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Investigating the association between the administration of SGLT-2 inhibitors and the risk of urinary tract infection; a systematic review and meta-analysis

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ABSTRACT

Introduction: Sodium-glucose transporter 2 (SGLT-2) inhibitors induce glycosuria. Therefore, using a meta-analysis study, this study aimed to evaluate the correlation between SGLT2 inhibitor administration and urinary tract infection (UTI) risk.

Materials and Methods: In this systematic review and meta-analysis, we conducted searches on Scopus, PubMed, Web of Science, Cochrane, and Google Scholar without time limitations up to October 16, 2023. Data were analyzed using STATA 14 software, and a significance level of $P < 0.05$ was considered.

Results: The combination of 11 studies revealed that the use of SGLT2 inhibitors, when compared to glucagon-like peptide-1 (GLP-1) receptor agonists, reduced the risk of UTI (OR = 0.77; 95% CI: 0.62, 0.95) and when compared to insulin (OR = 0.74; 95% CI: 0.63, 0.87). However, the administration of SGLT2 inhibitors, when compared to dipeptidyl peptidase-4 (DPP-4) inhibitors (OR = 1.09; 95% CI: 0.90, 1.32), sulfonylureas (OR = 1.35; 95% CI: 0.88, 2.05), biguanide initiators (OR = 1.14; 95% CI: 1.05, 1.24), thiazolidinediones (OR = 1.19; 95% CI: 0.58, 2.44), and other antidiabetic drugs (OR = 1.20; 95% CI: 0.92, 1.57), did not increase the risk of UTI. The administration of dapagliflozin (OR = 1.51; 95% CI: 0.60, 3.81), canagliflozin (OR = 1.22; 95% CI: 0.47, 3.15), and empagliflozin (OR = 3.22; 95% CI: 2.97, 3.48) showed associations with UTI risk. Furthermore, the correlation between SGLT2 inhibitors use and UTI risk was observed in cohort studies (OR = 1.14; 95% CI: 0.98, 1.32), cross-sectional studies (OR = 0.86; 95% CI: 0.64, 1.14), in males (OR = 1; 95% CI: 0.72, 1.40), and females (OR = 1.17; 95% CI: 0.91, 1.52).

Conclusion: Empagliflozin, in contrast to dapagliflozin and canagliflozin, increases the risk of UTI.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (CRD42023479548) and Research Registry (UIN: reviewregistry1742) websites.

Implication for health policy/practice/research/medical education:
No statistically significant correlation was found between dapagliflozin and canagliflozin and UTI risk. However, empagliflozin use was found to increase the risk of UTIs. Our meta-analysis suggests that dapagliflozin and canagliflozin may not increase the risk of UTIs, however, empagliflozin administration should be carefully monitored for this potential side effect.

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Meta-analysis

Introduction

Sodium-glucose transporter 2 (SGLT-2) inhibitors are a novel class of antidiabetic drugs that have recently found widespread use in the management of chronic heart failure and chronic kidney disease (1,2). They are recommended as one of several options for second-line diabetes treatment. Empagliflozin and canagliflozin are preferred second-line therapies for patients with cardiovascular diseases in clinical guidelines (3). Diabetes itself increases the risk of urinary tract infection (UTI) up to fourfold, which subsequently elevates the risk of complications, hospitalization, and mortality (4). SGLT2 inhibitors inhibit glucose reabsorption in the proximal renal tubules (5). Consequently, unabsorbed glucose is excreted in the urine, creating an environment conducive to bacterial and fungal growth (5,6). This process leads to glucosuria, which theoretically may contribute to bacterial and UTIs (5).

Although SGLT-2 inhibitors were found to be correlated with an increasing risk of genital infections (7,8), their specific connection to UTIs is less clear, and previous studies have reported contradictory findings (9-11). In fact, in 2015, the U.S. Food and Drug Administration warned about the increased risk of UTIs in cases of using SGLT-2 inhibitors (12). However, some studies have reported that SGLT2 inhibitors do not increase the risk of UTIs compared to the control group (8,13,14). Therefore, the objective of our systematic review and meta-analysis is to synthesis the results of previous studies and investigate the relationship between the use of SGLT2 inhibitors and the risk of UTIs.

Materials and Methods

Study design

This systematic review and meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (15) and was registered in the international Prospective Register of systematic Reviews (PROSPERO).

Search strategy

We conducted a comprehensive search of the Scopus, PubMed, Web of Science, Cochrane databases, and Google Scholar search engines without time restrictions up to October 16, 2023. The search incorporated Medical Subject Headings (MeSH) keywords, including "Urinary Tract Infections," "Infection, Urinary Tract," "Sodium-Glucose Transporter 2 Inhibitors," "Gliflozin," and "SGLT-2 Inhibitors." These keywords were combined using logical operators (AND, OR), and the list of studies that entered the meta-analysis process was thoroughly reviewed. Below is an example of the search strategy on PubMed: (Urinary Tract Infections [Title/Abstract] OR Infection, Urinary Tract) AND (Sodium-Glucose Transporter 2 Inhibitors [Title/Abstract] OR Gliflozin [Title/Abstract] OR SGLT-2 Inhibitors).

Inclusion criteria

Studies encompassing cohort, cross-sectional, and randomized controlled trials (RCTs) that investigated the association between the use of SGLT-2 inhibitors and the risk of UTIs were included in this meta-analysis.

PICO components

- Population: Studies exploring the relationship between the use of SGLT-2 inhibitors and the risk of UTIs.
- Intervention: The use of SGLT-2 inhibitors.
- Comparison: The control group, comprising placebo or other anti-diabetic drugs.
- Outcomes: The odds ratio of the association between SGLT-2 inhibitors and the risk of UTIs.

Exclusion criteria

Studies reporting individual cases, duplicate studies, narrative reviews, low-quality studies, those lacking complete text, studies without the necessary data for data analysis, and studies that reported the relationship between SGLT-2 inhibitor use and urinary and reproductive infections combined.

Quality assessment

Quality assessment was conducted using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (16). The final score, 22 questions, ranged from 0 to 44. Any study with a final score below 14 was excluded from the review; however, in this study, no exclusions were made. Among the reviewed studies, one RCT was identified, and to assess its quality, the risk bias of clinical trials study was evaluated by Cochrane Collaboration's tool (17). This tool consists of seven questions, each evaluating important aspects of clinical trial methodology. Each question has three response options: high risk of bias, low risk of bias, and unclear. Following this stage, disagreements regarding the answers to the questions were resolved through consensus between the two assessors, leading to a clear choice.

Data extraction

Two reviewers extracted independently. They recorded the data according to a checklist, which included the following information: first author's name, study type, patient age, comparison group, year, country, sample size, odds ratio (OR) for the association between SGLT-2 inhibitor use and the risk of UTIs, along with its 95% confidence interval. In cases of disagreement, the third reviewer evaluated the extracted data and resolved any discrepancies.

Statistical analysis

The logarithm of the OR was calculated for each study and subsequently combined. The I^2 was conducted to evaluate heterogeneity. This study, the I^2 statistic

was classified into three categories for heterogeneity assessment (less than 25% as low heterogeneity, between 25% and 75% as moderate heterogeneity, and more than 75% as high heterogeneity) (18). A random-effects model was employed in the present study ($I^2 = 97.7\%$). Data analysis was conducted using STATA 14 software, with a significance level set at $P < 0.05$.

Results

After searching the databases mentioned in the methodology section of the paper, 869 articles were identified. Upon examination of the study titles, 284 duplicate articles were excluded. The remaining 585 studies were reviewed, and from this subset, 39 articles were eliminated due to unavailability of their full text. The complete texts of the remaining 501 articles were assessed, and 490 additional articles were excluded based on other exclusion criteria. Ultimately, 11 articles entered the systematic review and meta-analysis process (Figure 1).

In this meta-analysis, 11 studies were examined (9 cohort studies, 1 cross-sectional study, and 1 randomized controlled trial). Additional article information meeting the criteria is presented in Table 1.

Figure 2 demonstrates that SGLT2 inhibitors did not significantly increase the overall risk of UTIs compared to the control group (OR = 1.09, 95% CI: 0.96, 1.25).

When comparing the administration of SGLT2 inhibitors with glucagon-like peptide-1 (GLP-1) receptor agonist (OR = 0.77, 95% CI: 0.62, 0.95) and with insulin (OR = 0.74, 95% CI: 0.63, 0.87), a decreased risk of UTIs was observed. However, when comparing SGLT2 inhibitors with DPP-4 (OR = 1.09, 95% CI: 0.90, 1.32), sulfonylureas (OR = 1.35, 95% CI: 0.88, 2.05), biguanide initiators (OR = 1.14, 95% CI: 1.05, 1.24), thiazolidinediones (OR = 1.19, 95% CI: 0.58, 2.44), and other antidiabetic medications (OR = 1.20, 95% CI: 0.92, 1.57), no significant increase in the risk of UTIs was observed, and no statistically significant association was detected in this context (Figure 3).

The relationship between the use of SGLT2 inhibitors and the risk of UTIs in cohort studies yielded an OR of 1.14 (95% CI: 0.98, 1.32). In the cross-sectional study, the OR was 0.86 (95% CI: 0.64, 1.14). These associations were not statistically significant (Figure 4).

When assessing the association between the use of SGLT2 inhibitors and the risk of UTIs in males, the OR was 1 (95% CI: 0.72, 1.40), and in females, the OR was

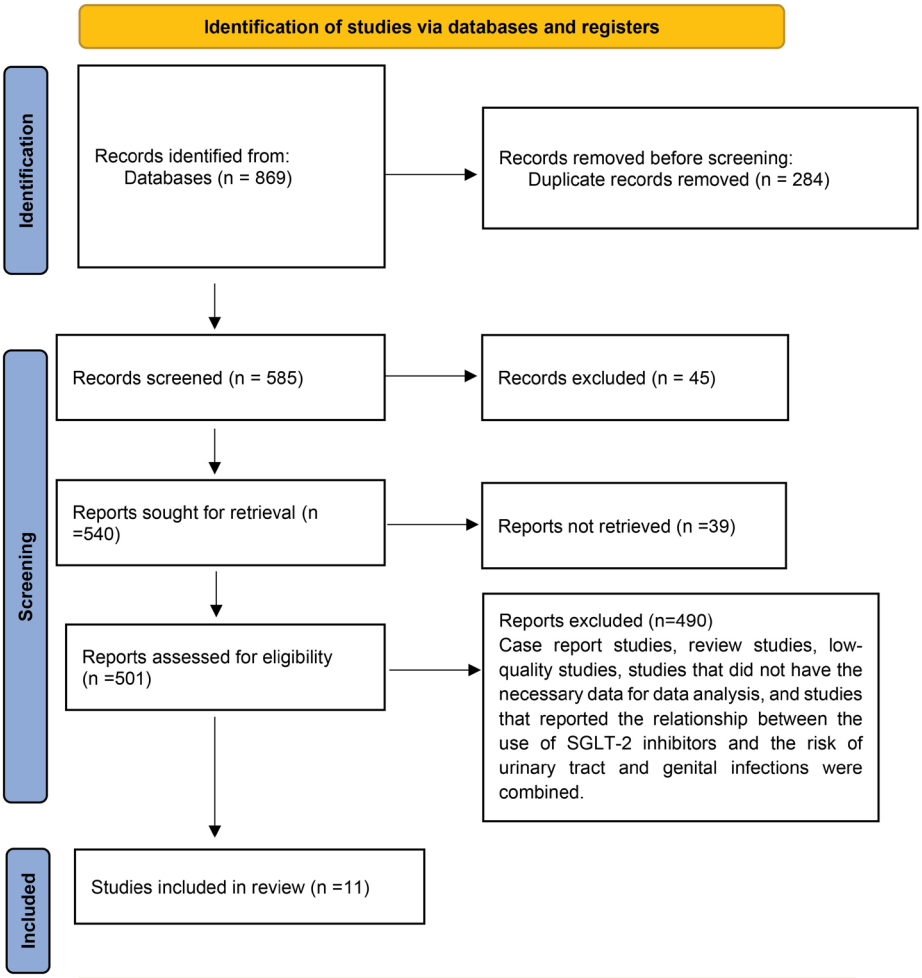

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Background information of the articles that entered the systematic review and meta-analysis process

First author, year of publication	Country	Type of study	Sample size	Mean age (y)	Compared to	During the study period
Alkabbani W, 2022 (19)	Canada	Cohort	14852	> 18	DPP-4	Jan 2005 and Nov 2018
Alkabbani W, 2022 (19)	Canada	Cohort	13667	> 18	Sulfonylureas	Jan 2005 and Nov 2018
Alkabbani W, 2022 (19)	Canada	Cohort	2101	> 18	GLP-1	Jan 2005 and Nov 2018
Alkabbani W, 2022 (19)	Canada	Cohort	5006	> 18	Thiazolidinediones	Jan 2005 and Nov 2018
Alkabbani W, 2022 (19)	Canada	Cohort	7804	> 18	Insulin	Jan 2005 and Nov 2018
Gadzhanova S, 2017 (20)	Australia	Cohort	NR	NR	DPP-4	between 1 Jan 2012 and 1 Sep 2015
Anan G, 2023 (M) (21)	Japan	Cross-sectional	978003	NR	Other drugs	As of May 31, 2023
Anan G, 2023 (W) (21)	Japan	Cross-sectional	685353	NR	Other drugs	As of May 31, 2023
Dave CV, 2019 (8)	USA	Cohort	123752	> 18	DPP-4	Mar 2013 to Sep. 2015
Dave CV, 2019 (8)	USA	Cohort	111978	> 18	GLP-1	Mar 2013 to Sep. 2015
Lega IC, 2019 (13)	Canada	Cohort	NR	NR	DPP-4	
Uitrakul S, 2022 (22)	Thailand	Cohort	853	NR	Other drugs	between 1 Jan 2019 and 30 June 2021
Yang H, 2022 (23)	Korea	Cohort	NR	NR	DPP-4	from 2014 to 2017
Yang H, 2022 (23)	Korea	Cohort	NR	NR	Sulfonylureas	from 2014 to 2017
Yang H, 2022 (23)	Korea	Cohort	NR	NR	Thiazolidinediones	from 2014 to 2017
Takeuchi Y, 2021 (24)	Japan	Cohort	NR	NR	DPP-4	between Apr 2014 and Mar 2015
Takeuchi Y, 2021 (24)	Japan	Cohort	NR	NR	Biguanide initiators	between Apr 2014 and Mar 2015
Akkus E, 2023 (25)	Turkey	Cohort	130	62	Other drugs	between Feb and Sep 2022
Tada K, 2022 (26)	Japan	Cohort	14526398	NR	Other drugs	NR
Nicolle LE, 2012 (27)	Canada	RCT	451	52.9	Placebo	NR

NR, Not reported; DPP-4, Dipeptidyl peptidase-4 inhibitor; GLP-1, Glucagon-like peptide-1.

1.17 (95% CI: 0.91, 1.52). These relationships also did not achieve statistical significance (Figures 5 and 6).

In the analysis based on the type of SGLT2 inhibitors, it was observed that the relationship between the use of dapagliflozin and the risk of UTIs resulted in an OR of 1.51 (95% CI: 0.60, 3.81) and the relationship between the use of canagliflozin and the risk of UTIs showed an OR of 1.22 (95% CI: 0.47, 3.15). These associations were not statistically significant. However, using empagliflozin was associated with a significant increase in the risk of UTIs, with an OR of 3.22 (95% CI: 2.97, 3.48) (Figures 7 to 9).

Discussion

In the examination of 11 studies, the overall use of SGLT2 inhibitors did not increase the risk of UTIs, except for empagliflozin, which was associated with an increased

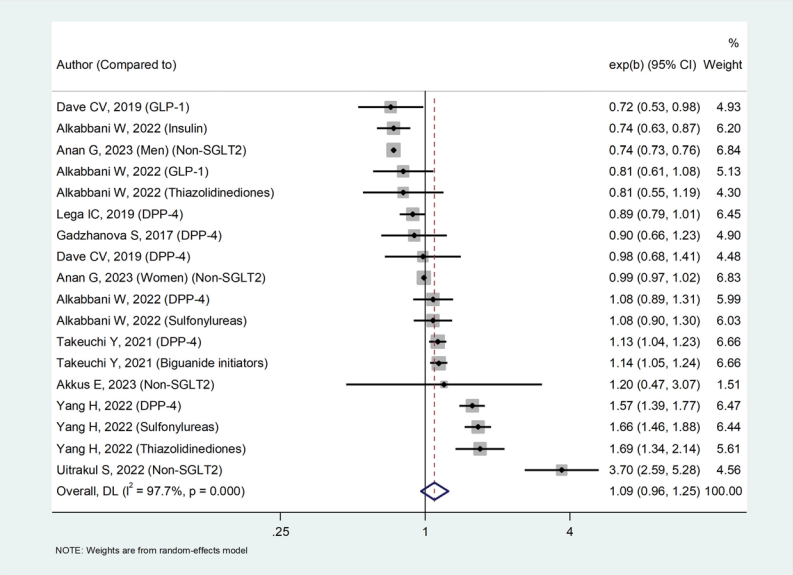

Figure 2. Forest plot of the association between SGLT2 inhibitors administration and risk of urinary tract infection with its 95% confidence interval.

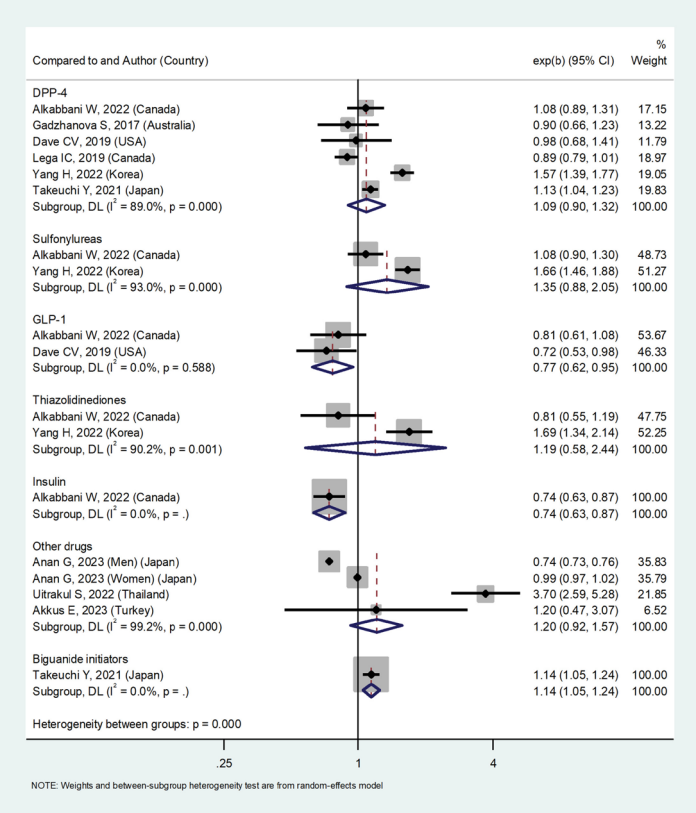

Figure 3. Forest plot of the association between SGLT2 inhibitors administration and risk of urinary tract infection by control group.

risk. Furthermore, when compared to GLP-1 receptor agonists, SGLT2 inhibitors reduced the risk of UTIs by 23%, and when compared to insulin, 26%. However, other relationships did not exhibit statistical significance.

In line with the meta-analysis conducted by Borovac and colleagues, the risk of UTIs in patients with heart failure who administered SGLT2 inhibitors did not significantly differ from those on placebo (RR: 1.09, 95% CI: 0.94–1.26) (28). In a network meta-analysis by Wang et al, the aim was to investigate the risk of urinary and

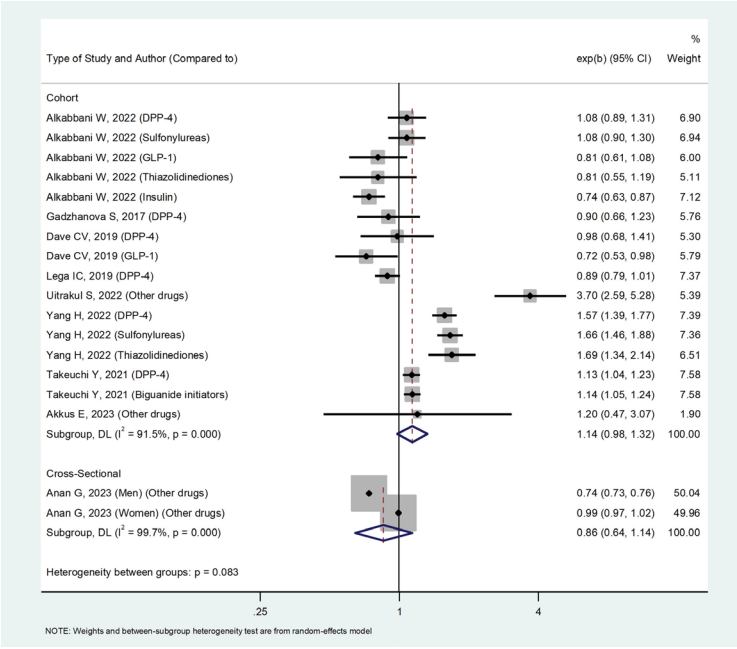

Figure 4. Forest plot of the association between SGLT2 inhibitors administration and risk of urinary tract infection by type of study.

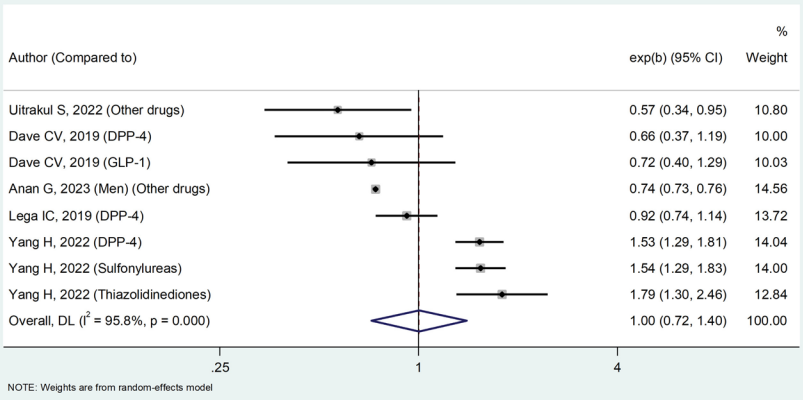

Figure 5. Forest plot of the association between SGLT2 inhibitors administration and risk of urinary tract infection in male.

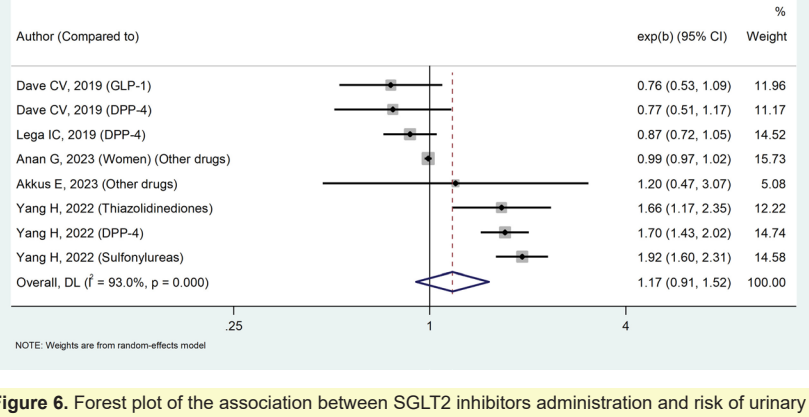

Figure 6. Forest plot of the association between SGLT2 inhibitors administration and risk of urinary tract infection in female.

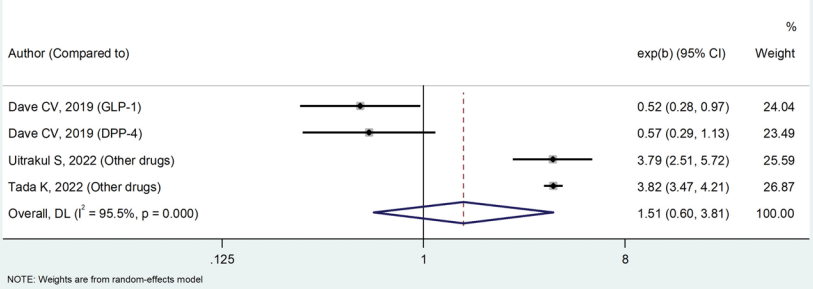

Figure 7. Forest plot of the association between dapagliflozin administration and risk of urinary tract infection.

genital infections in patients with type 2 diabetes. The results revealed that SGLT2 inhibitors did not lead to an increased risk of UTIs (29). These findings align with the results of our study. While our study had a different study population from the one in Borovac JA's meta-analysis, our results corroborate their findings, demonstrating that the use of SGLT2 inhibitors is not a risk factor for UTIs in patients with heart disease and diabetes.

In the meta-analysis conducted by Donnan and colleagues, there was no statistically significant association between the use of SGLT2 inhibitors and UTIs in patients with type 2 diabetes compared to other antidiabetic medications or placebo, except dapagliflozin, which, at a high dose, was associated with an increased risk of UTIs (OR: 1.30, 95% CI: 1.09–1.57) (30). In a previous meta-analysis performed by Li and colleagues, the administration of canagliflozin, dapagliflozin, and empagliflozin was linked to an increased risk of genital

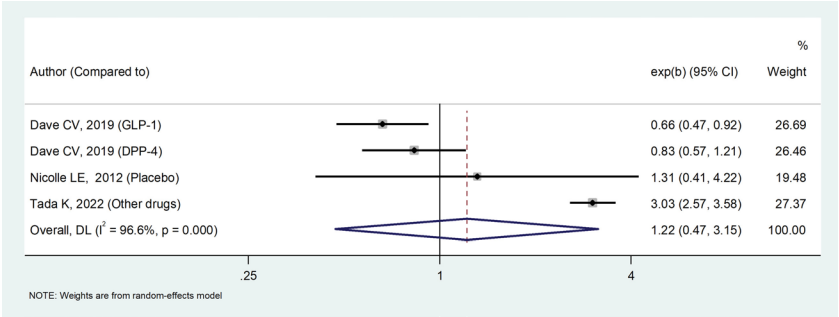

Figure 8. Forest plot of the association between canagliflozin administration and risk of urinary tract infection.

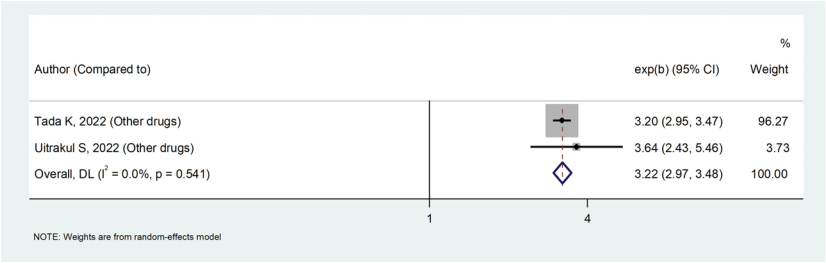

Figure 9. Forest plot of the association between empagliflozin administration and risk of urinary tract infection.

infections compared to placebo, with dapagliflozin having an OR of 3.21 (95% CI: 2.08-4.93) and canagliflozin having an OR of 5.23 (95% CI: 3.86-7.09). However, only dapagliflozin at a 10 mg dose was associated with an increased risk of UTIs compared to placebo (RR: 1.33, 95% CI: 1.10–1.61) (7). The results of a meta-analysis by Puckrin et al showed that SGLT-2 inhibitors reduced the risk of genital infections compared to placebo (RR: 3.37, 95% CI: 2.89–3.93) and the active comparator (RR: 3.89, 95% CI: 3.14 -4.82) increase. However, the risk of UTI was not increased with SGLT-2 inhibitors compared with placebo (RR: 1.03, 95% CI: 0.96–1.11) or active comparator (RR: 1.08, 95% CI: 0.93–1.25). In subgroup analysis, only dapagliflozin 10 mg was associated with an increased risk of UTI compared with placebo (RR: 1.33, 95% CI: 1.10–1.61)(10). These studies suggested that the administration of SGLT2 inhibitors is a risk factor for genital infections. Still, apart from dapagliflozin, which increases the risk of UTIs, other SGLT2 inhibitors do not have a statistically significant impact on the occurrence of UTIs. This finding does not align with our study, as our research indicated that empagliflozin is a risk factor for UTIs. At the same time, other SGLT2 inhibitors do not have a statistically significant effect. It is worth noting that differences in the study population, the number of studies, and the sample size in these studies may account for the discrepancies in the results.

Conclusion

In summary, the overall use of SGLT2 inhibitors does not increase the risk of UTIs. There was no statistically significant association between dapagliflozin and canagliflozin and the risk of UTIs. However, empagliflozin use was found to increase the risk of UTIs. Furthermore, when compared to insulin and GLP-1 receptor agonist, SGLT2 inhibitors reduced the risk of UTIs by 26% and 23%, respectively. However, no statistically significant differences were observed when comparing SGLT2 inhibitors with other antidiabetic medications. Additionally, there was no statistically significant association between patient gender and the type of studies with the impact of SGLT2 inhibitor use on the risk of UTIs. Based on the above results, it can be concluded that the use of dapagliflozin and canagliflozin not only does not pose a risk for UTIs but may perform better compared to insulin and GLP-1 receptor agonist. It is recommended that in patients prone to UTIs, dapagliflozin and canagliflozin be considered for prescription instead of Insulin and GLP-1 receptor agonist.

Limitations of the study

One of the limitations of this study was the inability to assess the impact of SGLT2 inhibitor use on the risk of UTIs based on patient age and drug dosage. The second limitation was the non-uniform distribution of study types among the studies under investigation, as out of the 11 studies, only one was cross-sectional, and one was a randomized clinical trial, while the rest were cohort studies. The third limitation was that some of the studies under investigation did not specify the type of SGLT2

inhibitor used in the study.

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Authors' contribution

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Writing–reviewing & editing: Nasim Zaman samghabadi, Sonia Razmjou, Ramin Haghighi, Roya Raeisi Jaski, Alireza Habibzadeh, and Mahdi Behi.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023479548) and Research Registry website (Unique Identifying Number (UIN): reviewregistry1742). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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