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ORIGINAL RESEARCH

Microvascular Outcomes in Patients with Type 2 Diabetes Treated with Vildagliptin vs. Sulfonylurea: A Retrospective Study Using German Electronic Medical Records

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ABSTRACT

Introduction: Preliminary data suggest that dipeptidyl peptidase-4 (DPP-4) inhibitors may reduce microvascular events, but there is a little evidence to support this from adequate real-world studies. This study aimed to compare microvascular outcomes between patients-prescribed vildagliptin and those prescribed sulfonylurea (SU).

Methods: This retrospective cohort study was conducted on a large sample from the German electronic medical records database IMS Lifelink Disease Analyzer. We used propensity score-matched samples of patients prescribed either vildagliptin or SU. Exposure was defined as therapy (SU or vildagliptin); primary outcomes were a diagnosis of retinopathy, nephropathy, neuropathy, or diabetic foot ulcer over the observation period in patients with no previous record of these outcomes. Secondary outcome was a composite of any primary outcome occurring in the observation period.

Results: In total, 16,321 patients prescribed SU and 4481 prescribed vildagliptin met the inclusion criteria. After propensity score matching, each sample comprised 3015 patients. Mean age was 63.7/64.6 years for SU/vildagliptin, respectively, with mean disease duration of 3.2/3.1 years, and mean treatment duration of 2.5/2.3 years. Treatment with vildagliptin was associated with a significant lower incidence of retinopathy [odds ratio (OR) = 0.55, $P = 0.0004$], neuropathy (OR 0.71, $P = 0.0001$), and composite outcome (OR 0.70, $P < 0.0001$). Incidences of nephropathy and diabetic foot ulcer were lower for vildagliptin, but not significantly so (OR 0.90, $P = 0.3920$; OR 0.76, $P = 0.0742$, respectively). There were

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no significant differences in incident rate ratios (all $P > 0.05$).

Conclusion: Treatment with vildagliptin was associated with a reduced incidence of microvascular complications, especially neuropathy and retinopathy, compared to treatment with SU in this clinical practice setting.

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Keywords: Diabetes; DPP-4 inhibitors; Endocrinology; Microvascular complications; Real-world evidence; Vildagliptin

INTRODUCTION

Diabetes mellitus is a progressive and chronic disease which is a major healthcare problem worldwide. According to the World Health Organization, 347 million people worldwide have diabetes (both types 1 and 2) [1], and the number is estimated to rise to 592 million by 2035, as forecasted by the International Diabetes Federation [2]. Type 2 diabetes mellitus (T2DM) results from a combination of insulin resistance and insulin deficiency. It is the most prevalent type of diabetes, accounting for 95% or more of all diabetes cases globally [3].

Diabetes can lead to many serious microvascular degenerative complications (e.g., retinopathy, nephropathy, and neuropathy) resulting into an increased risk of morbidity and mortality and with this significant health care system costs [4]. Hence, while, ideally, the treatment of diabetes demands a holistic approach that can address various complications associated with diabetes, the primary target of achieving an adequate blood glucose level as measured by hemoglobin A1c (HbA1c) level seems still essential. In fact, in previous studies in patients with T2DM, an association between the degree of hyperglycemia and a high risk of microvascular complications has been shown [5, 6]. Several prospective observational studies have outlined the role of intensive glucose control in reducing the risk of microvascular complications in diabetes [7, 8]. Some of the important drugs that are widely used in the treatment of T2DM are metformin, sulfonylureas, and thiazolidinediones class of molecules [4].

Dipeptidyl peptidase-4 (DPP-4) inhibitors were introduced in the treatment of T2DM in 2006 [9]. DPP-4 is an endogenous aminopeptidase enzyme which degrades incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). DPP-4 inhibitors impart their action by increasing the endogenous concentrations of GLP-1 and GIP that are released in response to food intake [10, 11]. The increased concentration of GLP-1 and GIP lead to insulin secretion by pancreatic β-cells, decreased glucagon secretion, and reduction in liver glucose production. Due to their efficacy, good tolerability, low risk of hypoglycemia, and body-weight neutrality, DPP-4 inhibitors have gained importance in the treatment of T2DM [12]. Vildagliptin (Galvus®; Novartis Pharma AG) is an oral antidiabetic agent from the DPP-4 inhibitor class of drugs. It is indicated in Europe in the treatment of T2DM on its own (monotherapy) in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to contraindications or intolerance; together with metformin, a thiazolidinedione or a sulfonylurea (dual therapy); or together with a sulfonylurea and metformin (triple therapy). Vildagliptin is also indicated for use in combination with insulin (with or without metformin) when diet and

exercise plus a stable dose of insulin do not provide adequate glycemic control [3].

Several studies have indicated importance of sulfonylureas or insulin to reduce the risk of microvascular complications [13]. However, there is no adequate comparative data available on the role of a relatively new molecule, i.e., a DPP-4 inhibitor vildagliptin, in treating the microvascular complications associated with T2DM. In this study, we used real-world evidence to evaluate the role of vildagliptin in treating microvascular complications associated with T2DM and compared it with sulfonylurea. The main objectives were to evaluate the incidence of microvascular complications of diabetes between the two treatment groups, i.e., vildagliptin vs. sulfonylurea, as well as, to investigate time needed for the development of these complications between patients in the above-mentioned populations.

METHODS

Study Design

The main objective of the study was to compare the incidence of the defined and confirmed microvascular event outcomes following exposure to one of two therapies: vildagliptin and sulfonylurea. To achieve this objective, a retrospective cohort study design was used in which exposure, outcome, and possible confounding variables were measureable. Since the source of data was longitudinal electronic medical record (EMR), the cohorts were defined by diagnoses and exposures recorded historically, with outcomes tracked over the course of the study period. As such, there was no need for patient informed consent and ethical committee approval according to the German and European law.

Settings

Patients' data was extracted from IMS Lifelink EMR Disease Analyzer (DA), Germany. This database captures data from German patients who visit a representative panel of physicians composed of both general practitioners and specialists. The panel was constituted through stratified sampling of physicians at national level with annual turn-over of 10–20% of the sample. The records of patients who visit the panel were de-identified and sent to a central EMR database in IMS Health. The content of the patient records was then coded through the appropriate coding systems [Anatomical Therapeutic Chemical (ATC) Classification System for drugs and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) for diagnoses]. The information of the database is updated monthly. Due to non-interventional nature of the present study, it did not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. The analyzed data was from the period of January 2007 to December 2013.

Participants

Participants were patients with T2DM treated in an outpatient care as per recorded in IMS Lifelink EMR DA Germany database in the defined study period. Inclusion criteria included having a record of diagnosis of T2DM before or at the time of inclusion (as defined by ICD-10 code E11), treatment initiation by either vildagliptin or sulfonylurea, at least 6 months of continuous treatment (the index date was the date of initiation on therapy), continuous available follow-up in the database as defined by at least one visit every 6 months, and aged greater than 40 years.

The exclusion criteria included a recorded history of microvascular complications before treatment by one of the above medications and concurrent treatment by both vildagliptin and sulfonylurea.

History of each microvascular complication was considered as an exclusion criterion for when it was analyzed as the outcome. The exclusion criterion of previous microvascular event was applied separately for each type of event. For example, for the outcome of retinopathy, patients were selected for the analysis if they had no previous record of retinopathy, and for the outcome of nephropathy, patients were selected if they had no previous history of nephropathy. Hence, patients excluded from the analysis of one outcome may be included in the analysis of a different outcome. For the combined outcome, patients were excluded if they have a record of any previous event.

To avoid confounding between comparison groups of vildagliptin vs. sulfonylurea, matched samples were created using propensity score matching (see "Statistical Analysis" subsection for details).

Outcomes

The primary endpoint was defined as the first recorded occurrence of diabetic nephropathy (ICD-10 codes: E11.2, E14.2), diabetic retinopathy (ICD-10 codes: E11.3, E14.3), diabetic neuropathy (ICD-10 codes: E11.4, 14.4), and diabetic foot syndrome (DFS; through natural language processing, as there is no ICD-10 code for this pathology).

In addition, a combined endpoint of first recorded occurrence of nephropathy, retinopathy, neuropathy, or DFS was computed. The secondary endpoint was the time from initiation of therapy to the first occurrence of either nephropathy, retinopathy, neuropathy, or DFS. DFS was identified through textual analysis of the physicians' notes which captured associated events, such as amputation, gangrene, etc.

Statistical Analysis

Descriptive statistics were calculated for all study variables and consist of number and percentage for categorical variables, as well as mean, median, minimum, maximum, and standard deviation for continuous variables with 95% confidence interval (CI).

The primary outcomes, as defined above, were assessed by unadjusted and adjusted odds ratios (ORs; with 95% CI), expressing the difference in risk of microvascular events (individual and combined) for patients prescribed vildagliptin or sulfonylurea. CIs were estimated using the Miettinen–Nurminen method. Secondary outcomes (time-to-microvascular event) were analyzed using Kaplan–Meier survival curves and the log-rank test. Incident rate ratios (IRR) were also calculated for different microvascular complications comparing two treatment groups (vildagliptin vs. sulfonylurea).

To account for potential confounding factors between two study groups (vildagliptin vs. sulfonylurea), matched samples were created using propensity score matching, i.e., the vildagliptin and sulfonylurea groups were selected to have similar profiles of propensity scores. The propensity scores were derived from the probability of treatment assignment conditional on the following confounding factors (covariates): age, sex, line of therapy, HbA1c score, duration of disease (<5 years vs. ≥ 5 years), duration of treatment, previous hypoglycemic events, co-prescribed medications, and number of co-morbidities.

These confounding factors could act as potential sources of bias in evaluating main objectives of the study, and hence, patients with similar demographic and clinical characteristics in two study groups (matched samples) were pooled. Propensity score-based matching criteria with respect to various confounding factors were used to derive matched samples between two study groups. Propensity scores were generated using a logistic regression model and matched using a genetic algorithm for closest matching based on propensity scores and covariate balance. The distribution of propensity scores and covariates was examined by group to allow for the degree of matching to be quantified (see Fig. 1).

A preliminary feasibility study was conducted to determine the sample size. Based on the data collected for the feasibility study, we estimated the frequency of microvascular complications (combined endpoint) for patients prescribed sulfonylurea as 11.9%, with a reduction of 4.1% for patients prescribed vildagliptin, and hence, the revised sample size requirement for the main study was 3144 patients for 95% power at the 0.01 significance level. All calculations were performed using R 3.0.2.

RESULTS

Participants and Cohort Characteristics

To investigate incidences of microvascular complications and time required for occurrence of such microvascular complications, data for two groups of patients that have exposures to either vildagliptin or sulfonylurea were retrieved. Data were extracted from IMS Lifelink DA database in German population during the study time period (52,187 vs. 12,958 patients in vildagliptin and sulfonylurea groups respectively). Several inclusion and exclusion criteria were applied (see "Methods" section for details) to select patients with certain characteristics in each study group. This led to 16,321 and 4481 patients in sulfonylurea and vildagliptin study

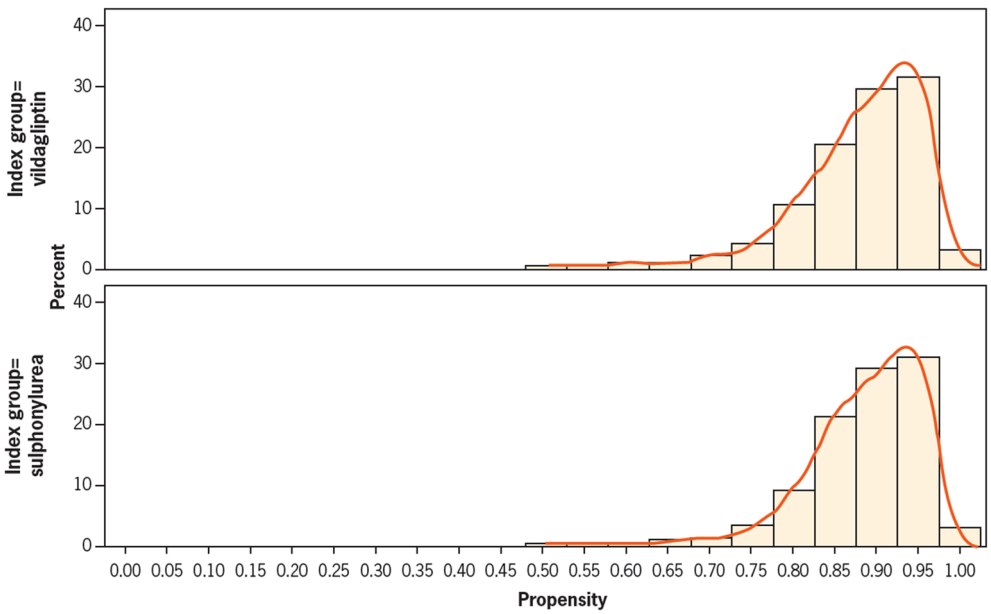

Fig. 1 Distribution of propensity scores for vildagliptin and sulfonylurea samples

groups, respectively. Detailed list of number of patients at each stage in each study group after applying various inclusion/exclusion criteria are mentioned in Table 1.

Patients in two cohorts (unmatched samples) differed with respect to several demographic and clinical characteristics, e.g., age, sex, line of therapy, HbA1c level, duration of disease and treatment, co-prescribed medications, and co-morbid conditions (supporting information, Tables S1 and S2). Matched samples contained 3015 patients in both sulfonylurea and vildagliptin study groups. Various comparable demographic and clinical characteristics of patients in matched samples in both study groups are described in Tables 2 and 3.

Incidences of Microvascular Complications

Primary endpoint of the present investigation was to measure the first occurrence of microvascular complications in diabetic patients which were assigned to vildagliptin or sulfonylurea treatments. Particularly incidences for retinopathy, nephropathy, neuropathy, DFS, or composite (occurrence of any of above complications) outcomes were measured

Table 1 Selection of participants in each study group

Variable	Vildagliptin	Sulfonylurea
First prescription (study window)	12,958	52,187
Age at index date above 40 years	12,637	51,492
Continuous treatment in the same practice (≥1 visit each half-year during at least 1 year before and after index date	8226	35,476
With a type II diabetes diagnosis on/before index date	6046	21,939
No insulin prescriptions at baseline/during follow-up	5938	21,511
No prescriptions of sulfonylurea and vildagliptin at the same time	4481	16,321
Duration of follow-up time (days)		
Minimum	183	183
Median	734	911
Mean	803.8	1045.5
SD	404.7	626.4
Maximum	2196	2727
Number of prescriptions per patient per year		
Minimum	0.86	0.52
Median	17.65	22.41
Mean	20.76	26.09
SD	13.42	16.59
Maximum	124.64	232.45

SD standard deviation

Table 2 Descriptive data (matched samples)

Variable	Vildagliptin	Sulfonylurea
N	3015	3015
Age (years)		
Mean (SD)	64.6 (10.9)	63.7 (10.7)
Minimum	40	40
Maximum	95	98
Sex (*N*, %)		
Male	1731 (57.4%)	1641 (54.4%)
Female	1284 (42.6%)	1372 (45.6%)
Line of therapy		
1st line	25.1%	18.6%
2nd line	52.2%	58.5%
3rd line	18.7%	16.3%
4th or higher line	3.4%	4.6%
HbA1c		
N (%) available	3015	3015
Mean (SD)	7.61 (1.47)	7.64 (1.37)
Minimum	4.6	3.6
Maximum	19.0	16.1
Duration of disease (years)		
Mean (SD)	3.1 (3.4)	3.2 (3.4)
Minimum	0.0	0.0
Maximum	20.4	20.9
Duration of treatment (years)		
Mean (SD)	2.3 (2.6)	2.5 (2.8)
Minimum	0.0	0.0
Maximum	18.2	16.9
Previous hypoglycemic event (*N*, %)	19 (0.63%)	23 (0.77%)

HbA1c hemoglobin A1c, *SD* standard deviation

between two matched sample study arms (Table 4, data for unmatched samples are available in supporting information, Table S3).

Incidences of each microvascular complications, i.e., retinopathy, nephropathy, neuropathy, DFS, or composite, appeared higher in the sulfonylurea study arm when compared with the vildagliptin arm (Table 4). To enable direct comparison between study arms, ORs based on incidences for each

Table 3 Clinical characteristics (matched samples)

Clinical characteristic	Vildagliptin	Sulfonylurea
Co-prescribed medications (*N*, %)		
Antihypertensives (C03, C07, C08, C09)	2505 (83.1%)	2472 (82.0%)
Lipid modifying agents (C10)	1424 (47.2%)	1420 (47.1%)
Other DPP-4 (A10 N excluding vildagliptin)	109 (3.61%)	305 (10.1%)
GLP-1 (A10S)	70 (2.32%)	96 (3.2%)
Metformin (A10 J)	2629 (87.2%)	2559 (85.0%)
SGLT 2 (A10P)	39 (1.3%)	25 (0.9%)
Alpha glucosidase inhibitors (A10L)	33 (1.1%)	41 (1.4%)
Glinides (A10 M)	89 (3.0%)	79 (2.6%)
Glitazone (TZD) (A10 K)	43 (1.4%)	76 (2.6%)
Insulin (A10C)	297 (9.9%)	332 (11.0%)
Co-morbid conditions (*N*, %)		
Hypertension (I10)	2591 (86.0%)	2558 (85.0%)
Peripheral vascular disease (I739, E115, E145)	381 (12.6%)	470 (15.6%)
Hyperlipidemia (E78)	1851 (61.4%)	1852 (61.4%)
Prior stroke (I63,64)	115 (3.81%)	151 (5.01%)
Myocardial infarction (I21-23, I252)	209 (7.0%)	201 (6.67%)
Ischemic heart disease (I24,25)	822 (27.3%)	934 (31.0%)
Angina pectoris (I20)	242 (7.4%)	272 (8.3%)
Renal failure (N18, N19)	390 (13.0%)	334 (11.1%)
Depression (F32, 33)	729 (24.2%)	878 (29.1%)
Dementia (F01, F03, G30)	155 (5.2%)	230 (7.6%)
Charlson Comorbidity Score		
Mean (SD)	2.32 (1.66)	2.39 (1.66)
Minimum	0	0
Maximum	13	20

GLP-1 glucagon-like peptide-1, *SD* standard deviation

microvascular complication for vildagliptin vs. sulfonylurea treatments were calculated. Treatment with vildagliptin was found to be associated with a significantly lower incidences of retinopathy (OR 0.55, 95% CI 0.39–0.77, $P = 0.0004$), neuropathy (OR 0.71, 95% CI 0.60–0.85, $P = 0.0001$), and composite outcome (OR 0.70, 95% CI 0.61–0.82, $P < 0.0001$; Table 5 and Fig. 2). Differences were non-significant for nephropathy (OR

Table 4 Incidences of microvascular events (matched samples)

Microvascular event	Vildagliptin	Sulfonylurea
	3015	3015
Retinopathy		
Patients with no retinopathy prior to index date	2948	2934
Retinopathy during all available follow-up period (*N*)	54	97
Retinopathy during all available follow-up period (%)	1.8%	3.3%
Time-to-first retinopathy diagnosis (years)	1.2	2.6
Neuropathy		
Patients with no neuropathy prior to index date	2891	2919
Neuropathy during all available follow-up period (*N*)	144	160
Neuropathy during all available follow-up period (%)	5.0%	5.5%
Time-to-first neuropathy diagnosis (years)	1.5	2.6
Nephropathy		
Patients with no nephropathy prior to index date	2728	2708
Nephropathy during all available follow-up period (*N*)	256	343
Nephropathy during all available follow-up period (%)	9.4%	12.7%
Time-to-first nephropathy diagnosis (years)	1.4	2.3
DFS		
Patients with no DFS prior to index date	2965	2968
DFS during all available follow-up period (*N*)	80	104
DFS during all available follow-up period (%)	2.7%	3.5%
Time-to-first DFS diagnosis (years)	1.7	2.1
Composite endpoint (any event)		
Patients with no event prior to index date	2563	2553
Event during all available follow-up period (*N*)	366	489
Event during all available follow-up period (%)	14.3%	19.1%
Time-to-first event diagnosis (years)	1.4	2.4

DFS diabetic foot syndrome

0.90, 95% CI 0.72–1.14, $P = 0.3920$) and DFS (OR 0.76, 95% CI 0.57–1.03, $P = 0.0742$). No significant differences in IRRs were found between two treatment arms (Table 6; Fig. 3, all $P > 0.05$).

DISCUSSION

A retrospective cohort observational study was carried out to investigate any advantage of the relatively new DPP-4 inhibitors class of a drug

Table 5 OR for the occurrence of microvascular events for vildagliptin vs. sulfonylurea (matched samples)

Adjusted	OR	95% CI	*P* value
Composite endpoint	0.70	0.61–0.82	<0.0001
Retinopathy	0.55	0.39–0.77	0.0004
Nephropathy	0.90	0.72–1.14	0.3920
Neuropathy	0.71	0.60–0.85	0.0001
Diabetic foot syndrome	0.76	0.57–1.03	0.0742

CI confidence interval, *OR* odds ratio

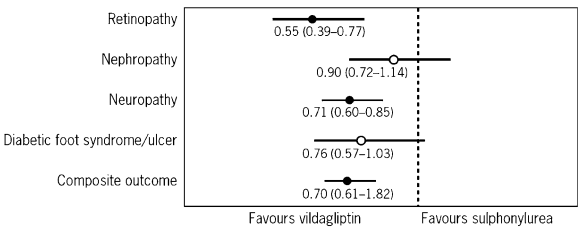

Fig. 2 Odds ratio (95% confidence intervals) for the occurrence of microvascular events for vildagliptin vs. sulfonylurea (matched samples)

Table 6 IRRs for vildagliptin vs. sulfonylurea (matched samples)

Adjusted	IRR	95% CI	*P* value
Composite endpoint	0.99	0.87–1.14	0.9285
Retinopathy	0.73	0.53–1.02	0.0680
Nephropathy	1.20	0.96–1.50	0.1121
Neuropathy	0.99	0.84–1.16	0.8647
Diabetic foot syndrome	1.02	0.76–1.37	0.8792

CI confidence interval, *IRR* incident rate ratio

vildagliptin over sulfonylurea in treating microvascular complications associated with T2DM.

Our investigations in the present study indicate that treatment with vildagliptin is associated with lower overall incidences of microvascular events, particularly significant were retinopathy and neuropathy, when compared with sulfonylurea. Microvascular

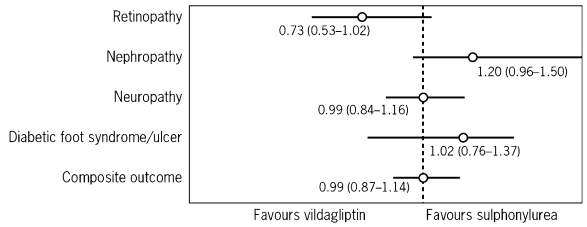

Fig. 3 Incident rate ratios (95% confidence intervals) for vildagliptin vs. sulfonylurea (matched samples)

complications associated with T2DM affect the retina, nerves, and kidney leading to the reduced quality of life of patients. Time-to-event analysis based on the IRR demonstrated no statistically significant differences in time required for the occurrence of various microvascular complications between two study groups (vildagliptin vs. sulfonylurea).

Relevant patients' data for the present study were extracted from the IMS Lifelink EMR DA database for the German population. The study design (retrospective cohort study) prevents any claims to have established causal effects based on the observed associations. A further limitation of database studies using EMR data is the suboptimal recording of information by physicians. However, in this study, the assumption could be made that this suboptimal recording affects both exposure groups (vildagliptin vs. sulfonylurea) in the same way, and thus, under-reporting may not be an issue for this real-world evidence comparison. Nevertheless, any conclusion regarding the absolute incidence of each microvascular complication shall be handled with caution. In addition, the under-reporting can potentially reduce the effect size, the amount of which cannot be estimated from the study data. It is likely that patients' exposure to vildagliptin or sulfonylurea was determined by their profile which, in its turn, affects the development of microvascular complications. We have tried to reduce or

eliminate this confounding effect using propensity scoring to generate comparable groups between two treatments. Comparable groups of patients with respect to age, sex, HbA1c level, duration of disease and treatment, and existing co-morbid conditions between two treatments (vildagliptin vs. sulfonylurea) ensured a high internal validity of our findings. In addition, validity and representativeness of the IMS Lifelink EMR DA database have already been investigated for its use in pharmacoepidemiological studies [14].

DPP-4 inhibitors have shown potential for the management of T2DM, as corroborated by conducted clinical trials that have indicated safety and efficacy of vildagliptin and other DPP-4 inhibitors in the treatment of T2DM [15–20]. Vildagliptin is well-tolerated and produces clinically meaningful reduction in blood glucose level without promoting weight gain or inducing hypoglycemia [21]. Recent studies have shown advantages of vildagliptin in T2DM treatment in elderly [22] and overweight/obese patients [23]. The benefit of DPP-4 inhibitors in addressing cardiovascular risks associated with T2DM when compared with, e.g., the metformin therapy was also investigated in several studies [12, 24, 25].

Considering microvascular complications associated with T2DM, role of intensive glucose control therapies in treating such microvascular complications has been investigated in several trials. In the UK Prospective Diabetes Study (UKPDS) trial (ISRCTN75451837), it was reported that each 1% reduction in mean HbA1c with intensive glucose therapies (sulfonylurea or insulin) was associated with 37% reductions in risk of microvascular complications [7]. An even more pronounced effect with reductions of 54% in microvascular complications was observed in the Diabetes Control and Complications Trial (DCCT; ClinicalTrials.gov identifier: NCT00360815) [26]. Similar observations regarding the benefit of intensive glucose treatment in microvascular complications were reported in Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [27] and Action to Control Cardiovascular Risk in Diabetes (ACCORD; ClinicalTrials.gov identifier: NCT00000620) [28] trials.

Several pilot studies were also conducted to investigate whether relatively new classes of DPP-4 inhibitors have any effect on microvascular complications associated with T2DM. A recent small (50 patients with T2DM), placebo-controlled, double blind, crossover trial has demonstrated that treatment with saxagliptin (a DDP-4 inhibitor) for 6 weeks could be advantageous in early microvascular changes [29]. In another pilot study, treatment with vildagliptin for 8 weeks in 47 patients with T2DM has shown the significantly reduced decreased albumin/creatinine ratio [30]. Similarly, vildagliptin has shown improved healing features for chronic foot ulcers in patients with T2DM [31]. Several pre-clinical studies also observed the importance of DPP-4 inhibitors in treating microvascular complications associated with diabetes [32–35]. Most of the studies on humans investigating importance of DPP-4 inhibitors in microvascular complications were preliminary and short-term studies, and further large and long-term trials are required to corroborate these findings. Our present observational study has attempted to fill in the gaps in establishing role of a DPP-4 inhibitor vildagliptin in treating microvascular complications associated with T2DM by directly comparing it with the sulfonylurea treatment.

The comparative evidence basis investigating different available therapeutic options in treating T2DM and its complications is sparse

[36]. Hence, there is a high-demand of the comparative effectiveness research between various available treatment options for T2DM. However, lengthy and costly clinical trials limit such comparative effectiveness studies, especially considering the fact that head-to-head comparisons between different treatments result into large number of combinations and permutations of drugs to be investigated. Nevertheless, real-world evidence solutions, as has been implemented in the present study, provide an effective alternative for direct comparisons between different therapeutic options available in the treatment of T2DM and its complications based on patients' data extracted from real-world settings. Such comparative effectiveness studies based on real-world data will be one step forward toward achieving the tailor-made, patient-centered approach for the treatment of a chronic disease, such as diabetes.

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Disclosures. Wlodzimierz M. Kolaczynski is an employee and Stock/Shareholder at Novartis Pharma AG. Matthew Hankins is an employee at IMS Health. Siew H. Ong is an employee at Novartis Pharma AG. Hartmut Richter is an employee at IMS Health. Andreas Clemens is an employee at Novartis Pharma AG. Massoud Toussi is an employee at IMS Health. Wlodzimierz M. Kolaczynski, Matthew Hankins, Siew H. Ong, Hartmut Richter, Andreas Clemens, and Massoud Toussi declare that they have no other conflict of interest other than those listed above.

Compliance with Ethics Guidelines. Data were de-identified and comply with the patient requirements of the Health Insurance Portability and Accountability Act (HIPAA). Therefore, Institutional Review Board approval was not required.

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