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Pancreatic safety of vildagliptin in patients with type 2 diabetes mellitus: A European, noninterventional, postauthorization safety study

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Abstract

This cohort study assessed the pancreatic safety of vildagliptin versus other noninsulin antidiabetic drugs (NIADs) based on data from five European electronic health care databases. Patients with type 2 diabetes aged ≥18 years on NIAD treatment were enrolled. Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated separately for acute pancreatitis and pancreatic cancer for vildagliptin (± other NIADs) compared with other NIADs using negative binomial regression. Approximately 2.8% of the enrolled patients (n = 738 054) used vildagliptin during the study, with an average follow-up time of 1.4 years. For acute pancreatitis, adjusted IRRs ranged between 0.89 andt 2.58 with all corresponding 95% CIs crossing 1. For pancreatic cancer adjusted IRRs ranged from 0.56 to 3.64, with the lower limit of 95% CIs >1 in some analyses. Post hoc sensitivity analyses taking latency time into account markedly lowered the risk estimates with corresponding 95% CIs crossing 1. Overall, the results do not suggest an increased pancreatitis risk with vildagliptin, while the observation for pancreatic cancer have to be interpreted carefully as this study was not designed to assess pancreatic cancer and rather be explained by certain underlying limitations including latency -time, chance findings and/or bias and confounding.

KEYWORDS
dipeptidyl peptidase-4 inhibitors, pancreatic cancer, pancreatitis, type 2 diabetes mellitus, vildagliptin

1 | INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors have gained popularity over the past decade owing to their robust efficacy and favourable effects on body weight and low risk of hypoglycaemia in patients with type 2 diabetes mellitus (T2DM).[1,2] The well-established benefit-risk profile of DPP-4 inhibitors however, has been challenged because of safety concerns regarding adverse pancreatic events (acute pancreatitis, pancreatic cancer) which was initially raised by postmarketing surveillance reports from the Food and Drug Administration Adverse Event Reporting System.[3] While some noninterventional studies[4,5] or meta-analyses of randomized controlled trials (RCTs)[6] reported an increased risk of pancreatic events, other studies did not find an increased risk.[7,8]

The ambiguity is further complicated because of the complex interplay between diabetes, pancreatitis and pancreatic cancer. Patients with T2DM are at twofold to threefold increased risk of developing pancreatitis compared to patients without T2DM.[9] Additionally, long-standing T2DM doubles the risk of pancreatic cancer, while presentation of new-onset diabetes in patients with pancreatic cancer is not uncommon.[10]

In the context of a noninterventional postauthorization vildagliptin safety study—undertaken as part of a commitment to the European Committee for Medicinal Products for Human Use (CHMP),[11] we conducted an exploratory analysis to assess the risk of acute pancreatitis and pancreatic cancer in patients with T2DM using vildagliptin or vildagliptin/metformin (as a fixed-dose combination) compared with other noninsulin antidiabetic drugs (NIADs).

2 | MATERIALS AND METHODS

2.1 | Study design and databases

For this population-based, analytical, multidatabase cohort study,[11] we used information from The Clinical Practice Research Datalink General practice OnLine Database (CPRD GOLD, UK), Intercontinental Marketing Statistics Disease Analyzer (IMS DA) Germany, IMS DA France, the Odense Pharmacoepidemiological Database (OPED) Denmark and the Swedish National Registers (NR).

2.2 | Patients and assessments

Patients with T2DM aged ≥18 years who were prescribed an NIAD other than vildagliptin were included. Patients with a history of cancer, HIV/AIDS and/or history of insulin use prior to start of follow-up were excluded. Starting from the index date (day of the first NIAD prescription on or after 01 Jan 2005) patients were followed up until the end of the study (June 2014), their transfer out of the database, date of first insulin prescription or death. Apart from patient demographics, information was collected on the number of visits to the doctor in the 6-12 months before cohort entry, smoking (only in CPRD GOLD and Swedish NR) and alcohol abuse, as well as exposure to other co-medications of interest within 6 months prior to the start of follow-up (= index date). Follow-up was divided into different NIAD exposure periods (current and noncurrent use, separately for vildagliptin and other NIADs). Patients could move between exposure categories and between NIAD classes; patients using vildagliptin concurrently with other NIADs were included in the vildagliptin cohort. The outcomes of interest (acute pancreatitis [ICD-10 code: K85] or pancreatic cancer [ICD-10 code: C25]) were identified using either Read (CPRD) or ICD-10 codes (remaining data sources). "Incident outcomes" were defined as the occurrence of a first event after the start of follow-up, excluding those patients with a prior recording of the outcome of interest on or before the start of follow-up. Incidence rates (IRs) and incidence rate ratios (IRRs) of acute pancreatitis and separately of pancreatic cancer were assessed as risk measures of the outcomes of interest across databases.

2.3 | Statistical analysis

It was estimated that 20 000 patient-years (PYs) of exposure with vildagliptin would provide 80% power (two-sided α, 0.05) to detect a twofold increase in risk for an event with an IR of 1.0 per 1000 PYs, assuming at least six patients will be accrued in the comparator NIAD cohort for each patient in the vildagliptin cohort. Demographics and other baseline characteristics were descriptively summarized by database and NIAD cohorts. IRs were calculated together with 95% confidence intervals (95% CIs), age- and sex-adjusted IRRs with 95% CIs were estimated using negative binomial regression. Statistical significance was assessed using adjusted *P*-values accounting for the false discovery rate. Where number of cases allowed, subgroup analyses were conducted by age (18-39, 40-64 and ≥65 years) and sex. In addition, a post hoc sensitivity analysis was performed excluding pancreatic cancer cases with <365 latency days between the initiation of vildagliptin or NIAD and pancreatic cancer diagnosis date and <365 days of cumulative vildagliptin or NIAD exposure prior to pancreatic cancer diagnosis. This sensitivity analysis was performed only for vildagliptin overall versus NIADs, but not for any subgroups.

2.3.1 | Ethics and good clinical practice

The protocol was endorsed by the Committee for Medicinal Products for Human Use (CHMP), and the study was conducted by the CPRD Group. Approvals were obtained from the Independent Scientific Advisory Committee (ISAC; for CPRD 09_069R) and the Danish Health Board.

3 | RESULTS

Of totally 738 054 included NIAD users, 20 973 (2.8%) received vildagliptin at any time during the study. The mean duration of follow-up for vildagliptin users was 1.4 years corresponding to 28 330 PYs of exposure. Overall, the baseline characteristics of patients were comparable between vildagliptin and other NIADs across databases (Table 1).

The age-/sex-adjusted IRRs for acute pancreatitis (vildagliptin vs. other NIADs) were 0.90 (95% CI: 0.22-3.60), 0.89 (95% CI: 0.65-1.24) and 2.58 (95% CI: 0.65-10.35) in CPRD GOLD, IMS DA Germany and Swedish NR, respectively (Figure 1). Due to zero cases in the vildagliptin group, both in IMS DA France and OPED, no IRRs were estimated.

The age-/sex-adjusted IRRs for pancreatic cancer for vildagliptin overall vs. other NIADs by databases are presented in Figure 2. There were no cases identified for pancreatic cancer in patients exposed to vildagliptin in the Danish and Swedish databases, only one case in association with vildagliptin use was reported in the French IMS DA (adjusted IRR, 0.56; 95% CI: 0.02-18.75). Six cases were identified in the CPRD GOLD group yielding an adjusted IRR of 3.64 (95% CI: 0.93-14.26; adjusted *P*-value 1.0); all identified cases associated with vildagliptin use from the CPRD GOLD were in the

TABLE 1 Baseline characteristics at the start of follow-up by database

Characteristic	CPRD GOLD (UK)		IMS DA (Germany)		IMS DA (France)		OPED (Denmark)		National Registers (Sweden)	
	NIAD N = 211 327	Vildagliptin N = 1990	NIAD N = 206 576	Vildagliptin N = 13 286	NIAD N = 41 911	Vildagliptin N = 2 982	NIAD N = 23 725	Vildagliptin N = 923	NIAD N = 254 515	Vildagliptin N = 569
Age (y)	63 ± 14	59 ± 12	65 ± 13	63 ± 12	63 ± 12	62 ± 11	64 ± 13	61 ± 11	65 ± 12	60 ± 10
18-39	9484 (4.5)	108 (5.4)	5829 (2.8)	367 (2.8)	1082 (2.6)	65 (2.2)	940 (4.0)	33 (3.6)	4270 (1.7)	15 (2.6)
40-64	101 569 (48.1)	1255 (63.1)	87 379 (42.3)	6864 (51.7)	21 349 (50.9)	1721 (57.7)	11 102 (46.8)	516 (55.9)	125 609 (49.4)	372 (65.4)
≥65	100 274 (47.4)	627 (31.5)	113 368 (54.9)	6055 (45.6)	19 480 (46.5)	1196 (40.1)	11 683 (49.2)	374 (40.5)	124 636 (49.0)	182 (32.0)
Women	90 815 (43.0)	842 (42.3)	98 040 (47.5)	5703 (42.9)	17 765 (42.4)	1174 (39.4)	13 700 (57.7)	572 (62.0)	104 933 (41.2)	216 (38.0)
Men	120 512 (57.0)	1 148 (57.7)	108 536 (52.5)	7583 (57.1)	24 146 (57.6)	1808 (60.6)	10 025 (42.3)	351 (38.0)	149 582 (58.8)	353 (62.0)
BMI (kg/m^2)	31 ± 7	33 ± 7	31 ± 6	32 ± 6	—	—	—	—	30 ± 5	31 ± 6
<20	2685 (1.3)	9 (0.5)	594 (0.3)	32 (0.2)	—	—	—	—	1460 (0.6)	3 (0.5)
20-25	26 700 (12.6)	165 (8.3)	8308 (4.0)	486 (3.7)	—	—	—	—	42 751 (16.8)	68 (12.0)
26-29	68 791 (32.6)	591 (29.7)	22 431 (10.9)	1541 (11.6)	—	—	—	—	68 748 (27.0)	140 (24.6)
>30	110 178 (52.1)	1222 (61.4)	32 308 (15.6)	2649 (19.9)	—	—	—	—	96 251 (37.8)	249 (43.8)
Unknown	2973 (1.4)	3 (0.2)	142 935 (69.2)	8578 (64.6)	—	—	—	—	45 305 (17.8)	109 (19.2)
Diabetes duration (y)	4 ± 5	4 ± 5	1 ± 3	1 ± 3	1 ± 1	1 ± 1	2 ± 3	2 ± 3	4 ± 5	4 ± 5
Number of visits to GP in 6-12 mo prior	6 ± 5	5 ± 5	—	—	—	—	—	—	1 ± 4	1 ± 2
Comorbidities										
Alcoholism	4299 (2.0)	30 (1.5)	1668 (0.8)	102 (0.8)	295 (0.7)	11 (0.4)	312 (1.3)	11 (1.2)	1269 (0.5)	2 (0.4)
Hypertension	117 230 (55.5)	1035 (52.0)	1476 (0.7)	85 (0.6)	19 (<0.1)	1 (<0.1)	188 (0.8)	7 (0.8)	61 326 (24.1)	100 (17.6)
Smoking status										
Smoker	40 829 (19.3)	360 (18.1)	—	—	—	—	—	—	33 257 (13.1)	67 (11.8)
Ex-smoker	87 911 (41.6)	777 (39.0)	—	—	—	—	—	—	1628 (0.6)	2 (0.4)
Non-smoker	81 094 (38.4)	840 (42.2)	—	—	—	—	—	—	178 494 (70.1)	399 (70.1)
Unknown smoking status	1493 (0.7)	13 (0.7)	—	—	—	—	—	—	41 136 (16.2)	101 (17.8)

BMI, body mass index; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; DA, Disease Analyzer; GP, general practitioner; NIAD, noninsulin antidiabetic drug; OPED, Odense Pharmaco Epidemiological Database; SD, standard deviation; UK, United Kingdom.
Data are expressed as mean ± SD or n (%).

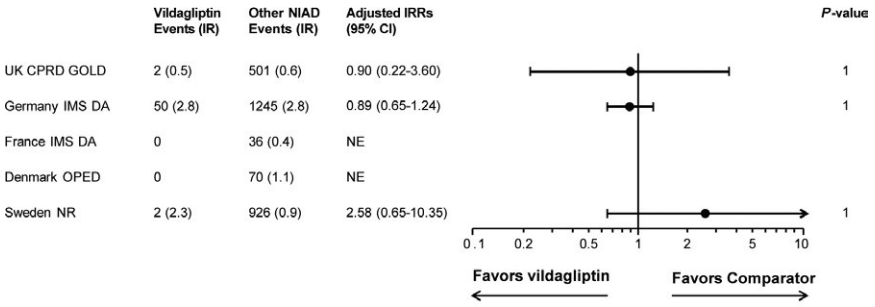

FIGURE 1 Adjusted incidence rate ratios of acute pancreatitis for the use of vildagliptin vs other NIADs. CI, confidence interval; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; IMS DA, Intercontinental Marketing Statistics Disease Analyzer; IR, incidence rate (per 1000 patient-y); IRRs, incidence rate ratios; NE, not evaluated (due to zero cases in the vildagliptin group); NIAD, noninsulin antidiabetic drug; NR, National Registers; OPED, Odense Pharmacoepidemiological Database

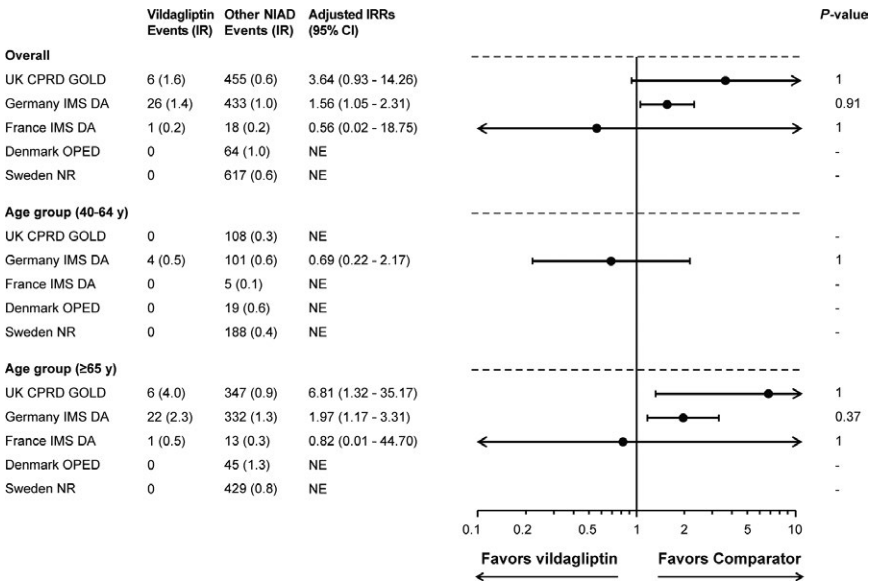

FIGURE 2 Adjusted incidence rate ratios of pancreatic cancer for the use of vildagliptin versus other NIADs by databases and age subgroups. CI, confidence interval; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; IMS DA, Intercontinental Marketing Statistics Disease Analyzer; IR, incidence rate (per 1000 patient-y); IRRs, incidence rate ratios; NE, not evaluated (due to zero cases in the vildagliptin group); NIAD, noninsulin antidiabetic drug; NR, National Registers; OPED, Odense Pharmacoepidemiological Database

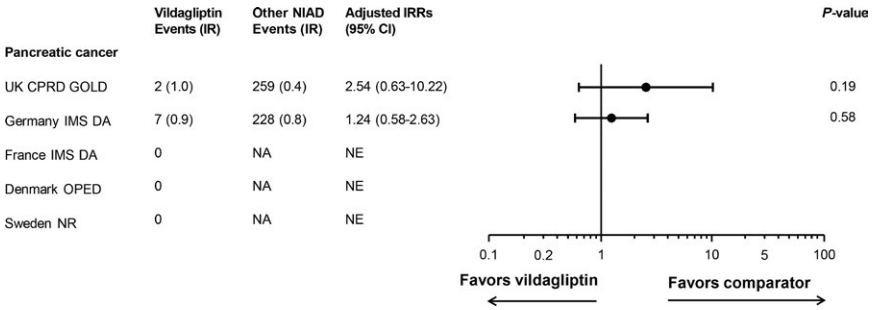

FIGURE 3 Post hoc sensitivity analysis: Adjusted incidence rate ratios of pancreatic cancer for the use of vildagliptin vs other NIADs. CI, confidence interval; CPRD GOLD, Clinical Practice Research Datalink General practice OnLine Database; IMS DA, Intercontinental Marketing Statistics Disease Analyzer; IR, incidence rate (per 1000 patient-y); IRRs, incidence rate ratios; NA, not available; NE, not evaluated (due to zero cases in the vildagliptin group); NIAD, noninsulin antidiabetic drug; NR, National Registers; OPED, Odense Pharmacoepidemiological Database

≥65 years age group. An increased risk of pancreatic cancer was also seen in IMS DA Germany with 26 cases identified in association with vildagliptin (adjusted IRR, 1.56; 95% CI: 1.05-2.31; adjusted *P*-value 0.91). Furthermore, subgroup analyses in IMS DA Germany showed increased IRRs in patients aged ≥65 years (adjusted IRR 1.97; 95% CI: 1.17-3.31; adjusted *P*-value 0.37) and in women (adjusted IRR 1.97; 95% CI: 1.04-3.75; adjusted *P*-value 1.0).

In the post hoc sensitivity analysis, after exclusion of cancer cases with <365 latency days between vildagliptin or NIAD start and cancer diagnosis, and/or <365 cumulative days of exposure to vildagliptin or NIADs, the number of cases of pancreatic cancer identified in the vildagliptin group decreased markedly in both CPRD GOLD (six to two cases) and IMS DA Germany (26 to 7 cases). A similar decrease in the number of pancreatic cancer cases was seen in the other NIAD groups from 455 to 259 in CPRD GOLD and 433 to 228 in IMS DA Germany. The corresponding adjusted IRR was 2.54 (95% CI: 0.63-10.22 adjusted *P*-value 0.19) in CPRD GOLD and 1.24 (95% CI: 0.58-2.63; adjusted *P*-value 0.58) in IMS DA Germany (Figure 3).

4 | DISCUSSION

The findings from the present multidatabase study revealed that use of vildagliptin is not associated with an increased risk of acute pancreatitis compared with other non-vildagliptin NIADs. No risk estimates were available for France and Denmark, and the data from CPRD GOLD and the Swedish NR were only based on a very low number of vildagliptin-associated pancreatitis cases resulting in risk estimates with wide CIs, while the IMS DA Germany data provided the most precise risk estimate (adjusted IRR 0.89; 95% CI: 0.65-1.24).

Our data are in line with the results from a meta-analysis of randomized studies for vildagliptin,[12] a meta-analysis for DPP-4 inhibitors based on observational data only[13] or of both, observational and RCTs[14] and various noninterventional studies[8,15] which reported no increased risk of acute pancreatitis compared to DPP-4 inhibitor nonusers. In contrast, a recent noninterventional study[5] and a meta-analysis of three large randomized DPP-4 inhibitor outcome trials (none of which included vildagliptin)[6] reported an increased risk of pancreatitis.

The conflicting results on the risk of acute pancreatitis in association with DPP-4 inhibitors as a class are difficult to explain. Some of the discrepancies with noninterventional studies may be explained by different study designs, limited sample size and follow-up and adjustment for confounding factors. Additionally, increased number of pancreatitis cases reported by doctors while prescribing DPP-4 inhibitors could be due to diagnostic bias as a result of warnings by regulatory agencies on the possible pancreatic adverse events associated with DPP-4 inhibitors.[5] Nevertheless, based on the currently available data, there is no evidence suggesting that vildagliptin is associated with an increased pancreatitis risk.

For pancreatic cancer, increased IRR estimates with corresponding lower bounds of the 95% CIs >1 were observed in CPRD GOLD and IMS DA Germany; however, corresponding adjusted *P*-values were >0.05. These findings suggestive of an increased risk have to be interpreted carefully due to several limitations associated with this analysis. The study was initially planned to assess various acute adverse events of interest, but not adverse events with a long latency period such as cancer. Four out of six pancreatic cancer cases identified from the vildagliptin group in CPRD were recorded within <1 year of initiation of vildagliptin therapy. Similarly, 17 (65%) out of 26 cases of pancreatic cancer identified in IMS DA Germany were recorded within <1 year of vildagliptin therapy, and notably in two cases, start of vildagliptin and pancreatic cancer diagnosis were on the same day. A possible causal relationship of pancreatic cancer in such a short period after initiating vildagliptin however, is unlikely. The findings may rather be explained by protopathic bias, that is, nondetected pancreatic cancer may have led to diabetes for which treatment with vildagliptin (or another NIAD) was initiated, thereby mistakenly suggesting an association with current vildagliptin (or NIAD) use. The post hoc sensitivity analyses taking latency time and cumulative exposure into consideration, strikingly reduced the number of cases, both for vildagliptin and other NIADS; accordingly, corresponding adjusted IRRs also relevantly decreased both in CPRD GOLD and IMA DA Germany with 95% CIs crossing 1.

Furthermore, the increased risk of pancreatic cancer seen with vildagliptin in the present study could have been biased due to allocation of all pancreatic cancer cases to vildagliptin, if a case occurred with current vildagliptin exposure, independent of either concomitant or prior (long-term) exposure to other NIADs. Additionally, chance findings due to multiple comparisons and confounding factors also need to be considered.

A meta-analysis of RCTs[6] and various large noninterventional studies[16-18] did not show an increased risk of pancreatic cancer in association with DPP-4 inhibitors.

In conclusion, this study suggests that the use of vildagliptin under real-world conditions is not associated with increased risk of pancreatitis compared with other NIADs. The increased risk of pancreatic cancer observed in some of the per protocol analyses are to be interpreted carefully as this study was originally not designed to assess pancreatic cancer and rather be explained by certain underlying limitations including latency time, chance findings and/or bias and other confounding factors (eg, smoking or alcoholism).

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CONFLICT OF INTEREST

R. W. is an employee of CPRD, London, UK. W. K., C. S. and R. S. are employees and own shares of Novartis Pharma AG, Basel,

Switzerland. S. L. is an employee and shareholder of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey.

AUTHOR CONTRIBUTIONS

All authors assume responsibility for the accuracy of the data interpretation, critically reviewed the manuscript at each draft stage and approved the manuscript for publication. R.W. contributed to study conception, data collection and analysis and interpretation of data. R.S. contributed to study conception, data analysis and interpretation of data; R.W. and R.S. also drafted the outline of the manuscript. S.L.-L., W.K. and C.S. contributed to the interpretation of data and critical review of the manuscript.

DATA ACCESSIBILITY

The data generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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