Assessing the risk of ketoacidosis due to sodium-glucose cotransporter (SGLT)-2 inhibitors in patients with type 1 diabetes: A meta-analysis and meta-regression

Assessing the risk of ketoacidosis due to Sodium-Glucose Co transporter (SGLT)-2 inhibitors in patients with Type 1 diabetes: a meta-analysis and meta-regression

RUNNING TITLE: predictors of SGLT-2 inhibitor-associated ketoacidosis in type 1 diabetes

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Abstract

Background. Sodium-Glucose Cotrransporter-2 (SGLT2) inhibitors (SGLT2i) showed benefits in type 1 diabetes mellitus (T1DM), but the risk of diabetic ketoacidosis (DKA) limits their use. Ability to predict DKA risk and therapeutic responses would enable appropriate patient selection for SGLT2i. We conducted a meta-analysis and meta-regression of randomized controlled trials (RCTs) evaluating SGLT2i in T1DM to assess moderators of the relative risk (RR) of DKA, of glycemic (HbA1c, fasting plasma glucose, continuous glucose monitoring parameters, insulin dose, insulin sensitivity indices) and nonglycemic (BMI, systolic BP, renal function, albuminuria, diabetic eye disorders) efficacy and of other safety outcomes (including hypoglycemia, infections, major adverse cardiovascular events, and death).

Methods and Findings. We searched MEDLINE, Cochrane Library, EMBASE, ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials;, WHO International Clinical Trials Registry Platform, European Union Clinical Trials Register, International Standard Randomised Controlled Trial Number (ISRCTN) registry, other electronic sources through Aug 30th, 2020, for RCTs comparing SGLT2i with active comparators or placebo in adult patients with T1DM.

Reviewers extracted data for relevant outcomes, performed random effects meta-analyses, subgroup analyses, and multivariable meta-regression. The strength of evidence was summarized using the GRADE approach.

Among 9914 records identified, 18 placebo-controlled RCTs (7396 participants, 50% males, mean age 42 yrs (range 23-55 yrs), 5 different SGLT2i evaluated), were included.

Main outcome measures were effect sizes and moderators of glycemic and non-glycemic efficacy and of safety outcomes**.**

In a multivariable meta-regression model, baseline BMI (β=0.439[95%CI: 0.211,0.666], p<0.001) and estimated Glucose Disposal Rate (eGDR) (β=-0.766[-1.276,-0.256], p=0.001) were associated with the

relative risk of DKA (RR: 2.81; 95%CI:1.97,4.01; p<0.001, R^2=61%). A model including also treatment-related parameters (insulin dose change-to-baseline insulin sensitivity ratio and volume depletion) explained 86% of variance across studies in the risk of DKA (R^2=86%).

The association of DKA with a BMI>27 kg/m^2 and with an eGDR<8.3 mg/kg/min was confirmed also in subgroup analyses.

Among efficacy outcomes, the novel findings were a reduction in albuminuria (WMD: -9.91, 95% CI: -16.26, -3.55 mg/g, p=0.002), and in relative risk of diabetic eye disorders (RR: 0.27[0.11, 0.67], p=0.005) associated with SGLT2i.

A SGLT2i dose-response gradient was consistently observed for main efficacy outcomes, but not for adverse events(AEs).

Overall, predictors of DKA and of other AEs differed substantially from those of glycemic and non-glycemic efficacy.

A limitation of our analysis was the relatively short (≤52 weeks) duration of included RCTs. The potential relevance for clinical practice needs also to be confirmed by real-world prospective studies

Conclusions. In T1DM, the risk of DKA and main therapeutic responses to SGLT2i are modified by baseline BMI and insulin resistance, total insulin dose reduction-to-baseline insulin sensitivity ratio and by volume depletion, which may enable the targeted use of these drugs in patients with the greatest benefit and the lowest risk of DKA.

Author Summary

Why Was This Study Done?

- Sodium-glucose Cotransporter-2 inhibitors (SGLT2i) are recommended for type 2 diabetes for their substantial glycemic and non-glycemic benefits.
- In type 1 diabetes (T1DM) their use is significantly limited by the increased risk of diabetic ketoacidosis (DKA), a serious adverse event (AE).
- Currently, there are no data on factors predicting the risk of DKA and therapeutic response to SGLT2i in T1DM.
- Knowing predictors of the risk of DKA and of therapeutic response would enable T1DM patient selection with the highest benefit-to-risk ratio from SGLT2i treatment.

What Did the Researchers Do and Find?

- We explored moderators of the risk of DKA and of main efficacy and safety outcomes associated with SGLT2i treatment in a meta-analysis and multiple meta-regression of 18 randomized trials enrolling 7396 T1DM patients treated with SGLT2i or placebo.
- In a multivariate meta-regression model, the risk of SGLT2i-associated DKA was largely explained by four independent parameters: BMI>27 kg/m^2, an estimated Glucose Disposal Rate (eGDR)<8.3 mg/kg/min, indicative of insulin resistance, a higher total insulin dose reduction-to-baseline insulin sensitivity ratio, and dehydration.
- The factors associated with therapeutic effectiveness differed substantially from risk factors of DKA and of other AEs.
- a dose-response relationship with increasing SGLT2i doses was observed for main efficacy outcomes, but not for the risk of DKA and for other adverse events.

What Do These Findings Mean?

- in T1DM, the risk of DKA risk and therapeutic responses SGLT2i treatment are predictable using clinically available parameters.
- Predictors of the risk of DKA and other adverse events radically differ from those of therapeutic effectiveness.
- If confirmed by real-world prospective studies , the results of our analysis may enable the targeted use of SGLT2i in patients with T1DM who have the greatest benefit and the lowest risk of DKA from the use of these drugs.

.**KEY-WORDS:** sodium glucose co-transport-2 (SGLT2) inhibitors, diabetes treatment, SGLT, DKA

ABBREVIATIONS

ADA: American Diabetes Association; BP: blood pressure; DKA: diabetic ketoacidosis; EASD: European Association for the Study of Diabetes; EOT: end of treatment; FPG: fasting plasma glucose; LDL: low density lipoprotein; HDL: high density lipoprotein; GTI: genital tract infection. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; SGLT: sodium glucose co-transporter; T1D: type 1 diabetes mellitus; TID: daily total insulin dose; UTI: urinary tract infection; WMD: weighted mean difference

Introduction

The prevalence of type 1 diabetes mellitus (T1DM) is rising at a yearly rate of ~3% [1,2]. Patients with T1DM achieve glycemic targets in only 30% of cases and are encumbered by the unwanted effects of insulin therapy [3]. Hence, several adjunctive therapies to insulin have been proposed to satisfy the largely unmet medical need of this patient population. Sodium-glucose Cotransporter-2 (SGLT2) inhibitors (SGLT2i) block the SGLT-2 transporter in the proximal renal tubule, resulting in glycosuria and natriuresis [4]. SGLT2i are now recommended for patients with Type 2 diabetes (T2DM) and showed glycaemic and non-glycaemic benefits in T1DM as well, including improved glycemic control and glycemic variability, decreased insulin dose requirement, blood pressure and body weight reduction [5,6].

In T1DM, however, SGTL2i treatment has to be weighed against an increased risk of diabetic ketoacidosis (DKA)[7,8], a serious, life-threatening adverse event (AE), which dominates the safety profile of these drugs. The risk of DKA varies widely across different randomized controlled trials (RCTs) and factors underlying such variation in DKA risk are unknown.

This uncertainty is reflected by the diverse positions of drug regulatory agencies, with the same SGLT2i being either approved an adjunct to insulin in patients with T1DM inadequate glycaemic control [9,10], or approved with restriction to patients with a body mass index (BMI)$\geq$27 kg/m^2 [11,12,13] despite the lack of data regarding the risk of DKA in overweight individuals, or rejected because of the risk of DKA deemed excessively high [14,15]. An evidence-based precision medicine tool to stratify T1DM patients for individual benefit-risk ratio of SGLT2i use is unavailable, as is a systematic review of the evidence to assess predictors of the risk of DKA, which could enable a safer use of these drugs in T1DM [16,17,18].

We conducted a meta-analysis and meta-regression of randomized controlled trials (RCTs) in T1DM to explore factors associated with the risk of DKA and with other efficacy and safety outcomes in adults treated with SGLT2i.

Methods

Data Sources and Searches

We searched English and non-English language publications through Aug 30th, 2020 on the following databases and clinical trial registries: Ovid MEDLINE, Ovid MEDLINE Epub Ahead of Print, Ovid MEDLINE In-Process, EMBASE, Cochrane Database of Systematic Reviews, Epistemonikos, ClinicalTrials.gov, Cochrane CENTRAL Register of Controlled Trials;, World Health Organization International Clinical Trials Registry Platform, European Union (EU) Clinical Trials Register, International Standard Randomized Controlled Trial Number (ISRCTN) registry, Australian New Zealand Clinical Trials Registry, and additional national clinical trial registries (full list in **S1 text**). No language restrictions were applied. We also searched drug regulatory agencies' and drug manufacturers' websites for relevant documents, and the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) meeting abstracts, which were subjected to the same assessment as regular articles [19,20,21].

We contacted authors of relevant papers by e-mail to verify results and methodological quality of retrieved articles and drug manufacturers to inquire about further published and unpublished trials. Additionally, we manually scanned reference lists from trials, review articles and reports to identify any other relevant data.

Search terms and search strategies

The search terms and examples of search strategies are provided in **S1 text**.

Study Selection

Inclusion criteria: English and non-English articles reporting RCTs with participants aged>18 yrs, of any sex or ethnic origin, comparing SGLT2i with placebo or active comparators as adjunct therapy to insulin in T1DM.

Exclusion criteria were: non-human studies, non-controlled or non-randomized trials, letters/case reports, articles not reporting outcomes of interest or primary data (editorials, reviews).

Outcomes

Primary outcome : we were primarily interested in exploring the association between the RR of definite DKA (see **S1 text**) [18,22] and different study-level moderators. To this aim, we performed a meta-analysis followed by univariable and multivariable meta-regression.

We conducted the same analyses for secondary outcomes, which were grouped into three broad sets (glycemic efficacy, non-glycemic efficacy, and safety outcomes other than DKA) and are tabulated in **Table 1** and detailed in **S1 text** [23**,**24,25,26,27,28,29,30].

Data extraction and Risk-of-Bias assessment. Two reviewers (GM, RG) extracted data independently and in duplicate by using a predefined electronic data collection form, based on the Cochrane Handbook for Systematic Reviews of Intervention; discrepancies were arbitrated by a third reviewer and resolved by]consensus. The agreement between the 2 reviewers for selection and validity assessment of trials was scored by Kappa coefficient.

The quality of RCTs was assessed by the Cochrane Collaboration Risk-of-Bias (RoB) Tool [31]. Sponsorship bias was also included in the RoB tool. The 2018 Agency for Healthcare Research and Quality (AHRQ) recommendations caution against equating industry sponsorship with high risk of bias and automatically downgrading the evidence for industry sponsorship [32]. Therefore, for all included trials we systematically assessed a pre-specified list of eight items in trial designing, conducting and reporting, which have been empirically linked to the risk of biased outcomes in industry-funded trials and are not captured by the six domains of the RoB tool[33,34,35,36,37,38,39]**(S2 Table 1).**

Different doses of SGLT2 inhibitors were classified into high-, moderate or low-dose subgroups based on the potency of the drugs and the dose categorization adopted in clinical trials [4] (**S1 text).**

When trials evaluated different SGLT2i doses, we presented data separately for each dose arm and split sample size of the placebo group evenly among different dose comparisons (Cochrane Handbook for Systematic Reviews of Intervention, chapter. 7.6-7.8 and 16.1.3). For the same RCT reported by several publications on different follow-up periods, the longest follow-up period was assessed.

Publication bias was examined using funnel plots and the Egger test.

Data Synthesis, Analysis. The analysis was carried out in concordance with the Cochrane Handbook of Systematic Reviews of Interventions [31] using RevMan Version 5.3.5 (Nordic Cochrane Center, Copenhagen, Denmark)[40] and Stata, release 11.2 (StataCorp, College Station, Texas) and was reported according to PRISMA guidelines [41]. Treatments were evaluated on an intention-to-treat principle.

We calculated weighted mean differences (WMDs) and 95% CIs for continuous outcomes using an inverse variance random-effects model. For dichotomous outcomes, we calculated Risk Ratios (RRs) and 95% CIs by using the random-effects Mantel–Haenszel approach with significance set at P=0.05. We conservatively used a random-effects model assuming a substantial variability in treatment effect size across studies.

Statistical heterogeneity was quantified using the I^2 statistic with values of 25%, 50%, and 75% consistent with low, moderate, and high degrees of heterogeneity, respectively [42]: with I^2 values ≥50%, we planned to explore individual study characteristics and those of subgroups of the main body of evidence.

Subgroup analyses

We also planned *a priori* subgroup analysis to explore potential effects on outcome measures of the following conditions:

-duration of diabetes (< 20 vs. ≥ 20 yr);

-baseline HbA1c levels (>8% vs. ≤ 8%);

-baseline BMI (>27 vs. ≤27 kg/m^2);

-baseline insulin resistance, defined by an estimated Glucose Disposal rate (eGDR)<8.3 vs. ≥8.3 mg/kg/min) [25];

-renal function stage: inclusion or exclusion of patients with impaired renal function (estimated Glomerular Filtration rate, eGFR <60 ml/min/1.73 m^2);

-study duration: <24 vs. ≥24 weeks;

-background therapy (pre-treatment insulin optimization vs. stable insulin therapy);

-additionally, we planned to explore potential differences among individual SGLT2 inhibitors by conducting separate analyses for each drug when sufficient data were available.

Dose-response analysis

We explored interactions between different SGLT2i doses and all outcomes primarily by comparing different dose groups within head-to-head trials, as the within-trial approach has a lower risk of ecological bias than the across-trial approach [43]; we verified robustness of this approach in ruling out dose-response relationship by using also an across-trial comparison and meta-regression. The "across-trial" approach has a higher risk of ecological bias but a higher power than the within-trial approach, thus allowing ruling out dose-response interactions with higher confidence.

Grading of Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the strength of evidence at outcome level and determine confidence in summary estimates for clinically relevant comparisons and outcomes [44]. Three reviewers graded inconsistency, risk-of-bias, indirectness, imprecision, and publication bias for evidence related to seven efficacy outcomes (HbA1c, time-in-range, eGDR, BMI, sysBP, eGFR, albuminuria) and seven safety outcomes [DKA, severe hypoglycemia, urinary tract infections (UTIs), genital tract infections (GTIs), eye disorders, volume depletion, major dverse cardiovascular events (MACE)].

Meta-Regression Analyses

When ≥8 comparisons were available (Cochrane Handbook of Systematic Reviews of Intervention (chapter 9.6.4), the effect of different study level moderators on each outcome were assessed by meta-regression analysis (random effects model, within-study variance estimated with the restricted maximum-likelihood method, Knapp-Hartung adjustment applied to compute SEs of the estimated coefficients to calculate summary effect estimates [45,46]. We specified *a priori* study level moderators based on existing literature and explored novel factors based on known pathophysiological data [16,17,18].

In meta-regression of the primary outcome (DKA) we classified moderators into baseline risk factors (to identify baseline risk factors for subsequent DKA) and treatment-related risk factors (to assess the moderating effects of treatment-related changes in different parameters on the risk of DKA), although overlaps were expected.

Baseline risk factors of incident DKA

Baseline risk factors included patient-related factors [age, gender, ethnicity (% Caucasian/Asian/Hispanic/Black vs other ethnicities), continuous subcutaneous infusion (CSI) users(%),Total Insulin Dose (TID)(IU/d), diabetes duration, BMI, HbA1c, fasting plasma glucose (FPG), eGDR, renal function stage, fasting blood β-hydroxybutyrate (BHB) level], and study design-related factors [study duration, study sample size, SGLT2i dose, SGLT2i drug, pre-randomization insulin optimization vs no optimization, Risk-of-Bias (high/unclear vs low)].

Treatment-related risk factors of DKA were: first, parameters regarding insulin dose adjustment, as excessive insulin dose reduction is a key contributor to DKA, but the exact extent of insulin dose down-titration increasing the risk of DKA is unclear. We evaluated the association of the risk of DKA with the following parameters: total/basal/bolus ID changes (% initial ID), ratio of changes in TID to baseline BMI (d-TID/BMI) or to baseline Relative Insulin Sensitivity (RIS) (d-TID/baseline RIS). We hypothesized that, rather than the absolute insulin dose reduction, the risk of DKA could depend on the extent of TID reduction relative to initial insulin resistance: the impact of a given insulin dose down-

titration on ketogenesis would be expected to be larger in the presence of higher baseline insulin resistance, which would enhance unrestricted lipolysis of free fatty acids (FFAs) from adipose tissue to the liver to fuel ketogenesis. This effect could be captured by the ratio of TID reduction to baseline RIS or BMI better than by % reduction in initial insulin dose. Second, residual insulin-SGLT2 inhibitor (INS-SGLT2i) effect, defined as the difference between the observed TID reduction and the predicted TID reduction (expressed as % of baseline TID) calculated from the 24-hour urinary glucose excretion (see **S1 tex**t) [47]. Third, changes in the following parameters: BMI (%), HbA1c (%), FPG (mg/dL), insulin sensitivity (eGDR, RIS change), fasting blood BHB level, eGFR changes, volume depletion events, UTIs, GTIs, respiratory infections.

Categorical variables were included in the model by means of dummy variables. SGLT2i dose variable in the regression equation was treated categorically, with the lowest dose coded as the baseline amount and moderate and high doses with a single increment increase.

Due to the considerable number of covariates, permutation test (using 1000 reallocations) was used for assessing the true statistical significance of an observed meta-regression finding [48]. Moderators that were significant at univariable analyses were included in a multivariable meta-regression model. To measure the strength of a moderator we compared the meta-regression models with the meta-analysis without covariates and estimated the percentage of heterogeneity explained by a moderator. The index R^2 value (defined as the ratio of explained to total variance) was used to determine the proportion of variance accounted for by different moderators.

We tested 3 different meta-regression models: model 1 (including baseline predictors that were significantly associated with the risk of DKA at univariable analysis), which identifies moderators of the risk of subsequent development of SGLT2i-associated DKA; model 2 (including treatment-related factors associated with DKA at univariable analysis), which identifies moderators of the risk of DKA during SGLT2i treatment; model 3 (including both baseline and treatment-related moderators of the risk of DKA), which accounts for interactions between baseline and treatment-related moderators and provide an overall ability to predict the across study variance in the RR of DKA.

We planned to conduct the same meta-regression analyses for other outcomes (HbA1c, BMI, systolic BP, eGFR, ACR, diabetic eye disorders, severe hypoglycemia, UTI, GTI, volume depletion) to obtain a thorough profile of moderators of SGLT2i efficacy and safety in T1DM.

Sensitivity analyses

We planned to verify consistency and robustness of our findings by repeating the meta-analysis and meta-regression with alternative effect measures (odds ratio vs. relative risk), pooling methods (Peto's method vs. Mantel-Hanszel, as Peto's OR is less biased and most powerful at event rates below 1%) [49], statistical models (fixed vs. random effects), by excluding RCTs where we imputed values and RCTs at high risk of bias in any domains of the RoB tool.

We also re-ran Model 1 and Model 2 as fully-adjusted multivariable models, including all candidate moderators, with the upper limit number of moderators for each model set at n/2 (where n is the number of observations), with statistical significance set at 0.15 to select variables from Model 1 and 2 to be included in Model 3 [50,51].

Finally, a leave-one-out sensitivity analysis was also performed by repeating the meta-analysis and meta-regression, each time with 1 of the included studies omitted, to see whether any one study had a disproportionately large influence on the effect estimates.

Management of missing data.

We planned to manage missing data by contacting via e-mail the corresponding authors. Where this was unsuccessful, we planned to follow the approach described in Cochrane Handbook of Systematic Reviews of Intervention (chapter 7.6-7.8 and 16.1.3) [31] (**S1 text**).

The protocol of the meta-analysis was submitted as a module assignment for the Systematic Review module and internally peer-reviewed at HUMANITAS University Gradenigo Hospital Institutional Review Board and is available at our Institution at request (e-mail: direzione.sanitaria@gradenigo.it).

The protocol of the meta-analysis was registered at the Joanna Briggs Institute (JBI) SYSTEMATIC REVIEW PUBLIC REGISTER (registration number: 2020-04-17).

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Ethical approval: The protocol of the meta-analysis was internally peer reviewed at Humanitas University Gradenigo Hospital's institutional review board and approved on Jan 20th, 2020. The entire protocol is available at our institution at request to the corresponding author.

Data sharing: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request

Results

The flow of study selection is reported in **Figure 1**. At the end of selection, 24 records describing 18 placebo-controlled RCTs [7396 participants, 50% males, mean age 42 yrs (range 23-55 yrs) mean duration 19 weeks (range 1-52 weeks)] were included in the meta-analysis. Five RCTs evaluated dapagliflozin [52,53,54,55,56,57,58], 2 RCTs evaluated ipragliflozin [59, 60], 1 RCT evaluated canagliflozin [61,62,63], 4 RCTs evaluated empagliflozin [64,65,66,67], 6 RCTs evaluated sotagliflozin [68,69,70,71,72,73,74,75] (main trial characteristics reported in **S2 Table 1A**).

No ongoing or planned RCTs with SGLT2i in T1DM were detected.

All included RCTs compared SGLT2i with placebo on background insulin treatment.

13 RCTs (5673 participants) compared different SGLT2i doses with placebo. Overall, 38 comparisons were available for the meta-analysis.

Eight RCTs adopted insulin dose optimization prior to randomization [57,58,61,66,67,73,74].

Eleven RCTs excluded patients with impaired renal function (eGFR<60 ml/min/1.73 m^2) [52,54,57,58,59,60,61,64,67,68,72], seven RCTs excluded patients with severe (stage 4: eGFR<30 ml/min/1.73 m^2) renal impairment [55,66,70,73,74,75].

Overall, the quality of included RCTs was good. One RCT [54] had high risk-of-bias in four domains and another RCT had a high risk of sponsorship bias [67] (**S2 Table 1B).**

The median (range) diabetes duration of participants was 19.4 yrs (11-25 yrs).

Participants' baseline characteristics were equally balanced between the study arms and in all RCTs dropout rates were generally low and balanced across arms. No trial used the last-observation-carried-forward (LOCF) approach to impute missing observations, which were imputed as nonresponse for dichotomous outcomes; for continuous outcomes, mixed-effects model for repeated measures (MMRM) statistics based on the restricted maximum likelihood method for estimation was used.

The risk of bias summary for individual RCTs and the risk of bias graph for each item across included RCTs are detailed in **S1 Table 1B** and summarized in **S3 Figure 1-2.**

The analysis of Funnel plots and the Egger test ($p>0.59$ for all outcomes) did not find any evidence of small-study effects **(S3 Figure 3A-Q).**

No values had to be imputed for the meta-analysis during data extraction.

The agreement between the 2 reviewers for study selection was 0.91 and for quality assessment of trials was 0.90.

Diabetic ketoacidosis (DKA)

The definition of DKA was consistent across all RCTs. Compared with placebo, SGLT2i were associated with an increased risk of DKA (RR 2.81, 95%CI: 1.97-4.01, $p<0.001$; N comparisons=38, I^2=0%, 7396 participants, trial duration ranging 1-52 weeks) **(Figure 2A).** Individual effect estimates varied widely (range 0.34 to 11.81), confirming that I^2 statistics has low power to detect heterogeneity in the presence of rare events and wide 95%CI and the appropriateness of meta-regression analysis [45].

Subgroup analysis revealed the risk of DKA was increased in RCTs with a mean baseline BMI>27 kg/m^2, and with a mean baseline eGDR<8.3 mg/kg/min, indicative of insulin resistance, but not in RCTs with a mean baseline BMI≤27 kg/m2 or a baseline eGDR≥8.3 mg/kg/min (**S2 Table 2**).

In univariable analysis, four baseline parameters [BMI, HbA1c, eGDR, total insulin dose (TID)] and 5 treatment-related parameters [change in BMI, eGDR, and RIS, change in ratio of TID-to-baseline RIS and volume depletion events] were associated with the risk of DKA (**Figure 3; S2 Table 3**).

In a multivariable meta-regression model including only baseline parameters (Model 1), BMI and eGDR independently predicted incident DKA, explaining 61% of between-study variance in the RR of DKA(R^2=61%, **Table 2**).

In a multivariable model including only treatment-related parameters (Model 2), the change in TID (%)-to-baseline RIS ratio and volume depletion events were independently associated with between-study variance in the RR of DKA (R^2=39%, **Table 2**).

In a multivariable model (Model 3) including all (baseline and treatment-related) parameters associated with DKA at univariable analysis, four parameters [baseline BMI and eGDR, TID change (%)-to-baseline RIS ratio and volume depletion events] were independently associated with between-study variance in the RR of DKA (R^2=86%) (**Table 2**).

Glycaemic efficacy outcomes

HbA1c

Compared with placebo, SGLT2i treatment was associated with a reduction in HbA1c (WMD -0.37%, 95%CI: -0.41 to -0.33%, p<0.001, I^2=4%, N-comparisons=29, 7243 participants) (**Figure 2B**). Subgroup and univariable meta-regression analyses revealed that HbA1c change was associated with SGLT2i dose, pre-randomization insulin optimization and eGDR change, but not with baseline BMI or HbA1c or with treatment duration (**S2 Table 2, S2 Table 4**). In a multivariable meta-regression model including baseline and treatment-related factors, only SGLT2i dose predicted HbA1c changes (R^2=68%) (**Table 2**).

Other glycaemic efficacy outcomes

The results of meta-analysis for other glycaemic efficacy outcomes are reported in **Table 3** and in **S3 Figure 4-6: c**ompared with placebo, SGLT2i increased UGE (g/d) improved fasting plasma glucose

(FPG, mg/dL), CGM parameters time-in-range (%) and MAGE (mg/dL), daily total/basal/bolus insulin dose and insulin sensitivity indices.

Non-glycaemic outcomes

The results of meta-analysis for non-glycaemic efficacy outcomes are reported in **Table 3.**

BMI

Compared with placebo, SGLT2 inhibitors reduced BMI (WMD -3.20%, 95%CI : -3.54 to -2.86%, p<0.001, I^2=47%, N-comparisons=39, 7396 participants) (**Table 3, S3 Figure 7A**).

Subgroup and univariable meta-regression analysis revealed that BMI change was associated with four baseline moderators (TID, BMI, eGDR, and SGLT2i dose) and with two treatment-related moderators (eGDR change and DKA) (**S2 Table 2**, **S2 Table 5**).

In a multivariable meta-regression model including baseline and treatment-related factors (Model 3), SGLT2i dose and eGDR change were independently associated with BMI changes (R^2=63%)(**Table 2**).

Systolic Blood pressure (sysBP)

Compared with placebo, SGLT2 inhibitors reduced sysBP (WMD -3.81 mmHg, 95%CI: -4.49 to -3.12, p<0.001, I^2=0%, N-comparisons=39, 7396 participants) **(Table 3, S3 Figure 7B**).

At univariable meta-regression, baseline sysBP and SGLT2i dose were associated with sysBP changes (**S2 Table 6**). In a multivariable meta-regression model (Model 3) only SGLT2i dose was associated with sysBP changes (R^2=62%) (**Table 2**).

Renal effects: eGFR and urinary ACR

Compared with placebo, SGLT2i were associated with a slight reduction in eGFR (WMD: -0.78, 95% CI: -1.29 to -0.26 ml/min/1.73 m^2, p=0.003, I^2=0%, N comparisons=39, 7396 participants) (**Table 3, S3 Figure 8A**). Subgroup analysis revealed that the eGFR reduction was observed only in RCTs lasting <24 weeks, but not in RCTs of longer duration (**S2 Table 2**). Univariable and multivariable meta-regression analysis confirmed study duration was the only moderator of eGFR changes (**S2 Table 7, Table 2**).

Urinary ACR was evaluated in 4 RCTs (trial duration ranging 4-52 weeks, mean baseline ACR in the microalbuminuric range). Pooled analysis of these RCTs showed SGLT2i treatment decreased ACR (WMD: -9.91, 95% CI : -16.26 to -3.55 mg/g, p=0.002, I_2=0%, N comparisons=8, 3052 participants **(Table 3, S3 Figure 8B).**

On meta-regression analysis, SGLT2i dose and MAGE were independently associated with ACR change **(Table 2, S2 Table 8).**

Diabetic eye disorders

In the pooled dataset, 14 cases of diabetic eye disorders occurred: 11 incident cases of haemorragic retinopathy, 1 case of macular oedema, 1 case of glaucoma and 1 case of vision loss).

Compared with placebo, SGLT2i were associated with a 73% lower risk of eye-related disorders (RR 0.27, 95%CI: 0.11-0.67, p=0.005; I^2=0%, N comparisons=39, 7396 participants) **(S3 Figure 9F).**

The effect was accounted for by a lower incidence of haemorragic retinopathy (RR 0.27, 95%CI: 0.10-0.72, p=0.009; N comparisons=38, I^2=0%, 7396 participants). Subgroup analysis revelated the effect was statistically significant only in RCTs of duration ≥24 weeks (S2 **Table 2**).

On meta-regression analysis, changes in time-in-range(%) were independent risk factors for diabetic eye disorders (**Table 2, S2 Table 9).**

Safety outcomes other than DKA

The effect of SGLT2 inhibitors on all AEs is summarized in **S2 Table 10.**

The definition of hypoglycemia and severe hypoglycemia was consistent across all RCTs. Compared with placebo, SGLT2i did not affect the risk of hypoglycemia, severe hypoglycemia, UTIs, MACE, cancer, all-cause death (**S3 Figure 9A-C, S3 Figure 9G**).

Compared with placebo, SGLT2i increased the risk of GTIs (RR 3.18, 95%CI: 2.49-4.06, p<0.001; I^2=0%, N-comparisons=39, 7396 participants)(**S3 Figure 9D).**

In a multivariable meta-regression model, the risk of GTI was independently associated with baseline TID and by changes in FPG(**Table 2, S2 Table 11**).

SGLT2i treatment was also associated with an increased risk of volume depletion events (RR: 1.53, 95%CI: 1.03-2.28, p=0.03; I^2=0%, N comparisons=39, 7396 participants) **(S3 Figure 9E).**

Subgroup analysis revealed the risk of volume depletion increased in RCTs with a mean baseline eGDR<8.3 mg/kg/min, indicative of insulin resistance, but not in RCTs with a mean baseline eGDR≥8.3 mg/kg/min(**S2 Table 2**).

On meta-regression analysis, baseline eGDR and changes in eGDR were independently associated with RR of volume depletion events (**Table 2, S2 Table 12).**

Dose-response analysis

We analysed dose-response interactions within the 13 RCTs (5673 participants) that evaluated different SGLT2i doses: a significant dose-response gradient for low doses vs. moderate doses vs. high doses was noted for HbA1c (%), FPG (mg/dL), time-in-range (%), total/basal/bolus insulin dose (%), eGDR (%), RIS, BMI (%), sysBP (mmHg), urinary ACR (mg/g) (**Table 4**).

We didn't find any relationship between different SGLT2i doses and AEs. The results of the within-trial comparison were all confirmed by the across-trial approach.

Analysis of individual SGLT2i

We noted no clear evidence that individual drugs had different effects on DKA and on other efficacy and safety outcomes (all I^2≤20%). However, sotagliflozin slightly reduced the risk of severe hypoglycaemia, as previously reported [13] (**S2 Table 13**).

Sensitivity analyses

Sensitivity analysis conducted by excluding RCTs at high risk of bias in any domain, by repeating meta-analysis and meta-regression using alternative effect measures, pooling methods, statistical models, by using one-step fully adjusted multivariable models and leave-one-out meta-analysis, confirmed robustness of the main analysis (**S2 Table 14-16, S3 Figure 10).**

Grading of Evidence

Quality of evidence was downgraded to moderate for MACE for imprecision (**S2 Table 17**).

Discussion

The main findings of our meta-analysis and meta-regression of RCTs evaluating SGLT2i in T1DM are the following: first, in multivariable meta-regression, baseline BMI and insulin resistance were independently associated with the risk of DKA, explaining 61% of variance across studies in the RR of DKA. A model including two additional parameters (ratio of TID change-to-insulin sensitivity and volume depletion) explained 86% of variance in DKA risk. These findings were confirmed by results of subgroups analysis.

Second, moderators of DKA risk differed substantially from those of efficacy outcomes, indicating a selection of T1DM patients with the highest benefit/risk ratio with SGLT2i is feasible.

Third, a consistent dose-response gradient with increasing SGLT2i doses was observed for major efficacy outcomes, but not for DKA and other AEs.

Fourth, among non-glycaemic benefits, we disclosed signals for renal and eye protection associated with SGLT2i treatment.

Patients with T1DM need adjunctive therapies to improve glycaemic control and mitigate unwanted effects of insulin [1,2,3]. SGLT2i confer extensive glycaemic and nonglycaemic benefits, which however must be weighed against the risk of DKA in T1DM.

To date, there is no evidence-based precision medicine strategy to predict SGLT2i-associated therapeutic responses to SGLT2i, minimize DKA risk and help select patients with the greatest benefit-to-risk ratio from these drugs. We therefore performed meta-analysis and multivariable meta-regression to disclose independent study-level moderators of risk of DKA and of main efficacy and safety outcomes in patients with T1DM treated with SGLT2i.

We found that four independent study-level moderators explained 86% of the variance among studies in DKA risk (**Table 2**).

The two baseline moderators, BMI and eGDR, together explained 61% of the across-study variance in DKA risk (**Table 2**): patients with overweight and with insulin resistance may be at increased risk of DKA because they are more prone to unrestricted FFA lipolysis from their increased triglyceride stores during the negative glucose balance and insulin dose down-titration induced by SGLT2i [76]. Notably, the analysis of the regression plot (**Figure 2A**) indicates that the DKA risk starts to increase with BMI≥ 27.00 kg/m^2, which coincides with the cut-off of approval for SGLT2i in Europe [11,12].

The two independent treatment-related moderators were the ratio of TID reduction (%)-to-baseline insulin sensitivity and volume depletion events, which together explained 37% of across-study variance in DKA risk.

Excessive insulin dose reduction plays a key role in DKA by enhancing lipolysis and ketogenesis [76], but the exact cut-off of insulin down-titration which augments DKA risk is unclear: we could not confirm the cut-offs suggested by experts (20% of initial TID or 10% of initial basal ID) [18] , which were derived from a post-hoc analysis of a small phase 2 RCT [53]. Rather, we found the risk of DKA during insulin dose down-titration was related to individual insulin sensitivity at baseline: the higher insulin resistance, the more cautious TID reduction should be to prevent unrestricted lipolysis and ketogenesis. More specifically, the analysis of the regression plot **(Figure 2H)** indicates that DKA risk starts to increase when the ratio of TID change (%)-to-baseline IS falls below -20.

Volume depletion was the fourth independent predictor of DKA, consistent with recent experimental evidence demonstrating dehydration and insulinopenia are both necessary and sufficient to trigger SGLT2i-associated DKA, through hypothalamic-pituitary-adrenal axis activation, catecholamine and corticosterone axis stimulation and increased adipose tissue lipolysis [77]. Hence, dehydration would be a central target for DKA prevention in patients with T1DM treated with SGLT2i.

In summary, our multivariable model suggests that patients with T1DM who are overweight and insulin resistant are at higher risk of DKA when they rapidly reduce insulin dose and are volume depleted, as these conditions concur to trigger unrestricted lipolysis and ketogenesis.

Among non-glycaemic benefits, a novel finding of our analysis were the signals for renal and eye protection associated with SGLT2i, with reduced albuminuria and risk of diabetic eye disorders. These two outcomes were associated with an improvement in CGM metrics rather than in HbA1c, consistent with emerging evidence that glucose swings are major contributors to microvascular complications [24].

The transient eGFR decline observed in the initial 24 weeks of treatment vanished in RCTs of longer duration **(S2 Table 2**), and could be ascribed to the enhanced afferent arteriolar tone with SGLT2i, which reduce intraglomerular pressure and relieve glomerular hyperfiltration and barrier damage [78,79].

If future RCTs of longer duration translate the observed renal and eye-related effects into hard outcomes, the clinical benefit of SGLT2i may be particularly valuable in patients with T1DM who are at lower DKA risk and have established microvascular complications.

The optimal dose of SGLT2i is also debated: based on individual trial findings [66], some suggested the lowest dose has equal effectiveness and higher safety than moderate-high doses.

Conversely, we documented a consistent dose-response gradient with increasing SGLT2i dosage for most glycaemic and non-glycaemic benefits, but not for DKA and other AEs (**Table 4**).

These findings suggest potential benefits of increasing SGLT2i doses may outweigh the risks of DKA, at least in patients not at increased risk of DKA and within the time frame of included RCTs.

Finally, while some discouraged SGLT2i use in T1DM patients with higher HbA1c levels [18], based on a reported increased incidence of DKA in general T1DM population with HbA1c>10% [80], we did not find a direct relationship between baseline HbA1c and the risk of DKA (**Figure 3B).** Hence, it may be reasonable not to withhold these drugs in patients at greater therapeutic need who are compliant to DKA risk mitigation recommendations.

Clinical policy implications

Our analysis suggests that the risk of DKA is not uniformly distributed across T1DM population; rather,

simple, clinical risk factors are associated with the risk of DKA and with other efficacy and safety outcomes in patients with T1DM treated with SGLT2i.

If confirmed by real-world prospective studies, the results of our analysis may enable the targeted use of SGLT2i in patients with T1DM who have the greatest benefit and the lowest risk of DKA from the use of these drugs.

These findings may be implemented into DKA risk mitigation strategies to appropriately select those patients with a higher baseline benefit-risk ratio from SGLT2i therapy and to inform protocols targeting appropriate TID down-titration and dehydration prevention.

Strengths and limitations

Strengths and limitations of our analysis derive from the characteristics of included evidence: strengths include the high percentage of explained variance in DKA risk, the good methodological quality of included RCTs, the thorough assessment of efficacy and safety outcomes and the relevant impact of extracted evidence on clinical policy and decision-making.

Limitations are the relatively short duration of included trials, which prevented assessment of long-term outcomes. Furthermore, we analysed study-level characteristics, which do not necessarily correspond to individual patient characteristics, including adherence to prescribed DKA risk mitigation strategies. However, individual patient data are rarely available, as most RCTs are sponsored by industry.

For several outcomes the event rate was low and 95% confidence intervals correspondingly wide, mandating caution in interpreting the absence of statistical significance. Finally, the extrapolation of our findings from RCT analysis to real-world needs confirmation, as participants enrolled in RCTs are inherently different from patients in the realities of clinical practice.

Conclusion

The data presented show that routinely available clinical parameters are associated with the risk of DKA and the therapeutic response to SGLT2i, and that factors associated with therapeutic response differ from those associated with unwanted effects of SGLT2i treatment. These findings may thus represent an initial step toward benefit-risk optimization of SGLT2i use in T1DM. Future studies should refine the

predictive ability of our model and assess the clinical benefits of implementing this strategy in real-world practice.

Supporting information

S1. Supplementary text

S2. Supplementary Tables

S3. Supplementary Figures

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Author contributions:

Giovanni Musso: took substantial part in conception and design of the article, data collection and elaboration, drafting of the article, final approval of the manuscript, agreement to be accountable for all aspects of the work

Antonio Sircana: took substantial part in data acquisition and interpretation, revising critically the article, final approval of the manuscript, agreement to be accountable for all aspects of the work.

Francesca Saba: took substantial part in data acquisition and interpretation, revising critically the article, final approval of the manuscript, agreement to be accountable for all aspects of the work.

Maurizio Cassader: took substantial part in data acquisition and interpretation, revising critically the article, final approval of the manuscript, agreement to be accountable for all aspects of the work.

Roberto Gambino: took substantial part in data acquisition and interpretation, revising critically the article, final approval of the manuscript, agreement to be accountable for all aspects of the work.

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Table 1. Glycemic and non-glycemic efficacy outcomes and safety outcomes evaluated in the meta-analysis.

Glycaemic efficacy outcomes	
Outcome	**Comments/description**
HbA1c (%)	changes in HbA1c (%) from baseline.
Fasting Plasma Glucose (FPG)	changes in FPG (mg/dL) from baseline
Time-in-range 70-180 mg/dL (%)	% of daily glucose readings between 70 and 180 mg/dL over each 24-h period during continuous glucose monitoring (CGM)
Mean amplitude of glucose excursion (MAGE)(mg/dL)	average of all glucose excursion that exceeded 1 SD over each 24-h period during CGM. MAGE is an index of glycaemic variability.
Urinary glucose excretion (UGE, g/24 hr)	daily urinary glucose excretion
Daily total insulin dose (TID) changes (%)	[(end-of treatment TID-initial TID)/initial TID] x 100%
Daily basal insulin dose (ID) changes (%)	[(end-of treatment basal ID-initial basal ID)/initial basal ID] x 100%
Daily bolus ID changes (%)	[(end-of treatment bolus ID-initial bolus ID)/initial bolus ID] x 100%
Estimated Glucose Disposal Rate (eGDR) changes (%)	[(end-of treatment eGDR-initial eGDR)/initial eGDR] x 100%
Relative Insulin Sensitivity (RIS) changes (%)	[(end-of treatment RIS-initial RIS)/initial RIS] x 100%
Non-glycaemic efficacy outcomes	
Outcome	**Comments/description**
BMI changes (%)	[(end-of treatment BMI-initial BMI)/initial BMI] x 100%

SysBP changes (mmHg)	[(end-of treatment sysBP-initial sysBP)/initial sysBP]
eGFR changes (ml/min/1.73 m^2)	[(end-of treatment eGFR-initial eGFR)/initial eGFR]
ACR changes (mg/g)	[(end-of treatment ACR-initial ACR)/initial ACR]
Diabetic Eye disorders	including development of haemorrhagic retinopathy/vitreous haemorrhage, retinal detachment, macular edema), glaucoma, or vision loss(as defined by the International Clinical Disease Severity Scale[29].
Safety outcomes	
Definite diabetic ketoacidosis (DKA)	anion-gap metabolic acidosis with ketone increase without a satisfactory alternative cause for anion-gap acidosis [18,22, 26].
Hypoglycaemia	Blood glucose < 70 mg/dL [26].
Severe hypoglycaemia(SH)	SH was defined as an event consistent with hypoglycemia when any of the following three conditions occurred [26]: • the patient had an episode of suspected hypoglycemia treated with carbohydrate or with glucagon that required the assistance of others to treat, because the neurologic impairment was severe enough to prevent self-treatment. • the patient lost consciousness during the episode • the patient had a seizure during the episode
Urinary tract infections (UTIs)	-
Genital tract infections (GTIs)	-
Upper respiratory infections	-

MACE	cardiovascular death, myocardial infarction, stroke, hospitalization due to heart failure or unstable angina, or coronary revascularization
Limb amputation	-
Bone fracture	-
Gastrointestinal events: nausea, vomiting, diarrhea	-
Renal events	defined according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred items version 15.1(**supplementary text**).
Volume depletion events	defined according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred items version 15.1(**supplementary text**).
Drug-induced liver injury	-
Venous thromboembolism	-
Cancer	-
Serious adverse event (AE)	Any untoward medical occurrence that results in death, a life-threaten, patient hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or if that requires medical intervention to prevent one of the outcomes listed above.
All-cause death	-

Abbreviations: ACR: albumin-to-creatinine ratio; eGFR: estimated Glomerular Filtration Rate; ID: insulin dose; MACE: major adverse cardiovascular events; MAGE: Mean Amplitude of Glucose Excursions;TID: total daily insulin dose.

Table 2. Multivariable meta-regression models for moderatos of different efficacy and safety outcomes. Only statistically significant moderators at univariable meta-regression were included in the models.

Diabetic ketoacidosis (DKA)														
Moderator	**N comparisons**	**N participants**	**Multivariable model 1 (baseline predictors)**				**Multivariable model 2 (treatment-related predictors)**				**Multivariable model 3 (all predictors)**			
			ß (95%CI)	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**
Baseline BMI (kg/m2)	**38**	**7396**	0.439 (0.211, 0.666)	0.118	**0.0001**	**61%**	-	-	-	-	0.399 (0.121, 0.667)	0.136	**0.006**	**86%**
Baseline HbA1c (%)	**38**	**7396**	-0.475 (-1.388, 0.437)	0.576	0.415		-	-	-	-	-0.309 (0.118, -0.736)	0.218	0.431	
Baseline eGDR (mg/kg/min)	**38**	**7396**	-0.766 (-1.276, -0.256)	0.260	**0.001**		-	-	-	-	-0.631 (-1.243, -0.021)	0.312	**0.028**	
Baseline TID (IU/d)	**38**	**7396**	0.049 (-0.021, 0.119	0.036	0.437		-	-	-	-	0.031 (-0.085, 0.147)	0.059	0.348	
BMI change (%)	**38**	**7396**	-	-	-	-	-0.312 (-0.688, 0.064)	0.192	0.104	**37%**	-0.394 (-0.811, 0.023)	0.213	0.128	
eGDR change (%)	**38**	**7396**	-	-	-	-	0.215 (-0.214, 0.530)	0.194	0.193		0.197 (-0.013, 0.407)	0.105	0.109	
RIS change $(I.U./kg)^{-1}$	**38**	**7396**	-	-	-	-	-4.385 (-1.744, -10.513	3.127	0.541		-2.180 (-9.991, 5.631)	3.985	0.713	
TID change(%) (%)/baselineRIS ratio ($IU^2/kg/d$)	**38**	**7396**	-	-	-	-	-0.048 (-0.057, -0.039)	0.004	**0.007**		-0.037 (-0.047, -0.027)	0.005	**0.010**	
Volume depletion events	**38**	**7396**	-	-	-	-	0.352 (0.193, 0.475)	0.06	**0.009**		0.296 (0.098, 0.494)	0.101	**0.011**	

Moderator	N comparisons	N participants	Multivariable model 1 (baseline predictors)				Multivariable model 2 (treatment-related predictors)				Multivariable model 3 (all predictors)			
			ß (95%CI)	SE	P	R^2	ß (95%CI)	SE	P	R^2	ß (95%CI)	SE	P	R^2
HbA1c(%)														
SGLT2 inhibitor dose	**38**	**7396**	-0.065 (-0.122, -0.009)	0.028	**0.005**	**56%**	-	-	-	-	-0.068 (-0.126, -0.010)	0.029	**0.009**	**68%**
Pre-randomization insulin optimization	**38**	**7396**	0.050 (-0.039, 0.138)	0.045	0.269		-	-	-	-	0.083 (-0.011, 0.177)	0.048	0.085	
Change in eGDR(%)	**38**	**7396**	-	-	-		-0.024 (-0.045,-0.002)	0.010	**0.031**	**28%**	-0.026 (-0.054, 0.001)	0.015	0.061	
BMI (%)														
Total ID (IU/d)	**38**	**7396**	-0.004 (-0.075,-0.066)	0.036	0.904	**58%**	-	-	-	-	-0.005 (-0.069, -0.060)	0.033	0.889	**63%**
BMI (kg/m^2)	**38**	**7396**	-0.148 (-0.418, 0.123)	0.138	0.284		-	-	-	-	0.092 (-0.179, 0.362)	0.138	0.506	
eGDR(mg/kg/min)	**38**	**7396**	-0.032 (-0.567, 0.503)	0.045	0.907		-	-	-	-	-0.216 (-0.693, -0.262)	0.244	0.376	
SGLT2 inhibitor dose	**38**	**7396**	-0.773 (-1.177, -0.365)	0.205	**<0.0001**		-	-	-	-	-0.433 (-0.827, -0.039)	0.199	**0.002**	
eGDR change (%)	**38**	**7396**	-	-	-	-	-0.331 (-0.453,-0.209)	0.062	**<0.0001**	**34%**	-0.326 (-0.488, -0.164)	0.083	**0.0008**	
DKA	**38**	**7396**	-	-	-	-	-0.080 (-0.163,-0.004)	0.043	0.069		-0.071 (-0.167, -0.025)	0.049	0.147	

Systolic BP (mmHg)															
			Multivariable model 1 (baseline predictors)				Multivariable model 2 (treatment-related predictors)				Multivariable model 3 (all predictors)				
Moderator	**Ncomparisons**	**Nparticipants**	**ß (95%CI)**	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**		**R^2**
Baseline sysBP(mmHg)	**38**	**7396**	0.147 (-0.043, 0.336)	0.097	0.129	**62%**	-	-	-	-	0.147 (-0.043, 0.336)	0.097	0.129		
SGLT2 inhibitor dose	**38**	**7396**	-1.349 (-2.490, -0.208)	0.581	**0.012**		-	-	-	-	-1.349 (-2.490, -0.208)	0.581	**0.012**		**62%**
eGFR(ml/min/1.73 m^2)															
Renal function stage	**38**	**7396**	-0.068 (-0.901, 0.766)	0.425	0.873	**51%**	-	-	-	-	-0.068 (-0.901, 0.766)	0.425	0.873		
Study duration(wk)	**38**	**7396**	0.030 (0.002, 0.058)	0.011	**0.038**		-	-	-	-	0.030 (0.002, 0.058)	0.011	**0.038**		**51%**
Albumin-to-creatinine ratio (ACR, mg/g)															
SGLT2 inhibitor dose	**38**	**7396**	-9.977 (-16.076, -3.878)	3.812	**0.004**	**56%**	-	-	-	-	-7.926 (-13.929, -1.923)	3.369	**0.010**		**69%**
Time-in-range (%) change	**31**	**3050**	-	-	-		0.364 (-1.707, 2.434)	1.056	0.731	**41%**	0.260 (-1.911, 0.430)	1.107	0.815		
MAGE (mg/dL) change	**31**	**3050**	-	-	-		1.151 (0.445, 1.857)	0.360	**0.009**		0.973(0.344, 1.602)	0.321	**0.011**		

Diabetic eye disorders														
Moderator	**N comparisons**	**N participants**	**Multivariable model 1 (baseline predictors)**				**Multivariable model 2 (treatment-related predictors)**				**Multivariable model 3 (all predictors)**			
			ß (95%CI)	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**
SGLT2 inhibitor dose	**38**	**7396**	-0.742 (-1.443, -0.041)	0.317	**0.031**	**49%**	-	-	-	**66%**	-0.555 (-1.903, 0.793)	0.688	0.587	
Time-in-range(%) change	**31**	**3050**	-	-	-		-0.117 (-0.211, -0.004)	0.049	**0.009**		-0.111 (-0.201, -0.014)	0.037	**0.010**	**64%**
Genital Tract Infections (GTIs)														
Total ID (IU/d)	**38**	**7396**	0.047 (0.040, 0.901)	0.022	**0.011**		-	-	-	-	0.042 (0.002, 0.080)	0.020	**0.043**	
BMI (kg/m^2)	**38**	**7396**	0.089 (-0.172, 0.349)	0.133	0.504	**32%**	-	-	-	-	-0.134 (-0.553, 0.285)	0.214	0.531	
eGDR(mg/kg/min)	**38**	**7396**	-0.237 (-0.710, 0.235)	0.241	0.325		-	-	-	-	-0.237 (-0.810, 0.336)	0.292	0.417	
FPG change(mg/dL)	**38**	**7396**	-	-	-	-	0.032 (0.005, 0.060)	0.014	**0.012**	**39%**	0.030 (0.002, 0.058)	0.014	**0.039**	**61%**
BMI change(%)	**38**	**7396**	-	-	-	-	-0.274 (-0.676, 0.129)	0.205	0.183		-0.292 (-0.720, 0.136)	0.218	0.181	
eGDR change (%)	**38**	**7396**	-	-	-	-	0.044 (-0.169, 0.258)	0.109	0.683		0.041 (-0.221, 0.304)	0.134	0.758	

Volume depletion events														
Moderator	**N comparisons**	**N participants**	**Multivariable model 1 (baseline predictors)**				**Multivariable model 2 (treatment-related predictors)**				**Multivariable model 3 (all predictors)**			
			ß (95%CI)	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**	**ß (95%CI)**	**SE**	**P**	**R^2**
Baseline eGDR (mg/kg/min)	**38**	**7396**	-0.698 (-1.250, -0.145)	0.279	**0.009**	**42%**	-	-	-		-0.645 (-1.272,-0.019)	0.320	**0.014**	
eGDR change (%)	**38**	**7396**	-	-	-	-	0.097 (0.055, 0.181)	0.043	**0.021**	**31%**	0.054 (-0.126 0.233)	0.092	0.560	**59%**
DKA	**38**	**7396**	-	-	-	-	-0.068 (-0.091, -0.228)	0.081	0.399		-0.005 (-0.182, 0.173)	0.090	0.958	

Abbreviations.

*R^2 is the ratio of explained to total variance and indicates the proportion of variance accounted for by different moderators.

eGDR: estimated Glucose Disposal rate; RIS: relative insulin sensitivity; TID: daily Total Insulin Dose

Table 3: Summary of main findings of meta-analysis for glycemic and non-glycemic efficacy outcomes.

Glycemic efficacy outcomes					
Outcome	**Comparisons (n)**	**Participants (n)**	**Effect estimate [95%CI]**	**P**	**I^2 (%)**
HbA1c(%)	**29**	**7243**	**WMD: -0.37 (-0.41, -0.33)**	**<0.001**	**4**
Fasting Plasma Glucose(FPG)	**39**	**7396**	**WMD: -19.20 (-22.28, -16.12)**	**<0.001**	**0**
Time-in-range(%)	**31**	**3050**	**WMD: +9.87 (+8.75, +10.99)**	**<0.001**	**10**
MAGE(mg/dL)	**38**	**3050**	**WMD: -15.91 (-17.95, -13.86)**	**<0.001**	**0**
Daily TID(%)	**39**	**7396**	**WMD: -10.60 (-11.72, -9.47)**	**<0.001**	**17**
Daily basal ID(%)	**39**	**7396**	**WMD: -12.37% (-14.15, -10.59)**	**<0.001**	**38**
Daily bolus ID(%)	**39**	**7396**	**WMD: -9.81% (-11.45, -8.18)**	**<0.001**	**18**
estimated Glucose Disposal Rate (eGDR)(%)	**39**	**7396**	**WMD: +11.06% (+10.16, +11.96)**	**<0.001**	**33**
Relative Insulin Sensitivity (RIS)(%)	**39**	**7396**	**WMD: +10.44% (+9.49, +11.39)**	**<0.001**	**48**
Non-glycemic efficacy outcomes					
Outcome	**Comparisons (n)**	**Participants (n)**	**Effect estimate [95%CI]**	**P**	**I^2 (%)**
BMI(%)	**39**	**7396**	**WMD: -3.20% (-3.54, -2.86)**	**<0.001**	**47**
SysBP(mmHg)	**39**	**7396**	**WMD:-3.81mmHg (-4.49, -3.12)**	**<0.001**	**0**
eGFR(ml/min/1.73 m^2)	**39**	**7396**	**WMD: -0.78 (-1.29, -0.26)**	**0.003**	**0**
ACR(mg/g)	**8**	**3052**	**WMD: -9.91 (-16.26, -3.55)**	**0.002**	**0**
Diabetic Eye disorders	**39**	**7396**	**RR: 0.38 (0.10, 1.40)**	**0.005**	**0**

Abbreviations: ACR: albumin-to-creatinine ratio; eGFR: estimated Glomerular Filtration Rate; ID: insulin dose; MAGE: Mean Amplitude of Glucose Excursions; TID: total daily insulin dose.

Table 4. Dose-response interaction: within-trial analysis of the pooled data from RCTs evaluating multiple SGLT2 inhibitor doses.

Outcome	SGLT2 inhibitor high dose vs. moderate dose	SGLT2 inhibitor high dose vs. low dose	SGLT2 inhibitor moderate dose vs. low dose
DKA	1.00 (0.70, 1.45) I^2=0%, p=0.98, N =13, 3577 participants	2.55 (0.60, 10.88) I^2=0%, p=0.30, N =7, 675 participants	2.91 (0.59, 14.29) I^2=0%, p=0.29, N =7, 675 participants
HbA1c(%)	-0.08 (-0.15, -0.01) I^2=0%, p=0.008, N =10, 3498 participants	-0.17 (-0.27, -0.07) , I^2=12%, p=0.0006, N =4, 634 participants	-0.16 (-0.29, -0.06) , I^2=0%, p=0.01, N =4, 634 participants
FPG (mg/dL)	-7.59(-12.38, -2.80), I^2=25, p=0.01, N =13, 3577 participants	-24.60 (-38.91, -10.28), I^2=23%, p=0.00008, N =7, 675 participants	-7.51 (-15.16, -1.15), I^2=0%, p=0.02, N =7, 675 participants
Time-in-Range (%)	2.05(0.33, 3.78), I^2=0%, p=0.01, N =11, 1821	6.07(3.28, 8..85), I^2=0%, p<0.0001, N =6, 498 participants	4.80(1.33, 8.27), I^2=0%, p=0.007, N =6, 214 participants
MAGE(mg/dL)	-2.14(-5.81, 1.54), I^2=28%, p=0.25, N =11, 1821 participants	-2.95(-9.99, 4.09), I^2=26%, p=0.41, N =6, 498 participants	-4.76(-18.45, 8.94), I^2=32%, p=0.50, N =6, 214 participants
Total insulin dose (%)	-3.14(-6.78, 11.98), I^2=0%, p=0.0003, N =13, 3577 participants	-7.01(-9.76, -4.53), I^2=0%, p<0.00001, N =7, 677 participants	-2.52(-4.99, -0.16), I^2=0%, p=0.04, N =7, 677 participants
Basal insulin dose (%)	-3.33(-4.85, -1.83), I^2=1%, p=0.0001, N =13, 3577 participants	-4.61(-8.04, -1.34), I^2=0%, p=0.01, N =7, 677 participants	-1.23(-4.39, 1.93), I^2=0%, p=0.45, N =7, 677 participants

Bolus insulin dose (%)	-4.58(-8.06, -1.10), I^2=30%, p=0.01, N =13, 3577 participants	-7.35(-11.56, -3.03), I^2=0%, p=0.001, N =7, 677 participants	-3.55(-6.93, -0.35), I^2=0%, p=0.04, N =7, 677 participants
eGDR (mg/kg/min)	2.34(1.36, 3.03), I^2=0, p<0.00001, N =13, 3577 participants	5.85 (1.63, 9.67), I^2=30%, p=0.001, N =7, 677 participants	3.75 (0.95, 6.54), I^2=35%, p=0.009, N =7, 677 participants
RIS	1.14(0.34, 1.71), I^2=0, p=0.004, N =13, 3577 participants	3.81 (1.48, 5.62), I^2=38%, p=0.003, N =7, 677 participants	3.35(1.47, 5.24), I^2=23%, p=0.0005, N =7, 677 participants
BMI (%)	-0.89(-1.20,- 0.53), p<0.0001, N =13, 3577participants	-1.00 (-1.87, -0.23), I^2=0%, p=0.01, N =7, 677 participants	-0.84 (-1.38, -0.30), I^2=10%, p=0.002, N =7, 677 participants
Systolic BP (mmHg)	-1.29(-2.19,-0.19), p=0.03, N =13, 3577 participants	-2.82 (-4.85, -1.21), I^2=0%, p=0.02, N =7, 677 participants	-1.76(-4.37, -0.86), I^2=21%, p=0.04, N =7, 677 participants
eGFR (ml/min/1.73 m^2)	0.18(-0.46, 0.82), p=0.40, N =13, 3577 participants	-0.13(-1.50, 1.85), p=0.85, N =7, N =7, 677 participants	-0.35(-1.80, 1.10, p=0.64, N =7, I^2=0%, 677 participants
Urinary ACR (mg/g)	-6.20 (-10.59, -0.08), I^2=0%, p=0.04, N =4, 1086 participants	-7.20 (-14.59, -0.08), I^2=NA, p=0.04, N =1, 38 participants	-7.40 (-15.32, -0.52), I^2=NA, p=0.04, N =1, 38 participants
Eye disorders	0.25(0.03, 2.21), p=0.21, N =13, 3577 participants	0.36 (0.04, 3.24), I^2=0%, p=0.36, N =6, 677 participants	0.36(0.02, 8.05), I^2=0%, p=0.52, N =6, 677 participants

Hypoglycemia	0.98(0.85, 1.15), p=0.71, N =13, 3577 participants	1.00 (0.94, 1.06), I^2=0%, p=0.98, N =6, 677 participants	0.99(0.93, 1.05), I^2=0%, p=0.92, N =6, 677 participants
Severe hypoglycemia	0.47(0.13, 1.79), p=0.31, N =13, 3577 participants	0.76 (0.45, 1.24), I^2=0%, p=0.29, N =6, 677 participants	0.80(0.55, 1.05), I^2=0%, p=0.10, N =6, 677 participants
UTI	0.68(0.30, 1.78), p=0.41, N =13, 3577 participants	1.22 (0.92, 1.64), I^2=0%, p=0.89, N =6, 677 participants	0.89(0.84, 1.25), I^2=0%, p=0.39, N =6, 677 participants
GTI	1.11(0.89, 1.33), p=0.34, N =13, 3577 participants	1.64 (0.90, 3.01), I^2=0%, p=0.19, N =6, 677 participants	1.46 (0.79, 1.72), I^2=0%, p=0.23, N =6, 677 participants
Volume depletion events	0.94(0.58, 1.54), p=0.82, N =13, 3577 participants	2.17 (0.62, 7.53), I^2=0%, p=0.23, N =6, 677 participants	2.54 (0.69, 9.33), I^2=0%, p=0.16, N =6, 677 participants
MACE	1.08(0.18, 1.98), p=0.82, N =13, 3577 participants	0.92 (0.37, 2.32), I^2=0%, p=0.39, N =6, 677 participants	1.18 (0.40, 3.39), I^2=0%, p=0.86, N =6, 677 participants

Abbreviations: ACR: albumin-to-creatinine ratio; DKA: diabetic ketoacidosis; FPG: fasting plasma glucose; MAGE: major amplitude of glucose excursions; eGDR: estimated Glucose Disposal Rate; RIS: relative Insulin Sensitivity; eGFR: estimated glomerular Filtration Rate; MACE: major adverse cardiovascular events; GTI: genital tract infections, UTI: urinary Tract Infections.