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SGLT-2 inhibitors and ketoacidosis: a disproportionality analysis in the World Health Organization's adverse drug reactions database

Short title: Gliflozins and severe ketoacidosis

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Abstract

Introduction: SGLT-2 inhibitors, also called gliflozins, are a new class of drugs used in type 2 diabetes. Since their marketing, several cases of ketoacidosis, including life-threatening conditions, were reported with their use. The objective of this study was to investigate the disproportionality of pharmacovigilance reports of serious ketosis between gliflozins and other drugs used for type 2 diabetes.

Methods: We performed a case-non-case study within the World Health Organization's pharmacovigilance database, VigiBase. From January 2013 to March 2016, we selected all reports of serious adverse drug reaction associated with glucose-lowering drugs in patients aged 40 years and older. Cases were reports of serious ketosis and non-cases were all other serious adverse drug reactions. We studied the disproportionality of reports of serious ketosis for gliflozins by calculating Reporting Odds Ratios (ROR) with their 95% confidence interval (95% CI). We also measured the disproportionality before the warnings issued by the U.S. and European medicines agencies.

Results: A total of 68,555 notifications were selected. We identified 487 cases of serious ketosis exposed to gliflozins. Serious ketosis was significantly more frequently reported with gliflozins than with other glucose-lowering drugs (adjusted ROR 15.5; 95% CI: 12.8 - 18.7). The disproportionality of gliflozins reports was also found before the warning of the medicines agencies.

Conclusion: Our study shows a significant and early pharmacovigilance signal which suggests an increased risk of serious ketoacidosis associated with the use of gliflozins in patients with diabetes. Further studies are needed to further characterize the potential risk of ketoacidosis with gliflozin use.

Key words

SGLT-2 inhibitors, gliflozins, adverse drug reactions, ketoacidosis, disproportionality analysis

Introduction

Marketed for the first time in 2013, sodium glucose transporter 2 (SGLT2) inhibitors, also called gliflozins, are a new class of drugs used in the treatment of type 2 diabetes. This class includes drugs such as dapagliflozin, canagliflozin, empagliflozin, ipragliflozin or ertugliflozin. Gliflozins are indicated in patients with type 2 diabetes in monotherapy or in combination with other glucose-lowering drugs such as metformin or insulin. By inhibiting the sodium glucose transporters in the proximal tubule of the kidney, gliflozins reduce the renal reabsorption of glucose and therefore lead to increased glycosuria and reduced glycemic levels [1]. In addition to their antihyperglycemic and diuretic effects in diabetic patients, gliflozins might be associated with potentially dangerous side effects including severe ketoacidosis, an adverse reaction that has been suspected following several post-marketing life-threatening cases. Ketoacidosis is an excessive acidity of the blood caused by the accumulation of ketone bodies which are by-products of fatty acids oxidation. Ketoacidosis generally occurs in patients with type 1 diabetes lacking insulin or under conditions that require increased glucose intake, and usually presents with severe hyperglycemia associated with glycosuria and ketonuria causing dehydration, potentially resulting in fatal shock. In preclinical and clinical development of gliflozins, ketoacidosis had not been specifically identified. The risk of serious ketosis associated with gliflozins has been a concern since the U.S. Food and Drug Administration (FDA) issued an alert bulletin in May 2015 based on the description of 73 reported cases in the United States [2] while, in Europe, 102 similar cases were recorded in the Eudravigilance database [3]. Unlike generally described diabetic ketoacidosis, the majority of the cases did not show a major rise in blood glucose, thus they were characterized as euglycemic.

In order to investigate the potential risk of ketoacidosis associated with gliflozins, we performed a pharmacovigilance study in a large international pharmacovigilance database by measuring the disproportionality of reports of serious ketosis between gliflozins and other drugs used for type 2 diabetes.

Materials and methods

Data source

Data were extracted from VigiBase, a database managed by the World Health Organization (WHO), which anonymously records more than 13 million spontaneous reports of adverse drug reactions (Individual Case Safety Report, ICSR) from more than 120 countries members of the WHO International Drug Monitoring Program [4]. Information retrieved from the database included the patient's sex and age at the onset time of the adverse reaction, the clinical description of the drug adverse reactions with date of onset and seriousness criterion, the country of origin, the type of reporter (healthcare professionals, pharmaceutical industries or patients), the exposure to drugs with prescription dates, daily dosage, route of administration, indication, and the accountability of each drug in the adverse reaction (based on criteria defining the drug as suspect, concomitant or interacting), and the evolution of the adverse reaction. Drug adverse reactions were described according to the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1) [5] and were considered serious when they resulted in death, were life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or in congenital anomalies or birth defects [6]. Drugs were classified using the Anatomical Therapeutic Chemical (ATC) classification [7].

Study population

We extracted from VigiBase all the reports of adverse drug reactions considered serious, occurring in patients over 40 years (since younger patients are more likely to present type 1 diabetes), associated with the use at least one glucose-lowering drugs including insulins, between January 2013 and March 2016.

Study design

The disproportionality of reports for serious ketosis associated with gliflozins was studied by performing a case-non-case study. This design allows the calculation of Reporting Odds Ratios (ROR), which compare the exposure to gliflozin between cases and non-cases in order to detect pharmacovigilance signals in adverse drug reaction databases [8, 9]. Cases were patients with serious ketosis defined by the

report of a drug adverse reaction considered as serious and coded with the following MedDRA preferred terms: *"acetonaemia"*, *"blood ketone body"*, *"blood ketone body Increased"*, *"blood ketone body present"*, *"diabetic ketoacidosis"*, *"ketoacidosis"*, *"ketosis urine ketone body"* and *"urine ketone body present."* All other serious drug adverse reactions were considered non-cases.

Exposure definition

Exposure to gliflozins was defined by the mention in the report of an exposure to at least one gliflozin (ATC code A10BK) for any level of accountability (suspect, concomitant or interacting) for which the chronology was considered compatible (*i.e.* the adverse reaction occurred after initiation of the drug).

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the case reports. In the primary analysis, RORs of serious ketosis and corresponding 95 % confidence interval (95% CI) for gliflozins compared to other glucose-lowering drugs were calculated using logistic regression models adjusted for age, gender, reporting region, reporting year, notifier type and exposure to other glucose-lowering drugs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 [DPP-4] inhibitors, glucagon like peptide 1 [GLP-1] agonists, and insulins). Following the media coverage of a potential pharmacovigilance signal, a notoriety effect is generally observed resulting in a relative over-reporting of the drug adverse reaction of interest, which can skew the analysis of disproportionality [10]. In order to study the presence of a notoriety bias, we performed a secondary analysis stratified before and after May 15th 2015, when was issued by the U.S. FDA the first communication about a potential risk of ketoacidosis associated with gliflozins [2]. Other secondary analyses included stratifications according to gender, age categories and the presence of at least one insulin in the notification. We also performed two sensitivity analyses. First, we repeated the primary analysis among selected notifications reported by healthcare professionals only. This analysis allows to control for the potential misclassification due to reports that would not have been medically confirmed. Second, we restricted our exposure definition to take into account exposure to gliflozins only when these drugs were considered as suspect in the notification (in this analysis, notifications mentioning a gliflozin as concomitant

drug or in interaction were considered non-exposed). This analysis allows to study the pharmacovigilance signal from the cases with the strongest accountability. All models were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Descriptive statistics

Between January 2013 and March 2016, 68,555 notifications met the study criteria (Figure 1). In total, 842 cases of serious ketosis were reported and among these cases, 484 (57.7%) were exposed to gliflozins. Table 1 shows the characteristics of serious ketosis reports according to exposure to gliflozins. Mean age of serious ketosis cases exposed to a gliflozin was 55.7 years. Exposed cases were in majority reported by a healthcare professional (93.0%). Median time to onset of ketosis was approximately 1.3 months in patients exposed to gliflozins and 79.5% recovered from the adverse reaction. Reports of serious ketosis associated with gliflozins originated more frequently from the United States (64.7%) followed by Great Britain (12.2%) Gliflozins were associated with metformin in 47.3% of cases and with insulin in 38.4%. In comparison, cases not exposed to gliflozin were predominantly reported by non-healthcare professional (58.5%), showed longer median time to onset (8.9 months) and were mainly treated with insulin (84.1%). Figure 2 shows the evolution of the number of notification of serious ketosis associated with gliflozins between 2013 and 2016. Notifications of serious ketosis associated with gliflozins were notably increased after the first warning of the U.S. FDA in May of 2015.

Primary analysis

Table 2 shows the results of the disproportionality analysis of serious ketosis case reports associated with gliflozins (and types of gliflozins) compared to other glucose-lowering drugs. Serious ketosis was more than 15 times more frequently reported with gliflozins than with other glucose-lowering drugs (adjusted ROR 15.47; 95% CI: 12.82 - 18.65). Except for ertugliflozin which was sparsely used, the different types of gliflozins were all associated with an increased reporting of serious ketosis. Empagliflozin showed a greater disproportionality signal than other gliflozins (adjusted ROR 35.91; 95% CI: 23.65 - 54.52). Results for other variables included in the model

are shown in Supplementary Table 1. We noted that advancing age was negatively associated with serious ketosis notification. Ketoses were also more frequently reported among women (ROR 1.39; 95% CI: 1.19-1.63). There was a smaller but significant positive association for insulin (ROR 3.45; 95% CI: 2.90 - 4.11) and inhibitors of alpha-glucosidase (ROR 2.79; 95% CI: 1.55 - 5.03), a negative association for GLP-1 agonists (0.68; 95% CI: 0.52 - 0.89) and a strong negative association for thiazolidinediones (ROR 0.04; 95% CI: 0.02 - 0.07).

Secondary analyses

Disproportionality analysis of serious ketosis reports associated with gliflozins stratified according to the date of the first FDA warning is presented in Table 3. For all gliflozins for which the calculation of ROR was possible, a statistically significant disproportionality signal was found before the warning of the FDA with, however, a lower ROR than after the warning (adjusted RORs 3.21 [95% CI: 2.08 - 4.96] and 24.61 [95% CI: 19.23 - 31.51], respectively). Analyses stratified according to age or gender provided similar ROR estimates than the primary analysis (data not shown). Table 4 presents the secondary analysis stratified according to the report of insulin use. Gliflozins showed a disproportionality signal of serious ketosis whether insulin use was reported or not, with higher ROR estimates in the absence of insulin than the main analysis (adjusted ROR 38.93 [95% CI: 27.08 - 55.97])

Sensitivity analyses

The analysis of disproportionality restricted to adverse events reported only by healthcare professionals showed a stronger positive association with gliflozins than the main analysis (adjusted ROR 22.77; 95% CI 17.87 - 19.15) (Supplementary Table 2). Similar estimates were found when considering exposure to gliflozins only when they were notified as suspect (adjusted ROR 21.71; 95% CI: 15.85 - 29.74) (Supplementary Table 3).

Discussion

Summary of findings

In this study, we showed that serious ketoses were significantly more frequently notified (as to 15 times) with gliflozins than with other glucose-lowering drugs, empagliflozin showing a more important disproportionality than other gliflozins. Disproportionality of notifications of serious ketosis with gliflozins was also present before the warning of the drug agencies and was consistent in additional analyses.

Discussion of the results and comparison to the literature

Our findings support, as a pharmacovigilance signal, the hypothesis of a risk of serious ketosis associated with gliflozins. The increased reporting of serious ketosis for gliflozins was observed consistently for the different subtypes of gliflozins, suggesting a class effect.

In 2015, the U.S. FDA and the European Medicines Agency (EMA) identified 175 reported cases of ketoacidosis associated with the use of gliflozins and raised concerns about this potential risk [2, 3]. Cases occurred in treated patients with gliflozin for type 2 diabetes as well as for type 1 diabetes for which it is an off-label use. Unlike diabetic ketoacidosis usually described, most cases showed normal or moderately increased serum glucose levels, a feature which is likely to cause delays in the diagnosis and treatment of these cases [11]. In several described cases, ketoacidosis have been triggered by factors such as infection, kidney failure, trauma, reduced food or water intake, hypoxemia, alcohol abuse or lower doses of insulin [3]. During the EMPA-REG OUTCOME trial, four cases of ketoacidosis were reported among the 4687 patients treated by empagliflozin [12]. Retrospectively analyzed the frequency of ketoacidosis reported in clinical trials of gliflozins was less than 0.1% [13]. In the literature, several case reports have described life-threatening ketoacidosis in patient treated with gliflozin (mainly with canagliflozin, dapagliflozin or empagliflozin) in the presence, in some cases, of normal blood glucose levels [11, 14–16].

In our study, serious ketoses were more frequently notified in younger patients and in women, which is consistent with the literature which describes younger age and female gender as risk factors for the occurrence of ketoacidosis [17–20]. Our main analyses were adjusted on age and gender and secondary stratifications

according to these factors did not modify our results. Notifications of ketosis were more frequent in the United States and in Europe as it is generally observed in VigiBase. No cases have been reported in France because, to date, France is one of the European countries where gliflozins are not yet marketed. The increased reporting of ketosis observed with insulin could actually account for the increased risk of ketoacidosis in patient with type 1 diabetes mainly treated with insulin. Furthermore, decreased or discontinued insulinotherapy is considered to be a precipitating factor for gliflozin-associated ketosis [21]. Our secondary analyses revealed that disproportionality signals for gliflozins were present whether insulin use was reported or not, with greater RORs in the absence of insulin, suggesting that type 1 diabetes or modified insulinotherapy did not influence our main findings. The negative association observed with GLP-1 agonists may be related to the inhibition of glucagon secretion by the GLP-1 which results in decreased hepatic glucose production [22]. The negative association with thiazolidinediones could be explained by the recent controversies about these products (cardiovascular risk and rosiglitazone; bladder cancer and pioglitazone), which resulted in a large number of notifications for these products. In computing the ROR corresponding to thiazolidinediones, such notifications were recorded as non-exposed non-cases and tended to decrease the ROR estimates. We could not find any explanation for the weaker signal observed with inhibitors of alpha-glucosidase. However, based on 15 and 17 exposed cases respectively, results concerning inhibitors of alpha-glucosidase and thiazolidinediones may also represent chance findings.

Potential mechanisms

The risk of ketoacidosis is associated with several factors such as peripheral insulin resistance, overproduction of hormones glucagon or growth hormone, post-operative period, alcohol intake, infection, recurrent diseases, food restriction, pregnancy, psychological problems, or use of drugs such as corticosteroids, thiazides, sympathomimetic or pentamidine [11, 13, 14, 16, 19]. The potential role of gliflozins in the occurrence of euglycemic ketoacidosis is not fully understood but may involve the following factors [23]: i) gliflozins are associated with a paradoxical increase in hepatic glucose production and fasting plasma glucagon concentrations which may be responsible for increased hepatic ketone production, especially when glycogen stores are depleted (during fasting or low carbohydrate intake); ii) gliflozins might

increase the tubular reabsorption of ketones and thus worsen the levels of plasma ketones by reducing their renal elimination; iii) because of their diuretic effect, gliflozins are associated with significant volume depletion, which could contribute to worsen the symptoms of ketoacidosis; iv) gliflozins are associated with an increased risk of infections (especially genital and urinary infections), which are known triggers of ketoacidosis; v) it has been shown that patients treated with gliflozins were more likely to present low serum bicarbonate which could worsen the risk of acidosis.

Strength and limits of the study

One of the strengths of this study is the use of Vigibase, the world's largest database of spontaneous reports of adverse drug reaction, which ensures sufficient statistical power to detect signals about rare effects such as drug-induced ketoacidosis. Our study population is likely to be representative of patients using these drugs because lower income countries that have no effective pharmacovigilance system and do not participate in Vigibase, generally do not have access to new diabetes treatments. In addition, pharmacovigilance data reflect the conditions of actual use of glucose-lowering drugs, in a more realistic setting than data from clinical trials. Furthermore, we were able to retrieve from Vigibase information on factors potentially associated with ketosis reports and we adjusted our analyzes for these factors. Finally, serious ketoses being the subject of communications from American and European medicines agencies, we were able to verify that the signal was present before these warnings, allowing us to consider that our main findings were not likely influenced by a notoriety bias.

Nevertheless, as a study of disproportionality in pharmacovigilance databases, our study presents some limitations. First, we could not measure the real risk of adverse drug reaction but the differences in the rate of notifications by the calculation Reporting Odds Ratios [24]. However, by analyzing real-life surveillance data, cases-non-case studies help to highlight pharmacovigilance signals that have demonstrated in the past their usefulness for detecting drug risks [24, 25]. Second, the issue of under-reporting of adverse drug reactions is a major disadvantage inherent to studies using pharmacovigilance databases. Notification rate for serious effects strongly varies depending on many factors but has been estimated to range approximately from 5% to 10% [26]. Applying this rate to the 487 exposed cases included in our study, the hypothetical number of actual cases of serious ketosis exposed to gliflozins

could be 4870 to 9740. Under-reporting is generally lower for newly marketed drugs and serious effects, which is the case in our study. Hence, we cannot exclude that cases of serious ketosis have been notified differentially with gliflozins compared to other diabetes medications and that it could have affected our estimates of disproportionality. Third, despite our multiple adjustments, the lack of data on potential risk factors such as the accurate medical history of the patient were not taken into account in our analysis. Fourth, in our study, the statistical unit was the notification of adverse reactions. It is possible that some patients have been subject to several notifications that count as multiple events in our database. The anonymization of notifications and the lack of unique identifier per patient did not allow us to identify potential multiple records of the same patient. However multiple notifications of serious adverse reactions during the 3-year period should not be in substantial numbers and do not seem a major obstacle to the study of disproportionality. Fifth, the possible errors in the diagnoses of serious ketosis could have led to information bias. However, this potential bias is limited in one hand by the standardization of the collection of adverse reaction by pharmacovigilance centers, and in other hand by the consistent results of our sensitivity restricted on medically confirmed cases of serious ketosis. Similarly, the sensitivity analysis considering as exposed only the notifications in which gliflozins were coded as suspect suggests that errors in exposure classification does not seem to have biased our results. Finally, the results regarding less used gliflozins such as ipragliflozin (available in Japan only) and ertugliflozin were based on very few cases and cannot be interpreted with confidence.

Conclusion

Despite the limitations inherent to disproportionality analyses of adverse drug reactions, we identified a strong and early pharmacovigilance signal that suggests a risk of serious ketosis associated with the gliflozin class of drugs. Vigilance must be observed in the future about this potential risk. Other studies, including longitudinal studies in large population samples, are needed to confirm this pharmacovigilance signal and better understand the mechanisms and the risk factors of ketoacidosis associated with gliflozins.

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All authors participated in the study design. JLF acquired the data. ABN did the statistical analyses and wrote the initial draft. All authors critically revised the manuscript.

All authors declare that they have no conflicts of interest.

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Table 1. Characteristics of serious ketosis cases according to gliflozin exposure.

Characteristics	Gliflozin users (n = 484)	Gliflozin non users (n = 358)	Total (n = 842)
Age, years, mean (SD)	55.7 (10.1)	54.0 (10.9)	55.5 (10.5)
Age, n (%)			
40-49	147 (30.7)	126 (36.6)	273 (33.1)
50-59	168 (35.1)	112 (32.6)	280 (34.0)
60-69	111 (23.2)	64 (18.6)	175 (21.3)
70-79	44 (9.1)	33 (9.6)	77 (9.4)
80-89	8 (1.7)	9 (2.6)	17 (2.1)
≥ 90	1 (0.2)	0 (0.0)	1 (0.1)
Unknown	5	14	19
Gender, n (%)			
Males	208 (43.0)	137 (38.4)	345 (41.0)
Females	276 (57.0)	220 (61.6)	496 (59.0)
Unknown	0	1	1
Notifier type, n (%)			
Physician	272 (61.5)	78 (23.1)	350 (44.9)
Pharmacist	59 (13.4)	27 (8.0)	86 (11.0)
Physician or pharmacist	1 (0.2)	2 (0.6)	3 (0.4)
Other health care professional	79 (17.9)	33 (9.8)	112 (14.4)
Non health care professional	31 (7.0)	197 (58.5)	228 (29.3)
Unknown	42	21	63
Time to onset, month, median (P25-P75)	1.3 (0.3-3.3)	8.9 (0.27-24.6)	1.5 (0.3-6.5)
Time to onset, n (%)			
< 1 week	21 (18.4)	8 (25.0)	29 (19.9)
1-2 weeks	17 (14.9)	1 (3.1)	18 (12.3)
0.5-1 month	16 (14.0)	2 (6.2)	18 (12.3)
1-2 months	12 (10.5)	2 (6.3)	14 (9.6)
2-3 months	14 (12.3)	0 (0.0)	14 (9.6)
3-6 months	15 (13.2)	1 (3.1)	16 (10.9)
6-12 months	17 (14.9)	3 (9.4)	20 (13.7)
12-24 months	2 (1.8)	7 (21.9)	9 (6.2)
≥ 24 months	0 (0.0)	8 (25.0)	8 (5.5)
Unknown	370	326	696
Country, n (%)			
United States	313 (64.7)	258 (72.1)	571 (67.8)
United Kingdom	59 (12.2)	24 (6.7)	83 (9.9)
Japan	23 (4.7)	28 (7.8)	51 (6.1)
Germany	17 (3.5)	11 (3.1)	28 (3.3)
Spain	22 (4.6)	4 (1.1)	26 (3.1)
Italy	3 (0.6)	7 (1.9)	10 (1.2)
India	5 (1.0)	0 (0.0)	5 (0.6)
Republic of Korea	0 (0.0)	2 (0.5)	2 (0.2)
France	0 (0.0)	7 (1.9)	7 (0.8)
Other countries	42 (8.7)	17 (4.7)	59 (7.0)

Characteristics	Gliflozin users (n = 484)	Gliflozin non users (n = 358)	Total (n = 842)
Evolution, n (%)			
Fatal	4 (1.5)	7 (4.1)	11 (2.6)
Not recovered/ Not resolved	14 (5.4)	11 (6.5)	25 (5.8)
Recovered /resolved with sequelae	1 (0.4)	0 (0.0)	1 (0.2)
Recovering/ resolving	34 (13.2)	25 (14.7)	59 (13.8)
Recovered/ resolved	205 (79.5)	127 (74.7)	332 (77.6)
Unknown	226	188	414
Reporting year, n (%)			
2013	1 (0.2)	28 (7.8)	29 (3.4)
2014	14 (2.9)	135 (37.7)	149 (17.7)
2015	352 (72.7)	166 (46.4)	518 (61.5)
2016	117 (24.2)	29 (8.1)	146 (17.4)
Type of gliflozin, n (%)			
Canagliflozin	261 (53.9)	0 (0.0)	261 (53.9)
Dapagliflozin	147 (30.4)	0 (0.0)	147 (30.4)
Empagliflozin	57 (11.8)	0 (0.0)	57 (11.8)
Ertugliflozin	19 (3.9)	0 (0.0)	19 (3.9)
Ipragliflozin	19 (3.9)	0 (0.0)	19 (3.9)
Unknown	0	358	358
Onset year, n (%)			
≤ 2010	0 (0.0)	30 (35.3)	30 (12.1)
2011	0 (0.0)	5 (5.9)	5 (2.0)
2012	0 (0.0)	16 (18.8)	16 (6.5)
2013	21 (12.9)	11 (12.9)	32 (12.9)
2014	47 (28.8)	15 (17.7)	62 (25.0)
2015	95 (58.3)	8 (9.4)	103 (41.5)
Unknown	321	273	594
Ketosis preferred terms, n (%)			
<i>Diabeticketoacidosis</i>	345 (71.3)	272 (76.0)	617 (73.3)
<i>Ketoacidosis</i>	88 (18.2)	52 (14.5)	140 (16.6)
<i>Urine ketone body present</i>	16 (3.3)	11 (3.1)	27 (3.2)
<i>Blood ketone body increased</i>	8 (1.6)	4 (1.1)	12 (1.4)
<i>Ketosis</i>	10 (2.1)	5 (1.4)	15 (1.8)
<i>Ketonuria</i>	9 (1.9)	0 (0.0)	9 (1.1)
<i>Blood ketone body</i>	0 (0.0)	7 (1.9)	7 (0.8)
<i>Acetonaemia</i>	2 (0.4)	3 (0.8)	5 (0.6)
<i>Blood ketone body present</i>	3 (0.6)	2 (0.6)	5 (0.6)
<i>Diabeticketoacidotichyperglycaemic coma</i>	1 (0.2)	2 (0.6)	3 (0.4)
<i>Urine ketone body</i>	2 (0.4)	0 (0.0)	2 (0.2)
Other antidiabetic drugs, n (%)			
Insulin	186 (38.4)	301 (84.1)	487 (57.8)
Metformin	229 (47.3)	68 (19.0)	297 (35.3)
Sulfonylureas	633 (19.1)	9499 (14.6)	10132 (14.8)
Thiazolidinedione	194 (5.9)	28943 (44.4)	29137 (42.5)
Alpha glucosidase inhibitors	113 (3.4)	1393 (2.1)	1506 (2.2)
DPP-4 inhibitors	821 (24.8)	9281 (14.2)	10102 (14.7)
GLP-1 agonists	265 (8.0)	5039 (7.7)	5304 (7.7)

Table 2. Disproportionality analysis of serious ketosis reports associated with gliflozins compared to other antidiabetic drugs.

Drug	Cases	Non-cases	Crude ROR (95% CI)	Adjusted ROR* (95%CI)
Any gliflozin	484	2827	31.03 (26.93-35.75)	15.47(12.82-18.65)
Canagliflozin	261	1307	36.19 (30.58-42.84)	14.33 (11.53-17.80)
Dapagliflozin	147	645	41.31 (33.58-50.81)	19.48 (14.91-25.44)
Empagliflozin	97	57	106.50 (75.56-150.11)	35.91 (23.65-54.52)
Ertugliflozin	0	1	-	-
Ipragliflozin	19	777	4.43 (2.9-7.07)	4.86 (2.60-9.08)
Other antidiabetics	358	64886	1 [Reference]	1 [Reference]

* Adjusted for age, gender, reporting region, reporting year, notifier type and other antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 agonists, and insulins).

Table 3. Disproportionality analysis of serious ketosis reports associated with gliflozins stratified according the FDA warning date.

Drug	Cases	Non-cases	Crude ROR (95%CI)	adjusted ROR * (95%CI)
Before, May 15th 2015				
Any gliflozins	32	952	6.93 (4.76-10.10)	3.21 (2.08-4.96)
Canagliflozin	18	400	9.28 (5.69-15.16)	3.50 (2.03-6.01)
Dapagliflozin	9	289	6.43 (3.27-12.64)	3.29 (1.53-7.06)
Empagliflozin	0	9	-	-
Ertugliflozin	0	0	-	-
Ipragliflozin	5	254	4.06 (1.66-9.94)	2.15 (0.67-6.29)
Other antidiabetic	220	45411	1 [Reference]	1 [Reference]
After, May 15th 2015				
Any gliflozins	452	1875	34.01 (27.94-41.39)	24.61 (19.23-31.51)
Canagliflozin	243	907	37.81 (30.36-47.07)	22.68 (17.20-29.90)
Dapagliflozin	138	356	54.70 (42.257 70.82)	30.21 (28.85-41.77)
Empagliflozin	57	88	91.41 (62.95 -132.72)	40.36 (25.96-62.75)
Ertugliflozin	0	1	-	-
Ipragliflozin	14	523	3.78 (2.17-6.59)	8.68 (3.88-19.44)
Other antidiabetic	138	19475	1 [Reference]	1 [Reference]

* Adjusted for age, gender, reporting region, reporting year, notifier type and other antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 agonists, and insulins).

Table 4. Disproportionality analysis of serious ketosis reports associated with gliflozins stratified according the report of insulin use in the notification.

Drug	Cases	Non-cases	Crude ROR (95%CI)	adjusted ROR * (95%CI)
Insulin				
Any gliflozins	186	600	16.86 (13.80-20.60)	12.07 (9.28-15.70)
Canagliflozin	102	298	18.61 (14.47-23.95)	11.05 (8.08-15.13)
Dapagliflozin	48	171	15.27 (10.87-21.45)	11.23 (7.33-17.20)
Empagliflozin	31	15	112.41(60.05-210.41)	69.54 (33.14-145.94)
Ertugliflozin	0	1	-	-
Ipragliflozin	5	115	2.36 (0.96-5.83)	3.79 (1.25-11.55)
Other antidiabetic	301	16372	1 [Reference]	1 [Reference]
No insulin				
Any gliflozins	298	227	113.89 (85.52-151.68)	38.93 (27.08-55.97)
Canagliflozin	159	1009	134.12 (98.47-182.67)	44.04 (29.22-66.83)
Dapagliflozin	99	474	177.77 (126.76-249.30)	57.05 (36.83-88.37)
Empagliflozin	26	82	269.87 (161.74-450.27)	57.57 (31.54-105.07)
Ertugliflozin	0	0	-	-
Ipragliflozin	14	662	18.00 (9.98-32.45)	6.54 (2.96-14.42)
Other antidiabetic	57	48514	1 [Reference]	1 [Reference]

* Adjusted for age, gender, reporting region, reporting year, notifier type and other antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 agonists).

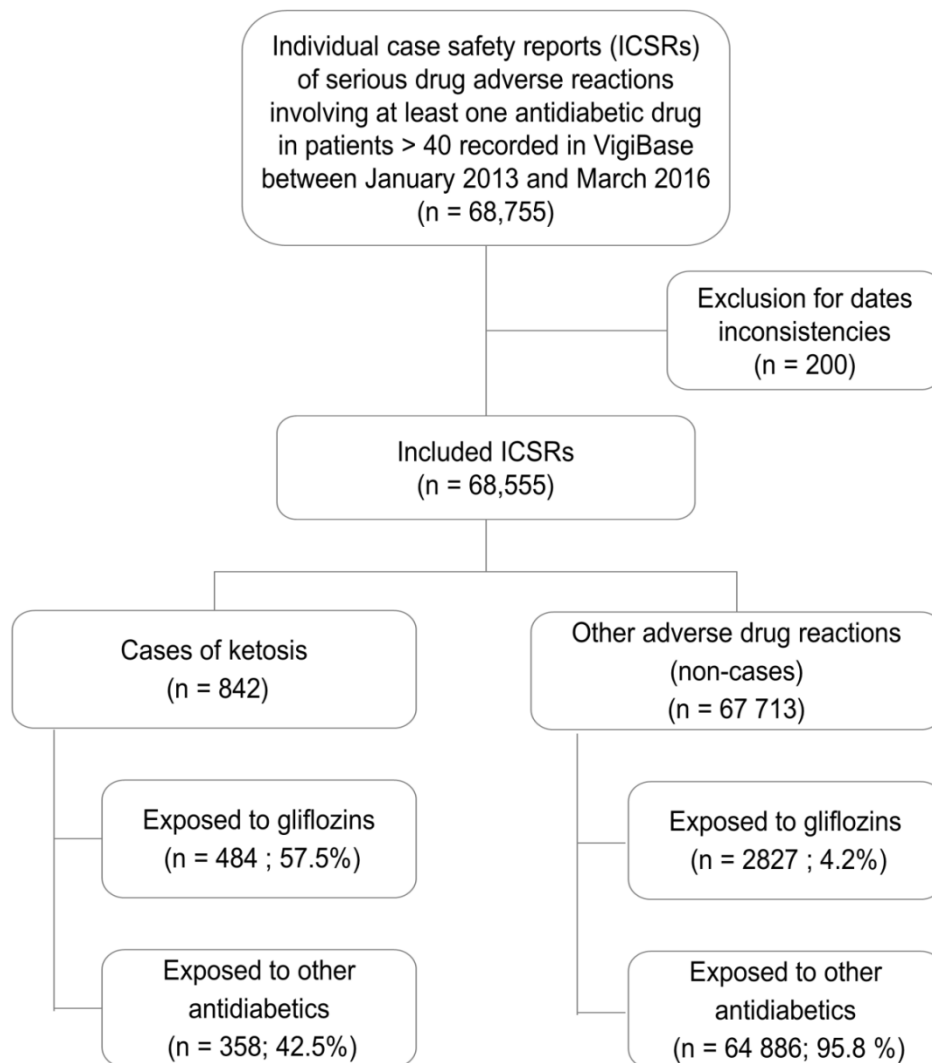


Figure 1. Numbers of reported cases of ketosis and corresponding non-cases according to exposure to gliflozins

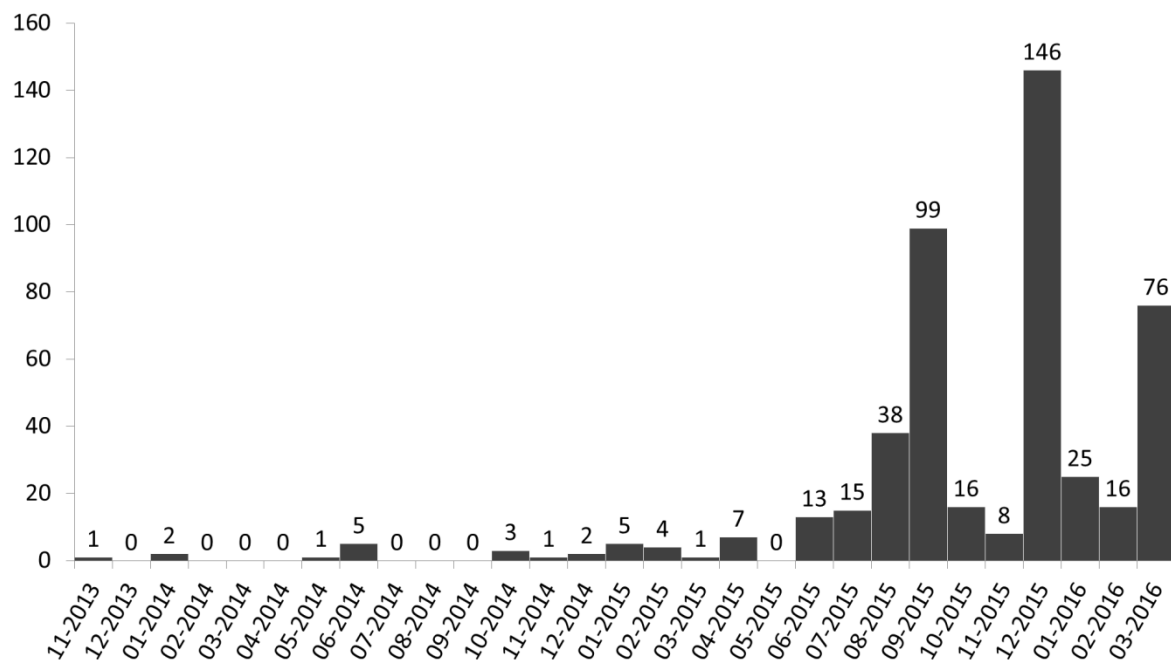


Figure 2. Evolution of the monthly number of serious ketosis cases reports associated with gliflozins in VigiBase between 2013 and 2016.