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Urinary Tract Infections and Fungal Infections Associated with Sodium-Glucose Co-transporter-2 (SGLT-2) Inhibitors and Metformin Combination: A Real-World Study from 2013 to 2023 Based on the FDA Adverse Event Reporting System (FAERS) Database

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ABSTRACT

Objective: This study aimed to compare the rates of urinary tract infections (UTIs) and fungal infections associated with metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, and their combination.

Materials and Methods: We collected data on UTIs and fungal infections related to metformin, SGLT-2 inhibitors, and their combinations from the FDA Adverse Event Reporting System (FAERS) database. We calculated the reporting odds ratio (ROR) and 95% confidence intervals (CI) to assess the risk associated with these adverse events when using these medications. We evaluated differences in categorical variables using the Chi-squared test.

Results: SGLT-2 inhibitors present a higher risk of UTIs and fungal infections compared to metformin. Empagliflozin showed the lowest risk of UTIs (ROR 0.928, 95% CI 0.858–1.005), while dapagliflozin exhibited the lowest risk of fungal infections (ROR 0.874, 95% CI 0.815–0.938). Additionally, patients using SGLT-2 inhibitors alone reported more cases of UTIs and fungal infections than those treated with a combination of SGLT-2 inhibitors and metformin (ROR>1).

Conclusion: SGLT-2 inhibitors are associated with an increased risk of UTIs and fungal infections compared to combination therapy with an SGLT-2 inhibitor and metformin. The reduced infection reports with combined SGLT-2 inhibitors and metformin therapy may be due to the potential antimicrobial activity of metformin.

Keywords: Adverse drug events, antidiabetic drugs, data mining, infection, pharmacovigilance.

INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are antidiabetic medications that have been approved by the U.S. Food and Drug Administration (FDA) for managing type 2 diabetes mellitus (T2DM) over the past decade.[1] Canagliflozin (CANA) was the first agent to receive FDA approval in

2013,[2] followed by dapagliflozin (DAPA), empagliflozin (EMPA), and ultimately, ertugliflozin (ERTU). Notably, SGLT-2 inhibitors provide cardiovascular and renal benefits, making them the preferred choice for treating T2DM patients with heart failure and chronic kidney disease.[3] Recent studies have further supported the increased use of SGLT-2 inhibitors due to their positive effects on heart failure with reduced ejection fraction and chronic kidney disease.[4]

SGLT-2 is primarily located in the proximal renal tubules and is involved in the reabsorption of urinary sodium and glucose.[5] SGLT-2 inhibitors block this reabsorption, thereby increasing the excretion of these substances through urine. This mechanism results in an antihyperglycemic effect.[5] However, the increase in glucose excretion via urine due to SGLT-2 inhibitors has been associated with adverse effects, notably urinary tract infections (UTIs) and genitourinary fungal infections. In response, the FDA added warnings about serious UTIs to the labels of SGLT-2 inhibitors in 2015.[6] Although the association between the risk of UTIs and SGLT-2 inhibitors has been debated in meta-analyses of clinical data, a meta-analysis of 77 trials found no difference in the risk of UTIs between SGLT-2 inhibitors and controls,[7] but did note an increased susceptibility to genital tract infections among SGLT-2 inhibitor users.[7] In four separate meta-analyses, DAPA was shown to have an elevated risk of UTIs, while all SGLT-2 inhibitors were linked to an increased risk of genital tract infections.[8–11] Despite these findings, the exact cause of the increased risk of UTIs due to the pharmacological actions of SGLT-2 inhibitors remains unclear.

SGLT-2 inhibitors are often used as secondary or tertiary treatment options in combination with metformin. Although metformin was introduced in Europe in 1958, it did not receive FDA approval until 1994[12] and continues to be the first-line treatment for T2DM. Beyond its antihyperglycemic effects, metformin is thought to have various pleiotropic effects, including antimicrobial activity.[13] Studies suggest a reduced risk of infection in patients with diabetes treated with metformin,[14,15] and it has been proposed as a potential antimicrobial agent against a variety of infections.[16] This indicates that combining SGLT-2 inhibitors with metformin may reduce the risk of UTIs and fungal infections. Accordingly, our study aims to compare UTIs and fungal infections associated with metformin, SGLT-2 inhibitors, or their combination using real-world data.

MATERIALS AND METHODS

Data Source and Study Design

Data were obtained from the FDA Adverse Event Reporting System (FAERS) database, a spontaneously reported adverse event database developed by the FDA for post-marketing safety surveillance to identify drug safety issues.[17] FAERS is the largest database of adverse event reports worldwide, containing over 26 million reports since 1969. Adverse events can be submitted by pharmaceutical companies, healthcare professionals, and patients.[18] The FAERS database provides access to patient sex, age, and weight, product name, generic name, reason for use, and year of adverse event; however, it lacks dosage information for the drugs. The FAERS database is publicly available for researchers to use in pharmacovigilance analyses,[19] and no ethical approval or informed consent is required, as the cases are anonymized by FAERS.

Table 1. Calculation of the reporting odds ratio (ROR)

	AEs of interest	All other AEs of interest	Total
Drug of interest	a	b	a + b
All other drugs of interest	c	d	c + d
	$ROR = \frac{a}{b} \times \frac{d}{c}$		

AEs: Adverse events; ROR: Reporting odds ratio.

The FAERS database search was conducted using the medications' generic names: "metformin hydrochloride," "canagliflozin," "canagliflozin/metformin hydrochloride," "empagliflozin," "empagliflozin/metformin hydrochloride," "dapagliflozin-dapagliflozin propanediol," "dapagliflozin propanediol/metformin hydrochloride," "ertugliflozin-ertugliflozin pidolate," and "ertugliflozin pidolate/metformin hydrochloride." As the first approved SGLT-2 inhibitor, canagliflozin, received approval in 2013,[2] adverse events occurring between 2013 and 2023 were included in the study. The analysis focused on urinary tract infection and fungal infection terms, which are the most common infection-related adverse events reported with canagliflozin. Types of infection less commonly reported in people using SGLT-2 inhibitors were not included in the study. Adverse events with identifiable pathogens (bacterial or fungal) were very few and thus excluded.

Disproportionality Analysis and Statistical Analysis

To facilitate a comparative analysis of the adverse event risk associated with these agents, the reporting odds ratio (ROR) and its corresponding 95% confidence intervals (CI) were calculated.[20] The formula for calculating ROR is presented in Table 1. ROR calculations were performed comparing metformin with SGLT-2 inhibitors, SGLT-2 inhibitors with their respective pharmacological subgroups, and SGLT-2

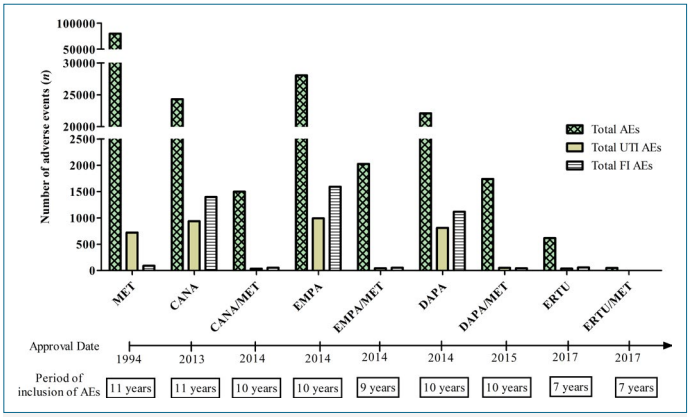

Figure 1. Total adverse events for metformin, SGLT-2 inhibitors, and their combinations. The timeline indicates the FDA approval dates for these medications and the duration of adverse events covered by this study, presented in years.

AEs: Adverse events; CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; FI: Fungal Infection; MET: Metformin HCl; UTI: Urinary tract infection.

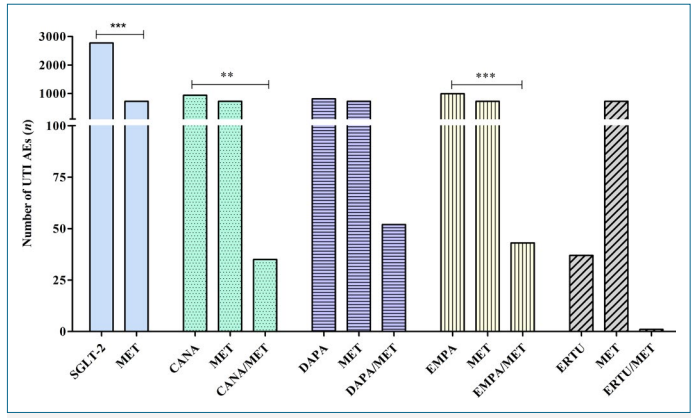

Figure 2. Number of UTIs associated with metformin, SGLT-2 inhibitors, and their combined usage. Statistical comparisons were conducted between the occurrence of UTIs related to SGLT-2 inhibitors and their combinations.

**: P<0.01; ***: P<0.001; AEs: Adverse Events; CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; MET: Metformin HCl; UTI: Urinary tract infection.

inhibitors both alone and in combination with metformin. The evaluation of the ROR value is as follows: ROR=1 indicates the drug of interest has no effect on the adverse events (AEs) of interest; ROR>1 indicates the drug of interest is associated with increased AEs of interest; and ROR <1 indicates the drug of interest is associated with reduced AEs of interest. Differences in categorical variables were evaluated using the Chi-square test. Statistical analyses were performed with GraphPad Prism software (USA), and p values <0.05 were considered statistically significant.

RESULTS

Characteristics of Case Reports and Descriptive Analysis

The FAERS database recorded a total of 79,700 adverse events associated with metformin and 75,090 adverse events associated with SGLT-2 inhibitors from 2013 through 2023. The most common adverse events reported for metformin during this period were lactic acidosis, acute kidney injury, diarrhea, hypoglycemia, and nausea. Among the SGLT-2 inhibitors, EMPA had the highest number of reported adverse events (n=28,062), followed by CANA (n=24,311), DAPA (n=22,102), and ERTU (n=615). Additionally, a total of 5,314 adverse events were reported for combinations of SGLT-2 inhibitors and metformin. Of these, the EMPA/metformin combination had the highest number of adverse events (n=2,026), followed by DAPA/metformin (n=1,740), CANA/metformin (n=1,418), and ERTU/metformin (n=50). Figure 1 displays these data. The number of adverse events reported for the recently FDA-approved SGLT-2 inhibitor ERTU is lower than those for other medications. This observation may be attributed to the drug being relatively new on the market or its limited prescription prevalence, thus ERTU results were not included in the discussion.

Demographic characteristics of reported cases of UTIs and fungal infections involving metformin, SGLT-2 inhibitors, and their combinations are presented in Appendix 1. Female patients using metformin or SGLT-2 inhibitors as monotherapy were found to have a higher risk of UTIs and fungal infections than males. The total incidence of UTIs and fungal infections was higher among individuals under 65 years of age compared with those over 65.

Analysis of UTIs Adverse Events

Between 2013 and 2023, a total of 722 UTIs were reported with metformin. Among the SGLT-2 inhibitors, EMPA exhibited the highest incidence of UTIs, followed by CANA and DAPA. ERTU reported the fewest cases. The ratios of the number of UTIs to the total number of adverse events for CANA, DAPA, and EMPA were 0.039, 0.037, and 0.035, respectively. However, the ratio of UTIs associated with metformin to the total number of adverse events is lower compared to SGLT-2 inhibitors (0.009). Additionally, the number of UTIs was lower with the combination of SGLT-2 inhibitors and metformin than with SGLT-2 inhibitors alone. This difference was statistically significant for CANA (p=0.0027) and EMPA (p=0.0008), as shown in Figure 2.

The ROR analysis indicates an increased risk of UTIs associated with SGLT-2 inhibitors compared to metformin

Table 2. Reporting odds ratio (ROR) and 95% confidence interval (CI) for UTIs associated with metformin and SGLT-2 inhibitors

	ROR	95% CI	p
SGLT-2 inhibitors vs. MET	4.198	3.865–4.559	<0.0001**
CANA vs. CANA/MET	1.676	1.191–2.358	0.0027*
CANA vs. other SGLT-2 inhibitors	1.067	0.985–1.157	0.1108
EMPA vs. EMPA/MET	1.688	1.240–2.299	0.0008**
EMPA vs. other SGLT-2 inhibitors	0.928	0.858–1.005	0.067
DAPA vs. DAPA/MET	1.235	0.929–1.642	0.1456
DAPA vs. other SGLT-2 inhibitors	0.988	0.909–1.074	0.7731
ERTU vs. ERTU/MET	3.137	0.421–23.360	0.239
ERTU vs. other SGLT-2 inhibitors	1.677	1.200–2.344	0.002*

*: P<0.01; **: P<0.001; CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; MET: Metformin HCl; SGLT-2: Sodium-Glucose Co-transporter 2.

(Table 2). Among the SGLT-2 inhibitors, ERTU exhibited the highest frequency of reported UTIs, while EMPA had the lowest incidence. Moreover, the ROR was greater than 1 for SGLT-2 inhibitors alone compared with those combined with metformin (Table 2).

Analysis of Fungal Infections Adverse Events

The occurrence of adverse events related to fungal infections was assessed across metformin and SGLT-2 inhibitors usage (Fig. 3). A total of 91 cases of fungal infections were reported in association with metformin. Among SGLT-2 inhibitors, EMPA exhibited the highest incidence of reported cases, followed by CANA and DAPA. ERTU had the lowest incidence of fungal infections. Among SGLT-2 inhibitors, CANA, DAPA, and EMPA showed comparable ratios of fungal infections to total adverse events (0.057, 0.057, and 0.051, respectively). Notably, the ratio of fungal infections relative to the total number of reported adverse events is lower for metformin compared to that for SGLT-2 inhibitors (0.001). When comparing SGLT-2 inhibitors and their combination with metformin, the combination therapies were associated with a reduced frequency of fungal infections. These differences were statistically significant for CANA (p=0.0003), DAPA (p<0.0001), and EMPA (p<0.0001) (Fig. 3).

The calculated ROR scores for fungal infections are provided in Table 3. Analysis of the ROR values reveals that SGLT-2 inhibitors exhibit increased susceptibility to fungal infections compared to metformin. Among the SGLT-2 inhibitors, fungal infections were reported most commonly with ERTU, CANA, EMPA, and DAPA, in that order. ROR scores were higher than 1 for SGLT-2 inhibitors both alone and in combination with metformin (Table 3).

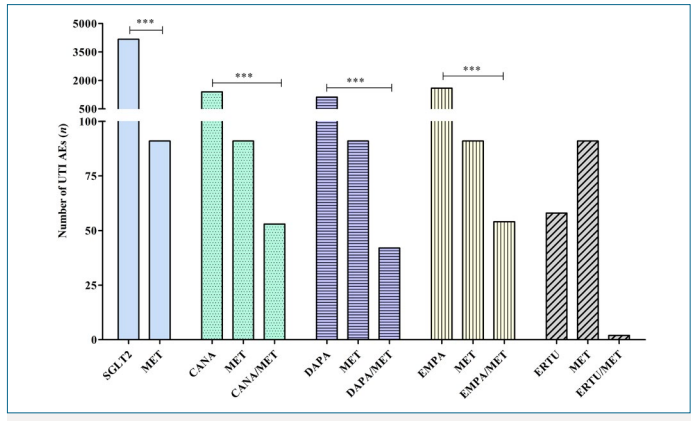

Figure 3. Number of fungal infections associated with metformin, SGLT-2 inhibitors, and their combinations. The number of fungal infections related to SGLT-2 inhibitors and their combinations was statistically compared.

***: p<0.001. AEs: Adverse Events; CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; FI: Fungal infection; MET: Metformin HCl.

DISCUSSION

SGLT-2 inhibitors, novel antidiabetic agents, decrease the blood glucose levels of diabetic patients by increasing glucose concentration in the urine. The increased risk of UTIs associated with SGLT-2 inhibitors is directly related to increased urinary glucose levels. The glucose-rich environments facilitates the growth rate and virulence of bacteria, consequently influencing microorganism pathogenicity.[21] In the presence of predisposing factors such as pH, temperature, nutrient deficiency, and particularly high glucose concentrations, certain pathogenic

Table 3. Reporting odds ratio (ROR) and 95% confidence interval (CI) for fungal infections associated with SGLT-2 inhibitors and metformin

	ROR	95% CI	p
SGLT-2 inhibitors vs. MET	51.39	41.74–63.27	<0.0001*
CANA vs. CANA/MET	1.661	1.256–2.196	0.0003*
CANA vs. other SGLT-2 inhibitors	1.056	0.989–1.128	0.106
DAPA vs. DAPA/MET	2.156	1.578–2.946	<0.0001*
DAPA vs. other SGLT-2 inhibitors	0.874	0.815–0.938	0.0002*
EMPA vs. EMPA/MET	2.196	1.668–2.892	<0.0001*
EMPA vs. other SGLT-2 inhibitors	1.039	0.974–1.108	0.241
ERTU vs. ERTU/MET	2.499	0.592–10.550	0.197
ERTU vs. other SGLT-2 inhibitors	1.784	1.359–2.343	<0.0001*

*: P<0.001; CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; MET: Metformin HCl; SGLT-2: Sodium-Glucose Co-transporter 2.

bacteria in the normal flora may become dominant and colonize more easily.[22] Patients with diabetes are also at a high risk for infections due to glucosuria, which facilitates bacterial growth and adhesion to the uroepithelium. Additionally, these patients have impaired immune function, inflammatory responses, and circulatory disorders.[22,23] Therefore, SGLT-2 inhibitors may increase the risk of infection in patients with diabetes by inducing glucosuria. However, despite the cautionary information on the package leaflet,[6] the consensus on the risk of UTIs associated with SGLT-2 inhibitors still need to be conclusive.[24] Our study revealed that EMPA exhibited the highest frequency of UTIs and fungal infections, followed by CANA and DAPA. The ratio of UTIs or fungal infections to total adverse events was similar for all three medications. Based on the calculated ROR values, both CANA and DAPA were more associated with UTIs than EMPA. This observation aligns with a meta-analysis demonstrating an increased UTI risk with DAPA compared to EMPA.[8] Conversely, the risk of fungal infections is more likely with CANA and EMPA compared to DAPA.

SGLT-2 inhibitors are often prescribed with metformin, a safe first-line antidiabetic agent for T2DM. This combination improves glycemic control without increasing the risk of hypoglycemia[25,26] and has been shown to have beneficial cardiometabolic properties compared to metformin alone.[27] Combined therapy has been suggested to be associated with substantial decreases in Hemoglobin A1c (HbA1c) and weight,[28] as well as cardiovascular and renal protection.[29] However, the combination of SGLT-2 inhibitors with metformin is related to an increased risk of metabolic acidosis[25] and diarrhea.[26] Despite these reports of adverse events, the combination of metformin and SGLT-2 inhibitors has a tolerable safety profile. In our study, we evaluated the UTIs and fungal infections associated with the combination of metformin and SGLT-2 inhibitors as reported in the FAERS database. Studies in the literature on ketoacidosis, acute renal failure, pancreatitis, Fournier's gangrene, and UTIs associated with SGLT-2 inhibitors through the FAERS database are extensive.[30–34] Our study differs from others in the literature as it specifically examines the relationship between the most commonly documented infectious adverse events and the combination of SGLT-2 inhibitors with metformin. Although the study by Mohammad et al.[35] evaluated the UTIs and genital fungal infections resulting from this combination, its short duration, lack of empagliflozin and metformin combination, and absence of ROR analyses distinguish our study from theirs. Furthermore, while that study[35] evaluated genital fungal infections, it did not include the keyword "fungal infection," which is the most commonly reported adverse event with SGLT-2 inhibitors. A retrospective cohort study indicated a significantly lower risk of UTIs in men with T2DM who used metformin.[36] Conversely, another cohort study found no substantial difference in UTI risk among patients with T2DM using metformin, although it did reveal a reduced risk of death from UTIs.[37] The number of fungal infections attributed to metformin is negligible compared to that with SGLT-2 inhibitors. A meta-analysis found that combining SGLT-2 inhibitors with metformin was associated with a reduced risk of genital infections compared to SGLT-2 inhibitor monotherapy, correlating with improved glycemic control in the combination group.[26] Another meta-analysis of 13 trials found that combined SGLT-2 inhibitors with dipeptidyl peptidase-4 inhibitors improved the risk of mycotic genital infections compared to metformin as an add-on therapy.[38] The number of UTIs and fungal infections associated with the combination therapy involving SGLT-2 inhibitors and metformin demonstrated a notable reduction compared to SGLT-2 inhibitor monotherapy. An observational

study examined the risk of UTIs following the concomitant use of SGLT-2 inhibitors and dipeptidyl peptidase-4 inhibitors, thiazolidinediones, or glinides, utilizing the FAERS database.[34] This study showed that using these antidiabetic drugs in combination with SGLT-2 inhibitors increased the risk of UTIs. However, this study did not encompass an evaluation of UTI risk with metformin and SGLT-2 inhibitors. In our study, SGLT-2 inhibitors as monotherapy are associated with a higher risk of UTIs and fungal infections compared to their combination with metformin, according to the ROR scores. The combination of SGLT-2 inhibitors and metformin may reduce the susceptibility of patients to infections due to the antimicrobial activity of metformin.[13] The possible mechanisms of metformin's antimicrobial activity include the inhibition of mitochondrial electron transport and bacterial gluconeogenesis.[37] The inhibition of mitochondrial electron transport can decrease the energy available for bacterial growth and colonization, while metformin may also limit bacterial gluconeogenesis and suppress the expression of bacterial virulence factors.[39]

CONCLUSION

Randomized, prospective, large-scale clinical trials should be conducted to establish the relationship between the drugs and the adverse events; however, these studies are time-consuming and costly. Therefore, the FAERS database can elucidate clinically important associations, thereby enhancing the clinical decision-making process. The results of our analysis of the FAERS database suggest that there may be an association between SGLT-2 inhibitors and the risk of UTIs and fungal infections. Additionally, the concurrent therapy involving an SGLT-2 inhibitor and metformin may be associated with a notable reduction in infection due to the potential antimicrobial effect of metformin. Our study highlights the potential benefits of combining these drugs to reduce the risk of infection linked to SGLT-2 inhibitors, and further research is needed to fully explore the therapeutic potential of combination therapy.

Author Contributions: Concept – ZŞA, AT; Design – ZŞA; Supervision – ZŞA; Data Collection and/or Processing – ZŞA; Analysis and/or Interpretation – ZŞA; Literature Search – ZŞA, AT; Writing – ZŞA, AT; Critical Reviews – ZŞA, AT.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Informed consent are not required in our study as the identity information of cases in FAERS is anonymized.

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Appendix 1. Characteristics of metformin and SGLT-2 inhibitors associated with UTIs and fungal infections adverse events from the FAERS database

	UTIs									Fungal infections								
	MET N=722	CANA N=937	CANA/ MET N=35	EMPA N=991	EMPA/ MET N=43	DAPA N=810	DAPA/ MET N=52	ERTU N=37	ERTU/ MET N=1	MET N=91	CANA N=1397	CANA/ MET N=53	EMPA N=1592	EMPA/ MET N=54	DAPA N=1119	DAPA/ MET N=42	ERTU N=58	ERTU/ MET N=2
Sex																		
Female	515	592	25	517	29	470	26	25	0	66	1007	36	1069	41	813	30	43	2
	(71.3%)	(63.2%)	(71.4%)	(52.2%)	(67.4%)	(58.0%)	(50.0%)	(67.6%)	(0.0%)	(72.5%)	(72.1%)	(67.9%)	(67.1%)	(75.9%)	(72.7%)	(71.4%)	(74.14%)	(100.0%)
Male	157	238	8	393	14	246	25	10	1	17	268	10	354	12	194	11	14	0
	(21.7%)	(25.4%)	(22.9%)	(39.7%)	(32.6%)	(30.4%)	(48.1%)	(27.0%)	(100.0%)	(18.7%)	(19.2%)	(18.9%)	(22.2%)	(22.2%)	(17.3%)	(26.2%)	(24.14%)	(0.0%)
Not specified	50	107	2	81	0	94	1	2	0	8	122	7	169	1	112	1	1	0
	(6.9%)	(11.4%)	(5.7%)	(8.2%)	(0.0%)	(11.6%)	(1.9%)	(5.4%)	(0.0%)	(8.8%)	(8.7%)	(13.2%)	(10.6%)	(1.9%)	(10.0%)	(2.4%)	(1.72%)	(0.0%)
Age																		
<65	256	336	17	266	8	234	13	6	1	41	332	15	344	11	227	14	8	1
	(35.5%)	(35.9%)	(48.6%)	(26.8%)	(18.6%)	(28.95%)	(25.0%)	(16.2%)	(100.0%)	(45.1%)	(23.8%)	(28.3%)	(21.6%)	(20.4%)	(20.3%)	(33.3%)	(13.79%)	(50.0%)
≥65	324	159	7	404	21	228	19	4	0	21	150	3	332	10	134	2	3	0
	(44.9%)	(17.0%)	(20.0%)	(40.8%)	(48.8%)	(28.1%)	(36.5%)	(10.8%)	(0.0%)	(23.1%)	(10.7%)	(5.7%)	(20.9%)	(18.5%)	(12.0%)	(4.8%)	(5.17%)	(0.0%)
Not specified	142	442	11	321	14	348	20	27	0	29	915	35	916	33	758	26	47	1
	(19.7%)	(47.2%)	(31.4%)	(32.4%)	(32.6%)	(43.0%)	(38.5%)	(73.0%)	(0.0%)	(31.9%)	(65.5%)	(66.0%)	(57.5%)	(61.1%)	(67.7%)	(61.9%)	(81.03%)	(50.0%)
Serious cases	681	702	34	632	35	574	43	4	1	61	335	16	178	7	204	14	1	0
(including	(94.3%)	(74.9%)	(97.4%)	(63.8%)	(81.4%)	(70.9%)	(82.7%)	(10.8%)	(100.0%)	(67.0%)	(24.0%)	(30.2%)	(11.2%)	(13.0%)	(18.2%)	(33.3%)	(1.72%)	(0.0%)
deaths)	43	16	1	19	1	32	3	0	1	1	3	0	3	0	2	0	0	0
Death	(6.0%)	(1.7%)	(2.9%)	(1.9%)	(2.3%)	(4.0%)	(5.8%)	(0.0%)	(100.0%)	(1.1%)	(0.2%)	(0.0%)	(0.2%)	(0.0%)	(0.2%)	(0.0%)	(0.0%)	(0.0%)

CANA: Canagliflozin; DAPA: Dapagliflozin; EMPA: Empagliflozin; ERTU: Ertugliflozin; FAERS: FDA Adverse event reporting system; MET: Metformin HCl; SGLT-2: Sodium-glucose Co-transporter 2; UTI: Urinary tract infection.