Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Brief Report

Nephrolithiasis and sodium-glucose co-transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials

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ARTICLE INFO

Article history:
Received 10 May 2019
Received in revised form
17 July 2019
Accepted 5 August 2019
Available online 8 August 2019

Keywords:
SGLT-2 inhibitors
Meta-analysis
Hyperuricemia
Nephrolithiasis

ABSTRACT

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) decreased serum uric acid in type 2 diabetes. Hyperuricemia is associated with an increased risk of nephrolithiasis. The present meta-analysis, performed on trials with duration ≥52 weeks in comparison with placebo or active comparators, suggests no effects of SGLT-2i on the risk of nephrolithiasis.

1. Introduction

SGLT-2 inhibitors have been recently introduced in the treatment of type 2 diabetes as glucose-lowering agents. In patients with preserved renal function, they are able to reduce blood glucose and HbA1c without inducing hypoglycaemia, unless combined with insulin or sulfonylureas [1]. In addition, the use of SGLT-2 inhibitors is associated with weight loss and reduction of blood pressure [2]. SGLT-2 inhibitors have been reported to reduce cardiovascular morbidity and/or mortality in high-risk patients [3–5]. The main side effect of SGLT-2 inhibitors is an increase in the risk of genital infections [6]. A modestly increased risk of urinary tract infections has also been observed in clinical trials [7], together with relatively rare events of volume depletion [7].

Nephrolithiasis is a common clinical condition, with an estimated lifetime prevalence in the US of 11 and 7% in men and women, respectively [8]. Diabetes is associated with an increased risk of nephrolithiasis [8]. Mechanisms underlying this association include acidification of urines (which facilitates the precipitation of urates) and increased oxalate urinary concentrations [9,10].

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https://doi.org/10.1016/j.diabres.2019.107808
0168-8227/

In addition to reducing blood glucose levels, SGLT2 inhibitors decrease serum uric acid levels [6,11] in patients with type 2 diabetes, including those with baseline hyperuricemia [12]. The reduction of circulating levels of uric acids could theoretically prevent the development of kidney stones [13]. In addition, the increase of urinary volume, and the consequent dilution of other solutes different from glucose, could reduce the risk of precipitation [14].

Davies et al [15], in a post hoc analysis of pooled data from four placebo-controlled phase III studies, did not observe any effect of canagliflozin on the incidence of nephrolithiasis; however, the number of observed events and the duration of trials (26 weeks) were insufficient to draw reliable conclusions.

2. Materials and methods

This manuscript reports a post-hoc analysis performed as an addendum to a previous meta-analysis [16] on SGLT-2 inhibitors (PROSPERO CRD42019119767; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID = CRD42019119767). This meta-analysis is reported following the criteria of PRISMA statement [17].

Briefly, a Medline search for canagliflozin OR dapagliflozin OR empagliflozin OR ertugliflozin OR ipragliflozin OR luseogliflozin OR tofogliflozin was performed, collecting all randomized clinical trials on humans up to December 1st, 2018, whereas completed but yet unpublished trials were searched in the www.clinicaltrials.gov register. All trials with a duration of at least 52 weeks, enrolling patients with type 2 diabetes, comparing approved doses of SGLT-2 inhibitors with placebo or other active comparators, were included. The identification of relevant abstracts, the selection of studies, and extraction were performed independently by the two of the authors (I.D. and B.N.), and conflicts resolved by the third investigator (M.M.).

For all published trials, results reported in published papers were used as the primary source of information, whereas results of unpublished trials were retrieved, if available, on www.clinicaltrials.gov. The quality of trials was assessed using the parameters proposed by the Cochrane Collaboration.

The principal endpoint was the incidence of nephrolithiasis, as reported by investigators as serious adverse event. Secondary endpoints included renal colic, hydronephrosis, and urinary retention, reported as serious adverse events, as defined in Table 1S of Supplementary materials.

Mantel-Haenszel odds ratio with 95% Confidence Interval (MH-OR) was calculated for all outcomes defined above, on an intention-to-treat basis. Heterogeneity was assessed by using I^2 statistics. Even when low heterogeneity was detected, a random-effects model was applied as the primary analysis, because the validity of tests of heterogeneity can be limited with a small number of component studies. To estimate possible publication/disclosure bias a funnel plots was examined for nephrolithiasis. All analyses were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

3. Results

Fig. 1 of Supplementary materials reports the trial flow summary. A total of 27 trials fulfilling the inclusion criteria was identified (3–5, and 1S–24S of Supplementary references); the principal characteristics of the included trials is reported in Table S2 of Supplementary Materials.

No publication bias was detected at visual analysis of Funnel plot (Fig. S2 Supplementary Materials). The overall quality of trials was satisfactory for most of the items of the Cochrane tool (Fig. S3 of Supplementary Material).

All available trials reported a complete list of treatment-emergent serious adverse events. Sixteen trials reported at least one case of nephrolithiasis (62 in SGLT-2 inhibitors and 44 in control group). Cases of renal colic, hydronephrosis, and urinary retention were 7, 12, 24 in SGLT2 inhibitors group and 5, 4, 8 in control group, respectively.

No association of SGLT-2 inhibitors with nephrolithiasis was observed (MH-OR 0.85 [0.57–1.26]; Fig. 1). I^2 statistics did not suggest any relevant heterogeneity. In subgroup analyses, risk of nephrolithiasis was 1.04 [0.51–2.13], 0.70 [0.35–1.41], 0.82 [0.43–1.60], and 1.48 [0.06–36.34], all $p > 0.50$, for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, respectively. When comparing SGLT-2 inhibitors with different comparators, the risk of nephrolithiasis was 0.69 [0.17–2.79], 0.87 [0.57–1.33], and 1.17 [0.06–24.66] (all $p > 0.050$) versus insulin secretagogues, placebo, and metformin, respectively.

Similarly, non between-group difference was detected in the risk of renal colic (MH-OR 0.70 [0.24–2.01]), hydronephrosis (MH-OR 1.06 [0.41–2.72]), and urinary retention (MH-OR 1.29 [0.63–2.64]; Figs. S4–S6 of Supplementary Material).

4. Discussion

The present meta-analysis does not show any relevant effect of SGLT-2 inhibitors on nephrolithiasis and related endpoints. Some pathophysiological mechanisms suggested a possible protective effect [11–13]; in particular, the reduction of uric acid excretion determined by the decrease of uricemia, and the dilution of urines induced by increased urinary volume, could theoretically lead to a lower risk of nephrolithiasis. However, such benefit cannot be detected in clinical trials. On the other hand, SGLT-2 inhibitors do not appear to increase the risk of urolithiasis.

The main strength of data from randomized controlled trials is the fact that randomization prevents many possible biases. In addition, large-scale, relatively long-term randomized trials are available for SGLT-2 inhibitors. In particular, cardiovascular safety trials provide a remarkable number of person-years of observation. For this reason, the number of recorded cases is remarkable. On the other hand, the outcomes considered in the present analysis were not among pre-specified endpoints of included trials; it is possible that some of the events were not classified as serious adverse events, raising the possibility of under-reporting. Furthermore, patients enrolled in trials are not fully representative of subjects receiving a drug prescription in routine clinical

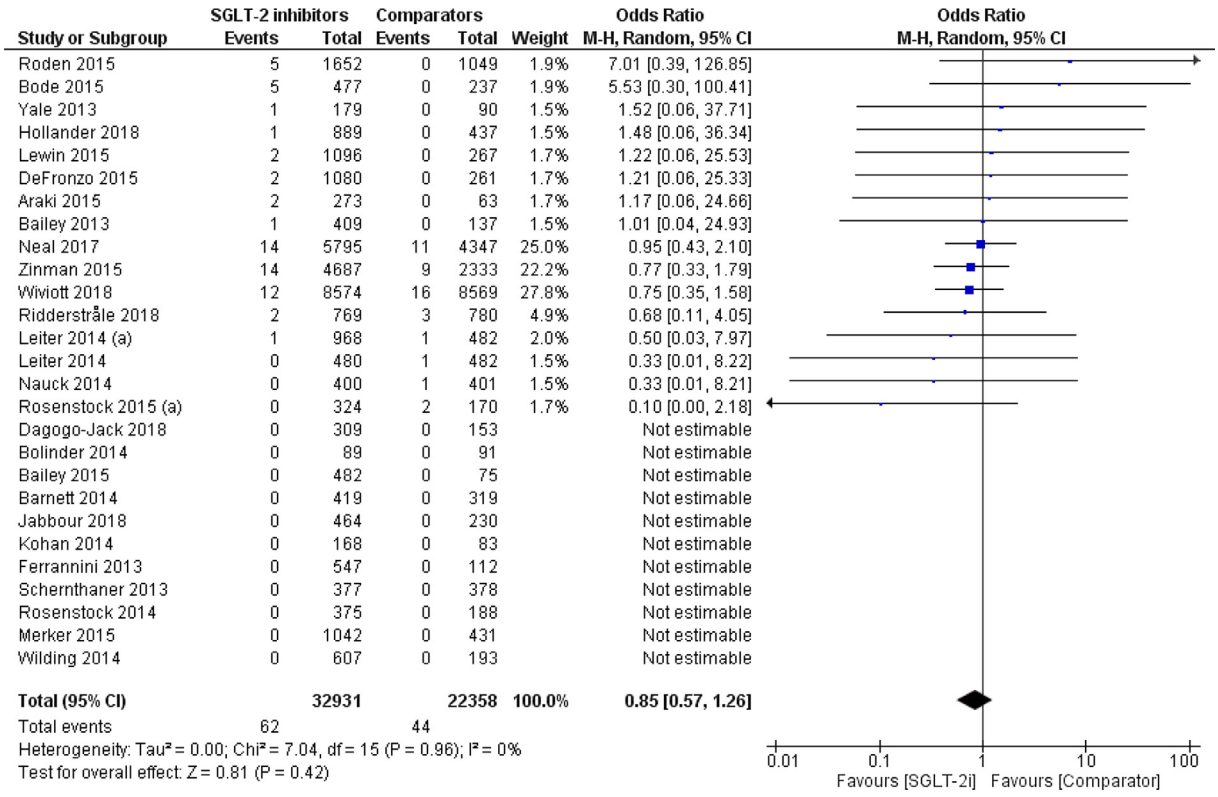

Fig. 1 – Risk of nephrolithiasis for SGLT-2 inhibitors versus different comparators (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

settings. In addition, minor differences in risk of nephrolithiasis between treatment groups may have been overlooked because of insufficient sample size. Large-scale retrospective observational studies could be a valuable source of additional information in this respect; however, it should be considered that events of nephrolithiasis, which do not lead to hospital admission in the majority of cases, can be difficult to capture in retrospective databases, with the risk of massive underreporting.

In conclusion, based on the results of available randomized controlled trials, treatment with SGLT-2 inhibitors appears to be neither beneficial nor detrimental with respect to nephrolithiasis. The possible effects of SGLT-2 inhibitors on urinary concentrations and solubility of urate and oxalate are not sufficient to determine relevant differences in clinical outcomes.

Acknowledgements

This research was performed independently of any funding as part of the institutional activity of the investigators.

Research involving Human Participants and/or Animals and Informed consent

For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

Claudia Cosentino has no conflicts of interest.

Ilaria Dicembrini has received speaking fees from Novonordisk.

Besmir Nreu is presently employee of Novo Nordisk.

Edoardo Mannucci has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Merck, Novartis, and Takeda.

Matteo Monami has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Bristol Myers Squibb.

All the authors approved the final version of this manuscript. Dr. Matteo Monami is the person who takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Contributor statements

Matteo Monami and Edoardo Mannucci were involved in each of the following points:

1. Design.
2. Data Collection.

3. Analysis.
4. Writing manuscript.

Ilaria Dicembrini, Claudia Cosentino, Besmir Nreu, were involved in each of the following points:

1. Data Collection.
2. Manuscript revision.

All the authors approved the final version of this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107808.

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