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BRIEF REPORT

Cardiovascular safety of vildagliptin in patients with type 2 diabetes: A European multi-database, non-interventional post-authorization safety study

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The aim of this non-interventional, multi-database, analytical cohort study was to assess the cardiovascular (CV) safety of vildagliptin vs other non-insulin antidiabetic drugs (NIADs) using real-world data from 5 European electronic healthcare databases. Patients with type 2 diabetes aged ≥18 years on NIAD treatment were enrolled. Adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for the outcomes of interest (myocardial infarction [MI], acute coronary syndrome [ACS], stroke, congestive heart failure [CHF], individually and as a composite) were estimated using negative binomial regression. Approximately 2.8% of the enrolled patients (n = 738 054) used vildagliptin at any time during the study, with an average follow-up time of 1.4 years, resulting in a cumulative current vildagliptin exposure of 28 330 person-years. The adjusted IRRs (vildagliptin [±other NIADs] vs other NIADs) were in the range of 0.61 to 0.97 (MI), 0.55 to 1.60 (ACS), 0.02 to 0.77 (stroke), 0.49 to 1.03 (CHF), and 0.22 to 1.02 (composite CV outcomes). The IRRs and their 95% CIs were close to 1, demonstrating no increased risk of adverse CV events, including the risk of CHF, with vildagliptin vs other NIADs in real-world conditions.

KEYWORDS

cardiovascular disease, DPP-4 inhibitor, observational study, type 2 diabetes, vildagliptin

1 | INTRODUCTION

Cardiovascular (CV) disease is a common cause of mortality among individuals with type 2 diabetes (T2D).[1] Coexistence of T2D and CV complications entails use of antidiabetic agents without additional CV safety burden. Regulatory authorities are rigorously evaluating the CV safety of newer antidiabetic agents and have issued guidance for conducting CV safety outcome studies.[2,3] Dipeptidyl peptidase-4 (DPP-4) inhibitors, since their launch in 2006, have gained wide acceptance globally for their favourable safety profile, particularly, for their low risk of hypoglycaemia and weight gain.[4]

Large CV outcome studies on DPP-4 inhibitors, including the SAVOR-TIMI 53, TECOS and EXAMINE trials (enrolling >36 000 patients), demonstrated no increased risk of major adverse CV events.[5–7] Additionally, a comprehensive meta-analysis of independently adjudicated CV events, including data from 40 randomized phase III/IV studies (enrolling >17 000 patients), has provided reassuring evidence of the CV safety of vildagliptin[8]; however, increased hospitalizations for heart failure (HF) were observed in patients receiving saxagliptin (SAVOR TIMI-53)[5] and

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alogliptin (EXAMINE)[7], thereby raising a safety concern regarding some DPP-4 inhibitors and the risk of HF. By contrast, findings from the TECOS study (sitagliptin),[6] and the VIVIDD study (vildagliptin)[9] did not show an increased risk of hospitalization for HF.

The present non-interventional study assessed whether vildagliptin (either as a single agent or as a fixed-dose combination with metformin) was associated with an increased risk of CV adverse events (AEs) including myocardial infarction (MI), acute coronary syndrome (ACS), stroke and congestive heart failure (CHF), individually, and as a composite outcome, compared with other non-insulin antidiabetic drugs (NIADs) in a real-world setting.

2 | MATERIALS AND METHODS

2.1 | Study design and databases

The present study had a population-based, analytical, multi-database cohort design with secondary use of data from 5 European electronic healthcare databases: the Clinical Practice Research Datalink General practice OnLine Database (CPRD GOLD), UK,[10] the Intercontinental Marketing Statistics (IMS) Disease Analyser (IMS DA), Germany,[11] the IMS DA, France,[11] the Odense Pharmaco-Epidemiological Database (OPED), Denmark,[12] and the Swedish National Registers (NR)[13] to assess the CV safety of vildagliptin (± other NIADs) relative to other NIADs. Additional information on the methodology is provided in File S1.

2.2 | Patients and study assessments

Patients with T2D aged ≥18 years with a new prescription of NIAD (including biguanides, sulphonylureas, glinides, thiazolidinediones, DPP-4 inhibitors, glucagon like peptide-1 analogues, α-glucosidase inhibitors, sodium glucose co-transporter-2 inhibitors, and amylin analogues) on or after January 1, 2005 were enrolled. The study included both prevalent and incident NIAD users. Patients with a history of cancer (excluding non-melanoma skin cancer), HIV/AIDS, and/or history of insulin use prior to the start of follow-up were excluded.

Patients were followed up from their index date (day of the first NIAD prescription post enrolment) to the earliest of the following: end of the study period; transfer out of the database; death; or date of first insulin prescription. Patient demographics including age, sex, NIAD use, duration of diabetes, year of cohort entry, specific comorbidities, and exposure to other co-medications of interest within 6 months prior to the start of follow-up were collected at the index date. Cardiac safety outcomes included incident MI, ACS, stroke and CHF, individually and as a composite outcome. Read/International Classification of Diseases (ICD)-10 codes were used to identify the outcomes of interest; endpoints were studied separately across databases. "Incident outcomes" were defined as the occurrence of a first event after start of follow-up, excluding those patients with a recording of the outcome of interest on or before the start of follow-up.

2.3 | Statistical analysis

It was estimated that 20 000 patient-years of exposure to vildagliptin would provide 80% power (2-sided $\alpha = .05$) to detect a 2-fold increase in risk for an event with an incidence rate (IR) of 1.0 per 1000 patient-years, assuming at least 6 patients would be accrued in the comparator NIAD cohort for each patient in the vildagliptin cohort. Demographics and other baseline characteristics were descriptively summarized as database and NIAD cohorts. The period of follow-up of patients was divided into periods of NIAD use. Patients could move over time between exposure categories and between NIAD types (vildagliptin, other NIAD); patients using vildagliptin concurrently with other NIADs were included in the vildagliptin cohort. Subgroup analyses were conducted by age (18-39, 40-64, and ≥65 years) and sex (men, women) in the cohort of patients with concomitant use of vildagliptin and TZDs and in patients with impaired renal function. Age- and sex-adjusted incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) for each of the individual outcomes were estimated using negative binomial regression. Statistical significance was assessed using adjusted *P* values accounting for the false discovery rate.[14]

2.4 | 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 Clinical Practice Research Datalink (CPRD) Group. Further approvals were obtained from the Independent Scientific Advisory Committee (ISAC; for CPRD 09_069R) and the Danish Health Board.

3 | RESULTS

3.1 | Baseline characteristics

Approximately 2.8% of the enrolled patients (n = 738 054) received vildagliptin (± other NIADs) at any time during the study. The average follow-up period for vildagliptin users was 1.4 years, resulting in 28 330 patient-years of cumulative current exposure to vildagliptin. Overall, the baseline characteristics were similar in all the cohorts across databases (Table 1). Overall, there were fewer women (44.0%), except in OPED (57.7% vs 42.3%). Patients in the vildagliptin cohort were slightly younger and had a higher BMI. Almost 50% of patients were using lipid-lowering drugs. Vildagliptin-exposed patients had a slightly lower prevalence of CV comorbidities. The comorbidities and co-medications at the start of follow-up were similar in the cohorts and are presented in Tables S1 and S2 (Supporting Information), respectively.

3.2 | Outcomes

3.2.1 | Myocardial infarction

The adjusted IRRs for MI (vildagliptin vs other NIADs) were <1 (range: 0.61-0.97) across the 5 databases (Figure 1); however, there was no statistically significant difference between the 2 groups

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	
	Vildagliptin N = 1990	NIADs N = 211 327	Vildagliptin N = 13 286	NIADs N = 206 576	Vildagliptin N = 2982	NIADs N = 41 911	Vildagliptin N = 923	NIADs N = 23 725	Vildagliptin N = 569	NIADs N = 254 515
Age, years	59 ± 12	63 ± 14	63 ± 12	65 ± 13	62 ± 11	63 ± 12	61 ± 11	64 ± 13	60 ± 10	65 ± 12
Age, n (%)										
18 to 39 years	108 (5.4)	9484 (4.5)	367 (2.8)	5829 (2.8)	65 (2.2)	1082 (2.6)	33 (3.6)	940 (4.0)	15 (2.6)	4270 (1.7)
40 to 64 years	1255 (63.1)	101 569 (48.1)	6864 (51.7)	87 379 (42.3)	1721 (57.7)	21 349 (50.9)	516 (55.9)	11 102 (46.8)	372 (65.4)	125 609 (49.4)
≥65 years	627 (31.5)	100 274 (47.4)	6055 (45.6)	113 368 (54.9)	1196 (40.1)	19 480 (46.5)	374 (40.5)	11 683 (49.2)	182 (32.0)	124 636 (49.0)
Women, n (%)	842 (42.3)	90 815 (43.0)	5703 (42.9)	98 040 (47.5)	1174 (39.4)	17 765 (42.4)	572 (62.0)	13 700 (57.7)	216 (38.0)	104 933 (41.2)
Men, n (%)	1148 (57.7)	120 512 (57.0)	7583 (57.1)	108 536 (52.5)	1808 (60.6)	24 146 (57.6)	351 (38.0)	10 025 (42.3)	353 (62.0)	149 582 (58.8)
BMI, kg/m^2	33 ± 7	31 ± 7	32 ± 6	31 ± 6	-	-	-	-	31 ± 6	30 ± 5
BMI, n (%)										
<20 kg/m^2	9 (0.5)	2685 (1.3)	32 (0.2)	594 (0.3)	-	-	-	-	3 (0.5)	1460 (0.6)
20 to 25 kg/m^2	165 (8.3)	26 700 (12.6)	486 (3.7)	8308 (4.0)	-	-	-	-	68 (12.0)	42 751 (16.8)
26 to 29 kg/m^2	591 (29.7)	68 791 (32.6)	1541 (11.6)	22 431 (10.9)	-	-	-	-	140 (24.6)	68 748 (27.0)
>30 kg/m^2	1222 (61.4)	110 178 (52.1)	2649 (19.9)	32 308 (15.6)	-	-	-	-	249 (43.8)	96 251 (37.8)
Unknown	3 (0.2)	2973 (1.4)	8578 (64.6)	142 935 (69.2)	-		-	-	109 (19.2)	45 305 (17.8)
Diabetes duration, years	4 ± 5	4 ± 5	1 ± 3	1 ± 3	1 ± 1	1 ± 1	2 ± 3	2 ± 3	4 ± 5	4 ± 5

Data are expressed as mean ± standard deviation, unless otherwise indicated.

	Vilda Events (IR)	Other NIADs Events (IR)	Adjusted incidence rate ratio** (95% CI)	P value
Myocardial Infarction				
UK CPRD Gold	11 (3.1)	3436 (4.5)	0.71 (0.39–1.30)	1*
Germany IMS DA	147 (8.4)	4036 (9.3)	0.78 (0.64–0.95)	0.02
France IMS DA	9 (2.2)	209 (2.3)	0.97 (0.16–5.83)	1*
Denmark OPED	7 (6.4)	457 (7.5)	0.78 (0.36–1.70)	1*
Sweden NR	4 (4.6)	8162 (8.2)	0.61 (0.23–1.63)	1*
Acute coronary syndrome				
UK CPRD Gold	12 (3.4)	4193 (5.6)	0.67 (0.38–1.21)	0.19
Germany IMS DA	143 (8.2)	4273 (9.9)	0.72 (0.60–0.88)	<0.01
France IMS DA	11 (2.7)	232 (2.6)	1.60 (0.29–8.81)	0.59
Denmark OPED	8 (7.4)	448 (7.4)	0.91 (0.44–1.90)	0.8
Sweden NR	4 (4.7)	9143 (9.2)	0.55 (0.21–1.45)	0.23
Stroke				
UK CPRD Gold	13 (3.6)	3925 (5.0)	0.77 (0.45–1.34)	1*
Germany IMS DA	185 (10.5)	6408 (15.0)	0.59 (0.50–0.70)	0.02*
France IMS DA	5 (1.2)	159 (1.8)	0.02 (0.00–0.12)	0.03*
Denmark OPED	4 (3.6)	503 (8.1)	0.42 (0.16–1.12)	1*
Sweden NR	1 (1.2)	8441 (8.5)	0.15 (0.02–1.08)	1*
CHF				
UK CPRD Gold	10 (2.7)	4669 (5.9)	0.51 (0.27–0.95)	1*
Germany IMS DA	481 (30.4)	13915 (36.3)	0.72 (0.64–0.81)	0.02*
France IMS DA	14 (3.4)	603 (6.8)	0.49 (0.28–0.85)	0.3*
Denmark OPED	14 (12.6)	687 (11.3)	1.03 (0.59–1.77)	0.93
Sweden NR	2 (2.3)	4395 (4.4)	0.61 (0.15–2.42)	1*
Composite of CV events				
UK CPRD Gold	41 (13.2)	9432 (14.7)	0.92 (0.67–1.27)	1*
Germany IMS DA	738 (53.1)	21488 (65.0)	0.66 (0.59–0.73)	0.02*
France IMS DA	36 (9.2)	1203 (14.2)	0.22 (0.10–0.47)	0.03*
Denmark OPED	26 (31.0)	1353 (28.7)	1.02 (0.69–1.50)	1.0*
Sweden NR	12 (14.3)	21700 (22.4)	0.69 (0.39–1.22)	1.0*

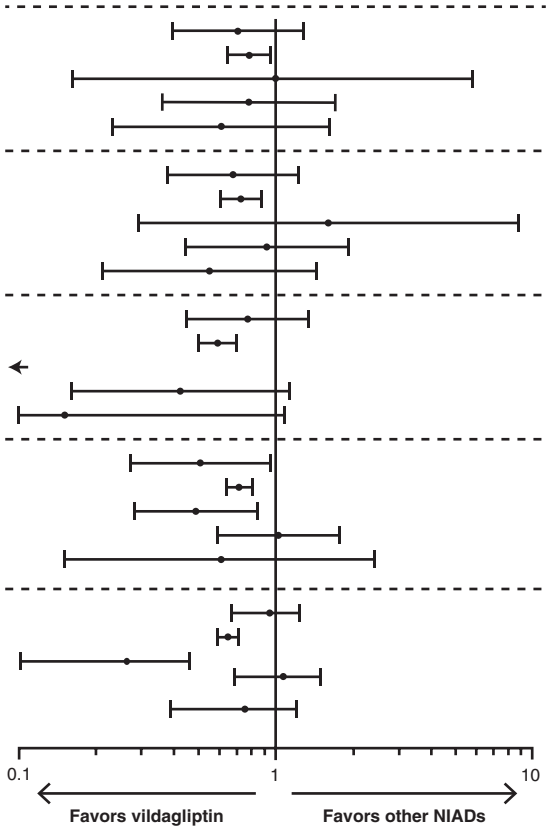

FIGURE 1 Incidence rate ratios of CV events for current use of vildagliptin vs other NIADs. Vilda, vildagliptin. *False discovery rate adjusted *P* values. **Adjusted for age and sex. IRRs for acute coronary syndrome in CPRD GOLD were also adjusted for co-medications; comorbidities; exposure to other DPP-4 inhibitors; SUs; and TZDs; diabetes duration; BMI; alcohol consumption status; smoking status; and year of cohort entry. IRRs for CHF in the Swedish NR were also adjusted for exposure to other DPP-4 inhibitors. For composite endpoints, IRRs in the Swedish NR were also adjusted for history of cardiomyopathy, hyperlipidaemia, and time-dependent exposure to biguanides, glinides and DPP-4 inhibitors

except for IMS DA, Germany (0.78, 95% CI 0.64-0.95; adjusted *P* value = .02).

3.2.2 | Acute coronary syndrome

The adjusted IRRs for ACS (vildagliptin vs other NIADs) were 0.55 to 1.60 (Figure 1). The IRR for IMS DA, France was >1 (1.60, 95% CI 0.29-8.81). There was no statistically significant difference between the 2 groups except for IMS DA, Germany (0.72, 95% CI 0.60-0.88; adjusted *P* value <.01).

3.2.3 | Stroke

The adjusted IRRs for stroke (vildagliptin vs other NIADs) were 0.02 to 0.77 (Figure 1). All adjusted IRR estimates were <1, with no statistically significant difference between the 2 groups, except for IMS DA, Germany (0.59, 95% CI 0.50-0.70; adjusted *P* value = .02) and IMS DA, France (0.02, 95% CI 0.00-0.12; adjusted *P* value = .03).

3.2.4 | Congestive heart failure

The adjusted IRRs for CHF (vildagliptin vs other NIADs) were 0.49 to 1.03. In 3 databases, the IRR and the upper limit of the 95% CI were <1, with the IRR in 1 database reaching statistical significance: CPRD GOLD (0.51, 95% CI 0.27-0.95), IMS DA, Germany (0.72, 95% CI 0.64-0.81; adjusted *P* value = .02), and IMS DA, France (0.49, 95% CI 0.28-0.85).

3.2.5 | Composite of CV events

The IRRs for the composite CV endpoint with vildagliptin vs other NIADs were 0.22 to 1.02. The IRRs and the upper limit of the 95% CIs were <1 for 2 databases: IMS DA, Germany (0.66, 95% CI 0.59-0.73; adjusted *P* value = .02), and IMS DA, France (0.22, 95% CI 0.10-0.47). Furthermore, no evidence of increased risk of individual outcomes or the composite of any CV event were observed in the subgroup analyses across the 5 databases (Tables S3-S7, Supporting Information).

4 | DISCUSSION

The present non-interventional, real-world data study with ~28 330 patient-years' exposure to vildagliptin provides further evidence of the CV safety of vildagliptin and that exposure to vildagliptin is not associated with an increased overall CV risk or risk of any of the studied CV outcomes (MI, ACS, stroke and CHF), when compared

with other NIADs. Recent findings from the SAVOR TIMI-53[5] and EXAMINE[7] trials raised questions regarding the safety of DPP-4 inhibitors with respect to HF. The present study showed that vildagliptin had a good safety profile, without increased risk of CHF or hospitalizations for HF across the 5 databases (adjusted IRR estimate ranged from 0.51 to 1.03). These results complement the data obtained from a large CV safety meta-analysis of vildagliptin (vs placebo and all non-vildagliptin treatments) including HF events (leading to hospitalization or new onset of HF [0.43% vs 0.45%; hazard ratio 1.08, 95% CI 0.68-1.70]),[8] the TECOS trial data (3.1% vs 3.1%; hazard ratio 1.00, 95% CI 0.83-1.20; $P = .98$)[6] and add further evidence with regard to the safety of DPP-4 inhibitors with respect to HF.

The generalizability of the data from CV outcome studies has been a matter of continuous debate. By virtue of their design, they focused on establishing safety in comparison with placebo, thus recruiting patients with high CV risk for faster accrual of events. By contrast, the broad inclusion/exclusion criteria of the present study, that is, any patient aged ≥18 years with an established diagnosis of T2D, constitute a real-world population. The population of the present study is more reflective of the majority of individuals with T2D whom clinicians care for on a daily basis.

The following limitations should nevertheless be considered while interpreting the results. Vildagliptin may have been preferentially prescribed to patients inadequately controlled with other NIADs, as a step before initiating insulin. The start of follow-up was earlier in calendar time in the group of non-vildagliptin NIAD users, while patients initiating vildagliptin at baseline are incident users; this may ultimately create a bias towards higher AE rates for vildagliptin users. The present study compared the IRs between vildagliptin and other NIAD therapies during period of current use; however, the IRs could also have been affected by prior exposure to antidiabetic agents. Data from the 5 databases are presented separately because differences in coding, healthcare settings and medical practice across databases limits the pooling of results. The analyses could not be adjusted for various potential confounding variables (such as smoking, alcohol use) because of the low numbers of patients with the outcome or with missing information on some variables across databases. Lastly, the average follow-up time on vildagliptin was relatively short at 1.4 years, therefore, these data do not provide information on the risks associated with longer-term therapy with vildagliptin.

In summary, the CV outcome analyses indicate that vildagliptin is not associated with an increased CV risk, including the risk of CHF, compared with other NIADs in real-world conditions. The current data complement the earlier CV safety meta-analysis of vildagliptin[9] and reflect the CV safety of vildagliptin in a broad population of patients with T2D.

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Conflict of interest

R. W. is an employee of CPRD, London, UK. F. d. V. was a senior epidemiologist at the CPRD, London, UK at the time the study was conducted. 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. C. C. was associated with Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA at the time the study was conducted; he is currently with Sanofi, Bridgewater, New Jersey. Novartis Pharma AG sponsored the study and had input into the study design, interpretation and writing of the report. The sponsor was not involved in data collection or analysis.

Author contributions

All authors assume responsibility for the accuracy of the data interpretation and approved the manuscript for publication. R. W. and F. d. V. contributed to study conception, data collection and analysis. R. S. contributed to study conception and data analysis; R. W. and R. S. drafted the first version of the manuscript; F. d. V., W. K., C. S., S. L. and C. C. helped with the critical review and finalization of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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