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Adverse events associated with sodium glucose co-transporter 2 inhibitors: an overview of quantitative systematic reviews

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Abstract

Background: Multiple published quantitative systematic reviews have reported on adverse events associated with the use of sodium glucose co-transporter 2 (SGLT-2) inhibitors in patients with type 2 diabetes mellitus.

Aims: To summarize and appraise the quality of evidence from quantitative systematic reviews assessing adverse events of SGLT-2 inhibitors.

Methods: We searched PubMed, EMBASE and the Cochrane Library for quantitative systematic reviews assessing SGLT-2 inhibitor safety. Two reviewers extracted data and assessed methodological quality using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool. Main outcomes included pooled and single study point estimaates (in the absence of pooled estimates) with corresponding 95% confidence intervals (CIs) of SGLT-2 inhibitors *versu*s placebo or active comparators for genitourinary infections, volume depletion, acute kidney injury, bone fractures, diabetic ketoacidosis, lower limb amputations, cancers, and other notable adverse events.

Results: Out of 1289 citations screened, 47 reviews assessed SGLT-2 inhibitor safety, of which 35 were of low quality. Canagliflozin, dapagliflozin and empagliflozin were consistently associated with an increased risk of genital tract infections *versu*s placebo (point estimates ranged from 2.5 to 9.8) and other antihyperglycemic agents (point estimates ranged from 2.7 to 12.0). Canagliflozin and dapagliflozin were associated with an increased risk of diabetic ketoacidosis. Canagliflozin was the only agent associated with an increased amputation risk; however, this was driven by results from a single trial program. Dapagliflozin was the only agent that exhibited a statistically significant increased risk of urinary tract infections. Empagliflozin was associated with a statistically significant increased risk of bladder cancer; however, this finding was susceptible to detection bias. None of the agents were associated with a statistically significant increased risk of acute kidney injury, or bone fractures compared to placebo or mixed (active or placebo) comparators. Upper 95% CI limits do not rule out clinically meaningful outcomes.

Conclusion: The majority of quantitative systematic reviews reporting on adverse events of SGLT-2 inhibitors were of low methodological quality. Despite almost 50 quantitative systematic reviews published on the safety of SGLT-2 inhibitors, clinicians are still left uncertain of the risks of important adverse effects.

Keywords: adverse events, harms, overview of reviews, SGLT-2 inhibitors, type 2 diabetes, umbrella reviews

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Plain Language Summary

SGLT-2 iInhibitor side effects: overview of reviews

Many published systematic reviews have reported on side effects associated with the use of sodium glucose co-transporter 2 (SGLT-2) inhibitors in patients with type 2 diabetes. We aimed to summarize and appraise the quality of evidence from quantitative systematic reviews assessing side effects of SGLT-2 inhibitors. Using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool, two authors extracted data and assessed the methods of included reviews. Main outcomes included reported pooled and single study point estimates for several SGLT-2 inhibitor side effects such as genital infections, bone fractures, lower limb amputations, increased blood acidity, among others. Of the reviews included in our study, 35 of the 47 reviews assessed were of low quality. Canagliflozin and dapagliflozin were associated with an increased risk of blood acidity in a 2020 review. Canagliflozin was the only agent associated with an increased amputation risk; however, this was driven by results from a single trial program. Dapagliflozin was the only agent that exhibited a significantly increased risk of urinary tract infections. Empagliflozin was associated with an increased risk of bladder cancer; however, this finding was susceptible to bias. None of the agents were associated with an increased risk of kidney injury or bone fractures.

Introduction

Sodium glucose co-transporter 2 (SGLT-2) inhibitors are a pharmacologically novel class of agents used in the treatment of type 2 diabetes mellitus. In 2013, the United States Food and Drug Administration (US FDA) approved canagliflozin as the first SGLT-2 inhibitor indicated for glycemic control in patients with type 2 diabetes.[1] This was soon followed by the approval of dapagliflozin and empagliflozin in 2014, among other SGLT-2 inhibitors internationally in subsequent years.[2] These agents achieve their glucose-lowering effect independent of insulin *via* inhibition of the sodium glucose co-transporter 2, expressed in the proximal tubule within the kidney.[1] Inhibition of these transporters, which are responsible for the reabsorption of glucose, facilitates blood glucose reduction *via* increased urinary excretion of glucose.[1]

There is a wide variety of benefits associated with SGLT-2 inhibitor use in the treatment of type 2 diabetes. These include, but are not limited to, significant reduction in hemoglobin A1C, weight loss (*via* caloric loss of increased renal glucose excretion), reduction in systolic and diastolic blood pressure (*via* increased diuresis) and lower risk of hypoglycemia compared to insulin secretagogues.[3] Moreover, canagliflozin and empagliflozin have demonstrated a reduction in major adverse cardiovascular events (MACEs) and delayed progression of nephropathy in patients with clinically established cardiovascular disease.[3] These benefits improve patient outcomes and quality of life, supporting SGLT-2 inhibitors' unique niche within type 2 diabetes pharmacotherapy. Clinical practice guidelines recommend SGLT-2 inhibitors as second or third-line agents, in addition to metformin, when additional glucose control is required.[3,4] Moreover, the American Diabetes Association guidelines recommend that a SGLT-2 inhibitor with demonstrated cardiovascular benefit be used in patients with established atherosclerotic cardiac disease, established kidney disease, or established heart failure.[4]

Despite these benefits, SGLT-2 inhibitors have been associated with numerous adverse events such as genitourinary tract infections and volume depletion due in part to their mechanism of action.[1] Health Canada (HC), the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued several SGLT-2 inhibitor-related communications to both consumers and healthcare professionals addressing multiple safety concerns, such as acute kidney injury (AKI), fractures and diabetic ketoacidosis (DKA).[5–11] Furthermore, numerous systematic reviews and meta-analyses have been

conducted to assess these safety outcomes, and others, associated with SGLT-2 inhibitor use. It is important to recognize that not all systematic reviews and meta-analyses exhibit the same level of methodological rigour and applicability to clinical practice. Given the rapid rise in SGLT-2 inhibitor use, clinicians may turn to these reviews for information on drug safety.[12] Therefore, we conducted an overview of systematic reviews, adapted from Cochrane Overviews, to provide clinicians, policy-makers and clinical guideline developers with a critical appraisal and summary of the best available evidence assessing the safety of SGLT-2 inhibitors used in the treatment of type 2 diabetes.[13]

Methods

The protocol for this study is registered with the PROSPERO international prospective register of systematic reviews (PROSPERO 2019: CRD42019135863).[14]

Eligibility criteria

We included systematic reviews of randomized clinical trials, cohort or case–control studies with a meta-analysis (quantitative systematic review) that evaluated SGLT-2 inhibitor safety and collected data on adverse events beyond hypoglycemia. Quantitative systematic reviews that did not describe their methods with a minimum of a systematic search strategy or include results on individual SGLT-2 inhibitor agents were excluded. Our outcomes of interest were total adverse events, serious adverse events, withdrawals due to adverse events, infections (such as genital mycotic infections, urinary tract infections and others), volume depletion-related events (such as orthostatic hypotension, dehydration, hypovolemia and others), AKI, bone fractures, DKA (both euglycemic and non-euglycemic), lower limb amputations, cancer and other notable adverse events reported in reviews meeting the inclusion criteria. We did not restrict the inclusion of quantitative systematic reviews based on the timing of adverse events following drug exposure. We restricted the language of included reviews to English.

Sources and searching

A search of bibliographic electronic databases and additional sources was used to identify potentially relevant quantitative systematic reviews for inclusion. First, PubMed, EMBASE and the Cochrane Library were searched from inception to 2 September 2020. Results were filtered in the search strategy with a systematic review filter when applicable. Second, we searched the table of contents from the following diabetes journals from 1 January 2011 to 2 September 2020: *Diabetes Care, Diabetologia, Diabetic Medicine, Diabetes Research and Clinical Practice*, *Diabetes*, *Obesity and Metabolism*, *Diabetes* and *The Lancet Diabetes and Endocrinology*. Third, we hand-searched the references of included systematic reviews. The search strategies used are available in Appendix 1.

Study selection

Two independent reviewers (R.P., K.N., W.A., Y.L., N.M., J.M.G.) screened the titles and abstracts of all potentially relevant citations. Subsequently, two independent reviewers screened the full texts of citations that were potentially relevant using a standardized study eligibility form. Disagreements were resolved by consensus or by a third reviewer (J.M.G.). Study selection is summarized in Figure 1.

Data extraction

One reviewer (R.P., K.N., W.A., Y.L., N.M., J.M.G.) extracted review-level data and recorded it on a standardized Google form developed for this study. Information was extracted on bibliographic details, research question(s)/objective(s), search strategies, the number of included studies, interventions and comparisons evaluated, outcomes reported and methods of analysis used. A 10% random sample of review-level data was checked for accuracy by a second reviewer (W.A.), and no discordances were noted. Two reviewers (R.P., K.N., W.A., Y.L., N.M.) extracted all pooled (irrespective of meta-analytical technique) and single study estimates (in the absence of a pooled estimate) from each included review and verification of all estimates was completed through consensus.

Quality assessment

Two independent reviewers assessed the quality of included systematic reviews using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) checklist.[11] AMSTAR 2 is a validated tool consisting of 16 domains that assess the methodological quality of systematic reviews

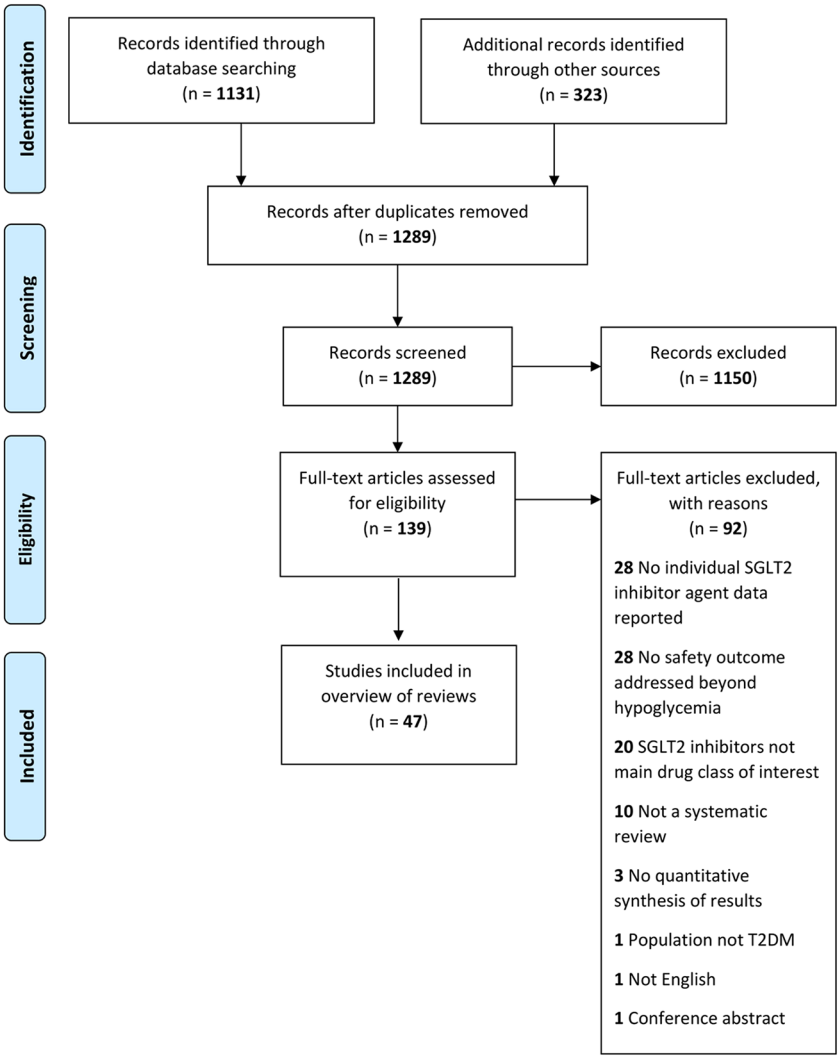

Figure 1. Flow diagram of study selection.

containing both randomized and non-randomized studies of interventions. All discordant AMSTAR 2 quality ratings between reviewers were resolved by consensus. Consistent with AMSTAR 2 published literature, systematic reviews having more than one critical flaw were rated as critically low quality, one critical flaw as low quality, more than one non-critical weakness as moderate quality, and no or one non-critical weakness as high quality. Domains 2, 4, 7, 9, 11, 13 and 15 are considered critical in AMSTAR 2.[15]

Analysis

We conducted a descriptive analysis of our results by summarizing the characteristics of reviews meeting the inclusion criteria, as well as safety outcome data for commonly used SGLT-2 agents worldwide (i.e. canagliflozin, dapagliflozin and empagliflozin). We tabulated the number of systematic reviews and number of pooled point estimates of treatment effect for all placebo and active treatment comparisons for SGLT-2 inhibitors. Point estimates included odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs) and mean differences (MDs). When applicable, we calculated summary descriptive statistics of review characteristics and findings (e.g. range of point estimates) and plotted the reported pooled and single study point estimates (in the absence of pooled results) using forest plots. We plotted the random effects estimate if both random and fixed effects point estimates were reported.

Results

We identified 1289 unique citations, of which 47 quantitative systematic reviews met our inclusion criteria (Figure 1 and Table 1).[16–62] Twenty-two reviews (47%) reported no funding source,[17–24,27,28,30–32,35,38,39,43,44,50,52,53,55] while nine reviews (19%) received funding from government,[25,26,29,37,40,41,51,54,59] five reviews (11%) received internal funding,[45–49] three reviews (6%) received foundational funding[16,34,36] and one review (2%) was funded by private industry.[57] A funding source was not disclosed in seven reviews (15%).[33,42,56,58,60–62] The median (interquartile range [IQR]) number of databases searched was four (2.5). The median (IQR) number of studies included was 27 (34). The geographical distribution of included reviews can be found in Figure 2. The complete AMSTAR 2 assessments and overall quality ratings for included systematic reviews is shown in Appendix 1, Supplemental Figure 1. Only one (2%) included review received an AMSTAR 2 quality rating of high.[44] Twenty-four (52%) reviews were considered critically low quality,[16–18,20–24,27–29,32,34,38–40,43,45,50,51,54,55,59,62] 11 (23%) reviews were considered low quality[19,33,46,47–49,52,56,57,60,61] and 11 (23%) reviews were considered moderate quality.[25,26,30,31,35–37,41,42,53,55] From the 47 included reviews, there were 958 point estimates reporting on 59 unique adverse effects. The most frequently reported estimates ($n=213$, 22%) were for urinary tract infection (Figure 3). There were 181 point estimates (19%) that were statistically significant (p-value <0.05). Associations for adverse events with specific SGLT-2 inhibitors are summarized below. See Supplemental Figures 1–140 in Appendix 2 for forest plots of extracted point estimates.

Canagliflozin

There were 312 point estimates reported for 50 adverse events from 37 reviews. Of these, 64 point estimates (20%) were statistically significant. Genital tract infections were consistently reported with canagliflozin use *versus* placebo and active comparators (34/37 point estimates from 12 reviews). In addition, an increased risk of lower limb amputations with canagliflozin use *versus* placebo and active comparators was observed (3/4 point estimates from four reviews). Included reviews reported some significant increases (4/19 point estimates from nine reviews) and decreases (3/19 point estimates from nine reviews) of any hypoglycemic events *versus* placebo, as well as one increased non-severe hypoglycemia event *versus* placebo (1/1 point estimate from one review). A significantly increased risk of any hypoglycemic event was reported in patients using canagliflozin in combination with metformin and sulfonylureas. In addition, canagliflozin was not consistently associated with a significant increase in volume depletion-related events (i.e. composite of dehydration, orthostatic hypotension and hypovolemia) *versus* placebo and active comparators (1/14 point estimates from five reviews). Hypovolemia *versus* placebo (1/1 point estimate from one review), as well as osmotic diuresis *versus* placebo and active comparators (4/8 point estimates from four reviews) were also associated with canagliflozin use. One review reported a significant association between canagliflozin and DKA *versus* placebo and active comparators (1/5 point estimates from four reviews). Canagliflozin use was inconsistently associated with composite renal adverse events (i.e. end-stage renal disease, doubling of serum creatinine, and death from renal or cardiovascular causes) *versus* placebo and active comparators (2/5 point estimates from two reviews). Significant associations were reported for canagliflozin users regarding increased pollakiuria *versus* placebo (1/1 point estimate from one review), serum magnesium (2/2 point estimates from one review) and nausea *versus* placebo (2/5 point estimates from one review). Canagliflozin was not consistently associated with a significant increase in total adverse events *versus* placebo (1/13 point estimates from six reviews). Significantly decreased risks of gastrointestinal cancer (2/3 point estimates from two reviews) and aspartate aminotransferase (AST; 1/1 point estimate from one review) with canagliflozin use *versus* placebo and active comparators were reported.

Dapagliflozin

There were 334 point estimates reported for 48 adverse events from 33 reviews. Of these, 71 point estimates (21%) were statistically significant. Both genital tract infections *versus* placebo and active comparators (32/48 point estimates from 12 reviews), as well as urinary tract infections *versus* placebo and active comparators (22/79 point estimates from 14 reviews) were significantly increased with dapagliflozin use. An increased risk of hypoglycemia was not consistently associated with dapagliflozin use *versus* placebo and active comparators (3/29

Table 1. Summary characteristics of 47 quantitative systematic reviews that evaluated adverse effects of either canagliflozin, dapagliflozin, or empagliflozin.

Characteristics	All reviews [47 (100%)]	Canagliflozin [37 (79%)]	Dapagliflozin [33 (70%)]	Empagliflozin [31 (66%)]
Year of study				
2012	2 (4)	0 (0)	2 (6)	0 (0)
2013	2 (4)	2 (5)	2 (6)	0 (0)
2014	4 (8)	2 (5)	2 (6)	1 (3)
2015	2 (4)	2 (5)	0 (0)	0 (0)
2016	8 (17)	7 (19)	4 (13)	5 (16)
2017	12 (26)	9 (24)	7 (21)	9 (29)
2018	8 (17)	7 (19)	7 (21)	8 (26)
2019	6 (13)	5 (15)	6 (18)	5 (16)
2020	3 (7)	3 (8)	3 (9)	3 (10)
Funding source				
No funding	22 (47)	18 (48)	15 (45)	11 (35)
Government	9 (19)	7 (19)	8 (24)	8 (26)
Internal funding	5 (11)	4 (11)	4 (13)	4 (13)
Foundation	3 (6)	2 (5)	2 (6)	3 (10)
Private industry	1 (2)	1 (2)	1 (3)	1 (3)
Not disclosed	7 (15)	5 (15)	3 (9)	4 (13)
Number of databases searched				
2	3 (7)	2 (5)	3 (9)	2 (6)
3	9 (19)	6 (16)	7 (21)	7 (23)
4	13 (28)	12 (32)	10 (30)	10 (32)
5	8 (17)	5 (15)	5 (16)	4 (13)
6+	14 (29)	12 (32)	8 (24)	8 (26)
Number of included studies				
⩽25	21 (45)	13 (36)	10 (30)	9 (29)
26–50	16 (35)	15 (40)	13 (38)	13 (42)
51–75	4 (8)	3 (8)	4 (13)	3 (10)
76–100	4 (8)	4 (11)	4 (13)	4 (13)
>100	2 (4)	2 (5)	2 (6)	2 (6)

(Continued)

Table 1. (Continued)

Characteristics	All reviews [47 (100%)]	Canagliflozin [37 (79%)]	Dapagliflozin [33 (70%)]	Empagliflozin [31 (66%)]
AMSTAR 2 quality rating				
Critically low	24 (52)	16 (44)	17 (52)	16 (52)
Low	11 (23)	10 (27)	8 (24)	6 (19)
Moderate	11 (23)	10 (27)	7 (21)	8 (26)
High	1 (2)	1 (2)	1 (3)	1 (3)

n = number of quantitative systematic reviews.
Note that meta-analysis techniques will not add to total meta-analyses conducted, as some systematic reviews used multiple techniques.
AMSTAR 2: A Measurement Tool to Assess Systematic Reviews 2.

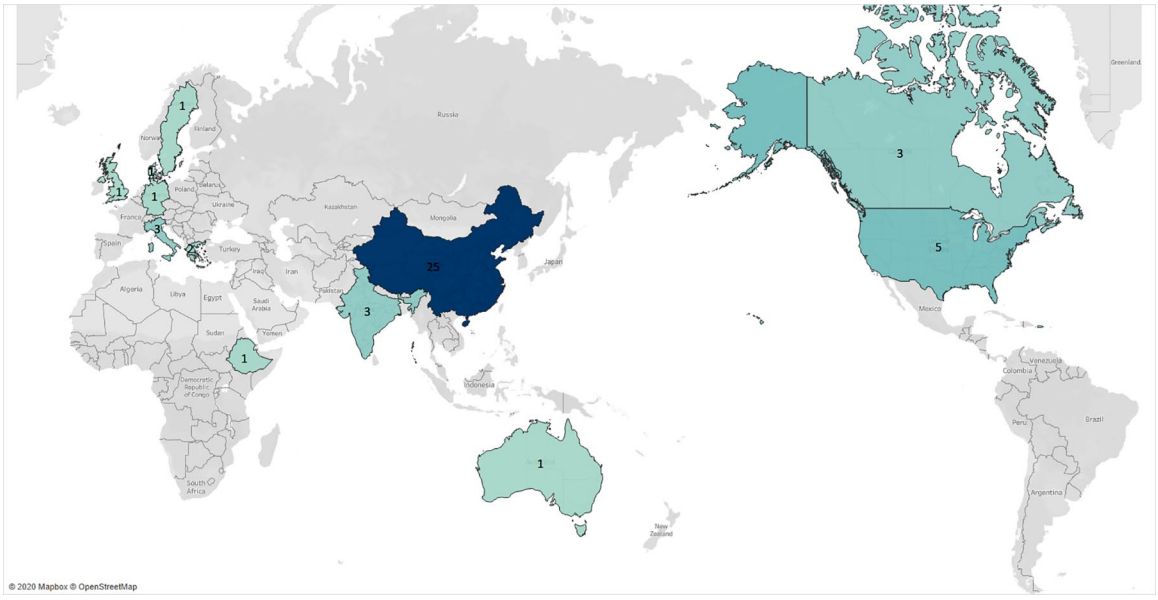

Figure 2. Geographical distribution of included quantitative systematic reviews (created using Tableau Professional 2019.2).

point estimates from seven reviews). Again, a significantly increased risk of hypoglycemia was reported in patients using a combination of dapagliflozin, metformin and sulfonylureas. A statistically significant increase in hypovolemia (1/5 point estimates from two reviews) and composite renal events (4/8 point estimates from two reviews) were also reported for dapagliflozin users. One review reported a significant association between canagliflozin and DKA *versus* placebo and active comparators (1/5 point estimates from four reviews). Dapagliflozin was associated with a significant increase in total adverse events *versus* placebo (2/2 point estimates from two reviews). Furthermore, serum magnesium (1/3 point estimates from one review) and serum phosphate concentrations (2/3 point estimates from one review) were significantly increased with dapagliflozin use.

Empagliflozin

There were 312 point estimates reported for 48 adverse events from 31 reviews. Of these, 52

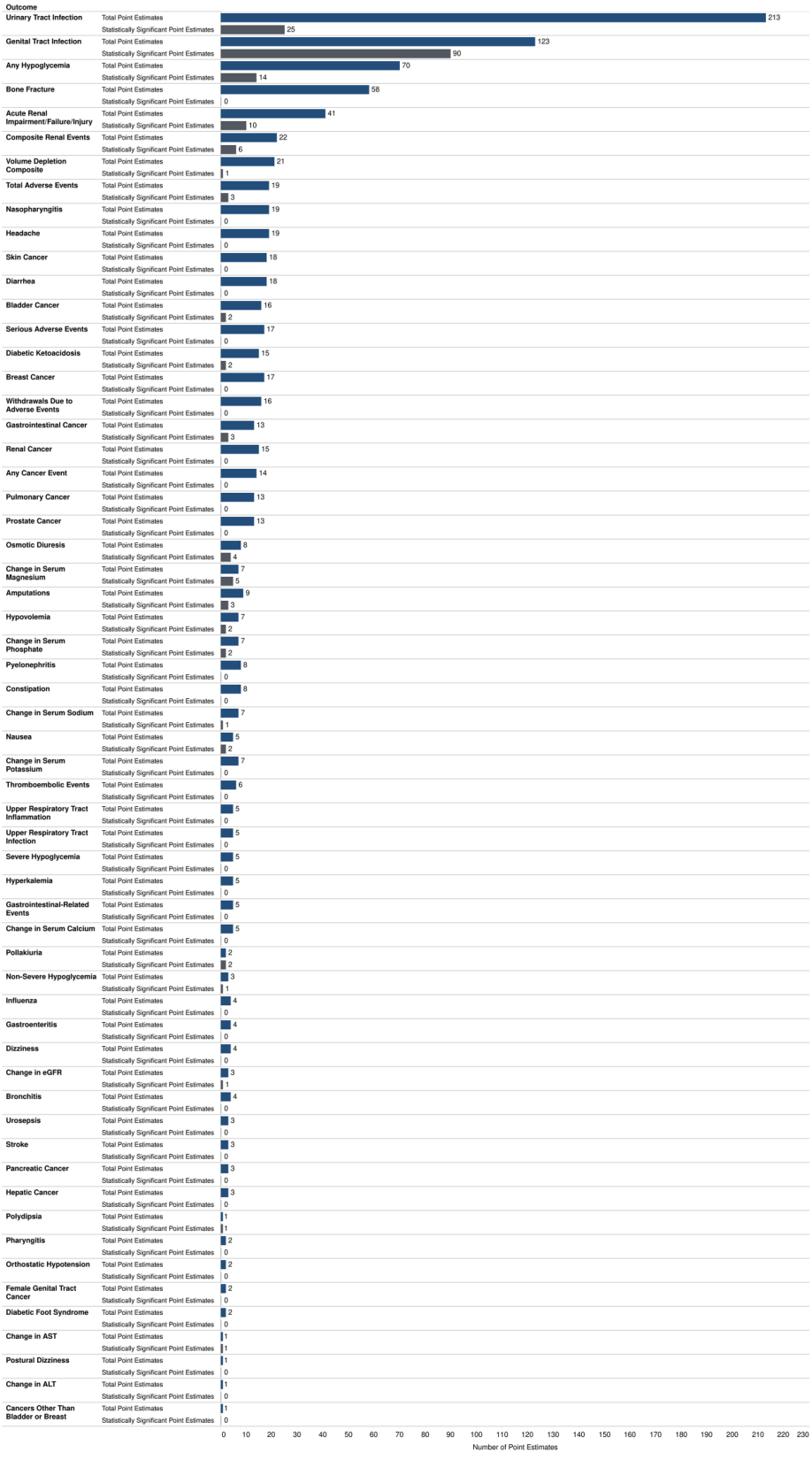

Figure 3. Distribution of total and statistically significant point estimates for all outcomes (created using Tableau Professional 2019.2).

point estimates (17%) were statistically significant. Empagliflozin was also associated with a significant increase in genital tract infections *versus* placebo and active comparators (24/38 point estimates from nine reviews). A significant increase of urinary tract infections with empagliflozin *versus* dapagliflozin was reported; however, only 4% of total comparisons demonstrated a significant association (3/71 point estimates from 12 reviews). Empagliflozin was inconsistently associated with a significant increase in hypoglycemia *versus* canagliflozin (2/22 point estimates from seven reviews), as well as a significant decrease in hypoglycemia risk *versus* placebo (2/22 point estimates from seven reviews). Furthermore, empagliflozin was associated with a significant decrease in renal composite events *versus* placebo and active comparators (6/9 point estimates from two reviews), as well as acute renal injury/impairment/failure (7/17 point estimates from five reviews). Empagliflozin was also associated with a statistically significant increase in pollakiuria (1/1 point estimate from one review), polydipsia (1/1 point estimate from one review), serum magnesium (2/2 point estimates from one review) and serum sodium (1/2 point estimates from one review) *versus* placebo. Furthermore, an association of bladder cancer with empagliflozin use *versus* placebo and active comparators was observed (2/8 point estimates from four reviews). One point estimate from a network meta-analysis reported a significantly increased association of gastrointestinal cancer with empagliflozin *versus* canagliflozin (1/6 point estimates from three reviews).[45]

Discussion

Our umbrella review identified 47 reviews reporting treatment associations between SGLT-2 inhibitors and one or more adverse events. Over 900 point estimates were reported, of which about one in five were statistically significant. These reviews reported on over 50 adverse events, of which the majority had very few contributing events. In fact, the only consistently reported adverse event that was more common in users, compared to placebo or active comparators, was genital tract infections. This adverse event was well described in large randomized clinical trials and is consistent with their mechanism of action – increased glucose exposure through the genitourinary tract is postulated to be the basis for an increase in genital infections as a class effect.[1] Moreover, based on the included reviews, it appears that SGLT-2 inhibitor agents may exhibit varying adverse effect profiles. Two examples are discussed below.

Canagliflozin appears to be uniquely associated with an increase in lower limb amputations. Amputation concerns arising from canagliflozin use was initially sparked by results from the landmark CANVAS program, which gathered together the results from the CANVAS and CANVAS-R trials.[63] Although the CANVAS program showed a 1.97-fold increase in amputation risk associated with canagliflozin use, recent data from the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial failed to substantiate this finding.[63,64] A recent systematic review inclusive of the CREDENCE trial also did not find a statistically significant association between canagliflozin use and lower limb amputations.[30] While inter-trial differences including study duration, daily canagliflozin doses, population sizes and trial durations may be related to the discrepancy in amputation risk, the exact source remains unclear.[63,64] It is important to note that part way through the CREDENCE trial, treatment assignment was interrupted for patients with risk factors for lower limb amputations. Furthermore, data from recently published observational studies indicate conflicting evidence regarding amputation risk with users of SGLT-2 inhibitors. A significantly increased risk of lower limb amputations in SGLT-2 inhibitor users *versus* GLP-1 agonists was reported in two studies.[65,66] However, another study reported no increased risk of amputation with canagliflozin users *versus* metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor (GLP-1) agonists, thiazolidinediones, sulfonylureas, insulin and other pharmacotherapies used in the management of type 2 diabetes.[67]

Interestingly, bladder cancer rates were exclusively increased in empagliflozin patients relative to placebo or active comparators *via* a network meta-analysis. This was largely driven by the results of the EMPA-REG OUTCOME according to the meta-analysis conducted by Tang *et al.* and Zinman *et al.*[48,68] With an overall low incidence of bladder cancer adverse events seen in this trial, including transitional cell carcinoma events, further studies are required to elucidate this association.[69] Gastrointestinal cancer rates were significantly decreased in canagliflozin users

when compared against placebo or active comparators. In particular, canagliflozin has strong SGLT-1 inhibition properties which partially occur in the gastrointestinal tract, thereby inhibiting intestinal epithelial cancer cell proliferation.[70] As empagliflozin has the lowest SGLT-1 selectivity out of all the three SGLT-2 inhibitor agents discussed, variations in receptor affinity may explain the differences seen with gastrointestinal cancer point estimates reported.[70] The aforementioned associations with cancers are hypothesis generating and require further mechanistic and epidemiological investigations.

Although other significant associations were reported among the included reviews, they should be interpreted with caution. For example, as reported in the results section there was a small number of point estimates suggesting an increased risk of hypoglycemia among SGLT-2 inhibitor users, which is likely to be due to concomitant hypoglycemic therapies. Agents with demonstrated hypoglycemia potential (i.e. sulfonylureas) were used in combination with SGLT-2 inhibitors in significant point estimates reporting increased hypoglycemia risk.[40,56] Notably, over 75% of the included reviews were either of low or critically low quality. Although the AMSTAR 2 checklist primarily evaluates the rigour of a systematic review rather than the quality of the included randomized control trials or observational studies, there remains a need for greater consistency across systematic reviews.[15] This is relevant, as systematic reviews are often considered by policy-makers and clinicians as important tools to summarize all relevant primary literature on a topic of interest. In addition, systematic reviews of harms have inherent challenges due in part to the large variation in the number and type of potential adverse events. Studies also vary in the definition of adverse events, the method and time course of ascertainment of such events, as well as baseline event rates. Indeed, there is not a commonly accepted set of SGLT-2 inhibitor safety outcomes that systematic reviews evaluated. The sparse number of events is another challenge of evaluating harms using meta-analyses, as there may be zero events. Although there are various correction techniques to account for zero events, these are applied inconsistently among reviews. As a result of these challenges, there is a patchwork of important safety outcomes that require further research, such as DKA, orthostatic hypotension and diabetic foot infections. Indeed, sparse events precluded precise estimates for ketoacidosis (i.e. the largest review inclusive of DKA events reported only 56 DKA events in 30,766 individuals receiving canagliflozin, dapagliflozin or empagliflozin).[37]

Importantly, the findings from our review must be interpreted in light of its limitations. First, our study only reports on adverse events captured in published systematic reviews that conducted a meta-analysis. We also limited our study to reviews that aimed to capture adverse events and therefore did not include reviews that were designed to evaluate effectiveness and incidentally reported safety events. Nonetheless, our study included the use of a published protocol and comprehensive search strategy, as well as the use of the standardized AMSTAR 2 checklist to provide greater consistency and reproducibility in evaluating quantitative systematic review methodology.[15] Notably, AMSTAR does not allow assessment of bias of the studies which were included within each systematic review. Thus, our study captured the available evidence regarding adverse effects associated with SGLT-2 inhibitor use in patients with type 2 diabetes mellitus. This consists of both frequently explored side effects (e.g. hypoglycemia, genital tract infections) as well as those which may be less commonly characterized (e.g. amputations, adverse renal events, volume depletion). Second, we did not meta-analyze the point estimates extracted from the included studies as this was beyond the scope of this overview. Our review intentionally summarizes and assesses the quality of systematic reviews of SGLT-2 inhibitor adverse events. Third, we did not assess individual studies included within each review. It is likely that substantial overlap exists among the studies included among the included systematic reviews.[71] Studies published earlier in time (e.g. EMPA-REG OUTCOME in 2015) will likely be included in more systematic reviews in comparison to studies published at a later date (e.g. CREDENCE in 2019), and therefore aggregated several times in different meta-analyses conducted. This may lead to repeated reporting of data across systematic reviews; however, assessing bias and study overlap for all primary literature contained within each review was outside the scope of our study. Furthermore, the results of large randomized clinical trials (e.g. CANVAS program for canagliflozin, DECLARE-TIMI 58 for dapagliflozin)[63,72]

may have driven results of many of the included reviews. For example, 13 of 34 included meta-analyses examining empagliflozin are driven by the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial.[68] Fourth, given the many ongoing efforts to discern further the adverse effects of SGLT-2 inhibitors, it is likely that additional studies are currently underway or have yet to be published. A 'living systematic review', or a systematic review that is regularly updated in accordance with changes in current evidence, would be significant as there are a number of pre-existing systematic reviews that primarily focus on specific adverse effect outcomes.[73] Finally, the limitations inherent in systematic reviews of harms as described above must be considered when interpreting our findings.

Conclusion

We found a dearth of high-quality quantitative systematic reviews reporting on adverse events of SGLT-2 inhibitors. The only consistent adverse events reported across reviews were that commonly used SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) are associated with an increased risk of genital infections. Given the low methodological quality of included quantitative systematic reviews and the limitations of systematic reviews for quantifying associations of rare adverse events, definitive conclusions regarding adverse events are premature. Further research is required, including well designed observational studies to quantify the adverse events of SGLT-2 inhibitors.

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Author contributions

RP, KN and JMG conceptualized the review. RP and KN wrote the first draft of the manuscript, made suggested changes from co-authors, and formatted the paper for publication. All authors partook in the review selection and critical appraisal processes, as well as provided intellectual feedback on manuscript drafts. All authors approved the final draft of the manuscript prior to submission.

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Conflict of interest

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are available within the article and its supplementary materials, as well as upon reasonable request.

Code availability

Custom code used in this overview of reviews is available upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

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