HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2019 September 05.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2018 June ; 27(6): 660–667. doi:10.1002/pds.4437.

Cardiovascular safety signals with dipeptidyl peptidase-4 inhibitors: A disproportionality analysis among high-risk patients

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Abstract

Purpose: In 2008, the US Food and Drug Administration (FDA) issued Draft Guidance on investigating cardiovascular risk with oral diabetic drugs, including dipeptidyl peptidase-4 inhibitors (DPP-4i).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 to 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 2 analyses and calculated the percent positive agreement for signals of disproportional reporting (SDRs) involving MACE.

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DISCLOSURES

Dr Alexander is Chair of the FDA's Peripheral and Central Nervous System Advisory Committee, serves as a paid consultant to QuintilesIMS, serves on the Advisory Board of MesaRx Innovations, and serves on OptumRx's National P&T Committee. This arrangement has been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. No other authors declare a potential conflict of interest.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

SUPPORTING INFORMATION

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

Results: Of 180.3 million adverse event reports, 13.4 million were for diabetic and cardiovascular drugs. In the cardiovascular subset, there was an 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 an SDR in both analyses. Overall, the cardiovascular subset elicited 11 more SDRs 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; pharmacoepidemiology; pharmacovigilance

1 | 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.[1] Many of these patients also experience medical complications such as coronary heart disease, stroke, nephropathy, neuropathy, and retinopathy.[2] 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.[3] 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.[4] Since the approval of the first DPP-4i, sitagliptin, in 2006, the US Food and Drug Administration (FDA) have approved 10 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 glucagon-like peptide-1 (GLP-1).[5] 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 antidiabetic products. Based on premarketing clinical trial data, adverse events are less severe than other treatment options but include acute pancreatitis.[6] 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.[7,8] However, while failing to reach statistical significance, one phase 4 trial suggested hospitalization for heart failure with saxagliptin use.[9]

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 (SDRs) 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.

2 | METHODS

2.1 | Data

We used postmarketing 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.[10] 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 to include all FDA approved drug products and exclude other FDA approved products such as biologics.[11] We excluded reports without a suspect medication (N = 3556), 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.

2.2 | Rationale of datasets and analytic approach

We conducted Bayesian disproportionality analyses using 2 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 noninsulin antihyperglycemic agents and drugs indicated for cardiovascular disease (“cardiovascular subset”). By using these 2 different sets, we were able to compare and contrast SDR between 2 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,[12] 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.[13]

2.3 | 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 (EBGM) of the relative reporting ratio. We used the DuMouchel multi-item gamma Poisson shrinkage method to derive and

rank the EBGM.[14] 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.[15–18] 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 an SDR for any drug-event combination.[19] Events were precoded 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 myocar-dial 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 Table S1. 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.

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.[20] 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.[7,21–23] 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 5 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 2 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.

3 | RESULTS

3.1 | 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. A total of 208 385 (0.1%) reports were for DPP-4i from patients with a median of 60 (inter-quartile range (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.

3.2 | 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 an 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 an 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) (Tables S2 to S4).

3.3 | 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 (Tables S2 to S4).

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 3 antihyperglycemic drug classes, there was general agreement in SDR between the 2 datasets for acute myocardial infarction and hemorrhagic stroke. However, there were 12 instances where the full dataset elicited an SDR, and the cardiovascular subset did not. There were 12 instances where the cardiovascular subset elicited an SDR, and the full dataset did not. All of the discordances in DPP-4i signals between the 2 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.

3.5 | 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 (percent positive agreement (PPA) = 33.3%) each had low percent positive agreement. The analyses of the full dataset and the cardiovascular subset each detected 12 unique SDRs.

3.6 | Stimulated reporting

Comparing the percent change between the 2 months after the regulatory events and 2 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.

4 | 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 SDRs 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 2 SDRs, 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 (ie, 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 SDRs for other MACE with distinct pathogenesis (eg, myocardial infarction). In examining percent positive agreement between analyses of the 2 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 used 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 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.[24] 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.[25] 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.[5] While this raises a concern for selection bias, alternative comparators such as thiazolidinediones are associated with cardiovascular risk,[26] while others such as SGLT2 inhibitors are associated with cardiovascular benefit.[27]

5 | 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. Longitudinal, observational research is needed to fully understand the association between DPP-4i use and cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This work was supported in part through the Johns Hopkins Center of Excellence in Regulatory Science and Innovation (U01 FD004977–03). The funding source had no role in the design and conduct of the study, analysis or interpretation of the data, and preparation or final approval of the manuscript prior to publication.

Funding information

Johns Hopkins Center of Excellence in Regulatory Science and Innovation, Grant/Award Number: U01 FD004977–03

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KEY POINTS

- The US Food and Drug Administration issued a warning for heart failure risk in diabetics with the use of dipeptidyl peptidase-4 inhibitors (DPP-4i) based on underpowered, post hoc analyses of clinical trials.
- We conducted Bayesian disproportionality analyses on adverse event reports to assess whether DPP-4i elicited signals of disproportional reporting (SDRs) for cardiovascular events in the full set of adverse event reports and among a subset implicating cardiovascular and diabetic drugs.
- We found 2 SDRs for heart failure among DPP-4i. Additionally, the cardiovascular subset elicited more SDRs for cardiovascular events than the full dataset.
- Our findings support the current Food and Drug Administration warning of heart failure risk with the use of DPP-4i.

TABLE 1

Bayesian signals of disproportional reporting (EB05[a] <2.0) for antihyperglycemic agents in full dataset and cardiovascular subset[b]

	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						
	Cardiac Failure Congestive		Sudden Death		Sudden Cardiac Death		Cerebrovascular Accident		Cerebral Infarction		Hemorrhagic Stroke		Ischemic Stroke	

	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)**
	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

[a] EB05: 90% lower bound of the empirical Bayes geometric mean of the relative reporting ratio.

[b] Excludes products with n = 0 reports, EB05 <0, or EBGM <0.

TABLE 2

Percent positive agreement between datasets[a]

			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	

	Full Dataset		Percent Positive Agreement, %
	SDR	No SDR	
Ischemic stroke	1	18	

Abbreviation: SDR, signal of disproportional reporting.

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