



Is There a Link Between Liraglutide and Pancreatitis? A Post Hoc Review of Pooled and Patient-Level Data From Completed Liraglutide Type 2 Diabetes Clinical Trials

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Diabetes Care 2015;38:1058–1066 | DOI: 10.2337/dc13-1210

OBJECTIVE

To report the incidence of pancreatitis in type 2 diabetes trials of liraglutide and details of all pancreatitis cases.

RESEARCH DESIGN AND METHODS

Data from Novo Nordisk–sponsored trials with liraglutide (phase 2 and 3; NN2211 identifiers) completed by 19 April 2013 were pooled. All pancreatitis cases were reviewed.

RESULTS

Total exposure to liraglutide and active comparators was 5,021 and 1,354 patient-years, respectively ($n = 6,345$ and $1,846$, respectively). Eight cases of acute pancreatitis (AP) with liraglutide and one with any comparator (glimepiride) were found. The incidence of AP was 1.6 cases/1,000 patient-years exposure (PYE) for liraglutide vs. 0.7 cases/1,000 PYE for total active comparators. One of the eight AP cases reported with liraglutide did not meet diagnostic criteria for AP. In six of these eight cases, recognized risk factors for AP were present and/or the onset of AP occurred >6 months after liraglutide initiation. All patients were receiving multiple medications. Four cases of chronic pancreatitis (CP) with liraglutide and none with comparators were found. One of these four cases fulfilled diagnostic criteria for CP; these criteria were not met or information was missing in the remaining three.

CONCLUSIONS

Based on the small number of cases observed, the incidences of reported AP and CP were numerically greater with liraglutide than with comparators. Not all cases fulfilled diagnostic criteria, and confounding variables were present in 75% of the AP cases with liraglutide therapy, precluding firm conclusions.

In 2007, the U.S. Food and Drug Administration (FDA) prompted an update of the exenatide twice daily label to include a warning for acute pancreatitis (1). This update was based on six acute pancreatitis cases in patients receiving exenatide twice daily in clinical trials together with several postmarketing case reports (1);

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Received 23 May 2013 and accepted 10 November 2014.

A slide set summarizing this article is available online.

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See accompanying articles, pp. 948, 951, and 1089

similar observations were made with liraglutide (2,3). Today, GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors carry warning text for acute pancreatitis on their labels (2,4–12).

A number of studies investigated the association between incretin-based therapies and pancreatitis, with varied conclusions (13–23). A systematic review and meta-analysis of 55 randomized clinical trials (33,350 patients) indicated an odds ratio (95% CI) for pancreatitis of 1.11 (0.57, 2.17) with incretin-based therapies versus control; estimates calculated by incretin therapy class (GLP-1 receptor agonists or DPP-4 inhibitors) showed similar results (23). In the same study, the authors described results of five observational studies without pooled analysis due to variation in outcome measures and data forms. Four of these observational studies showed no increased risk of pancreatitis associated with incretin exposure, but one (19) linked exenatide or sitagliptin use with a significantly increased odds of acute pancreatitis (use within 2 years vs. no use 2.07 [1.36, 3.13]) (23).

Since its initial approval for clinical use in 2009, mixed conclusions have been drawn in publications related to liraglutide and pancreatitis. At least 11 case reports suggested a relationship between liraglutide and pancreatitis, highlighting pancreatitis as a potential complication of therapy and suggesting caution when prescribing liraglutide (17). Meanwhile, a meta-analysis of 25 longitudinal studies (22 randomized controlled trials, 3 retrospective cohort analyses, 775,602 patients) concluded that liraglutide was not associated with an increased risk of acute pancreatitis (odds ratio [95% CI] 0.97 [0.21, 4.39]) (20). More recently, a liraglutide audit conducted by the Association of British Clinical Diabetologists reported that after 3,720 years of exposure to liraglutide across 6,010 patients, four cases of possible pancreatitis were documented. Likely causes were identified in three patients, and one patient had no etiological cause (24). The authors concluded that “people with type 2 diabetes are at greater risk of acute pancreatitis (hazard ratio between 1.5 and 2.8). Thus, the possibility of liraglutide-associated pancreatitis in ‘real-world’ clinical practice (0.027/100 patient-years) represents a very small risk” (24).

Based on a report showing pancreatic pathology in human tissue (15) and a claims database study indicating increased hospitalization for acute pancreatitis with sitagliptin or exenatide treatment (19), which were subsequently re-evaluated and criticized (25–27), both the European Medicines Agency (EMA) and the FDA initiated investigations regarding the pancreatic safety of incretin-based therapies. In February 2014, the EMA and FDA concluded that based on available data, the “assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data” (28). Until further information becomes available, pancreatitis will continue to be considered a risk associated with these therapies, and both agencies continue to monitor the safety signals. At the time of this writing, the EMA and FDA believed that “current knowledge is adequately reflected in the product information or labeling” (28). The current article reviews all cases of pancreatitis reported during Novo Nordisk-sponsored, randomized clinical trials of liraglutide as the primary investigational product for type 2 diabetes (Novo Nordisk trial identifiers prefixed with NN2211 only) completed by 19 April 2013.

RESEARCH DESIGN AND METHODS

All pancreatitis cases from intermediate- and long-term (phase 2 and 3), Novo Nordisk-sponsored, randomized clinical trials with liraglutide as the primary investigational product for the treatment of type 2 diabetes (Novo Nordisk trial identifiers prefixed with

NN2211 only) completed by 19 April 2013 are reported (ClinicalTrials.gov identifiers NCT01509755, NCT01508949, NCT00154414, NCT00318422, NCT01511172, NCT00154401, NCT00318461, NCT00294723, NCT00333151, NCT00331851, NCT00393718, NCT00395746, NCT00614120, NCT00518882, NCT00620282, NCT00856986, NCT00700817, and NCT01511198; completion date criterion applied because a small number of additional trials are currently ongoing). There was no preselection of cases. No cases of pancreatitis were reported in phase 1 studies, so these trials were excluded from analysis.

A Cochran-Mantel-Haenszel test was performed to estimate the relative risk of acute pancreatitis in the pooled liraglutide group versus the active comparator groups. Liraglutide was compared with two different active comparator groups (total active comparator group: glimepiride, rosiglitazone, insulin glargine, sitagliptin, and exenatide; active comparator group excluding sitagliptin and exenatide: glimepiride, rosiglitazone, and insulin glargine only). Calculations were performed using R version 2.14.2 (29) and SAS 9.1.3 (SAS System for PC; SAS Institute Inc., Cary, NC) software.

All pancreatitis cases were reviewed by the authors, including a clinical pancreatologist (W.M.S.). Patient-level details were compiled, including patient histories, concomitant medications, lipase and amylase levels, pancreatitis event latency, and outcomes.

RESULTS

Exposure to Liraglutide and Comparators

A total of 9,016 patients were included in the study. Total exposure to liraglutide, active comparator groups, and placebo are summarized in Table 1.

Table 1—Total exposure to liraglutide, active comparator groups, and placebo

	Exposure (patient-years)	Number of patients
Liraglutide (all doses)	5,021	6,345
1.2 mg once daily	1,215	3,072
1.8 mg once daily	2,726	1,417
Total active comparator group	1,354	1,846
Active comparator group excluding sitagliptin and exenatide	1,070	1,395
Placebo	397	825

Many of the patients received these interventions for <1 year. Patients receiving doses other than liraglutide 1.2 and 1.8 mg once daily were included in the study, and hence, the sum of exposure to liraglutide 1.2 and 1.8 mg once daily does not total to that for the liraglutide (all doses) category.

Incidence of Acute Pancreatitis With Liraglutide and Comparators

Acute pancreatitis was recorded for eight patients receiving liraglutide (0.13% of liraglutide-treated patients, six with liraglutide 1.8 mg [0.195% of liraglutide 1.8 mg–treated patients] and two with liraglutide 1.2 mg [0.141% of liraglutide 1.2 mg–treated patients]), and one receiving a comparator (glimepiride; 0.05% of all active comparator–treated patients). No cases were reported with any other comparator, including rosiglitazone, insulin glargine, sitagliptin, exenatide, and placebo. This absence of cases precluded the calculation of the relative risk of acute pancreatitis with liraglutide versus individual active comparators or placebo.

The reporting rate for acute pancreatitis was 1.6 cases/1,000 patient-years exposure (PYE) for liraglutide vs. 0.7 cases/1,000 PYE for total active comparators and 0.9 cases/1,000 PYE for comparators excluding sitagliptin and exenatide. The relative risk with liraglutide versus total active comparators was 2.1 (95% CI 0.3, 16.0; $P = 0.4478$) and 1.7 (0.2, 13.2; $P = 0.6241$) versus the active comparator group excluding sitagliptin and exenatide.

Review of Acute Pancreatitis Cases

Established criteria for the diagnosis of acute pancreatitis are presented in Table 2. Details of the nine cases of acute pancreatitis were compiled and are summarized in Table 3. Among the eight acute pancreatitis cases reported with liraglutide, one (case 1) did not fulfill the established criteria (30) for the diagnosis of acute pancreatitis (no significant upper abdominal pain and negative imaging results) (Table 3). In four

cases (cases 2, 3, 5, and 6), risk factors for acute pancreatitis (including gallstones, endoscopic retrograde cholangiopancreatography [ERCP] with sphincterotomy, and chronic calcific pancreatitis) were present. Two patients with acute pancreatitis were found to have gallstones on autopsy (case 2) or surgery (case 5); the latter also had a greater than threefold elevation of alanine aminotransferase levels on admission, which could be suggestive of a stone in the common bile duct. In one case (case 3), the patient was hospitalized for acute pancreatitis on the same day as an ERCP with sphincterotomy. One patient (case 6) had an acute exacerbation of chronic pancreatitis (computed tomography [CT] scan showed calcification of the pancreas). In addition, six patients (cases 1–6) had onset latencies (the time between starting the drug and the development of acute pancreatitis) of 196–668 days. All patients were receiving multiple concomitant medications in addition to liraglutide or comparator. Eight patients recovered, and one in the liraglutide arm (case 2) died.

Incidence of Chronic Pancreatitis With Liraglutide and Comparators

Chronic pancreatitis was recorded for four patients receiving liraglutide (0.06% of liraglutide-treated patients; three with liraglutide 1.8 mg and one with liraglutide 0.6 mg). There were no cases of chronic pancreatitis in patients receiving a comparator.

Review of Chronic Pancreatitis Cases

Criteria for the diagnosis of chronic pancreatitis are presented in Table 2 (31). Details of the four cases of chronic

pancreatitis reported are presented in Table 4. All chronic pancreatitis cases occurred in patients treated with liraglutide and other medications. Two patients (cases 1 and 2) did not describe upper abdominal pain as a symptom (Table 4). In case 1, a CT scan showed no pancreatic abnormality except nephrosclerosis; pancreatic findings from the CT scan were not reported for case 2. In the remaining two cases, imaging showed calcification in the head of the pancreas and a dilated pancreatic duct (case 3; consistent with chronic pancreatitis) or a swollen part of the pancreas between its head and corpus and an enlarged lymph node (case 4; findings not diagnostic of chronic pancreatitis). Thus, of the four cases of chronic pancreatitis, one had symptoms and imaging suggestive of the disease. The remaining three cases either did not have recorded symptoms or did not have imaging suggestive of chronic pancreatitis. The latency of the chronic pancreatitis events (the time between starting the drug and the development of chronic pancreatitis) ranged from 88 to 226 days. Three patients were considered not to have recovered; the outcome for one patient (case 3) is not known because this patient was lost to follow-up.

CONCLUSIONS

The results add important pooled and patient-level data to our knowledge regarding the pancreatic safety of incretin-based therapies. In this study, the incidence of reported acute pancreatitis was numerically greater with liraglutide than with comparators (1.6 cases/1,000 PYE in the liraglutide group, 0.7 cases/1,000 PYE in the total active comparator group, and 0.9 cases/1,000 PYE in the active comparator group excluding sitagliptin and exenatide). Prior studies in patients with type 2 diabetes (not being treated with incretin-based therapy) reported an incidence of acute pancreatitis of 0.5–5.6 events/1,000 PYE (22,32–34). A trend toward an increase in the relative risk of acute pancreatitis was seen in the liraglutide group versus the active comparator groups (2.1 [95% CI 0.3, 16.0], $P = 0.4478$ vs. all active comparators; 1.7 [0.2, 13.2], $P = 0.6241$ vs. active comparators excluding sitagliptin and exenatide), although this trend was based on very few cases. The CIs for the relative risk were wide, indicating an

Table 2—Criteria for the diagnosis of acute pancreatitis by international consensus (Atlanta classification) (30) and criteria for diagnosis of chronic pancreatitis (31)

The diagnosis of acute pancreatitis requires fulfillment of two of the following three features:

1. Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back)
2. Serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal
3. Characteristic findings of acute pancreatitis on CT scan and less commonly MRI or transabdominal ultrasonography

The diagnosis of chronic pancreatitis requires fulfillment of the following features:

1. Chronic continuous or intermittent upper abdominal pain lasting weeks, months, or years
2. Imaging (using sonography, CT, MRI, ERCP) consistent with chronic pancreatitis (calcium deposition in the pancreas, atrophy of the pancreas, dilated main pancreatic duct or secondary biliary radicles, presence of pseudocysts)

Table 3—Cases of acute pancreatitis in Novo Nordisk–sponsored type 2 diabetes clinical trials of liraglutide

Case number	Sex	Age (years)	BMI (kg/m ²)	Dose (mg/day)	Details of diagnosis	Additional case details	Latency (days)	Outcome
1	M	50	33.0	Liraglutide 1.8	<ul style="list-style-type: none"> No significant abdominal pain (bloating, flatulence) Lipase: greater than threefold ULN (peak: 589 units/L) Ultrasound was negative 	<ul style="list-style-type: none"> Peak amylase: 169 units/L Other drugs: metformin (13 months), valsartan/hydrochlorothiazide (9 months), esomeprazole, aspirin (9 days) 	274	Recovered
2	F	64	43.4	Liraglutide 1.8	<ul style="list-style-type: none"> Patient died suddenly 3 days after a colonoscopy for adenocarcinoma of the colon; cause of death on autopsy stated as acute and chronic pancreatitis Diagnosis based on autopsy No prior blood tests or imaging Abdominal pain after colonoscopy 	<ul style="list-style-type: none"> Lipase and amylase levels unavailable (no previous record made) Autopsy also showed gallstones Other drugs: propofol for sedation during the colonoscopy, simvastatin (21 months), lisinopril/hydrochlorothiazide, aspirin 	668	Fatal
3	F	47	28.3	Liraglutide 1.2	<ul style="list-style-type: none"> Patient presented with acute pancreatitis; an ERCP with sphincterotomy was performed on the same day Pain due to pancreatitis present Lipase: greater than threefold ULN (peak: 1,755 units/L) No imaging 	<ul style="list-style-type: none"> Peak amylase: 519 units/L; suspected sphincter of Oddi dysfunction Medical history: hyperlipidemia, abdominal pain Other drugs: escitalopram (14 months), bupropion (17 months), hyoscyamine (5 months) 	196	Recovered
4	M	64	31.5	Liraglutide 1.8	<ul style="list-style-type: none"> Abdominal pain Lipase: greater than threefold ULN (peak: 1,540 units/L) Amylase: greater than threefold ULN (peak: 538 units/L) CT scan showed peripancreatic inflammation 	<ul style="list-style-type: none"> Triglycerides: 208 mg/dL (normal range 30–185 mg/dL) Sonogram carried out 3 months after the acute pancreatitis event showed no gallstones Medical history: hypertension, hyperlipidemia, kidney stones; no history of gallstones or alcohol abuse Other drugs: glyburide (4 years), losartan (5 weeks), atenolol (5 weeks) 	419	Recovered
5	F	72	28.6	Liraglutide 1.8	<ul style="list-style-type: none"> Epigastric pain Amylase: greater than threefold ULN (peak: 1,651 units/L) 	<ul style="list-style-type: none"> No lipase information ALT: 121 units/L (normal range 7–31 units/L) Laparoscopic cholecystectomy showed multiple gallstones Medical history: hypertension, cervical dysplasia; no history of obesity or alcohol abuse Other drugs: enalapril, ranitidine, aspirin, sulfamethoxazole/trimetoprim 	313	Recovered

Continued on p. 1062

Table 3—Continued

Case number	Sex	Age (years)	BMI (kg/m ²)	Dose (mg/day)	Details of diagnosis	Additional case details	Latency (days)	Outcome
6	M	52	37.9	Liraglutide 1.8	<ul style="list-style-type: none"> Abdominal pain Lipase: greater than threefold ULN (peak: 1,542 units/L) 	<ul style="list-style-type: none"> No amylase information Sonogram showed fatty liver and no gallstones CT scan showed induration of fat around head of pancreas and punctate calcifications consistent with chronic pancreatitis Patient history: hyperlipidemia, coronary artery disease, GERD Other drugs: metformin (17 months), omeprazole (25 years), atorvastatin (21 months), clopidogrel (17 months), aspirin (5 years), ramipril (5 years), amlodipine (5 years), metoprolol (5 years), citalopram (5 years), bupropion (1 year) 	254	Recovered
7	M	61	26.9	Liraglutide 1.8	<ul style="list-style-type: none"> Left-side upper quadrant pain Lipase: greater than threefold ULN (12,215 units/L) CT scan showed evidence of acute pancreatitis 	<ul style="list-style-type: none"> No amylase information Patient recovered 5 days after liraglutide discontinuation No gallstones on CT scan ALT normal No triglyceride information Medical history: former alcohol abuse, acute pancreatitis, hypertension, hyperlipidemia Other drugs: ramipril, aspirin/dipyridamole, simvastatin, pantoprazole, metamizole 	59	Recovered
8	M	49	31.8	Liraglutide 1.2	<ul style="list-style-type: none"> Severe epigastric pain Amylase: greater than threefold ULN (peak: 698 units/L) CT scan and sonogram were negative 	<ul style="list-style-type: none"> No lipase information No gallstones on sonogram Medical history: hyperlipidemia, hypertension; no history of alcohol abuse Other drugs: metformin, aspirin, perindopril (4 years), atorvastatin (2 years) 	49	Recovered
9	F	59	38.7	Glimepiride 4	<ul style="list-style-type: none"> Amylase: greater than threefold ULN (peak: >2,000 units/L) CT scan and sonogram positive for acute pancreatitis 	<ul style="list-style-type: none"> No lipase information ALT and bilirubin normal Medical history: obesity, hyperlipidemia, hypertension; no history of alcohol abuse or gallstones; history of triglycerides at 1,590 mg/dL (markedly high levels) Other drugs: metformin (3 months), atenolol (6 years), fenofibrate (7 years), acenocoumarol (7 years), levothyroxine (4 years) 	62	Recovered

ALT, alanine aminotransferase; GERD, gastroesophageal reflux disease; ULN, upper limit of normal.

Table 4—Cases of chronic pancreatitis in Novo Nordisk–sponsored type 2 diabetes clinical trials of liraglutide

Case number	Sex	Age (years)	BMI (kg/m ²)	Liraglutide dose (mg/day)	Details of diagnosis	Additional case details	Latency (days)	Outcome
1	M	63	30.7	0.6	<ul style="list-style-type: none"> • Retrosternal burning/acid dyspepsia, flatulence, bloating • Peak amylase: 124 units/L • No lipase information reported • CT scan of abdomen showed no pancreatic abnormality except nephrosclerosis 	<ul style="list-style-type: none"> • Nausea and weakness • Other drugs: atenolol, ranitidine, gimepiride • Consumes alcohol daily 	170	Not recovered
2	M	69	28.0	1.8	<ul style="list-style-type: none"> • No description of abdominal pain at time of event • No lipase or amylase information reported • CT scan of abdomen conducted 2 months before event (due to upper abdominal pain), but pancreatic findings not reported • Sonogram showed evidence of chronic pancreatitis 	<ul style="list-style-type: none"> • Patient has asthma, COPD, and lung cancer • Medical history of abdominal distention and hypercholesterolemia • Denies alcohol abuse • Other medications: metformin (11 years), gimepiride (8 years), bedomethasone (9 months), ramipril (6 months) 	88	Not recovered
3	M	54	33.6	1.8	<ul style="list-style-type: none"> • Left-side upper quadrant pain • Amylase elevated two- to threefold (peak: 290 units/L) • No lipase information reported • Abdominal CT scan showed calcification in the head of the pancreas and dilated pancreatic duct 	<ul style="list-style-type: none"> • Nausea, sweating • No information regarding alcohol use • Esophagogastroduodenoscopy showed <i>Helicobacter pylori</i>-associated gastritis • Other drugs: metformin, ramipril, simvastatin, amlodipine, aspirin, allopurinol 	214	Unknown
4*	M	54	23.4	1.8	<ul style="list-style-type: none"> • Recurring abdominal pain for ~1 month • Amylase 1 day before diagnosis: 1.76 μkat/L (normal range 0–1.67 μkat/L); peak amylase: 2.83 μkat/L ~1 month after liraglutide discontinuation • Lipase 1 day before diagnosis: 1.3 μkat/L (normal range 0–1 μkat/L); peak lipase: 2.05 μkat/L ~1 month after liraglutide discontinuation • Sonogram showed swollen part of pancreas between its head and corpus • Endoscopic ultrasound showed enlarged lymph nodes near the neck of the pancreas 	<ul style="list-style-type: none"> • Nausea, vomiting for 1 day, black stools for 3 days • Gastroscopy showed peptic gastritis • Diarrhea for 3 days • Optic nerve swelling and diabetes retinopathy • Other drugs: perindopril, atorvastatin, aspirin, omeprazole 	226	Not recovered

COPD, chronic obstructive pulmonary disease. *Reported using the preferred term “pancreatitis-not acute.”

imprecise estimate of risk and low power to detect a difference in the incidence of acute pancreatitis between groups. Therefore, these statistical analyses should be considered as preliminary and inconclusive. Chronic pancreatitis also occurred more frequently with liraglutide than with comparators (four cases vs. zero cases; no statistical analyses conducted). To date, no drug has been implicated as causing chronic pancreatitis (35).

Upon review of all the reported pancreatitis cases, it was evident that not all of the cases fulfilled established diagnostic criteria. In one case of acute pancreatitis reported with liraglutide (case 1), acute pancreatitis was diagnosed in an individual with elevated lipase levels (more than three times the upper limit of the normal range) but without significant abdominal pain or imaging suggestive of the condition (Table 3). Therefore, this case did not fulfill the Atlanta criteria for the diagnosis of acute pancreatitis, as agreed on by international consensus (Table 2); note that as for all reported pancreatitis cases, it was nonetheless included in the statistical analyses. Serum lipase and amylase levels are elevated in ~13–20% and 6–8% of individuals with type 2 diabetes, respectively, who are not receiving GLP-1 receptor agonists or DPP-4 inhibitors and who do not have gastrointestinal symptoms (1–2% have threefold or greater lipase elevations) (36–39). Furthermore, in a 1-year longitudinal study, liraglutide raised serum lipase levels by a median of ~10 units/L (from 40 to 49 units/L; normal limit <60 units/L). This increase in lipase activity was unaccompanied by pancreatitis in 99.8% of cases and returned to baseline when liraglutide treatment was stopped (37). The significance of elevated lipase levels in patients with type 2 diabetes before starting a GLP-1 receptor agonist and the further rise after drug initiation is presently unclear. However, these data show that the presence of elevated serum levels of pancreatic enzymes in patients with type 2 diabetes not taking or taking GLP-1 receptor agonists needs to be interpreted with caution when diagnosing acute pancreatitis.

There is a substantial body of literature on drug-induced acute pancreatitis (40). The large majority of these reactions occur within the first 1–12 weeks

of exposure to the drug and are believed to be due to idiosyncratic or allergic reactions. In contrast, in six of the cases reported in the present study, the patients had been receiving liraglutide for 6–18 months before the acute pancreatitis event occurred. A mechanism has been proposed to explain a long latency between exposure to a GLP-1 receptor agonist or a DPP-4 inhibitor and an event of acute pancreatitis (41). GLP-1 receptor agonists have been reported to induce pancreatic duct gland hyperplasia or pancreatic intraepithelial neoplasia lesions in certain animal models. Authors have hypothesized that these structures, which develop over time, obstruct the small pancreatic ductules, leading to late-presenting acute pancreatitis (41). From a pathophysiologic point of view, how slow occlusion of the peripheral pancreatic ductules (should this occur with GLP-1 receptor agonists in humans) over a prolonged period may lead to acute pancreatitis is unclear. The main model of occlusion of pancreatic ducts leading to acute pancreatitis is gallstone occlusion, during which abrupt blockage by a gallstone leads to a sudden increase of pressure in the pancreatic ductular system (42).

One or more risk factors or causes for acute pancreatitis (gallstones, ERCP with sphincterotomy, chronic pancreatitis) were present in one-half of the acute pancreatitis cases observed with liraglutide, and all patients were taking multiple drugs. It is possible that GLP-1 receptor agonists may potentiate other established causes of acute pancreatitis. For example, it is possible that liraglutide, in combination with other medications, may predispose to pancreatitis. It is also possible that liraglutide may induce gallstone formation or cause a stone to migrate down the common bile duct. GLP-1 receptor agonists may cause a patient with established chronic pancreatitis to have an acute exacerbation of pancreatitis (case 6) (Table 3). Of the 37 of 3,137 subjects with a baseline history of pancreatitis in the observational EVIDENCE study, only one patient developed renewed symptoms of pancreatitis during 12 months of liraglutide therapy (43,44). However, the number of subjects was small, and any effects of liraglutide on pancreatitis recurrence over a period of several years remain unknown. The U.S. label for liraglutide

states that other antidiabetic therapies should be considered in patients with a history of pancreatitis (2), whereas the European label for liraglutide does not make specific recommendations with regard to treating these patients (9).

The safety profile of liraglutide is under continuous surveillance through meticulous routine pharmacovigilance, with any cases of pancreatitis being analyzed and reported to the health authorities. In addition, two pharmacoepidemiological studies of liraglutide are under way (using OptumInsight in a U.S. study and Clinical Practice Research Datalink in a U.K. study) that will supply substantial scientific information to this debate once completed. In an interim analysis of the study using OptumInsight, no significant elevation in the incidence of unadjudicated acute pancreatitis diagnoses with liraglutide versus non-GLP-1–based comparators over a median follow-up of 15 months has been found (187.5/100,000 PYE vs. 154.4/100,000 PYE, adjusted rate ratio 1.10 [0.81, 1.49]) (45).

The long-term cardiovascular outcome trial LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation) (46) in which 9,340 patients with type 2 diabetes are enrolled is expected to provide information regarding safety of up to 5 years' liraglutide exposure by 2016. Similar safety outcome trials are ongoing or have been completed for other incretin-based therapies. Of interest, the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53) and EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care) studies (long-term outcomes trials of DPP-4 inhibitors in patients with type 2 diabetes) indicated low incidences of pancreatitis with saxagliptin (confirmed acute pancreatitis: $n = 17$ [0.2%] vs. 9 [0.1%], $P = 0.17$) and alogliptin (acute pancreatitis: $n = 12$ [0.4%] vs. 8 [0.3%], $P = 0.50$) compared with placebo, with a numerical imbalance between arms (47,48).

In the present study, the incidences of reported acute and chronic pancreatitis were numerically greater with liraglutide than with comparators, but the small number of cases and the

confounding variables observed in several of the cases preclude firm conclusions. Combined data obtained from completed and multiple ongoing studies should provide more definitive evidence about whether incretin-based therapies cause pancreatitis. We share the current EMA and FDA view that any potential risk of pancreatitis is adequately reflected in the liraglutide label, which still carries a warning statement regarding pancreatitis (2,9).

Acknowledgments. The authors thank Henrik F. Thomsen (Novo Nordisk A/S) for contributing to the data analysis and Laura Elson (Watermeadow Medical, U.K. [supported by Novo Nordisk A/S, Copenhagen, Denmark]) for assistance with the preparation of the manuscript.

Duality of Interest. T.M.J. and K.S. are employees of Novo Nordisk A/S. W.M.S. serves as a member of the Steering Committee of the LEADER trial being conducted by Novo Nordisk and served as a consultant and expert witness with respect to exenatide for Amylin Pharmaceuticals and Eli Lilly and Company. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. T.M.J., K.S., and W.M.S. conducted the review of reported pancreatitis cases, interpreted the data, contributed to discussions, critically revised drafts of the article, and had final approval of the version for publication. T.M.J. 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.

Prior Presentation. Parts of this study were presented at the 2012 Joint Meeting of the American Pancreatic Association and International Association of Pancreatology, Miami, FL, 31 October–3 November 2012 (49). These data were subsequently incorporated into studies published by other authors (16,24). A short statement on six of the cases included in the case reviews was included in a letter to *The Annals of Pharmacotherapy* (35).

References

1. Amylin Pharmaceuticals Inc. and Eli Lilly & Company, 2007. Available from <http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm126437.pdf>. Accessed 22 March 2014
2. Prescribing information for liraglutide. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s020lbl.pdf. Accessed 26 March 2014
3. Questions and answers - safety requirements for Victoza (liraglutide). Available from <http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm198543.htm>. Accessed June 2014
4. Prescribing information for sitagliptin. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021995s028lbl.pdf. Accessed 26 March 2014
5. Prescribing information for saxagliptin. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022350s011lbl.pdf. Accessed 26 March 2014
6. Prescribing information for linagliptin. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201280s006lbl.pdf. Accessed 26 March 2014
7. Prescribing information for exenatide twice daily. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf. Accessed 26 March 2014
8. Prescribing information for exenatide once weekly. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022200s008lbl.pdf. Accessed 26 March 2014
9. Novo Nordisk A/S. Victoza [liraglutide] summary of product characteristics [article online], 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001026/WC500050017.pdf. Accessed 22 March 2014
10. Novartis Europharm Ltd. Galvus [vildagliptin] summary of product characteristics [article online], 2012. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000771/WC500020327.pdf. Accessed 22 March 2014
11. sanofi-aventis groupe. Lyxumia [lixisenatide] summary of product characteristics. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf. Accessed 22 March 2014
12. European Medicines Agency. Investigation into GLP-1-based diabetes therapies concluded [article online], 2013. Available from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001856.jsp&mid=WC0b01ac058004d5c1. Accessed 22 March 2014
13. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011;141:150–156
14. Lee PH, Stockton MD, Franks AS. Acute pancreatitis associated with liraglutide. *Ann Pharmacother* 2011;45:e22
15. Butler AE, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* 2013;62:2595–2604
16. Meier JJ, Nauck MA. Risk of pancreatitis in patients treated with incretin-based therapies. *Diabetologia* 2014;57:1320–1324
17. Franks AS, Lee PH, George CM. Pancreatitis: a potential complication of liraglutide? *Ann Pharmacother* 2012;46:1547–1553
18. Raschi E, Piccini C, Poluzzi E, Marchesini G, De Ponti F. The association of pancreatitis with antidiabetic drug use: gaining insight through the FDA pharmacovigilance database. *Acta Diabetol* 2013;50:569–577
19. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013;173:534–539
20. Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract* 2012;98:271–284
21. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010;33:2349–2354
22. Monami M, Dicembrini I, Martelli D, Mannucci E. Safety of dipeptidyl peptidase-4 inhibitors: a meta-analysis of randomized clinical trials. *Curr Med Res Opin* 2011;27(Suppl. 3):57–64
23. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ* 2014;348:g2366
24. Ryder REJ, Thong KY, Blann AD, et al.; ABCD Nationwide Liraglutide Audit Contributors. Liraglutide pancreatitis: the ABCD nationwide liraglutide audit. *Br J Diabetes Vasc Dis* 2013;13:253–259
25. Kahn SE. Incretin therapy and islet pathology: a time for caution. *Diabetes* 2013;62:2178–2180
26. Nauck MA. A critical analysis of the clinical use of incretin-based therapies: the benefits by far outweigh the potential risks. *Diabetes Care* 2013;36:2126–2132
27. Bonner-Weir S, In't Veld PA, Weir GC. Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies. *Diabetes Obes Metab* 2014;16:661–666
28. Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med* 2014;370:794–797
29. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2012. Available from <http://www.R-project.org>. Accessed 22 March 2014
30. Banks PA, Bollen TL, Dervenis C, et al.; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013;62:102–111
31. Forsmark CE. Chronic pancreatitis. In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th ed. Feldman M, Friedman L, Brand L, Eds. Philadelphia, Saunders/Elsevier, 2010, p. 998–999
32. 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
33. Girman CJ, Kou TD, Cai B, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab* 2010;12:766–771
34. Gonzalez-Perez A, Schlienger RG, Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care* 2010;33:2580–2585

35. Steinberg WM. Comment: acute pancreatitis associated with liraglutide. *Ann Pharmacother* 2011;45:1169
36. Steinberg WM, Rosenstock J, DeVries JH, Thomsen AB, Svendsen CB, Wadden TA. Elevated serum lipase activity in adults with type 2 diabetes and no gastrointestinal symptoms (Abstract). *Gastroenterology* 2012;142(Suppl. 1):S93–S94
37. Steinberg WM, DeVries JH, Wadden TA, Jensen CB, Svendsen CB, Rosenstock J. Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with once daily GLP-1 analog liraglutide (Abstract). *Gastroenterology* 2012;142(Suppl. 1):S850–S851
38. Lando HM, Alattar M, Dua AP. Elevated amylase and lipase levels in patients using glucagonlike peptide-1 receptor agonists or dipeptidyl-peptidase-4 inhibitors in the outpatient setting. *Endocr Pract* 2012;18:472–477
39. Malloy J, Gurney K, Shan K, Yan P, Chen S. Increased variability and abnormalities in pancreatic enzyme concentrations in otherwise asymptomatic subjects with type 2 diabetes. *Diabetes Metab Syndr Obes* 2012;5:419–424
40. Badalov N, Baradaran R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007;5:648–661; quiz 644
41. Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care* 2013;36:2118–2125
42. Tenner S, Steinberg WM. Acute pancreatitis. In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th ed. Feldman M, Friedman L, Brand L, Eds. Philadelphia, Saunders/Elsevier, 2010, p. 963–964
43. Gourdy P, Penfornis A, Charpentier G, et al. Effectiveness and tolerability with liraglutide among patients with type 2 diabetes. 1-year data from EVIDENCE: a 2-year, prospective, follow up, post-marketing study. Poster presented at the 49th Annual Meeting of the European Association for the Study of Diabetes, 27 September 2013, Barcelona, Spain. Available from <http://www.easdvirtualmeeting.org/resources/6203>. Accessed 26 March 2014
44. Gourdy P, Penfornis A, Charpentier G, et al. Effectiveness and persistence with liraglutide among patients with type 2 diabetes. One year data from EVIDENCE: a 2-year, prospective, follow up, post-marketing study (Abstract). *Diabetologia* 2013;56(Suppl. 1):S369
45. Funch D, Gydesen H, Tornøe K, Major-Pedersen A, Chan KA. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. *Diabetes Obes Metab* 2014;16:273–275
46. Marso SP, Poulter NR, Nissen SE, et al. Design of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. *Am Heart J* 2013;166:823–830
47. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327–1335
48. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–1326
49. Jensen TM, Saha K, Steinberg WM. Assessment of acute pancreatitis in liraglutide type 2 diabetes trials. *Pancreas* 2012;41:1370–1371