Journal of Diabetes and Its Complications xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

# Comparative risk for cardiovascular diseases of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas in combination with metformin: Results of a two-phase study

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ARTICLE INFO

*Article history:*
Received 6 January 2016
Received in revised form 7 April 2016
Accepted 16 May 2016
Available online xxxx

*Keywords:*
Adverse drug effects
Combination therapy
Diabetes type 2
Health insurance data
Pharmacoepidemiological research database

ABSTRACT

*Aims:* The aim was to assess whether the use of additional data from the Disease Management Program (DMP) diabetes mellitus type 2 to minimize the potential for residual confounding will alter the estimated risk of either myocardial infarction, ischemic stroke or heart failure in patients with type 2 diabetes using sulfonylureas compared to dipeptidyl peptidase-4 (DPP-4) inhibitors in addition to metformin based on routine health care data.
*Methods:* We conducted a nested two-phase case–control study using claims data of one German health insurance from 2004 to 2013 (phase 1) and data of the DMP from 2010 to 2013 (phase 2). Adjusted odds ratios (ORs) for the combined cardiovascular event myocardial infarction, ischemic stroke or heart failure were calculated using a two-phase logistic regression.
*Results:* Phase 1 comprised 3179 patients (289 cases; 2890 controls) and phase 2 comprised 1968 patients (168 cases; 1800 controls). We observed an adjusted OR of 0.83 for the combined cardiovascular event (95% CI: 0.61–1.13).
*Conclusions:* We observed a non-significantly reduced risk for cardiovascular diseases in patients using DPP-4 inhibitors compared to sulfonylureas in addition to metformin. This finding was not altered by the inclusion of additional information of the DMP in the analysis. However, due to the low power of this study, further studies are needed to reproduce our findings.



## 1. Introduction

Cardiovascular diseases are major complications in patients with type 2 diabetes and responsible for the high mortality rate among diabetic patients (Juutilainen, Lehto, Ronnemaa, Pyorala, & Laakso, 2008; Morrish, Stevens, Fuller, Keen, & Jarrett, 1991; UK Prospective Diabetes Study (UKPDS) Group, 1998). Since most patients will receive oral antidiabetic drugs (OADs) in the course of the disease to achieve glycemic targets, a focus of the OAD therapy should also be on the reduction of cardiovascular events (Inzucchi et al., 2012). Based on the recommendations of the German National Disease Management Guideline, metformin is the first choice of medication (Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), & (AWMF), A. d. W. M. F., 2013). If a monotherapy of metformin fails to achieve glycemic targets, a combined therapy of metformin and a second OAD class is recommended. Besides the commonly used sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors are increasingly used since their market introduction in 2007 (Freichel & Mengel, 2014).

The added benefit of DPP4-ihibitors compared to sulfonylureas is controversially discussed. The Institute for Quality and Efficiency in Health Care (IQWiG) rated DPP-4 inhibitors to have no added benefit compared to sulfonylureas (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)). However, sulfonylureas have been shown to be associated with weight gain and an increased risk of hypoglycemia (Nathan et al., 2009). Furthermore, studies on the cardiovascular risk of both sulfonylureas and DPP-4 inhibitors in combination with metformin showed conflicting results. A meta-analysis

Conflict of interest statement: Iris Pigeot is head and Dirk Enders and Bianca Kollhorst are employees of an institute that occasionally performs studies sponsored by pharmaceutical industries. These companies include Bayer, Celgene, GSK, Mundipharma, Novartis, Sanofi, Sanofi Pasteur MSD, and STADA. Roland Linder, Susanne Engel and Frank Verheyen are working for the Scientific Institute of the Techniker Krankenkasse (TK) for Benefit and Efficiency in Health Care (WINEG). The mission of the WINEG is to investigate the value of innovations and new programmatic approaches within the statutory health insurance framework. The authors declare that because they belong to the TK, a potential conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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http://dx.doi.org/10.1016/j.jdiacomp.2016.05.015
1056-8727/

of seven observational studies found a 43% increased risk of being hospitalized or to die due to a cardiovascular event for patients with a combined therapy of metformin and sulfonylurea compared to the study-specific reference group (Rao, Kuhadiya, Reynolds, & Fonseca, 2008). However, the studies included in the meta-analysis were heterogeneous, especially regarding the definition of the reference group.

DPP-4 inhibitors, at first sight, seem to have a protective effect concerning cardiovascular diseases. For instance, a meta-analysis of clinical trials showed a decreased risk for major cardiovascular events compared to placebo or sulfonylurea (Monami, Ahrén, Dicembrini, & Mannucci, 2013; Monami, Genovese, & Mannucci, 2013). In the SAVOR TIMI-53 clinical trial, use of the DPP-4 inhibitor saxagliptin compared to placebo did not lead to an increased risk of an overall cardiovascular event. However, users of saxagliptin had an increased risk of heart failure compared to placebo (Scirica et al., 2013, 2014). The hypothesis of an increased risk of heart failure among users of DPP-4 inhibitors was supported in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial (Monami, Dicembrini, & Mannucci, 2014). Contrary to this, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) found that adding the DPP-4 inhibitor sitagliptin to usual care did not alter the risk for heart failure compared to placebo (Green et al., 2015). Two recently conducted large observational studies showed a decreased risk of heart failure for users of DPP4-inhibitors compared to sulfonylureas (Fadini et al., 2015) and no differential risk between DPP-4 inhibitors compared to sulfonylureas (Fu et al., 2016). Furthermore, the latter study investigated the risk between the two DPP-4 inhibitors sitagliptin and saxagliptin but found no differential risk as well.

Studies explicitly comparing both sulfonylureas and DPP-4 inhibitors in addition to metformin are scarce. One clinical trial observed a significantly decreased risk of major cardiovascular events for the DPP-4 inhibitor linagliptin compared to the sulfonylurea glimepiride in addition to metformin (Gallwitz et al., 2012). One observational study based on the United Kingdom Clinical Practice Research Datalink (CPRD) found no difference between the two combination therapies regarding the risk of major cardiovascular events (Yu, Yin, & Azoulay, 2015). However, occurrence of heart failure was not investigated in these studies. A recently conducted observational study based on data of Korean national health insurances observed an increased risk of total cardiovascular disease but not of heart failure for a combination of metformin and sulfonylureas compared to metformin and DPP-4 inhibitors (Seong et al., 2015).

Since a comparison between the effect of sulfonylureas and DPP-4 inhibitors in addition to metformin on the overall cardiovascular risk is unclear and large randomized controlled trials to compare these two medications are still missing, recommendations for physicians must be based on high-quality observational studies including studies based on routine data from health insurances. However, these studies typically lack information on important confounders, e.g., lifestyle factors and laboratory parameters.

The objective of this study is to investigate whether the estimated risk of either myocardial infarction, ischemic stroke or heart failure in patients with type 2 diabetes using sulfonylureas compared to DPP-4 inhibitors in addition to metformin will alter if routine data from a large German health insurance are analyzed in combination with data from the Disease Management Program (DMP) diabetes type 2 to minimize the potential for residual confounding. Data from the DMP diabetes type 2 comprise additional information on HbA1c-values, BMI and smoking status. Since only a subset of the patients with diabetes is enrolled in the DMP, the objective of our study was pursued by using a two-phase approach to analyze the data (Collet, Schaubel, Hanley, Sharpe, & Boivin, 1998). The general idea of this approach is to use the whole information of patients contained in both data sources and to account for information on disease status, exposure and important confounders that is available for all patients. Such a two-phase approach is generally more efficient than a complete-case analysis (Breslow & Chatterjee, 1999).

## 2. Subjects, materials and methods

### 2.1. Data sources

This study was based on two data sources.

Data for the first phase were obtained from the German Pharmacoepidemiological Research Database (GePaRD), which currently comprises data of more than 20 million patients of four statutory health insurances (SHI) in Germany. The database includes demographic characteristics, information on diagnoses from hospital admissions and ambulatory physician visits as well as reimbursed outpatient prescriptions. Ambulatory and inpatient diagnoses are coded according to the German modification of the International Classification of Diseases (ICD-10 GM). Prescriptions are uniquely classified by the anatomical–therapeutical–chemical (ATC) code and the defined daily dose (DDD). The database was described in detail elsewhere (Behr, Andersohn, & Garbe, 2010). This study was based on data from one SHI with about 8.7 million insurants from the years 2004 to 2013.

Second phase data were obtained from the records of the DMP diabetes type 2 of the same SHI that provided the health insurance data. DMPs are special health care plans offered by the German SHIs to insurants with selected chronic diseases in order to provide a structured approach to care. Patients enrolled in the DMP diabetes type 2 visit a physician at least every six months. The record of a visit includes information on BMI, lifestyle variables such as smoking, laboratory parameters (e.g., HbA1c-value), examinations of eyes and feet and recommendations and referrals of the physician. DMP data from 2010 to 2013 were considered for this study.

The data from both data sources were pseudonymized and linked using the pseudonymized identifiers.

### 2.2. Study design

We conducted a nested two-phase case–control study. Therefore, an overall cohort of patients receiving a combined therapy of two antidiabetic drugs was identified first. From this overall cohort, we selected those patients for whom the metformin monotherapy failed and who were additionally treated with DPP-4 inhibitors or sulfonylureas thereafter.

#### 2.2.1. Overall cohort: patients with a combined antidiabetic therapy

We included patients in the cohort at the time of the first prescription of a metformin, sulfonylurea (glibenclamide, glibornuride, gliquidone, gliclazide, glimepiride), DPP-4 inhibitor (sitagliptin, vildagliptin, saxagliptin), thiazolidinedione (rosiglitazone, pioglitazone), alpha-glucosidase inhibitor (acarbose, miglitol), glinid (repaglinid, nateglinid) or incretin mimetic (exenatide, liruglatide, lixisenatide) after being continuously insured for nine months without a prescription of any antidiabetic drug. Further, patients needed to have a subsequent prescription of an antidiabetic drug class other than the initial prescription to be included in the cohort. Cohort entry in the overall cohort was then defined as the date of the first prescription of the second antidiabetic drug. Cohort exit was defined as the end of the continuous insurance period (allowing gaps of 14 days without insurance membership), end of the study (December 31st, 2013) or death, whichever came first.

Patients who did not receive a prescription of the initial antidiabetic drug class after cohort entry were excluded, because we assumed that these patients switched from one medication to another instead of taking the second drug class additionally. Patients younger than 18 years or without an ambulatory or inpatient diagnosis of diabetes mellitus (ICD-10 GM E11 or E14) in the nine months before the first prescription of an antidiabetic drug until cohort exit were further excluded to ensure a cohort of type 2 diabetes patients. Since data of the DMP were only available from 2010 to 2013, patients with

Please cite this article as: Enders, D., et al., Comparative risk for cardiovascular diseases of dipeptidyl peptidase-4 inhibitors vs. sulfonylureas in combination with metformin: Resul..., *Journal of Diabetes and Its Complications* (2016), http://dx.doi.org/10.1016/j.jdiacomp.2016.05.015