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Dipeptidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study

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Abstract

Aims—Dipeptidyl-peptidase-4 inhibitors (DPP-4i) have been implicated with an increased pancreatic cancer risk. We therefore compared pancreatic cancer incidence and diagnostic work-up among initiators of DPP-4i versus sulfonylureas (SU) and thiazolidinediones (TZD).

Methods—Medicare claims data were examined in a new-user active-comparator cohort study. Patients >65 years with no prescriptions for DPP-4i, SU or TZD at baseline were included if they had at least two claims for the same drug within 180 days. Using an as-treated approach and propensity score-adjusted Cox models, we estimated hazard ratios (HR) and 95% confidence intervals (CI) for pancreatic cancer. Diagnostic work-up was compared using risk ratios (RR).

RESULTS—In the DPP-4i vs SU comparison, there were 18,179 DPP4i initiators of which 26 developed pancreatic cancer (follow-up time interquartile range 5–18 months). In the DPP-4i vs TZD comparison there were 29,366 DPP-4i initiators and 52 developed pancreatic cancer. The hazard of pancreatic cancer with DPP-4i was lower relative to SU (HR=0.6, CI 0.4–0.9) and similar to TZD (HR=1.0, CI 0.7–1.4). Excluding first 6 months of follow-up to reduce the potential for reverse causality did not alter results. Probability of diagnostic work-up post-initiation among DPP-4i initiators (79.3%) was similar to TZD (74.1%) (RR=1.06, CI 1.05–1.07) and SU (74.6%) (RR=1.06, CI1.05–1.07). The probability of diagnostic workup pre-index was ~80% for all cohorts.

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Conclusion—Though limited by sample size and the observed duration of treatment in the US, our well-controlled population based study suggests no increased short-term pancreatic cancer risk with DPP-4i relative to SU or TZD.

Introduction

Dipeptidyl-peptidase-4 inhibitors (DPP-4i) were introduced in the United States in 2006 to improve glycemic control in adults with type 2 diabetes. Sitagliptin was the first in class, followed by saxagliptin (2008), linagliptin (2011) and alogliptin (2012).[1] There is considerable interest in these drugs due to their tolerability (apart from nasopharyngitis), body-weight neutrality and ease of use [1,2], but only limited data are available on their safety. In 2009, the Food and Drug Administration (FDA) issued a safety communication regarding post-marketing reports of acute pancreatitis in patients using sitagliptin or sitagliptin/metformin.[3] Subsequently, manufacturers of these drugs revised the labels to include information regarding reports of acute pancreatitis, recommending that their use be promptly discontinued if pancreatitis was suspected while using these products.[3–5] In 2011, an analysis of the FDA Adverse Events Reporting System (FAERS) demonstrated increased rates of pancreatitis and pancreatic cancer with incretin-mimetics compared to other antihyperglycemic therapies. Pancreatic cancer rate with sitagliptin was found to be 2.7 times the rate in the control group, raising concern about a potential adverse effect.[6] The FAERS analysis has been criticized mainly due to the limitations of the FAERS database; including the lack of denominator, disproportionate reporting, confounding and inconsistencies in exposure and outcome ascertainment.[7,8] In March 2013, Butler et al [9] examined pancreata from brain-dead organ donors and found increased pancreatic mass, exocrine cell proliferation and dysplasia in organ donors treated with incretin-mimetics (7 sitagliptin, 1 exenatide) compared with diabetic patients on other antihyperglycemic agents and non-diabetic controls. The authors suggested that these observations are compatible with an increased pancreatic cancer risk in those treated with incretin-mimetics.[9] However, this study is limited by small numbers (n=34), poor matching on baseline characteristics and absence of information about treatment duration.[10] Following this, the FDA issued a drug safety communication announcing that it is evaluating such reports but that it had “not reached any new conclusions about safety risks with incretin-mimetics”.[11] Recently two trials (SAVOR-TIMI 53 and EXAMINE) evaluating the cardiovascular effects of DPP-4i were reported. [12,13] The SAVOR-TIMI compared saxagliptin versus placebo over median 2.1 years follow-up and evaluated pancreatic cancer as a safety outcome but found no indication for an increased risk (5 events with saxagliptin versus 12 with placebo).[12] The EXAMINE trial comparing alogliptin versus placebo found no reports of pancreatic cancer over about 1.5 years of median follow-up in 5380 patients.[13]

There have been many pharmacoepidemiologic studies examining acute pancreatitis with DPP-4i [14–16], but none on pancreatic cancer. We therefore compared the pancreatic cancer incidence after initiation of DPP-4i versus sulfonylureas (SU) and thiazolidinediones (TZD) using 2006–2011 Medicare claims data which reflect the diabetes burden and treatment in older adults. We conducted this study despite the limited timeframe of available Medicare Part D data on dispensed drugs because of the imperative of conducting well-controlled studies in light of the hypothesis generated in relatively uncontrolled studies as

treatment decisions are being made on a daily basis. While not intended to be definitive, the data presented are the first to examine a well-defined high-risk population, using the state-of-the-art new-user active-comparator study design, rigorous confounding control, and various sensitivity analyses.

Methods

The study was reviewed and approved by the University of North Carolina Chapel Hill Institutional Review Board (IRB # 12-1466). Before scrutinizing the data or conducting analyses, the study protocol was registered in the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) electronic register of studies (http://www.encepp.eu/encepp/viewResource.htm?id=3411).

Study population

We conducted a new-user active-comparator cohort study using a 20% random sample of Medicare beneficiaries >65 years with fee-for-service Part A (hospital coverage), B (outpatient care) and D (dispensed prescription drugs) enrollment in at least one month during a calendar year from January 1, 2007 (2006 for Part A and B) to December 31, 2011. Medicare is the largest public health insurance program in the US, covering >98% of adults 65 years or older.[17] This data contains information about demographics, enrollment, diagnoses, procedures and prescription drugs for each enrollee.[17]

From this population, we identified two new-user active-comparator cohort pairs (supplementary figures 1,2) mimicking a clinical treatment decision: 1. initiators of DPP-4i versus SU (not exposed to DPP-4i or SU in the previous 6 months) and 2. initiators of DPP-4i versus TZD (not exposed to DPP-4i or TZD in the previous 6 months). Prevalent users in the 6 months before initiation were excluded (example, in the DPP-4i vs SU comparison, patients could be on any antihyperglycemic drugs other than DPP-4i and SU in the 6 months pre-initiation). A DPP-4i initiator with no previous prescription of SU and TZD would be eligible for inclusion in both comparisons (DPP-4i vs SU and DPP-4i vs TZD). Since the drugs of interest are indicated for diabetes management, patients were not required to have a diabetes claim for cohort inclusion. Drug initiation was defined as the first prescription of the drug with the index date defined as the date of dispensing. Patients needed to have at least 6 months of continuous Part D enrollment and at least 12 months parts A and B enrollment pre-index. To ensure that patients were actually started on the drugs, we restricted our cohorts to patients with a second prescription for the same drug dispensed within 6 months after the index prescription and follow-up started from the second fill date. Finally, using a sensitive definition of ICD-9-CM codes and procedure codes (Supplemental table 1), we excluded patients with evidence of cancer or cancer-related procedures any time before the start of follow-up.

Outcome

The outcome was incident pancreatic cancer defined as at least two inpatient or outpatient claims with ICD-9-CM codes 157.xx within two months.[18] This definition has been shown to have high specificity (minimize false positives, yield unbiased relative risk

estimates) for other cancers in a Medicare population.[18] We analyzed the data using both as-treated (preferred in studies of adverse outcomes) and an intent-to-treat approach (preferred here because the induction period for pancreatic cancer is thought to be long). In the as-treated analysis, patients were followed up from the second prescription until: the outcome, discontinuation (no new prescription for the initiated drug, within days-supply plus a 180 days grace period to allow for dose adjustment/irregular use), switching or augmentation with the comparator drug, death, end of enrollment, or December 31, 2011. In the intent-to-treat approach patients were not censored when they stopped/switched/augmented therapy, but were followed until the outcome occurred, death, end of enrollment, or December 31, 2011. Patients with a diagnosis of any non-pancreatic cancer (except non-melanoma skin cancer) during follow-up were censored at that point since diagnostic-work-up or treatment of other cancers may affect the incidence of pancreatic cancer.

Confounding control and analysis

We estimated propensity scores using a number of baseline variables. Comorbidities and health care utilization were assessed during the 12 months pre-index and use of other drugs was assessed during the 6 months pre-index. Using these variables, we predicted the probability for initiating DPP-4i versus SU and DPP-4i versus TZD for each patient (the propensity score) using two separate logistic regression models.[19] We implemented the estimated propensity scores using weights that led to the “standardization” of covariates in the SU and TZD groups to the covariate distribution observed in DPP-4i initiators. This was achieved by assigning a weight of 1 to the treated (DPP-4i) and a weight of (propensity score/(1-propensity score)) to SU and TZD.[20] This weighting creates pseudo-populations of SU and TZD initiators with similar covariate distribution as in DPP-4i initiators. This covariate balance across groups allows us to estimate the unconfounded treatment effect in a population of patients similar to those actually initiating DPP-4i.[20, 21] Our weighted analysis thus answers the question “what would have happened to patients who initiated DPP-4i if they had initiated SU or TZD, instead”.[22]

After checking covariate balance in the pseudo-populations we computed weighted Kaplan Meier plots to check the proportional hazards assumption. We then fit Cox proportional hazards models in the weighted pseudo-populations with treatment as the only independent variable to compare pancreatic cancer incidence among initiators of DPP-4i vs SU and DPP-4i vs TZD.

Diagnostic procedures

Studies assessing cancer risk after a new diabetes diagnosis have raised concerns about differential cancer detection biasing the association between diabetes and cancer.[23, 24] The potential for detection bias also presents methodological challenges in studies assessing cancer risk with antihyperglycemic drugs. It is possible that patients initiating DPP-4i may undergo increased diagnostic screening just before and after drug initiation, which may lead to increased discovery of pancreatic cancer in the DPP-4i group relative to SU/TZD. To address this we compared the use of diagnostic procedures (Supplemental table 2) in 6 months before and after the index date among initiators of DPP-4i versus SU and TZD using risk ratios and 95% confidence intervals.

Sensitivity analyses

We conducted sensitivity analyses using a 6 month induction period (excluding first 6 months of follow-up). This was done in order to reduce the potential for a spurious drug-pancreatic cancer association due to pre-clinical pancreatic cancer leading to hyperglycemia and initiation of antihyperglycemic therapy (reversed causality).[25, 26] Bias resulting from reversed causality would be strongest immediately following treatment initiation. Second, we compared the pancreatic cancer incidence in DPP-4i initiators versus a combined comparison group of SU and TZD initiators.

Results

Tables 1 and 2 present the baseline covariates for each comparison. DPP-4i initiators had a mean age ~75 years and ~35% were men. Compared with DPP-4i initiators, SU initiators were more likely to be men, less likely to have connective tissue diseases, neuropathy or retinopathy and less likely to be on other antihyperglycemics, statins, angiotensin receptor blockers and beta-blockers during baseline (table 1). The SU initiators were also less likely to have had lipid testing and influenza vaccinations than the DPP-4i initiators. The TZD initiators were more likely to be men and non-white compared to the DPP-4i initiators (table 2). The prevalence of comorbidities and use of other antihyperglycemics, antihypertensives (except ACE inhibitors), statins was lower in TZD compared to the DPP-4i group. TZD initiators were also slightly less likely to get influenza vaccinations or lipid testing. In the column ‘effect of channeling’, we present the multivariable effect of these covariates on channeling between initiating DPP-4i versus comparators. After weighting (weighted SU/TZD columns, tables 1,2), all covariates in the weighted SU and TZD pseudo-populations are identical to the distribution of the DPP-4i initiators. This indicates that we were able to balance cohorts on all measured covariates which removes any confounding by these variables.

Table 3 presents incidence rates for pancreatic cancer per 100,000 person-years, time-to-event, and the crude and adjusted (weighted) hazard ratios comparing DPP-4i with SU and TZD. In the as-treated analysis, based on 26 events among 18,179 DPP-4i initiators and 177 events among 63,746 SU initiators, the adjusted HR was 0.62 (CI: 0.41, 0.94). There were 52 pancreatic cancers among 29,366 DPP-4i initiators and 54 events among 26,332 TZD initiators leading to an adjusted HR of 0.97 (CI: 0.65, 1.43). Overall these results indicate no increased short-term hazard of pancreatic cancer with DPP-4i relative to SU, nor with DPP-4i relative to TZD. Using the intent-to-treat approach (table 3), the adjusted HR was 0.68 (CI: 0.47, 1.00) for DPP-4i vs SU and 0.88 (CI: 0.62, 1.23) for DPP4i vs TZD. As shown in figure 1, similar relations were observed in those on drugs for a longer time. Figure 2 presents results stratified by duration of use since initiation. Based on a total of 53 events among 6,994 DPP-4i and 31,603 SU initiators on therapy for one year or more, we found no indication of an increased pancreatic cancer incidence with DPP-4i (HR=0.68, CI: 0.28, 1.61). In the DPP-4i versus TZD comparison, there were 11,768 DPP-4i and 12,690 TZD initiators on treatment for one year or more and the hazard ratio of pancreatic cancer based on 22 events was 0.62 (0.26, 1.51).

To reduce the potential of reverse causality, we repeated the as-treated analyses excluding the first 6 months of follow-up. In the DPP-4i vs SU comparison, this yielded 12,332 DPP-4i and 49,265 SU initiators and a total of 100 pancreatic cancers resulting in an adjusted hazard ratio of 0.73 (CI: 0.40, 1.32). In the DPP-4i vs TZD comparison, there were 21,020 DPP-4i and 21,562 TZD initiators and 51 pancreatic cancers with an adjusted hazard ratio of 0.71 (CI: 0.40, 1.25).

We also compared DPP-4i initiators with a combined group of SU or TZD initiators such that no patient had a prescription of any of these three drugs in the 6 months pre-initiation. Using an as-treated approach, this yielded 17,166 DPP-4i initiators and 69,729 initiators of SU/TZD and an adjusted hazard ratio of 0.71 (CI: 0.47, 1.08) indicating no increased pancreatic cancer incidence with DPP-4i relative to SU and TZD combined.

We did not find any difference in the risk of diagnostic work-up in the 6 months before and after drug initiation (Supplemental table 3). We performed this analysis to address the potential for increased diagnostic work-up in DPP-4i that could bias towards a higher incidence due to diagnosing some preclinical pancreatic cancers. In the 6 months post-index, the risk of diagnostic work-up was between 74.1 to 79.3% in all groups. The probability of diagnostic work-up among initiators of DPP-4i was similar to SU (RR: 1.06; CI: 1.05,1.07) and TZD initiators (RR: 1.06; CI: 1.05,1.07). In the 6 months pre-index, the risk of diagnostic work-up was similar in all groups (81.0–86.8%).

Conclusions

We found no evidence of increased short-term pancreatic cancer incidence with DPP-4i versus SU or TZD in our new-user active-comparator cohort study based on a 20% random sample of all currently available Medicare claims. Our study is limited by the short treatment duration, both as a function of actual treatment dynamics (as-treated analysis – follow-up IQR 5–18 months, median 10 months) and the availability of data (intent-to-treat - IQR 6–26 months, median 14 months). However, we required the patients to have two prescriptions of the same drug and started follow-up from the second prescription. The mean (median) time between the two prescriptions was approximately 1.5 (1) months (Supplemental table 4) indicating that the patients were on treatment for a slightly longer period than reported. Our approach of excluding patients with any cancer between the first and the second prescription can affect generalizability of results to all patients initiating these drugs, but the number of patients excluded was very small (<100 in each group) so that this is negligible. Short follow-up is likely to be an issue for the next few years since none of the clinical trials are planned for >5 years and real-world treatment patterns do not allow long-term follow-up of patients. Given the likely long induction period for pancreatic cancer it may be impossible to detect differences in cancer initiation between DPP-4i and comparators in our study. However our approach of synchronizing patients on diabetes severity and baseline pancreatic cancer risk likely makes the distribution of early stage preclinical cancers similar in DPP-4i versus comparators and we should thus be able to detect a difference in cancer promotion.

A recent meta-analysis among diabetic patients reported increased odds of pancreatic cancer with SU use versus non-use (although there was considerable heterogeneity across all studies that could not be explained by study design, setting or location), and no difference in odds with TZD use versus non-use.[27] Our observation of a slightly lower adjusted hazard of pancreatic cancer with DPP-4i versus SU could be a function of only 26 events in the DPP-4i group and also a potentially increased pancreatic cancer risk with SU which could make DPP-4i appear protective. Therefore these results should be interpreted with caution and additional data are needed to investigate this further. For each comparison, the results did not change among long term drug users as shown in figures 1 and 2.

Our results were robust to changes in analysis approaches and varying induction periods. We found little evidence for differential diagnostic work-up in DPP-4i initiators, indicating that differential outcome detection bias is less of a concern in our study.

Our results are contrary to those in the aforementioned FAERS analysis and the histologic study on human pancreata which suggested an increased pancreatic cancer risk with DPP-4i.[6,9] The limitations of these studies clearly warranted further investigation using large population-based healthcare data and state-of-the-art non-experimental methods.

A strength of our study is the use of a new-user active-comparator cohort design which is analogous to a head-to-head clinical trial [28] and mimics the most relevant clinical decision (‘which treatment to initiate’ rather than ‘treatment or not’). It allows synchronizing follow-up in all cohorts which is the basis for sensitivity analyses of induction periods.[28] Specifically, we identified initiators of DPP-4i or comparators after a 6 month washout. Potential confounders were measured before drug initiation thereby avoiding the problem of controlling for covariates potentially affected by prevalent treatment.[28] The covariate balance achieved by our propensity score weighting reassures us about absence of confounding by these covariates. Using active comparators helped balance the groups on diabetes severity, baseline pancreatic cancer risk (particularly important since diabetes is a risk factor for pancreatic cancer) and addressed confounding by indication and frailty. Given that many plausible predictors of treatment choice were already balanced by using an active comparator (before propensity score implementation), we may be more inclined to make the assumption that unmeasured confounding is not a major concern in our study, although we can never be certain about this point.

Compared to SU and TZD, DPP-4i initiators were more likely to get statins, influenza vaccines or blood lipids tested suggesting that DPP-4i initiators are more likely to follow guidelines of disease prevention, i.e., healthy users.[29] However, we successfully balanced the cohorts of DPP-4i and SU and TZD initiators on all these factors using weighting and this would tend to reduce imbalances of unmeasured factors associated with measured healthy user behaviors.[30]

Our study should be interpreted in the context of its limitations. As outlined above, the main limitation is short duration of follow-up and the results should be cautiously accepted. The follow-up time in the DPP-4i group was slightly shorter than the follow-up for comparators (supplemental table 5), but Cox models do not require equal person-time to be valid. The

relatively constant slope of the Kaplan-Meier plots provide some reassurance that cancer risk in DPP-4i initiators are not increasing in the second year; however no implications can be made at this time about longer periods of exposure. Our study also had limited number of outcomes and number of DPP-4i initiators. DPP-4i were introduced in the US only in 2006 while SU and TZD have been on the market for a longer time, which might explain the small number of DPP-4i initiators as many potential candidates were excluded because of prior exposure to SU/TZD. Limited number of outcomes may be attributed to the fact that pancreatic cancer is a rare disease.[31] However, the median age at pancreatic cancer diagnosis is 71 years and the Medicare data is likely to have the highest power to study this outcome compared to other claims data from equivalent years. Based on the pancreatic cancer rates in the general US population reported by National Cancer Institute's Surveillance Epidemiology and End Results (SEER), we calculated the expected number of events for our study population and compared it to the observed events in our data.[32] The ratio of observed to expected events was between 2–3 implying that that our study population had more than twice the number of pancreatic cancer events than the general US population, consistent with the fact that diabetic individuals have a 2-fold increased pancreatic cancer risk compared with the general population.[33, 34] In separate analyses (data not shown), we attempted to examine incident pancreatic cancer with the GLP-1 receptor agonists. However, the sample size was even more restricted, precluding robust analysis. Since GLP-1 receptor agonists and DPP-4i potentiate incretin action through different mechanisms and the exact spectrum of adverse events is uncertain, we did not combine these into a single analysis.[8]

There is a possibility of reverse causality affecting our study. Patients with preclinical pancreatic cancer may have worsening of their diabetes leading to initiation of antihyperglycemic treatments. However, our results did not change even after excluding the first 6 months of follow-up. We would have liked to extend this to 12 months or longer but were limited by treatment dynamics and data availability.

Finally, we could not adequately control for potential risk factors for pancreatic cancer like smoking, body mass index (BMI) since they not well-measured in Medicare claims.[35–37] However, we used chronic obstructive pulmonary disease as a proxy for smoking and balanced the comparison groups on this variable. We could not statistically adjust for BMI. However, BMI is only weakly associated with pancreatic cancer and therefore not adjusting for it is not expected to affect our results.[37]

In summary, we did not find an increased short-term pancreatic cancer risk after initiation of DPP-4i versus SU or TZD in older diabetic patients. This study does not establish the safety of DPP-4i – but uses real-world treatment patterns to present the first alternate view of the situation in contrast to the reports of increased risk from non-population based studies with similar or even lesser exposure and events. Given the short follow-up, ourstudy could not assess long term risk and therefore physicians should cautiously interpret the results while using them to guide clinical decisions. Further research should continue to assess the risk as more data become available as recently suggested.[38–41] Meanwhile, our results will help prudent clinicians and patients to make reasonable treatment decisions based on the currently available evidence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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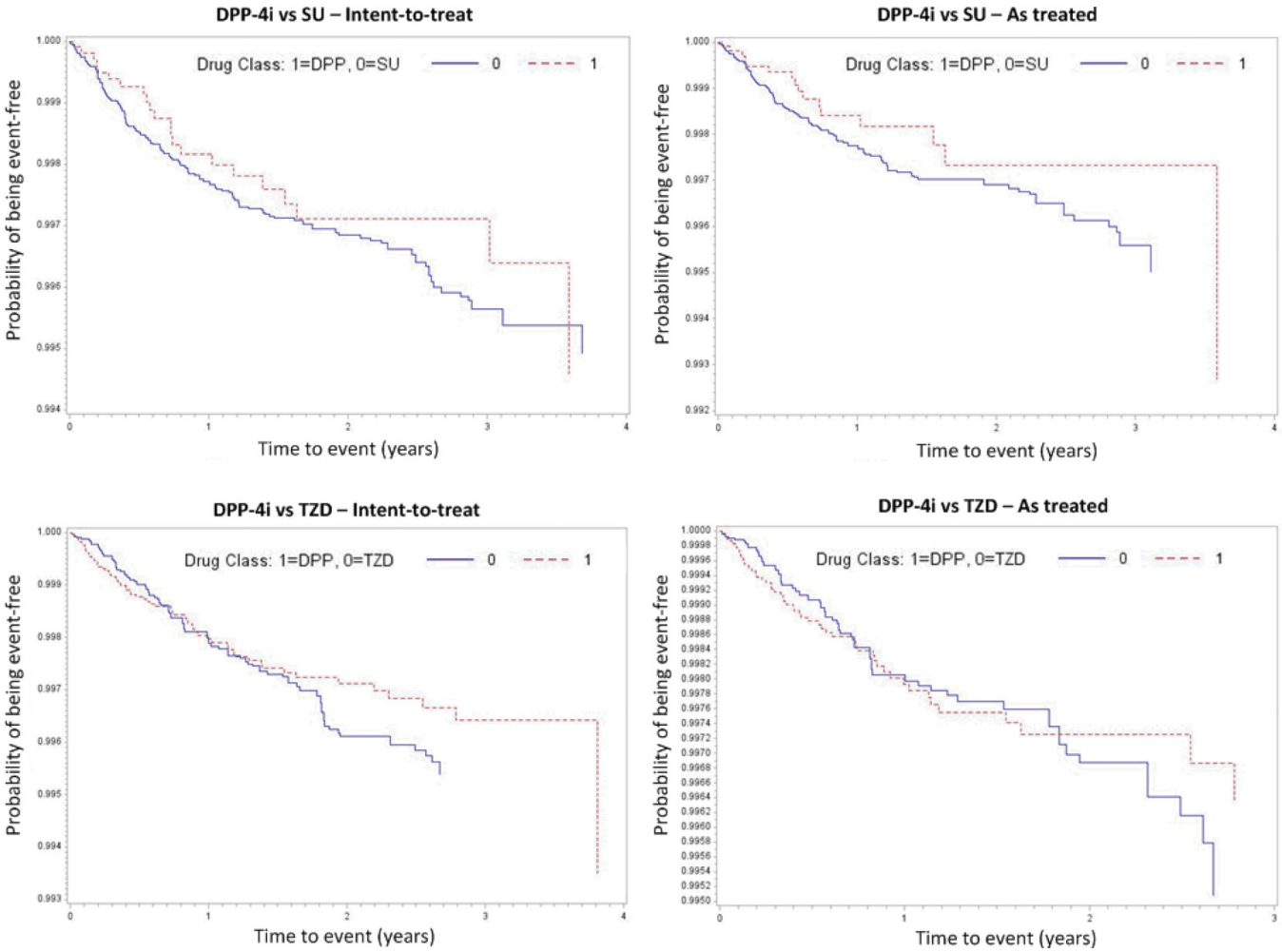
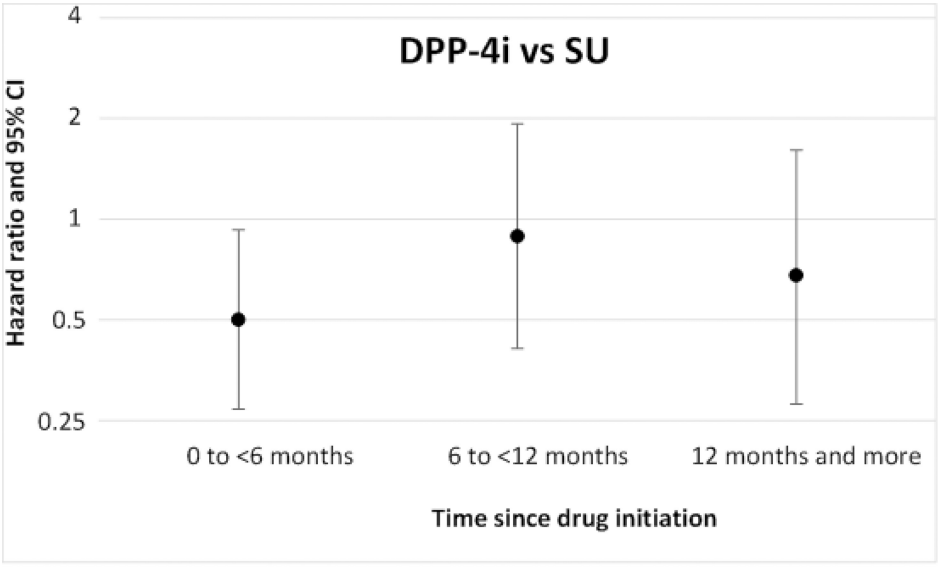


Figure 1. Kaplan-Meier plots of time to event for pancreatic cancer with dipeptidyl-peptidase-4 inhibitors (DPP-4i), sulfonylureas (SU) and thiazolidinediones (TZD)

For the graphs titled 'DPP vs SU' red dotted line = DPP-4i and blue solid line = SU For graphs titled 'DPP vs TZD', red dotted line = DPP-4i and blue solid line = TZD



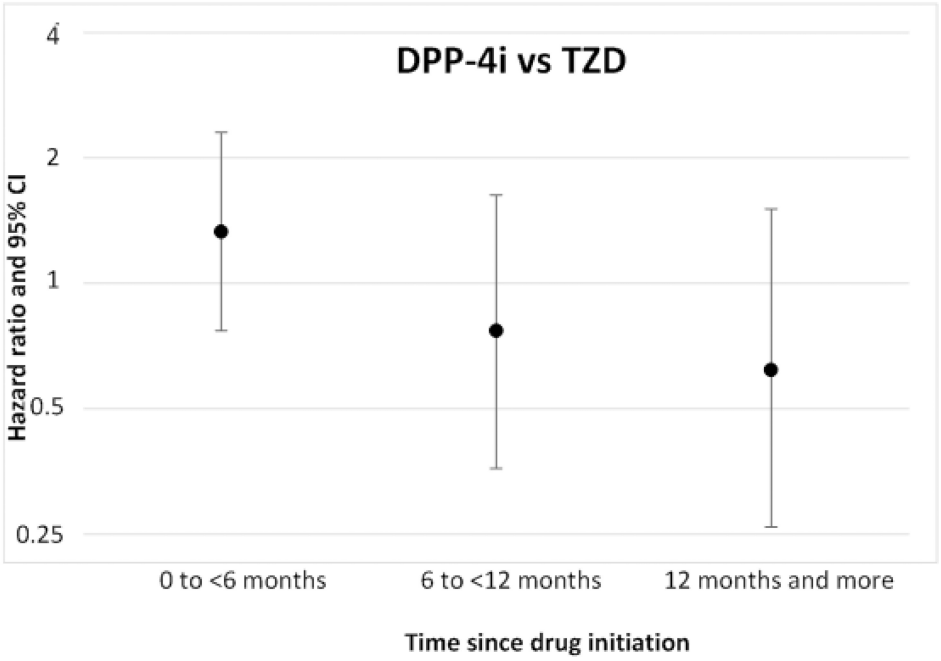


Figure 2. Hazard ratios and 95% CI for pancreatic cancer stratified by time since drug initiation

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Table 1

Distribution of selected baseline characteristics in initiators of dipeptidyl-peptidase-4 inhibitors (DPP-4i) and sulfonylureas (SU) [a]

	DPP-4i (n = 18,179)		SU (n = 63,746)		Effect of channeling[b]			weighted SU[c]
	N	%	N	%	Odds ratio	95% CI		%
Age Mean (SD)	75.28 (7.00)		75.60 (7.28)		0.997	0.951	1.045	75.53 (7.22)
66 to 75 years old	10428	57.36	35632	55.90	-	-	-	57.44
76 to 85 years old	5916	32.54	20884	32.76	-	-	-	32.72
86 years and above	1835	10.09	7230	11.34	-	-	-	9.84
Male	6566	36.12	25340	39.75	0.892	0.860	0.925	36.06
White	13486	74.18	48907	76.72	0.766	0.728	0.805	74.20
Black	1925	10.59	7694	12.07	0.669	0.624	0.717	10.67
Other	2768	15.23	7145	11.21	Reference			15.13
Comorbidities[d]								
Connective tissue disease	6354	34.95	19307	30.29	1.143	1.102	1.186	34.96
Depression	3089	16.99	10262	16.10	1.001	0.955	1.049	17.01
Chronic obstructive pulmonary disease	3516	19.34	12972	20.35	0.941	0.90	0.985	19.4
Chronic kidney disease	3381	18.6	10923	17.14	0.995	0.947	1.046	18.77
Congestive heart failure	4588	25.24	15939	25.00	1.015	0.969	1.064	25.37
Diabetic neuropathy	3751	20.63	9631	15.11	1.212	1.159	1.268	20.72
Diabetic nephropathy	1542	8.48	3961	6.21	1.131	1.056	1.213	8.60
Diabetic retinopathy	2974	16.36	7721	12.11	1.107	1.054	1.163	16.49
Diabetic cataract	51	0.28	111	0.17	1.111	0.788	1.567	0.28
Gastrointestinal disorders	158	0.87	550	0.86	1.031	0.859	1.237	0.86
Alcohol use [e]	192	1.06	804	1.26	0.975	0.828	1.148	1.06
Tobacco use [e]	48	0.26	142	0.22	1.135	0.811	1.588	0.27
Pancreatitis	211	1.16	690	1.08	1.072	0.914	1.257	1.18
Medication use[f]								
Insulin	3823	21.03	9232	14.48	1.495	1.428	1.566	21.20

	DPP-4i (n = 18,179)		SU (n = 63,746)		Effect of channeling[b]			weighted SU[c]
	N	%	N	%	Odds ratio	95% CI		%
Metformin	9386	51.63	27902	43.77	1.269	1.224	1.314	51.95
Thiazolidinediones	3983	21.91	7567	11.87	1.892	1.811	1.977	22.27
Angiotensin converting enzyme inhibitors	6068	33.38	21806	34.21	0.953	0.917	0.990	33.57
Angiotensin receptor blockers	5403	29.72	12393	19.44	1.471	1.412	1.532	29.91
Statins	11908	65.50	35028	54.95	1.251	1.205	1.298	65.64
Loop diuretics	4771	26.24	16443	25.79	0.931	0.891	0.974	26.3
Other diuretics	4625	25.44	16923	26.55	0.906	0.871	0.942	25.54
Beta blockers	8989	49.45	28689	45.01	1.096	1.057	1.135	49.49
Calcium channel blockers	6238	34.31	19790	31.05	1.055	1.017	1.095	34.35
Healthcare utilization[d]								
Blood tests	1759	9.68	5104	8.01	1.111	1.048	1.178	9.73
Lipid panel	15719	86.47	49572	77.76	1.476	1.405	1.551	86.59
Influenza vaccinations	9997	54.99	31990	50.18	1.121	1.083	1.16	55.04

[a] Initiation defined as no dispensed prescriptions for DPP-4i or SU during the 6 months before initiation and filling a second prescription of the same drug/drug class within 6 months after the first prescription

[b] Channeling between initiation of DPP-4i versus initiation of SU; odds ratios from multivariable logistic regression model including all covariates presented in the table (i.e., the propensity score model); odds ratios >1.0 indicate more likely to be initiated on DPP-4i than SU

[c] Pseudo-population of SU initiators weighted to the distribution of covariates of the DPP-4i initiators using the propensity score to balance covariates (and therefore control for confounding)

[d] Measured in the 12 months before drug initiation

[e] Tobacco use and alcohol use and abuse defined using ICD-9-CM codes may be underestimated.

[f] Measured in the 6 months before drug initiation

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Table 2

Distribution of selected baseline characteristics in initiators of dipeptidyl-peptidase-4 inhibitors (DPP-4i) and thiazolidinediones (TZD) [a]

	DPP-4i (n = 29,366)		TZD (n = 26,332)		Effect of channeling[b]			weighted TZD[c]
	N	%	N	%	Odds ratio	95% CI		%
Age Mean (SD)	75.61 (7.10)		74.64 (6.70)		0.945	0.901	0.992	75.62 (7.50)
66 to 75 years old	16407	55.87	16100	61.14	-	-	-	55.60
76 to 85 years old	9782	33.31	8130	30.87	-	-	-	33.65
86 years and above	3177	10.82	2102	7.98	-	-	-	10.74
Male	10590	36.06	10609	40.29	0.884	0.852	0.916	35.94
White	22245	75.75	18628	70.74	1.321	1.259	1.387	75.77
Black	3059	10.42	3140	11.92	1.060	0.99	1.134	10.40
Other	4062	13.83	4564	17.33	(reference)			13.83
Comorbidities[d]								
Connective tissue disease	9966	33.94	7763	29.48	1.108	1.067	1.15	34.08
Depression	4709	16.04	3712	14.10	1.003	0.955	1.054	16.15
Chronic obstructive pulmonary disease	5595	19.05	3999	15.19	1.080	1.030	1.133	18.88
Chronic kidney disease	5790	19.72	4031	15.31	1.114	1.058	1.172	19.70
Congestive heart failure	7740	26.36	4373	16.61	1.430	1.361	1.502	26.41
Diabetic neuropathy	6478	22.06	4813	18.28	1.114	1.066	1.164	22.24
Diabetic nephropathy	2660	9.06	1954	7.42	1.040	0.971	1.114	9.12
Diabetic retinopathy	5260	17.91	4432	16.83	1.010	0.965	1.058	17.92
Diabetic cataract	83	0.28	73	0.28	0.988	0.716	1.364	0.28
Gastrointestinal disorders	256	0.87	208	0.79	1.006	0.834	1.215	0.86
Alcohol use [e]	316	1.08	258	0.98	1.132	0.954	1.342	1.10
Tobacco use [e]	78	0.27	59	0.22	1.086	0.769	1.534	0.26
Pancreatitis	318	1.08	243	0.92	1.071	0.902	1.273	1.08
Medication use[f]								
Insulin	5409	18.42	4445	16.88	0.977	0.932	1.024	18.51

	DPP-4i (n = 29,366)		TZD (n = 26,332)		Effect of channeling[b]			weighted TZD[c]
	N	%	N	%	Odds ratio	95% CI		%
Metformin	16805	57.23	14282	54.24	1.208	1.165	1.253	57.68
Sulfonylureas	13530	46.07	11352	43.11	1.051	1.015	1.089	46.25
Angiotensin converting enzyme inhibitors	10907	37.14	9899	37.59	0.949	0.914	0.986	37.20
Angiotensin receptor blockers	8184	27.87	5982	22.72	1.216	1.166	1.269	28.11
Statins	19331	65.83	15466	58.73	1.206	1.163	1.252	65.85
Loop diuretics	8294	28.24	5025	19.08	1.245	1.189	1.304	28.26
Other diuretics	7831	26.67	6861	26.06	0.99	0.952	1.03	26.48
Beta blockers	15350	52.27	11288	42.87	1.217	1.174	1.261	52.23
Calcium channel blockers	10334	35.19	8440	32.05	1.049	1.011	1.088	35.39
Healthcare utilization[d]								
Blood tests	2675	9.11	2261	8.59	1.032	0.972	1.096	9.08
Lipid panel	25483	86.78	22105	83.95	1.196	1.138	1.258	87.01
Influenza vaccinations	16325	55.59	13427	50.99	1.112	1.074	1.151	55.79

[a] Initiation defined as no dispensed prescriptions for DPP-4i or TZD during the 6 months before initiation and filling a second prescription of the same drug/drug class within 6 months after the first prescription

[b] Channeling between initiation of DPP-4i versus initiation of TZD; odds ratios from multivariable logistic regression model including all covariates presented in the table (i.e., the propensity score model); odds ratios >1.0 indicate more likely to be initiated on DPP-4i than TZD

[c] Pseudo-population of TZD initiators weighted to the distribution of covariates of the DPP-4i initiators using the propensity score to balance covariates (and therefore control for confounding)

[d] Measured in the 12 months before drug initiation

[e] Tobacco use and alcohol use and abuse defined using ICD-9-CM codes may be underestimated.

[f] Measured in the 6 months before drug initiation

Table 3

Pancreatic cancer incidence among initiators [a] of dipeptidyl-peptidase-4 inhibitors (DPP-4i), sulfonylureas (SU) and thiazolidinediones (TZD)

Comparison	Drug	Number of new-users	Events	time to event in years interquartile range (median)	Total person-years	Incidence (per 100,000 person years)	Unadjusted HR (95% CI) [b]	Adjusted HR (95%CI) [c]
As treated analysis								
DPP-4i vs SU	DPP-4i [d]	18,179	26	0.36 – 1.45 (0.75)	18,813	138.20	0.63 (0.39, 0.91)	0.62 (0.41, 0.94)
	SU	63,746	177	0.55 – 1.85 (0.99)	80,768	219.15	1.00 (reference)	1.00 (reference)
DPP-4i vs TZD	DPP-4i [d]	29,366	52	0.43 – 1.50 (0.79)	31,333	165.96	0.97 (0.66, 1.42)	0.97 (0.65, 1.43)
	TZD	26,332	54	0.57 – 1.71 (0.96)	32,261	167.38	1.00 (reference)	1.00 (reference)
Intent to treat analysis								
DPP-4i vs SU	DPP-4i	18179	35	0.48 – 2.25 (1.16)	25,902	135.12	0.64 (0.45, 0.91)	0.68 (0.47, 1.00)
	SU	63746	213	0.66 – 2.51 (1.48)	103,652	205.50	1.00 (reference)	1.00 (reference)
DPP-4i vs TZD	DPP-4i	29,366	63	0.52 – 2.22 (1.18)	41675	151.17	0.93 (0.66, 1.30)	0.88 (0.62, 1.23)
	TZD	26,332	75	0.93 – 2.73 (1.81)	48925	153.29	1.00 (reference)	1.00 (reference)

[a] Initiation defined as no dispensed prescriptions for the drugs being compared during the 6 months before initiation and filling a second prescription of the same drug/drug class within 6 months after the first prescription

[b] Hazard ratios and their 95 % confidence intervals from Cox proportional hazards models for pancreatic cancer with baseline treatment as the only independent covariate

[c] Hazard ratios adjusted for variables in Table 1 and 2 using propensity score weighting (standardized to DPP-4i population)

[d] Number of DPP-4i initiators different in both cohorts because for the DPP-4i vs SU comparison, patients could be on any diabetes medication (including TZD) except for DPP-4i and SU during the washout period. Similarly for the DPP-4i versus TZD comparison, patients could be on any other drugs except DPP-4i and TZD.