# Supplementary Tables

## Supplementary Table 1 panel A. Characteristics of included randomized controlled trials

| Author | N-participants | Study duration (week) | Study Arms | Age (yr) | Gender (%M) | Bodyweight (kg) / BMI (kg/m$^2$) | Initial HbA1c (%) | Diabetes duration (yr) | Background treatment / Daily TID (IU/kg) | Dropout rate(%) | Renal function |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sands 2015** | 33 | 4 | Sota 400 mg | 45 | 50 | 74.2 kg / 27.1 kg/m$^2$ | 7.94 | 18.5 | Insulin 0.6 IU/kg | 0% | eGFR≥60 ml/min/1.73 m$^2$ |
| | | | placebo | 44 | 47 | 72.7 kg / 26.2 | 7.98 | 16.8 | Insulin 0.6 IU/kg | 0% | |
| **Bode 2017** | 87 | 12 | Sota 400 mg | 23 | 49 | 83.8 kg / 29.0 | 9.9 | 12 | Insulin 0.8 IU/kg | 0% | eGFR≥45 ml/min/1.73 m$^2$ |
| | | | placebo | 22 | 45 | 80.7 kg / 27.9 | 9.7 | 12 | Insulin 0.8 IU/kg | 4.8% | |
| **Baker 2017** | 141 | 12 | Sota 400 mg | 45 | 57 | 84.1 kg / 29 | 8.1 | 24 | Insulin 0.7 IU/kg | 0% | eGFR≥60 ml/min/1.73 m$^2$ |
| | | | Sota 200 mg | 47 | 47 | 81.9 kg / 28 | 8.1 | 24 | Insulin 0.7 IU/kg | 0% | |
| | | | Sota 75 mg | 42 | 40 | 78.1 kg / 27 | 8.0 | 23 | Insulin 0.7 IU/kg | 2.7% | |
| | | | placebo | 48 | 42 | 89.6 kg /31 | 8.0 | 27 | Insulin 0.7 IU/kg | 2.7% | |

**SupplementaryTable 1. Characteristics (panel A) and Risk of Bias (panel B) of included trials.**

| Author | N-participants | Study duration (week) | Study Arms | Age (yr) | Gender (%M) | Bodyweight (kg) / BMI (kg/m$^2$) | Initial HbA1c (%) | Diabetes duration (yr) | Background treatment / Daily TID (IU/kg) | Dropout rate | Renal function |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Garg 2017** | 1402 | 24 | Sota 400 mg | 43 | 51 | 82.4 kg/ 28.3 | 8.2 | 20 | Insulin 0.7 IU/kg | 13% | eGFR≥45 ml/min/1.73 m$^2$ |
| | | | placebo | 42 | 48 | 81.6/28.1 | 8.2 | 20 | Insulin 0.7 IU/kg | 11% | |
| **Buse 2018** | 793 | 52 | Sota 400 mg | 46 | 46 | 86.5 kg/29.6 | 7.6 | 24 | Insulin 0.7 IU/kg | 10% | eGFR≥45 ml/min/1.73 m$^2$ |
| | | | Sota 200 mg | 47 | 48 | 86.9 kg/29.8 | 7.6 | 25 | Insulin 0.7 IU/kg | 9% | |
| | | | placebo | 45 | 51 | 87.3 kg/29.6 | 7.5 | 24 | Insulin 0.7 IU/kg | 12% | |
| **Danne 2018** | 782 | 52 | Sota 400 mg | 41 | 51 | 81.9 kg/ 27.9 | 7.7 | 19 | Insulin 0.7 IU/kg | 8% | eGFR≥45 ml/min/1.73 m$^2$ |
| | | | Sota 200 mg | 42 | 53 | 81.9 kg/ 27.9 | 7.7 | 18 | Insulin 0.7 IU/kg | 8% | |
| | | | placebo | 40 | 52 | 81.1 kg/ 27.5 | 7.7 | 18 | Insulin 0.7 IU/kg | 8% | |

| Supplementary Table 1 panel BRisk of Bias of included randomized controlled trials | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Author** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and èpersonnel** | **Blinding pf outcome assesment** | **Incomplete outcome data** | **Selective reporting** | **Other: sponsorship bias** |
| **Sands 2015** | Low risk. Computer generated list | Low risk. Central allocation, web-based randomization | Low risk. Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor) | Low risk. Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessors) | Low risk. No patients dropped out | Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication | Low risk. The Robert and Janice McNair Foundation partly funded the study |
| **Bode 2017** | Low risk. Computer generated list | Low risk. Central allocation, web-based randomization | Low risk. Quadruple masking | Low risk. Quadruple masking | Low risk. Low dropout rate: | Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication | Low risk. JDRF partly funded the study |
| **Baker 2017** | Low risk. Computer generated list | Low risk. Central allocation, web-based randomization | Low risk. Quadruple masking | Low risk. Quadruple masking | Low risk. Low dropout rate: | Low risk. Prespecified outcomes available on a clinical trial database and all reported in publication | Low risk. Industry funded but no high risk of bias feature encountered* |

| Panel B(continued). Risk of Bias of included randomized controlled trials | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Author** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and èpersonnel** | **Blinding pf outcome assesment** | **Incomplete outcome data** | **Selective reporting** | **Other: sponsorship bias** |
| **Garg 2017** | Low risk. Computer generated list | Low risk Central allocation, web-based randomization | Low risk Quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor) | Low risk Quadruple masking | Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse. | Low risk Prespecified outcomes available on a clinical trial database and all reported in publication | Low risk Industry funded but no high risk of bias feature encountered* |
| **Buse 2018** | Low risk. Computer generated list | Low risk Central allocation, web-based randomization | Low risk Quadruple Masking | Low risk Quadruple masking | Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse. | Low risk Prespecified outcomes available on a clinical trial database and all | Low risk Industry funded but no high risk of bias feature encountered* |
| **Danne 2018** | Low risk. Computer generated list | Low risk Central allocation, web-based randomization | Low risk Quadruple Masking | Low risk Quadruple masking | Low risk Low dropout rate: Missing observations at EOT imputed as nonresponse. | Low risk Prespecified outcomes available on a clinical trial database and all | Low risk Industry funded but no high risk of bias feature encountered* |

**Abbreviations**: eGFR: estimated glomerular filtration rate;JDRF: Juvenile Diabetes Research Foundation; Sota: sotagliflozin; TID: total insulin dose

[a]Insulin dose optimization during the 6 weeks preceding randomization(target: FPG 80-130 mg/dL and 2hr-PPG<180 mg/dL)

*__Assessment of sponsorship bias__: in the presence of industry sponsorship, the following list of 8 items in trial designing, conducting or reporting, empirically linked by existing literature to biased outcomes in industry-funded trials and not captured by the Cochrane Risk of Bias domains, were assessed: if any one item was present, the trial was downgraded to "high risk of bias".

**Item a**:unclearclinical relevance of outcome measures: the clinical relevance of trial outcomes is not supported by international guidelines (American Association for the study of Diabetes-ADA or European Association for the Study of Diabetes-EASD guidelines).

**Item b**: if active comparator was used: inadequacy of doses timing or way of administration,

**Item c**: -deviationsfrom study protocol or original protocol changes or amendments after trial initiation

**Item d**: post-hoc selection of the major findings and endpoints

**Item e**: use of last observation carried forward analysis to impute missing data

**Item f**:on-treatment outcome reporting /absence of data and safety monitoring board

**Item g**:absence of sponsor-independent statistician and data analysis

**Item h**: early trial termination before the endpoint recorded on clinical trial registries

**Supplementary Table 2.** Characteristics of randomized controlled trials(RTCs) with sotagliflozin excluded from this meta-analysis.

| Phase 1 trials | | | | |
|---|---|---|---|---|
| **Official Title (author/ year of publication) ClinicalTrials.gov ID number** | **Drug (dose)** | **N-participants (actual or anticipated)** | **Duration (week)** | **Year of registration Status** |
| Effect of Rifampicin on the Pharmacokinetics and Pharmacodynamics of Sotagliflozin NCT03063580 | Sota 400 mg | 16 | 7.5 | 2017 Completed |
| Oral Contraceptive DDI Study NCT02494609 | Sota 400 mg | 30 | 4 | 2015 Active, not recruiting |
| PK Study of Sotagliflozin in Subjects With Hepatic Impairment NCT02471274 | Sota 400 mg | 32 | 1 | 2015 Completed |
| Interaction study to evaluate the Effects of Mefenamic Acid on the Pharmacokinetics and Pharmacodynamics of Sotagliflozin in Healthy Male and Female Subjects. NCT03070678 | Sota 400 mg | 16 | 8 | 2017 Completed |
| A Drug to Drug Interaction Study of Sotagliflozin With Midazolam and Metoprolol. NCT02940379 | Sota 200 mg or 400 mg | 24 | 8 | 2016 Completed |
| Sotagliflozin Bioequivalence Study NCT03211195 | Sota 200 mg | 76 | 9 | 2017 Completed |
| A Study to Evaluate the Effect of Food on the Pharmacokinetics of Sotagliflozin and to Explore the Relative Bioavailability in Healthy Subjects. NCT03174548 | Sota 200 mg | 14 | 9 | 31/05/2017 Completed |
| A Drug to Drug Interaction Study of Sotagliflozin With Hydrochlorothiazide NCT03387657 | Sota 200 mg | 16 | 2 | 2018 Completed |
| Comparison of Sotagliflozin Prototype Tablets With | Sota | 12 | 9 | 2017 |

| | | | | |
|---|---|---|---|---|
| Reference Tablet in Healthy Subjects<br>NCT03310944 | 400 mg | | | Completed |
| A Bioequivalence Study Testing Two Formulations of Sotagliflozin in Healthy Male and Female Subjects Under Fasted Conditions<br>NCT03776227 | Sota 200 mg or 400 mg | 58 | 14 | 2018<br>Active, not yet recruiting, |
| A Phase 1, Open-label, Parallel-group Study to Evaluate Sotagliflozin Safety and Pharmacokinetics in Subjects With Varying Degrees of Renal Function,<br>NCT02647918 | Sota 200 mg | 44 | 1 | 2015<br>Active, Not recruiting |
| A Drug-Drug Interaction Study Between Sotagliflozin and Ramipril<br>NCT03414723 | Sota 400 mg | 1 | 9 | 2018<br>Completed |
| **Randomized trials in type 2 diabetes mellitus(T2DM)** | | | | |
| **Official Title<br>(author/ year of publication)<br>ClinicalTrials.gov ID** | **Sota dose** | **N-participants (actual or anticipated)** | **Duration (week)** | **Year of registration<br>Status** |
| A Randomized, Open-Label, Three-Way Crossover Study of Two Oral Formulations of LX4211 in Subjects With Type 2 Diabetes Mellitus<br>NCT01188863 | Sota 150 mg or 300 mg | 15 | 4 | 2012<br>Completed |
| A Study to Evaluate the Pharmacodynamic Effects of Single-Dose Co-Administration of LX4211 With Januvia® in Type 2 Diabetics<br>NCT01441232 | Sota 400 mg | 18 | 3 | 2015<br>Completed |
| Pharmacodynamic and Pharmacokinetic Effects of LX4211 in Subjects With Type 2 Diabetes and Renal Impairment<br>NCT01555008 | Sota 400 mg | 31 | 1 | 2015<br>Completed |
| Safety and Efficacy of LX4211 With Metformin in Type 2 Diabetes Patients With Inadequate Glycemic Control on Metformin<br>NCT01376557 | Sota 75 mg, 200 mg, 400 mg | 299 | 12 | 2015<br>completed |
| Efficacy and Safety of Sotagliflozin Versus Placebo in Chinese Patients With Type 2 Diabetes Mellitus Not Adequately Controlled by Diet and Exercise<br>NCT03760965 | Sota 200 mg or 400 mg | 369 | 24 | 29/11/2018<br>Recruiting, |

| | | | | |
|---|---|---|---|---|
| Efficacy and Safety of Sotagliflozin Versus Placebo in Chinese Patients With Type 2 Diabetes Mellitus Not Adequately Controlled by Metformin With or Without Sulfonylurea<br>NCT03761134 | Sota 200 mg or 400 mg | 369 | 24 | Recruiting 29/11/2018 |
| Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF Trial)<br>NCT03521934 | Sota 200 mg or 400 mg | 4000 | 32 | Recruiting30 /04/2018 |
| Comparison of Pharmacodynamic Effects of Sotagliflozin and Empagliflozin in T2DM Patients With Mild to Moderate Hypertension<br>NCT03462069 | Sota 400 mg | 40 | 8 | Recruiting 06/03/2018 |
| Efficacy and Bone Safety of Sotagliflozin Dose 1 and Dose 2 Versus Placebo in Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control.(SOTA-BONE Trial)<br>NCT03386344 | Sota 200 mg or 400 mg | 360 | 24 | Active, not recruiting 21/12/2017 |
| Efficacy and Safety of Sotagliflozin Versus Glimepiride and Placebo in Subjects With Type 2 Diabetes Mellitus That Are Taking Metformin Monotherapy(SOTA-GLIM trial)<br>NCT03332771 | Sota 200 mg or 400 mg | 930 | 52 | Active, Not recruiting 02/11/2017 |
| Efficacy and Safety of Sotagliflozin versus Placebo and Empagliflozin in Subjects with Type 2 Diabetes Mellitus who have Inadequate Glycemic Control while taking a DPP4 Inhibitor Alone or with Metformin(SOTA-EMPA trial)<br>NCT03351478 | Sota 400 mg | 700 | 26 | Active, not recruiting |
| Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk(SCORED trial)<br>NCT03315143 | Sota 200 mg vs. 400 mg | 1500 | 5 years | Active, recruiting 04/10/2017 |
| Efficacy and Safety of Sotagliflozin versus Placebo in Subjects with Type 2 Diabetes Mellitus who have inadequate glycemic control while Taking Insulin Alone or with Other Oral Antidiabetic Agents(SOTA-INS trial)<br>NCT03285594 | Sota 200 mg vs. sota 400 mg | 560 | 96 | Active, not recruiting 2017 |
| Safety and Efficacy Study of Sotagliflozin on Glucose Control in Patients With Type 2 Diabetes, Moderate Impairment of Kidney Function, and Inadequate Blood Sugar Control (SOTA-CKD3 trial) | Sota 200 mg vs. sota 400 mg | 780 | 52 | Active, Not recruiting 03/08/2017 |

| | | | | |
|---|---|---|---|---|
| NCT03242252 | | | | |
| A Study to Evaluate Safety and Effects of Sotagliflozin Dose 1 and Dose 2 on Glucose Control in Patients With Type 2 Diabetes, Severe Impairment of Kidney Function and Inadequate Blood Sugar Control.(SOTA-CKD4 trial) NCT03242018 | Sota 200 mg vs. sota 400 mg | 276 | 52 | Active, Not recruiting 03/08/2017 |
| Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus on Background of Sulfonylurea Alone or With Metformin NCT03066830 | Sota 400 mg | 500 | 26 | Active, Not recruiting 24/02/2017 |
| Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus Not Currently Treated With Antidiabetic Therapy NCT02926937 | Sota 400 mg | 400 | 26 | Active, Not recruiting 05/10/2016 |
| Efficacy and Safety of Sotagliflozin Versus Placebo in Patients With Type 2 Diabetes Mellitus on Background of Metformin NCT02926950 | Sota 200 mg vs. sota 400 mg | 500 | 26 | Active, Not recruiting 05/10/2016 |
| **Randomized trials in Congestive Heart Failure** | | | | |
| **Official Title (author/ year of publication) ClinicalTrials.gov ID number** | **Drug (dose)** | **N-participants (actual or anticipated)** | **Duration (week)** | **Year of registration Sstatus** |
| Safety, Tolerability and Pharmacodynamic Activity of Sotagliflozin in Hemodynamically Stable Patients With Worsening Heart Failure. NCT03292653 | Sota 200 mg or 400 mg | 81 | 5 | Active, Recruiting 04/12/2017 |

**Abbreviations**: UGE: urinary glucose excretion; T2D: type 2 diabetes mellitus; OAD: Oral Antidiabetic Agents; Sota: sotagliflozin

**Supplementary Table 3**. Results of subgroup and sensitivity analysis.

| Treatment duration | | |
|---|---|---|
| **Outcome** | **treatment duration ≤12 weeks** | **treatment duration >12 weeks** |
| **HbA1c(%)** | -0.37 (-0.56, -0.18), $I^2$=0%, p=0.0001, N =5 comparisons, 261 participants | -0.36(-0.47, -0.26), $I^2$=12%, p<0.00001, N =5 comparisons, 2977 participants |
| **FPG(mg/dL)** | -16.74 (-28.49, -5.00), $I^2$=10%, p=0.005, N =5, 261 participants | -16.77 (-23.05, -10.49), $I^2$=25%, p<0.00001, N=5, 2977 participants |
| **2h-PPG (mg/dL)** | -38.72 (-52.27, -25.16), $I^2$=20%, p<0.00001, N=5, 261 participants | -40.10(-63.73, -16.47), $I^2$=30%, p=0.001, N=5, 278 participants |
| **Total insulin dose (IU/d)** | -9.51 (-17.91, -1.81), $I^2$=0%, p=0.009, N=5, 261 participants | -9.16 (-11.40, -6.92), $I^2$=36%, p<0.00001, N=3, 2977 participants |
| **Basalinsulin dose (IU/d)** | -5.33 [-10.49,-1.49], $I^2$=0%, p=0.03, N=3, 261 participants | -8.89 (-11.16, -6.61) $I^2$=0%, p<0.00001, N=5, 2977 participants |
| **Bolus insulin dose (IU/d)** | -13.77 [-23.04, -3.50] $I^2$=34%, p=0.0004, N =5, 261 participants | -9.51 (-13.10, -5.92), $I^2$=24%, p<0.00001, N=5, 2977 participants |
| **Time-in-Range (%)** | 11.31(6.75,15.87) $I^2$=0%, p<0.00001, N=2, 120 participants | 8.88(4.25, 13.51) $I^2$=36%, p=0.0002, N=4, 278 participants |
| **Body weight change (%)** | -2.63(-4.09, -1.17), $I^2$=0%, p=0.0004, N=5, 261 participants | -3.67(-4.25, -3.10), $I^2$=0%, p<0.00001, N=5, 2977 participants |
| **SystolicBP(mmHg)** | -8.65(-12.49, -4.81), $I^2$=34%, p=0.0004, N=5, 285 participants | -3.61(-4.55, -2.66), $I^2$=0%, p<0.00001, N=5, 2977 participants |
| **DiastolicBP(mmHg)** | -2.13 (-4.00, -0.27), $I^2$=0%, p=0.02, N=3, 285 participants | -1.36 (-1.93, -0.80), $I^2$=0%, p<0.00001, N=3, 2977 participants |
| **eGFR (ml/min/1.73 $m^2$)** | -2.26(-4.41, -0.11), $I^2$=0%, p=0.04, N=5, 261 participants | -0.42(-1.15, 0.32), $I^2$=0%, p=0.26, N=5, 2977 participants |
| **Albumin-creatinine ratio (ACR)(mg/g)** | No studies | -14.57(-26.87, -2.28), $I^2$=0%, p=0.02, N=3, 2977 participants |
| **Hypoglycemia (events per patient-year)** | -9.82(-16.00, -1.48), $I^2$=0%, p=0.01, N=3, 261 participants | -9.71(-15.05, -4.38), $I^2$=0%, p<0.00001, N=3, 2977 participants |
| **Severe hypoglycemia** | 0.41(0.13, 1.28), $I^2$=0%, p=0.12, N=5, 261 participants | 0.72(0.51, 1.04), $I^2$=0%, p=0.08, N=5, 2977 participants |
| **DKA** | 1.23(0.31, 4.94) $I^2$=0%, p=0.77, N=5, 261 participants | 5.89(2.60, 13.36), $I^2$=0%, p<0.00001, N=5, 2977 participants |
| **UTI** | 0.70(0.20, 2.42), $I^2$=0%, p=0.57, N=5, 261 participants | 0.99(0.71, 1.37), $I^2$=0%, p<0.00001, N=5, 2977 participants |

| | | |
|---|---|---|
| **GTI** | 1.21(0.30, 4.86), $I^2$=0%, p=0.79, N=35 261 participants | 3.36(2.27, 4.96), $I^2$=0%, p<0.00001, N=5, 2977 participants |
| **Diarrhea** | 1.70(1.08, 2.77), $I^2$=0%, p=0.04, N=5, 261 participants | 1.59(1.12, 2.24), $I^2$=0%, p=0.009, N=5, 2977 participants |
| **Volume depletion events** | 2.62 (1.18, 5.82), $I^2$=3%, p=0.02, N=5, 261 participants | 1.37 (0.30, 2.19), $I^2$=0%, p=0.68, N=5, 2977 participants |
| **MACE** | No events, N =5 comparisons, 261 participants | 1.05(0.46, 2.43), $I^2$=0%, p=0.91, N=10, 2977 participants |
| **Initial HbA1c levels** | | |
| **Outcome** | **initial HbA1c levels < 8%** | **initial HbA1c levels ≥8%** |
| **HbA1c(%)** | -0.27 (-0.35, -0.19), $I^2$=0%, p<0.00001, N =5 comparisons, 1608 participants | -0.44(-0.52, -0.36), $I^2$=0%, p<0.00001, N =5 comparisons, 1630 participants |
| **FPG (mg/dL)** | -14.77 [-23.25, -6.30], $I^2$=25%, p=0.0006, N =3, 1608 participants | -19.83 [-26.51, -13.15], $I^2$=0%, p<0.00001, N =3, 1630 participants |
| **2h-PPG (mg/dL)** | -39.82(-56.70, -22.94), $I^2$=8%, p<0.00001, N =5, 311 participants | -38.74 [-55.81, -21.67], $I^2$=4%, p<0.00001, N =4, 228 participants |
| **Total insulin dose (IU/d)** | -9.23 (-12.12, -6.33), $I^2$=39%, p<0.00001, N =5 comparisons, 1608 participants | -9.04(-11.48, -6.59), , $I^2$=0%, p<0.00001, N =5 comparisons, 1630 participants |
| **Basal insulin dose (IU/d)** | -8.19 (-10.84, -5.55), $I^2$=0%, p<0.00001, N =5 comparisons, 1608 participants | -7.76 (-11.23, -4.29), $I^2$=0%, p<0.00001, N =5 comparisons, 1630 participants |
| **Bolus insulin dose (IU/d)** | -9.94(-14.84, -5.05), $I^2$=32%, p<0.00001, N =5 comparisons, 1608 participants | -9.77(-14.01, -5.52), $I^2$=0%, p<0.00001, N =5 comparisons, 1630 participants |
| **Time-in-Range(%)** | 8.88(4.25, 13.5), $I^2$=0%, p=0.0002, N =4, 278 participants | 11.31(6.75, 15.87), $I^2$=0%, p<0.00001, N =2, 120 participants |
| **Body weight change(%)** | -3.66(-4.44, -2.87), $I^2$=30%, p<0.00001, N =5 comparisons, 1608 participants | -3.50(-3.96, -3.03), $I^2$=0%, p<0.00001, N =5 comparisons, 1630 participants |
| **SystolicBP (mmHg)** | -3.27 (-4.76, -1.78), $I^2$=0%, p<0.0001, N =5 comparisons, 1608 participants | -6.67(-10.38, -2.96), $I^2$=0%, p=0.0004, N =5 comparisons, 1630 participants |
| **DiastolicBP (mmHg)** | -1.42(-2.20, -0.65), $I^2$=0%, p=0.0003, N =5 comparisons, 1608 participants | -1.44(-2.20, -0.69), $I^2$=0%, p=0.0002, N =5 comparisons, 1630 participants |
| **eGFR (ml/min/1.73 $m^2$)** | -1.35 (-2.26, -0.44), $I^2$=0%, p=0.004, N =5, 1608 participants | -1.07 (-2.35, -0.29), $I^2$=0%, p=0.21, N =5, 1630 participants |
| **Albumin-creatinine ratio (ACR)(mg/g)** | -13.92(-27.36, -0.48), $I^2$=0%, p=0.04, N=4, 1608 participants | -20.10(-40.25, -0.63), $I^2$=NA, p=0.04, N =1, 1402 participants |
| **Hypoglycemia** | -13.47(-20.90, -6.03), $I^2$=0%, p=0.004, | -6.12(-10.96, -1.28), $I^2$=0%, p=0.01 N=5, |

| | | |
|---|---|---|
| **(events per patient-ear)** | N=5, 1608 participants | 1630 participants |
| **Severe Hypoglycemia** | 0.69(0.46, 1.02), $I^2$=0%, p=0.07, N=5, 1608 participants | 0.71(0.36, 1.43), $I^2$=0%, p=0.34, N =5, 1630 participants |
| **DKA** | 6.62(2.04, 21.48), $I^2$=0%, p=0.002, N=5, 1608 participants | 2.21(0.43, 11.42), $I^2$=0%, p=0.34, N =5, 1630 participants |
| **UTI** | 0.86(0.48, 1.56), $I^2$=0%, p=0.62, N =3, 1608 participants | 0.96(0.57, 1.59), $I^2$=0%, p=0.86, N =3, 1630 participants |
| **GTI** | 3.39(1.53, 7.52), $I^2$=14%, p<0.003, N =5, 1608 participants | 2.97(1.71, 5.19), $I^2$=0%, p=0.0001, N =5, 1630 participants |
| **Diarrhea** | 1.50 (0.97, 2.29), $I^2$=0%, p=0.07, N =5, 1608 participants | 0.98 (0.32, 3.01), $I^2$=0%, p=0.98, N =5, 1630 participants |
| **Volume depletion Events** | 1.89 (0.76, 4.68), $I^2$=0%, p=0.17, N =5, 1608 participants | 2.68 (0.93, 7.73), $I^2$=0%, p=0.0001, N =5, 1630 participants |
| **MACE** | 0.89(0.33, 2.44), $I^2$=0%, p=0.82, N =5, 1608 participants | 5.03(0.24, 104.55), $I^2$=0%, p=0.30, N =5, 1630 participants |
| **Duration of diabetes** | | |
| **Outcome** | **duration of diabetes<20 yr** | **duration of diabetes≥20 yr** |
| **HbA1c (%)** | -0.33(-0.44, -0.22), $I^2$=0%, p<0.00001, N =4 comparisons, 902 participants | -0.36(-0.46, -0.25),, $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **FPG (mg/dL)** | -17.18(-31.70, -2.66), $I^2$=0%, p=0.01, N =4 comparisons, 902 participants | -18.19(-23.76, -12.62), $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **2h-PPG (mg/dL)** | -51.96(-67.00, -36.92), $I^2$=0%, p<0.00001, N =4 comparisons, 262 participants | -29.94(-42.98, -16.89), $I^2$=16%, p<0.00001, N =5, 277 participants |
| **Total insulin dose (IU/d)** | -7.16(-9.79, -4.53), $I^2$=0%, p<0.00001, N =4 comparisons, 902 participants | -9.75(-12.21, -7.28),, $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **Basal insulin dose (IU/d)** | -5.83 (9.47, -2.19), $I^2$=0%, p=0.002, N =4 comparisons, 902 participants | -9.14(-11.72, -6.56),, $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **Bolus insulin dose (IU/d)** | -9.42(-14.79, -4.04), $I^2$=0%, p=0.0006, N =4 comparisons, 902 participants | -9.18 (-13.47, -4.90),, $I^2$=20%, p<0.00001, N =6, 2336 participants |
| **Time-in-Range(%)** | 11.53(8.21, 14.84), $I^2$=0%, p<0.00001, N =4 comparisons, 262 participants | 7.69(1.52, 13.89), $I^2$=0%, p=0.02, N =2, 136 participants |
| **Body weight change (%)** | -3.13(-3.82, -2.44), $I^2$=0%, p<0.00001, N =4 comparisons, 902 participants | -3.13(-3.82, -2.44), $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **SystolicBP (mmHg)** | -3.50(-5.72, -1.28), $I^2$=0%, p=0.0002, N =4 comparisons, 902 participants | -4.01(-5.33, -2.70), $I^2$=13%, p<0.00001, N =6, 2336 participants |
| **DiastolicBP (mmHg)** | -1.24(-2.27, -0.21), $I^2$=0%, p=0.02, N =4 comparisons, 902 participants | -1.51(-2.14, -0.87), $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **eGFR** | -1.36(-2.47, -0.26), $I^2$=0%, p=0.02, N =4 | -0.66(-1.36, -0.04), $I^2$=0%, p=0.04, N =6, |

| | | |
|---|---|---|
| **(ml/min/1.73 $m^2$)** | comparisons, 902 participants | 2336 participants |
| **Albumin-creatinine ratio (ACR)(mg/g)** | -20.45(-33.12, -7.77), $I^2$=0%, p=0.002, N =2 comparisons, 782 participants | -15.71(-32.62, 1.21), $I^2$=0%, p=0.01, N =3, 1798 participants |
| **Hypoglycemia (events per patient-year)** | -13.68(-21.90, -5.46), $I^2$=0%, p=0.001, N =4 comparisons, 902 participants | -7.58(-11.24, -1.91), $I^2$=0%, p=0.006, N =6, 2336 participants |
| **Severe Hypoglycemia** | 0.68(0.36, 1.31), $I^2$=0%, p=0.25, N =4 comparisons, 902 participants | 0.70(0.47, 1.05), $I^2$=0%, p=0.08, N =6, 2336 participants |
| **DKA** | 4.60(1.82, 15.73), $I^2$=0%, p=0.006, N =4 comparisons, 902 participants | 4.30(1.98, 9.31), $I^2$=0%, p=0.0002, N =6, 2336 participants |
| **UTI** | 1.13(0.62, 2.07), $I^2$=0%, p=0.69, N =4 comparisons, 902 participants | 0.91(0.63, 1.32), $I^2$=0%, p=0.73, N =6, 2336 participants |
| **GTI** | 3.76(1.73, 8.16), $I^2$=0%, p=0.0008, N =4 comparisons, 902 participants | 2.95(1.92, 4.52), $I^2$=0%, p<0.00001, N =6, 2336 participants |
| **Diarrhea** | 1.85 (0.93, 3.68), $I^2$=0%, p=0.08, N =4 comparisons, 902 participants | 1.39 (0.92, 2.09), $I^2$=0%, p=0.12, N =6, 2336 participants |
| **Volume depletion events** | 1.55 (0.63, 3.83), $I^2$=0%, p=0.34, N =4 comparisons, 902 participants | 2.10 (0.92, 4.85) , $I^2$=0%, p=0.12, N =6, 2336 participants |
| **MACE** | 2.02(0.34, 12.13), $I^2$=0%, p0.44, N =4 comparisons, 902 participants | 0.82(0.17, 3.92), $I^2$=0%, p0.80, N =6, 2336 participants |
| **Background therapy** | | |
| **Outcome** | **stable insulin therapy** | **pre-randomization insulin optimization** |
| **HbA1c (5)** | -0.44(-0.52, -0.36), $I^2$=0%, p<0.00001, N =6, 1663 participants | -0.37(-0.45, -0.29), $I^2$=0%, p<0.00001, N =4, 1575 participants |
| **FPG (mg/dL)** | -20.21(-27.60, -12.83), $I^2$=0%, p<0.00001, N =6, 1663 participants | -13.46(-20.49, -6.43), $I^2$=0%, p=0.0002, N =4, 1575 participants |
| **2h-PPG (mg/dL)** | -38.72(-52.27, -25.16), $I^2$=19%, p<0.00001, N =5, 261 participants | -40.10 (-63.73, -16.47), $I^2$=0%, p=0.0009, N =4, 278 participants |
| **Total insulin dose (IU/d)** | -9.26(-11.66, -6.87), $I^2$=0%, p<0.00001, N =6, 1663 participants | -8.94(-11.98, -5.89), $I^2$=0%, p<0.00001, N =4, 1575 participants |
| **Basal insulin dose (IU/d)** | -7.38(-10.71, -4.04), $I^2$=0%, p<0.00001, N =6, 1663 participants | -8.47(-11.18, -5.76), $I^2$=0%, p<0.00001, N =4, 1575 participants |
| **Bolus insulin dose(IU/d)** | -10.12(-15.07, -5.16), $I^2$=0%, p<0.0001, N =6, 1663 participants | -8.51(-12.57, -4.45), $I^2$=0%, p<0.0001, N =4, 1575 participants |
| **Time-in-Range(%)** | 11.31(6.75, 15.87), $I^2$=0%, p<0.00001, N =6, 120 participants | 9.35(5.50, 13.21), $I^2$=0%, p<0.00001, N =4, 311 participants |
| **Body weight change(%)** | -3.48(-3.95, -3.02), $I^2$=0%, p<0.00001, N =6, 1663 participants | -3.70(-4.58, -2.83), $I^2$=0%, p<0.00001, N =4, 1575 participants |

| | | |
|---|---|---|
| **SystolicBP (mmHg)** | -6.67(-10.38, -2.96), $I^2$=0%, p=0.0004, N =6, 1663 participants | -3.27([-4.76, -1.78), $I^2$=0%, p<0.0001, N =4, 1575 participants |
| **DiastolicBP (mmHg)** | -1.43(-2.18, -0.69), $I^2$=0%, p=0.0002, N =6, 1663 participants | -1.43(-2.22, -0.65), $I^2$=0%, p=0.0004, N =4, 1575 participants |
| **eGFR (ml/min/1.73 $m^2$)** | -0.98(-1.70, -0.23), $I^2$=0%, p=0.03, N =6, 1663 participants | -1.37(-2.22, -0.52), $I^2$=0%, p=0.002, N =4, 1575 participants |
| **Albumin-creatinine ratio (ACR)(mg/g)** | -20.10(-39.57, -0.63), $I^2$=0%, p=0.04, N =1, 1402 participants | -13.92(-27.36, -0.48), $I^2$=0%, p=0.04, N =4, 1575 participants |
| **Hypoglycemia (events per patient-year)** | -7.23(-12.05, -2.40), $I^2$=0%, p=0.01, N =6, 1663 participants | -13.32(-20.81, -5.83), $I^2$=0%, p=0.0005, N =4, 1575 participants |
| **Severe Hypoglycemia** | 0.70 (0.37, 1.04), $I^2$=0%, p=0.08, N =6, 1663 participants | 0.68(0.46, 1.02), $I^2$=0%, p=0.06, N =4, 1575 participants |
| **DKA** | 3.08(1.32, 7.17), $I^2$=0%, p=0.009, N =6, 1663 participants | 6.90(1.91, 24.89), $I^2$=0%, p=0.003, N =4, 1575 participants |
| **UTI** | 0.89 (0.54, 1.45), $I^2$=0%, p=0.64, N =6, 1663 participants | 1.03(0.68, 1.55), $I^2$=0%, p0.90, N =4, 1575 participants |
| **GTI** | 2.64(1.55, 4.49), $I^2$=0%, p=0.0003, N =6, 1663 participants | 3.68(2.17, 6.24), $I^2$=0%, p<0.00001, N =4, 1575 participants |
| **Diarrhea** | 1.59 (1.03, 2.46), $I^2$=0%, p=0.04, N =6, 1663 participants | 1.51 (1.07, 2.26], $I^2$=0%, p=0.04, N =4, 1575 participants |
| **Volume depletion events** | 2.23 [0.90, 7.44], $I^2$=0%, p=0.08, N =6, 1663 participants | 1.80 (0.70, 4.65), $I^2$=0%, p=0.22, N =4, 1575 participants |
| **MACE** | 0.89(0.33, 2.44), $I^2$=0%, p=0.82, N =6, 1663 participants | 1.03 (0.24, 10.55) $I^2$=0%, p=0.78, N =4, 1575 participants |
| **Renal function at baseline** | | |
| **Outcome** | **eGFR≥60 ml/min/1.73 $m^2$** | **eGFR≥45 ml/min/1.73$m^2$** |
| **HbA1c (%)** | -0.39 (-0.63, -0.14), $I^2$=0%, p=0.0002, N =4, 174 participants | -0.37 (-0.46, -0.27), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **FPG (mg/dL)** | -18.29 (-32.87, -3.71), $I^2$=28%, p=0.01, N =4, 174 participants | -17.46(-23.00, -11.92), $I^2$=6%, p<0.00001, N =6, 3064 participants |
| **2h-PPG (mg/dL)** | -33.81(-46.92, -20.69), $I^2$=2%, p<0.00001, N =4, 174 participants | -45.63(-63.51, -27.75), $I^2$=21%, p<0.00001, N =5, 365 participants |
| **Total insulin dose (IU/d)** | -8.46 (-15.13, -1.79), $I^2$=20%, p=0.01, N =4, 174 participants | -9.03(-11.14, -6.92), $I^2$=9%, p<0.00001, N =6, 3064 participants |
| **Basal insulin dose (IU/d)** | -8.51 [-15.60,- 0.59], $I^2$=8%, p=0.03, N =4, 174 participants | -8.57 (-10.77, -6.36), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **Bolus insulin dose (IU/d)** | -17.55 (-26.14, -8.96), $I^2$=0%, p=0.01, N =4, 174 participants | -9.04 (-12.21, -5.86), $I^2$=6%, p<0.00001, N =4, 3064 participants |

| | | |
|---|---|---|
| **Time-in-Range(%)** | 11.80 (3.50, 20.10), $I^2$=NA, p=0.005, N =1, 33 participants | 9.44 (5.88, 12.99), $I^2$=17%, p<0.00001, N =5, 365 participants |
| **Body weight change (%)** | -2.98 (-5.02, -0.95), $I^2$=0%, p=0.0006, N =4, 174 participants | -3.64 (-4.16, -3.11), $I^2$=35%, p<0.00001, N =6, 3064 participants |
| **SystolicBP (mmHg)** | -7.93(-13.06, -2.80), $I^2$=0%, p=0.0002, N =4, 174 participants | -3.71(-4.64, -2.78), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **DiastolicBP (mmHg)** | -1.53(-2.59, -0.46), $I^2$=28%, p=0.005, N =4, 174 participants | -1.51(-2.33, -0.70), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **eGFR (ml/min/1.73 $m^2$)** | -1.21(-3.99, -0.57), $I^2$=0%, p=0.04, N =4, 174 participants | -0.78 [-1.42, -0.15], $I^2$=0%, p=0.02, N =6, 3064 participants |
| **Albumin-creatinine ratio (ACR)(mg/g)** | No study | -14.57(-26.87, -2.28), $I^2$=0%, p=0.02, N =5, 2977 participants |
| **Hypoglycemia (events per patient-year)** | -9.70 [-19.50, -3.11], $I^2$=0%, p=0.01, N =4, 174 participants | -9.47 (-14.55, -4.38), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **Severe Hypoglycemia** | 0.49 (0.11, 2.06), $I^2$=0%, p=0.33, N =4, 174 participants | 0.71 (0.50, 1.01), $I^2$=0%, p=0.06, N =6, 3064 participants |
| **DKA** | 8.06(1.04, 22.25), $I^2$=0%, p=0.04, N =4, 174 participants | 4.72 (1.99, 11.21), $I^2$=0%, p=0.0002, N =6, 3064 participants |
| **UTI** | 0.35 (0.08, 1.59), $I^2$=0%, p=0.91, N =4, 174 participants | 1.01 (0.73, 1.40), $I^2$=0%, p=0.76, N =6, 3064 participants |
| **GTI** | 2.29 (1.07, 7.71), $I^2$=0%, p=0.04, N =4, 174 participants | 3.38 (2.30, 4.98), $I^2$=0%, p<0.00001, N =6, 3064 participants |
| **Diarrhea** | 1.50 [1.08, 3.10], $I^2$=0%, p=0.04, N =4, 174 participants | 1.53 (1.09, 2.14), $I^2$=0%, p=0.03, N =6, 3064 participants |
| **Volume depletion events** | 3.85 (0.89, 6.48), $I^2$=0%, p=0.13, N =4, 174 participants | 2.23 (0.91, 4.60), $I^2$=0%, p=0.33, N =6, 3064 participants |
| **MACE** | No events, N =4, 174 participants | 1.06 (0.40, 2.82), $I^2$=0%, p=0.91, N =6, 3064 participants |

## Sensitivity analysis: Peto Odds Ratio, fixed-effect model

| **Outcome** | **OR(95%CI), $I^2$, statistical significance, N-comparisons, participants** |
|---|---|
| **Severe Hypoglycemia** | 0.68(0.46, 0.98), $I^2$=0%, p=0.04,N=10, 3238 participants |
| **DKA** | 3.92 (2.37, 6.47), $I^2$=0%, p<0.00001, N=10, 3238 participants |
| **UTI** | 0.98(0.71, 1.37), $I^2$=0%, p=0.92, N=10, 3238 participants |
| **GTI** | 2.85(2.10, 3.87), $I^2$=0%, p<0.00001, N=10, 3238 participants |
| **Diarrhea** | 1.55 (1.11, 2.16), $I^2$=0%, p=0.01, N=10, 3238 participants |

| | |
|---|---|
| **Nausea-vomiting** | 0.97(0.32, 2.96), $I^2$=0%, p=0.96, N=10, 3238 participants |
| **Headache** | 1.69(0.26, 11.04), $I^2$=0%, p=0.58, N=10, 3238 participants |
| **Sinusitis** | 1.07(0.06, 18.62), $I^2$=0%, p=0.91, N=10, 3238 participants |
| **Nasopharyngitis** | 1.07(0.14, 8.39), $I^2$=0%, p=0.91, N=10, 3238 participants |
| **Renal events** | 1.19(0.57, 2.45),$I^2$=0%, p=0.65, N=10, 3238 participants |
| **Acidosis-related Events** | 3.70 (2.80, 4.90), $I^2$=0%, p<0.00001, N=10, 3238 participants |
| **Volume depletion events** | 2.64 (1.44, 4.83), $I^2$=0%, p=0.01, N=10, 3238 participants |
| **Bone fractures** | 0.70(0.39, 1.25), $I^2$=0%, p=0.23, N=10, 3238 participants |
| **Amputation** | 3.40(0.26, 18.38)$I^2$=0%, p=0.38, N=10, 3238 participants |
| **Suspected drug-duced liver injury** | 1.01(0.09, 11.13), $I^2$=0%, p=0.99, N=10, 3238 participants |
| **Serious AEs** | 1.13(0.86, 1.48), $I^2$=0%, p=0.39, N=10, 3238 participants |
| **AEs leading to Discontinuation** | 1.57 (1.06, 2.34), $I^2$=0%, p=0.02, N=10, 3238 participants |
| **MACE** | 1.15(0.48, 2.80), $I^2$=0%, p=0.75, N=10, 3238 participants |
| **Cancer** | 0.67(0.22, 2.11), I2=0%, p=0.75, N=10, 3238 participants |
| **All-cause deaths** | 0.19 (0.03, 1.51), $I^2$=0%, p=0.12, N=10, 3238 participants |

Abbreviations: AE: adverse events; FPG: fasting plasma glucose; MACE: major adverse cardiovascular outcomes DKA: diabetic ketoacidosis; GTI: genital tract infections; PPG: postprandial plasma glucose; UTI: urinary tract infections

**Supplementary Table 4**. Dose-response interactions: within-trial analysis of the pooled data from three RCTs[28,30,31]. Only statistically significant interactions between evaluated outcomes and sotagliflozin doses are reported.

| Outcome | Sotagliflozin 200 mg vs. 75 mg | Sotagliflozin 400 mg vs. 200 mg |
|---|---|---|
| **HbA1c(%)** | -0.24 (-0.62, 0.14) $I^2$=NA, p=0.22, N =1, 70 participants | -0.22 (-0.28, -0.12) , $I^2$=0%, p=0.001, N =3, 1119 participants |
| **FPG (mg/dL)** | 0.0 (-14.06, 14.06), $I^2$=NA, p=1.00, 1.0 N =1, 70 participants | -9.82 (-17.05, -2.58), $I^2$=0%, p=0.008, N =3, 1119 participants |
| **2h-PPG (mg/dL)** | -8.00(-27.46, 11.46), $I^2$=NA, p<0.00001, N =1, 70 participants | -20.51 (-33.98, -7.03), $I^2$=0%, p=0.003, N =3, 1119 participants |
| **Total insulin dose (%)** | 2.60(-6.78, 11.98), $I^2$=0%, p=0.77, N =1, 70 participants | -5.25(-7.66, -2.84), $I^2$=0%, p<0.0001, N =3, 1119 participants |
| **Basalinsulin dose (%)** | -0.10(-11.11, 10.91), $I^2$=0%, p=0.99, N =1, 70 participants | -4.64(-8.64, -0.64), $I^2$=0%, p=0.01, N =3, 1119 participants |
| **Bolus insulin dose (%)** | -2.80(-8.48, 14.08), $I^2$=0%, p=0.89, N =1, 70 participants | -7.85(-11.96, -3.75), $I^2$=0%, p=0.0002, N =3, 1119 participants |
| **Time-in-range(%)** | No study | 6.48(2.97, 9.99), $I^2$=0%, p=0.0003, N =2, 185 participants |
| **Average daily Glucose(mg/dL)** | No study | -11.02(-17.70, -4.33), $I^2$=0%, p=0.001, N =2, 185 participants |
| **Urinary glucose Excretion(g/24 hr)** | 16.00(3.06, 28.94), p=0.03, N =1, 70 participants | 13.00(-1.78, 27.78), p=0.20, N =1, 70 participants |
| **Body weight (%)** | -1.33(-3.37, 0.71), p=0.20, N =1, 70 participants | -0.96 (-1.55, -0.37), $I^2$=0%, p=0.001, N =3, 1119 participants |
| **Systolic BP(mmHg)** | 1.60(-7.42, 10.62), p=0.53, N =1, 70 participants | -2.51 (-3.83, -1.20), $I^2$=0%, p=0.0002, N =3, 1119 participants |
| **eGFR (ml/min/1.73 $m^2$)** | -0.26(-4.95, 4.43), p=0.91, N =1, 70 participants | 1.05(0.11, 2.12], p=0.03, N =1, N =3, 1119 participants |
| **Urinary albumin/creatinine ratio (ACR)(mg/g)** | No study | -12.29 (-26.81, -1.23), $I^2$=0%, p=0.03, N =3, 1049 participants |

**Supplementary Table 5: Summary of main findings of meta-analysis for safety outcomes in included RCTs**

| Outcome | Studies (n) | Events/Participants (n/N) | | Effect estimate [95%CI] | $I^2$ (%) |
|---|---|---|---|---|---|
| | | Sotagliflozin | Control | | |
| **Hypoglicemia(events per patient-year)** | **6** | **87/1912** | **98/1326** | **MD: -7.69 (-13.25, -2.13)** | **0** |
| **Severe hypoglycemia** | **6** | **68/1912** | **57/1326** | **RR: 0.69 (0.49, 0.98)** | **0** |
| **Diabetic ketoacidosis (DKA)** | **6** | **61/1912** | **6/1326** | **RR: 3.93 (1.94, 7.96)** | **0** |
| **Occurring at blood glucose>250 mg/dL n(% total events)** | | 42 (69%) | 4 (67%) | | |
| **Occurring at blood glucose≥150-250 mg/dL n(% total events)** | | 19(31%) | 2(33%) | | |
| **Occurring at blood glucose<150-mg/dL n(% total events)** | | 0 (0%) | 0 (0%) | | |
| **Urinary tract infections (UTIs)** | **6** | **96/1912** | **63/1326** | **RR: 0.97 (0.71, 1.33)** | **0** |
| **Genital mycotic infections (GTIs)** | **6** | **161/1912** | **31/1326** | **RR: 3.12 (2.14, 4.54)** | **0** |
| **Diarrhea** | **6** | **114/1912** | **46/1326** | **RR: 1.50 (1.08, 2.10)** | **0** |
| **Nausea-vomiting** | **6** | **8/ 1912** | **7/1326** | **RR: 0.60 (0.12, 2.94)** | **0** |
| **Headache** | **6** | **3/1912** | **2/1326** | **RR: 1.59 (0.30, 8.33]** | **0** |
| **Sinusitis** | **6** | **1/1912** | **1/1326** | **RR: 1.07 [0.06, 15.62)** | **0** |
| **Nasopharingytis** | **6** | **2/1912** | **2/1326** | **RR: 1.07 (0.13, 8.67)** | **0** |
| **Renal events** | **6** | **21/1912** | **11/1326** | **RR: 1.16 (0.56, 2.40)** | **0** |
| **Acidosis-related events** | **6** | **187/1912** | **32/1326** | **RR: 3.85 (2.33, 6.36)** | **23** |
| **Volume depletion events** | **6** | **38/1912** | **8/1326** | **RR: 2.19 (1.10, 4.36)** | **0** |
| **Bone fractures** | **6** | **29/1912** | **23/1326** | **RR: 0.71 (0.40, 1.24)** | **0** |
| **Amputation** | **6** | **2/1912** | **0/1326** | **RR: 3.02** | **0** |

| | | | | | |
|---|---|---|---|---|---|
| | | | | **(0.31, 29.09)** | |
| **Suspected drug-induced liver injury** | **6** | **2/1912** | **1/1326** | **RR: 0.44 (0.07, 2.76)** | **0** |
| **Venous thromboembolism** | 6 | 0/1877 | 0/1888 | - | - |
| **Serious AEs** | **6** | **109/1912** | **143/1326** | **RR: 1.29 (0.89, 1.82)** | **0** |
| **AEs leading to discontinuation** | **6** | **81/1912** | **31/1326** | **RR: 1.34 (0.78, 2.30)** | **25** |
| **Hypoglycemia** | | **1 (1%)*** | **3(3%)*** | | |
| **Severe hypoglycemia** | | **4(6%)*** | **3(5%)*** | | |
| **Diabetic ketoacidosis (DKA)** | | **23(38%)*** | **1(17%)*** | | |
| **Urinary tract infections (UTIs)** | | **3(3%)*** | **4(6%)*** | | |
| **Genital tract infections (GTIs)** | | **9(6%)*** | **3(10%)*** | | |
| **Diarrhea** | | **8(7%)*** | **3(7%)*** | | |
| **Volume depletion events** | | **1(4%)*** | **1(12%)*** | | |
| **Major adverse cardiovascular outcomes (MACE)** | **6** | **15/1912** | **7/1326** | **RR: 1.06 (0.40, 2.82)** | **0** |
| **AMI** | | 8 | 3 | | |
| **Stroke** | | 1 | 2 | | |
| **Hospitalization for HF/UA** | | 0 | 0 | | |
| **Coronary revascularization** | | 6 | 2 | | |
| **Cancer** | **6** | **7/1912** | **4/1326** | **RR: 0.86 (0.25, 2.97)** | **0** |
| **Breast** | | 2 | 2 | | |
| **Lung** | | 3 | 2 | | |
| **Thyroid** | | 1 | 0 | | |
| **Melanoma** | | 1 | 0 | | |
| **All-cause death** | **6** | **1/1912** | **3/1326** | **RR: 0.35 (0.07, 1.70)** | **0** |

**Abbreviations:** AE : adverse events; VTE:Venousthromboembolism;Sota: sotagliflozin;TID: total daily insulin dose; plcb: placebo; HF: heart failure; UA: unstable angina.

*the percentage refers to the percentage of all patients experiencing that AE

For all outcomes, the length of follow-up ranged 4 to 52 weeks