



Amylase, Lipase, and Acute Pancreatitis in People With Type 2 Diabetes Treated With Liraglutide: Results From the LEADER Randomized Trial

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OBJECTIVE

To evaluate serum amylase and lipase levels and the rate of acute pancreatitis in patients with type 2 diabetes and high cardiovascular risk randomized to liraglutide or placebo and observed for 3.5–5.0 years.

RESEARCH DESIGN AND METHODS

A total of 9,340 patients with type 2 diabetes were randomized to either liraglutide or placebo (median observation time 3.84 years). Fasting serum lipase and amylase were monitored. Acute pancreatitis was adjudicated in a blinded manner.

RESULTS

Compared with the placebo group, liraglutide-treated patients had increases in serum lipase and amylase of 28.0% and 7.0%, respectively. Levels were increased at 6 months and then remained stable. During the study, 18 (0.4% [1.1 events/1,000 patient-years of observation] [PYO]) liraglutide-treated and 23 (0.5% [1.7 events/1,000 PYO]) placebo patients had acute pancreatitis confirmed by adjudication. Most acute pancreatitis cases occurred ≥ 12 months after randomization. Liraglutide-treated patients with prior history of pancreatitis ($n = 147$) were not more likely to develop acute pancreatitis than similar patients in the placebo group ($n = 120$). Elevations of amylase and lipase levels did not predict future risk of acute pancreatitis (positive predictive value $< 1.0\%$) in patients treated with liraglutide.

CONCLUSIONS

In a population with type 2 diabetes at high cardiovascular risk, there were numerically fewer events of acute pancreatitis among liraglutide-treated patients (regardless of previous history of pancreatitis) compared with the placebo group. Liraglutide was associated with increases in serum lipase and amylase, which were not predictive of an event of subsequent acute pancreatitis.

Glucagon-like peptide 1 (GLP-1) receptor agonists are established glucose-lowering drugs for treating type 2 diabetes (1). However, incretin-based therapies (GLP-1 receptor agonists and dipeptidyl peptidase 4 [DPP-4] inhibitors) are associated with increased levels of serum lipase and amylase, and a potential for an increased risk of acute pancreatitis has previously been raised (2–6). Current assessments from regulatory agencies in Europe and the U.S. indicate that pancreatitis should be considered a

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*The full list of LEADER Trial Investigators and Committee Members can be found in the Supplementary Data online.

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risk associated with incretin-based drugs until further data are available (7). Subsequently, analyses of pooled data from shorter phase III clinical trials of GLP-1 receptor agonists have noted an association with 38 cases of acute pancreatitis among 17,775 patient-years of observation (PYO) (event rate 2.1/1,000 PYO) compared with 9 cases after 5,863 PYO (event rate 1.5/1,000 PYO) (8). For DPP-4 inhibitors, though meta-analysis of shorter regulatory trials failed to show an association with pancreatitis (8), meta-analysis of the longer cardiovascular outcomes trials does suggest a small increased risk (9,10).

Due to the previous results and the lack of long-term data, pancreatitis continues to be of interest in studies of GLP-1 receptor agonists, particularly in studies where long-term safety data can be collected. Furthermore, serial amylase and lipase measurements have been suggested to predict the development of acute pancreatitis (11).

In the Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) trial, 9,340 patients with type 2 diabetes and high cardiovascular risk were randomized to the GLP-1 analog liraglutide or matching placebo, both in addition to standard of care, and followed for 3.5–5.0 years. The aim of the current study was to evaluate results from LEADER regarding the effects of liraglutide treatment on serum lipase and amylase and the number of cases of acute pancreatitis confirmed by adjudication.

RESEARCH DESIGN AND METHODS

Detailed methods have previously been published (12,13). Briefly, 9,340 patients were enrolled at 410 sites in 32 countries. Patients with type 2 diabetes at high risk for cardiovascular events were randomized 1:1 double-blind to either subcutaneous liraglutide 1.8 mg daily (or maximum tolerated dose) or placebo with a treatment period of 3.5–5.0 years and a 30 day follow-up period. Patients with a history of pancreatitis were not excluded. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Other prespecified outcomes included acute pancreatitis.

Serum lipase and amylase (pancreas specific) were measured at baseline and months 6 and 12. Thereafter, assessments

were repeated annually until the trial ended. No measurement was performed after the planned end-of-treatment visit. Serum pancreatic lipase and total amylase were measured in the fasting state in all patients using an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) performed by a central laboratory (ICON PLC, Dublin, Ireland). No patients had symptoms suggesting acute pancreatitis at baseline blood draw. The upper limit of normal (ULN) for the assays was 63 units/L for lipase and 100 units/L for amylase. Neither limit was adjusted for the distribution expected in patients with type 2 diabetes. More frequent tests for lipase and amylase were allowed at the discretion of the investigator. Baseline lipase activity and amylase activity among the study population have previously been reported (14). Per protocol, participants diagnosed with pancreatitis should be withdrawn from study medication by their care team.

Evaluation of Acute Pancreatitis

Pancreatitis was predefined by the trial protocol as a medical event of special interest. Revised Atlanta criteria were used for a confirmed diagnosis of acute pancreatitis and classified by severity (15) (Supplementary Table 1). For the diagnosis of acute pancreatitis, two or more of the following three criteria had to be fulfilled: 1) severe acute upper abdominal pain, 2) amylase and/or lipase threefold or more above the ULN ($\geq 3 \times$ ULN), and 3) characteristic findings on imaging (ultrasound, computed tomography [CT], or MRI) of the pancreas. Chronic pancreatitis was defined by characteristic imaging findings (ultrasound, CT, and MRI) with abnormal pancreatic function tests or characteristic histological findings. All potential cases of pancreatitis were adjudicated by an independent committee of experts, which was blinded to treatment. To ensure that potential events of pancreatitis were not missed for adjudication, a Medical Dictionary for Regulatory Activities search of the clinical database was performed to identify events for adjudication not already identified by study investigators. In those who developed acute pancreatitis as confirmed by adjudication, data were further analyzed post hoc as to whether gallstone disease was present at the time of pancreatitis event either on imaging (sonography, CT, MRI) or blood testing (threefold elevation of

the liver enzyme profile alanine aminotransferase/aspartate transaminase) (11). In addition, characteristics of the events not confirmed by adjudication were evaluated in a post hoc review by the sponsor.

Statistical Analysis

All analyses were prespecified (before database lock) unless marked otherwise. Due to a right-skewed distribution, observed geometric means for lipase and amylase levels are presented. The differences between treatment groups in lipase and amylase were estimated using a mixed effects model for repeated measurements adjusted for baseline covariates. Comparisons between groups were performed at 36 months, as this was the last annual visit with laboratory testing for the majority of the patients, given the minimum treatment period of 42 months. An analysis using a linear model with repeated measures (Mixed effect Model Repeat Measurement [MMRM]) assuming an unstructured covariance matrix was performed to evaluate the interaction between explanatory factors at baseline and treatment in relation to change from baseline for log-transformed levels of lipase and amylase, respectively, at each visit. Effects of each level in the factors were presented as the treatment ratio between liraglutide versus placebo at the 36-month visit. Explanatory factors were age, sex, BMI, smoking status, diabetes duration, glycated hemoglobin (HbA_{1c}), baseline lipase and amylase levels, medical history (including history of pancreatitis), estimated glomerular filtration rate, lipid levels, and use of certain medications. The interaction between baseline characteristics and allocated treatment (liraglutide vs. placebo) on the development of acute pancreatitis was examined using logistic regression. Correction for multiple comparisons in the analyses of baseline characteristics was performed using the Bonferroni method.

The analyses for risk of acute pancreatitis were based on a Cox proportional hazards model with treatment as a covariate. All randomized patients were included in the analyses, and patients without acute pancreatitis were censored on the day of their follow-up visit/withdrawal date or date of death. Events occurring after follow-up visit were not included. All analyses were performed

using SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 9,340 patients were randomized (4,668 to liraglutide and 4,672 to placebo, both added to standard of care). Of these, 96.8% completed a final visit, died, or had a primary outcome. The median and mean times of exposure to study medication were 3.52 and 3.07 years, respectively. The mean proportion of time on study drug was 84.0% for liraglutide and 82.0% for placebo, and 71.3% of patients were exposed for 3–5 years. The median observation time was 3.84 years in both groups. The median daily dose of liraglutide was 1.78 mg (interquartile range 1.54–1.79) including off-treatment periods. Of patients entering the study, 267 had a history of pancreatitis (147 and 120 in the liraglutide and placebo groups, respectively).

Baseline Characteristics

Baseline population characteristics have previously been published (13). The mean age of the population was 64.3 years, 64.3% of the population were male, and mean duration of diabetes was 12.9 years.

Lipase and Amylase Levels Over Time

The time course and magnitude of change in lipase and amylase over time are depicted in Fig. 1 (13). In the liraglutide arm, elevated levels of both enzymes were seen at 6 months and persisted for the duration of the study. Compared with placebo

and considering baseline characteristics, at 36 months liraglutide was associated with an estimated relative 28.0% increase in lipase (estimated treatment ratio 1.28 [95% CI 1.25–1.30]; $P < 0.001$). Observed mean lipase changed from 40.0 units/L to 55.2 units/L for liraglutide. Similarly, an estimated 7.0% (1.07 [95% CI 1.06–1.09]; $P < 0.001$) increase in amylase was seen with an observed amylase change from 59.4 units/L to 70.9 units/L for liraglutide. Results for both lipase and amylase were similar when only patients with an on-treatment laboratory value were included (data not shown).

Figure 2 shows the categorical maximum values of lipase and amylase over the course of the study. Of patients randomized to liraglutide, 51.3% experienced at least one elevated lipase level ($>ULN$) over time compared with 31.8% on placebo. In the liraglutide group, 8.3% of patients and in the placebo group 5.3% experienced increases of threefold or more in lipase at some point during the trial (Fig. 2). For amylase, 29.0% of liraglutide-treated patients and 22.9% of the placebo group had at least one elevated amylase level during the study (1.0% and 0.8%, respectively, had levels elevated by threefold or more).

Effect of Baseline Data on Lipase and Amylase Levels Over Time

The influence of baseline characteristics on increases in lipase and amylase over time is shown in Supplementary Table 2. With adjustment for multiple comparisons, only increased baseline lipase level was found to have a statistically significant

positive association with subsequent elevation of amylase.

Events Confirmed or Not Confirmed as Acute Pancreatitis by the Adjudication Process

Supplementary Table 3 presents details of the adjudication process for Event Adjudication Committee confirmed acute pancreatitis cases and which of the three diagnostic criteria (typical pain, elevated serum pancreatic enzymes $\geq 3 \times ULN$, and characteristic imaging findings) were met. In all cases, a minimum of two of these three criteria were met.

Supplementary Tables 4–6 present similar data for patients with events suggestive of acute pancreatitis but in whom the diagnosis of acute pancreatitis was not confirmed by the adjudication process. This information is based on post hoc review by the trial sponsor. The diagnosis was not confirmed by the Event Adjudication Committee in 50 liraglutide-treated or 21 placebo patients. For the majority of events in both treatment groups, patients had been clinically evaluated due to any abdominal pain or elevation in lipase or amylase levels. Information on presence or absence of pain, lipase and amylase levels, and imaging was available in the majority of cases but did not support a diagnosis of acute pancreatitis. There was no imbalance in diagnostic procedures performed and information available for the adjudication process between patients administered liraglutide or placebo.

Acute Pancreatitis

Acute pancreatitis events confirmed by adjudication were identified in 18 of the 4,668 liraglutide-treated patients (0.4%) and 23 of the 4,672 placebo-administered patients (0.5%) (Supplementary Table 7). One of 18 patients in the liraglutide group had 2 acute pancreatitis events (19 total events), and 8 patients in the placebo group had >1 event (31 total events) (Supplementary Table 7). The corresponding event rates were 1.1/1,000 PYO for the liraglutide group and 1.7/1,000 PYO for the placebo group (Supplementary Table 7). When we analyzed first acute pancreatitis events, there was a nonsignificant 22% reduction in the incidence (hazard ratio 0.78 [95% CI 0.42–1.44]) (Fig. 3). Results were similar (hazard ratio 0.73 [95% CI 0.35–1.54]) when only patients with events that occurred during days on treatment (+1 day) were included.

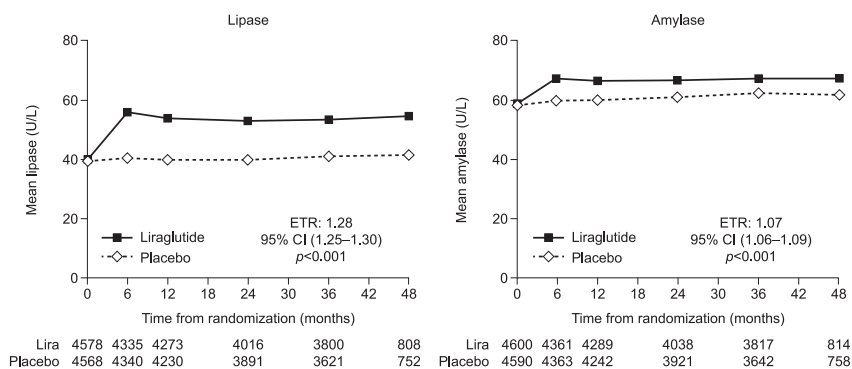


Figure 1—Lipase and amylase over time. Data are observed geometric means (full analysis set) (12). Estimated treatment ratios were calculated using a mixed model for repeated measurements. For amylase, 135 patients equally distributed between the liraglutide and placebo arms had missing information and were not included in the analysis. For lipase, 177 patients had missing information and were not included in the analysis. ETR, estimated treatment ratio; Lira, liraglutide; U, units.

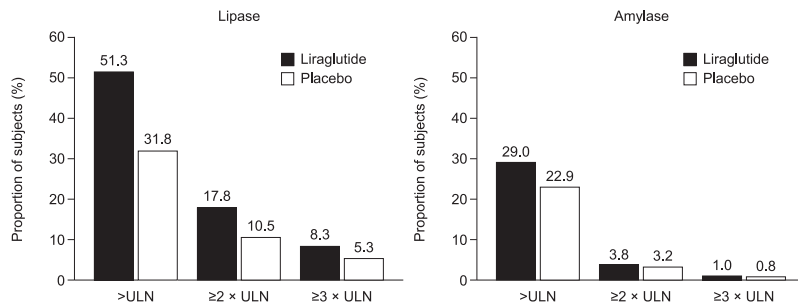


Figure 2—Maximum lipase and amylase levels by category. Data are presented as proportion of subjects with maximum lipase and amylase levels at scheduled measurements within the stated categories (>ULN, ≥2 × ULN, or ≥3 × ULN [full analysis set]).

Most acute pancreatitis events were mild according to modified Atlanta criteria (89.5% and 83.9% in the liraglutide and placebo groups, respectively) (Supplementary Tables 7 and 8). Six of the 18 patients in the liraglutide group had been off liraglutide for extended periods of time when the acute pancreatitis event occurred (28, 30, 103, 146, 634, and 637 days, respectively) (Supplementary Table 8). Gallstone disease was observed (by imaging and/or ≥3 × ULN elevations of alanine aminotransferase/aspartate transaminase) at the time of acute pancreatitis event for 7 of 18 (38.9%) compared with 10 of 23 (43.5%) patients in the liraglutide and placebo groups (*P* = 0.81) (Supplementary Table 8).

Two patients in the placebo group had chronic pancreatitis events confirmed by adjudication (Supplementary Table 7).

Figure 3 shows the time course of acute pancreatitis events, which was similar in both groups. No patients in the liraglutide group developed acute pancreatitis within the first 6 months of therapy.

In both groups, most cases of acute pancreatitis developed >12 months after beginning the trial (Supplementary Table 8). Of the patients who entered the trial with a history of pancreatitis, 2 of 147 (1.4%) in the liraglutide group and 6 of 120 (5.0%) in the placebo group had another event during the study.

Effect of Baseline Characteristics on Subsequent Development of Acute Pancreatitis

In Supplementary Table 9, the interaction between baseline characteristics and treatment on subsequent development of acute pancreatitis is shown. There was no statistically significant interaction between liraglutide or placebo administration and baseline characteristics on the risk of emergent acute pancreatitis.

Predictive Value of Lipase and Amylase

Table 1 and Supplementary Tables 10 and 11 show the predictive values of measuring lipase and amylase in predicting acute pancreatitis. Whether the data were analyzed using the >ULN or ≥3 × ULN,

positive predictive values for elevated serum levels of both enzymes was <1.0%. Supplementary Fig. 1 plots lipase and amylase over time in patients who subsequently developed acute pancreatitis, showing minimal elevations in levels measured at scheduled visits prior to the diagnosis of acute pancreatitis. Finally, in both the liraglutide and placebo groups there was no association between onefold or threefold elevated lipase and the subsequent risk of acute pancreatitis in patients without acute pancreatitis at the time of measurement (Supplementary Fig. 2). In fact, relatively more patients on placebo had categorical increases in enzyme levels prior to the attack of acute pancreatitis than for the liraglutide group, albeit numbers were small.

CONCLUSIONS

This randomized, double-blind trial comparing liraglutide and placebo added to standard of care in patients with type 2 diabetes and high cardiovascular risk is the largest and longest study to date exposing patients to the GLP-1 analog liraglutide. In the present report, liraglutide treatment was associated with a 28.0% increase in mean serum lipase and 7.0% increase in mean serum amylase compared with placebo. There were fewer acute pancreatitis events in the liraglutide group, and isolated liraglutide-associated elevations in lipase and amylase were not predictive of subsequent acute pancreatitis. Liraglutide was also associated with increases in the proportion of patients with elevated enzyme levels over the course of therapy, including some with threefold or more increases in lipase (albeit none of these had acute pancreatitis), findings consistent with prior studies of liraglutide in patients with normoglycemia, prediabetes, and diabetes (16). The current study did not evaluate pancreatic enzymes after liraglutide was discontinued, but prior work has shown that serum pancreatic enzymes return to baseline when liraglutide is stopped (17).

The cause of serum pancreatic enzyme elevations, especially lipase, induced by liraglutide is unknown. Indeed, the mechanisms by which pancreatic enzymes enter and exit the blood compartment have not been elucidated. One hypothesis is that enzymes enter the blood by passing through the basolateral membrane of the acinar cell allowing access into the blood (“spillover” of a minor percentage of the

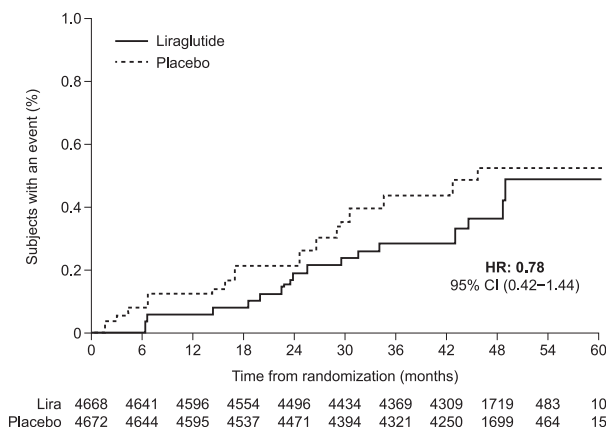


Figure 3—Time to confirmed acute pancreatitis. Kaplan-Meier plot of confirmed acute pancreatitis first index events (full analysis set). Values underneath the graph are number of subjects at risk, HR, hazard ratio; Lira, liraglutide.

Table 1—Predictive value of increased lipase or amylase levels for confirmed acute pancreatitis

	Liraglutide		Placebo	
	N	%	N	%
Lipase >ULN during trial	2,604		1,682	
Subsequent acute pancreatitis	7	0.27	11	0.65
Lipase $\geq 3 \times$ ULN during trial	339		216	
Subsequent acute pancreatitis	0	0.00	2	0.93
Amylase >ULN during trial	1,382		1,084	
Subsequent acute pancreatitis	3	0.22	5	0.46
Amylase $\geq 3 \times$ ULN during trial	38		35	
Subsequent acute pancreatitis	0	0.00	0	0.00

Data are for confirmed acute pancreatitis (full analysis set). Subjects are included in the elevated lipase or amylase category from the date of first elevation within the stated categories (>ULN and $\geq 3 \times$ ULN lipase or amylase). Hazard ratios and 95% CIs derived from data in this table are shown in Supplementary Fig. 2. %, percentage of subjects; N, number of subjects.

enzymes present in acinar cells). The elimination of lipase from the blood is thought in part to be due to renal degradation of the enzyme (18). Although previous studies reported controversial views on whether human pancreatic acinar cells express GLP-1 receptors (19,20), recent animal studies indicate that pancreatic acinar cells have GLP-1 receptors that, when stimulated, increase the production and secretion of pancreatic enzymes (20). However, increases in pancreatic secretion into the pancreatic ductular system and intestine alone do not explain higher levels in the blood. Along these lines, serum pancreatic enzymes do not rise after a meal despite an increase in pancreatic secretion (21). It appears possible that liraglutide somehow enhances the basolateral secretion of pancreatic enzymes, especially lipase, into the blood or may affect the degradation of lipase in the kidney. Alternative explanations are an increase in pancreatic exocrine weight due to stimulation of protein synthesis, as shown in rodents treated with liraglutide, with a likely stimulation of pancreatic enzyme synthesis as part of this general enhancement in protein synthesis (22), although similar effects have not been obvious in studying nonhuman primates (23). The changes in lipase and amylase may also be the consequence of changes in food preferences (as part of well-established reductions in appetite and caloric intake induced by liraglutide) (24,25) leading to altered expression of pancreatic enzymes specifically favoring the digestion of preferred substrates (26–28). Altogether, the mechanism of GLP-1 receptor stimulation with liraglutide

on serum lipase (and, less so, amylase) has not been sufficiently delineated.

Despite this background of increased lipase and amylase associated with liraglutide, the rate of acute pancreatitis was quite low overall and 22% lower in the liraglutide than in the placebo group, albeit not statistically significant. The liraglutide group also included six patients who were off liraglutide for 28–637 days when acute pancreatitis developed. The relationship between acute pancreatitis and drugs that have been stopped for long periods of time remains obscure. In pooled data from prior studies of the GLP-1 receptor agonists exenatide, liraglutide, and lixisenatide, an excess of acute pancreatitis was found compared with comparator treatments (2.1/1,000 PYO and 1.5/1,000 PYO, respectively) (8). The lower event rate for acute pancreatitis in the current study (1.1/1,000 PYO) compared with the rate reported in the analysis by Meier and Nauck (8) may be the result of adjudication in the current study; adjudication was not performed in all studies contributing to the pooled analysis.

The current study population consisted of patients with type 2 diabetes at high risk for cardiovascular events, which is different from populations previously studied. Interestingly, another recent cardiovascular outcomes trial for the once-weekly GLP-1 analog semaglutide reported a lower number of patients with acute pancreatitis events in the semaglutide versus placebo group (9 and 12 for semaglutide and placebo, respectively), as confirmed by adjudication (29). Similarly, the cardiovascular outcomes trial for the short-acting GLP-1 receptor

agonist lixisenatide reported five and eight patients with acute pancreatitis in the lixisenatide and placebo groups, respectively (30). Additional cardiovascular outcomes trials for other GLP-1 receptor agonists are expected to report in the coming years and may provide further data on this topic.

The time course of acute pancreatitis in both liraglutide and placebo groups was similar. The majority of patients in both groups had acute pancreatitis attacks after participating in the trial for >12 months. Most therapies associated with drug-induced pancreatitis are thought to be due to a hypersensitivity reaction (31). Hypersensitivity reactions tend to have much shorter latencies (the time interval between starting the drug and development of acute pancreatitis) of up to 12 weeks (32,33). Long latencies as seen in the present population suggest a different mechanism than hypersensitivity. Another possibility is the development of gallstones leading to gallstone pancreatitis. Patients with type 2 diabetes (not on GLP-1 receptor agonists) have an increased risk of developing gallstones and acute pancreatitis (6), and liraglutide therapy in patients without diabetes increases the risk of gallstones and acute cholecystitis compared with placebo (34). Gallstones may take an extended period of time to form, which may explain the latency between drug initiation and acute pancreatitis in some patients. In LEADER, an increased risk of development of acute gallstone disease was also observed in the liraglutide group compared with placebo (3.1% vs. 1.9%, $P < 0.001$) (13). Nevertheless, the observed imbalance in acute gallstone disease did not translate into an increased risk of gallstone-associated acute pancreatitis, since a similar proportion of pancreatitis events (38.9% vs. 43.5%) was found to be associated with signs of gallstone disease being present at the time of event in the liraglutide group compared with placebo. The protocol required all adverse events of acute gallstone disease to be reported; however, asymptomatic gallstones were not required to be reported, and furthermore, systematic clinical evaluation for gallstone disease at baseline in the LEADER trial was not part of the protocol.

It has been suggested that liraglutide may induce pancreatitis in patients with prior history of pancreatitis (35). In fact,

prescribing information for liraglutide advises exercising caution in patients with a history of acute pancreatitis and that other therapies should be considered. In the current study, pancreatitis was not an exclusion criterion for study entry, and in patients with prior history of pancreatitis, only 2 of 147 (1.4%) in the liraglutide group and 6 of 120 (5.0%) in the placebo group developed acute pancreatitis. Our results do not support the exclusion of patients with previous pancreatitis from treatment with GLP-1 receptor agonists in general terms and with liraglutide in particular. Nevertheless, the study protocol did not call for an active investigation to characterize previous pancreatic or biliary structural or functional damage.

The U.S. Food and Drug Administration and other regulatory authorities have mandated that studies involving GLP-1 receptor agonists monitor lipase and amylase levels under the assumption that this might predict patients' development of acute pancreatitis. This study and others (16) have shown that the positive predictive value of an isolated elevation of these enzymes for acute pancreatitis is very low (<1.0%). Indeed, in the population of all patients treated with liraglutide in the LEADER trial who developed substantially elevated serum lipase ($\geq 3 \times$ ULN) while being asymptomatic, none developed acute pancreatitis later in the trial. In fact, among patients with categorical enzyme elevations there were relatively more in the placebo group who subsequently developed acute pancreatitis (based on small numbers) (Supplementary Fig. 2). The reasons for this remain obscure.

The present analysis provides details on the blinded adjudication process (Supplementary Tables 3–6) that demonstrate sufficient data were available for either confirming or refuting the diagnosis of acute pancreatitis for those events that were adjudicated. These data also show that despite more suspected events sent for adjudication with liraglutide treatment (most likely due to lipase and amylase increases as well as abdominal pain) versus placebo, among those events not confirmed by adjudication, the extent of workup was similar between the two groups.

Strengths of the current study include its large population, placebo-controlled design, and relatively long-term observation time (for a minimum of 3.5 and up to 5.0 years). Serum samples were collected prospectively at specified intervals.

Finally, to ensure objective assessment of events of suspected acute pancreatitis, a committee blinded to treatment evaluated all cases and used the Atlanta criteria to confirm a diagnosis of acute pancreatitis. A potential weakness of this study is that the trial population only included patients with type 2 diabetes, the majority being men, with a higher mean age and longer diabetes duration than the wider population of patients with type 2 diabetes. Thus, our findings may not be generalizable. Another potential limitation is the low number of acute pancreatitis events, which leads to wide CIs, meaning that we cannot completely rule out a potential increased risk (Fig. 3). Finally, because patients could discontinue treatment or not reach the 36-month visit (if they discontinued the trial or died), the relationship between lipase levels and pancreatitis events could be diluted and/or the association between liraglutide treatment and risk of acute pancreatitis could be affected. However, analyses that included only the on-treatment population showed similar results to those of the intention-to-treat analyses, potentially due to the high degree of exposure in the trial.

In summary, this study confirmed and extended observations concerning the effect of liraglutide on the pancreas. In LEADER, numerically fewer events of acute pancreatitis were observed in liraglutide-treated patients compared with the placebo group. Liraglutide increased serum amylase, and especially lipase, and this increase plateaued and remained stable for the duration of the study. Liraglutide-induced elevations of lipase and amylase in asymptomatic patients were not predictive of the development of acute pancreatitis.

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