05)	12 (0.07)	NS	NS
Tetracyclines	21,073 (2.8)	1,132 (2.9)	NS	188 (2.8)	466 (2.9)	478 (2.9)	NS	NS
Risk factors (ICD-9): ≥1 claim during wash-in								
Pancreatic disease	455 (0.06)	53 (0.14)	<0.0001	4 (0.06)	22 (0.14)	27 (0.17)	NS	NS
Alcohol abuse	1,881 (0.25)	60 (0.16)	0.0002	7 (0.11)	20 (0.13)	33 (0.20)	NS	NS
Biliary stone disease	4,500 (0.60)	323 (0.84)	<0.0001	54 (0.83)	148 (0.94)	121 (0.74)	NS	NS
Hypertriglyceridemia	7,071 (0.95)	661 (1.71)	<0.0001	135 (2.06)	293 (1.85)	233 (1.43)	<0.001	<0.005
Cholestatic liver disease	2,253 (0.30)	104 (0.27)	NS	15 (0.23)	46 (0.29)	43 (0.26)	NS	NS
Pancreatitis								
Patient follow-up (years)	1.2 ± 0.4	0.7 ± 0.5	<0.0001	0.6 ± 0.5	0.8 ± 0.5	0.7 ± 0.5	<0.0001	<0.0001
New acute pancreatitis	1,746 (0.2)	154 (0.4)	<0.0001	22 (0.3)	67 (0.4)	65 (0.4)	NS	NS
Incidence of new acute pancreatitis (cases/100,000 patient-years)	190.5	563.9		569.9	554.4	571.9		

Data are means ± SD or *n* (%).

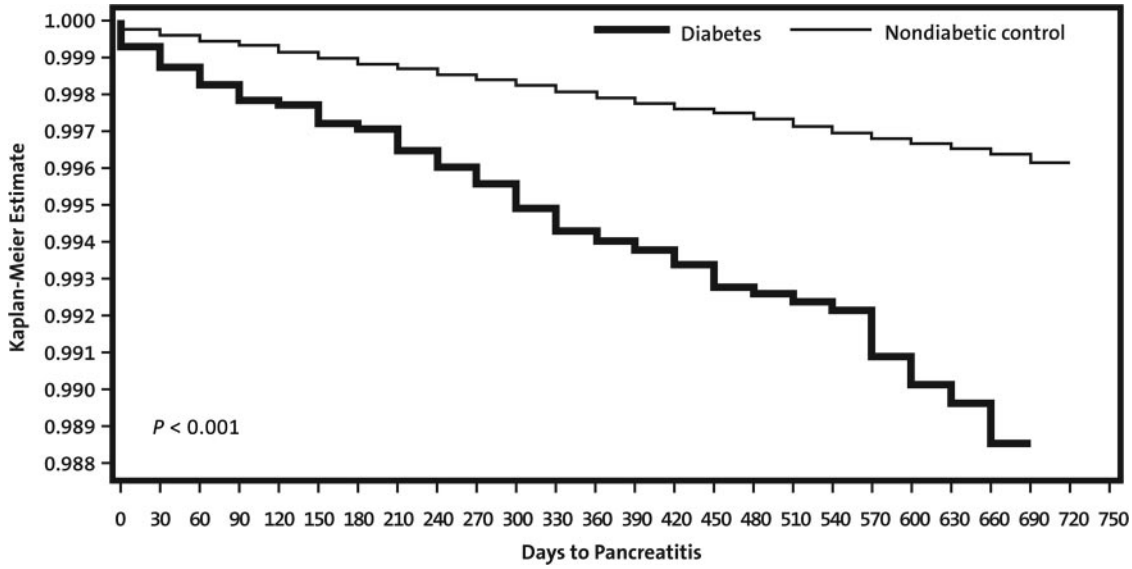

Figure 1—*Kaplan-Meier curve of acute pancreatitis in combined diabetic groups (exenatide, sitagliptin, diabetes control) and the nondiabetic control group.*

The incidence of acute pancreatitis in our diabetic cohort (5.63 cases per 1,000 patient years) is similar to that reported in a claims analysis reported by Noel et al. (8) (4.22 cases per 1,000 patient years). They reported a similar increased risk for acute pancreatitis (adjusted hazard ratio [HR] of 2.8), which was very similar to that in our study (adjusted HR of 2.1). In contrast, Girman et al. (11) recently reported a lower risk of acute pancreatitis in patients with type 2 diabetes (adjusted HR of 1.49). Because their analysis was performed using the U.K. General Practice Research Database, which contains clinical as well as claims data, they were able to adjust for data, such as incidence of obesity, that are probably underreported using claims data.

Our claims data analysis had the strength of allowing observation of a large number of patients treated with these drugs throughout the country. The data therefore have good generalizability to other insured populations across geographic regions. The differences in baseline characteristics are representative of the trends expected in clinical practice. Thus, diabetic patients were older than nondiabetic patients, were taking more medications, and had a higher chronic disease score. Both exenatide and sitagliptin group patients were taking multiple antidiabetes drugs as well as more lipid-lowering drugs and had higher chronic disease scores compared with those for the diabetic control group. These observations suggest that exenatide and sitagliptin may have been used later in the course of disease and in sicker patients. Exenatide, an injectable drug, was used more often in younger patients and in women. Exenatide is associated with weight loss and may be preferentially selected in obese patients for this reason. However, despite this potential indication bias, we did not find a higher incidence of acute pancreatitis in association with these drugs.

The study has numerous important limitations, and the results should be considered with these in mind. Most important, the nonrandom nature of the study may have introduced unmeasured confounders. For example, if prescribers were aware of the possible risks of pancreatitis associated with incretin-based therapy, they may have preferentially prescribed other antidiabetic medications to patients perceived to be at higher risk. This channeling bias could have inflated the risk of acute pancreatitis in diabetic patients taking control medications, masking a potential real increased risk with exenatide and sitagliptin. We attempted to minimize the effect of this bias by measuring and adjusting for risk factors for acute pancreatitis. However, our ability to detect patients at increased risk was limited to conditions detectable by medical and pharmacy claims. Our administrative claims dataset did not provide potentially relevant demographic and clinical details such as type and duration of diabetes, obesity, glycemic and lipid control, alcohol consumption, and acute pancreatitis that occurred before the baseline period. Although we ad-

Table 2—*Cox proportional hazards analysis for time to pancreatitis for diabetic and nondiabetic patients*

	(Adjusted age and sex) HR (95% CI)	*P* value	(Adjusted all) HR (95% CI)	*P* value
Diabetic patients	2.9 (2.5–3.5)	<0.0001	2.1 (1.7–2.5)	<0.0001
Age	1.0 (1.0–1.0)	NS	0.99 (0.98–0.99)	<0.005
Sex (female = 1)	1.2 (1.1–1.3)	<0.001	1.1 (1.0–1.2)	NS
Medical history				
Pancreatic disease			24.7 (18.4–33.3)	<0.0001
Alcohol abuse			6.2 (4.5–8.6)	<0.0001
Biliary stone disease			2.6 (1.9–3.5)	<0.0001
Hypertriglyceridemia			1.4 (0.9–2.0)	NS
Cholestatic liver disease			1.4 (0.9–2.3)	NS
CDS			1.021 (1.018–1.023)	<0.0001

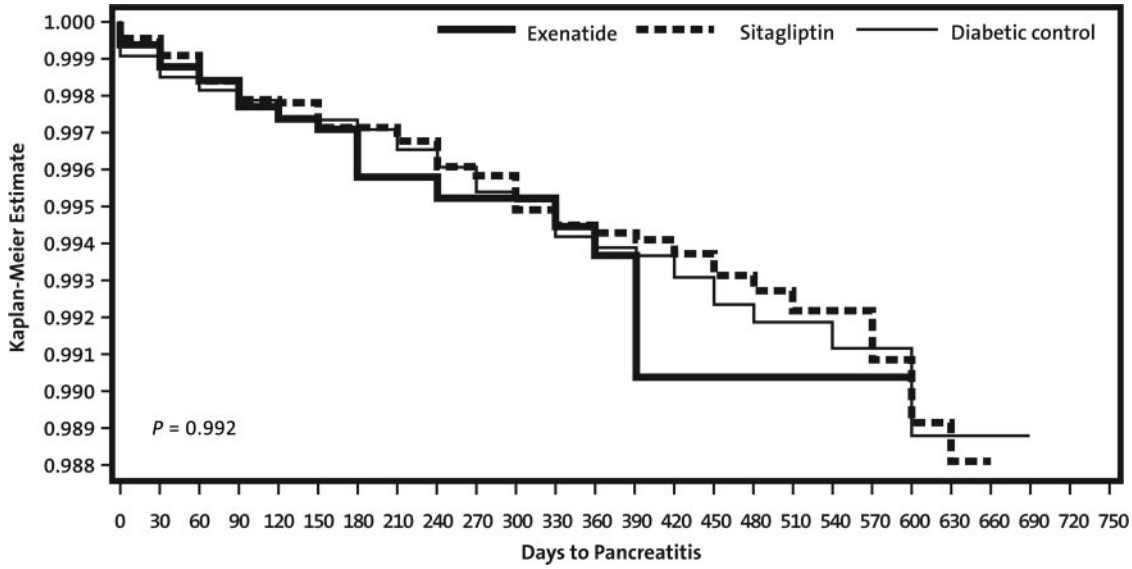

Figure 2—*Kaplan-Meier curve of acute pancreatitis in exenatide, sitagliptin, and diabetes control groups.*

justed the Cox model for hypertriglyceridemia, obesity, and alcohol abuse identified by medical claims, claims of these types are probably undercoded and inconsistently coded.

Data capture for patients included may not have been complete if there were secondary insurance policies that were not administered through Medco or if the patients paid for their medical costs out of pocket. There were likely to have been coding inaccuracies, which are an inherent limitation of claims data. Important to this analysis, the incidence of pancreatitis in this population may be overestimated because providers may have used the acute pancreatitis code when evaluating patients for "rule-out" pancreatitis. However, it is likely that these inaccuracies would affect the diabetic treatment group patients equally. Patients >63 years of age were excluded because of incomplete data. Our analyses did not include adjustment for medication dose or adherence, and we were not able to confirm that patients were actually taking medications for which claims were filed. We were also unable to investigate the interaction between exenatide and sitagliptin and risk factors for acute pancreatitis because of small numbers. The possibility of asymptomatic chronic pancreatitis and the potential for pancreatic carcinoma with long-term use, as suggested by some experts (12), was not investigated in this study. A few animal studies have shown incretinomimetic drugs to cause exocrine pancreatic duct hyperplasia that may eventually lead to acute or chronic pancreatitis or pancreatic carcinoma (13,14).

Despite these limitations, these data provide valuable information for practicing clinicians weighing potential reported benefits versus risks, including the FDA warning of increased pancreatitis. Although this retrospective analysis cannot rule out with certainty that an association between exenatide, sitagliptin, and acute pancreatitis exists, it appears that exenatide and sitagliptin may not be associated with a large increased risk of acute pancreatitis.

Treatment with the incretin-based therapies appears to be increasing, and there are several new agents that have come to market or may come soon. These agents are attractive in that they may allow treatment intensification while body weight is controlled through mechanisms associated with a low rate of hypoglycemia. Our findings did not reveal any increased risk of acute pancreatitis with exenatide and sitagliptin, but this retrospective study cannot rule out with certainty the existence of such an association.

Table 3—*Cox proportional hazards analysis for time to pancreatitis for diabetic patients*

	(Adjusted age and sex) HR (95% CI)	*P* value	(Adjusted all) HR (95% CI)	*P* value
Taking exenatide	1.0 (0.6–1.6)	NS	0.9 (0.6–1.5)	NS
Taking sitagliptin	1.0 (0.7–1.4)	NS	0.9 (0.7–1.3)	NS
Age	1.0 (1.0–1.0)	NS	1.0 (1.0–1.0)	NS
Sex (female = 1)	1.1 (0.8–1.6)	NS	1.1 (0.8–1.5)	NS
Medical history				
Pancreatic disease			31.7 (14.8–69.0)	<0.0001
Alcohol abuse			3.3 (0.5–23.6)	NS
Biliary stone disease			0.7 (0.2–3.0)	NS
Hypertriglyceridemia			0.8 (0.3–2.7)	NS
Cholestatic liver disease			2.8 (0.8–9.7)	NS
Chronic disease score			1.020 (1.012–1.027)	<0.0001

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

R.G. interpreted data and wrote the manuscript. W.C. collected data, conducted statistical analysis, and reviewed/edited the manuscript. M.P. conceived the study, participated in development of the statistical plan, and reviewed/edited the manuscript.

Parts of this study were presented in poster form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

We thank Lorraine Tully, Medco Health Solutions, for assistance with medical coding and Zhuliang Tao, Medco Health Solutions, for

statistical contributions. We thank Steven Haffner, Cindy Fenton, Steven Bowlin, Rocco Lulic, Inderpal Bhanderi, Glen Stettin, and Peter Juhn (all from Medco Health Solutions) for assistance through all study phases.

References

1. Ayoub WA, Kumar AA, Naguib HS, Taylor HC. Exenatide-induced acute pancreatitis. Endocr Pract 2010;16:80–83
2. Ahmad SR, Swann J. Exenatide and rare adverse events. N Engl J Med 2008;358:1970–1971; discussion 1971–2
3. Denker PS, Dimarco PE. Exenatide (exendin-4)-induced pancreatitis: a case report. Diabetes Care 2006;29:471
4. Tripathy NR, Basha S, Jain R, Shetty S, Ramachandran A. Exenatide and acute pancreatitis. J Assoc Physicians India 2008;56:987–988
5. Information for Healthcare Professionals: Exenatide (marketed as Byetta)—8/2008 update [online article]. Available from http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124713.htm. Accessed 7 February 2010
6. Sitagliptin (marketed as Januvia and Janumet) information [online article], 2009. Available from http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm183768.htm. Accessed 7 February 2010
7. Parks M, Rosebraugh C. Weighing risks and benefits of liraglutide—the FDA's review of a new antidiabetic therapy. N Engl J Med 2010;362:774–777
8. Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care 2009;32:834–838
9. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197–203
10. Dore DD, Seeger JD, Arnold Chan K. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared with metformin or glyburide. Curr Med Res Opin 2009;25:1019–1027
11. Girman CJ, Kou TD, Cai B, Alexander CM, O'Neill EA, Williams-Herman DE, Katz L. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. Diabetes Obes Metab 2010;12:766–771
12. Butler PC, Dry S, Elashoff R. GLP-1-based therapy for diabetes: what you do not know can hurt you. Diabetes Care 2010;33:453–455
13. Matveyenko AV, Dry S, Cox HI, Moshtaghian A, Gurlo T, Galasso R, Butler AE, Butler PC. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes 2009;58:1604–1615
14. Nachnani JS, Bulchandani DG, Nookala A, Herndon B, Molteni A, Pandya P, Taylor R, Quinn T, Weide L, Alba LM. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. Diabetologia 2010;53:153–159