Incidence of Pancreatitis and Pancreatic Cancer in a Randomized Controlled Multicenter Trial (SAVOR-TIMI 53) of the Dipeptidyl Peptidase-4 (DPP-4) Inhibitor Saxagliptin

OBJECTIVE
To determine the incidence of pancreatitis and pancreatic cancer in the SAVOR-TIMI 53 trial.

RESEARCH DESIGN AND METHODS
A total of 16,492 type 2 diabetic patients ≥40 years old with established cardiovascular (CV) disease or CV risk factors were randomized to saxagliptin or placebo and followed for 2.1 years. Outcome measures were investigator reported with blinded expert adjudication of total pancreatitis (acute and chronic) and reported cases of pancreatic cancer.

RESULTS
Trial investigators reported 35 events of pancreatitis in each treatment arm in 63 patients (33 [0.40%] in the saxagliptin arm and 30 [0.37%] in control arm), with a hazard ratio (HR) of 1.09 (95% CI 0.66–1.79, \( P = 0.80 \)). Adjudication confirmed pancreatitis in 24 patients (26 events) in the saxagliptin arm (0.29%) and 21 patients (25 events) in placebo arm (0.26%), with an HR of 1.13 (0.63–2.06, \( P = 0.77 \)). Cases of definite acute pancreatitis were confirmed in 17 (0.2%) vs. 9 (0.1%) (HR 1.88 [0.86–4.41], \( P = 0.17 \)), definite plus possible pancreatitis in 22 vs. 16 (HR 1.36 [0.72–2.64], \( P = 0.42 \)), and chronic pancreatitis in 2 vs. 6 (HR 0.33 [0.05–1.44], \( P = 0.18 \)) in the saxagliptin and placebo arms, respectively. No differences in time to event onset, concomitant risk factors for pancreatitis, investigator-reported causality from study medication or disease severity, and outcome were found between treatment arms. The investigators reported 5 and 12 cases of pancreatic cancer in the saxagliptin and placebo arms, respectively (HR 0.42 [0.13–1.12], \( P = 0.09 \)).

CONCLUSIONS
In the SAVOR-TIMI 53 trial, within 2.1 years of follow-up, risk for pancreatitis in type 2 diabetic patients treated with saxagliptin was low and apparently similar to placebo, with no sign of increased risk for pancreatic cancer. Further studies are needed to completely resolve the pancreatic safety issues with incretin-based therapy.
Several clinical features associated with type 2 diabetes and obesity are recognized risk factors for acute pancreatitis (1). Recently, concerns have been raised regarding long-term consequences of incretin therapy in type 2 diabetic patients. These concerns include possible triggers for acute pancreatitis and initiation or acceleration of histological changes, suggesting silent or clinical chronic pancreatitis with preneoplastic lesions and potentially pancreatic cancer (2,3). Although some reports have supported the linkage of type 2 diabetes treatment with dipeptidyl peptidase 4 (DPP-4) inhibitors or GLP-1 receptor agonists and increased risk of pancreatitis (4,5), others have not support this association (6–9).

The U.S. Food and Drug Administration requires the investigation of cardiovascular (CV) safety of new drugs for diabetes (10,11). Therefore, several randomized controlled CV safety studies with incretin-based therapies are ongoing or have recently been completed (12–15). These studies provide an opportunity to further evaluate additional safety events of interest, including effects on the pancreas.

**RESEARCH DESIGN AND METHODS**

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial evaluated the long-term CV safety and efficacy of saxagliptin in patients with type 2 diabetes at high risk for CV events (16). The TIMI Study Group and Hadassah Medical Organization designed the trial in collaboration with the sponsors. SAVOR-TIMI 53 was a randomized, double-blind, placebo-controlled, multicenter international intervention trial conducted between May 2010 and June 2013 in 788 medical centers in 26 countries. Patients with type 2 diabetes >40 years of age with established CV disease or ≥55 (men) and ≥60 (women) years of age with one or more CV risk factors were randomized 1:1 to receive 5 mg/day saxagliptin or placebo. In patients with moderate or severe renal failure, the saxagliptin dose was decreased to 2.5 mg/day. The protocol was approved by the ethics committees of all participating centers, and all patients gave written informed consent before enrollment. The full eligibility criteria have been previously published (16). In short, eligible patients had a documented history of type 2 diabetes, had an HbA1c between 6.5% and 12.0% (48–108 mmol/mol) during the 6 months before enrollment in the study, and were taking any antidiabetic drug except incretin-based therapy. To qualify for the established CV disease criteria, study subjects had to be at least 40 years old and have a history of a clinical event secondary to atherosclerosis involving the coronary, cerebrovascular, or peripheral vascular system. To qualify based on multiple risk factor criteria, study subjects had to be at least 55 (men) or 60 (women) years old and have at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking. Patients were ineligible if they were currently or previously (within 6 months) treated with an incretin-based therapy or had end-stage renal disease (long-term dialysis, renal transplant, or serum creatinine level >6.0 mg/dL). The baseline characteristic of the SAVOR-TIMI 53 participants were previously reported (17).

Patients were followed at the study sites by a minimum of one office visit every 6 months with either an additional phone call or office visit every 3 months. The patients also continued their usual medical care with their respective treating physicians, and the sites were instructed to maintain contact with these physicians.

Pancreatitis events were reported by the investigator as an adverse event (AE), a serious AE, and an event of special interest (EOSI). We systematically collected all events, investigators received specific training, and specific prospective electronic case report forms were used for event collection.

Pancreatitis events were blindly adjudicated by an external expert committee, which included two pancreatic disease experts (N.G. and M.M.L.). The classification of the pancreatitis events was decided on by an external expert committee and was in accordance with internationally accepted guidelines (18–20). Reported cases were classified into four categories: definite acute pancreatitis, possible acute pancreatitis, chronic pancreatitis, or unlikely to be pancreatitis. The predefined end point was the total number of adjudicated cases of pancreatitis. The diagnosis of acute pancreatitis was regarded as definite when at least two of the following three criteria from internationally accepted guidelines (18) were met: 1) acute onset of persistent, severe, epigastric pain often radiating to the back; 2) elevation in serum lipase or amylase to three times or more the upper limit of normal at the respective institution; and 3) characteristic findings of acute pancreatitis on diagnostic imaging (transabdominal ultrasound, contrast-enhanced computed tomography, or magnetic resonance imaging). To allow for greater sensitivity for a potential association with pancreatic disorders, we used a second category of possible acute pancreatitis (18), which included patients in whom reported atypical abdominal symptoms were not characteristic of pancreatitis (but were without an alternative explanatory diagnosis) plus at least one of the following: 1) elevated serum lipase or amylase levels to three times or more the upper limit of normal, 2) characteristic findings of acute pancreatitis on diagnostic imaging, or 3) a history of previous pancreatitis. Patients were classified as having chronic pancreatitis when either medical records documented or cross-sectional imaging confirmed the diagnosis. Symptoms were regarded as unlikely to be pancreatitis when none of the these definitions applied. Patients with definite or possible pancreatitis were assessed as having severe disease when single or multiple organ failure persisted for >48 h (19,20). Known risk factors for pancreatitis, including alcohol use, gallstone disease (including prior cholecystectomy), hypertriglyceridemia, hypercalcemia, recent endoscopic retrograde cholangiopancreatography, trauma, and concomitant drugs known to be associated with pancreatitis, were also evaluated. In addition, investigators were instructed to treat pancreatitis according to local guidelines and to continue or discontinue the study drug according to their clinical judgment. Of note, history of pancreatitis was not a contraindication for participation in the trial.

Pancreatic cancer cases were collected as AE and serious AE and like all cancer cases, as EOSI. We collected as much information as possible on each case, including medical records and pathology and imaging results. Each report was reviewed for accuracy and completeness by blinded study physicians.
by both the TiMI Study Group and by the sponsor.

**Statistical Analysis**

All analyses were performed with an intention to treat all patients who underwent randomization. Continuous variables are expressed as mean ± SD, median and interquartile range, or minimum and maximum values; categorical variables are expressed as frequencies and percentages. χ² or Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables are reported. Incidence of pancreatitis was calculated as the number of patients with pancreatitis divided by the total population at risk in the beginning of the study. In addition, the cumulative incidence of pancreatitis at the end of study was reported by Kaplan-Meier plots (Supplementary Fig. 1A–D). To determine the relative risk of pancreatitis and pancreatic cancer between the saxagliptin and placebo arms, Cox proportional hazard modeling using profile likelihood estimations with stratification by study design variables, baseline renal impairment, and baseline CV risk factors (including dyslipidemia (71.2%), hypertension (81.8%), BMI ≥ 30 kg/m² (53.6%), BMI ≥ 40 kg/m² (7.5%), estimated glomerular filtration rate ≤ 50 mL/min (15.6%), and current smoking (13.5%).

The total observation time was 16,884 person-years in the saxagliptin group and 16,761 person-years in placebo group. The study drug was prematurely discontinued less frequently in patients assigned to saxagliptin than to placebo (1,527 [18.4%] vs. 1,705 [20.8%], respectively, P < 0.001). A final vital status was assessed in 99.1% of patients. Twenty-eight patients were lost to follow-up. The median follow-up was 2.1 years (interquartile range 1.8–2.3 years), and maximum follow-up was 2.9 years.

Investigators reported a total of 35 events of pancreatitis in 33 patients in the saxagliptin arm and 35 events in 30 patients in the placebo arm (hazard ratio

| Table 1—Investigator-reported and adjudication-confirmed pancreatitis in SAVOR-TIMI 53 |

<table>
<thead>
<tr>
<th>Event</th>
<th>Saxagliptin overall (n = 8,280)</th>
<th>Placebo overall (n = 8,212)</th>
<th>P value (Fisher exact test)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-reported pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with pancreatitis events</td>
<td>33 (0.40)</td>
<td>30 (0.37)</td>
<td>0.80</td>
<td>1.09 (0.66–1.79)</td>
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<tr>
<td>Number of events of pancreatitis</td>
<td>35</td>
<td>35</td>
<td>0.99 (0.90–1.10)</td>
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<tr>
<td>Adjudication-confirmed pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with any pancreatitis event</td>
<td>24 (0.29)</td>
<td>21 (0.26)</td>
<td>0.77</td>
<td>1.13 (0.63–2.06)</td>
</tr>
<tr>
<td>Number of events of pancreatitis</td>
<td>26</td>
<td>25</td>
<td>1.03 (0.92–1.15)</td>
<td></td>
</tr>
<tr>
<td>Patients with definite acute pancreatitis events</td>
<td>17 (0.2)</td>
<td>9 (0.1)</td>
<td>0.17</td>
<td>1.88 (0.86–4.41)</td>
</tr>
<tr>
<td>Patients with acute pancreatitis, definite or possible</td>
<td>22 (0.3)</td>
<td>16 (0.2)</td>
<td>0.42</td>
<td>1.36 (0.72–2.64)</td>
</tr>
<tr>
<td>Patients with chronic pancreatitis events</td>
<td>2 (0.02)</td>
<td>6 (0.07)</td>
<td>0.18</td>
<td>0.33 (0.05–1.44)</td>
</tr>
<tr>
<td>Patients with any pancreatitis event*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of events (days)</td>
<td>21</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>13.7 (28.3)</td>
<td>38.5 (103.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.0 (3.0, 135.0)</td>
<td>12.0 (2.0, 494.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Action taken to study drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>4 (15.4)</td>
<td>5 (20.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose not changed</td>
<td>16 (61.5)</td>
<td>13 (52.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug interrupted</td>
<td>2 (7.7)</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug withdrawn</td>
<td>4 (15.4)</td>
<td>6 (24.0)</td>
<td></td>
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<tr>
<td>Outcome of the AE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved</td>
<td>21 (80.8)</td>
<td>21 (84.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovering</td>
<td>3 (11.5)</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resolved</td>
<td>2 (7.7)</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolved with sequelae</td>
<td>0</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>1 (4.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise indicated. HR and 95% CIs from a Poisson regression model. *Summary is at the event level; denominator is the total number of events for each treatment group. Eight pancreatic cases missing data on duration of events.
Pancreatitis was adjudicated in 24 patients (26 events) receiving saxagliptin and 21 (25 events) receiving placebo (HR 1.13 [95% CI 0.66–1.79]) (Table 1 and Supplementary Table 1). Pancreatitis was adjudicated to have either definite or possible acute pancreatitis (22 [0.3%] vs. 16 [0.2%], HR 1.36 [95% CI 0.72–2.64], Fisher exact test \( P = 0.42 \)) in the saxagliptin and placebo arms, respectively (Table 1 and Supplementary Fig. 1A). One case was adjudicated to have either acute pancreatitis and subsequently as chronic pancreatitis. Thirty-eight patients were adjudicated to have either definite or possible acute pancreatitis (22 [0.3%] vs. 16 [0.2%], HR 1.36 [95% CI 0.72–2.64], Fisher exact test \( P = 0.42 \)) in the saxagliptin and placebo arms, respectively (Table 1 and Supplementary Table 2). Pancreatitis was adjudicated in 24 patients (26 events) receiving saxagliptin and in 15 patients (93.8%) with acute pancreatitis receiving placebo (Fig. 1 and Supplementary Table 2). Risk factors in general and the number of risk factors per patient were distributed similarly between the two treatment arms (Supplementary Table 2 and Fig. 1). The blinded pancreatitis adjudication committee considered 19 cases as unlikely to be pancreatitis (9 in the saxagliptin arm and 10 in the placebo arm). All these cases did not have typical abdominal pain, increased pancreatic enzymes (more than three times the upper limit of normal) or imaging consistent with pancreatitis. The event was recovered in 16 (7 in the saxagliptin arm and 9 in the placebo arm) and not recovered in 2 in the saxagliptin arm (1 had hepatic cellular carcinoma) and 1 in the placebo arm (who had metastatic pancreatic cancer).

After inclusion in the study, the time to onset of symptoms of all adjudicated definite or possible acute pancreatitis, definite acute pancreatitis, or chronic pancreatitis did not differ between treatment arms. Events occurred at various time points during the treatment period, with no cluster of events in either treatment arm. The mean (SD) duration of events was 13.7 (28.3) vs. 38.5 (103.4) days in saxagliptin- or placebo-treated patients, respectively. The recovery rate from pancreatitis was similar between the two treatment arms (21 [80.8%] vs. 21 [84.0%]) were resolved, 2 [7.7%] vs. 1 [4.0%]) were not resolved, and 0 vs. 1 [4%] were resolved with sequelae in the saxagliptin vs. placebo arms, respectively. The number of patients who continued on the study medication despite pancreatitis was 16 (61.5%) in the saxagliptin arm compared with 13 (52.0%) in the placebo arm (Table 1).

Chronic pancreatitis was reported by the investigators in five patients receiving saxagliptin and four receiving placebo; adjudication confirmed chronic pancreatitis cases in the saxagliptin and placebo arms were similar (nine vs. nine, respectively), as was the frequency at which the study medication was discontinued due to pancreatitis (six vs. seven, respectively). Adjudicated reports of severe pancreatitis and deaths were similar between the saxagliptin and placebo arms (one case of severe pancreatitis in each arm, and no vs. one death in the saxagliptin vs. placebo arms, respectively) (Table 1).

Figure 1—Most common risk factors for pancreatitis identified in patients with pancreatitis, intention-to-treat population. Con., control; HyperTG, hypertriglyceridemia. (A high-quality color representation of this figure is available in the online issue.)
pancreatitis in two patients receiving saxagliptin (0.02%) and six receiving placebo (0.07%) (HR 0.33 [95% CI 0.05–1.44], Fisher exact test \( P = 0.18 \)) (Supplementary Fig. 1D). Pancreatic cancer was reported in 5 patients in the saxagliptin arm and 12 in the placebo arm (HR 0.42 [95% CI 0.13–1.12], Fisher exact test \( P = 0.09 \)), including 1 patient with a neuroendocrine tumor in the placebo arm.

CONCLUSIONS

The frequency of pancreatitis cases previously reported in epidemiological studies of diabetic patients aged \( >40 \) years versus the general population were 54.0 vs. 30.1 per 100,000 person-years, respectively (adjusted rate ratio 1.77 [95% CI 1.46–2.15]) (7). These numbers, however, are imprecise because of investigators’ reliance on epidemiological data rather than on prospective clinical studies. The SAVOR-TIMI 53 trial is the first prospective study in which pancreatitis was predefined as an EOSI. We systematically collected information regarding all pancreatitis events, using a similar process to that for the CV end points, and used an independent, blinded adjudication committee to ensure the quality of these adjudicated end points. This rigorous process provides important data regarding pancreatitis in type 2 diabetic patients, particularly regarding incretin-based therapy. To increase sensitivity for milder cases of pancreatitis, we used both the definite and the possible definition. However, because amylase and lipase levels were not routinely examined throughout the trial, and clinical visits were performed every 6 months (with a telephone call visit every 3 months in between), subclinical pancreatitis might have been missed. Post hoc analysis of studies that examined the levels of lipase and amylase in overweight/obese patients versus type 2 diabetic patients found a higher incidence of increased enzyme levels and higher variability within the same patient, among type 2 diabetic patients (21). The use of DPP-4 inhibitors might lead to a further increase and fluctuation in levels of amylase and lipase in asymptomatic patients (22). The clinical impact, however, of a diabetes-related as well as a drug-induced increase in amylase and lipase levels and their relation to subclinical pancreatitis are unclear.

The predefined end point of all cases of pancreatitis was similarly distributed between treatment arms (26 vs. 25 in the saxagliptin vs. placebo arms, respectively; HR 1.03 [95% CI 0.93–1.15]). However, there were numerical differences between the treatment arms regarding the subtypes of pancreatitis. In the saxagliptin arm, more cases of definite acute pancreatitis were found (17 vs. 9, HR 1.88 [95% CI 0.86–4.41]) and fewer cases of possible (5 vs. 7, HR 0.85 [95% CI 0.27–2.56]) and chronic (2 vs. 6, HR 0.33 [95% CI 0.05–1.44]) pancreatitis. None of these differences reached statistical significance, however. The meaning of statistical non-significance with such a small number of cases is limited. In addition, the numerical imbalance in the cases of definite acute pancreatitis that were also observed in the EXAMINE (Examination of Cardiovascular Outcomes: Alogliptin vs. Standard of Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome) trial (12 [0.4%] vs. 8 [0.3%] unadjudicated cases of pancreatitis in the alogliptin vs. placebo arm, respectively) (9) should not be dismissed without further investigation.

A possible slight increase in the risk for pancreatitis should be balanced with the favorable course and outcome of the rare pancreatitis cases. Both study arms had similar clinical outcomes as expressed by the length of hospitalization and similar high rates of recovery regardless of continuation or discontinuation of study drug, and no fatalities occurred in the saxagliptin arm. The investigators’ perception of most
pancreatitis events as mild might explain the high continuation rate of study drug in both the saxagliptin (61.5%) and the placebo (52%) arms. Finally, the low rate of recurrent events (two in the saxagliptin arm and three in the placebo arm), regardless of continuation or discontinuation of study drug, is also reassuring.

Patients with type 2 diabetes have an increased risk of developing acute pancreatitis, chronic pancreatitis, and pancreatic cancer (1,23) compared with the general population and even more so when known confounders, such as obesity (24) and CV disease (25), exist. Moreover, medications often used to treat diabetes comorbidities have been shown in population-based case-control studies to increase the risk of developing pancreatitis, including statins (odds ratio [OR] 1.44), ACE inhibitors (OR 1.5), antidepressants (OR 2.8), and nonsteroidal anti-inflammatory drugs (OR 2.7) (26). Previously published retrospective studies suggested that the relationship between incretin-based therapy and pancreatitis was nonrandomized and therefore uncontrolled for baseline known and unknown risk factors for pancreatitis. Pancreatitis cases were not blindly adjudicated, which may have led to a bias of overreporting among the incretin-treated patients (4,5,27). The current study is the first in our knowledge to prospectively adjudicate pancreatitis, and therefore, it provides a more precise estimate of the actual rate.

Whereas acute pancreatitis must be regarded as an incident condition that occurred during the treatment period of the study, the same argument does not hold for chronic pancreatitis because of the difficulty in excluding undiagnosed, preexisting chronic pancreatitis; therefore, a possible association with the respective treatment arm is less stringent (28). Following cases of chronic pancreatitis is important because data suggest that patients with chronic pancreatitis are at increased risk of pancreatic cancer (29–31). In the SAVOR-TIMI 53 trial, eight cases of chronic pancreatitis were confirmed by adjudication (two in the saxagliptin arm and six in the placebo arm), and all but one were reported after >300 days of exposure. Pancreatic cancer was reported in 5 patients in the saxagliptin arm and 12 (including 1 with neuroendocrine tumor) in the placebo arm (Fisher exact test P = 0.09). Although a reduction in pancreatic cancer risk has been suggested for antidiabetic drugs like metformin (32,33), such a protective effect is not assumed for saxagliptin. However, concerns about an increased pancreatic cancer or neuroendocrine tumor risk, as proposed by others in patients under relatively short exposure to DPP-4 inhibitors (2), could not be confirmed in the current study. It should be noted that the median follow-up period in the SAVOR-TIMI 53 trial was 2.1 years. Larger studies with longer follow-up periods are needed to confirm the findings.

The SAVOR-TIMI 53 trial did not completely resolve the issue of whether DPP-4 inhibitors are associated with a slight increase in the risk of pancreatitis (mainly milder cases). The possible risk should be properly judged in the context of the favorable outcome of these cases and the overall proven safety record of this group of drugs. This question will be further determined by the results of other ongoing DPP-4 inhibitors prospective outcome trials (34,35).

The SAVOR-TIMI 53 data do not support a pancreatic cancer signal. It is unlikely, however, that the effect of DPP-4 inhibitors on cancer risk and progression, particularly at specific cancer sites, will be fully addressed with randomized controlled clinical trials because of the follow-up time limitation. The combination of the ongoing large outcome studies with a well-balanced meta-analysis and continued large data-based surveys might further clarify this issue.

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