CARDIOVASCULAR SAFETY OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

by
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ABSTRACT

Objective: The proposed study will examine the association between the dipeptidyl peptidase-4 inhibitors (DPP-4i) drug class and the risk of major adverse cardiovascular events (MACE) in patients with diabetes.

Methods: In the surveillance portion of this dissertation, we utilized the Food and Drug Administration's Adverse Events Reporting System (FAERS) to conduct a Bayesian disproportionality analysis on reports for MACE associated with DPP-4i, to assess the association of DPP-4i with a cardiovascular subset of reports to the full database. These associations were quantified using the posterior distribution of the empirical Bayes lower bound (EB05) of the relative reporting ratio, among high- and low- risk populations. Next for the longitudinal analyses, we conducted retrospective, time to first MACE analyses of data from Truven Marketscan Commercial Claims and Encounters to compare new users of DPP-4i versus sulfonylurea and DPP-4i versus metformin. This association was measured using propensity score weighted Cox proportional hazards models, adjusted for baseline demographics, comorbidities, and concomitant medications. Propensity score weights, based on baseline clinical characteristics and concomitant medications, were calculated using a generalized boosted logistic regression model. This analysis was repeated in both individuals with established cardiovascular and/or kidney disease (high-risk cohort), as well as in individuals without these medical conditions (low-risk cohort).

Results: In the surveillance study, there was a safety signal for heart failure with linagliptin (EB05=2,782.47) and saxagliptin (EB05=2.40), myocardial infarction with alogliptin (EB05=290.11), and cerebral infarction with sitagliptin (EB05=2.80) in the cardiovascular subset of reports. Eight of fourteen possible MACE events had a percent positive agreement ≥50% for a drug-event safety signal in both the cardiovascular subset and the full dataset. Overall, the cardiovascular subset elicited 11 more safety signals for DPP-4i than the full dataset. In the longitudinal analysis of low-risk individuals, DPP-4i use was associated with lower risk for MACE than sulfonylurea use (adjusted Hazard Ratio (aHR)=0.87; 95% Confidence Interval (CI): [0.78, 0.98]), and no increased risk for MACE compared to metformin use (aHR=1.07; 95% CI: [0.97, 1.18]). Risk for acute myocardial infarction (aHR=0.70; 95% CI: [0.51, 0.96]), stroke (aHR=0.57; 95%CI: [0.41, 0.79]), and heart failure (aHR=0.57; 95% CI: 0.41, 0.79) with DPP-4i was lower compared to sulfonylureas. In the longitudinal analysis of high-risk individuals, DPP-4i was associated with lower risk for MACE than sulfonylurea (aHR=0.84; 95% CI: [0.7, 0.9]), and with no increased risk for MACE compared to metformin (aHR=1.07; 95% CI: [1.0, 1.2]).

Conclusions: This dissertation confirms the evidence that DPP-4i carry less risk for MACE compared to sulfonylureas in new users of antihyperglycemic therapy for type 2 diabetes. Additionally, DPP-4i and metformin are similar in risk of MACE. While the surveillance data showed a signal for heart failure with some DPP-4i, further prospective analyses of longitudinal data did not lead to evidence to support the drug label warning for increased risk of heart failure among high-risk patients with the use of DPP-4i.

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Abbreviations

CDC – Centers for Disease Control and Prevention
CV - Cardiovascular
DPP-4i – dipeptidyl peptidase-4 inhibitors
FAERS – Food and Drug Administration Adverse Event Reporting System
FDA – United States Food and Drug Administration
GLP-1 - glucogon-like peptide-1
MACE – major adverse cardiovascular events
NIH – National Institutes of Health
NHLBI – National Heart, Lung, and Blood Institute
T2DM – type 2 diabetes mellitus

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Table of Contents

SPECIFIC AIMS

Type 2 diabetes mellitus (T2DM) is a common and costly disease, affecting nearly 1/3 of the United States population and often presenting with many comorbidities, including cardiovascular disease[1]. Patients with T2DM can be treated with antihyperglycemic agents spanning nine drug classes, each with their respective risks and benefits. While these therapies allow patients to manage blood glucose levels, some come with side effects such as hypoglycemia or gastrointestinal upset. The United States Food and Drug Administration (FDA) has approved 15 dipeptidyl peptidase-4 inhibitors (DPP-4i) since 2006. This class of drug was thought to protect against acute cardiovascular events, making them a safer option to rosiglitazone and other thiazolidinediones, after a link between rosiglitazone and myocardial infarction was identified in 2007[2].

In February 2014, the FDA issued a Drug Safety Communication regarding increased risk of congestive heart failure (CHF) with the DPP-4i saxagliptin in response to the publication of results from the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial[3,4]. While SAVOR investigators collected baseline data on cardiovascular risk, it was limited to age and having one of three risk factors (hyperlipidemia, hypertension, or active smoking). Re-analysis of results suggested an increased risk of CHF compared to placebo; however, the trial was designed to assess CHF as part of a composite, secondary outcome[4]. As such, FDA convened an Advisory Committee to assess the data for increased risk of CHF with saxagliptin and look at data from the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial for alogliptin, which was conducted

in patients with acute coronary syndrome. Data regarding the co-primary endpoint of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke, showed no increased risk associated with alogliptin use[5]. While the Advisory Committee recognized the dangers of making post-hoc assessments on trial data, the re-analysis of both trials showed a non-statistically significant increased risk for CHF with DPP-4i use. FDA erred on the side of caution and placed a warning of generalized cardiovascular risk on the saxagliptin and alogliptin labels.

DPP-4i's are among the most common treatments for T2DM and many patients have comorbid cardiovascular diseases such as hypertension and hyperlipidemia. Data from SAVOR and EXAMINE do not suggest statistically significant increases in cardiovascular risk for these products, yet signal detection through spontaneous reports indicate that cardiovascular risk should be evaluated in a systematic manner for this class of drug[6]. With this discrepancy in mind, we used post-marketing adverse event and commercial claims data to assess whether safety concerns exhibited through spontaneous reporting are indicative of increased hazards of acute cardiovascular events and death among patients who have taken DPP-4i compared to those on sulfonylureas and metformin.

Specific Aim 1: To determine whether post-marketing surveillance of DPP-4i elicit a safety signal for an increased risk of acute cardiovascular events compared to sulfonylureas and metformin in (1) the full set of drug-related adverse event reports and (2) in a subset of adverse event reports consisting of all FDA-approved cardiovascular and diabetic drug products.

Hypothesis 1.1: There will be a safety signal for major adverse cardiovascular events associated with each DPP-4i drug in the full set of drug-related adverse event reports.
Hypothesis 1.2: There will be a safety signal for major adverse cardiovascular events associated with each DPP-4i drug in the subset of reports from cardiovascular and diabetic products.

Specific Aim 2: To compare the hazards of acute cardiovascular events or death with the use of DPP-4i versus sulfonylureas and metformin among treatment naïve patients *without* prior cardiovascular disease or renal impairment using commercial claims data.
Hypothesis 2.1: The hazard of acute cardiovascular events in individuals without cardiovascular disease or renal impairment is greater with DPP-4i than with sulfonylureas and metformin.

Specific Aim 3: To assess whether the hazards of acute cardiovascular events or death differ with the use of DPP-4i versus sulfonylureas and metformin among treatment naïve patients *with* prior cardiovascular disease and/or renal impairment using commercial claims data.
Hypothesis 3.1: The hazard of acute cardiovascular events in individuals with cardiovascular disease and/or renal impairment is greater with DPP-4i than with sulfonylureas and metformin.

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OVERVIEW

Type 2 diabetes mellitus (T2DM) is a common and chronic disease in the United States. The United States Centers for Disease Control and Prevention estimates that 9.4% of the United States population currently have diabetes[1]. This often presents with a host of comorbidities, including cardiovascular disease. In the following dissertation, we first provide a comprehensive review of the epidemiology of diabetes in the United States. Next, we consider the United States Food and Drug Administration (FDA) approved pharmacological treatment options for T2DM and the cardiovascular safety concerns with these products. Finally, we discuss the current evidence base and regulatory framework for assessing the cardiovascular safety of dipeptidyl peptidase-4 inhibitors (DPP-4i), one class of oral antihyperglycemic agents.

Following this overview, we present three papers that provide empiric examinations of the association between DPP-4i and cardiovascular events. In the first manuscript, we evaluate the relationship between DPP-4i and major adverse cardiovascular events spontaneously reported to the FDA Adverse Event Reporting System (FAERS). We assessed the presence of safety signals in both the full set of adverse event reports and a subset of reports for drugs indicated for cardiovascular and diabetic indications. This approach allowed us to determine whether there was disproportional reporting of major adverse cardiovascular events for DPP-4i overall and within the context of drugs commonly prescribed to diabetic patients at high risk for experiencing a major adverse cardiovascular event.

In the second manuscript, we used commercial claims data to investigate the association between DPP-4i use and major adverse cardiovascular events among patients

without a history of cardiovascular disease. We compare this association to that of sulfonylureas and metformin. By controlling for risk factors such as hypertension and hypercholesterolemia through surrogate markers of medications used to treat those conditions, we could better assess whether or not the risk of major adverse cardiovascular events were due to DPP-4i use or underlying cardiovascular disease.

In the third manuscript, we conducted a similar analysis in patients with a history of major adverse cardiovascular events and/or renal impairment (i.e. chronic kidney disease and acute kidney impairment). This group was identified by FDA in a 2008 Guidance for Industry as a vulnerable population, whose cardiovascular risk with the use of oral antihyperglycemic agents is poorly understood[2]. The clinical trial data regarding cardiovascular safety of DPP-4i submitted to FDA suggested that a prior history of cardiovascular disease and/or renal impairment modified the relationship between DPP-4i and major adverse cardiovascular events when compared to those without this medical history. By analyzing this cohort separately, we were able to investigate the association between DPP-4i use and major adverse cardiovascular events in this subgroup of interest.

Finally, we conclude with the implications of our findings in light of current evidence on the cardiovascular safety of DPP-4i. We discuss the potential impact on prescribing practices, patient safety, and regulatory guideline development.

BACKGROUND

Diabetes is common among patients with cardiovascular disease.

The CDC estimates that 30.3 million people suffer from diabetes in the United States, and 90-95% of these cases are T2DM patients[3]. Additionally an estimated 86 million Americans over age 20 are pre-diabetic[4]. This statistic becomes especially concerning in light of data showing that diabetes often presents with cardiovascular disease (CVD)[5]. These two diseases are often preceded by a cluster of symptoms commonly referred to as metabolic syndrome, which comprises of any three of the following five conditions: elevated fasting blood glucose, elevated waist circumference, elevated triglycerides, reduced HDL-C, and elevated blood pressure. Metabolic syndrome increases the risk of developing diabetes by five-fold; additionally, it increases the risk of CVD in the following 5-10 years by 50%[6]. Further complicating this relationship, diabetes often increases individual risk for cardiovascular disease[7]. An estimated 71% of diabetic patients over age 18 either have blood pressure greater than or equal to 140/90 mmHg or are currently taking antihypertensive medication[4].

There are many treatment options for patients with T2DM

Before physicians and patients pursue pharmaceutical therapies for T2DM, patients are often asked to make lifestyle modifications such as increased exercise and reduced dietary sugar and carbohydrate intake. When these actions show minimal or no effect on glycemic control, patients with T2DM can be treated with any combination of antihyperglycemic agents from nine classes, namely sulfonylureas, biguanides, meglitinides, thiazolidinediones, sodium/glucose cotransporter 2 (SLGT2) inhibitors,

alpha-glucosidase inhibitors, GLP-1 agonists, bile acid sequestrants, and DPP-4i. The American Academy of Clinical Endocrinologists recently released their prescribing algorithm for antihyperglycemic agents[8]. These agents are often prescribed in a step-wise fashion. Among mono-therapy options are metformin, DPP-4i, and sulfonylureas. As patients progress with the disease, dual-therapy can be initiated when HbA1c levels are ≥7.5%, and triple-therapy with the option for insulin treatment can be used when this is no longer effective. As T2DM is a metabolic disorder affecting insulin action and secretion, each of these drug classes works by either indirectly regulating the amount of glucose or the amount of insulin released into the blood.

Table 1. Drug Classes of Antihyperglycemic Agents for the Treatment of Type 2 Diabetes Mellitus

Treatment Class	**Mechanism of Action**	**Example Side Effect(s)**
Sulfonylureas	Stimulate pancreas to release more insulin	Hypoglycemia
Biguanides	Decrease glucose produced in liver	Diarrhea
Meglitinides	Stimulate pancreas to release more insulin	Hypoglycemia
Thiazolidinediones	Assist insulin effectiveness in muscle and fat; reduce glucose production in liver	Heart failure
DPP-4 Inhibitors	Prevent breakdown of GLP-1	Upper respiratory tract infection
SGLT2 Inhibitors	Blocks reabsorption of glucose in kidney	Limb amputations
α-glucosidase inhibitors	Blocks breakdown of starches in intestine	Gas and diarrhea
GLP-1 agonists	Prevent breakdown of GLP-1	Acute pancreatitis
Bile acid sequestrants	Not well understood; indicated for hypocholesterolemia	Flatulence and constipation

Many antihyperglycemic agents associated with cardiovascular events

On May 21, 2007 the FDA issued a Boxed Warning for Avandia (rosiglitazone), a thiazolidinedione, for a possible increased risk for myocardial infarctions. This warning was based on both an internal and external meta-analysis examining the association between rosiglitazone and myocardial infarction and death from cardiovascular events[9]. The trials included in these meta-analyses were small and primarily placebo-controlled; however, many were not powered or designed to detect cardiovascular events. At the time of the Nissen and Wolski review, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial was ongoing; later results would suggest an increased risk for heart failure but no increased risk for overall cardiovascular morbidity or mortality when compared to metformin and sulfonylurea[10]. The Avandia label was updated in August 2007 to include a warning that the drug might cause or exacerbate heart failure in some patients. Additionally, rosiglitazone was contraindicated for those with a prior history of the New York Heart Association class III or IV heart failure.

Over the next four years, FDA expanded the Risk Evaluation and Mitigation Strategies program for rosiglitazone containing products by restricting access to patients who were already successfully treated with these medications and those whose blood sugar could not be controlled with other anti-diabetic medications and did not wish to use pioglitazone-containing products. The data from RECORD was re-evaluated in 2011. At this time, possible bias was uncovered due to misclassification of cardiovascular events. The re-evaluation showed that there was no increased risk for heart attacks compared to metformin and sulfonylurea. Despite the eventual removal of these prescribing

restrictions, these actions prompted the development of a Guidance for Industry on evaluating cardiovascular risk with T2DM therapies and increased vigilance for cardiovascular events upon the approval of subsequent antihyperglycemic agents[2].

Association between DPP-4i and acute cardiovascular events remains unclear

One of the more recent classes of antihyperglycemic agents to be approved is DPP-4i. These treatments act by preventing the breakdown of glucogon-like peptide-1 (GLP-1)[11]. The breakdown of GLP-1 stimulates the release of insulin, improving glucose homeostasis. DPP-4i carry a low risk of hypoglycemia and are not associated with weight gain or gastrointestinal symptoms that are often commonly found with the use of other antihyperglycemic agents. Additionally, DPP-4i were initially thought to protect against major adverse cardiac events (MACE), making them a safer option to rosiglitazone and other thiazolidinediones, which have been linked to heart failure[9,12].

FDA issued a Drug Safety Communication in 2014 for generalized cardiovascular risk with the use of these products based on Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR), a placebo-controlled, phase 4 trial investigating cardiovascular risk with saxagliptin, and post-marketing surveillance data for saxagliptin, alogliptin, and sitagliptin[13,14]. Similar to the case of rosiglitazone, the weight of evidence supporting the Drug Safety Communication did not definitively point to an increased risk of cardiovascular events with the use of saxagliptin. Baseline data on cardiovascular risk for SAVOR showed that all patients either had multiple risk factors for cardiovascular disease or were diagnosed with cardiovascular disease[15]. Results suggested an increased risk of heart failure compared to placebo, but

SAVOR was only designed to assess heart failure as part of a composite, secondary outcome[14]. Common drawbacks of composite outcomes include interpreting the significance of results when they are not uniform across all components of the composite outcome[16]. In this case, interpreting the risk of one component of the composite could lead to possible type I error. Additionally, the composite outcome was a secondary outcome, calling into question its validity and reproducibility[17].

The Endocrinologic and Metabolic Drugs Advisory Committee also assessed the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) data for cardiovascular events associated with alogliptin. In contrast to SAVOR, EXAMINE was conducted in patients with acute coronary syndrome. Of the 5380 patients, 77.2% had previously suffered a myocardial infarction, and the remainder 22.6% had unstable angina[18]. These post-hoc analyses were assessed with due caution, especially since heart failure and other acute cardiovascular events are rare. Both trials showed a non-statistically significant increased risk for congestive heart failure with DPP-4i use in high-risk populations. However, out of an abundance of caution, FDA placed a warning of generalized cardiovascular risk on the labels of saxagliptin and alogliptin products. Noting that deaths from CVD are two- to eight-fold higher in T2DM patients, the drug label warnings on DPP-4i provide proactive protection for at-risk patients; however, these actions might inadvertently limit treatment options for patients when the evidence for their claims are less than conclusive.

Recently published data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial, which evaluated the primary composite outcome of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization

for unstable angina in patients >50 years old with established CVD, showed that sitagliptin was noninferior compared to placebo (HR=0.98, 95% CI: 0.83, 1.20, P=0.98)[19]. In addition to the TECOS trial, recent observational data from Taiwan's National Health Insurance Research Database also support no increased risk of acute cardiovascular events with the use of DPP-4i. DPP-4i treated patients were matched to non-DPP-4i treated patients on clinical and socio-demographic characteristics and followed for all-cause mortality (HR=0.79, 95% CI: 0.72, 0.87) and major adverse cardiovascular event (HR=0.79, 95%CI: 0.75, 0.83)[20]. While these studies suggest no increased risk for acute cardiovascular events, they were designed to assess composite outcomes. The benefit of spontaneously reported adverse events reports is their ability to detect specific, rare event signals without having to tease out composite outcomes.

Data Sources

FDA Adverse Event Reporting System

FDA currently collects adverse event reports for all of its regulated products through MedWatch, a passive adverse event surveillance system developed in 1993. This portal collects reports from patients, patient advocates, and providers. Additionally, manufacturers are required to submit spontaneously reported adverse event reports for their products within 15-days of receipt of the information by the applicant. Reports from both of these pathways are organized and entered into the FDA Adverse Events Reporting System (FAERS). This information was initially used to detect drug-event combinations in patients taking more than one product, since clinical trials submitted during the drug-approval process typically exclude these types of patients. Over time, the

system has evolved to collect information on the adverse event (date, duration, related laboratory test results), drug (manufacturer, dose, frequency, duration of treatment, route of administration, prescribed indication), patient background (age, sex, weight, concomitant medications), and event abatement upon dechallenge and rechallenge of suspect medication. Case reports are available free-of-charge and downloadable as FAERS Quarterly Data Files, via web access on the FDA website. FDA relies heavily on FAERS to detect safety issues in a larger, heterogeneous patient population[21].

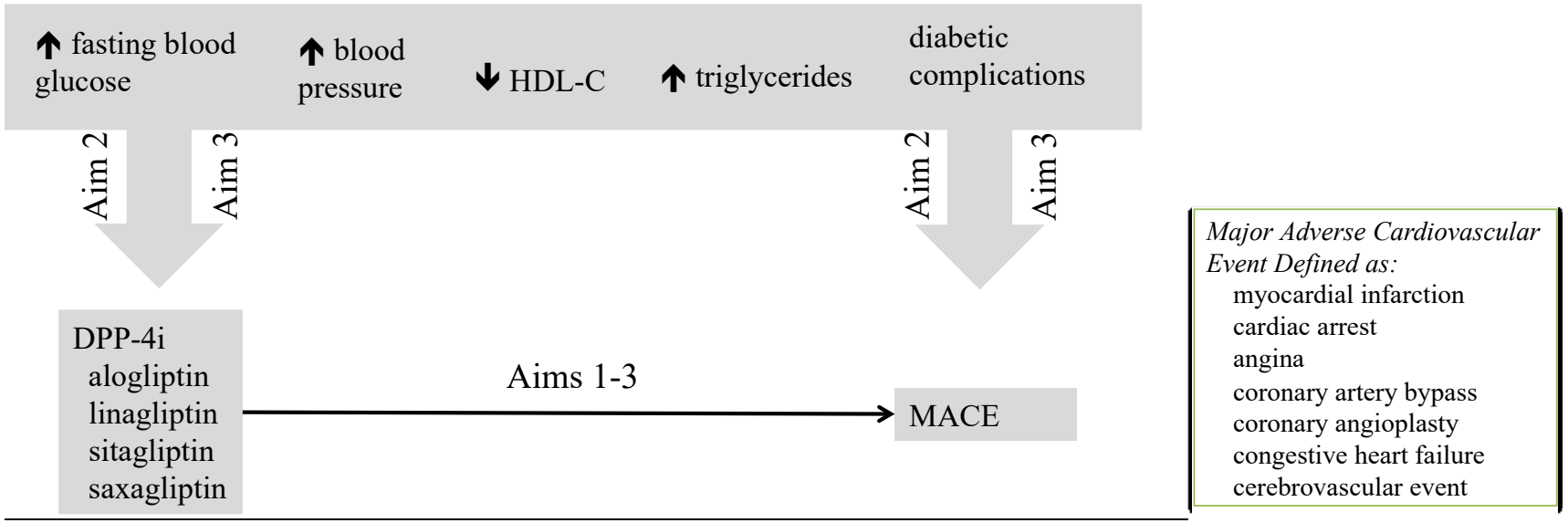
Truven Health Analytics MarketScan® Commercial Claims and Encounters Database

MarketScan Commercial Claims and Encounters Database (Commercial) contains linked medical and drug data for millions of Americans covered by approximately 350 payors. The data are representative of insured employees and their families, early retirees, Consolidated Omnibus Budget Reconciliation Act covered users, and Medicare Supplemental insurance holders. Insurance plans include fully- and partially-capitated fee-for-service, preferred provider organizations, exclusive provider organizations, point of service plans, indemnity plans, health maintenance organizations, and consumer-directed health plans. Employer database data consist of inpatient cases, inpatient services, outpatient services, capitated encounter records, enrollment counts, and outpatient prescription drug claims. There are currently data on 210 million unique patients in the database, spanning all 50 states since 1995. MarketScan is particularly equipped to provide additional clinical context to adverse events through this data linkage.

Conceptual Framework

This dissertation focused on the association between DPP-4i and major adverse cardiovascular events. In order to understand this association, we first assessed safety signals in the FAERS reports submitted to FDA to better understand whether the drug-event combination of DPP-4i therapy and major adverse cardiovascular events was greater than would be expected given the background risk in the full set of adverse event reports and in a subset of reports consisting of all adverse events reported for cardiovascular and diabetic drug products (AIM 1). Next, we examined the medical history of treatment naïve patients without a history of cardiovascular disease or renal impairment to assess whether the risk for major adverse cardiovascular events is increased with the use of DPP-4i compared to sulfonylureas and to metformin using a propensity score weighted Cox proportional hazard model, adjusting for individual demographics, comorbidities, and concomitant medications (AIM 2). Finally, we conducted a similar analysis in treatment naïve patients with a history of cardiovascular disease and/or renal impairment (AIM 3).

Figure 1. Conceptual Framework for Dissertation



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CARDIOVASCULAR RISK WITH DIPEPTIDYL PEPTIDASE-4 INHIBITORS: A DISPROPORTIONALITY ANALYSIS AMONG HIGH RISK PATIENTS

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ABSTRACT

Purpose: In 2008, the U.S. Food and Drug Administration (FDA) issued Draft Guidance on investigating cardiovascular risk with oral diabetic drugs, including dipeptidyl peptidase-4 inhibitors (DPP-4i). In 2014, underpowered, post-hoc analyses of clinical trials suggested an increased risk of heart failure with the use of these products. As such, we assessed disproportionate reporting of major adverse cardiac events (MACE) among reports for DPP-4i submitted to the FDA Adverse Event Reporting System (FAERS) from 2006-2015.

Methods. We assessed the empirical Bayes geometric mean (EBGM) and its lower bound (EB05) of the relative reporting ratio for MACE among DPP-4i reports in the full FAERS database and in a subset of reports limited to cardiovascular and diabetic drugs. We then compared the EB05 in these two analyses and calculated the percent positive agreement for signals of disproportional reporting (SDR) involving MACE.

Results. Of 180.3 million adverse event reports, 13.4 million were for diabetic and cardiovascular drugs. In the cardiovascular subset, there was a SDR for heart failure with linagliptin (EB05=2782.47) and saxagliptin (EB05=2.40), myocardial infarction with alogliptin (EB05=290.11), and cerebral infarction with sitagliptin (EB05=2.80). Of the 14 MACE, 8 had a percent positive agreement ≥50% for a SDR in both analyses. Overall, the cardiovascular subset elicited 11 more SDR for DPP-4i than the full dataset.

Conclusions. Postmarketing surveillance of DPP-4i through FAERS suggest increased reporting of MACE, supporting the current FDA warning of heart failure risk. This suggests the need for additional longitudinal, observational research into the association of DPP-4i and other MACE.

Keywords

Dipeptidyl peptidase-IV inhibitors; drug-related side effects and adverse reactions; heart failure; pharmacovigilance

Introduction

As of 2015, the Centers for Disease Control and Prevention estimate that 23.1 million people in the United States have diagnosed diabetes, 5% of whom have type 1 diabetes[8]. Many of these patients also experience medical complications such as coronary heart disease, stroke, nephropathy, neuropathy and retinopathy[23]. Following the approval of many new classes of medications, the mean number of diabetic medications prescribed per patient visit was 1.45 in 2007, an increase of 0.39 from 1994[24]. These treatments have a variety of novel mechanisms targeting the pancreas, liver, kidney, gastrointestinal tract, or muscle and fat tissues. While there are a variety of treatment options available, both providers and regulators seek to better understand the benefits and risks of these medications in postmarket settings.

Among the newest medicines, glitazones, incretins, and dipeptidyl peptidase-4 inhibitors (DPP-4i) have increased in market share since their introduction in 2003[25]. Since the approval of the first DPP-4i, sitagliptin, in 2006, the U.S. Food and Drug Administration (FDA) have approved ten additional single-ingredient or fixed-dosed combination DPP-4i. These treatments are approved as monotherapy as well as add-on therapy to metformin and act by preventing the breakdown of glucogon-like peptide-1 (GLP-1)[15]. The breakdown of GLP-1 stimulates the release of insulin, improving glucose homeostasis. DPP-4i have several appealing characteristics including a low risk of hypoglycemia as well as the absence of an association with weight gain or gastrointestinal symptoms that often limit the use of other anti-diabetic products. Based on premarketing clinical trial data, adverse events are less severe than other treatment options but include acute pancreatitis[26]. In addition, DPP-4i were initially thought to

protect against major adverse cardiac events (MACE), making them a safer option to rosiglitazone and other thiazolidinediones, which have been linked to heart failure[1,16]. However, while failing to reach statistical significance, one Phase 4 trial suggested hospitalization for heart failure with saxagliptin use[3].

Given continued interest in the cardiovascular safety of these products on the part of patients, clinicians, payers and regulators, we compared signals for disproportional reporting (SDR) for MACE for DPP-4i in the full set of drug-related FDA adverse event reports and a subset containing all of the adverse event reports for cardiovascular and diabetic drug products.

Methods

Data

We used post-marketing adverse event data submitted to the FDA Adverse Events Reporting System (FAERS) to assess whether safety concerns exhibited through spontaneous reporting were suggestive of an association between DPP-4i use and MACE. We accessed FAERS reports submitted to the FDA from October 1, 2006 to December 31, 2015 via the FAERS Quarterly Data Files published online by the FDA[27]. This time period captured adverse events submitted to FDA from October 16, 2006, when sitagliptin, the first DPP-4i, was approved. We then filtered the reports for FDA drug products using the list of brand and generic drugs in the FDA publication, Approved Drug Products with Therapeutic Equivalent Evaluations in order to include all FDA approved drug products and exclude other FDA approved products such as biologics[28]. We excluded reports without a suspect medication (N=3,556), adverse event (N=0) or

report number (N=0). Each drug-event combination in FAERS is listed as individual records and linked via report number. From these reports, we abstracted the report number, patient age, patient sex, suspect drug, concomitant medications, adverse event, and date of report.

Rationale of Datasets and Analytic Approach

We conducted Bayesian disproportionality analyses using two different sets of data. We use the full set of drug-related adverse event reports in FAERS ("full set") and a subset of reports submitted only for non-insulin antihyperglycemic agents and drugs indicated for cardiovascular disease ("cardiovascular subset"). By using these two different sets, we were able to compare and contrast SDR between two datasets with different assumptions regarding the Bayesian prior for the disproportionality analysis. In the overall body of FAERS reports, the Bayesian prior comprised of the general patient population and therefore assumed average risk for MACE. In the cardiovascular subset, the Bayesian prior assumed a higher risk for the patient population in that they were known to have diabetes or cardiovascular disease by virtue of the drugs they were on. In each dataset, we also compared the EB05 for DPP-4i to those of sulfonylureas and biguanides. We compared the results of DPP-4i with sulfonylureas due to their known cardiovascular risk[29], high utilization, and similar patient population to DPP-4i patients. We chose biguanides as a second comparison group due to their relatively low cardiovascular risk[30].

Analysis

We first characterized the patients for whom adverse event reports were submitted for DPP-4i, sulfonylureas, and biguanides in both the full set and cardiovascular subset.

We conducted disproportionality analyses on every drug-event combination in the full dataset to determine the Empirical Bayes geometric mean of the relative reporting ratio (EBGM). We used the DuMouchel multi-item gamma Poisson shrinkage method to derive and rank the EBGM[31]. The method allows for the comparison of reporting ratios of individual adverse events for a particular drug and the full database of adverse events. In this analysis, the full database serves as the Bayesian prior. This method has been extensively replicated for the use of data-mining in pharmacovigilance[32-35]. The EBGM allowed for valid assessments of relative reporting ratios even in the presence of small samples within the database. From these EBGMs we took the lower bound on the 90% credible interval to establish a threshold consistent with FDA practice of EB05 >2.0 to indicate a SDR for any drug-event combination[36]. Events were pre-coded with the latest version of preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) dictionary at the time of release in the FAERS quarterly data file. From the full list of SDR, we focused on the results pertaining to MACE. We defined major adverse cardiovascular events as any of the following MedDRA terms: acute myocardial infarction, atrioventricular block complete, cardiogenic shock, myocardial infarction, arteriosclerosis coronary artery, cardiac arrest, cardiac failure, cardiac failure congestive, sudden death, sudden cardiac death, cerebrovascular event, cerebral infarction, hemorrhagic stroke, and ischemic stroke.

For our cardiovascular subset of reports, we filtered the full dataset for all reports for suspect drugs that were FDA approved oral antihyperglycemic agents or cardiovascular medications listed in **Supplemental Table 1**. From the cardiovascular subset, we conducted the DuMouchel disproportionality analysis on each drug-event combination to determine the EB05. In this analysis, the oral antihyperglycemic agents and cardiovascular drugs served as the Bayesian prior. We then assessed the percent positive agreement for the signals for MACE between the cardiovascular subset and the full set of reports.

Finally, we compared the disproportionality results of MACE reporting for DPP-4i, sulfonylureas, and biguanides for the cardiovascular set and the full set of reports. We also calculated the percent positive agreement between signals for MACE with DPP-4i, sulfonylureas, and biguanides in the full dataset and the cardiovascular subset.

In order to determine whether or not reporting of MACE was sensitive to regulatory actions related to oral antihyperglycemic agents, we assessed the possibility of stimulated reporting of adverse events with DPP-4i using the methods previously described by Hoffman et al[37]. We first identified three actions that could have potentially stimulated the reporting of adverse events with oral antihyperglycemic agents: the 2007 FDA warning about cardiovascular risk with the use of rosiglitazone-containing products, the 2008 *FDA Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, and the 2014 FDA warning regarding the risk of congestive heart failure with the use of DPP-4i[1,2,7,38]. To assess whether these actions resulted in an increase in reporting, we then compared the period

after these actions to the period after sham actions. We chose sham action dates five fiscal quarters prior to the regulatory actions.

For each of the regulatory actions and sham actions, we calculated the percent change in the number of reports in the two quarters after the regulatory and sham actions and performed a Mann-Whitney test to assess statistically significant differences in percent change between the pairs.

This study was exempt from review by a Johns Hopkins University Institutional Review Board.

Results

Descriptive Statistics

There were a total of 180.4 million drug-event pairs in the full dataset and 13.4 million (7.4%) in the cardiovascular subset. 208,385 (0.1%) reports were for DPP-4i from patients with a median of 60 (IQR: 56, 71) years of age. Of reports associated with DPP-4i, the majority (51.8%) was from male patients, 37.1% listed concomitant medications, and 43.4% were attributed to a sitagliptin-containing product.

A total of 444,780 reports were for sulfonylureas. Of these, three-fifths involved males, the median patient age was 63 (IQR: 53, 73) years, 77.6% listed concomitant medications, and glimepiride was most commonly represented (59.0%). Additionally, 345,580 reports were for biguanides, involving patients with a median age of 62 (IQR:

53, 70) years of whom approximately one-half (51.5%) were male and 60.1% listed concomitant medications.

Full FAERS Dataset

For myocardial infarction, there was a signal with alogliptin (EB05=15.9) among the DPP-4i. Among the sulfonylureas and biguanides, chlorpropamide (EB05=27.9), glipizide (EB05=2.8), glipizide extended release (EB05=2.1), and metformin hydrochloride (EB05=6.7) elicited SDR for myocardial infarction. For cerebral infarction, there was one DPP-4i SDR with sitagliptin (EB05=2.5). With the sulfonylureas and biguanides, glimepiride (EB05=4.0) elicited a SDR for cerebral infarction.

Among the DPP-4i FAERS reports in this dataset, sitagliptin (EB05=0.5) and sitagliptin combined with metformin (EB05=0.4) had reports of congestive heart failure; however, these did not cross the threshold for a potential SDR. In contrast, the following sulfonylurea-containing products elicited a SDR for congestive heart failure: glimepiride (EB05=2.4), glimepiride with pioglitazone hydrochloride (EB05=2.4), glimepiride with rosiglitazone maleate (EB05=7.3), glipizide (EB05=4.8), glyburide (EB05=3.3), and glyburide with metformin hydrochloride (EB05=2.7) (**eTable 2, 3, 4**).

Report Subset with Diabetes and Cardiovascular Drugs

Similar to the full dataset, the subset of reports from cardiovascular drugs had a signal for myocardial infarction with alogliptin (EB05=4.5), saxagliptin (EB05=10.0), chlorpropamide (EB05=13.4), glipizide (EB05=2.01), glipizide extended release (EB05=17.6), and metformin hydrochloride (EB05=3.2). For cerebral infarction, there

was a signal with sitagliptin (EB05=2.8) and none among the sulfonylureas and biguanides. Also in this subset, there was no statistically significant signal for congestive heart failure with any DPP-4i or biguanide. However, the following sulfonylurea-containing products elicited a signal for congestive heart failure: glipizide (EB05=23.7), and glimepiride and rosiglitazone maleate (EB05=2.4). The DPP-4i, linagliptin (EB05=2782.5) and saxagliptin (EB05=2.4) elicited signals for heart failure (**Supplemental Tables eTable 2, 3, 4**).

Comparison of SDR by Dataset

There were 2 signals for MACE in the Bayesian disproportionality analysis of the full dataset compared to 12 with the cardiovascular subset among DPP-4i (**Table 1**). Overall among the three antihyperglycemic drug classes, there was general agreement in SDR between the two datasets for acute myocardial infarction and hemorrhagic stroke. However, there were 12 instances where the full dataset elicited a SDR, and the cardiovascular subset did not. There were 12 instances where the cardiovascular subset elicited a SDR, and the full dataset did not. All of the discordances in DPP-4i signals between the two datasets showed a signal in the cardiovascular subset but not in the full dataset. However, for the sulfonylureas 11 of the 12 signal discrepancies showed a signal in the full dataset and not in the cardiovascular subset. There was 1 discrepancy among the biguanides.

Percent Positive Agreement Between Full Set and Cardiovascular Set

Table 2 shows the percent positive agreement between the full dataset and the cardiovascular subset for DPP-4i, sulfonylureas and biguanides, respectively. Of the 14 MACE of interest, 5 had a percent positive agreement ≥50%, suggesting that surveillance for a subset of reports from patients who may be at heightened risk of MACE has utility in detecting additional SDR. Among the reports from patients who may be expected to experience MACE, there was greater detection of congestive heart failure, atrioventricular block complete, cerebrovascular accident, and cerebral infarction. The lowest percent positive agreement was with arteriosclerosis coronary artery, sudden death, and cerebrovascular accident each with 0% percent positive agreement. Heart failure (PPA=33.3%) and congestive heart failure (PPA=33.3%) each had low percent positive agreement. The analyses of the full dataset and the cardiovascular subset each detected 12 unique SDR.

Stimulated Reporting

Comparing the percent change between the two months after the regulatory events and two months after the sham events showed no statistically significant results for the 2007 rosiglitazone warning about cardiovascular risk (W=54.0, p=0.5), the 2008 FDA Guidance for Industry (W=41.0, p=1.0), or the 2014 FDA warning for DPP-4i risk of heart failure (W=56.0, p=0.5). Therefore, we did not detect evidence of stimulated reporting.

Discussion

In this disproportionality analysis of FDA adverse event reports, we examined the relative reporting ratio for MACE with the use of DPP-4i. Among a subset of adverse events reports that are generated from a group of patients with a high risk for cardiovascular events, there was an increase in reporting of MACE for sitagliptin, saxagliptin, linagliptin, and alogliptin. These SDR suggest that even among a group of reports where one would expect to see high numbers of reports for these events, the DPP-4i class stands out. In addition to the previously reported association with heart failure, our results suggest that DPP-4i adverse event reporting is increased for multiple MACE. Finally, we found that creating a subset of reports from drugs associated with diabetes and cardiovascular disease allowed for detection of additional MACE reporting.

Interestingly, our analyses of the cardiovascular risks of DPP-4i using the full FAERS dataset only identified two SDR, whereas our use of the cardiovascular subset elicited 12 distinct signals. By contrast, we identified fewer cardiovascular signals using the full rather than the subset when examining sulfonylureas (20 vs 10) and biguanides (8 vs. 9). This suggests that for products where there is a known association with cardiovascular events with those products (i.e. sulfonylureas), signal detection in the full FAERS dataset is sensitive enough to detect potential SDR. However, for products where association is tenuous, a subset with reports from a high-risk patient population may be more sensitive to capture additional SDR for further investigation.

As the purpose of disproportionality analyses is hypothesis generation, this evidence cannot independently support FDA actions. While prior evidence suggested that DPP-4i were associated with heart failure, we were interested in investigating

whether or not there were additional SDR for other MACE with distinct pathogenesis (e.g., myocardial infarction). In examining percent positive agreement between analyses of the two datasets, the cardiovascular subset can allow for greater sensitivity to detect SDR associations that might be confounded by comorbidities commonly found with diabetes. This methodology of subsetting the adverse event reports to a high-risk pool of patients has utility in identifying SDR for further investigation.

Our approach of honing in on a subset of adverse events reports from similar drugs or a high-risk population provides opportunities for increasing the sensitivity of Bayesian signal detection. Given that signal detection methods are primarily utilized by regulatory agencies for hypothesis generation about drug safety issues, increasing sensitivity is desirable especially in cases where comorbidities may act like confounders. In this example, we were able to highlight additional MACE aside from heart failure that could be further investigated in longitudinal studies. This method allows for increased vigilance for specific risk groups without the high resource allocation an FDA Risk Evaluation and Mitigation Strategies (REMS) program would require.

The FDA has acknowledged the limitations of its current signal detection methods and is actively seeking novel approaches to its surveillance activities. Two points of concern with current practices are the threshold of EB05=2.0 and residual confounding[39]. Through restriction of the Bayesian prior to adverse event reports stemming from a pool of patients with related illnesses, our approach can reduce the level of residual confounding. Additionally, as the EB05=2.0 threshold is considered a minimal threshold for further investigation of a drug safety concern, regulators can adjust this threshold based on the restricted patient population and their unique health concerns. For instance,

if this analysis approach were applied to a subset of reports associated with oncology products, regulators might increase the threshold for action on a non-life-threatening adverse event.

Our study had several limitations. The FAERS dataset is primarily a case report dataset initially developed to detect drug-drug interactions[40]. In this study, we were mining the data for single-drug adverse event associations. Despite previously established low cardiovascular risk, 8 of the 14 MedDRA terms elicited SDR for biguanides, our negative control. Causality remains unclear without further investigation, because the majority (60.1%) of the biguanide reports listed concomitant medications. Nonetheless, our use of negative and positive controls provides additional context when comparing the results between the full set and cardiovascular subset for DPP-4i.

Second, the level of missing covariates in the FAERS dataset did not allow for extensive analysis of the potential effect of demographic and medical characteristics that could affect the association between DPP-4i and MACE. Additionally potential underreporting in the FAERS system does not capture the true number of adverse events in the general population. Finally, DPP-4i are currently recommended as a first line diabetic therapy and are commonly prescribed to patients with more advanced diabetes than those on metformin or sulfonylureas[15]. While this raises a concern for selection bias, alternative comparators such as thiazolidinediones are associated with cardiovascular risk[14], while others such as SGLT2 inhibitors are associated with cardiovascular benefit[41].

Conclusions

We found evidence to suggest further investigation of MACE SDR associated with DPP-4i. While the analysis of the full dataset suggests a possible increase in reporting of MACE with the use of DPP-4i, the results from the cardiovascular subset show utility in identifying additional SDR. This novel approach to pharmacovigilance contrasts with the current approach of conducting surveillance on the entire exposed population, irrespective of risk level. Conducting signal detection in subsets of reports stemming from high-risk populations allows regulators to hone in on the most vulnerable members of the exposed population. Longitudinal, observational research is needed to fully understand the association between DPP-4i use and cardiovascular events.

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Table 1: Bayesian signals of disproportional reporting (EB05† <2.0) for antidiabetic agents in full dataset and cardiovascular subset ‡

	Acute Myocardial Infarction		Atrioventricular Block Complete		Cardiogenic Shock		Myocardial Infarction		Arteriosclerosis Coronary Artery		Cardiac Arrest		Cardiac Failure	
	Full Set (N = 126,823)	CV Subset (N = 27,146)	Full Set (N = 34,538)	CV Subset (N = 10,061)	Full Set (N = 59,134)	CV Subset (N = 10,394)	Full Set (N = 328,431)	CV Subset (N = 67,602)	Full Set (N = 61,010)	CV Subset (N = 14,027)	Full Set (N = 464,712)	CV Subset (N = 49,987)	Full Set (N = 322,345)	CV Subset (N = 45,574)
DPP-4 Inhibitors														
alogliptin	◆1.34	◆0.68					◆15.89	◆4.48					◆0.16	◆0.03
linagliptin											◆0.29	◆0.28		◆3126.03
saxagliptin								◆9.98		◆81.01		◆7.17		◆2.41
sitagliptin	◆1.65	◆0.81			◆0.93	◆0.52	◆0.95	◆0.46	◆0.90	◆0.39	◆0.46	◆0.71	◆0.16	◆1.01
sitagliptin; metformin							◆0.26	◆0.05			◆0.16	◆0.13		
sitagliptin; metformin ER	◆0.45	◆0.14												
Sulfonylureas														
chlorpropamide							◆27.94	◆13.41						
glimepiride	◆1.98		◆9.92		◆1.23		◆1.69		◆4.13		◆0.75		◆0.62	
glimepiride; pioglitazone HCL														
glimepiride; rosiglitazone maleate														
glipizide	◆139.18	◆33.46	◆0.79		◆1.71	◆3.34	◆2.75	◆2.01	◆0.98	◆0.07	◆0.73	◆0.45	◆0.28	◆0.22
glipizide ER	◆0.45	◆0.21					◆36.59	◆17.55			◆0.26	◆0.21		
glyburide	◆1.13	◆0.55	◆7.66	◆2.50	◆1.04	◆0.58	◆1.34	◆0.65	◆0.90	◆0.39	◆1.95	◆1.67	◆0.27	◆0.90
glyburide; metformin HCL	◆0.91	◆0.46	◆0.19	◆0.48	◆4.57	◆2.58	◆2.09	◆1.03			◆44.11	◆38.48	◆0.43	◆0.31
Biguanides														
metformin HCL	◆0.58	◆0.28	◆12.70	◆4.15	◆4.06	◆2.25	◆6.71	◆3.22	◆0.59	◆0.25	◆0.24	◆0.24	◆16.12	◆6.45
metformin HCL ER								◆1.31						

◆ EB05 <2.0 ◆ EB05 ≥2.0

† EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio

‡ Excludes products with n=0 reports, EB05 <0, or EBGM <0

Table 1 (cont'd): Bayesian signals of disproportional reporting (EB05† <2.0) for antidiabetic agents in full dataset and cardiovascular subset ‡

	Cardiac Failure Congestive		Sudden Death		Sudden Cardiac Death		Cerebrovascular Accident		Cerebral Infarction		Hemorrhagic Stroke		Ischemic Stroke	
	Full Set (N = 359,336)	CV Subset (N = 66,952)	Full Set (N = 74,163)	CV Subset (N = 8,493)	Full Set (N = 55,841)	CV Subset (N = 11,327)	Full Set (N = 183,283)	CV Subset (N = 36,271)	Full Set (N = 122,372)	CV Subset (N = 12,910)	Full Set (N = 30,587)	CV Subset (N = 5,563)	Full Set (N = 27,260)	CV Subset (N = 6,054)
DPP-4 Inhibitors														
alogliptin			◆1.97	◆3.57				◆606.37	◆0.26	◆0.07				
linagliptin							◆0.33	◆0.31						
saxagliptin		◆0.97		◆30.99		◆98.70		◆3.15		◆0.38				◆14.04
sitagliptin	◆0.51	◆0.28	◆0.10	◆0.06			◆1.45	◆0.74	◆2.47	◆2.81	◆0.25	◆0.12	◆0.13	◆0.04
sitagliptin; metformin	◆0.43	◆0.23	◆0.15	◆0.06			◆0.06	◆0.01						
sitagliptin; metformin ER							◆0.34	◆0.80						
Sulfonylureas														
chlorpropamide														
glimepiride	◆2.44	◆1.34	◆0.32				◆2.11	◆1.09	◆3.97		◆0.42		◆9.54	
glimepiride; pioglitazone HCL	◆2.42	◆1.64					◆0.49	◆0.25						
glimepiride; rosiglitazone maleate	◆7.28	◆2.38					◆3.16	◆1.77						
glipizide	◆4.79	◆23.67	◆0.39				◆0.77	◆0.46	◆0.14		◆0.67		◆0.49	
glipizide ER	◆1.65	◆0.92					◆0.52	◆0.26						
glyburide	◆3.29	◆1.79	◆0.54	◆0.42			◆1.82	◆0.93	◆1.72	◆1.94			◆0.75	◆0.35
glyburide; metformin HCL	◆2.66	◆1.48					◆1.38	◆0.73	◆0.12	◆0.08				
Biguanides														
metformin HCL	◆1.20	◆0.65	◆1.54	◆2.26	◆62.94	◆18.14	◆2.68	◆1.37	◆0.60	◆0.67	◆5.04	◆2.81	◆87.66	◆27.52
metformin HCL ER		◆1.30					◆0.77	◆0.75						

◆ EB05 <2.0 ◆ EB05 ≥2.0

† EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio

‡ Excludes products with n=0 reports, EB05 <0, or EBGM <0

Table 2. Percent positive agreement between datasets†

			Full Dataset		Percent Positive Agreement
			SDR	No SDR	
Cardiovascular Subset	SDR	Acute myocardial infarction	1	0	100.0%
		Atrioventricular block complete	2	0	66.7%
		Cardiogenic shock	2	1	66.7%
		Myocardial infarction	5	1	71.4%
		Arteriosclerosis coronary artery	0	1	0.0%
		Cardiac arrest	1	1	50.0%
		Cardiac failure	1	2	33.3%
		Cardiac failure congestive	2	0	33.3%
		Sudden death	0	3	0.0%
		Sudden cardiac death	1	1	50.0%
		Cerebrovascular accident	0	1	0.0%
		Cerebral infarction	1	0	50.0%
		Hemorrhagic stroke	1	0	100.0%
		Ischemic stroke	1	1	33.3%
	No SDR	Acute myocardial infarction	0	20	
		Atrioventricular block complete	1	18	
		Cardiogenic shock	0	18	
		Myocardial infarction	1	14	
		Arteriosclerosis coronary artery	1	19	
		Cardiac arrest	0	19	
		Cardiac failure	0	18	
		Cardiac failure congestive	4	15	
		Sudden death	0	18	
		Sudden cardiac death	0	19	
		Cerebrovascular accident	3	17	
		Cerebral infarction	1	19	
		Hemorrhagic stroke	0	20	
		Ischemic stroke	1	18	

† There were 21 total drug event combinations involving DPP-4i, sulfonylureas, and biguanides with major adverse cardiac events.

SUPPLEMENTARY MATERIAL

eTable 1: Drugs used in Cardiovascular Subset

FDA Approved DPP-4 Inhibitors
- alogliptin
- alogliptin and metformin
- alogliptin and pioglitazone
- linagliptin
- linagliptin and empagliflozin
- linagliptin and metformin
- sitagliptin
- sitagliptin and metformin
- sitagliptin and metformin extended release
- saxagliptin
- saxagliptin and metformin extended release

FDA Approved Sulfonylureas
- chlorpropamide
- glimepiride
- glimepiride and pioglitazone hydrochloride
- glimepiride and rosiglitazone maleate
- glipizide
- glipizide extended release
- glyburide
- glyburide and metformin hydrochloride

*FDA Approved Biguanides**
- metformin hydrochloride
- metformin hydrochloride extended release

FDA Approved GLP-1 Agonists
- albiglutide
- dulaglutide
- exenatide synthetic
- liraglutide recombinant

FDA Approved Thiazolidinediones
- alogliptin benzoate and pioglitazone hydrochloride
- metformin hydrochloride and rosiglitazone maleate
- metformin hydrochloride and pioglitazone hydrochloride
- metformin hydrochloride and pioglitazone hydrochloride extended release
- pioglitazone hydrochloride
- rosiglitazone maleate

*FDA Approved SGLT2 Inhibitors**
- canagliflozin
- canagliflozin and metformin
- dapagliflozin
- dapagliflozin and metformin extended-release
- empagliflozin
- empagliflozin and linagliptin
- empagliflozin and metformin

*FDA Approved Meglitinides**
- nateglinide
- repaglinide
- repaglinide and metformin hydrochloride

*FDA Approved α-Glucosidase Inhibitors**
- miglitol

acarbose

FDA Approved Statins

pravastatin sodium
atorvastatin calcium
simvastatin
cerivastatin sodium
lovastatin
fluvastatin sodium extended release
rosuvastatin
pitavastatin
fluvastatin sodium
atorvastatin calcium; ezetimibe
extended release niacin; lovastatin

FDA Approved Fibrates

fenofibrate
choline fenofibrate

FDA Approved Niacin/Nicotinic Acid

niacin extended release

FDA Approved Bile Acid Sequestrants

colestipol
cholestyramine
colesevelam

FDA Approved Beta-Blockers

acebutolol hydrochloride
atenolol
atenolol; chlorthalidone
betaxolol hydrochloride
bisoprolol fumarate
bisoprolol fumarate; hydrochlorothiazide
carvedilol
carvedilol phosphate
labetalol hydrochloride
metoprolol tartrate
metoprolol tartrate; hydrochlorothiazide
nadolol
nebivolol
penbutolol sulfate
propranolol hydrochloride
propranolol hydrochloride extended release
propranolol hydrochloride sustained release
sotalol hydrochloride
timolol maleate
bendroflumethiazide; nadolol
hydrochlorothiazide; propranolol hydrochloride
hydrochlorothiazide; metoprolol succinate
metoprolol succinate extended release
pindolol

FDA Approved Angiotensin II Receptor Blockers

eprosartan mesylate
valsartan
telmisartan
hydrochlorothiazide; valsartan
hydrochlorothiazide; telmisartan
candesartan cilexetil
eprosartan mesylate; hydrochlorothiazide
nesiritide recombinant

olmesartan medoxomil
amlodipine besylate; hydrochlorothiazide; olmesartan medoxomil
azilsartan kamedoxomil; chlorthalidone
azilsartan kamedoxomil
irbesartan
hydrochlorothiazide; irbesartan
losartan potassium
sacubitril; valsartan
nebivolol hydrochloride; valsartan

FDA Approved Angiotensin Converting Enzyme Inhibitors

lisinopril
enalapril maleate/diltiazam malate
trandolapril
captopril; hydrochlorothiazide

FDA Approved Calcium Channel Blockers

diltiazem hydrochloride
verapamil extended release
verapamil
verapamil hydrochloride sustained release
enalapril maleate; felodipine
isradipine extended release
amlodipine besylate; olmesartan medoxomil
amlodipine besylate; atorvastatin calcium
clevidipine
aliskiren hemifumarate; amlodipine besylate
aliskiren hemifumarate; amlodipine besylate; hydrochlorothiazide
nimodipine
amlodipine besylate; perindopril arginine

FDA Approved Antiplatelet Agents

clopidogrel bisulfate
eptifibatide
anagrelide hydrochloride
prasugrel hydrochloride
vorapaxar sulfate
ticlodipine
dipyridamole
cangrelor
aspirin; omeprazole

FDA Approved Diuretics

atenolol; chlorthalidone
azilsartan kamedoxomil; chlorthalidone
fendolopam mesylate
hydrochlorothiazide; spironolactone
spironolactone

FDA Approved Anticoagulants

apixaban
ardeparin sodium
argatroban
bivalirudin
dabigatran etexilate mesylate
edoxaban tosylate
rivaroxaban
ticagrelor
tinzaparin sodium
warfarin sodium

FDA Approved Nitrates

hydralazine hydrochloride; isosorbide dinitrate
isosorbide
isosorbide dinitrate
isosorbide mononitrate
nitroglycerin
riociguat

FDA Approved Antihypertensive
treprostinil

FDA Approved Antianginals
ranolazine

FDA Approved Endothelin Receptor Antagonist
ambrisentan
macitentan

FDA Approved Dyslipidemic Agents
icosapent ethyl
omega-3 carboxylic acids

FDA Approved Direct Renin Inhibitor
aliskiren hemifumarate

FDA Approved MTP Inhibitors
lomitapide mesylate

FDA Approved Thiazides
bendroflumethiazide
chlorothiazide
chlorthalidone
hydroflumethiazide
indapamide
methyclothiazide
metolazone
polythiazide

FDA Approved Vasodilators
hydralazine hydrochloride
hydralazine hydrochloride; hydrochlorothiazide
hydralazine hydrochloride; hydrochlorothiazide; reserpine
hydralazine hydrochloride; reserpine
minoxidil
nitroglycerin
nitroprusside

FDA-Approved Alpha Adrenoreceptor Agonists
chlorthalidone; clonidine hydrochloride
chlorthiazide; methyldopa
clonidine
clonidine hydrochloride
guanabenz acetate
hydrochlorothiazide; methyldopa
methyldopa
methyldopa hydrochloride

eTable 2: Summary of safety signals for DPP-4 Inhibitors†

		Bayesian Disproportionality in Full Dataset (N=180,399,180)		Bayesian Disproportionality in Cardiovascular Subset (N=17,575,517)	
Adverse Event	**Drug**	**EB05‡**	**EBGM‡**	**EB05‡**	**EBGM‡**
Cardiac Disorders					
acute myocardial infarction	alogliptin	1.34	1.94	0.68	0.93
	sitagliptin	1.65	2.00	0.81	0.97
	sitagliptin and metformin	0.45	3.54	0.14	0.81
cardiogenic shock	sitagliptin	0.93	1.34	0.52	0.74
myocardial infarction	alogliptin	**15.89**	**19.78**	**4.48**	**5.57**
	saxagliptin			**9.98**	**12.12**
	sitagliptin	0.95	1.11	0.46	0.53
	sitagliptin and metformin	0.26	0.94	0.05	0.27
arteriosclerosis coronary artery	saxagliptin			**81.01**	**142.85**
	sitagliptin	0.90	1.25	0.39	0.53
cardiac arrest	linagliptin	0.29	10.73	0.28	17.20
	saxagliptin			**7.17**	**7.56**
	sitagliptin	0.46	0.70	0.71	1.13
	sitagliptin and metformin	0.16	0.44	0.13	0.70
cardiac failure	alogliptin	0.16	0.45	0.03	0.18
	linagliptin			**3126.03**	**5657.48**
	saxagliptin			**2.41**	**2.66**
	sitagliptin	0.16	0.21	1.01	1.34
cardiac failure congestive	saxagliptin			0.97	1.24
	sitagliptin	0.51	0.61	0.28	0.33
	sitagliptin and metformin	0.43	0.65	0.23	0.35
Generic Disorders and Administration Site Conditions					
sudden death	alogliptin	1.97	5.73	**3.57**	**7.82**
	saxagliptin			**30.99**	**32.93**
	sitagliptin	0.10	0.19	0.06	0.15
	sitagliptin and metformin	0.15	0.40	0.06	0.32
sudden cardiac death	saxagliptin			**98.70**	**103.74**

†Excludes products with n=0 reports, EB05 <0, or EBGM <0

‡ EBGM = empirical Bayes geometric mean of the relative reporting ratio; EB05=90% lower bound of EBGM

eTable 2 (cont'd): Summary of safety signals for DPP-4 Inhibitors†

		Bayesian Disproportionality in Full Dataset (N=180,399,180)		Bayesian Disproportionality in Cardiovascular Subset (N=17,575,517)	
Adverse Event	**Drug**	**EB05‡**	**EBGM‡**	**EB05 ‡**	**EBGM‡**
Nervous System Disorders					
cerebrovascular accident	alogliptin			**606.37**	**1069.46**
	linagliptin	0.33	73.47	0.31	21.83
	saxagliptin			**3.15**	**4.33**
	sitagliptin	1.45	1.71	0.74	0.87
	sitagliptin and metformin	0.06	0.14	0.01	0.07
	sitagliptin and metformin extended release	0.34	771.41	0.80	229.17
cerebral infarction	alogliptin	0.26	0.97	0.07	0.40
	saxagliptin			0.38	0.88
	sitagliptin	**2.47**	**2.93**	**2.81**	**3.27**
hemorrhagic stroke	sitagliptin	0.25	0.47	0.12	0.26
ischemic stroke	saxagliptin			**14.04**	**19.82**
	sitagliptin	0.13	0.28	0.04	0.13

†Excludes products with n=0 reports, EB05 <0, or EBGM <0

‡ EBGM = empirical Bayes geometric mean of the relative reporting ratio; EB05=90% lower bound of EBGM

eTable 3: Summary of safety signals for Sulfonylureas†

		Bayesian Disproportionality in Full Dataset (N=180,399,180)		Bayesian Disproportionality in Cardiovascular Subset (N=17,575,517)	
Adverse Event	**Drug**	**EB05‡**	**EBGM§**	**EB05‡**	**EBGM§**
Cardiac Disorders					
acute myocardial infarction	glimepiride	1.98	2.22		
	glipizide	**139.18**	**167.58**	**33.46**	**38.15**
	glipizide extended release	0.45	0.86	0.21	0.41
	glyburide	1.13	1.36	0.55	0.66
	glyburide and metformin hydrochloride	0.91	1.45	0.46	0.70
atrioventricular block complete	glimepiride	**9.92**	**10.86**		
	glipizide	0.79	1.11		
	glyburide	**7.66**	**8.75**	**2.50**	**2.86**
	glyburide and metformin hydrochloride	0.19	0.56	0.48	**3.33**
cardiogenic shock	glimepiride	1.23	1.74		
	glipizide	1.71	2.11	**3.34**	**4.28**
	glyburide	1.04	1.39	0.58	0.76
	glyburide and metformin hydrochloride	**4.57**	**6.46**	**2.58**	**3.55**
myocardial infarction	chlorpropamide	**27.94**	**34.82**	**13.41**	**16.70**
	glimepiride	1.69	1.82		
	glipizide	**2.75**	**2.94**	**2.01**	**2.27**
	glipizide extended release	**36.59**	**38.75**	**17.55**	**18.58**
	glyburide	1.34	1.49	0.65	0.72
	glyburide and metformin hydrochloride	**2.09**	**2.59**	1.03	1.24
arteriosclerosis coronary artery	glimepiride	**4.13**	**4.94**		
	glipizide	0.98	1.24	0.07	0.19
	glyburide	0.90	1.19	0.39	0.51
cardiac arrest	glimepiride	0.75	0.82		
	glipizide	0.73	0.81	0.45	0.59
	glipizide extended release	0.26	0.41	0.21	0.35
	glyburide	1.95	2.11	1.67	1.80
	glyburide and metformin hydrochloride	**44.11**	**52.51**	**38.48**	**44.83**

† Excludes products with n=0 reports, EB05 <0, or EBGM <0
‡ EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio
§ EBGM: empirical Bayes geometric mean of the relative reporting ratio

eTable 3 (cont'd): Summary of safety signals for Sulfonylureas†

		Bayesian Disproportionality in Full Dataset (N=180,399,180)		Bayesian Disproportionality in Cardiovascular Subset (N=17,575,517)	
Adverse Event	**Drug**	**EB05‡**	**EBGM§**	**EB05‡**	**EBGM §**
cardiac failure	glimepiride	0.62	0.69		
	glipizide	0.28	0.34	0.22	0.34
	glyburide	0.27	0.34	0.90	1.45
	glyburide and metformin hydrochloride	0.43	0.63	0.31	0.47
cardiac failure congestive	glimepiride	**2.44**	**2.69**	1.34	1.46
	glimepiride and pioglitazone hydrochloride	**2.42**	**18.34**	1.64	5.96
	glimepiride and rosiglitazone maleate	**7.28**	**16.34**	**2.38**	**5.31**
	glipizide	**4.79**	**5.01**	**23.67**	**27.09**
	glipizide extended release	1.65	2.15	0.92	1.17
	glyburide	**3.29**	**3.52**	1.79	1.91
	glyburide and metformin hydrochloride	**2.66**	**3.19**	1.48	1.73
Generic Disorders and Administration Site Conditions					
sudden death	glimepiride	0.32	0.44		
	glipizide	0.39	0.54		
	glyburide	0.54	0.75	0.42	0.60
sudden cardiac death	glipizide	0.35	0.51		
Nervous System Disorders					
cerebrovascular accident	glimepiride	**2.11**	**2.45**	1.09	1.24
	glimepiride and pioglitazone hydrochloride	0.49	1.47	0.25	0.75
	glimepiride and rosiglitazone maleate	**3.16**	**4.91**	1.77	2.50
	glipizide	0.77	0.89	0.46	**0.64**
	glipizide extended release	0.52	0.88	0.26	0.45
	glyburide	1.82	2.06	0.93	1.05
	glyburide and metformin hydrochloride	1.38	1.93	0.73	0.98
cerebral infarction	glimepiride	**3.97**	**4.32**		
	glipizide	0.14	0.20		
	glyburide	1.72	2.03	1.94	2.26
	glyburide and metformin hydrochloride	0.12	0.25	0.08	0.28
hemorrhagic stroke	glimepiride	0.42	0.76		
	glipizide	0.67	0.97		
ischemic stroke	glimepiride	**9.54**	**11.27**		
	glipizide	0.49	0.76		
	glyburide	0.75	1.19	0.35	0.54

† Excludes products with n=0 reports, EB05 <0, or EBGM <0
‡ EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio
§ EBGM: empirical Bayes geometric mean of the relative reporting ratio

eTable 4: Summary of safety signals for Biguanides†

		Bayesian Disproportionality in Full Dataset (N=180,399,180)		Bayesian Disproportionality in Cardiovascular Subset (N=17,575,517)	
Adverse Event	**Drug**	**EB05‡**	**EBGM§**	**EB05‡**	**EBGM§**
Cardiac Disorders					
acute myocardial infarction	metformin hydrochloride	0.58	0.71	0.28	0.34
atrioventricular block complete	metformin hydrochloride	**12.70**	**13.85**	**4.15**	**4.52**
cardiogenic shock	metformin hydrochloride	**4.06**	**4.59**	**2.25**	**2.52**
myocardial infarction	metformin hydrochloride	**6.71**	**6.98**	**3.22**	**3.35**
	metformin hydrochloride extended release			1.31	**2.35**
arteriosclerosis coronary artery	metformin hydrochloride	0.59	0.77	0.25	0.33
cardiac arrest	metformin hydrochloride	0.24	0.28	0.24	0.28
cardiac failure	metformin hydrochloride	**16.12**	**17.31**	**6.45**	**6.94**
cardiac failure congestive	metformin hydrochloride	1.20	1.31	0.65	0.71
	metformin hydrochloride extended release			1.30	**2.32**
Generic Disorders and Administration Site Conditions					
sudden death	metformin hydrochloride	1.54	2.46	**2.26**	**3.35**
sudden cardiac death	metformin hydrochloride	**62.94**	**67.32**	**18.14**	**19.34**
Nervous System Disorders					
cerebrovascular accident	metformin hydrochloride	**2.68**	**2.92**	1.37	1.49
	metformin hydrochloride extended release	0.77	6.24	0.75	3.17
cerebral infarction	metformin hydrochloride	0.60	0.73	0.67	0.81
hemorrhagic stroke	metformin hydrochloride	**5.04**	**5.84**	**2.81**	**3.24**
ischemic stroke	metformin hydrochloride	**87.66**	**101.97**	**27.52**	**31.15**

† Excludes products with n=0 reports, EB05 <0, or EBGM <0
‡ EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio
§ EBGM: empirical Bayes geometric mean of the relative reporting ratio

DIPEPTIDYL PEPTIDASE-4 INHIBITOR USE AND CARDIOVASCULAR EVENTS IN LOW-RISK PATIENTS WITH DIABETES: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Purpose: Cardiovascular safety of Dipeptidyl peptidase-IV inhibitors (DPP-4i) is poorly understood for patients with type 2 diabetes. Understanding this risk is especially important given that type 2 diabetes independently increases an individual's risk for cardiovascular disease. Clinical trials investigating this association focused on patients with high cardiovascular risk; however, this approach excludes the majority of new users of antihyperglycemic therapy who do not have a history of cardiovascular or renal disease. As such, we investigated the risk of major adverse cardiovascular events (MACE) associated with the use of DPP-4i among patients with diabetes, without established cardiovascular disease or renal disease. Because DPP-4i are recognized for their low cardiovascular risk, we restricted to this "low-risk" patient population to control for potential confounding due to existing cardiovascular disease or renal disease.

Methods: Using a new-user, cohort design, we analyzed Truven Marketscan Commercial Claims and Encounters from 2010-2015 for commercially insured patients with diabetes, without a history of cardiovascular disease and/or chronic kidney disease to determine the association between DPP-4i and MACE. We compared time to first MACE for DPP-4i to sulfonylurea and DPP-4i to metformin using propensity score weighted Cox proportional hazards, adjusting for demographics, baseline comorbidities, concomitant medications, and cumulative exposure. Additionally, we assessed the association between DPP-4i and the secondary outcomes of heart failure, acute myocardial infarction, and stroke.

Results: Of 445,701 individuals, 30,267 (6.79%) used DPP-4i, 52,138 (11.70%) used sulfonylureas, and 367,908 (82.55%) used metformin. Incidence for MACE with DPP-4i (21.45 per 1,000 person-years) was lower than sulfonylurea (24.87 per 1,000 person-years) and comparable to metformin (17.61 per 1,000 person-years). After adjustment, DPP-4i use was associated with lower risk than sulfonylurea use (aHR=0.87; 95% CI: [0.78, 0.98]), and similar risk to metformin use (aHR=1.07; 95% CI: [0.97, 1.18]). Risk for acute myocardial infarction (aHR=0.70; 95% CI: [0.51, 0.96]), stroke (aHR=0.57; 95%CI: [0.41, 0.79]), and heart failure (aHR=0.57; 95% CI: 0.41, 0.79) with DPP-4i was statistically significantly lower compared to sulfonylureas.

Conclusions: Among low-risk individuals, DPP-4i use was associated with lower risk for MACE compared to sulfonylureas and no increased risk for MACE compared to metformin. These findings suggest that DPP-4i is a low cardiovascular risk option for low-risk patients initiating antihyperglycemic treatment.

Keywords

Dipeptidyl peptidase-IV inhibitors; drug-related side effects and adverse reactions; major adverse cardiovascular events; pharmacoepidemiology

Introduction

Type 2 diabetes is prevalent in 9.4% of the United States population, affecting individuals of different races, ages, and socio-economic backgrounds[1]. The long-term micro- and macro-vascular complications of diabetes compound the public health impact of the disease[2]. Additionally, diabetes often presents in patients with multiple comorbidities, many of which affect the cardiovascular system[3]. Of the 7.2 million hospital discharges for patients with diabetes in 2014, 1.5 million were for cardiovascular events[1]. Altering the risk for major adverse cardiovascular events (MACE) involves a nuanced understanding of a patient's blood glucose levels, comorbidities, and vascular complications.

Further complicating this risk management, clinical trials and retrospective cohort studies have linked some oral antihyperglycemic drug classes, such as thiazolidinediones[4] and sulfonylureas[5] to an increased risk of MACE. Determining whether these associations are due to underlying cardiovascular disease or to adverse reactions from a particular drug remains a challenge for regulators and practitioners[6]. One newer class of oral antihyperglycemic agents, dipeptidyl peptidase-IV inhibitors (DPP-4i), has elicited increased reports of MACE to the United States Food and Drug Administration Adverse Event Reporting System[7,8]. These drugs were initially believed to be cardio-protective in pre-market clinical pharmacology studies[9]. However, postmarketing clinical trials[10-12] and retrospective, insurance claims-based cohort studies[13-15] have reported inconsistent data regarding the cardiovascular safety of DPP-4i. Additionally, the clinical trials have focused primarily on individuals with established cardiovascular disease, while the

insurance claims-based cohort studies have focused on all diabetic patients exposed to DPP-4i, irrespective of established cardiovascular or renal disease. Given that the majority of new users of oral antihyperglycemic agents do not have established cardiovascular or renal disease, we sought to better understand cardiovascular safety of DPP-4i for this population in a real-world setting.

Using a nationwide commercial claims database, we investigated the association between DPP-4i therapy and MACE. We restricted the study population to those without diagnosed cardiovascular disease or renal disease and compared the risk of MACE among new users of DPP-4i to that of metformin and of sulfonylurea. By restricting the population to those without a baseline risk, we were able to assess whether DPP-4i was associated with increased risk for MACE among a large subtype of patients initiating antihyperglycemic treatment. Underlying cardiovascular disease and renal disease confound the relationship between DPP-4i therapy and MACE. As such, prescribers have different prescribing considerations depending on an individual's cardiovascular risk. We were interested in this low risk population, as any difference in risk for MACE with DPP-4i would inform the prescribing of DPP-4i. Current package labels in the US only include warnings about the need for caution when prescribing these drugs to patients with a history of cardiovascular and/or renal disease.

Methods

Study Design and Data Source

To investigate the association between DPP-4i and MACE, we conducted a retrospective cohort study of commercially insured patients, using data from Truven Marketscan Commercial Claims and Encounters from January 2010 through December 2015. This database captures individual-level linked patient claims and encounter data for approximately 25 million individuals annually. The de-identified data contains information on patient demographics, inpatient and outpatient services as well as prescription drug claims.

Study Population

We identified patients with type 2 diabetes as those with at least one prescription for an oral antihyperglycemic agent and either HbA1c greater than 6.5% twice, fasting glucose greater than 126 mg/dL twice on different days, random glucose > 200 mg/dL twice on different days, one inpatient diagnosis (International Classification of Diseases, $9^{th}/10^{th}$ Revisions (ICD-9(10)): 250x (E11.9), 357.2 (E11.42), 366.41 (E11.36), 362.01-362.07 (E11.3*)), or outpatient diagnosis (ICD-9(10): 250x (E11.9), 366.41 (E11.36), 362.01-362.07 (E11.3*)) twice on different days. We included patients if they received at least one prescription for an FDA-approved DPP-4i, sulfonylurea, or metformin (**eTable 1**). The index date for follow-up was assigned as the date of first filled prescription for one of these products. The baseline period was defined as the six-month period preceding this.

We excluded individuals if they met any of the following criteria: 1) less than six months of continuous medical and prescription enrollment, 2) less than 12-weeks of continuous exposure to exposure group drugs, 3) insulin use during baseline period, 4) treatment with other oral or injectable antihyperglycemic agents in baseline period, 5) below the age of 35, 6) cardiovascular disease or renal disease in baseline, and 7) missing age or sex information. We followed patients until the first of the following events: 1) first evidence of a major adverse cardiovascular event (MACE), 2) end of continuous medical or prescription enrollment, 3) switch in antihyperglycemic agent treatment or addition of another antihyperglycemic agent, 4) 14-days after then last date of exposure to exposure group drug, or 5) study end date of December 31, 2015.

We identified individuals with established cardiovascular disease through ICD-9/10 codes for myocardial infarction, complete atrioventricular block, cardiogenic shock, coronary artery disease, chronic heart failure, stroke, cerebral infarction, atrial fibrillation, or coronary artery bypass graft in the six-month baseline period. We also defined renal disease through ICD-9/10 codes for chronic kidney disease or acute renal failure in the six-month baseline period.

Definition of Exposure

The three exposure groups consisted of new users of DPP-4i, sulfonylurea, and metformin, respectively. We also created an indicator variable for cumulative exposure, defined as the number of days an individual was exposed to the exposure group drug. In the event of an individual initiating more than one of these drug classes at baseline, they

were assigned to all relevant exposure groups. We used a negative control (metformin) and a positive control (sulfonylurea) in this study for two reasons: 1) the population of new users of DPP-4i is similar to that of sulfonylurea; however, sulfonylurea is carries cardiovascular risk; 2) metformin carries low cardiovascular risk; however, new users of metformin have less severe diabetes.

Definition of Outcomes

We defined our primary composite outcome of MACE as the first of any of the following events: myocardial infarction, cardiac arrest, coronary artery bypass graft, coronary angioplasty, heart failure, and stroke. Myocardial infarction[16,17], cardiac arrest[18], coronary artery bypass graft[16], coronary angioplasty[16], heart failure[19], and stroke[20] were identified through validated ICD-9/10 algorithms. For conditions/procedures without validated ICD-10 algorithms, we deferred to the Chronic Conditions Warehouse[21]. We excluded all-cause mortality from the primary composite outcome, because we did not have information on deaths occurring outside of the inpatient setting. Our secondary outcomes were acute myocardial infarction, stroke, and heart failure.

Definition of Covariates

We assessed possible confounding due to individual demographics, concomitant medications, and comorbidities. We conducted literature searches of similar studies[17,22-24], consulted clinical guidance[25-28], and regulatory documents[29] to identify covariates of interest. We created indicator variables for individuals' age and sex. We accounted for

comorbidities such as hypertension, asthma, peripheral vascular disease, and neuropathy using the Clinical Classification Software (CCS) developed by the Agency for Healthcare Research and Quality. The CCS was only available for conditions coded in ICD-9. For inpatient and outpatient medical service records using ICD-10, we cross-referenced ICD-9 codes with their ICD-10 equivalents. Additionally, we identified the use of concomitant medication such as statins, hormone replacement therapy, bronchodilators, and diuretics via National Drug Codes (NDC). Finally we categorized individuals based on their disease severity using the Adjusted Diabetes Comorbidities Severity Index (aDCSI)[30-32]. A full list of covariates used in the analysis is contained in **eTable 2**.

Propensity Score

We first identified all available covariates without an association to the exposure that were associated to the primary outcome in order to increase precision[33]. Next, we used the Toolkit for Weighting and Analysis of Nonequivalent Groups (*twang)* package developed by the RAND Corporation[34] to compute the propensity scores and associated weights used in the analysis to balance the covariates between exposure groups. This package allows for propensity scores estimation in the presence of multiple exposure groups. Using generalized boosted regression models, we optimized the selection of covariates for the propensity score calculation. We used the standardized mean difference (SMD) to measure the balance of covariates before and after weighting. Propensity score weighting reduced the SMD from a maximum of 0.15 to less than 0.01 (**eFigure 1)**. We then used the average treatment effect on the treated (ATT) propensity score weights to estimate the treatment effect of DPP-4i.

Statistical Analysis

We used chi-square statistics for categorical covariates and the Kruskal-Wallis test for continuous covariates to compare differences at baseline between new users of DPP-4i, sulfonylurea, and metformin. Next, we used exact Poisson tests to compute the incidence rate differences for the primary and secondary outcomes between new users of DPP-4i and those of sulfonylurea and metformin, respectively. Additionally, we checked for differences in time to first MACE distributions using a Kolmogorov-Smirnov test. We calculated propensity score weighted crude and adjusted Cox proportional hazards for the association between new use of DPP-4i and the primary and secondary outcomes compared to new use of sulfonylureas and metformin. We included indicators for age, sex, baseline comorbidities, and concomitant medication in the adjusted models (**eTable 3**). We plotted the scaled Schoenfeld residuals to check for covariates that violated the proportional hazards assumption. We stratified the Cox proportional hazards model by covariates that violated the proportional hazards assumption. Finally, we included natural regression spline terms with knots at 180-, 365-, and 540-days to account for changes in the underlying hazard function with increasing cumulative exposure, which was defined as the total number of days exposed to the exposure group drug[35]. All analyses were conducted in R, version 3.3.3.

Sensitivity Analyses

To check the robustness of our results, we first assessed possible sensitivity of our results to the latency of the period after drug discontinuation. We lagged this period for 14-, 7-, and 30-days after the last day of exposure to drug. Next, we recalculated the

primary analysis without individuals exposed to more than one exposure group to determine whether our results were sensitive to the inclusion of those individuals.

The study was exempted from review by a Johns Hopkins Institutional Review Board.

Results

Subject Inclusion and Characteristics

We first identified 12,166,812 individuals with diabetes from January 2010-December 2015 through commercial claims. Most individuals in each exposure group were male (DPP-4i: 58.86%, sulfonylureas: 58.19%, metformin: 51.34%) (**Figure 1**). More individuals on DPP-4i (41.51%) and sulfonylureas (44.52%) were aged 55 and older compared to those on metformin (36.37%). After applying the inclusion and exclusion criteria above, the study population consisted of 445,701 individuals. There were 30,267 (6.79%) new users of DPP-4i, 52,138 (11.70%) who initiated sulfonylureas, and 367,908 (82.55%) who started metformin. Less than one percent of included individuals were new users of both DPP-4i and metformin, and 17,070 (3.83%) were new users of both sulfonylureas and metformin.

Individuals in each exposure group differed in their baseline characteristics (**Table 1**). There were more male new users of sulfonylureas (58.19%) than DPP-4i (56.86%) or metformin (51.34%). Most individuals in each group were exposed for 12 months or less (DPP-4i: 77.94%; sulfonylurea: 76.27%; metformin: 72.41%). Many

individuals in this study cohort experienced micro-vascular complications of diabetes. New users of DPP-4i had neuropathy (7.53%), retinopathy (5.48%), and peripheral vascular disease (2.79%) in the baseline period. Among new users of sulfonylurea, 6.93% had neuropathy, 5.04% had retinopathy, and 2.17% had peripheral vascular disease. Metformin users had the lowest proportion of peripheral vascular disease (1.87%), retinopathy (3.50%), and nephropathy (0.54%). Additionally, a higher percentage of DPP-4i initiators (22.3%) used angiotensin II receptor blockers in baseline compared to sulfonylurea (16.2%) and metformin (16.5%) initiators. Statin use was also higher in DPP-4i initiators (42.5%) than sulfonylurea (37.5%) and metformin (37.9%). Differences in baseline characteristics between exposure groups were diminished after propensity score weighting (**eTable 6**).

Association Between Treatment and Major Adverse Cardiovascular Events

The median follow-up for first occurrence of MACE was 341 days [interquartile range (IQR): 196, 580], and there were no significant differences in follow-up time between exposure groups (**eFigure 2**). The absolute difference in incidence rates for the primary composite outcome was statistically significantly greater for DPP-4i (21.45 per 1,000 person-years) compared to metformin (17.61 per 1,000 person years). DPP-4i was also associated with a lower incidence rate of MACE than sulfonylurea (24.87 per 1,000 person-years) (**Table 2**). This difference was also seen in the secondary outcomes of acute myocardial infarction (DPP-4i: 2.45 per 1,000 person-years vs. sulfonylurea: 3.72 per 1,000 person-years), stroke (DPP-4i: 2.21 per 1,000 person-years vs. sulfonylurea: 4.08 per 1,000 person-years), and heart failure (DPP-4i: 2.21 per 1,000 person-years vs.

sulfonylurea: 4.02 per 1,000 person-years). There were no differences in incidence between DPP-4i and metformin for the secondary outcomes.

After adjustment for baseline characteristics, introducing spline terms for every six months of cumulative exposure, and propensity score weighting, there was an association between DPP-4i and MACE compared to sulfonylurea and MACE (adjusted hazard ratio (aHR): 0.87, 95% confidence interval (CI): 0.78, 0.98). In contrast, there was no difference in risk for MACE with DPP-4i compared to metformin (aHR: 1.07, 95% CI: 0.97, 1.18) (**Table 3**).

There were also differences in risk seen for the secondary outcomes between exposure groups. In the adjusted analyses, there was a lower risk for acute myocardial infarction associated with DPP-4i (aHR: 0.70, 95% CI: 0.51, 0.96) compared to sulfonylurea (aHR: 0.95, 95% CI: 0.72, 1.27). Risk for stroke was also lower with DPP-4i (aHR: 0.57, 95% CI: 0.41, 0.79) compared to sulfonylurea (aHR: 0.81, 95% CI: 0.60, 1.09). Finally DPP-4i (aHR: 0.57, 95% CI: 0.41, 0.79) was associated with a lower risk for heart failure compared to sulfonylurea (aHR: 1.04, 95% CI: 0.77, 1.40). There were no statistically significant associations between the secondary outcomes and DPP-4i when compared to metformin in the adjusted or unadjusted analyses (**Table 3**).

Sensitivity Analyses

After removing individuals with more than one exposure group, there were a total of 426,328 individuals in the study cohort. Analysis results did not qualitatively differ

after removal of these individuals (**eTable 3**). Additionally, results were not sensitive to changes in the latency period after the last dose of exposure for the primary analysis results when lagging the latency period by 7-days or 30-days (**eTable 4**).

Discussion

In this retrospective cohort analysis of commercial claims data for individuals with diabetes and without a history of cardiovascular disease or chronic kidney disease, DPP-4i use was associated with 13% lower risk of MACE compared to sulfonylureas, and a similar risk of MACE when compared to metformin. DPP-4i was also shown to be associated with a decreased risk for acute myocardial infarction, stroke, and heart failure when compared to sulfonylurea. These results contribute to the existing data from signal detection of adverse event reports, clinical trials, and other cohort analyses examining the association of DPP-4i and MACE in low cardiovascular risk patients with diabetes.

The results of this study align with those of previous clinical trials and observational studies of cardiovascular safety of DPP-4i. Unlike the three completed clinical trials comparing DPP-4i and placebo[11,36,37]; however, our study population consisted of individuals with low-risk for MACE but in a real-world setting with multiple comorbidities and concomitant medications. Our results confirm that DPP-4i are similar to metformin and potentially safer than sulfonylureas with regards to risk of MACE in a low-risk subset of new users. Additionally, our analysis compared DPP-4i to other common first-line therapies, as opposed to assessing it as add-on therapy compared to placebo, and showed a decreased risk for MACE compared to sulfonylureas. Of note, we

did not find increased risk for heart failure with the use of DPP-4i, contrasting with the results of the EXamination of CArdiovascular OutcoMes with AlogliptIN versus Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) trial[10] and the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI) trial[11]. This could be due to our restricting the study cohort to low-risk individuals.

Similar to our study, a 2015 longitudinal study of the Taiwan National Health Insurance Research Database showed lower risk for MACE associated with DPP-4i compared to sulfonylurea as add-on therapy to metformin (aHR: 0.68, 95% CI: 0.55, 0.83)[13]. Our study population expanded on this approach through the inclusion of individuals exposed to only metformin.

This analysis had two notable strengths. The first of these was the use of a low-risk population together with a new user design. This approach allowed us to hone in on a common prescribing scenario, as many patients initiating oral antihyperglycemic therapy are middle-aged and do not have cardiovascular disease or renal disease. Understanding whether or not diabetic treatment in this population increases patient risk for MACE is critical to managing their care due to the close link between cardiovascular disease and diabetes[38].

There were also limitations with our analysis. The first of these was the inclusion of individuals into more than one exposure group at baseline. We recognize that this

could have potentially led to misclassification[39]. Excluding patients who were exposed to multiple drug groups of interest would have resulted in a 32.7% reduction in our population of individuals exposed to sulfonylurea, potentially threatening the generalizability of our results. As such, we assessed the sensitivity of our results to their inclusion and found them to be robust. The second limitation was our inability to account for time-varying hazards. We attempted to address this by introducing natural regression spline terms with knots at 6-, 12-, and 18-months of cumulative exposure. This allowed us to account for possible changes in baseline hazard with increasing cumulative exposure. Third, there is the potential for informative censoring due to a change in exposure status. We assessed sensitivity of our results to this approach to censoring and found them to be insensitive to the lagged latency period after the last day of exposure. Additionally, MACE primarily occurred within the first year of exposure and extending the latency period past 30-days would have unlikely changed our results and could have potentially led to misclassification. Finally due to limitations of the dataset, we were unable to assess key unmeasured variables. The first of these was mortality, which we could not include as a component of the primary composite outcome or as a competing risk. We also did not have data on body mass index, a correlate of cardiovascular disease. Third, our study population consisted of younger, low-risk patients with diabetes below age 65. As we were interested in those with low-cardiovascular risk, this younger cohort was representative of this patient subtype.

Conclusion

Among a commercially insured patient population with diabetes and low-risk for major adverse cardiovascular events in the United States, our results provide evidence of decreased risk for MACE when comparing DPP-4i versus sulfonylurea. Additionally, we found that DPP-4i carried similar risk for MACE when compared to metformin. These results were also reflected in several individual components of the composite outcome, namely acute myocardial infarction, stroke, and heart failure. Finally, our results suggest that DPP-4i is a low cardiovascular risk option for low-risk patients initiating antihyperglycemic treatment. Additionally our findings of no association with increased risk for heart failure in a low-risk population suggests that the current drug label warning for caution in prescribing saxagliptin and alogliptin in patients with prior cardiovascular disease is sufficient. Further research is needed to investigate whether this association between DPP-4i and MACE is similar in high-risk populations.

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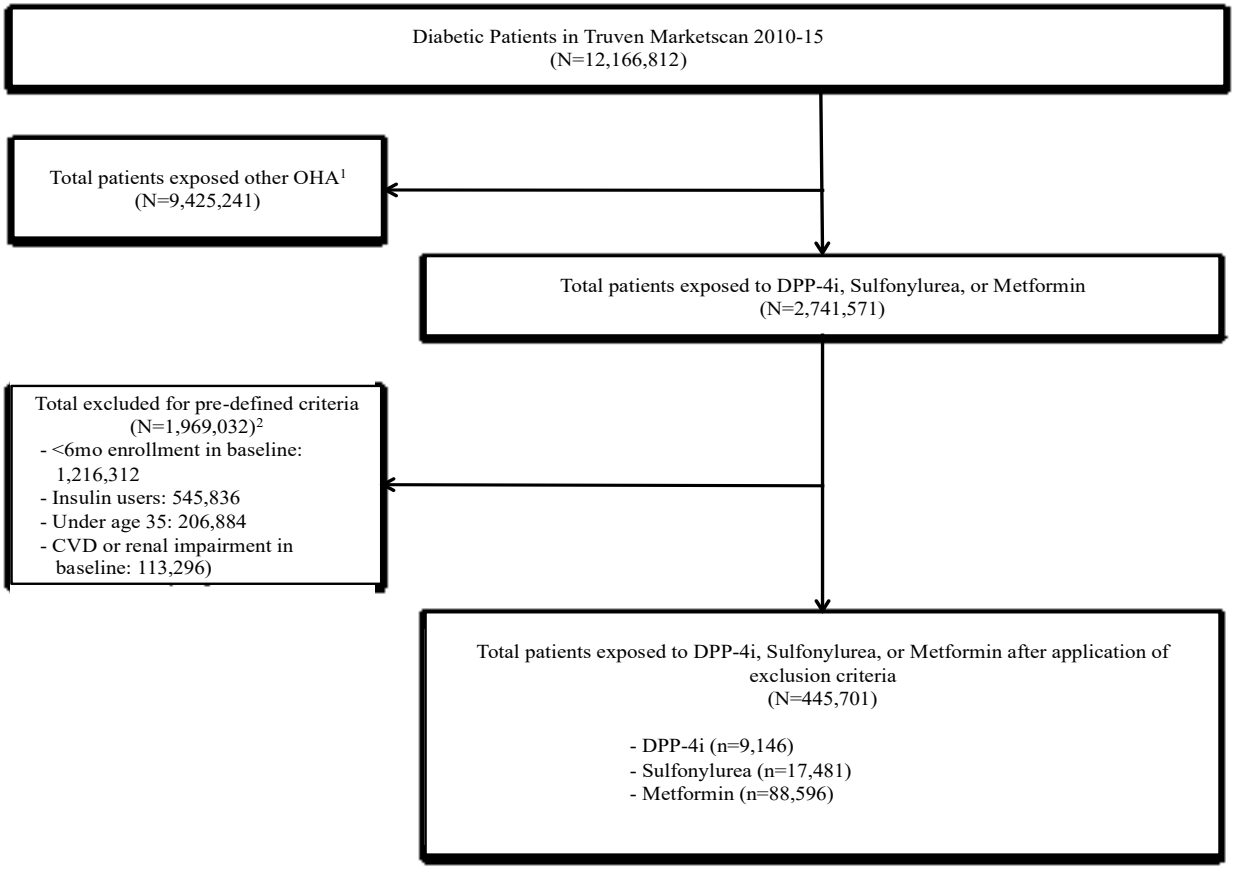
TABLES AND FIGURES

Figure 1. Cohort derivation and sample attrition



[1] OHA = oral antihyperglycemic agents
[2] Subcategories are not mutually exclusive

Table 1. Baseline demographics and medical characteristics

	DPP-4i (n=30,267)		Sulfonylureas (n=52,138)		Biguanides (n=367,908)	
	N	%	N	%	N	%
Demographics						
Male	17,209	56.86	30,340	58.19	188,882	51.34
Age						
35-44	5,562	18.38	9,578	18.37	82,260	22.36
45-54	12,140	40.11	19,348	37.11	151,847	41.27
55-64	12,565	41.51	23,212	44.52	133,801	36.37
Location (Region)						
Northeast	5,829	19.26	7,358	14.11	56,186	15.27
North Central	5,614	18.55	10,635	20.40	79,433	21.59
South	14,926	49.31	25,108	48.16	160,626	43.66
West	3,391	11.20	8,203	15.73	65,961	17.93
Unknown	507	1.68	834	1.60	5,702	1.55
Cumulative Exposure						
<6 months	13,110	43.31	24,428	46.85	141,469	38.45
6-12 months	10,481	34.63	15,339	29.42	124,943	33.96
12-18 months	3,456	11.42	5,971	11.45	49,787	13.53
>18 months	3,220	10.64	6,400	12.28	51,709	14.05
Comorbidities in Baseline						
Asthma	1,823	6.02	2,578	4.94	25,700	6.99
Peripheral Vascular Disease	845	2.79	1,134	2.17	6,886	1.87
Ischemic heart disease	1,201	3.97	1,861	3.57	11,364	3.09
Hypertension	18,907	62.47	30,789	59.05	215,790	58.65
Retinopathy	1,659	5.48	2,630	5.04	12,870	3.50
Eye disease	8,009	26.46	11,759	22.55	86,274	23.45
Renal disease	7,390	24.42	11,008	21.11	84,100	22.86
Atrial fibrilation	2,070	6.84	2,988	5.73	26,749	7.27
Neuropathy	2,280	7.53	3,612	6.93	27,841	7.57
Nephropathy	279	0.92	589	1.13	2,000	0.54
aDCSI Score						
0	30,115	99.50	51,845	99.44	366,471	99.61
1+	152	0.50	293	0.56	1,437	0.39
Dual Exposures						
Sulfonylureas		0.00		0.00	17,070	4.64
Metformin	2,303	7.61	17,070	32.74		0.00
DPP-4 inhibitors		0.00		0.00	2,303	0.63

Table 1 (cont'd). Baseline demographics and medical characteristics

	DPP-4i (n=30,267)		Sulfonylureas (n=52,138)		Biguanides (n=367,908)	
	N	%	N	%	N	%
Concomitant Medications at Baseline						
ACE inhibitors	5,856	19.35	11,255	21.59	84,735	23.03
angiotensin II receptor blockers	6,746	22.29	8,467	16.24	60,645	16.48
antidepressants	4,648	15.36	6,933	13.30	71,046	19.31
antiplatelets	3,609	11.92	5,353	10.27	46,484	12.63
Asthma medication	819	2.71	1,225	2.35	10,656	2.90
α-Glucosidase inhibitors	58	0.19	80	0.15	184	0.05
benzodiazepines	3,195	10.56	4,844	9.29	46,310	12.59
beta blockers	4,165	13.76	7,640	14.65	57,142	15.53
bile acid sequestrants	526	1.74	644	1.24	4,081	1.11
blood thinners and anticoagulants	538	1.78	968	1.86	7,207	1.96
calcium channel blockers	2,876	9.50	5,298	10.16	35,658	9.69
cardioselective beta blockers	1,405	4.64	2,229	4.28	14,101	3.83
diuretics	4,399	14.53	7,324	14.05	66,953	18.20
cholinergics	12	0.04	16	0.03	184	0.05
hormone replacement therapy	923	3.05	1,100	2.11	14,562	3.96
fibrates	2,668	8.81	3,462	6.64	23,955	6.51
niacin	607	2.01	905	1.74	6,533	1.78
nitrates	217	0.72	482	0.92	2,975	0.81
NSAIDs	5,844	19.31	8,935	17.14	83,764	22.77
bronchodilators	3,123	10.32	4,195	8.05	43,808	11.91
inhaled steroids	4,830	15.96	6,603	12.66	70,760	19.23
oral corticosteroids	6,421	21.21	9,127	17.51	90,048	24.48
erythropoietan	6	0.02	22	0.04	22	0.01
ophthalmic drugs	618	2.04	1,000	1.92	6,262	1.70
disease-modifying antirheumatic drugs	543	1.79	882	1.69	6,891	1.87
biologic response modifiers	171	0.56	259	0.50	1,930	0.52
peripheral neuropathic treatments	1,265	4.18	1,474	2.83	14,991	4.07
statins	12,852	42.46	19,534	37.47	139,601	37.94
thiazide diuretics	5,195	17.16	8,895	17.06	79,174	21.52

Table 2. Incidence rates of primary composite outcome, acute myocardial infraction, stroke, and heart failure among new users of DPP-4 inhibitors, sulfonylureas, and metformin

Outcome, *n*	**DPP-4 Inhibitors**	**DPP-4 Inhibitors v. Sulfonylureas**	**DPP-4 Inhibitors v. Metformin**
Primary Composite Outcome	450	910	5,445
Total person years	20,982	36,595	309,151
Rate per 1,000 person years	21.45	24.87	17.61
Median [IQR] observation time, days	187 [107, 314]	173 [104, 317]	225 [134, 384]
Rate difference (95% CI)	--	**-3.42 [-5.98, -0.86]**	**3.83 [1.80, 5.87]**
Acute Myocardial Infarction	52	138	791
Total person years	21,236	37,060	312,411
Rate per 1,000 person years	2.45	3.72	2.53
Median [IQR] observation time, days	189 [108, 317]	176 [104, 321]	227 [135, 388]
Rate difference (95% CI)	--	**-1.28 [-2.19, -0.36]**	-0.08 [-0.77, 0.61]
Stroke	47	151	786
Total person years	21,239	37,027	312,438
Rate per 1,000 person years	2.21	4.08	2.52
Median [IQR] observation time, days	189 [108, 317]	175 [104, 321]	227 [135, 388]
Rate difference (95% CI)	--	**-1.87 [-2.77, -0.86]**	-0.07 [-0.76, 0.62]
Heart Failure	47	149	602
Total person years	21,238	37,052	312,548
Rate per 1,000 person Years	2.21	4.02	1.93
Median [IQR] observation time, days	189 [108, 317]	175 [104, 321]	227 [135, 388]
Rate difference (95% CI)	--	**-1.81 [-2.71, -0.90]**	0.52 [-0.16, 1.21]

[1] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke, death

[2] Incidence rate difference per 1,000 person-years

[3] IQR = interquartile range

Table 3. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, acute myocardial infraction, stroke, and heart failure compared to Sulfonylureas and Metformin

	Hazard Ratios for DPP-4 Inhibitors Use			
Reference Group	**Primary Composite Outcome[3]**	**Acute Myocardial Infarction**	**Stroke**	**Heart Failure**
Sulfonylureas				
HR [95% CI][1]	**0.86 [0.77, 0.97]**	**0.69 [0.50, 0.95]**	**0.54 [0.39, 0.75]**	**0.58 [0.42, 0.81]**
aHR [95% CI][2]	**0.87 [0.78, 0.98]**	**0.70 [0.51, 0.96]**	**0.57 [0.41, 0.79]**	**0.57 [0.41, 0.79]**
Metformin				
HR [95% CI][1]	1.08 [0.98, 1.19]	0.91 [0.69, 1.21]	0.80 [0.59, 1.07]	1.05 [0.78, 1.41]
aHR [95% CI][2]	1.07 [0.97, 1.18]	0.95 [0.72, 1.27]	0.81 [0.60, 1.09]	1.04 [0.77, 1.40]

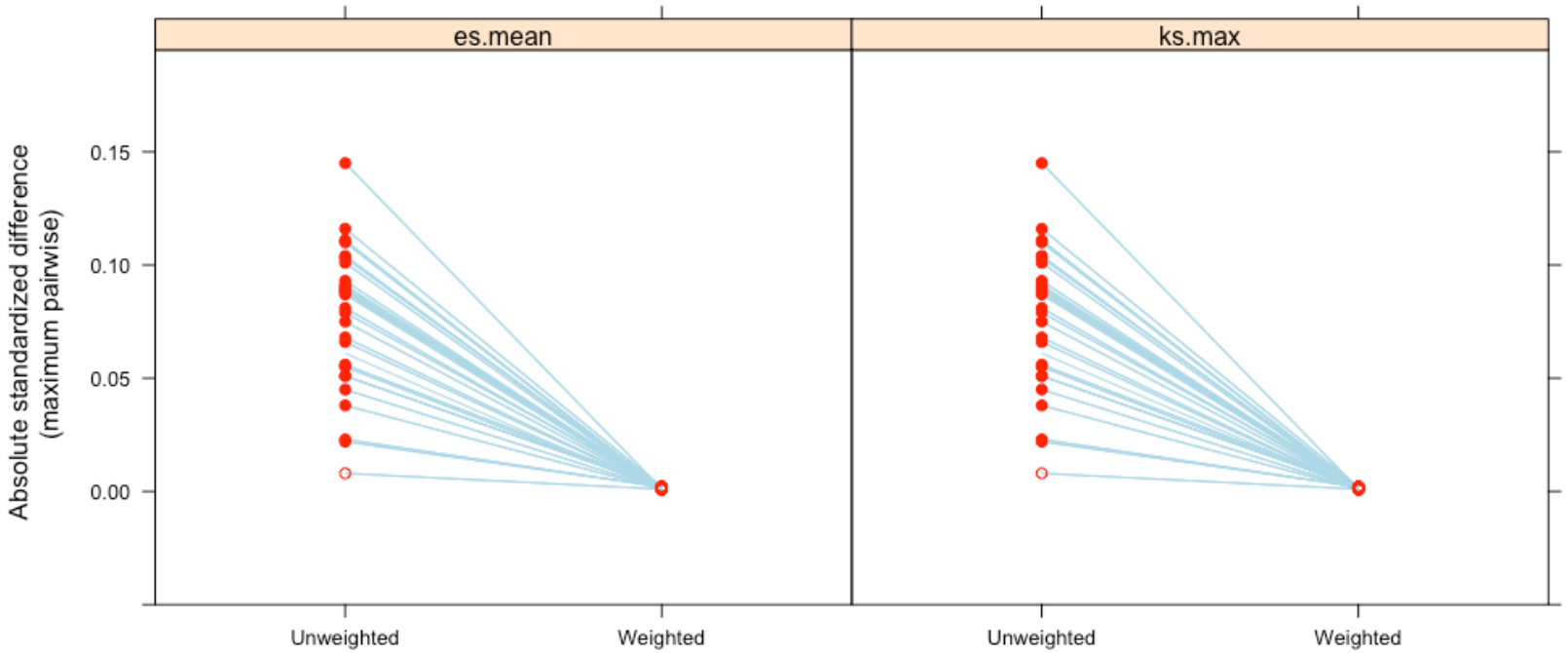
[1] Propensity score weighting only

[2] Propensity score weighting, spline terms for cumulative exposure, and demographics, comorbidities, and concomitant medications as regressors and stratifiers

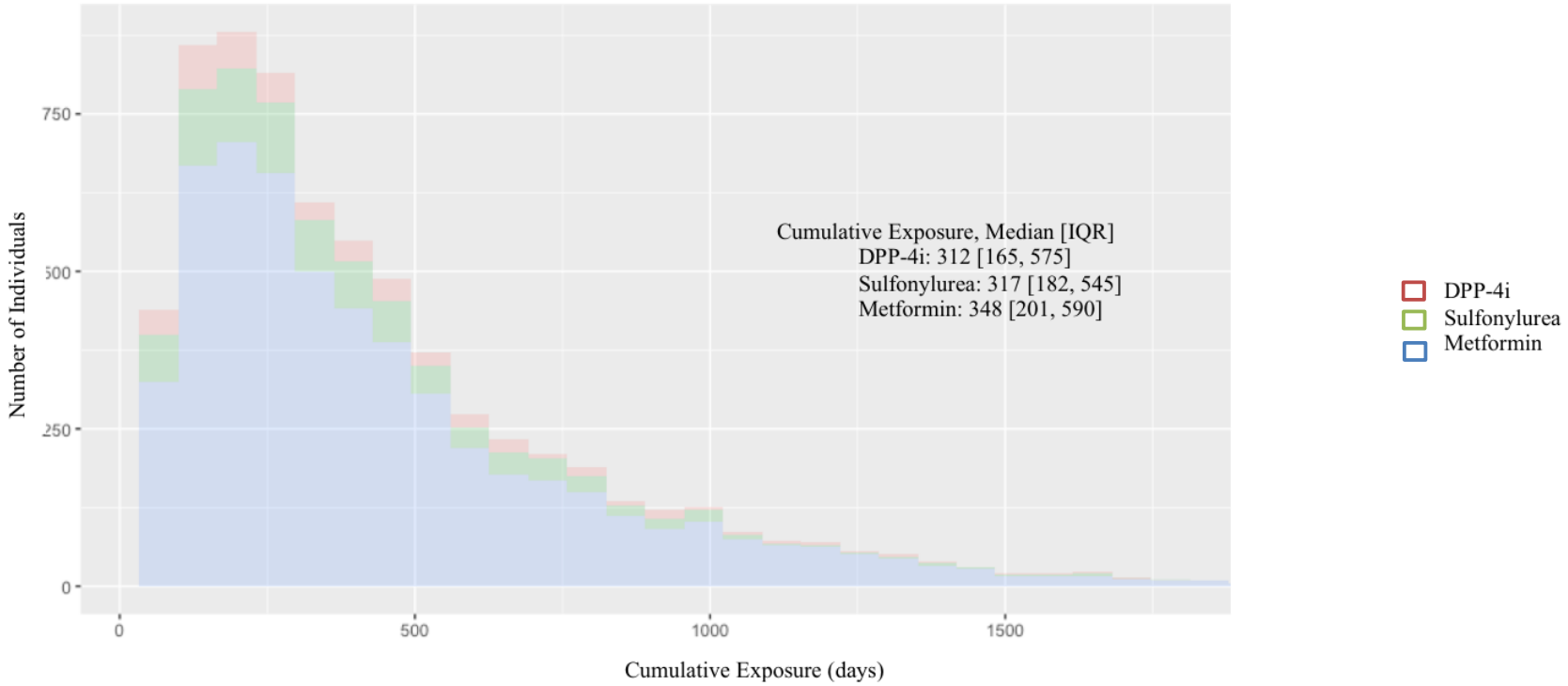
[3] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke, death

SUPPLEMENTARY MATERIAL

eFigure 1. Absolute standardized mean differences before and after propensity score weighting



eFigure 2. Distributions of cumulative exposure as measured in days for individuals with events



eTable 1. Categorization of drugs into exposure groups

FDA Approved DPP-4 Inhibitors

alogliptin
alogliptin and metformin
alogliptin and pioglitazone
linagliptin
linagliptin and empagliflozin
linagliptin and metformin
linagliptin and metformin extended release
sitagliptin
sitagliptin and metformin
sitagliptin and metformin extended release
saxagliptin
saxagliptin and metformin extended release

FDA Approved Sulfonylureas

chlorpropamide
glimepiride
glimepiride and pioglitazone hydrochloride
glimepiride and rosiglitazone maleate
glipizide
glipizide extended release
glyburide
glyburide and metformin hydrochloride
tolazamide
tolbutamide

FDA Approved Biguanides

metformin hydrochloride
metformin hydrochloride extended release

eTable 2. Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	Stratifier
Demographics				
Male	X	X		X
Age	X	X		X
Location (Region)	X			
Cumulative Exposure	X			X
Comorbidities in Baseline				
Asthma	X	X		
Peripheral vascular disease	X	X		
Ischemic heart disease	X			
Hypertension	X	X	X	
Retinopathy	X	X		
Eye disease	X	X	X	
Renal disease	X		X	
Atrial fibrilation	X			
Neuropathy	X	X	X	
Nephropathy	X			
aDCSI Score	X			
Dual Exposures			X	
Sulfonylureas	X		X	
Metformin	X		X	
DPP-4 inhibitors	X			
Concomitant Medications at Baseline				
ACE inhibitors	X	X		
alpha agonists	X			
analgesics	X			
angiotensin II receptor blockers	X	X	X	
anti Veg-F	X			
anticoagulants	X			
antidepressants	X	X		
antiplatelets	X	X		X

eTable 2 (cont'd). Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	Stratifier
Concomitant Medications at Baseline				
aspirin	X			
benzodiazepines	X	X	X	
beta blockers	X	X		X
beta blockers (ophthalmic)	X			
bile acid sequestrants	X			
biologic response modifiers	X			
blood thinners and anticoagulants	X			X
bronchodilators	X	X		X
calcium channel blockers	X	X	X	
carbonic anhydrase inhibitors	X			
cardioselective beta blockers	X	X		
cholinergics	X			
disease-modifying antirheumatic drugs	X	X		
diuretics	X	X		
erythropoietan	X			
fibrates	X	X		
hormone replacement therapy	X	X		
inhaled steroids	X	X		X
leukotrine modifiers	X			
loop diuretics	X			
MAOI	X			
niacin	X			
nitrates	X			
NSAIDs	X	X		X
ophthalmic drugs	X			
oral corticosteroids	X	X		
other asthma medication	X			
peripheral neuropathic treatments	X	X	X	
phosphodiesterase-4 inhibitors	X			
potassium sparing diuretics	X			
prostaglandins	X			
SNRI	X			

eTable 2 (cont'd). Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	Stratifier
Concomitant Medications at Baseline				
SSRI	**X**			
statins	**X**	**X**	**X**	
theophyllines	**X**			
thiazide diuretics	**X**	**X**	**X**	
tricyclic antidepressants	**X**			
vasodilators	**X**			
α-Glucosidase inhibitors	**X**			

eTable 3. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, showing sensitivity to individuals with more than one exposure group

	Hazard Ratios for DPP-4 Inhibitors Use	
Reference Drug	**Allowing for dual exposure**	**Disallowing dual exposure**
Sulfonylureas		
HR (95% CI)[1]	**0.86 [0.77, 0.97]**	**0.86 [0.76, 0.96]**
aHR (95% CI)[2]	**0.87 [0.78, 0.98]**	**0.87 [0.77, 0.97]**
Metformin		
HR (95% CI)[1]	1.08 [0.98, 1.19]	1.10 [1.00, 1.21]
aHR (95% CI)[2]	1.07 [0.97, 1.18]	1.10 [1.00, 1.21]

[1] Propensity score weighting only

[2] Propensity score weighting, spline terms for cumulative exposure, and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eTable 4. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, showing sensitivity to latency after drug discontinuation

	Hazard Ratios for DPP-4 Inhibitors Use		
Reference Drug	**14-day lag censor**	**7-day lag censor**	**30-day lag censor**
Sulfonylureas			
HR (95% CI)[1]	**0.86 [0.77, 0.97]**	**0.85 [0.75, 0.96]**	**0.86 [0.77, 0.96]**
aHR (95% CI)[2]	**0.87 [0.78, 0.98]**	**0.85 [0.76, 0.96]**	**0.87 [0.78, 0.97]**
Metformin			
HR (95% CI)[1]	1.08 [0.98, 1.19]	1.07 [0.96, 1.18]	1.07 [0.98, 1.18]
aHR (95% CI)[2]	1.07 [0.97, 1.18]	1.09 [0.98, 1.21]	1.11 [1.01, 1.21]

[1] Propensity score weighting only

[2] Propensity score weighting, spline term for cumulative exposure, and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eTable 5. Weighted and unweighted hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome

	Hazard Ratios for DPP-4 Inhibitors Use
Reference Drug	**Hazard Ratio [95% CI]**
Sulfonylureas	
Unweighted HR (95% CI)[2]	**0.87 [0.78, 0.97]**
HR (95% CI)[3]	**0.86 [0.77, 0.97]**
aHR (95% CI)[4]	**0.87 [0.78, 0.98]**
Metformin	
Unweighted HR (95% CI)[2]	1.10 [1.00, 1.21]
HR (95% CI)[3]	1.08 [0.98, 1.19]
aHR (95% CI)[4]	1.07 [0.97, 1.18]

[1] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke, death

[2] Adjusted for demographics, comorbidities, and concomitant medications

[3] Propensity score weighting only

[4] Propensity score weighting, spline term for cumulative exposure, and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eTable 6. Pre- and Post-weighting distribution of covariates across exposure groups

	DPP4i	Sulfonylureas				Metformin			
		Pre-weighting		Post-weighting		Pre-weighting		Post-weighting	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Male	0.57	0.58	**<0.01**	0.57	0.96	0.51	**<0.01**	0.57	0.83
Age	0.18	0.18	**<0.01**	0.18	0.91	0.22	**<0.01**	0.18	0.98
Region	0.19	0.14	**<0.01**	0.19	1.00	0.15	**<0.01**	0.19	1.00
Peripheral vascular disease	0.97	0.98	**<0.01**	0.97	0.80	0.98	**<0.01**	0.97	0.84
Asthma	0.94	0.95	**<0.01**	0.94	0.89	0.93	**<0.01**	0.94	0.87
Eye disease	0.74	0.77	**<0.01**	0.74	0.77	0.77	**<0.01**	0.74	0.94
Hypertension	0.38	0.41	**<0.01**	0.37	0.74	0.41	**<0.01**	0.38	0.84
Neuropathy	0.92	0.93	**<0.01**	0.92	0.92	0.92	0.83	0.93	0.76
Retinopathy	0.95	0.95	**0.01**	0.95	0.90	0.97	**<0.01**	0.95	0.87
Benzodiazepine	0.89	0.91	**<0.01**	0.89	0.96	0.87	**<0.01**	0.89	0.75
Fibrates	0.91	0.93	**<0.01**	0.91	0.91	0.93	**<0.01**	0.91	0.84
Antidepressants	0.97	0.98	**<0.01**	0.97	0.99	0.96	**<0.01**	0.97	0.81
Oral corticosteroids	0.79	0.82	**<0.01**	0.79	0.85	0.76	**<0.01**	0.79	0.76
Inhaled steroids	0.84	0.87	**<0.01**	0.84	0.83	0.81	**<0.01**	0.84	0.80
Bronchodilators	0.90	0.92	**<0.01**	0.90	0.94	0.88	**<0.01**	0.90	0.91
ACE inhibitors	0.81	0.78	**<0.01**	0.81	0.92	0.77	**<0.01**	0.81	0.80
Antiplatelets and blood thinners	0.88	0.90	**<0.01**	0.88	0.93	0.87	**<0.01**	0.88	0.77
Hormone replacement therapy	0.97	0.98	**<0.01**	0.97	0.91	0.96	**<0.01**	0.97	0.82
NSAIDs	0.81	0.83	**<0.01**	0.81	0.74	0.77	**<0.01**	0.81	0.83
Angiotensin II receptor blockers	0.78	0.84	**<0.01**	0.78	0.95	0.84	**<0.01**	0.78	0.79
Beta blockers	0.86	0.85	**<0.01**	0.86	0.87	0.84	**<0.01**	0.86	0.79
Cardioselective beta blockers	0.95	0.96	**0.01**	0.95	0.90	0.96	**<0.01**	0.95	0.90
Diuretics	0.15	0.14	0.05	0.15	0.90	0.18	**<0.01**	0.15	0.97
Statins	0.58	0.63	**<0.01**	0.58	0.94	0.62	**<0.01**	0.58	0.98
Peripheral neuropathic agents	0.96	0.97	**<0.01**	0.96	0.95	0.96	0.38	0.96	0.80
Calcium channel blockers	0.90	0.90	**<0.01**	0.90	0.88	0.90	0.28	0.90	0.76
Disease-modifying antirheummatic agents	0.98	0.98	0.28	0.98	0.84	0.98	0.33	0.98	0.84
Thiazide diuretics	0.83	0.83	0.7	0.83	0.82	0.78	**<0.01**	0.83	0.81

DIPEPTIDYL PEPTIDASE-4 INHIBITOR USE AND CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS WITH DIABETES: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Purpose: Cardiovascular safety of dipeptidyl peptidase-IV inhibitors (DPP-4i) among high-risk patients, such as those with established cardiovascular or kidney disease, is poorly understood. These individuals make up a fraction of new users of antihyperglycemic agents; however, their comorbidities increase their underlying cardiovascular risk, potentially confounding the relationship between DPP-4i use and major adverse cardiovascular events (MACE). In this study, we investigated the risk of MACE associated with the use of DPP-4i among individuals with diabetes, comorbid with cardiovascular disease, chronic kidney disease, and/or acute renal impairment.

Methods: Using a retrospective, new-user, cohort design, we analyzed Truven Marketscan Commercial Claims and Encounters from 2010-2015. We studied commercially-insured patients with diabetes, comorbid with cardiovascular disease and/or renal impairment to determine the association between DPP-4i and MACE. We compared outcomes with use of DPP-4i to sulfonylureas and to metformin using a propensity score weighted Cox proportional hazards model, adjusting for demographics, baseline comorbidities and concomitant medications. Additionally, we separately assessed the association between DPP-4i and heart failure, acute myocardial infarction, and stroke.

Results: In our cohort of 113,296 individuals, 8.1% used DPP-4i, 15.4% used sulfonylurea, and 78.2% used metformin. MACE incidence with DPP-4i was less than with sulfonylurea (-30.20 per 1,000 person-years; IQR [-40.5, -19.9]) and comparable to

that with metformin (7.75 per 1,000 person-years; IQR: [-0.5, 16.0]). After adjustment, DPP-4i were associated with a lower risk of MACE than sulfonylurea (aHR=0.84; 95% CI: [0.7, 0.9]); similar to that with metformin (aHR=1.07; 95% CI: [1.0, 1.2]). No significant associations were seen in the secondary outcomes after adjustment.

Conclusions: Among high-risk patients, DPP-4i were associated with a lower risk of MACE than sulfonylureas, with MACE hazards comparable to that with metformin use.

Keywords

Dipeptidyl peptidase-IV inhibitors; drug-related side effects and adverse reactions; major adverse cardiovascular disease; pharmacoepidemiology

Introduction

Diabetes afflicts nearly 26 million people in the United States, who often have very high morbidity and mortality[1,2]. Individuals with diabetes have high rates of cardiovascular disease (CVD)[3], including peripheral arterial disease and cerebrovascular disease, and treatment choices need to be made in light of these serious and prevalent comorbidities.

One important class of medicines to treat Type 2 diabetes are the dipeptidyl peptidase-IV inhibitors (DPP-4i); these drugs slow the breakdown of GLP-1, inhibiting glucagon release and increasing insulin release[4]. Five medications in this class have been approved by the FDA since 2006, for use alone or in combination, and they rank third in utilization after biguanides and sulfonylurea with 8% of antidiabetic drug prescriptions[5].

DPP-4i(s) were initially believed to be protective against major adverse cardiovascular events (MACE), evidenced through pre-approval clinical trials[6]. Given high rates of cardiovascular disease among diabetics[7,8], as well as longstanding regulatory interest in the potential adverse cardiovascular events associated with diabetes treatments[9], evidence of such a cardioprotective effect would be of high regulatory, clinical and marketing importance. However, despite this early evidence from pre-approval studies, postmarketing surveillance reports[10,11] and data from Phase 4 clinical trials[12-14] suggest elevated risks of MACE, specifically heart failure.

In this retrospective study, we focused on patients at elevated baseline risk, specifically those with history of cardiovascular disease and/or renal disease (i.e. chronic kidney disease and acute kidney impairment), comparing the rates of adverse cardiovascular events among DPP-4i users with that of comparable users of metformin and sulfonylurea. Our inclusion of patients with renal disease stemmed from results of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial, which showed that renal disease was independently associated with increased risk for MACE[15]. We were interested in this elevated risk population, because if a discernable effect were present, it would likely be seen in this high-risk population.

METHODS

Study Design and Data Source

We conducted a population-based, retrospective cohort with a new user design using data from Truven Health MarketScan Commercial Claims and Encounters from January 2010 through December 2015. MarketScan houses linked paid claims and encounter data from approximately 350 payers, covering more than 25 million individuals annually. The data consists of de-identified individual-level healthcare utilization data including demographic characteristics and information on inpatient and outpatient medical claims and pharmacy claims.

Cohort Derivation

We included individuals with type 2 diabetes having at least one prescription for an oral antihyperglycemic agent and either HbA1c greater than 6.5% twice, fasting glucose greater than 126 mg/dL twice on different days, random glucose > 200 mg/dL twice on different days, one inpatient diagnosis of for diabetes (ICD-9(10): 250x (E11.9), 357.2 (E11.42), 366.41 (E11.36), 362.01-362.07 (E11.3*)) or outpatient diagnosis for diabetes (ICD-9(10): 250x (E11.9), 366.41 (E11.36), 362.01-362.07 (E11.3*)) twice on different days. For inclusion, individuals needed to have filled at least one prescription for a DPP-4i, a sulfonylurea, or metformin (**eTable 1)**. We assigned an index date as the date of the first filled prescription for one of these products, and the baseline period was defined as the preceding six-month period. We used International Classification of Diseases, 9th and 10th Revisions (ICD-9/10) codes (**eTable 2)** from inpatient and outpatient records to identify those with a history of cardiovascular disease and/or renal impairment for inclusion into the study.

We excluded individuals based on: 1) without continuous medical or pharmacy enrollment in the six-month baseline period; 2) below the age of 35; 3) with insulin use during the baseline period; 4) patients on dialysis in the baseline period; 5) less than 12-weeks of exposure to index treatment; or 6) treatment with other oral antihyperglycemic agents in the baseline period. We followed patients until the first of either: date of major adverse cardiovascular event or censoring at 14-days after the last date of exposure, switch in anti-hyperglycemic treatment or addition of another anti-hyperglycemic agent, end in medical or pharmacy enrollment, or study end date of 31 December 2015.

Definition of Exposure

We assigned patients to an exposure group based on their first prescription of DPP-4i, sulfonylurea, or metformin. In the event of multiple drug class prescriptions on the index date, patients were counted in all relevant exposure groups.

Definition of Outcome

We defined our primary composite outcome as the first of any of the following events: myocardial infarction, cardiac arrest, coronary artery bypass graft, coronary angioplasty, heart failure, or stroke. Our secondary outcomes were acute myocardial infarction, stroke, and heart failure. We used validated algorithms to identify myocardial infarction[16], cardiac arrest[17], coronary artery bypass graft[16], coronary angioplasty[16], heart failure[18], and stroke[19]. For conditions/procedures without validated ICD-10 algorithms, we deferred to the Chronic Conditions Warehouse[20].

Definition of Covariates

We used the peer-reviewed literature[21-24], clinical guidelines[25-29] and expert opinion[9,30] in order to identify key covariates of interest (**eTable3**). We assessed possible confounding due to patient age and sex; cardiovascular risk factors including hypertension and hypercholesterolemia, diabetic complications, diabetic severity as measured by the Adjusted Diabetes Comorbidities Severity Index (aDCSI)[31-33], and other common comorbidities such as cerebrovascular disease, ischemic heart disease, asthma, and rheumatoid arthritis. Comorbidities coded under ICD-9 were identified using the

Clinical Classification Software (CCS) developed by the Agency for Healthcare Research and Quality[34]. As CCS was not updated with ICD-10 codes at the time of analysis, we cross-referenced these ICD-9 codes with their ICD-10 equivalents. Additionally, we used National Drug Codes to assess for possible confounding due to concomitant medications including statins, angiotensin converting enzymes (ACE) inhibitors, platelet aggregation inhibitor, calcium channel blockers, angiotensin II receptor blockers, beta-blockers, diuretics, nitrates, and inhaled corticosteroids.

Propensity Score

We used the Toolkit for Weighting and Analysis of Nonequivalent Groups (*twang)* package developed by the RAND Corporation[35] to compute the propensity scores and associated weights used in the analysis to balance the covariates between exposure groups. To do so, we identified all available covariates with an association to the primary outcome but without an association to the exposure in order to increase precision[36]. Next, we used generalized boosted regression models to optimize the selection of covariates for the propensity score calculation. The *twang* package allows for propensity scores estimation in the presence of multiple exposure groups. We used the standardized mean difference (SMD) to measure balance of covariates before and after weighting. Propensity score weighting reduced the SMD from a maximum of 0.23 to less than 0.01 (**eFigure 2)**. We used the average treatment effect on the treated (ATT) propensity score weights to estimate the treatment effect of DPP-4i.

Statistical Analysis

Using chi-square statistics for categorical covariates and the Kruskal-Wallis test for continuous covariates, we compared differences at baseline between new users of DPP-4i, sulfonylurea, and metformin. We used exact Poisson tests to compare absolute differences in incidence rates for the primary and secondary outcomes for new users of DPP-4i compared to those of sulfonylurea and metformin. Additionally, we checked for differences in time-to-event distributions using a Kolmogorov-Smirnov test. Using the propensity score weights described above, we calculated weighted crude and adjusted Cox proportional hazards for the association between new use of DPP-4i and the primary and secondary outcomes compared to new use of sulfonylureas and metformin. For the adjusted hazard ratios, we included indicators for age, sex, cumulative exposure, baseline comorbidities, and concomitant medication (**eTable 3**). Additionally, we checked for covariates that violated the proportional hazards assumption by plotting the scaled Schoenfeld residuals. We stratified the Cox proportional hazards model by these covariates. We also used spline terms for cumulative exposure. Finally, we included an indicator for individuals included in multiple exposure groups. All analyses were conducted in R, version 3.3.3.

Sensitivity Analyses

To check the robustness of our results, we first assessed possible sensitivity of our results to the latency of the period after drug discontinuation. We followed patients for 14-, 7-, and 30-days after the last day of exposure to drug. Next, we recalculated the

primary analysis without patients with acute renal failure at baseline to determine whether our results were sensitive to the inclusion of those patients.

The study was exempted from review by the appropriate Johns Hopkins Bloomberg School of Public Health Institutional Review Board

RESULTS

Subject Inclusion and Characteristics

We identified 12,166,812 individuals with diabetes from 2010-2015. After applying our inclusion and exclusion criteria, there were 113,296 individuals in our cohort (**Figure 1**). Of these, 9146 (8.1%) were new users of DPP-4i, 17481 (15.4%) initiated sulfonylureas, and 88596 (78.2%) started metformin. Three percent of included patients were new users of both DPP-4i and metformin, and 1,524 (1.3%) were new users of both sulfonylureas and metformin.

More sulfonylurea users (60.4%) were male compared to DPP-4i (58.5%) or metformin (52.2%) users. **(Table 1)** Approximately half of patients in each exposure group had a cumulative exposure to the treatment of interest less than or equal to 6 months (DPP-4i: 54.0%; sulfonylureas: 56.3%; metformin: 53.7%). Rates of cardiovascular disease were higher among users of metformin than their counterparts, while kidney disease was more prevalent among users of sulfonylureas (17.2%) and DPP-4i (15.0%) than metformin (7.1%). Differences between users of DPP-4i,

sulfonylurea, and metformin diminished after application of propensity score weighting (**eTable 4)**.

Association between treatment and major adverse cardiovascular events (MACE)

The median time until the primary outcome was 160 days (interquartile range [IQR] 92- 296 days) and there was no statistically significant difference in time-to-event distributions across the therapeutic classes examined (**eFigure 2**). After propensity score weighting and adjusting for baseline demographics, clinical characteristics, and concomitant medications, the incidence rate for the primary outcome was statistically significantly lower, by 30.2 per 1000 person-years, among new users of DPP-4i compared to sulfonylureas (**Table 2**). There was a non-statistically significant increase in the incidence rate for the primary outcome among new users of DPP-4i's compared to metformin (91.25 per 1,000 person-years vs. 79.46 per 1,000 person-years). Among the secondary outcomes, the incidence rate for heart failure was significantly less (4.07 per 1,000 person-years vs. 7.56 per 1,000 person-years) for new users of DPP-4i compared to sulfonylurea. The incidence rates for the secondary outcomes were not significantly different between DPP-4i and metformin.

After propensity score weighting and adjustment for baseline demographics, clinical characteristics, and concomitant medications, the risk of MACE was less with new use of DPP-4i compared to with new use of sulfonylurea (adjusted hazard ratio [aHR] 0.84, 95% confidence interval [CI] 0.7-0.9). There was not a statistically

significant difference in risk of MACE with DPP-4i as compared with metformin (aHR 1.07, CI 1.0-1.2) (**Table 3**).

There was a statistically significant association for heart failure in the propensity score weighted analysis comparing DPP-4i to sulfonylurea (HR 0.95, CI [0.4-0.9); however, after adjusting for potential confounders, the association was attenuated and no longer statistically significant. DPP-4i was also not statistically significantly associated with acute myocardial infarction when compared to sulfonylureas (aHR 0.95, CI 0.7-1.4) or metformin (aHR 1.32, CI 1.0-1.2), nor was there a statistically significant association between DPP-4i and stroke when compared to sulfonylureas (aHR 1.08, CI 0.9-1.4) or metformin (aHR 1.16, CI 1.0-1.4).

Sensitivity Analyses

Results of analyses excluding patients with acute renal failure showed qualitatively similar results to those including these patients (**eTable 6**). Similarly, results were not sensitive to changes in the latency period after the last dose of exposure for the primary analysis results, nor did they differ substantively when lagging the latency period by 7-days or 30-days (**eTable 7**).

DISCUSSION

In this longitudinal study of commercial claims data for patients with diabetes, comorbid with cardiovascular disease and/or renal disease, new use of DPP-4i was associated with less risk for MACE compared to sulfonylureas, and a comparable risk

compared to metformin. New use of DPP-4i was not shown to be associated with the following individual components of MACE: heart failure, stroke, or acute myocardial infarction. These results expand upon the body of evidence examining the association of DPP-4i and MACE in patients at higher risk for cardiovascular events.

Overall, our results corroborated those of previous clinical trials and observational studies of cardiovascular safety of DPP-4i. Our analysis detected no increased risk for MACE with the use of DPP-4i similar to the conclusions in the three completed clinical trials comparing DPP-4i and placebo[12,13,37]. Unlike these trials however, our study population consisted of a high-risk group of patients in a real-world setting with multiple comorbidities and concomitant medications. Additionally, our study allowed us to compare DPP-4i to other available therapies, namely sulfonylureas and metformin, showing a decreased risk for MACE when compared to sulfonylureas.

Three notable observational studies provide additional context to our results. First, a 2015 administrative claims study of patients with diabetes and chronic kidney disease admitted for acute myocardial infarction in the Taiwan National Health Insurance Research Database also showed no increased risk for MACE when comparing patients on sitagliptin to those not on sitagliptin[24]. Expanding on this approach, our study design included patients with a host of cardiovascular conditions at baseline, making our results more generalizable to high-risk patients with diabetes. The second study of 127,555 patients in the Italian Nationwide OsMed Health-DB database showed decreased risk in hospitalization for heart failure risk associated with DPP-4i compared to sulfonylurea

(HR=0.78; 95% CI: [0.62, 0.97])[38]. This suggests that the increased risk for MACE in our comparison might be driven by differences in risk for heart failure. This is partially evident in the statistically significant unadjusted hazard ratio for heart failure as a secondary outcome (**Table 3**). Finally, a study of Medicare patients with diabetes compared cardiovascular risk of DPP-4i to sulfonylurea and thiazolidinediones and found no increased risk in patients over age 65[39]. While our study was limited to a patient population under age 65, our results are similar to those found in a study of older patients.

A major strength of our study is the identification of a high-risk cohort through the use of a large administrative database. The results of the SAVOR TIMI-53 trial suggested that renal impairment was independently associated with adverse cardiovascular outcomes, even after adjusting for cardiovascular risk factors[15]. As such, our decision to restrict the study cohort to patients with diabetes, comorbid with cardiovascular disease and renal impairment allowed us to hone in on a patient population identified by FDA as more appropriate for the study of this drug-event association. In a 2008 Guidance for Industry[9], regulators noted that such patients are often excluded from pre-approval clinical trials, and recommended studies of the association between oral antihyperglycemic agents and MACE should include high-risk patients.

Our study also had limitations. First, we included patients using multiple therapies of interest (e.g., both DPP-4i and sulfonylureas) at baseline. While this may have led to potential misclassification, their exclusion would have resulted in a much

smaller and less generalizable sample [40]. Second, our new user design did not account for time-varying hazards for MACE. We partially addressed this by including spline terms for cumulative exposure to account for changes in baseline hazard. Third, our analyses are subject to potential informative censoring due to a change in exposure status. However, our results were insensitive to the lagged latency period after the last day of exposure, and since most events occurred within the first year of exposure, extending the latency period past 30-days would have been unlikely to have changed our results and could have potentially led to misclassification. Finally, we were unable to assess mortality as a component of the primary composite outcome or as a competing risk due to limitations in the dataset.

CONCLUSION

Our results provide evidence of decreased risk for MACE when comparing DPP-4i versus sulfonylurea in a commercially insured patient population with diabetes, comorbid with cardiovascular disease and renal impairment in the United States. Additionally, we found that there was no difference in risk of MACE for these patients when comparing DPP-4i and metformin. Further studies are needed to determine differences in risk for individual components of the composite outcome, particularly heart failure. Finally, the decreased risk seen with DPP-4i use compared to sulfonylurea is more likely due to cardiovascular risk associated with sulfonylurea rather than protective effects of DPP-4i, as there was no difference in effect between DPP-4i and metformin, which carries little cardiovascular risk.

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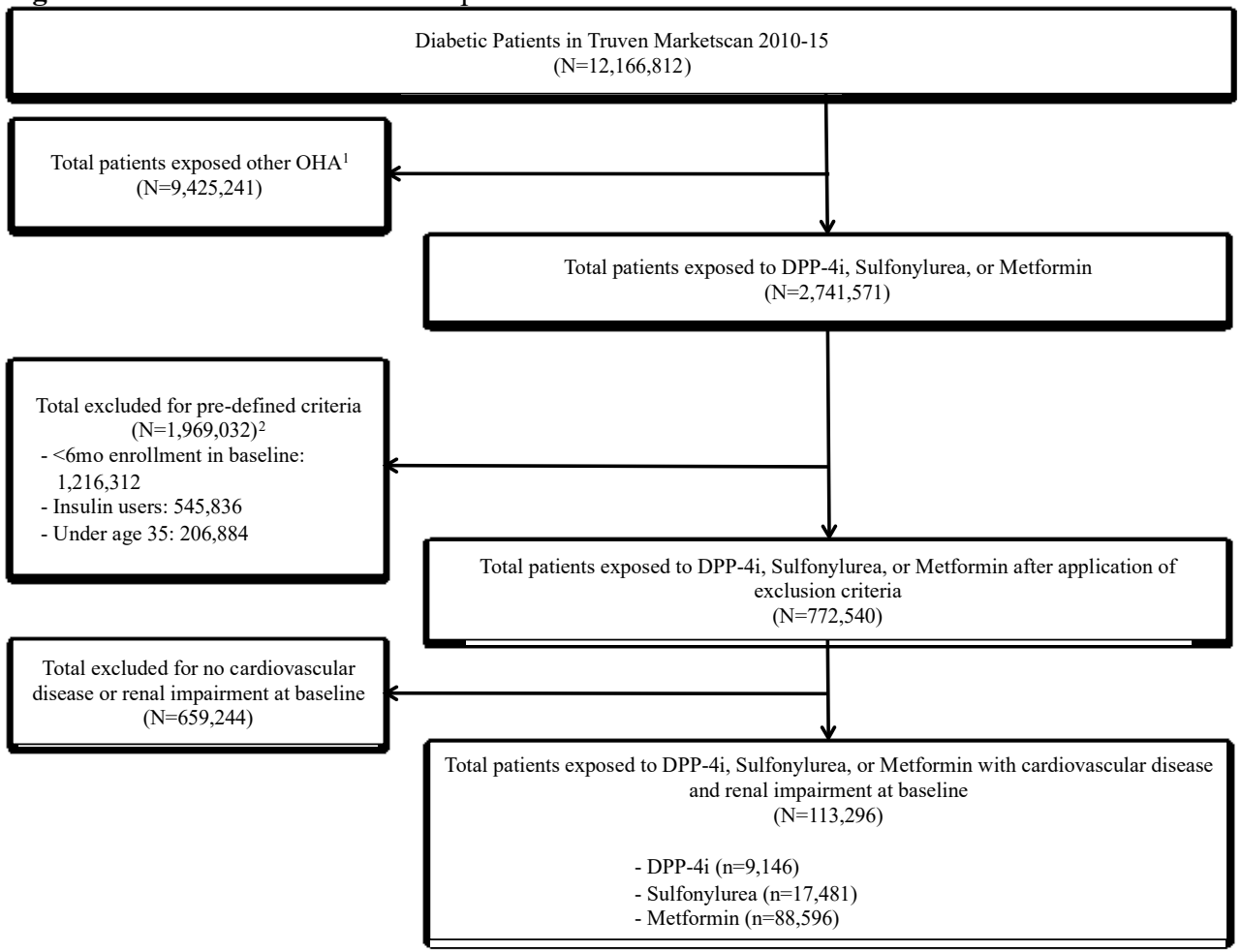
TABLES AND FIGURES

Figure 1. Cohort derivation and sample attrition



[1] OHA = oral antihyperglycemic agents [2] Subcategories are not mutually exclusive

Table 1. Baseline demographics and medical characteristics

	DPP-4i (n=9,146)		Sulfonylureas (n=17,481)		Metformin (n=88,596)	
	N	%	N	%	N	%
Male sex	5,351	58.5	10,559	60.4	46,224	52.2
Age, years						
35-44	877	9.6	2,066	11.8	11,755	13.3
45-54	2,815	30.8	5,147	29.4	29,238	33.0
55-64	5,454	59.6	10,268	58.7	47,603	53.7
Cumulative Exposure, months						
<6 months	4,943	54.0	9,838	56.3	47,534	53.7
6-12 months	2,580	28.2	4,326	24.7	23,869	26.9
12-18 months	848	9.3	1,665	9.5	8,713	9.8
>18 months	775	8.5	1,652	9.5	8,480	9.6
Comorbidities in Baseline						
Cardiovascular disease	8,187	89.5	15,359	87.9	84,138	95.0
Kidney disease (chronic and acute)	1,372	15.0	3,011	17.2	6,263	7.1
Cerebrovascular disease	1,574	17.2	2,931	16.8	14,391	16.2
Ischemic heart disease	3,926	42.9	7,374	42.2	35,242	39.8
Hypertension	7,501	82.0	13,902	79.5	68,723	77.6
Eye disease	3,149	34.4	5,289	30.3	28,809	32.5
Renal disease[1]	4,029	44.1	7,243	41.4	34,718	39.2
Acute renal failure	465	5.1	1,126	6.4	2,118	2.4
Neuropathy	1,320	14.4	2,270	13.0	12,573	14.2
Nephropathy	559	6.1	1,330	7.6	2,455	2.8
aDCSI[2] Score						
0	5,813	63.6	11,326	64.8	61,295	69.2
1	1,203	13.2	2,055	11.8	10,806	12.2
2	1,358	14.8	2,738	15.7	11,290	12.7
3+	772	8.4	1,362	7.8	5,205	5.9

[1] Includes diseases of kidneys, ureters, and bladders; inclusive of acute renal failure.
[2] aDCSI = Adapted Diabetes Complications Severity Index

Table 1 (cont'd). Baseline demographics and medical characteristics

	DPP-4i (n=9,146)		Sulfonylureas (n=17,481)		Metformin (n=88,596)	
	N	%	N	%	N	%
Dual Exposures						
Sulfonylureas	0	0.0	0	0.0	1,524	1.7
Metformin	3,451	37.7	1,524	8.7	0	0.0
DPP-4 inhibitors	0	0.0	0	0.0	3,451	3.9
Concomitant Baseline Medications						
ACE inhibitors	2,022	22.1	3,643	20.8	20,522	23.2
Angiotensin II receptor blockers	2,380	26.0	3,346	19.1	18,410	20.8
Antidepressants	2,132	23.3	3,378	19.3	24,832	28.0
Antiplatelets	2,871	31.4	4,729	27.1	28,182	31.8
Asthma medication	4,599	50.3	7,531	43.1	48,709	55.0
Benzodiazepines	1,842	20.1	2,905	16.6	20,485	23.1
Beta blockers	2,832	31.0	5,208	29.8	28,437	32.1
Blood thinners and anticoagulants	496	5.4	820	4.7	4,924	5.6
Calcium channel blockers	1,507	16.5	2,762	15.8	13,754	15.5
Cardioselective beta blockers	940	10.3	1,632	9.3	7,767	8.8
Diuretics	1,737	19.0	3,016	17.3	19,258	21.7
Nitrates	807	8.8	1,342	7.7	7,924	8.9
Peripheral neuropathic treatments	688	7.5	944	5.4	6,867	7.8
Statins	4,699	51.4	7,484	42.8	41,933	47.3
Thiazide diuretics	1,875	20.5	3,335	19.1	21,306	24.0

Table 2. Incidence rates of primary composite outcome, acute myocardial infraction, stroke, and heart failure among new users of DPP-4 inhibitors, sulfonylureas, and metformin

Outcome, *n*	**DPP-4 Inhibitors**	**DPP-4 Inhibitors v. Sulfonylureas**	**DPP-4 Inhibitors v. Metformin**
Primary Composite Outcome	510	1,301	4,781
Total person years	5,578	10,696	57,134
Rate per 1,000 person years	91.25	121.63	79.46
Median [IQR] observation time, days	160 [92, 286]	144 [75, 288]	163 [93, 300]
Rate difference (95% CI)	-	**-30.20 [-40.5, -19.9]**	7.75 [-0.5, 16.0]
Acute Myocardial Infarction	54	132	450
Total person years	5,898	11,487	60,159
Rate per 1,000 person years	9.16	11.49	7.06
Median [IQR] observation time, days	167 [98, 297]	161 [90, 308]	172 [100, 314]
Rate difference (95% CI)	-	-2.34 [-5.5, 0.8]	1.68 [-0.9, 4.2]
Stroke	141	268	1,202
Total person years	5,839	11,380	59,592
Rate per 1,000 person years	24.15	23.55	20.17
Median [IQR] observation time, days	167 [97, 295]	159 [90, 305]	171 [99, 311]
Rate difference (95% CI)	-	0.60 [-4.3, 5.5]	3.98 [-0.2, 8.1]
Heart Failure	24	87	240
Total person years	5,912	11,512	60,277
Rate per 1,000 person years	4.06	7.56	3.98
Median [IQR] observation time, days	168 [98, 298]	161[90,308]	172 [100, 314]
Rate difference (95% CI)	-	**-3.50 [-5.8, -1.2]**	0.08 [-1.6, 1.8]

[1] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke

[2] Incidence rate difference per 1,000 person-years

[3] IQR = interquartile range

Table 3. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, acute myocardial infraction, stroke, and heart failure compared to sulfonylureas and metformin

	Hazard Ratios for DPP-4 Inhibitors Use			
Reference Drug	**Primary Composite Outcome[3]**	**Acute Myocardial Infarction**	**Stroke**	**Heart Failure**
Sulfonylureas				
HR (95% CI)[1]	**0.77 [0.7, 0.9]**	0.81 [0.6, 1.1]	1.03 [0.8, 1.3]	**0.59 [0.4, 0.9]**
aHR (95% CI)[2]	**0.84 [0.7, 0.9]**	0.95 [0.7, 1.4]	1.08 [0.9, 1.4]	0.71 [0.4, 1.1]
Metformin				
HR (95% CI)[1]	0.98 [0.9, 1.1]	1.13 [0.9, 1.5]	1.12 [0.9, 1.3]	0.94 [0.6, 1.4]
aHR (95% CI)[2]	1.07 [1.0, 1.2]	1.32 [1.0, 1.8]	1.16 [1.0, 1.4]	1.19 [0.8, 1.8]

[1] Propensity score weighting only

[2] Propensity score weighting and demographics, comorbidities, and concomitant medications as regressors and stratifiers

[3] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke

SUPPLEMENTARY MATERIAL

eTable 1. Categorization of drugs into exposure groups

FDA Approved DPP-4 Inhibitors
- alogliptin
- alogliptin and metformin
- alogliptin and pioglitazone
- linagliptin
- linagliptin and empagliflozin
- linagliptin and metformin
- linagliptin and metformin extended release
- sitagliptin
- sitagliptin and metformin
- sitagliptin and metformin extended release
- saxagliptin
- saxagliptin and metformin extended release

FDA Approved Sulfonylureas
- chlorpropamide
- glimepiride
- glimepiride and pioglitazone hydrochloride
- glimepiride and rosiglitazone maleate
- glipizide
- glipizide extended release
- glyburide
- glyburide and metformin hydrochloride
- tolazamide
- tolbutamide

*FDA Approved Biguanides**
- metformin hydrochloride
- metformin hydrochloride extended release

eTable 2. ICD9/10 codes to identify patients with cardiovascular disease and renal impairment

Criterion	Codes	
acute myocardial infarction	410.XX	
	V12.50	
	I21*	
	I25.2	
angina	413.9	
	V12.54	
	I20*	
arteriosclerosis coronary artery	414.01	
	I25.10	
atrial fibrilation	427.31	
	I48*	
atrioventricular block complete	426.0	
	I44.2	
cardiac failure	398.91	428.22
	402.01	428.23
	402.11	428.30
	402.91	428.31
	404.01	428.32
	404.03	428.33
	404.11	428.40
	404.13	428.41
	404.91	428.42
	404.93	428.43
	428.0	428.9
	428.1	V12.59
	428.20	I50*
	428.21	
cardiogenic shock	785.51	
	R57.0	
	R57.9	
cerebral infarction	434.91	433.91
	434.9	433.9
	434.11	433.21
	434.1	433.2
	434.01	346.6
	433.01	346.62
	433	346.51
	433.11	346.53
	433.1	346.52
	433.3	V12.54
	433.81	I63*
	433.8	

cerebrovascular accident	434.91 V12.54 I63.50 Z86.73	
coronary artery bypass graft	36.1x I25.810	
hemmorhagic stroke	432.9 V12.54 I61*	
ischemic stroke	434.11 V12.54 I63*	
myocardial infarction	429.7 429.79 412 411 V12.50 I21*	
stroke	430 431 433.01 433.11 433.21 433.31 433.81 433.91 434.00 434.01 434.10 434.11 434.90 434.91	435.0 436 997.02 V12.54 Z86.73 I61 I62 I63 I65 I66 I67 I68 I69

eTable 3. Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	**Stratifier**
Demographics				
Male	**X**	**X**		**X**
Age	**X**	**X**		**X**
Location (Region)	**X**			
Cumulative Exposure	**X**			**X**
Comorbidities in Baseline				
MACE	**X**	**X**	**X**	
Kidney disease	**X**	**X**	**X**	
Cerebrovascular disease	**X**	**X**		**X**
Congestive heart failure	**X**			
Ischemic heart disease	**X**	**X**	**X**	
Hypertension	**X**	**X**	**X**	
Retinopathy	**X**			
Eye disease	**X**	**X**	**X**	
Renal disease	**X**	**X**		**X**
Acute renal failure	**X**			
Atrial fibrilation	**X**			
Neuropathy	**X**	**X**	**X**	
Nephropathy	**X**	**X**	**X**	
aDCSI Score	**X**	**X**		**X**
Dual Exposures				
Sulfonylureas	**X**			
Metformin	**X**		**X**	
DPP-4 inhibitors	**X**		**X**	

eTable 3 (cont'd). Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	Stratifier
Concomitant Medications at Baseline				
α-Glucosidase inhibitors	X			
ACE inhibitors	X	X	X	
alpha agonists	X	X		
analgesics	X			
angiotensin II receptor blockers	X	X	X	
anti Veg-F	X			
anticoagulants	X	X		
antidepressants	X	X	X	
antiplatelets	X	X		X
aspirin	X	X		
asthma medication	X	X	X	
benzodiazepines	X	X	X	
beta blockers	X	X		X
beta blockers (ophthalmic)	X			
bile acid sequestrants	X			
biologic response modifiers	X			
blood thinners and anticoagulants	X	X	X	
bronchodilators	X	X		
calcium channel blockers	X	X	X	
carbonic anhydrase inhibitors	X			
cardioselective beta blockers	X	X	X	
cholinergics	X			
disease-modifying antirheumatic drugs	X			
diuretics	X	X	X	
erythropoietan	X	X		
fibrates	X			
GLP-1 agonists	X			
hormone replacement therapy	X			
inhaled steroids	X	X		
leukotrine modifiers	X	X		

eTable 3 (cont'd). Covariates used in propensity score model and adjusted Cox proportional hazards model

Covariate	Measured	Included in Propensity Score Model	Included in adjusted Cox PH Model	
			Covariate	**Stratifier**
Concomitant Medications at Baseline				
loop diuretics	**X**	**X**		
MAOI	**X**	**X**		
meglitinides	**X**			
niacin	**X**	**X**		
nitrates	**X**	**X**	**X**	
NSAIDs	**X**			
ophthalmic drugs	**X**			
oral corticosteroids	**X**	**X**		
peripheral neuropathic treatments	**X**	**X**	**X**	
phosphodiesterase-4 inhibitors	**X**			
potassium sparing diuretics	**X**	**X**		
prostaglandins	**X**	**X**		
SGLT-2 inhibitors	**X**			
SNRI	**X**	**X**		
SSRI	**X**	**X**		
statins	**X**	**X**		**X**
theophyllines	**X**			
thiazide diuretics	**X**	**X**	**X**	
thiazolidinediones	**X**			
tricyclic antidepressants	**X**	**X**		
vasodilators	**X**	**X**		

eTable 4. Pre- and Post-weighting distribution of covariates across exposure groups

	DPP4i	Sulfonylurea				Metformin			
		Pre-weighting		Post-weighting		Pre-weighting		Post-weighting	
	Mean	Mean	p-value	Mean	p-value	Mean	p-value	Mean	p-value
Male	0.59	0.60	**<.001**	0.59	0.93	0.52	**<.001**	0.58	0.91
Age Group	0.10	0.12	**<.001**	0.10	0.98	0.13	**<.001**	0.10	0.99
Cardiovascular disease	0.10	0.12	**<.001**	0.11	0.96	0.05	**<.001**	0.10	0.85
Kidney Disease	0.85	0.83	**<.001**	0.85	0.94	0.93	**<.001**	0.85	0.92
Cerebrovascular disease	0.83	0.83	0.36	0.83	0.87	0.84	**0.02**	0.83	0.95
Ischemic heart disease	0.57	0.58	0.24	0.57	0.84	0.60	**<.001**	0.57	0.90
Hypertension	0.18	0.20	**<.001**	0.18	0.97	0.22	**<.001**	0.18	0.94
Eye disease	0.66	0.70	**<.001**	0.66	0.87	0.67	**<.001**	0.66	0.95
Renal disease	0.56	0.59	**<.001**	0.56	0.77	0.61	**<.001**	0.56	0.88
Neuropathy	0.86	0.87	**<.001**	0.86	0.93	0.86	0.53	0.86	0.92
Nephropathy	0.94	0.92	**<.001**	0.94	0.98	0.97	**<.001**	0.94	0.87
aDCSI score	0.64	0.65	**<.001**	0.64	0.99	0.69	**<.001**	0.64	1.00
Benzodiazepines	0.80	0.83	**<.001**	0.80	0.95	0.77	**<.001**	0.80	0.93
Antidepressant	0.77	0.81	**<.001**	0.77	0.92	0.72	**<.001**	0.77	0.91
ACE inhibitors	0.78	0.79	**0.02**	0.78	0.92	0.77	**0.02**	0.78	0.95
Antiplatelets	0.69	0.73	**<.001**	0.69	0.91	0.68	0.41	0.69	0.94
Angiotensin II receptor blockers	0.74	0.81	**<.001**	0.74	0.78	0.79	**<.001**	0.74	0.97
Beta blockers	0.69	0.70	0.05	0.69	0.98	0.68	**0.03**	0.69	0.97
Cardioprotective beta blockers	0.90	0.91	**0.01**	0.90	0.86	0.91	**<.001**	0.90	0.98
Diuretics	0.81	0.83	**<.001**	0.81	0.94	0.78	**<.001**	0.81	0.92
Nitrates	0.91	0.92	**<.001**	0.91	0.87	0.91	0.70	0.91	0.87
Statins	0.49	0.57	**<.001**	0.49	0.87	0.53	**<.001**	0.49	0.88
Peripheral neuropathic agents	0.92	0.95	**<.001**	0.93	0.87	0.92	0.44	0.93	0.89
Calcium channel blockers	0.84	0.84	0.15	0.83	0.96	0.84	**0.02**	0.84	0.92
Thiazide diuretics	0.79	0.81	**0.01**	0.79	0.95	0.76	**<.001**	0.79	0.86
Asthma medication	0.50	0.57	**<.001**	0.50	0.79	0.45	**<.001**	0.50	0.98
Blood thinners and anticoagulants	0.95	0.95	**0.01**	0.95	0.94	0.94	0.59	0.95	0.95

eTable 5. Incidence rates of primary composite outcome, acute myocardial infraction, stroke, and heart failure among new users of DPP-4 inhibitors, sulfonylureas, and metformin, showing sensitivity to latency period after drug discontinuation

Outcome, *n*	**DPP-4 Inhibitors**	**DPP-4 Inhibitors v. Sulfonylureas**	**DPP-4 Inhibitors v. Metformin**
14-day lag censor	510	1,301	4,781
Total person years	5,578	10,696	57,134
Rate per 1,000 person years	91.25	121.63	79.46
Median [IQR] observation time, days	160 [92, 286]	144 [75, 288]	163 [93, 300]
Rate difference (95% CI)	-	**-30.20 [-40.5, -19.9]**	7.75 [-0.5, 16.0]
7-day lag censor	510	1,301	4,781
Total person years	4,593	9,044	47,268
Rate per 1,000 person years	110.82	143.85	96.05
Median [IQR] observation time, days	127 [78, 233]	118 [68, 237]	130 [79, 247]
Rate difference (95% CI)	-	**-32.81 [-45.2, -20.4]**	9.89 [-0.2, 19.9]
30-day lag censor	567	1,438	5,379
Total person years	7,107	13,176	71,923
Rate per 1,000 person years	79.78	109.14	74.79
Median [IQR] observation time, days	207 [116, 352]	185 [90, 358]	211 [118, 381]
Rate difference (95% CI)	-	**-29.36 [-38.0, -20.7]**	4.99 [-1.9, 11.9]

[1] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke

[2] Incidence rate difference per 1,000 person-years

[3] IQR = interquartile range

eTable 6. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, showing sensitivity to patients with acute renal failure at baseline

	Hazard Ratios for DPP-4 Inhibitors Use	
Reference Drug	**Including patients with acute renal failure at baseline**	**Excluding patients with acute renal failure at baseline**
Sulfonylureas		
HR (95% CI)[1]	**0.77 [0.7, 0.9]**	**0.77 [0.7, 0.8]**
aHR (95% CI)[2]	**0.84 [0.7, 0.9]**	**0.83 [0.7, 0.9]**
Metformin		
HR (95% CI)[1]	0.98 [0.9, 1.1]	0.97 [0.9, 1.1]
aHR (95% CI)[2]	1.07 [1.0, 1.2]	1.08 [1.0, 1.2]

[1] Propensity score weighting only

[2] Propensity score weighting and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eTable 7. Hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome, showing sensitivity to latency after drug discontinuation

	Hazard Ratios for DPP-4 Inhibitors Use		
Reference Drug	**14-day lag censor**	**7-day lag censor**	**30-day lag censor**
Sulfonylureas			
HR (95% CI)[1]	**0.77 [0.7, 0.9]**	**0.78 [0.7, 0.9]**	**0.76 [0.7, 0.8]**
aHR (95% CI)[2]	**0.84 [0.7, 0.9]**	**0.85 [0.7, 0.9]**	**0.81 [0.7, 0.9]**
Metformin			
HR (95% CI)[1]	0.98 [0.9, 1.1]	0.98 [0.9, 1.1]	0.96 [0.9, 1.0]
aHR (95% CI)[2]	1.07 [1.0, 1.2]	1.09 [1.0, 1.2]	1.05 [0.9, 1.2]

[1] Propensity score weighting only

[2] Propensity score weighting and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eTable 8. Weighted and unweighted hazard ratios for the association between DPP-4 inhibitor use and primary composite outcome

	Hazard Ratios for DPP-4 Inhibitors Use
Reference Drug	**Hazard Ratio [95% CI]**
Sulfonylureas	
Unweighted HR (95% CI)[2]	**0.81 [0.7, 0.8]**
HR (95% CI)[3]	**0.77 [0.7, 0.9]**
aHR (95% CI)[4]	**0.84 [0.7, 0.9]**
Metformin	
Unweighted HR (95% CI)[2]	1.06 [1.0, 1.2]
HR (95% CI)[3]	0.98 [0.9, 1.1]
aHR (95% CI)[4]	1.07 [1.0, 1.2]

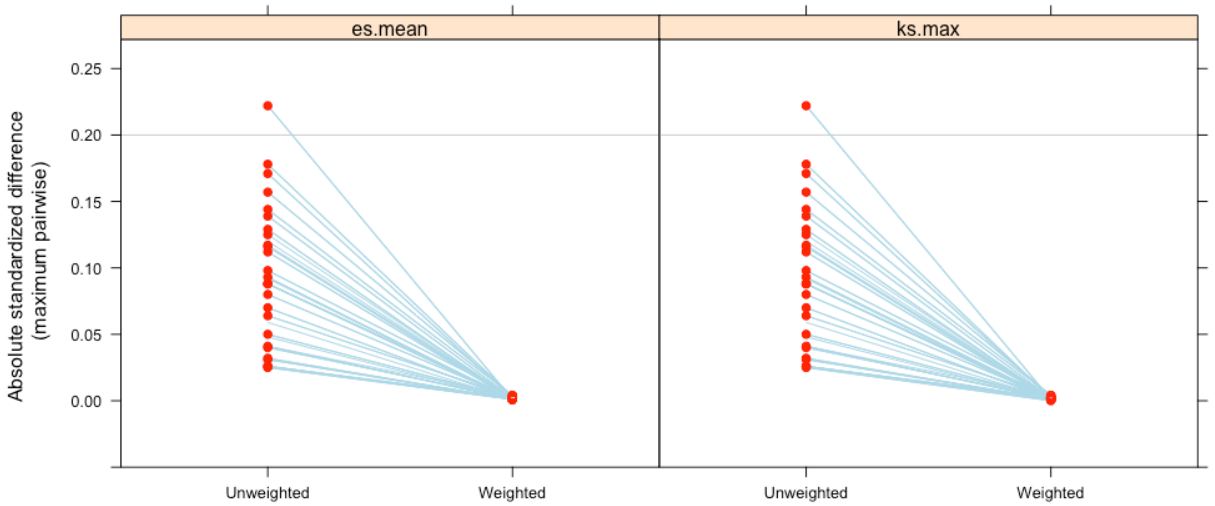
[1] Primary composite outcome includes myocardial infarction, cardiac arrest, coronary artery bypass, coronary angioplasty, heart failure, stroke

[2] Adjusted for demographics, comorbidities, and concomitant medications

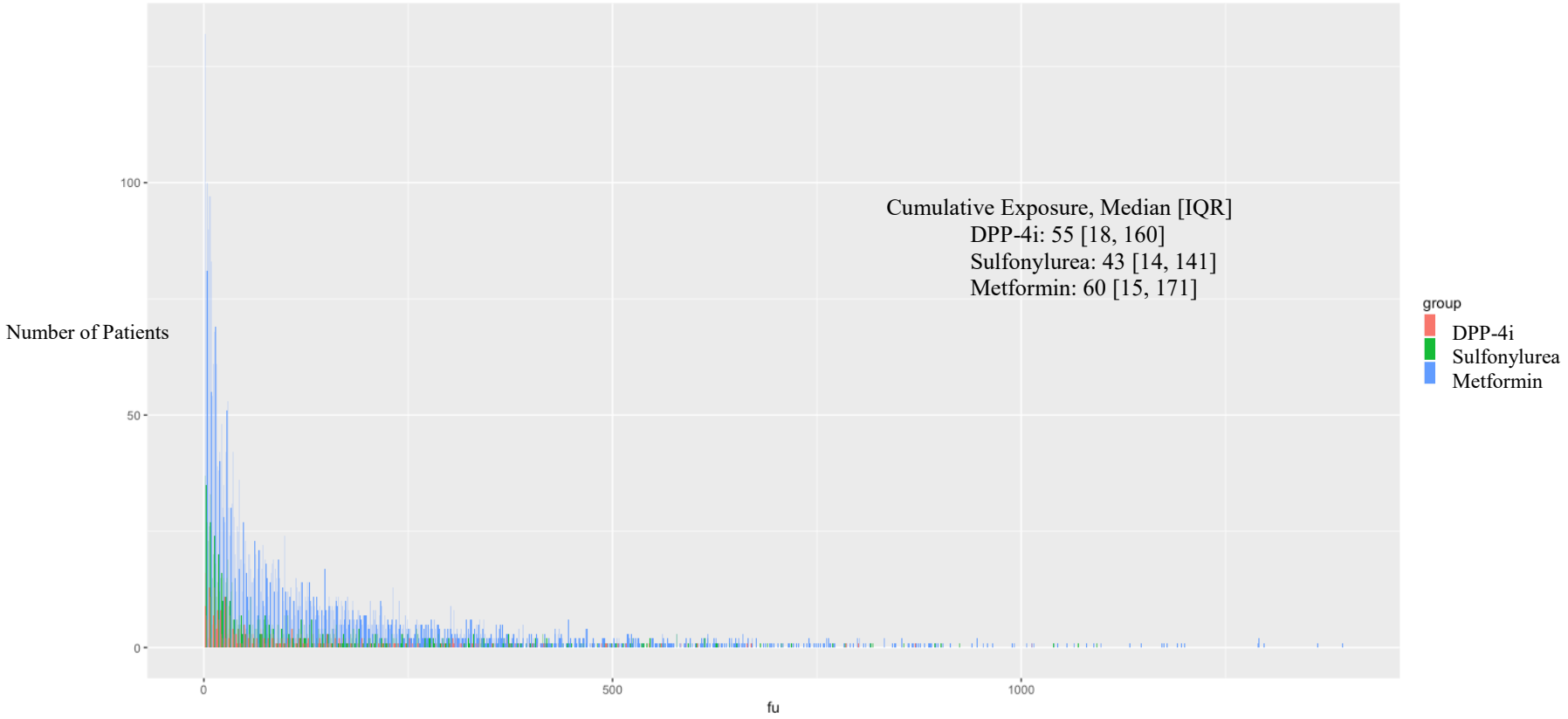
[3] Propensity score weighting only

[4] Propensity score weighting and demographics, comorbidities, and concomitant medications as regressors and stratifiers

eFigure 1. Absolute standardized mean differences before and after propensity score weighting.



eFigure 2. Distributions of cumulative exposure as measured in months for patients with events



CONCLUSION

Public Health Implications

Through our surveillance and retrospective analyses, we found evidence to suggest that while there was increased reporting to FDA of MACE associated with DPP-4i use, further investigation of both low-and high-risk individuals with diabetes revealed that DPP-4i had lower risk for MACE compared to sulfonylureas and comparable risk for MACE compared to metformin. This supports the use of DPP-4i as a safer first-line therapy than sulfonylurea for T2DM in both high- and low-risk individuals with <7.1% HbA1c[1].

Our surveillance study (Aim 1) identified additional MACE events that might potentially be associated with DPP-4i among high-risk individuals, namely myocardial infarction and cerebral infarction. Though we were underpowered to analyze the association between DPP-4i and every individual component of MACE in the retrospective cohort study of high-risk individuals (Aim 3), we did identify acute myocardial infarction as a secondary outcome. After controlling for baseline characteristics, we found no evidence of increased risk for acute myocardial infarction with DPP-4i compared to sulfonylurea or metformin. Further research is needed to determine whether the increased reporting for cerebral infarction is associated with DPP-4i use.

While this dissertation was not designed to look at the cardiovascular safety of individual drugs in Aim 2 and 3, we performed signal detection for individual drugs in

Aim 1. If there were a difference amongst DPP-4i, we would expect to see them between peptidomimetic (sitagliptin, saxagliptin) and nonpeptidomimetic (alogliptin, linagliptin) products. One mechanism of action for DPP-4i is to form a covalent bond with Ser630 in the active site. Peptidomemetic DPP-4i typically have greater selectivity for DPP-4i, whereas nonpeptidomimetic DPP-4i have poor selectivity, and are more likely to bond with DPP-8 or DPP-9. This action can lead to inhibition of T-cell activation and proliferation[2]. In turn, inhibition of T_{REG} activation has been associated with lower cardioprotection[3]. From our Aim 1 results however, both peptidomimetic and nonpeptidomimetic DPP-4i elicited cardiovascular safety signals.

Finally, the decreased risk seen with DPP-4i use compared to sulfonylurea is more likely due to cardiovascular risk associated with sulfonylurea rather than protective effects of DPP-4i, as there was no difference in effect between DPP-4i and metformin, which carries little cardiovascular risk.

The results of our study carry implications for patient care, clinician prescribing behavior, and regulatory actions. This dissertation provides evidence that DPP-4i are a viable alternative to sulfonylureas for first-line therapy in new users of non-insulin antihyperglycemic drug therapy. A 2016 meta-analysis of 179 clinical trials and 25 observational studies examining the comparative effectiveness of monotherapy found that metformin carried a better cardiovascular safety profile that sulfonylurea[4]. These findings align with the results of this dissertation, suggesting that both metformin and DPP-4i are safer alternatives for newly treated patients with diabetes. Our Aim 2 and 3 results show that for patients with different cardiovascular risk profiles, DPP-4i carry similar risks between high- and low-risk patients when compared to sulfonylurea and

metformin. This has implications for physicians determining the best treatment for new patients, for whom they may not have a complete understanding of their cardiovascular risk. Our results suggest that DPP-4i are a low-cardiovascular risk option, along with metformin, for first line treatment. Finally, our results did not support the current FDA label warning for increased risk of heart failure with the use of saxagliptin or alogliptin among patients with high cardiovascular risk. These results contribute to the current body of evidence used as regulatory guidance in evaluating the cardiovascular safety of DPP-4i.

Review of Aim 1

In the surveillance portion of the dissertation, we used a disproportionality analysis of FDA adverse event reports to detect safety signals, as measured by relative reporting ratios, for DPP-4i reports for MACE. In the subset of adverse events reports that were generated from a group of patients with at high-risk for cardiovascular events, there was an increase in reporting of MACE for sitagliptin, saxagliptin, linagliptin, and alogliptin. These signals suggested that even among a group of reports where one would expect to see high numbers of reports for these events, the DPP-4i class stood out. Our results showed signals for multiple components of MACE in addition to the previously reported association with heart failure.

Finally, we found that creating a subset of reports from drugs associated with diabetes and cardiovascular disease allowed for detection of additional MACE reporting. This approach contrasted with the analysis of the cardiovascular risks of DPP-4i using the full FAERS dataset. In this latter analysis, only two signals were detected, whereas our use of the cardiovascular subset elicited 12 distinct signals. We saw that for products

where there is a known association with cardiovascular events with those products (i.e. sulfonylureas), signal detection in the full FAERS dataset is sensitive enough to detect potential signals. However, for products where association is tenuous, a subset with reports from a high-risk patient population may be more sensitive to capture additional signals for further investigation.

Review of Aim 2

In this retrospective cohort analysis of commercial claims data for individuals with diabetes and without a history of cardiovascular disease or chronic kidney disease, DPP-4i use was associated with 13% lower risk of MACE compared to sulfonylureas, and a similar risk of MACE when compared to metformin. Our results also showed decreased risk for the secondary outcomes of acute myocardial infarction, stroke, and heart failure when comparing DPP-4i to sulfonylurea. Contrasting with the results of the EXamination of CArdiovascular OutcoMes with AlogliptIN versus Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) trial[5] and the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI) trial[6], we did not find increased risk for heart failure with the use of DPP-4i. This is likely due to our study population restriction to low-risk individuals. Understanding whether or not diabetic treatment in this population increases patient risk for MACE is critical to managing their care due to the close link between cardiovascular disease and diabetes[7].

Review of Aim 3

In this longitudinal study of commercial claims data for patients with diabetes, comorbid with cardiovascular disease and/or renal disease, new use of DPP-4i was associated with less risk for MACE compared to sulfonylureas, and a comparable risk compared to metformin. New use of DPP-4i was not shown to be associated with the following individual components of MACE: heart failure, stroke, or acute myocardial infarction. These results expand upon the body of evidence examining the association of DPP-4i and MACE in patients at higher risk for cardiovascular events.

Study Limitations

Limitations in Aim 1

One important limitation of the study was the nature of surveillance used by FDA to collect the adverse event reports that populate FAERS. This system relies heavily upon spontaneous reporting from patients, providers, and patient advocates as well as required reporting from drug manufacturers. Because FAERS collects data through passive surveillance, the number of adverse events reported to FDA potentially underestimates the true level of risk with drug products. Another limitation with these data is the amount of missing information regarding patient medical history, concomitant medications, and drug manufacturer. While the adverse event reporting form contains fields for these elements, they are often missing the requested data, or the information must be requested through the Freedom of Information Act. This level of missing data did not allow for extensive analysis of the FAERS reports.

Limitations in Aims 2 and 3

Our longitudinal analyses were limited by our decision to use first line therapies as comparators. Many oral antihyperglycemic agents that qualify as first-line therapy are often prescribed concomitantly with a second first-line drug. We were left to include individuals into more than one exposure group at baseline. We recognized that this could have potentially led to misclassification[8]. Excluding patients who were exposed to multiple drug groups of interest would have resulted in a reduced sample size, threatening the generalizability of our results. As such, we assessed the sensitivity of our results to their inclusion and found them to be robust.

Another limitation of the dataset was our inability to assess key unmeasured variables. The first of these was mortality, which we could not include as a component of the primary composite outcome or as a competing risk. We also did not have data on body mass index, a correlate of cardiovascular disease. Finally, we were unable to capture date on individuals over the age of 65.

Study Strengths

We used the results of the surveillance study (Aim 1) as a hypothesis-generating tool to better inform the design of the retrospective cohort studies (Aim 2 and 3). While prior evidence suggested that DPP-4i were associated with heart failure, we were interested in investigating whether or not there were additional signals for other MACE with distinct pathogenesis (e.g., myocardial infarction). Our method of subsetting the adverse event reports to a high-risk pool of patients showed utility in identifying signals

for further investigation. The cardiovascular subset allowed for greater sensitivity to detect signals that might have been confounded by comorbidities commonly found with diabetes. Also, by restricting the Bayesian prior to adverse event reports stemming from a pool of patients with related illnesses, our approach reduced the level of residual confounding.

Our retrospective cohort analyses benefited from many characteristics of the dataset, including a large, generalizable, patient population, inpatient and outpatient medical encounters data, linked prescription and medical encounters data, and six years of follow-up. We leveraged these strengths to conduct separate analyses of high- and low-risk individuals with diabetes initiating treatment with DPP-4i. This approach allowed us to tailor the covariates in each analysis to each study cohort, thereby acknowledging that baseline cardiovascular disease and renal disease may confound the relationship between DPP-4i and MACE.

In conclusion, this dissertation contributes to the ongoing work investigating the cardiovascular risk of oral antihyperglycemic agents. We did not find evidence of increased risk for MACE with the use of DPP-4i.

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List of Tables

Background

Cardiovascular Risk with Dipeptidyl Peptidase-4 inhibitors: A disproportionality analysis among high risk patients

Dipeptidyl Peptidase-4 inhibitor use and Cardiovascular Events in low-risk patients with diabetes: a retrospective cohort study

Dipeptidyl Peptidase-4 inhibitor use and Cardiovascular Events in high-risk patients with diabetes: a retrospective cohort study

List of Figures

Background

Dipeptidyl Peptidase-4 inhibitor use and Cardiovascular Events in low-risk patients with diabetes: a retrospective cohort study

Dipeptidyl Peptidase-4 inhibitor use and Cardiovascular Events in high-risk patients with diabetes: a retrospective cohort study

Appendix 1: Adapted R code for *'PhViD'* package

```
##########################################################################
##########################################################################
#
#   Simplified version of PhViD package and associated GPS Command
#
##########################################################################
##########################################################################


setwd("/Users/Sheriza/dpp4 inhibitors/FAERS/")
rm(list=ls())
# Load data frame with drugname, pt, and N
# Duplicates have been removed for this dataset
load("newdata.rda")

# source("https://bioconductor.org/biocLite.R")
# biocLite("LBE")
# LBE allows for estimation of false discovery rate (FDR)
library(LBE)

##########################################################################
# Original Code:
##########################################################################

# Create a data frame with the marginal probabilities for each drug-event combo
   #signaldat <- data.frame(newdata)
   #library(PhViD)
   #signaldat <- as.PhViD(signaldat, MARGIN.THRES = 1)
   #system.time(signaldat<-as.PhViD(newdata, MARGIN.THRES = 1))

# Disproportionality analysis and signal detection
   #gps <- GPS(signaldat, RR0 = 1, MIN.n11 = 2, DECISION = 3,
   #      DECISION.THRES = 0.05,
   #      RANKSTAT = 1, TRONC = FALSE, TRONC.THRES = 1,
   #      PRIOR.INIT = c(alpha1 = 0.2, beta1 = 0.06, alpha2 = 1.4,
   #                  beta2 = 1.8, w = 0.1), PRIOR.PARAM = NULL)

# Problematic error message after as.PhViD command:
# Error in tapply(y, by, sum) : total number of levels >= 2^31




##########################################################################
# Deconstructed Code to Compare Data With New Code:
##########################################################################

## with all data
```

```
library(data.table)

dim(newdata)
length(levels(newdata$drugname))
length(levels(newdata$pt))
newdata$drugname<-factor(newdata$drugname)
length(levels(newdata$drugname))
newdata$pt<-factor(newdata$pt)
length(levels(newdata$pt))

newdata<-newdata[1:round(nrow(newdata)/2),]
newdata$drugname<-factor(newdata$drugname)
length(levels(newdata$drugname))
newdata$pt<-factor(newdata$pt)
length(levels(newdata$pt))
dim(newdata)
tallydata <- count.dups(newdata)

setwd("/Users/Sheriza/dpp4 inhibitors/FAERS/")
rm(list=ls())
load("newdata.rda")
library(data.table)
dim(newdata)
length(levels(newdata$drugname))
length(levels(newdata$pt))
newdata$drugname<-factor(newdata$drugname)
length(levels(newdata$drugname))
newdata$pt<-factor(newdata$pt)
length(levels(newdata$pt))
dta<-newdata[!grepl("^\\.{1,}$", newdata$drugname),]
dta<-dta[!grepl("^\\'{1,}$", dta$drugname),]
dta<-dta[!grepl("^\\,{1,}$", dta$drugname),]
dta<-dta[dta$drugname!="",]
```

```
##############################################################################
# Corrected Code
##############################################################################
rm(list=ls())
setwd("/Users/Sheriza/dpp4 inhibitors/FAERS/")
library(PhViD)
library(data.table)

# New function to create dataframe with drug, pt, n11, n.1, n1.
# Effectively this function is a substitute for as.PhViD
new_function<-function(dta){
 require(plyr)
 data <- dta
 data[, 1] <- as.factor(dta[, 1])
 data[, 2] <- as.factor(dta[, 2])
 data[, 3] <- as.double(dta[, 3])

 coln <- names(data)
 names(data)[3] <- "n11"

 cat("Summing over drugnames")
 n1dot<-ddply(data, .(drugname), summarize, n1d=sum(n11, na.rm=T), .progress="text")
 cat("Summing over adverse effects")
 ndot1<-ddply(data, .(pt), summarize, nd1=sum(n11, na.rm=T), .progress="text")
 cat("Merging...")
 all<-merge(data, ndot1, by="pt", all=T)
 all<-merge(all, n1dot, by="drugname", all=T)
 colnames(all)<-c("drugname", "pt", "n11", "n.1", "n1.")
 all<-all[order(all$drugname, all$pt),]
 data<-as.matrix(all[,c(3,5,4)])
 rownames(data)<-paste0(all$drugname, " ", all$pt)
 L<-all[,c(1,2)]

 N<-sum(data[,"n11"], na.rm=T)

 RES <- vector(mode = "list")
 RES$L <- L
 RES$data <- data
 RES$N <- N
 RES
}


load("newdata.rda")
newdata<-newdata[sample(1:nrow(newdata), size = round(nrow(newdata)/3)),]
# Check characteristics of raw data
dim(newdata)
length(levels(newdata$drugname))
length(levels(newdata$pt))
newdata$drugname<-factor(newdata$drugname)
length(levels(newdata$drugname))
newdata$pt<-factor(newdata$pt)
length(levels(newdata$pt))
```

```
dta<-newdata[!grepl("^\\.{1,}$", newdata$drugname),]
dta<-dta[!grepl("^\\'{1,}$", dta$drugname),]
dta<-dta[!grepl("^\\,{1,}$", dta$drugname),]
dta<-dta[!grepl("^\\-{1,}$", dta$drugname),]
dta<-dta[dta$drugname!="",]

unique_drugs<-unique(as.character(dta$drugname))
unique_drugs<-unique_drugs[order(unique_drugs)]
head(unique_drugs)
unique_pt<-unique(as.character(dta$pt))
unique_pt<-unique_pt[order(unique_pt)]
head(unique_pt)

unique_drugs[grepl("acetaminophen", unique_drugs, ignore.case=T)&
        grepl("oxycodone", unique_drugs, ignore.case=T)]

# Duration for new as.PhViD
function_baksh<-new_function(dta)

head(function_baksh$data)
tail(function_baksh$data)

#############################################################################
# GPS parameters according to Szarfman et al
#############################################################################
source("GPS_v2.R")
gps <- GPS2(DATABASE=function_baksh,
      RR0 = 1,
      MIN.n11 = 1,
      DECISION = 3,
      DECISION.THRES = 2,
      RANKSTAT = 2,
      TRONC = F,
      TRONC.THRES = 0,
      PRIOR.INIT = c(alpha1= 0.2, beta1= 0.06, alpha2=1.4, beta2=1.8, w=0.1),
      PRIOR.PARAM = NULL)


#############################################################################
# Query for drugs or events of interest
#############################################################################

library(PhViD)
options(max.print = 9999999)
PhViD.search(RESULT, DRUG = NULL, EVENT = NULL)
#alogliptin <- capture.output(PhViD.search(gps, DRUG = "ALOGLIPTIN", EVENT = NULL))
#cat("Alogliptin Signals" , alogliptin, file = "alogliptin.csv", sep = ",", append = TRUE)

# where RESULT is the name of the results file
# Replace "NULL" with DRUG and/or EVENT of interest
```

Curriculum Vitae

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SKILLS SUMMARY

PhD candidate with over six years of federal regulatory experience in pharmacoepidemiology, spanning drug utilization, adverse event signal detection, and bioequivalence trial design. Strong interest in novel methods in pharmacoepidemiology research. Trained in the FDA Adverse Events Reporting System, Marketscan Commercial, R, and SAS.

EDUCATION AND CERTIFICATIONS

Ph.D. [in progress]	*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health*
Certificate 2015	*Risk Science and Public Policy, Johns Hopkins University*
MPH 2009	*Department of Epidemiology and Department of International Health, Boston University School of Public Health*
B.A. 2007	*Health & Societies and English, University of Pennsylvania*

PROFESSIONAL EXPERIENCE

Research Assistant, 2015-Present, Center for Clinical Trials and Evidence Synthesis, Johns Hopkins Bloomberg School of Public Health

Research Assistant, 2014-2015, Risk Sciences and Public Policy Institute, Johns Hopkins University

Epidemiologist, 2012-2014, CDER/OPS/IO, The United States Food and Drug Administration

ORISE Fellow, 2009-2012, CDER/OPS/IO, The United States Food and Drug Administration

Research Assistant, 2009, Pathways to Wellness, Boston, MA

Quality Assurance Intern, 2008, Sabin Vaccine Institute, Washington, DC

Junior Epidemiologist, 2007, CDER/OPaSS/ODS/DDRE, The United States Food and Drug Administration

PROFESSIONAL ACTIVITIES

Memberships

International Society for Pharmacoepidemiology (ISPE), *2015-Present*
Society for Clinical Trials, *2013-Present*
American Public Health Association, *2008-2013*

EDITORIAL ACTIVITIES

Ad hoc Reviewer

Trials
Drug Safety

HONORS AND AWARDS

Johns Hopkins Center for Excellence in Regulatory Science and Innovation (CERSI) Scholar*, Johns Hopkins Bloomberg School of Public Health* (2016-present)
Center for Drug Safety and Effectiveness Scholar*, Johns Hopkins Bloomberg School of*
Public Health (2015-present)
Office of Pharmaceutical Science Employee Recognition Award, *CDER/OPS/IO, The United*
States Food and Drug Administration, (2012)

PUBLICATIONS

Journal Articles (Peer-reviewed)

1. **Baksh SN**, Demarco MM, Segal JB, Alexander GC. (In press). Cardiovascular safety signals with dipeptidyl peptidase-4 inhibitors: a disproportionality analysis among high-risk patients. *Pharmacoepidemiology and Drug Safety*. 2018 Apr; [Epub ahead of print].
2. Chang HY, Singh S, Mansour O, **Baksh SN**, Alexander GC. Association between sodium-glucose cotransporter-2 (SGLT-2) inhibitors and lower extremity amputation: A retrospective cohort study. *JAMA Internal Medicine*. 2018 Aug; [Epub ahead of print].

3. Mansour O, Chang HY, **Baksh SN**, Alexander GC, Singh S. Risk of hospitalization and cardiovascular events among patients using sodium-glucose cotransporter 2 (SGLT2) inhibitors: A retrospective cohort study. [Manuscript under review].
4. Nachman KE, Fain KM, Smith TJ, **Baksh SN**, Fox MA. Comparability of toxicological evaluation approaches for veterinary and human pharmaceuticals, environmental chemicals, and food and food additives across seven US federal programs. *Environmental Health Perspectives.* [Manuscript under review].
5. Fox MA, **Baksh SN**, Lam J, Resnick B. Building the future of Environmental Public Health Tracking: Proceedings and recommendations of an expert panel workshop. *Journal of Environmental Health*. 2017 Jun; 79(10):14-9.
6. Chingcuanco, F, Segal JB, Kim SC, Alexander GC. Bioequivalence of biosimilars tumor necrosis factor-α inhibitors compared with their reference biologics: A systematic review. *Annals of Internal Medicine*. 2016 Oct; 165(8):565-74. [Acknowledgement for research].
7. **Baksh SN**, Gellad WF, Alexander GC. Maximizing the Post-Approval Safety of Flibanserin: A Role for Regulators, Clinicians, and Patients. *Drug Safety*. 2016 May; 39(5):375-80.
8. Botvinick M, Bylsma LM. Regularization in short-term memory for serial order. *Journal of Experimental Psychology: Learning, memory and cognition.* 2005 Mar; 31(2):351-8. [Acknowledgement for research].

Book Chapters

1. Zolnik, BS, **Baksh, SN**, Sadrieh, N. (2012). "Challenges in the development of nanotechnology based ophthalmic systems" in Thassu D and Chader G *Ocular Drug Delivery Systems: Barriers and Application of Nanoparticulate Systems* (pp. 95-109). London: Taylor and Francis/Informa Health.

PART II

TEACHING

Courses

Johns Hopkins Bloomberg School of Public Health
Teaching Assistant, 317.600.81, *Introduction to Risk Sciences and Public Policy (online)*, 2016-2017
Teaching Assistant, 317.605.01, *Methods in Quantitative Risk Assessment,* 2017
Lead Teaching Assistant, 317.600.01, *Introduction to Risk Sciences and Public Policy*, 2014-2016
Teaching Assistant, 340.645.01, *Introduction to Clinical Trials,* 2016-2017
Teaching Assistant, 317.615.01, *Topics in Risk Assessment*, 2016
Teaching Assistant, 340.601.01, *Principles of Epidemiology*, 2015-2016
Teaching Assistant, 317.610.81, *Risk Policy, Management, and Communication (online)*, 2015
Teaching Assistant, 317.610.01, *Risk Policy, Management, and Communication*, 2014, 2016
Tutor, 340.601.01, *Principles of Epidemiology*, 2014

Coursera
Teaching Assistant, Johns Hopkins University, *Design and Interpretation of Clinical Trials,* 2016

Moelis Access Science, Netter Center for Community Partnerships
Instructor, *Neuroscience,* 2005-2007

Agatston Urban Nutrition Initiative, Netter Center for Community Partnerships
Curriculum Developer, *Nutrition,* 2006-2007

Guest Lectures

Senior-Level High School Biology Class. *Introduction to Public Health*, Western High School, November 2015

Risk Policy, Management, and Communication (317.610.01). *Current Events in Risk Sciences: Mixing Medications and Dietary Supplements*. Johns Hopkins Bloomberg School of Public Health, November 2014

Middle School Science. *Environmental Health*. St. John the Evangelist Elementary School, March 2010

PRESENTATIONS

1. **Baksh S**, DeMarco MM, Segal JB, Alexander GC. "Safety signals for major adverse cardiovascular events as a composite outcome with dipeptidyl peptidase-4 inhibitors in the FDA Adverse Event Reporting System." International Society for Pharmacoepidemiology 33rd ICPE [Conference]. Montreal, Canada. August 26, 2017.
2. Mitchell C, **Baksh S**, et al. *Study to Understand Fall Reduction and Vitamin D in You (STURDY): A Bayesian adaptive randomized clinical trial to study vitamin D supplements for fall prevention in older adults.* [Centennial Poster Session – Johns Hopkins University School of Public Health – November 3, 2015].
3. Fox M, **Baksh S**, Lam J. "Case studies of acceptable risk: paving the way for the risk-specific dose". Society for Risk Analysis Annual Meeting [Conference]. Denver, CO. December 2014.
4. Nachman K, Fain K, Smith T, **Baksh S**, Fox M. "Transparency considerations for toxicological evaluation approaches for veterinary and human pharmaceuticals, environmental chemicals, and food and food additives across seven US federal programs". Society for Risk Analysis Annual Meeting [Conference]. Denver, CO. December 2014.
5. **Baksh, S**, Zolnik, B, Sadrieh, N. "Analysis of Approved Generic Antiepileptic Drugs: Evaluation of post-marketing data submitted to FDA's Medwatch (Part 1 of 2)". American Association of Pharmaceutical Scientists Annual Meeting and Exposition [Conference]. Chicago, IL. 14 Oct. 2012.
6. Zolnik, B., **Baksh, S.**, Sadrieh, N. "Analysis of Approved Generic Antiepileptic Drugs: Evaluation of pharmacokinetic data from bioequivalence (BE) studies submitted to the FDA (Part 2 of 2)". American Association of Pharmaceutical Scientists Annual Meeting and Exposition [Conference]. Chicago, IL. 14 Oct. 2012.
7. **Baksh, S.** *Divalproex Sodium: An In-depth Analysis of Adverse Events and Current and Proposed Bioequivalence Standards for Generic Extended Release Antiepileptic Drugs* [Presentation – Office of Surveillance and Epidemiology - October 2011].
8. **Baksh, S.** *Single-funder and multiple-funder NTD vaccine development strategies and research productivity*. [Boston University School of Public Health MPH Thesis - May 2009].
9. **Baksh, S.** *Effects of Acupuncture and CAM Therapy on the Digestive Side Effects of ARV Therapy.* [Poster Session – Boston University School of Public Health Practicum Poster Session - April 2009]
10. **Baksh, S.** *Impediments to accessing health care in the English-speaking Caribbean.* [University of Pennsylvania Undergraduate Thesis - May 2007]