The Risk of Acute Pancreatitis After Initiation of Dipeptidyl Peptidase 4 Inhibitors: Testing a Hypothesis of Subgroup Differences in Older U.S. Adults

Jin-Liern Hong,[1] John B. Buse,[2] Michele Jonsson Funk,[1] Virginia Pate,[1] and Til Stürmer[1]

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OBJECTIVE

To examine whether dipeptidyl peptidase 4 inhibitors (DPP-4I) increase acute pancreatitis risk in older patients and whether the association varies by age, sex, and history of cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS

We conducted a cohort study of DPP-4I initiators versus thiazolidinedione (TZD) or sulfonylurea initiators using U.S. Medicare beneficiaries, 2007–2014. Eligible initiators were aged 66 years or older without history of pancreatic disease or alcohol-related diseases. Patients were followed up for hospitalization due to acute pancreatitis and censored at 90 days after treatment changes. Weighted Cox models were used to estimate the hazard ratio (HR) for acute pancreatitis. Analyses were performed overall as well as within subgroups defined by age, sex, and CVD history.

RESULTS

We found no increased risk of acute pancreatitis comparing 49,374 DPP-4I initiators to 132,223 sulfonylurea initiators (weighted HR 1.01; 95% CI 0.83–1.24) and comparing 57,301 DPP-4I initiators to 32,612 TZD initiators (weighted HR 1.11; 95% CI 0.76–1.62). Age and sex did not modify the association. Among patients with CVD, acute pancreatitis incidence was elevated in initiators of DPP-4I and sulfonylurea (2.3 and 2.4 per 1,000 person-years, respectively) but not in TZD initiators (1.5). Among patients with CVD, higher risk of acute pancreatitis was observed with DPP-4I compared with TZD (weighted HR 1.84; 95% CI 1.02–3.35) but not compared with sulfonylurea.

CONCLUSIONS

Our study provides evidence that DPP-4I is not associated with an increased risk of acute pancreatitis in older adults overall. The positive association observed in patients with CVD could be due to chance or bias but merits further investigation.

Incretin-based drugs reduce hyperglycemia in patients with type 2 diabetes. These drugs include dipeptidyl peptidase 4 inhibitors (DPP-4I) and glucagon-like peptide 1 receptor agonists (GLP-1RA). While the clinical benefit of incretin-based drugs has been proven for controlling blood glucose level (1–3), there have been concerns about an increased risk of acute pancreatitis (4,5). Meta-analyses of randomized clinical trials

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

[2]Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Corresponding author: Jin-Liern Hong, jlhongtw@email.unc.edu.

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(RCTs) have provided conflicting results. In 2014, a meta-analysis of 55 RCTs with incretin-based drugs found no effect of these drugs on the risk of acute pancreatitis (6). However, meta-analyses of three recent cardiovascular outcome RCTs involving DPP-4I among patients with diabetes with established cardiovascular disease (CVD) or risk factors for CVD reported a 1.8-fold increase in the risk of acute pancreatitis compared with standard therapy (7,8). One possible explanation for the discrepancy is that these three RCTs had larger sample sizes and longer follow-up (1.5–3 years). Alternatively, the discordant results may suggest that the effect of DPP-4I on acute pancreatitis is restricted to a subgroup of patients, e.g., patients with CVD (9).

Several observational studies based on large health care databases have examined the association between DPP-4I and acute pancreatitis. Most of the observational studies found no increased risk of acute pancreatitis associated with DPP-4I (10–21), whereas three have reported positive associations (22–24). No study has specifically investigated older Americans and subgroups of patients, including the impact of prior CVD on the association of DPP-4I with acute pancreatitis. Although CVD is not generally recognized as an independent risk factor for acute pancreatitis, a population-based study has shown that CVD appears to increase the risk of acute pancreatitis (25). Given that age and sex are also risk factors for acute pancreatitis (26), the potential interaction of age and sex with the effect of DPP-4I on acute pancreatitis also merits further exploration.

We conducted a cohort study to examine the risk of acute pancreatitis after initiation of DPP-4I versus other second-line treatment of diabetes with clinical equipoise in older Medicare beneficiaries and to explore whether the association between DPP-4I and acute pancreatitis is modified by history of CVD, age, or sex. The large sample size allowed us to assess incretin-associated risk for pancreatitis within subgroups of Medicare beneficiaries to provide insights into the discordant results of the effects of DPP-4I on acute pancreatitis.

RESEARCH DESIGN AND METHODS

Study Population

This cohort study was conducted within a 20% random sample of fee-for-service Medicare beneficiaries with concurrent Medicare Part A (inpatient), Part B (outpatient), and Part D (dispensed drugs) coverage in at least one month between 2007 and 2014. Medicare provides medical coverage for citizens aged 65 years and older, with certain disabilities, or with end-stage renal disease.

Within the Medicare population, we selected two study cohorts. Cohort one included new users of DPP-4I or sulfonylurea; cohort two included new users of DPP-4I or thiazolidinedione (TZD). We chose sulfonylurea and TZD as active comparators because DPP-4I, sulfonylurea, and TZD are the recommended second-line oral treatments for type 2 diabetes (27,28). New use was defined as initiation of DPP-4I or the comparator (i.e., sulfonylurea or TZD) without use of incretin-based drugs (i.e., DPP-4I and GLP-1RA) or the comparator in the 12 months before initiation. Patients were also required to be aged 66 years or older at initiation, to have $\geq$12 months of continuous Medicare Parts A, B, and D coverage before initiation, and to have at least one refill of the same drug within the days supply plus a grace period of 90 days, therefore increasing the likelihood that included individuals were taking the drug. The date of the first refill prescription was defined as the index date. Patients were excluded if they had a diagnosis code indicating chronic or acute pancreatitis, other pancreatic diseases, pancreatic cancer, or alcohol abuse, alcohol-related diseases, hepatitis, or consequences of alcoholism (i.e., hepatic encephalopathy, portal hypertension, hepatorenal syndrome, other sequelae of chronic liver disease, gastroesophageal laceration-hemorrhage syndrome, and cirrhosis of liver without mention of alcohol) before the index date. Given concerns regarding an increased risk of heart failure with TZD use (29), cohort two (DPP-4I and TZD) excluded patients with a diagnosis code for heart failure before initiation.

Outcome and Follow-up

The outcome was hospitalization for acute pancreatitis identified by an inpatient claim with a primary discharge diagnosis of acute pancreatitis (ICD-9-CM code 577.0). The outcome date was defined as the date of hospital admission.

Patients were considered exposed to the index drug (e.g., DPP-4I or sulfonylurea) until 90 days after drug discontinuation, switch to, or subsequent addition of the other drug of interest (e.g., adding a sulfonylurea in initiators of DPP-4I or vice versa). Discontinuation was defined as no further refill within the days supply plus a 90-day grace period. Patients were not censored at the time of subsequent addition of GLP-1RA during follow-up. All patients were followed up from the index date until the earliest of the following: the end of drug exposure; hospitalization for acute pancreatitis; death; disenrollment from Medicare Part A, B, or D; or end of study (31 December 2014).

Covariates and Confounding Control

We used propensity score weighting to control for confounding. For each patient, we estimated the probability of receiving DPP-4I versus the comparator (i.e., sulfonylurea or TZD) using multivariable logistic regression models. The propensity score model included potential confounders, known risk factors for pancreatitis, prior use of antihyperglycemic drugs, markers of frailty, and health care utilization. To implement propensity score weighting, we defined the weights as 1 for DPP-4I initiators and the odds of the propensity score for the comparator group (i.e., standardized morbidity ratio weighting) (30).

All covariates were defined based on data from the 12 months prior to initiation. We considered age, sex, and CVD history as potential effect modifiers. Age was calculated as the calendar year of initiation minus the birth year and was further categorized as $<$75 or $\geq$75 years. History of CVD (yes/no) was defined as the presence of any diagnosis code for major CVD. Major CVD included ischemic heart disease, cerebrovascular disease, and heart failure (DPP-4I vs. sulfonylurea comparison only).

Statistical Analysis

We calculated the incidence rate of hospitalization for acute pancreatitis (cases per 1,000 person-years) for each group. We estimated the crude and standardized morbidity ratio–weighted hazard ratios (HRs) and corresponding 95% CIs using Cox proportional hazards models with robust variance. A previous pooled analysis of three trials of DPP-4I in patients with CVD showed that the cumulative incidence of acute pancreatitis in DPP-4I and placebo groups started to diverge after 1 year of follow-up (7). Thus, we estimated HRs stratified by follow-up time (0–1, 1–2, $>$2 years).

To assess heterogeneity by age, sex, and CVD history, we examined the association between DPP-4I and the risk of acute pancreatitis in various subgroups stratified by age category (<75 and ≥75 years), sex (male and female), and presence or absence of CVD at initiation. We reestimated the propensity score within each subgroup to ensure balance of baseline characteristics. All analyses were first conducted in the study cohort of DPP-4I and sulfonylurea and were repeated within the study cohort of DPP-4I and TZD.

We conducted five sensitivity analyses to evaluate the consistency of our main results. First, we varied the length of the latency period, ranging from 0 to 720 days, to evaluate the robustness of the latency assumption of 90 days in the main analysis. Second, we conducted a sensitivity analysis ignoring any subsequent treatment changes (i.e., based on initial treatment choice only). Follow-up started on the index date and ended with hospitalization for acute pancreatitis, death, disenrollment of Medicare Part A or B, or end of study. Third, we required all cohorts to have prior use of metformin (at least one prescription during the 12 months before initiation) to limit the population to those initiating second-line therapy. In addition, we repeated the main analysis censoring patients at the time of subsequent addition of GLP-1RA during follow-up. Last, because the 1-year look-back period may fail to capture relevant comorbid conditions and medications, we conducted an analysis in which we used all available data to define comorbidities and previous medication use.

All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

RESULTS

During the study period from 2007 to 2014, cohort one included 49,374 DPP-4I initiators and 132,223 sulfonylurea initiators, and cohort two included 57,301 DPP-4I initiators and 32,612 TZD initiators. Table 1 presents demographic and clinical characteristics at baseline across treatment groups. Compared with initiators of sulfonylurea and TZD, DPP-4I initiators had similar age distributions but were more likely to have prior use of statins and metformin, diabetes complications, and CVD at initiation (Table 1). In addition, regular physician office visits and treatment initiation between 2012 and 2014 were strongly associated with higher probabilities of receiving DPP-4I rather than sulfonylurea or TZD. After propensity score weighting, baseline characteristics of sulfonylurea and TZD initiators were comparable to those of DPP-4I initiators.

Over 74,021 and 230,484 person-years of follow-up, we identified 150 DPP-4I initiators and 467 sulfonylurea initiators hospitalized for acute pancreatitis, for an incidence rate of 2.0 (95% CI 1.7–2.4) and 2.0 (95% CI 1.9–2.2) per 1,000 person-years, respectively (Table 2). No increased risk of acute pancreatitis after DPP-4I initiation was found consistently before or after propensity score weighting (weighted HR 1.01; 95% CI 0.83–1.24). The results were similar when comparing DPP-4I to TZD initiators (weighted HR 1.11; 95% CI 0.76–1.62). Analyses stratified by follow-up time also showed no difference in the risk of acute pancreatitis between DPP-4I and the comparator drugs.

Figure 1 presents the crude incidence rate of acute pancreatitis and propensity score–weighted HRs for each subgroup of interest (see Supplementary Table 1 for the crude HRs). The incidence rate of acute pancreatitis was higher among patients with CVD (DPP-4I, 2.3 per 1,000 person-years; sulfonylurea, 2.4 per 1,000 person-years) than among those without CVD (DPP-4I, 1.8 per 1,000 person-years; sulfonylurea, 1.7 per 1,000 person-years). Compared with sulfonylurea, DPP-4I was not associated with acute pancreatitis within any subgroup of patients based on age (<75 or ≥75 years), sex (male or female), or presence or absence of CVD. In cohort two, DPP-4I, as compared with TZD, was not associated with an increased risk of acute pancreatitis within subgroups of patients based on age or sex. However, among patients with CVD, DPP-4I initiators had a higher incidence rate of acute pancreatitis (2.2 per 1,000 person-years) than TZD initiators (1.5 per 1,000 person-years), for a crude HR of 1.45 (95% CI 0.91–2.29). The association became stronger after propensity score weighting (weighted HR 1.84; 95% CI 1.02–3.35).

All sensitivity analyses were consistent with no increased risk of acute pancreatitis after DPP-4I initiation among older patients (Supplementary Tables 2–13). In the sensitivity analysis where we required patients to have received metformin prior to initiation of DPP-4I or the comparators, we observed an increased risk associated with DPP-4I as compared with TZD (weighted HR 2.45; 95% CI 1.20–5.02) in the subgroup with CVD but not among those without CVD and not when compared with sulfonylurea (Supplementary Table 7). This positive association was attenuated in the sensitivity analysis that ignored treatment changes during follow-up: weighted HR 1.12 (95% CI 0.79–1.59) in the analysis without required prior use of metformin (Supplementary Table 4); weighted HR 1.35 (95% CI 0.90–2.04) in the sensitivity analysis requiring prior use of metformin (Supplementary Table 8). In the sensitivity analysis in which we used all available data to define CVD and other comorbidities, the association between DPP-4I and the risk of acute pancreatitis became stronger when comparing DPP-4I to TZD among patients with CVD (weighted HR 2.30; 95% CI 1.20–4.0) (Supplementary Table 11).

CONCLUSIONS

DPP-4I are widely used for the treatment of type 2 diabetes, a risk factor for pancreatitis. Despite substantial attention to the pancreatic safety of incretin-based drugs, an increased risk of acute pancreatitis has not been evident in premarketing clinical trials or postmarketing observational studies. Recent cardiovascular outcome trials of DPP-4I demonstrated trends toward increased risk of acute pancreatitis in patients with clinical CVD (7,8). We sought to evaluate the risk of acute pancreatitis in older patients with diabetes who initiated DPP-4I compared with other second-line treatment (TZD or sulfonylurea) and to investigate whether CVD at initiation was associated with increased risk of acute pancreatitis or modified any increased risk relative to comparators. We found that DPP-4I was not associated with an increased risk of acute pancreatitis compared with alternative treatments among U.S. older patients with diabetes. However, we observed higher incidences of acute pancreatitis among patients with CVD at baseline than those among patients without CVD. These findings may imply that

Table 1—Baseline characteristics of the new users of DPP-4I versus sulfonylurea and the new users of DPP-4I versus TZD, respectively

	Cohort 1: DPP-4I and SU			Cohort 2: DPP-4I and TZD		
Characteristic	DPP-4I (*N* = 49,374)	SU (*N* = 132,223)	Weighted SU*	DPP-4I (*N* = 57,301)	TZD (*N* = 32,612)	Weighted TZD*
Age, years						
Median	74	74	74	74	72	74
Interquartile range	70–81	69–81	70–81	69–80	68–78	70–80
Male	19,443 (39.4)	55,969 (42.3)	(39.3)	22,943 (40.0)	14,136 (43.3)	(40.7)
Race						
White	36,842 (74.6)	102,979 (77.9)	(74.6)	43,746 (76.3)	23,814 (73.0)	(77.9)
Black	5,471 (11.1)	16,241 (12.3)	(11.1)	6,106 (10.7)	3,891 (11.9)	(9.9)
Others	7,061 (14.3)	13,003 (9.8)	(14.3)	7,449 (13.0)	4,907 (15.0)	(12.3)
Medication						
ACEI	22,341 (45.2)	64,205 (48.6)	(45.2)	27,276 (47.6)	16,182 (49.6)	(47.0)
ARB	16,352 (33.1)	30,639 (23.2)	(33.4)	17,734 (30.9)	7,885 (24.2)	(31.5)
β-Blocker	25,601 (51.9)	68,075 (51.5)	(51.8)	28,056 (49.0)	13,472 (41.3)	(49.3)
Calcium channel blocker	18,096 (36.7)	46,363 (35.1)	(36.6)	20,881 (36.4)	10,440 (32.0)	(36.1)
Loop diuretics	13,367 (27.1)	37,037 (28.0)	(27.2)	9,785 (17.1)	4,586 (14.1)	(17.4)
Other diuretics	19,516 (39.5)	50,445 (38.2)	(39.5)	22,594 (39.4)	12,160 (37.3)	(39.4)
Statins	35,200 (71.3)	82,758 (62.6)	(71.4)	40,600 (70.9)	20,937 (64.2)	(71.0)
Metformin	33,052 (66.9)	74,750 (56.5)	(67.6)	41,081 (71.7)	20,806 (63.8)	(71.4)
SU	NA†	NA†	NA†	27,105 (47.3)	15,119 (46.4)	(48.9)
TZD	11,253 (22.8)	17,811 (13.5)	(22.9)	NA‡	NA‡	NA‡
Insulin	10,258 (20.8)	19,988 (15.1)	(21.2)	9,123 (15.9)	4,827 (14.8)	(15.8)
Comorbidity						
Retinopathy	7,435 (15.1)	14,682 (11.1)	(15.3)	8,598 (15.0)	4,476 (13.7)	(15.0)
Nephropathy	4,273 (8.7)	8,706 (6.6)	(8.8)	4,455 (7.8)	1,959 (6.0)	(8.1)
Neuropathy	9,924 (20.1)	20,055 (15.2)	(20.3)	10,780 (18.8)	4,757 (14.6)	(19.5)
COPD	9,969 (20.2)	27,142 (20.5)	(20.1)	7,817 (13.6)	3,865 (11.9)	(13.7)
Chronic kidney disease	14,689 (29.8)	36,893 (27.9)	(29.9)	14,659 (25.6)	6,564 (20.1)	(26.3)
Depression	8,361 (16.9)	20,559 (15.5)	(17.0)	7,933 (13.8)	3,651 (11.2)	(13.7)
Heart failure	10,954 (22.2)	29,108 (22.0)	(22.3)	NA‡	NA‡	NA‡
Ischemic heart disease	19,623 (39.7)	48,499 (36.7)	(39.8)	18,341 (32.0)	8,165 (25.0)	(32.5)
PVD	10,566 (21.4)	24,238 (18.3)	(21.4)	9,783 (17.1)	4,330 (13.3)	(17.1)
Cerebrovascular disease	11,249 (22.8)	28,178 (21.3)	(22.8)	10,778 (18.8)	4,971 (15.2)	(18.6)
Hyperlipidemia	41,231 (83.5)	98,470 (74.5)	(83.6)	47,697 (83.2)	23,828 (73.1)	(84.2)
Gallstones	1,750 (3.5)	4,330 (3.3)	(3.5)	1,569 (2.7)	699 (2.1)	(2.8)
Cancer	8,205 (16.6)	21,221 (16.0)	(16.6)	9,063 (15.8)	4,040 (12.4)	(16.0)
Health care utilization						
Flu shot	26,614 (53.9)	64,477 (48.8)	(53.8)	31,253 (54.5)	14,651 (44.9)	(55.8)
HbA_{1c} test	43,303 (87.7)	102,609 (77.6)	(87.8)	51,102 (89.2)	25,424 (78.0)	(89.7)
Lipid test	40,316 (81.7)	94,650 (71.6)	(81.7)	47,403 (82.7)	23,653 (72.5)	(83.6)
Emergency room visit	18,227 (36.9)	51,445 (38.9)	(37.0)	17,449 (30.5)	8,256 (25.3)	(30.4)
No. of physician office visits						
0	2,954 (6.0)	14,475 (10.9)	(6.0)	3,489 (6.1)	4,349 (13.3)	(5.8)
1–6	15,668 (31.7)	49,962 (37.8)	(31.6)	19,350 (33.8)	12,883 (39.5)	(33.2)
7–12	15,593 (31.6)	37,434 (28.3)	(31.6)	19,159 (33.4)	9,374 (28.7)	(34.1)
≥13	15,159 (30.7)	30,352 (23.0)	(30.8)	15,303 (26.7)	6,006 (18.4)	(27.0)
Days of hospitalization						
0	36,701 (74.3)	94,020 (71.1)	(74.2)	47,140 (82.3)	27,861 (85.4)	(82.0)
1–3	2,420 (4.9)	6,697 (5.1)	(4.9)	2,651 (4.6)	1,327 (4.1)	(4.7)
4–6	3,543 (7.2)	10,789 (8.2)	(7.2)	3,433 (6.0)	1,564 (4.8)	(6.3)
7–12	3,019 (6.1)	9,403 (7.1)	(6.1)	2,151 (3.8)	1,015 (3.1)	(3.7)
≥13	3,691 (7.5)	11,314 (8.6)	(7.6)	1,926 (3.4)	845 (2.6)	(3.3)
Calendar year						
2008	5,119 (10.4)	22,172 (16.8)	(10.3)	4,704 (8.2)	8,751 (26.8)	(8.1)
2009	4,540 (9.2)	20,400 (15.4)	(9.2)	5,037 (8.8)	7,767 (23.8)	(8.8)
2010	5,650 (11.4)	19,013 (14.4)	(11.4)	6,107 (10.7)	6,138 (18.8)	(10.6)
2011	8,666 (17.6)	18,283 (13.8)	(17.3)	9,004 (15.7)	3,712 (11.4)	(15.3)
2012	9,238 (18.7)	17,166 (13.0)	(18.6)	10,445 (18.2)	1,970 (6.0)	(17.5)
2013	8,158 (16.5)	18,450 (14.0)	(16.7)	11,033 (19.3)	2,177 (6.7)	(19.5)
2014	8,003 (16.2)	16,739 (12.7)	(16.5)	10,971 (19.1)	2,097 (6.4)	(20.2)

Data are *N* (%) or (%) unless otherwise specified. ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; NA, not applicable; PVD, peripheral vascular disease; SU, sulfonylurea. *Weighted by standardizing to their distribution in DPP-4I initiators by using weights of 1 for DPP-4I initiators and the odds of the estimated propensity score for SU or TZD initiators. The propensity score model included all the variables listed in the table. †For DPP-4I and SU comparison cohorts, eligible new users were those who did not receive either DPP-4I or SU before the first prescription. ‡For DPP-4I and TZD comparison cohorts, eligible new users were those who did not receive either DPP-4I or TZD before the first prescription and did not have history of heart failure.

Table 2—Incidence rate and HR for acute pancreatitis by study cohort, overall and stratified by follow-up time

Analysis	Cohort	No. of patients	AP events	Follow-up years		AP rate per 1,000 person-years (95% CI)	HR (95% CI)	
				Total	Median (IQR)		Crude	Weighted
Overall								
	DPP-4I	49,374	150	74,021	1.05 (0.60–2.03)	2.0 (1.7–2.4)	1.00 (0.83–1.20)	1.01 (0.83–1.24)
	SU	132,223	467	230,484	1.24 (0.67–2.43)	2.0 (1.9–2.2)	1.00	1.00
Stratified by follow-up time								
0–1 year	DPP-4I	49,374	70	39,207	1.00 (0.60–1.00)	1.8 (1.4–2.3)	0.89 (0.68–1.17)	0.94 (0.70–1.25)
	SU	132,223	218	108,823	1.00 (0.67–1.00)	2.0 (1.8–2.3)	1.00	1.00
1–2 years	DPP-4I	25,636	44	18,255	0.97 (0.40–1.00)	2.4 (1.8–3.2)	1.09 (0.78–1.54)	1.07 (0.73–1.56)
	SU	76,329	126	57,109	1.00 (0.48–1.00)	2.2 (1.9–2.6)	1.00	1.00
>2 years	DPP-4I	12,551	36	16,559	0.97 (0.45–1.88)	2.2 (1.6–3.0)	1.14 (0.79–1.65)	1.11 (0.74–1.67)
	SU	41,304	123	64,553	1.24 (0.55–2.35)	1.9 (1.6–2.3)	1.00	1.00
Overall								
	DPP-4I	57,301	159	86,795	1.07 (0.64–2.03)	1.8 (1.6–2.1)	1.11 (0.85–1.43)	1.11 (0.76–1.62)
	TZD	32,612	87	52,383	1.14 (0.70–2.09)	1.7 (1.3–2.0)	1.00	1.00
Stratified by follow-up time								
0–1 year	DPP-4I	57,301	84	46,007	1.00 (0.64–1.00)	1.8 (1.5–2.3)	1.19 (0.82–1.73)	1.19 (0.71–2.01)
	TZD	32,612	42	27,433	1.00 (0.70–1.00)	1.5 (1.1–2.1)	1.00	1.00
1–2 years	DPP-4I	30,289	39	21,382	0.94 (0.39–1.00)	1.8 (1.3–2.5)	1.22 (0.71–2.12)	1.05 (0.46–2.43)
	TZD	18,215	19	12,741	0.93 (0.36–1.00)	1.5 (1.0–2.3)	1.00	1.00
>2 years	DPP-4I	14,537	36	19,406	0.99 (0.45–1.90)	1.9 (1.3–2.6)	0.87 (0.52–1.44)	0.93 (0.50–1.74)
	TZD	8,672	26	12,209	1.08 (0.45–2.02)	2.1 (1.5–3.1)	1.00	1.00

AP, acute pancreatitis; IQR, interquartile range; SU, sulfonylurea.

the recent cardiovascular outcome trials could detect the association between DPP-4I and acute pancreatitis because they recruited patients with clinical CVD who are at higher risk of developing acute pancreatitis.

A number of observational studies have examined the association between DPP-4I and acute pancreatitis (10–24). Although few studies reported a positive association (22–24), the more rigorous observational studies designed to reduce the potential for bias consistently showed no association between DPP-4I and acute pancreatitis. For example, a large, multicountry, population-based cohort study comparing use of DPP-4I to use of two oral antihyperglycemic drugs found no increased risk of acute pancreatitis overall or across databases from different countries (19). Our study also supports that finding by showing no increased risk of acute pancreatitis after initiation of DPP-4I in older Medicare patients.

We found a higher risk of acute pancreatitis for DPP-4I, compared with TZD, among patients with CVD at baseline, however. The results are compatible with the findings from three large cardiovascular outcome trials of DPP-4I in patients with established CVD (7,8,31–33). A higher risk of acute pancreatitis in the DPP-4I group compared with the placebo group was observed in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial (12 cases in alogliptin group vs. 8 cases in placebo) (31), in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53) trial (17 cases in saxagliptin group vs. 9 cases in placebo) (32), and in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (23 cases in sitagliptin group vs. 12 cases in placebo) (33). Meta-analysis of these three trials yielded an odds ratio (OR) of 1.78 (95% CI 1.13–2.81) (7,8). Another meta-analysis of RCTs investigating incretin-based drugs also showed higher risks of acute pancreatitis associated with incretin-based drugs in the large trials of patients with CVD (OR 1.53; 95% CI 1.02–2.29) (9). The test for interaction, however, showed no statistically significant heterogeneity between RCTs with and without CVD, likely because the RCTs without CVD had small sample sizes, resulting in a small number of events and an imprecise overall estimate with a wide CI that completely overlapped the relatively precise estimate from RCTs with CVD. To our knowledge, there is no biological explanation why the effect of DPP-4I on acute pancreatitis would be confined to patients with CVD. These RCT results may merely reflect that these large RCTs with long follow-up recruited patients with diabetes who were at higher risk, and therefore the trials were more likely to detect the difference.

In our study, however, the increased risk of acute pancreatitis among patients with CVD was not seen when comparing DPP-4I to sulfonylurea. Plausibly, both DPP-4I and sulfonylurea initiators with CVD had increased risks of acute pancreatitis, leading to the absence of an association. In our older population with diabetes, the incidence rate of acute pancreatitis was approximately 2 per 1,000 person-years. Among patients with CVD, we observed the incidence rate per 1,000 person-years was 2.2 vs. 1.5 in DPP-4I versus TZD initiators and was 2.3 vs. 2.4 in DPP-4I versus sulfonylurea initiators, indicating elevated risks in both DPP-4I and sulfonylurea initiators but not in TZD initiators. Alternatively, this could imply that TZD initiators with CVD had a lower risk of pancreatitis. TZDs are contraindicated in patients with heart failure and their cardiovascular safety has received much attention; thus, patients with CVD initiating TZD might be particularly healthy compared with those with CVD initiating DPP-4I or sulfonylurea. Although measured covariates were well-balanced by propensity score weighting in the subgroup of patients with CVD who initiated DPP-4I versus TZD (Supplementary Table 14), TZD initiators may have been more likely to have mild CVD conditions, as the severity of CVD was largely unobservable

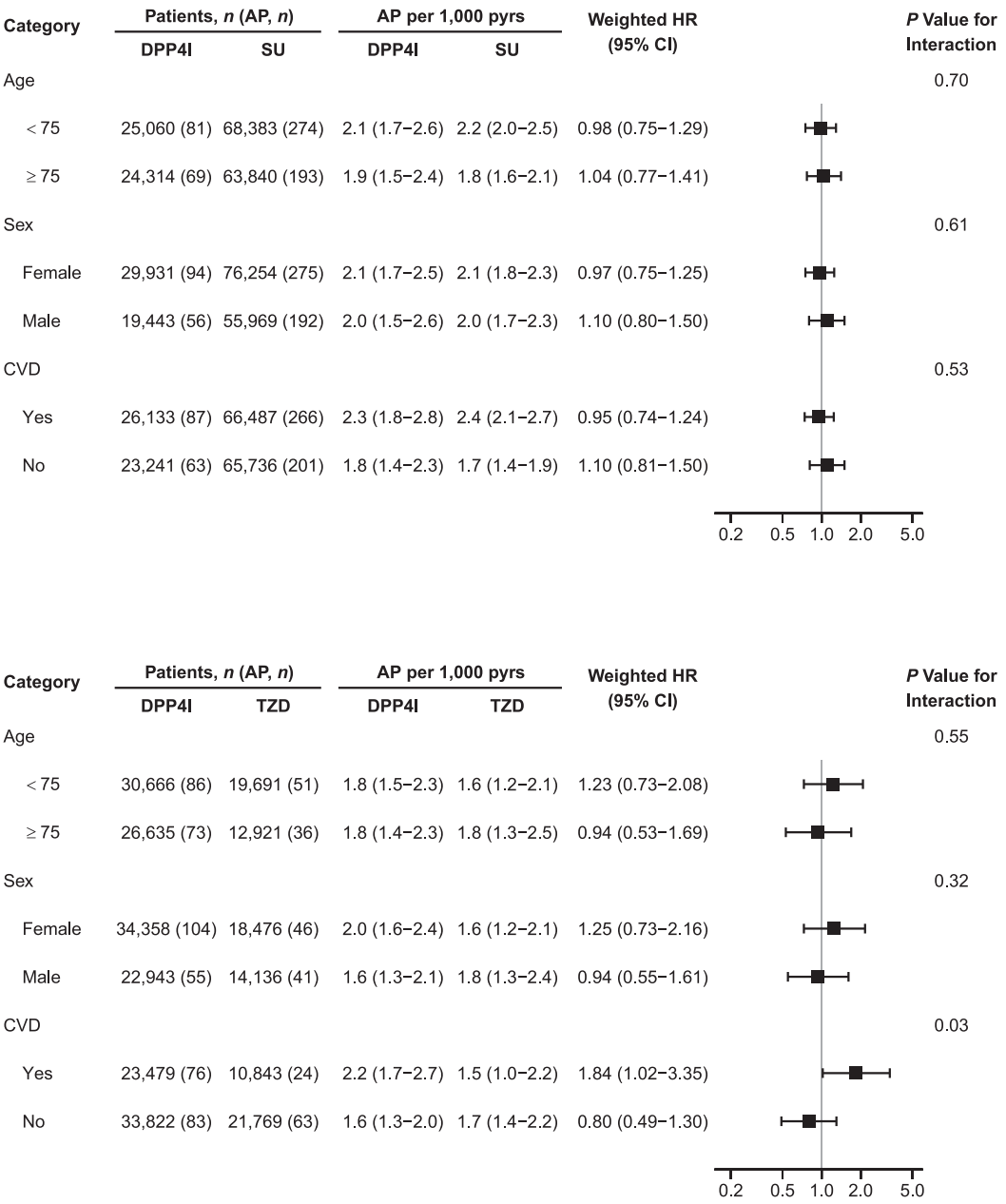

Figure 1—Incidence rate and HR for acute pancreatitis (AP) by study cohort in the subgroup analyses stratified by age category, sex, and CVD at baseline. The crude HR is provided in Supplementary Table 1. *P* values for interaction were based on Wald tests in Cox models. We did not adjust the results for multiple comparisons because we present all interactions that we assessed (40). pyrs, person-years; SU, sulfonylurea.

in our study. Thus, the positive association observed in the subgroup of patients with CVD may be attributable to differences in disease severity between DPP-4I and TZD initiators.

The increased risk of acute pancreatitis associated with DPP-4I initiation among patients with CVD was largely attenuated in the sensitivity analysis which ignored subsequent treatment changes. We varied the length of the latency period in the subgroup of patients with CVD and found a clear trend toward the null with increasing length of the latency period (Supplementary Table 15). This may indicate that the positive association observed in the main analysis based on actual exposure to treatment could suffer from selection bias by prognostic factors such as adherence. However, the analysis based on actual treatment exposure is preferred in studies addressing adverse outcomes. In addition, chance could be another explanation for the positive association confined within the DPP-4I and TZD comparison in the analysis based on actual exposure to treatment. There were only 24 cases of acute pancreatitis in the TZD group in the main analysis based on actual exposure to treatment, but there were 78 cases in the analysis ignoring subsequent treatment changes.

Our results in the subgroups should be interpreted with caution and only in light of a hypothesis. Subgroup analyses have been criticized for lack of power and higher chances of false-positive results owing to multiple statistical testing (34–36). Despite a large sample size, our study suffers from the same issues by analyzing multiple subgroups separately without a prior hypothesis. Thus, there is a possibility

that the positive associations we observed in a selected subgroup are completely due to chance.

Our study has other limitations. First, this study is limited by the short duration of treatment. In this study, the median duration of treatment was about 1 year, whereas the large trials showing increased risk of acute pancreatitis associated with DPP-4I had median duration of treatment ranging from 1.5 to 3 years (31–33). Our relatively short treatment duration reflects the dynamic diabetes regimen in a real-world population. When we stratified the analysis by duration of treatment, we found that use of DPP-4I for more than 2 years was not associated with an increased risk of acute pancreatitis overall. Second, the validity of defining acute pancreatitis based on diagnosis codes in claims data is not ideal. We used admission to a hospital with a primary discharge diagnosis of acute pancreatitis to improve specificity (37). However, we cannot exclude the possibility that we underestimated the true association between DPP-4I and acute pancreatitis because of low sensitivity and less than perfect specificity of the outcome measurement. We also acknowledge that the new users included in our study may not be true new users because the 1-year washout period may be relatively short to identify true new users. Although the new user design with active comparators is known to reduce bias attributable to unmeasured confounding (38), our study could still be subject to unmeasured confounding by length of diabetes and alcohol use, potential factors for acute pancreatitis. We have conducted a sensitivity analysis restricting the study population to those with prior use of metformin who initiated the studied drugs as the second-line treatment and were more likely to have similar length of diabetes. This sensitivity analysis showed results consistent with the primary analysis. Although we excluded patients with codes for alcohol-related diseases, hepatitis, or consequences of alcoholism, our study population may still include patients with alcohol dependency. This problem is exacerbated by the Centers for Medicare and Medicaid Services' redaction of substance abuse claims (39). However, alcohol dependence is unlikely to strongly affect the choice of DPP-4I or TZD. Although patients with alcoholism may be less likely to receive sulfonylurea because of their higher risks for hypoglycemia, this cannot explain why we did not observe an increased risk of acute pancreatitis comparing initiators of DPP-4I and sulfonylurea.

Although our study provides evidence of no increased risk of acute pancreatitis after DPP-4I initiation in the overall U.S. older population with diabetes, we found that patients with diabetes with CVD had higher risks of acute pancreatitis than those without CVD. We also observed a higher risk of acute pancreatitis associated with DPP-4I, as compared with TZD, among a subgroup of patients with CVD at baseline. We cannot exclude the possibility that this positive association is due to chance, unmeasured confounding, or selection bias. Our findings should not alter physicians' treatment decision for patients with diabetes in general, but caution may be warranted in older patients with clinical CVD at higher risk for pancreatitis.

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