CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

Pancreatic Safety of Sitagliptin in the TECOS Study

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OBJECTIVE

We evaluated the incidence of acute pancreatitis and pancreatic cancer in patients with type 2 diabetes and cardiovascular disease who were treated with sitagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i).

RESEARCH DESIGN AND METHODS

In the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) study, a cardiovascular safety study of sitagliptin, all suspected cases of acute pancreatitis and pancreatic cancer were collected prospectively for 14,671 participants during a median follow-up time of 3 years, and were adjudicated blindly.

RESULTS

Baseline differences were minimal between participants confirmed to have no pancreatic events, acute pancreatitis, or pancreatic cancer. Among those participants randomized to receive sitagliptin, 23 (0.3%) (vs. 12 randomized to receive placebo [0.2%]) had pancreatitis (hazard ratio 1.93 [95% CI 0.96–3.88], $P = 0.065$; 0.107 vs. 0.056/100 patient-years), with 25 versus 17 events, respectively. Severe pancreatitis (two fatal) occurred in four individuals allocated to receive sitagliptin. Cases of pancreatic cancer were numerically fewer with sitagliptin (9 [0.1%]) versus placebo (14 [0.2%]) (hazard ratio 0.66 [95% CI 0.28–1.51], $P = 0.32$; 0.042 vs. 0.066 events/100 patient-years). Meta-analysis with two other DPP-4i cardiovascular outcome studies showed an increased risk for acute pancreatitis (risk ratio 1.78 [95% CI 1.13–2.81], $P = 0.01$) and no significant effect for pancreatic cancer (risk ratio 0.54 [95% CI 0.28–1.04], $P = 0.07$).

CONCLUSIONS

Pancreatitis and pancreatic cancer were uncommon events with rates that were not statistically significantly different between the sitagliptin and placebo groups, although numerically more sitagliptin participants developed pancreatitis and fewer developed pancreatic cancer. Meta-analysis suggests a small absolute increased risk for pancreatitis with DPP-4i therapy.

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Increased risks of pancreatitis and pancreatic carcinoma are linked to type 2 diabetes, obesity, and insulin resistance in epidemiological studies and animal models (1). Dipeptidyl peptidase-4 inhibitors (DPP-4is) have become widely adopted as effective and well-tolerated glucose-lowering agents since the introduction of sitagliptin in 2006 (2). A potential association between DPP-4i treatment and pancreatitis and pancreatic cancer was suggested in 2009, based on studies in rats carrying the human islet amyloid polypeptide transgene treated with sitagliptin, in which increased pancreatic ductal turnover, ductal metaplasia, and isolated pancreatitis were observed (3). Although subsequent preclinical studies have not confirmed this

finding (4,5), this potential association has triggered intense interest and clinical assessment. Pharmacovigilance efforts, epidemiological studies, and meta-analysis of randomized control studies with DPP-4is have suggested a small increase in or no increased risk of pancreatitis (6) or pancreatic cancer (7), but they all have methodological limitations.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) assessed the long-term cardiovascular safety of adding sitagliptin to usual care, compared with usual care alone, in patients with type 2 diabetes and established cardiovascular disease during a 3-year median follow-up period (8). We describe the presentation, features, and incidence of pancreatitis and pancreatic cancer cases confirmed in TECOS, and perform a meta-analysis of these events with two recently reported DPP-4i cardiovascular safety trials, the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction (SAVOR-TIMI) 53 trial (9,10) and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial (11).

RESEARCH DESIGN AND METHODS

The TECOS study (Clinical trial reg. no. NCT00790205, clinicaltrials.gov) rationale and design (12) as well as its primary outcomes and safety measures (6) have been reported previously. Briefly, 14,735 participants from 38 countries were enrolled in the study between December 2008 and July 2012. Eligible participants were ≥50 years old with type 2 diabetes, cardiovascular disease, and HbA_{1c} values of 6.5–8.0% (48–64 mmol/mol), and on stable-dose monotherapy or dual-combination therapy with metformin, pioglitazone, or sulfonylurea, or insulin with or without metformin. Study subjects were randomized double-blind to sitagliptin or placebo at dosing appropriate for their estimated glomerular filtration rate. Patients with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 were not eligible for enrollment. Patients with a history of pancreatitis were not excluded from the study. Treatment for type 2 diabetes and its comorbidities was provided by usual care providers based on local guidelines. The addition of any antihyperglycemic agents, other than a glucagon-like peptide 1 receptor agonist or an open-label DPP-4i, was permitted, but rosiglitazone use was discouraged. The intent-to-treat (ITT) population comprised 14,671 participants with a median follow-up period of 3.0 years (interquartile range 2.3–3.8, maximum 5.7). Overall, 95.1% of participants allocated to receive sitagliptin and 94.1% allocated to receive placebo completed the study, with premature study medication discontinuation occurring in 26.1% and 27.5% of participants, respectively. Vital status was determined at study end for 97.5% of participants. The study was managed and all data were adjudicated and analyzed by academic partners (Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit).

Event Ascertainment and Adjudication

A Clinical Events Committee (CEC) adjudicated all cases of pancreatitis and cancer reported by investigators, recorded as adverse events, or identified in source documentation for other events. The CEC was independent of both the sponsor and the TECOS Executive Committee, and remained blinded to study treatment assignment. Information related to pancreatitis events was collected systematically in the trial database, including relevant symptoms, laboratory and imaging data, concomitant medication usage, and the investigator's suspected etiology of the event. Relevant hospital and clinic records as well as laboratory and imaging reports were also requested for CEC review. All such cases were first reviewed by a gastroenterologist and then forwarded to the CEC for a second phase of independent review and finalization of adjudication. To confirm a diagnosis of acute pancreatitis, medical records or a clinical narrative prepared by the study sites had to document symptoms (abdominal pain or vomiting) and objective evidence of pancreatic inflammation—either elevated pancreatic enzymes (amylase or lipase more than three times the upper limit of normal for the assay or in patients with chronic pancreatitis, enzyme elevations more than two times the upper limit of normal) or evidence of pancreatitis documented by imaging (abdominal computed tomography, magnetic resonance imaging, or ultrasound showing diffuse and inhomogeneous gland enlargement) (see Supplementary Data). Confirmed cases were further characterized as either "severe," if there was evidence of organ failure (i.e., systolic blood pressure <90 mmHg, partial pressure of oxygen in arterial blood <60 mmHg, serum creatinine level >2 mg/dL after rehydration, or estimated gastrointestinal blood loss of >500 mL in 24 h) or local complications demonstrated on imaging (i.e., pancreatic necrosis, abscess, or acute pseudocyst), or "mild" (8).

Table 1—Confirmed pancreatitis and pancreatic cancer events in the TECOS Study

	Patients				Events	
	Sitagliptin (n = 7,332)	Placebo (n = 7,339)	HR (95% CI)	P	Sitagliptin	Placebo
ITT analysis						
Acute pancreatitis	23 (0.107)	12 (0.056)	1.93 (0.96–3.88)	0.065	25 (0.113)	17 (0.077)
Severe	4	0			4	0
Mild	19	11			21	16
Unknown	0	1			0	1
Pancreatic cancer	9 (0.042)	14 (0.066)	0.66 (0.28–1.51)	0.32		
Per-protocol analysis						
Acute pancreatitis	20 (0.104)	11 (0.058)	1.80 (0.86–3.76)	0.12	21 (0.109)	12 (0.063)
Pancreatic cancer	9 (0.047)	10 (0.054)	0.91 (0.37–2.25)	0.85	. . .	. . .

Data are n (events per 100 patient-years of follow-up) or n, except where indicated. Some patients had more than 1 event.

Information related to malignant/neoplastic events was also collected systematically in the trial database. Investigators reported classification (malignancy vs. benign neoplasm), primary site, type, stage, and extent, as well as the date of onset and whether the malignancy/neoplasm was clinically evident prior to randomization. Relevant hospital and clinic records, and laboratory, imaging, and pathology reports were requested for CEC review. All such cases were first reviewed by an oncologist and then forwarded to the CEC for a second phase of review and finalization of adjudication. Charter-defined malignancies included new malignancy or first recurrence during the study period of a previously diagnosed malignancy. All confirmed charter-defined malignancies were categorized by site or type. Confirmed pancreatic cancers were also subcategorized as pancreatic endocrine or exocrine tumors, or as uncertain types of pancreatic malignancy. No patient had both pancreatitis and pancreatic cancer confirmed during the study.

Statistical Analysis

Descriptive statistics from the adjudication process are presented to provide a sense of the nature of these events in the TECOS study. Definition of the per-protocol population is provided in the study protocol (8). Unless otherwise stated, continuous variables are summarized as the median (interquartile range), and categorical variables are categorized as number (percentage). The baseline characteristics of patients in whom pancreatitis, pancreatic cancer, or neither were diagnosed were compared with Wilcoxon rank sum, χ^2, and Fisher exact tests.
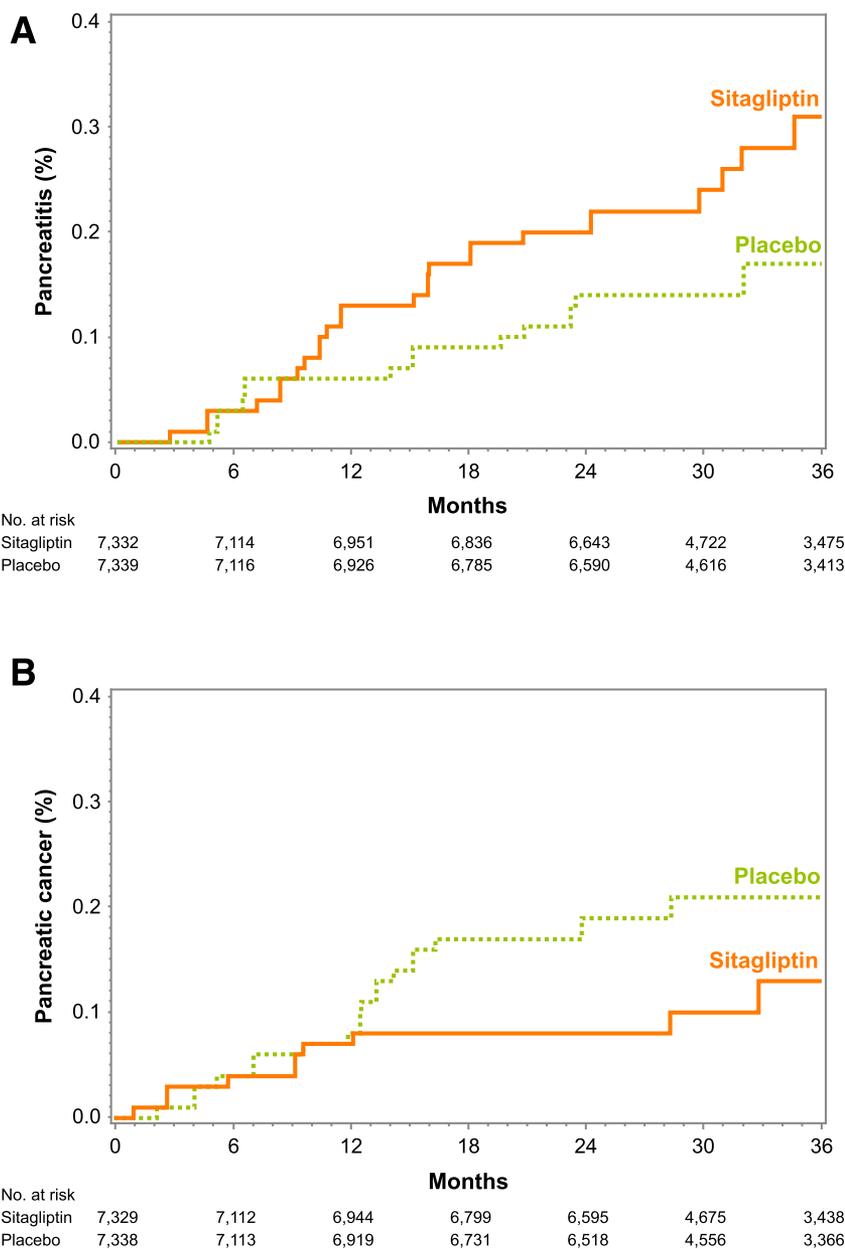
The time-to-pancreatic-event analyses used Cox proportional hazards regression models and are presented as hazard ratio (95% CI). Hazard ratios and P values for treatment effect are provided for both the ITT and per-protocol populations. The ITT population includes all events regardless of treatment compliance. The per-protocol end points are those that occurred before a major protocol violation in patients who took at least one dose of study medication. Event rates are shown as the number and as events per 100 patient-years of follow-up. Kaplan-Meier rates over the first 3 years for pancreatic events are plotted separately for the sitagliptin and placebo groups in the ITT population.

Meta-analyses were performed on data from the SAVOR-TIMI 53 trial, the EXAMINE trial, and the TECOS study using random-effects models on summative data for pancreatitis and pancreatic cancer outcomes. Heterogeneity among studies was assessed using the Cochran Q test and I^2 index. Odds ratios and 95% CIs are shown with forest plots. Comprehensive Meta Analysis version 2.0 software (Biostat, Inc., Englewood, NJ) was used for these analyses. Except where noted, data were analyzed using SAS version 9.4.

RESULTS

The ITT population comprised 14,671 individuals. Relevant baseline characteristics for the 14,613 participants who had no reported pancreatic event, 35 with confirmed pancreatitis, and 23 with confirmed pancreatic cancer are presented in the Supplementary Appendix (Supplementary Table 1). Differences in baseline characteristics among these participants were generally minimal, but smoking history differed by category ($P = 0.015$). For those with pancreatitis, pancreatic cancer, or no pancreatic event, the proportions of participants

A

No. at risk

Sitagliptin	7,332	7,114	6,951	6,836	6,643	4,722	3,475
Placebo	7,339	7,116	6,926	6,785	6,590	4,616	3,413

B

No. at risk

Sitagliptin	7,329	7,112	6,944	6,799	6,595	4,675	3,438
Placebo	7,338	7,113	6,919	6,731	6,518	4,556	3,366

Figure 1—Cumulative proportion of participants with confirmed acute pancreatitis (*A*) and confirmed pancreatic cancer (*B*) by treatment group as a function of time.

who were current smokers were 23%, 13%, and 11%, respectively. Participants with pancreatic cancer were more likely to have smoked previously (65%) than those with pancreatitis (31%) or no pancreatic event (40%). Additionally, there was a similar imbalance with respect to racial distribution, particularly a lower representation of pancreatic cancer among Asians and perhaps an increase in pancreatitis among blacks. The average age of those with confirmed pancreatic events was 66 years.

Confirmed acute pancreatitis events are shown in Table 1. The 7,332 participants assigned to receive sitagliptin had 21,508 patient-years of follow-up, whereas those assigned to receive placebo had 21,325 patient-years of follow-up. Among participants randomized to receive sitagliptin, pancreatitis developed in 23 participants (0.3% of the ITT population, 0.107/100 patient-years) compared with 12 participants who received placebo (0.2% of the ITT population, 0.056/100 patient-years; hazard ratio 1.93 [95% CI 0.96–3.88], P = 0.065), with these participants having 25 and 17 events, respectively. Four participants in the sitagliptin group experienced a severe pancreatitis event (two fatal events), with no severe events in the placebo group. One pancreatitis event of unknown severity was reported for the placebo group, with all remaining cases adjudicated as "mild" in severity.

Figure 1A shows the cumulative proportion of participants with acute pancreatitis as a function of time, with no notable differences between groups in event rates during the first 9 months. Through 3 years of follow-up, there appears to be a fairly linear rate of cases for each treatment assignment. The median times to the diagnosis of acute pancreatitis were 1.42 years (interquartile range 0.80–2.66 years) and 1.44 years (interquartile range 0.54–1.94 years), respectively, in the sitagliptin and placebo groups.

The characteristics of the confirmed pancreatitis events for participants allocated to sitagliptin or placebo are listed in Table 2. The majority of case patients in both groups had symptoms, elevated pancreatic enzyme levels, and imaging evidence of pancreatitis. Investigators reported a suspected cause of pancreatitis (alcohol, biliary disease, or a history of pancreatitis) in 60.0% of events in sitagliptin-treated participants compared

Table 2—Characteristics of pancreatitis events among sitagliptin- and placebo-treated participants in the TECOS study

Characteristic	Sitagliptin (N = 25)	Placebo (N = 17)
Symptoms		
Abdominal pain	22 (88)	17 (100)
Vomiting	11 (44)	5 (29)
Evidence of pancreatic inflammation		
Elevated pancreatic enzymes	15 (60)	14 (82)
Amylase or lipase >3× upper limit of normal	13	13
In patients with chronic pancreatitis, amylase, or lipase >2× upper limit of normal	2	1
Documented by imaging	18 (72)	7 (41)
Investigator reported pancreatitis etiology		
Known or suspected etiology*	15 (60)	8 (47)
Alcohol	2	0
Biliary	9	3
History of pancreatitis	6	6
Other	1	1
Unknown†	10 (40)	9 (53)
Severity indices		
Severe pancreatitis	4 (16)	0 (0)
Evidence of organ failure‡	1	0
Local complications on imaging	4	0
Pancreatic necrosis	3	0
Pancreatic abscess	2	0
Pancreatic pseudocyst	1	0
Pancreatitis resulting in death§	2	0

Data are n (%) or n. *Investigator reported. †Events where study drug was reported as a possible cause are included in the category for unknown. ‡The patient with evidence of organ failure had renal failure (serum creatinine >2 mg/dL after rehydration), pulmonary insufficiency (P_{AO_2} <60 mmHg), and shock (systolic blood pressure <90 mmHg). §The deaths resulting from pancreatitis occurred in one patient with a history of alcohol use and one with a known history of chronic biliary pancreatitis.

with 47.1% in placebo-treated participants; biliary disease and/or a history of pancreatitis were present in 11 of 23 patients in the sitagliptin group (13 of 25 events) compared with 2 of 12 patients in the placebo group (7 of 17 events). The number of patients without a suspected cause was similar in the two treatment groups (10 and 9, respectively). Additional characteristics for the four case patients with severe pancreatitis in the sitagliptin group are also presented in Table 2. The characteristics of case patients with suspected pancreatitis referred for adjudication but not confirmed are available in the Supplementary Appendix (Supplementary Table 2).

Confirmed pancreatic cancer cases are shown in Table 1 for the ITT population with numerically fewer participants in the sitagliptin group (N = 9, 0.1%, 0.042 events/100 patient-years) compared with the placebo group (N = 14, 0.2%, 0.066 events/100 patient-years) (hazard ratio 0.66 [95% CI 0.28–1.51], P = 0.32). Pancreatic cancer resulted in death in seven of the sitagliptin case

patients and nine of the placebo case patients. The median times to the diagnosis of pancreatic cancer were 0.80 years (interquartile range 0.48–2.36 years) and 1.05 years (interquartile range 0.59–1.27 years), respectively, in the sitagliptin and placebo groups. Figure 1B shows the cumulative proportion of participants with pancreatic cancer as a function of time, with no notable differences among groups in event rates during the first 12 months.

The per-protocol analyses shown in Table 1 excluded relatively few confirmed cases of pancreatitis or pancreatic cancer but tended to move the hazard ratios toward unity for both of these outcomes.

Meta-analysis of the data from the three cardiovascular outcome trials with DPP-4i reported to date (Fig. 2) shows a statistically significant increased risk of acute pancreatitis for DPP-4i therapy (risk ratio 1.78 [95% CI 1.13–2.81], P = 0.01) without evidence of heterogeneity. Meta-analysis for pancreatic cancer showed a nonsignificant
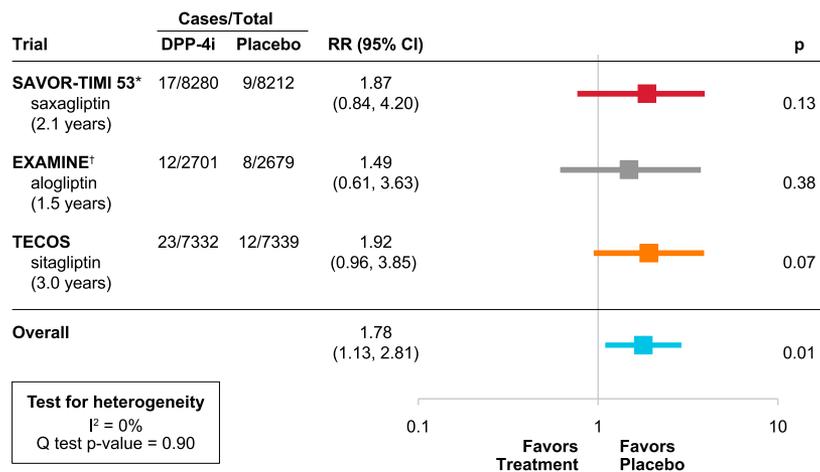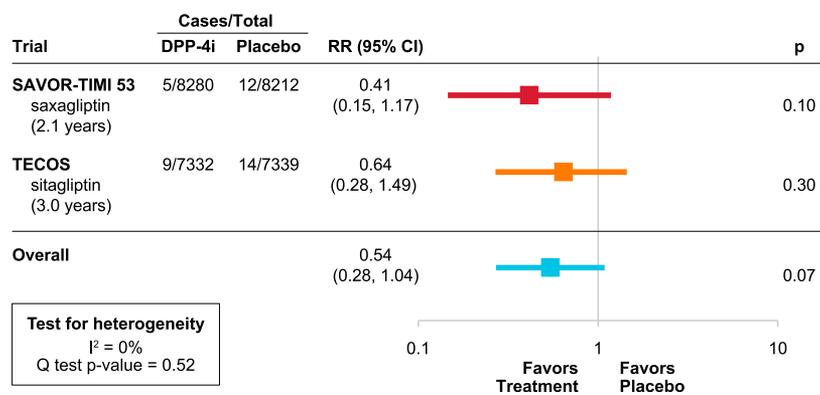
Figure 2—Meta-analysis of pancreatitis (*A*) and pancreatic cancer (*B*) in the SAVOR-TIMI 53 trial, the EXAMINE trial, and the TECOS study. It is noted that the SAVOR-TIMI 53 trial used different criteria than the TECOS study for the adjudication of pancreatitis, and that in the EXAMINE trial pancreatitis was not adjudicated and no pancreatic cancer cases were reported. *Ref. 9; †Ref. 11.

risk factors, and it is unclear to what extent sitagliptin contributed to the pancreatitis in each case. That said, the finding of other potential etiologies should not provide reassurance that treatment with sitagliptin was perhaps not a contributor, as the alternative hypothesis would be that treatment with sitagliptin magnifies the penetrance of risk factors on pancreatitis development and severity.

The per-protocol analysis of individuals with recent or ongoing treatment with study medication provides a similar result for the ITT analysis with a modestly lower point estimate for risk and wider CI (hazard ratio 1.80 [95% CI 0.86–3.76], $P = 0.12$). With the small number of events, it is not possible to ascribe particular risk factors for acute pancreatitis for the population as a whole (see Supplementary Appendix). Although a history of pancreatitis was not a TECOS exclusion criterion, the risk of acute pancreatitis with sitagliptin exposure in those participants with a history of pancreatitis cannot be estimated as this information was not recorded systematically at baseline.

Pancreatic cancer was also an uncommon event in the TECOS study (0.054 events/100 patient-years). Numerically, there were fewer cases of pancreatic cancer with sitagliptin treatment than with placebo treatment, but the difference was not statistically significant. The per-protocol analysis for pancreatic cancer essentially eliminates the discrepancy between arms. Although the median 3-year follow-up period during the TECOS study is longer than in many other diabetes outcome trials, it is insufficient to permit a robust assessment of the long-term risk of pancreatic cancer.

SAVOR-TIMI 53 (9) and EXAMINE (11) are two recently reported, double-blind, placebo-controlled, cardiovascular safety trials of DPP-4is that evaluated saxagliptin and alogliptin, respectively. These trials have important differences with the TECOS study Both the SAVOR-TIMI 53 and EXAMINE trials enrolled patients with a wider range of HbA$_{1c}$ levels at diagnosis and a shorter duration of study treatment exposure. The SAVOR-TIMI 53 trial used different criteria in the adjudication of pancreatitis, whereas the EXAMINE trial did not adjudicate cases of pancreatitis and reported no cases of pancreatic cancer. These factors preclude head-to-head comparisons of the rates of pancreatitis and could impact on the

effect of DPP-4i (risk ratio 0.54 [95% CI 0.28–1.04], $P = 0.07$) without evidence of heterogeneity.

CONCLUSIONS

The TECOS study was a global, double-blind, placebo-controlled clinical trial of sitagliptin in individuals ≥50 years of age with type 2 diabetes and established cardiovascular disease. The TECOS study demonstrated, on a background of usual care, that there was no difference between treatment groups in the rates of major cardiovascular events, heart failure, or death from any cause. This study examined whether there was an association between the use of sitagliptin and pancreatic disease.

The overall rate of confirmed acute pancreatitis was low (0.095 events/100 patient-years) with a numerically increased

but not statistically significant risk for acute pancreatitis with sitagliptin therapy (0.107/100 patient-years for sitagliptin treatment vs. 0.056/100 patient-years for placebo treatment). The clinical presentation of acute pancreatitis with regard to symptoms and onset during the study period was similar in the two treatment groups. Recurrent episodes of pancreatitis occurred in two participants treated with sitagliptin (both had one recurrence) and two participants treated with placebo (one with a single recurrence and one with four recurrences). Cases of confirmed severe acute pancreatitis were rare, but numerically greater with sitagliptin treatment compared with placebo treatment (four vs. zero, including two fatal cases). For both fatal cases, an etiology other than study treatment was suspected. Pancreatitis is often associated with multiple

meta-analysis presented here, which means that these findings should therefore be interpreted with caution.

The primary goal of the Tecos study was to examine the cardiovascular safety of sitagliptin. The trial demonstrated unequivocal evidence for no increased risk of major cardiovascular events, heart failure, or all-cause mortality. Sitagliptin was associated with good tolerability and glycemic efficacy. These analyses of acute pancreatitis and pancreatic cancer from the TECOS study, and the meta-analysis with two other large, well-conducted studies involving other members of the DPP-4i class of drugs, provide prescribers and patients greater precision around the question of pancreatic safety. Although conclusions are limited by the small numbers of events over a limited period of follow-up, information collected from these double-blind, randomized, placebo-controlled trials provide the most robust data available currently to quantify the risk of pancreatic outcomes associated with DPP-4i therapy. It may be that some cases of subclinical pancreatitis could have been missed, but similar findings from the three trials suggest that there is a small increased risk of acute pancreatitis with DPP-4i therapy. For sitagliptin, the magnitude of excess risk based on the results of the TECOS study is estimated to be ~1 additional case/1,000 patient-years, although severe and fatal cases occurred in the sitagliptin group. If this difference had been statistically significant, the number needed to harm would have been 1,974 to have 1 additional affected individual with pancreatitis. Pancreatic cancer, a condition that is almost uniformly fatal, occurred in roughly half as many participants as pancreatitis, and the risk did not appear to be increased with sitagliptin. Longer-term pharmacovigilance and pharmacoepidemiological studies of DPP-4is will be required to provide greater insights into the pancreatic safety of this drug class.

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