1. ABSTRACT

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	Invokana
Name of Active Ingredient(s)	JNJ-28431754 (Canagliflozin)

Protocol No.: RRA-21651

Title of Study: Incidence of Diabetic Ketoacidosis among Patients with Type 2 Diabetes Mellitus Treated with SGLT2 inhibitors or Other Antihyperglycemic Agents- A Retrospective, Observational, New-User Cohort Study Using 4 Administrative Claims Databases in the US

Sponsor's Responsible Medical Officer: Gary Meininger, MD, Janssen Research & Development

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Names and Affiliations of Principal Investigator(s):

Norman Rosenthal, MD
Janssen Research & Development
PPD
USA

Study Center(s): United States

Publication (Reference): None

Study Period: 01 Apr 2013 to 31 Dec 2017

Background and Rationale: Diabetic ketoacidosis (DKA) is a serious acute metabolic complication of diabetes. In February 2016, the European Medicines Agency (EMA) concluded that rare events of DKA, including life-threatening ones, have occurred in patients taking sodium glucose co-transporter 2 inhibitors (SGLT2i) for type 2 diabetes mellitus (T2DM) and a number of these cases have been atypical, with patients experiencing DKA with lower than expected blood sugar levels. The EMA adopted the recommendation of Pharmacovigilance Risk Assessment Committee (PRAC) to list DKA as a rare adverse reaction in the product information of SGLT2i and implement risk management measures to minimize the risk. Following these recommendations, we conducted a post-authorization safety study to further evaluate the risk of DKA in T2DM patients taking SGLT2i.

Research Questions and Objectives:

Research Questions of this study are

- What are incidence rates of DKA among 'real-world' patients diagnosed with T2DM taking various AHAs, including SGLT2i?
- Is SGLT2i treatment associated with a higher incidence of DKA hospitalization compared with other AHAs among patients with T2DM having similar baseline characteristics?

Objectives of this study are

Primary Objective:

- To compare the incidence of DKA among patients diagnosed with T2DM and pair-matched on exposure propensity scores (PS) for new use of any SGLT2i versus new use of various other AHAs.

Secondary Objective(s):

- To compare the incidence of DKA among patients diagnosed with T2DM and pair-matched on exposure PS for new use of individual SGLT2i versus new use of various other AHAs
- To estimate the incidence rate of DKA for new users of SGLT2i and new users of other AHAs among patients diagnosed with T2DM
- To estimate and compare the incidence of DKA among patients with T2DM, stratified by age group, sex, history of DKA, and insulin use, respectively
- To identify potential precipitating events and evaluate risk factors for incident DKA

Study Design: Retrospective, observational, new-user cohort study using administrative claims databases

Setting: Patients with a diagnosis of T2DM preceding ≥1 prescription claims for the pre-specified AHAs from 01 April 2013 to the last day of data in each of the 4 large US administrative claims databases (varying from 31 December 2016 to 31 December 2017)

Patient Population and Study Size: Patients who had a diagnosis of T2DM preceding new use of an SGLT2i or at least one pre-specified comparator AHAs during the study period and had at least 365 days of continuous enrollment prior to the first day of new drug exposure (index date) were eligible for this study. T2DM patients were defined using 2 algorithms. The broad definition required diagnosis of T2DM but no type 1 diabetes (T1DM) or secondary diabetes (SDM) on or before the exposure index date. The narrow definition had additional requirements with intent to exclude patients who might have T1DM or SDM that were misclassified as T2DM. For pair-wise comparative analyses, the eligible patients in the respective target and comparator cohort were 1:1 matched on the exposure propensity scores (PS) to adjust for the baseline covariates imbalance in the comparative cohorts. Only PS-matched patients were included in comparative analyses.

Variables and Data Sources: Exposure to the target and comparator AHAs were identified from the prescription records in each claims database. The target AHAs were SGLT2i, including the class as the primary target AHA and 3 individual agents (canagliflozin, dapagliflozin, empagliflozin) as the secondary target AHA. The non-SGLT2i comparator AHAs included 7 primary comparators, 1) sulfonylureas (SU), 2) dipeptidyl peptidase-4 inhibitors (DPP-4i), 3) glucagon-like peptide-1 agonists (GLP-1a), 4) thiazolidinediones (TZD), 5) insulin, 6) metformin, 7) insulinotropic AHAs combined as one group (DPP-4i, GLP-1a, SU, nateglinide, repaglinide), and one secondary comparator 8) other miscellaneous AHAs. The outcome of interest was the first DKA event that occurred after the index date of an AHA new-user cohort and was identified from diagnosis code recorded in inpatient or ER claims. Due to limited availability and biased collection of laboratory data in the databases used for this study, we were unable to categorize cases to typical or atypical DKA. Baseline covariates were evaluated based on claims data in the 365 days or more prior to the exposure index date. Four US administrative claims databases (IBM MarketScan® Commercial Claims and Encounters [CCAE], IBM MarketScan® Medicaid [MDCD], IBM MarketScan® Medicare Supplemental [MDCR], and Optum© De-identified Clinformatics® Data Mart Database – Socio-Economic Status [OPTUM]) were used for this study. Each database contained inpatient admission records, outpatient services, prescription drugs, eligibility status, and costs of services.

Statistical Methods: Incidence rates of DKA were calculated as the number of incident cases divided by total time-at-risk. Intent-to-treat (ITT) was the primary cohort follow-up strategy, in which time-at-risk started from the day after the drug exposure index date and ended at the time of the incident DKA diagnosis, disenrollment, or the end of the database coverage. Per-protocol (PP) / on treatment was the sensitivity follow-up strategy, where censoring was applied to the time-at-risk at the initiation of non-index AHAs and the discontinuation of the index AHA. For descriptive analyses, crude incidence rates of DKA, distribution of risk factors for DKA, and the events preceding DKA occurrence were examined across each AHA new-user cohort. For comparative analyses, exposure PS were estimated using the large-scale regularized regression of the large number of baseline covariates. One-to-one PS matching was used to balance the baseline characteristics of the target and comparator cohorts. Cox proportional hazards models conditioning on the PS-matched pairs were used to estimate the hazard ratios (HR) of DKA among the new users of SGLT2i (class and individual agents) compared with non-SGLT2i comparator AHAs. P-value were calibrated using the negative control outcomes to address potential systematic bias. HRs and 95% CI were estimated in each database separately. Where I^2 was <40%, a pooled HR was estimated using a random effects approach to combine the estimates across 4 databases. Sensitivity analyses were conducted to assess the robustness of results.

RESULTS:

PARTICIPANTS AND PATIENT CHARACTERISTICS: Of the 4 claims databases, the CCAE database provided the largest sample size for all AHA new-user cohorts and the MDCD database provided the smallest sample size for most cohorts. Using the broad definition of T2DM, the number of new users of SGLT2i class ranged from 11,141 in MDCD to 152,728 in CCAE, the number of new users of primary comparator AHAs ranged from 5,687 TZD users in MDCD to 329,839 metformin users in CCAE. The number of eligible new users were fewer when using the narrow definition of T2DM, ranging from 7,779 users in MDCD to 130,708 users in CCAE for SGLT2i class and from 3,982 TZD users in MDCD to 271,723 metformin users in CCAE for comparator AHAs. Across all AHA new-user cohorts, the mean age ranged from 47.9 to 75.5 years, the percentage of females ranged from 41.0% to 72.1%.

OUTCOME DATA: Using the broad definition of T2DM, the crude incidence rates of DKA identified from diagnosis code in inpatient or ER claims during the ITT time-at-risk period ranged from 2.33 to 9.47 / 1000 person-years (PYs) in the new users of the SGLT2i (class and individual agents), from 1.38 to 15.8 / 1000 PYs in the new users of non-SGLT2i comparator AHAs. The corresponding crude incidence rates using the narrow definition of T2DM ranged from 0.95 to 4.15 / 1000 PYs in the SGLT2i cohorts and from 0.75 to 7.94 / 1000 PYs in the comparator cohorts. The proportion of fatal DKA was overall low.

MAIN RESULTS: Using the broad definition of T2DM, a significantly increased risk of DKA was observed in the new users of SGLT2i class compared with 5 pre-specified non-SGLT2i AHA groups. The pooled HR (95% CI) of DKA for SGLT2i new users across 4 databases was 1.53 (1.31-1.79) compared with SU, 1.28 (1.11-1.47) compared with DPP-4i, 1.34 (1.12-1.60) compared with GLP-1a, 1.31 (1.11-1.54) compared with metformin, and 1.38 (1.15-1.66) compared with insulinotropic AHAs. When using the narrow definition of T2DM to exclude T1DM patients who might be misdiagnosed as T2DM, the risk of DKA was not significantly higher among the new users of SGLT2i class compared with DPP-4i, GLP-1a, or metformin, but remained increased compared with SU, with a pooled HR of 1.43 (95% CI: 1.01-2.01). The risk of DKA also appeared trending higher in 3 out of 4 databases for SGLT2i compared with insulinotropic AHAs, a combination group that included SU, with no pooled estimate across databases due to unacceptable heterogeneity. The new users of SGLT2i had a significantly lower risk of DKA compared with insulin new users (pooled HR of 0.74 and 0.70 using the broad and narrow T2DM definition, respectively), and a similar risk of DKA compared with TZD. The risk of DKA for the new user of individual SGLT2i agents versus non-SGLT2i AHAs appeared generally similar to that for the SGLT2i class, but with greater variations in HRs across individual databases.

OTHER ANALYSES: The crude incidence rates of DKA were higher in patients with prior use of insulin and history of DKA. The SGLT2i new users had a higher proportion of patients receiving the insulin prescription prior to the index date compared with non-SGLT2i AHAs except for GLP-1a. Other risk factors for DKA and events that occurred prior to DKA (hospitalization, surgery, and infections) were similarly distributed across the AHA new-user cohorts.

DISCUSSION AND CONCLUSION:

DISCUSSION:

Our study conducted comprehensive analyses to evaluate the risk of DKA among T2DM patients treated with SGLT2i in 4 large-scale US claims databases. Using the broad T2DM definition and based on the pooled HRs in meta-analysis across 4 databases, our study found that the new users of SGLT2i had a moderate, but statistically significant, increased risk of DKA compared with the new users of several pre-specified non-SGLT2i AHA groups. When using the narrow T2DM definition, the risk of DKA remained significantly increased in the SGLT2i new users only when compared with SU (in meta-analysis) and insulinotropic AHA (in only one database, possibly driven by SU component). Since DKA occurs more frequently in T1DM patients, the differences in associations between using the broad and narrow T2DM definitions suggest that the increased risk of DKA in the SGLT2i new users might be attributed to the use of SGLT2i in unrecognized or misclassified T1DM patients. Given the limitation in using an algorithm of diagnosis and prescription claims to define T2DM, misclassification remains possible even in the patients identified with the narrow definition. On the other hand, our descriptive analyses suggest that the SGLT2i new users may be in a more advanced stage of diabetes with both insulin resistance and insulin deficiency; our comparative analyses showed for the new users of SGLT2i, there was an increased risk of DKA compared with the new users of SU and a decreased risk compared with the new users of insulin with both T2DM definitions. These findings support one possible explanation that in the SGLT2i users, diminished beta-cell function may be a predisposing factor for the development of DKA, but the risk can be managed if the exogenous supply of insulin was maintained. The current clinical recommendations on the use of SGLT2i and the Summary of Product characteristics for SGLT2i are in line with this hypothesis.

This study was subject to the limitations of observational study research using administrative claims data, including potential misclassification, missing data, residual confounding, and small sample size in select comparisons.

CONCLUSIONS:

In this large, observational, retrospective cohort study using claims databases, an increased risk of DKA was observed for the new users of SGLT2i compared with the new users of several non-SGLT2i AHAs using the broad T2DM definition. When using the narrow T2DM definition to exclude possible misclassified T1DM patients, the risk of DKA remained increased only when compared with SU. A trending association in favor of insulinotropic AHAs versus SGLT2i may be largely driven by SU. The association of individual SGLT2i agents with the risk of DKA appeared generally similar across agents of the SGLT2i class. These data suggest that the positive association between SGLT2i and the risk of DKA may be in part due to potential misdiagnosis of T1DM as T2DM. Nevertheless, based on the meta-analysis estimates, the current study also could not rule out an increased risk of DKA associated with SGLT2i therapy even in a well-defined T2DM population.