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ORIGINAL RESEARCH

Real-Life Effectiveness and Tolerability of Vildagliptin and Other Oral Glucose-Lowering Therapies in Patients with Type 2 Diabetes in Germany

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ABSTRACT

Introduction: Metformin is an established first-line treatment for patients with type 2 diabetes mellitus (T2DM), but treatment intensification with other oral antidiabetes drugs (OADs) is usually required over time. Effectiveness of diabetes control with vildagliptin and vildagliptin/metformin was a 1-year, large observational study of 45,868 patients with T2DM across 27 countries which assessed effectiveness and safety of vildagliptin as add-on therapy to other OADs versus other comparator OAD combinations. Here, we present the data from Germany.

Methods: Patients inadequately controlled with monotherapy were eligible only after the add-on treatment was finalized. Patients were assigned to either vildagliptin or comparator OADs [sulfonylureas, thiazolidinediones, glinides, α-glucosidase inhibitors or metformin, excluding dipeptidyl peptidase 4 (DPP-4) inhibitors or glucagon-like peptide-1 mimetic/analogues]. The primary efficacy endpoint was the proportion of patients achieving a glycosylated hemoglobin (HbA_{1c}) reduction of >0.3% without peripheral edema, hypoglycemia, discontinuation due to a gastrointestinal event or weight gain ≥5%. One secondary efficacy endpoint was the proportion of patients achieving HbA_{1c} <7% without hypoglycemia and weight gain. Change in HbA_{1c} from baseline to study endpoint and safety were assessed.

Results: Of 8,887 patients enrolled in Germany, 6,679 received vildagliptin and 1,695 received other OADs. The mean ± SD baseline age, HbA_{1c}, and T2DM duration were 62.8 ± 11.0 years, 7.7 ± 1.2%, and 5.8 ± 4.9 years, respectively. The proportion of patients achieving the primary (34.5% vs. 30.5%, $p < 0.01$) and secondary (25.4% vs. 21.7%, $p = 0.01$)

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endpoints was higher with vildagliptin than comparator OADs. Vildagliptin showed a numerically greater reduction in HbA_{1c} (0.7%) from baseline vs. comparator OADs (0.6%). The overall incidence of adverse events was similar.

Conclusion: In real life, treatment with vildagliptin is associated with a higher proportion of patients reaching target HbA_{1c} without hypoglycemia and weight gain compared with other OADs in Germany.

Keywords: Diabetes; Dipeptidyl peptidase 4 inhibitors; Endocrinology; Glycosylated hemoglobin; Observational study; Oral antidiabetes agents; Real life; Type 2 diabetes mellitus; Vildagliptin

INTRODUCTION

The prevalence of diabetes in Germany has been predicted to increase in the next two decades with about 3.9 million people aged 55–74 years affected by type 2 diabetes mellitus (T2DM) in 2030 [1]. This would result in a 79% increase in annual costs between 2010 and 2040 [2].

T2DM is a progressive disease and its long-term management warrants intensification of treatment and a patient-centric approach based on benefits and risks for the individual concerned [3]. Metformin is often recommended as the first-line treatment for patients with T2DM, but addition of other antihyperglycemic agents is usually required over time [3]. Sulfonylureas (SUs) are commonly used in patients when metformin monotherapy fails to achieve glycemic control. However, use of SUs is associated with adverse effects such as hypoglycemia and weight gain [4].

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control by increasing α- and β-cell responsiveness to glucose. Vildagliptin as monotherapy or in combination has been shown to be weight neutral with no additional risk of hypoglycemia [5–7]. The weight neutrality and low risk of hypoglycemia with DPP-4 inhibitors has also been confirmed from a recent meta-analysis that assessed the safety and efficacy of all available second-line antihyperglycemic therapies in patients with T2DM inadequately controlled by metformin monotherapy [8].

Pragmatic real-life observational studies are designed to provide a closer look into routine clinical practice and thus can serve as additional evidence to randomized clinical trials, which are conducted in a predefined patient population under controlled conditions [9–11].

Effectiveness of Diabetes control with vildaGliptin and vildagliptin/mEtformin (EDGE) was a prospective, 1-year, real-life observational study conducted across 27 countries that assessed the effectiveness and tolerability of vildagliptin added to monotherapy with an oral antidiabetes drug (OAD) (vildagliptin cohort), compared with other OAD combinations (comparator OAD cohort) [12]. Here, we present the results of a post hoc analysis from the EDGE study in patients with T2DM in Germany.

METHODS

Study Design and Patients

Of the 45,868 patients enrolled in the EDGE study, 8,887 patients were enrolled in Germany (Fig. 1a). Patients with T2DM, aged >18 years inadequately controlled on OAD monotherapy with an SU, metformin, thiozolidinediones (TZD), glinide or α-glucosidase inhibitor were

eligible. Patients receiving DPP-4 inhibitors other than vildagliptin, incretin mimetics/analogues or insulin, requiring three or more OADs, or having a history of hypersensitivity to study drugs were excluded.

The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors. All participants provided a written or oral informed consent before participation in the study.

Physicians chose antidiabetic treatment for their patients at their own discretion. To avoid bias for a particular choice of treatment by the physician, enrolment of patients was agreed only after the treatment decision was made. The term 'index therapy' was used to represent the combination treatment initiated at enrolment.

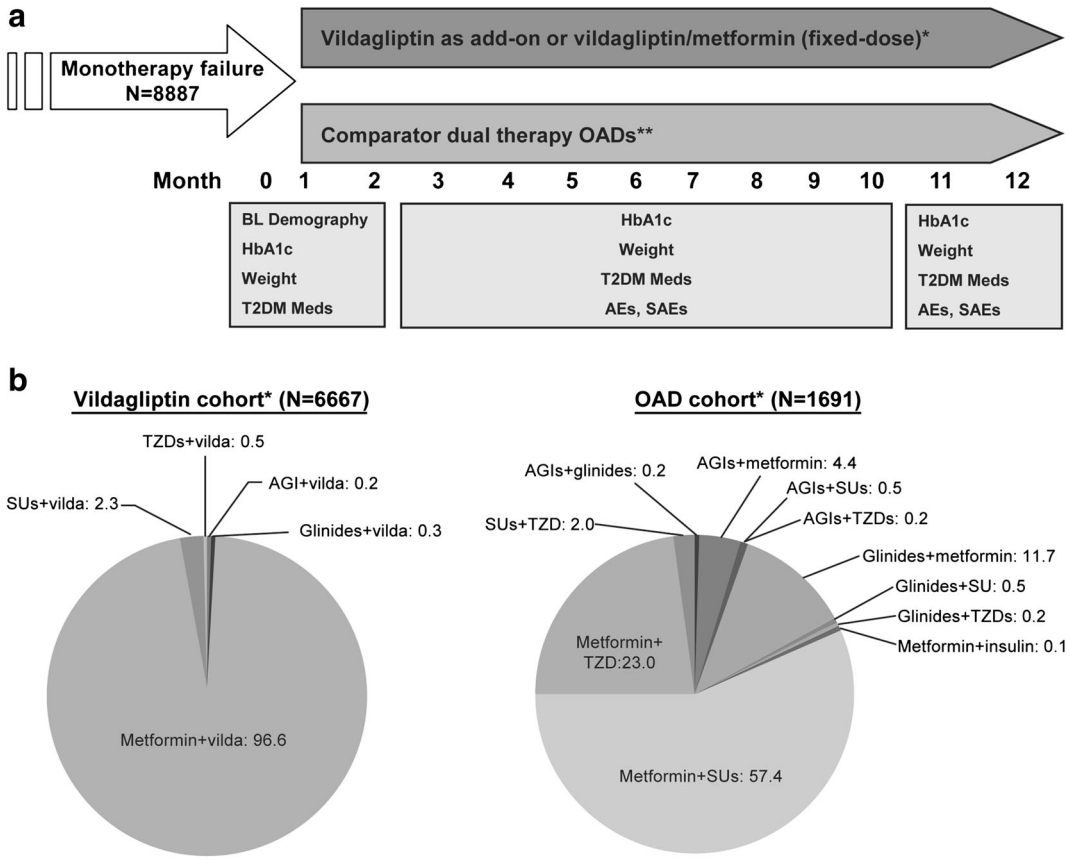

Fig. 1 **a** Study design of German subgroup analysis. *Vildagliptin cohort: T2DM patients newly initiating vildagliptin as add-on dual therapy or newly initiating vildagliptin/metformin (fixed-dose) from non-vildagliptin monotherapy. **Comparator OAD cohort: T2DM patients newly initiating therapy with OADs other than vildagliptin (defined as SU, metformin, TZDs, metiglinides, α-glucosidase inhibitors as add-on dual therapy) except as add-on to vildagliptin, other DPP-4 inhibitors, or GLP-1 mimetics/analogues. *AEs* Adverse events, *BL* baseline, HbA_{1c} glycosylated hemoglobin, *OADs* oral antidiabetes drugs, *SAEs* severe adverse events, *T2DM* type 2 diabetes mellitus, *TZDs* thiozolidinediones. **b** Percentage of patients taking index medication (ITT population). *AGI* α-glucosidase inhibitor, *ITT* intention-to-treat, *OAD* antidiabetes drugs, *SU* sulphonylurea, *TZD* thiazolidinedione, *vilda* vildagliptin. *Initial (prior) monotherapy is given first within a treatment. For 12 patients in the vildagliptin cohort and 4 in the comparator cohort, it was not possible to identify the index medication

For any index therapy, a fixed-dose combination, if available, was allowed. Details of the subjects and study design are reported elsewhere [12].

Efficacy and Safety Assessments

The primary efficacy endpoint was the proportion of patients having a treatment response of HbA_{1c} reduction >0.3% from baseline to 12-month endpoint without peripheral edema, hypoglycemic event, discontinuation due to a gastrointestinal event, or weight gain ≥5%. One of the secondary efficacy endpoints was the proportion of patients achieving HbA_{1c} <7.0% without hypoglycemic events and weight gain ≥3% in patients with baseline HbA_{1c} ≥7% at 12-month endpoint (responder rate). Change in HbA_{1c} from baseline to 12-month endpoint (analysis not pre-specified in the protocol) and the number of hypoglycemic events were also evaluated in this post hoc analysis. Hypoglycemia was defined as presence of symptoms suggestive of hypoglycemia including mild and severe events that resolved promptly on administration of oral carbohydrate. Safety assessments including body weight, adverse events (AEs) and serious AEs (SAEs) were recorded.

Statistical Analysis

Descriptive statistics were used for these post hoc analyses. The per protocol (PP) population was a subset of the intention-to-treat (ITT) population without protocol deviation and was used for the analysis of efficacy endpoints. Data were censored if patients changed index therapy. A binary logistic regression model was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for the probability of success in achieving the primary and secondary endpoints with the vildagliptin cohort versus the comparator OAD cohort. Patients whose outcomes could not be categorized as a success or failure (e.g., due to missing HbA_{1c} or body weight data at the 12-month endpoint) were considered non-evaluable. These non-evaluable patient data were considered failures in the calculation of the OR for success. The OR expresses odds in favor of success with vildagliptin combination relative to odds in favor of success with comparator OADs. Only unadjusted ORs were reported for the primary and secondary endpoints in this post hoc analysis. The change in HbA_{1c} in both groups was not pre-specified in the protocol, HbA_{1c} drop was adjusted with HbA_{1c} baseline by using the analysis of co-variance (ANCOVA) model.

RESULTS

Patient Demographics and Baseline Characteristics

Of the 8,887 patients enrolled from Germany in the EDGE study, 513 patients (377 in the vildagliptin cohort and 124 in the comparator OAD cohort plus 12 without cohort assigned) were excluded due to inadequate source documentation or problems with quality or accuracy of data entry. The remaining ITT population, used for baseline demographics and safety analyses, comprised patients receiving dual therapy with newly prescribed vildagliptin ($n = 6,679$) or a non-vildagliptin OAD added to prior monotherapy ($n = 1,695$) (Table 1). The PP population comprised 6,501 patients in the vildagliptin cohort, and 1,686 patients in the comparator OAD cohort.

The demographic and baseline characteristics of patients in the ITT population are summarized in Table 2. After initiating combination therapy 6,439 patients

Table 1 Patient populations and flow

Enrolled[a]	8,887	
No cohort assignment	12	
	Vildagliptin cohort	**Comparator OAD cohort**
Assigned to	7,056	1,819
No adequate source documentation at site; lack of quality and accuracy of data entry	377	124
ITT[b]	6,679	1,695
Patients completed, *n* (%)	4,934 (73.9)	1,386 (81.8)
Patients discontinued, *n* (%)	1,745 (26.1)	309 (18.2)
Lost to follow-up	821 (47.0)	129 (41.7)
Administrative	664 (38.1)	147 (47.6)
Unsatisfactory therapeutic effect	84 (4.8)	6 (1.9)
Subject withdrew consent	49 (2.8)	12 (3.9)
Patients with ≥1 protocol deviation	48 (2.8)	3 (1.0)
Adverse events	32 (1.8)	2 (0.6)
Abnormal laboratory values	16 (0.9)	2 (0.6)
Subject's condition no longer requires study drug	15 (0.9)	0
Death	13 (0.7)	8 (2.6)
Missing	2	0
Abnormal test procedure results	1 (0.1)	0
Per protocol[c]	6,501	1,686

OAD oral antidiabetes drugs

[a] The enrolled population includes all patients who gave documented informed consent

[b] The intent-to-treat (ITT) population is a subset of the enrolled population and includes all patients who were assigned to new treatment at study start

[c] The per protocol (PP) population is a subset of the ITT population, who completed the study without any major protocol deviation. It was used for the analyses of effectiveness endpoints

(96.6% of the vildagliptin cohort) received metformin–vildagliptin and 971 patients (57.4% of the comparator OAD cohort) received metformin–SUs (Fig. 1b).

Efficacy and Safety Assessments

The primary endpoint was reached in 34.5% and 30.5% of patients in the vildagliptin and comparator OAD cohorts, respectively, with unadjusted OR 1.2 (95% CI 1.07, 1.35; $p < 0.01$) significantly in favor of vildagliptin. In the vildagliptin cohort, a higher proportion of patients reached the responder rate of HbA_{1c} <7.0% without hypoglycemia and weight gain when compared with comparator OAD cohort (vildagliptin, 25.4%; comparator OADs, 21.7%), with an unadjusted OR of 1.23 (95%

Table 2 Demographic and patient baseline characteristics [intention-to-treat (ITT) population]

Characteristic	Vildagliptin cohort ($N = 6,679$)	Comparator OAD cohort ($N = 1,695$)	Total ($N = 8,374$)
Age (years)	62.4 ± 11.1	64.5 ± 10.6	62.8 ± 11.0
Gender, *n* (%)			
Male	3,641 (54.5)	888 (52.4)	4,529 (54)
Female	3,038 (45.5)	807 (47.6)	3,845 (46)
BMI (kg/m^2)	30.9 ± 5.5	30.0 ± 5.1	30.7 ± 5.4
HbA_{1c} (%)	7.8 ± 1.2	7.6 ± 1.2	7.7 ± 1.2
Duration of T2DM (years)	5.7 ± 4.9	6.2 ± 5.0	5.8 ± 4.9

Data are mean ± SD unless specified otherwise

BMI body mass index, *ITT* intention-to-treat, *SD* standard deviation, *T2DM* type 2 diabetes mellitus, *HbA_{1c}* glycosylated hemoglobin, *OAD* oral antidiabetes drugs

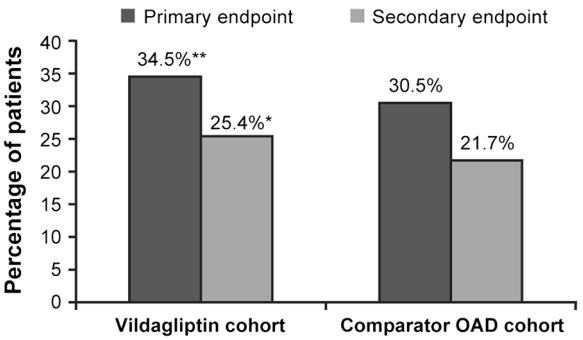

Fig. 2 Percentage of patients achieving primary and secondary efficacy endpoints. $^{**}p < 0.01$ for unadjusted odds ratio of 1.2 (95% CI 1.07, 1.35) in favor of vildagliptin. $^{*}p = 0.01$ for unadjusted odds ratio of 1.2 (95% CI 1.05, 1.43) in favor of vildagliptin. Primary endpoint: proportions of patients experiencing decreased HbA_{1c} of >0.3%, without hypoglycemia, weight gain, peripheral edema, or gastrointestinal side-effects. Secondary endpoint: proportion of patients reaching HbA_{1c} <7% with no hypoglycemic events and weight gain. *OAD* oral antidiabetes drugs, *HbA_{1c}* glycosylated hemoglobin

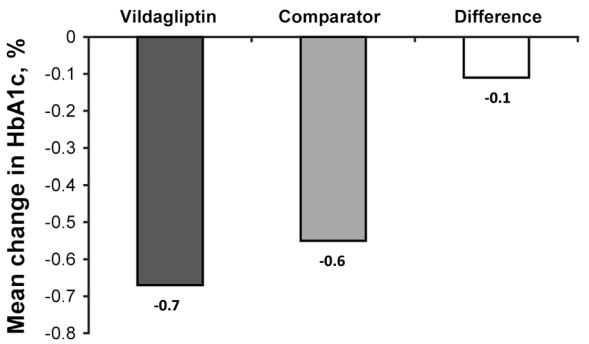

Fig. 3 Mean change in glycosylated hemoglobin (HbA_{1c}) from baseline to study endpoint

CI 1.05, 1.43; $p = 0.01$) in favor of vildagliptin (Fig. 2).

After 1-year of treatment, HbA_{1c} decreased in both cohorts from baseline to endpoint (−0.7% in the vildagliptin cohort vs. −0.6% in the comparator OAD cohort), with a mean treatment difference of −0.11% (95% CI −0.17, −0.06) in favor of vildagliptin (Fig. 3).

Overall, 342 patients (5.1%) in the vildagliptin cohort and 86 patients (5.1%) in the comparator OAD cohort reported AEs. The overall occurrence of SAEs was low in both the cohorts: 62 patients reported SAEs in the vildagliptin cohort (0.9%) and 16 in the comparator cohort (0.9%). However, none of the SAEs were suspected to be drug-related. A total of eight patients (0.1%) reported hypoglycemia in the vildagliptin cohort vs. four patients in the comparator OAD cohort (0.2%). The mean decrease in body weight from

baseline was 1.21 kg in the vildagliptin cohort vs. 0.37 kg in the comparator OAD cohort with a between-treatment difference of −0.84 kg ($p < 0.001$).

DISCUSSION

The present study provides real-life data regarding the effectiveness and tolerability of vildagliptin combinations compared with other OAD combinations in patients with T2DM in Germany. The results demonstrate that vildagliptin as an add-on to other OAD monotherapy provides better glycemic control than comparator OADs, without peripheral edema, hypoglycemic events, discontinuation due to a gastrointestinal event, or weight gain ≥5%.

The responder rate of HbA_{1c} <7.0% without hypoglycemia and weight gain observed in the present analyses is consistent with those from a post hoc analysis of data from a 2-year, randomized controlled study that compared vildagliptin 50 mg bid with glimepiride as add-on to metformin [13]. In that study, the proportion of patients reaching the composite endpoint was higher in the vildagliptin-treated patients (29.8%) than glimepiride-treated patients (19.4%) [13].

The HbA_{1c} drop seen in the present post hoc analysis (−0.7% with vildagliptin cohort vs. −0.6% with comparator OAD) is comparable with the HbA_{1c} drop observed with vildagliptin vs. other OADs (−0.9% vs. −0.6%) in a large 6-month observational study in Germany [14].

Current treatment guidelines recommend that it is important to avoid weight gain and hypoglycemia in addition to achieving glycemic targets [3]. The findings from the present post hoc analyses demonstrated that treatment with vildagliptin resulted in more patients achieving glycemic targets without weight gain and increased risk of hypoglycemia, which is in line with those recommendations.

Overall, vildagliptin was well tolerated and had a good safety profile. Additionally, no new safety findings or those related to any recently discussed events in a controlled, randomized setting in high-risk cardiovascular (CV) populations treated with DPP-4 inhibitors such as increased hospitalization due to congestive heart failure (CHF) [15, 16], were identified in this cohort. Treatment with vildagliptin is not usually associated with an increased risk of hypoglycemia. In the present study there were slightly more hypoglycemic events with other OADs as compared with vildagliptin. It should be noted that voluntary reporting of AEs might have led to unnoticed or under-reported events, which is also a limitation of the present study.

Furthermore, being an open-label, real-life, observational study by design, physicians could have selected any drug based on their clinical judgment, resulting in an imbalance in treatment arms, clearly favoring the DPP-4 inhibitor, vildagliptin (6,679 patients in the vildagliptin cohort vs. 1,695 patients in the comparator OAD cohort). Moreover, the patients were recruited both in specialty centers and centers of routine care, which might have resulted in poor quality and missing data, thus, impacting the overall results. Such data should have ideally been excluded from the effectiveness analyses.

CONCLUSION

The study results demonstrate that in real-life clinical practice, vildagliptin is associated with a numerically greater HbA_{1c} drop and a higher proportion of patients reaching target HbA_{1c}

without tolerability findings compared with other OADs in patients with T2DM in Germany.

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All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. R. Göke has received fees for consultancy, advisory boards, speaking, travel or accommodation from AstraZeneca, Bayer, Berlin-Chemie, BMS, Lilly, MSD, Novartis, Sanofi Aventis, Roche and UCB.

M. Dworak is an employee of Novartis and owns stocks within the company.

G. Bader is an employee of Novartis.

Compliance with ethics. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors. All participants provided a written or oral informed consent before participation in the study.

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