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Clinical Adverse Events of High-Dose vs Low-Dose Sodium–Glucose Cotransporter 2 Inhibitors in Type 2 Diabetes

A Meta-Analysis of 51 Randomized Clinical Trials

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J Clin Endocrinol Metab. 2020;105(11)

Abstract and Introduction

Abstract

Aims: The aims of this work are to assess the clinical adverse events (AEs) of high-dose vs low-dose sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) in patients with type 2 diabetes mellitus (T2DM).

Methods: We searched MEDLINE, EMBASE, and Cochrane Library from January 1, 2006 to March 10, 2020, for identifying eligible randomized clinical trials (RCTs) that reported AEs by high-dose and low-dose SGLT2 inhibitors in T2DM patients. Random-effects models was used to obtain summary relative risks (RRs) with associated 95% CIs. Prespecified subgroup analyses according to individual SGLT2 inhibitors and follow-up duration, and leave-one-out sensitivity analysis were conducted.

Results: A total of 51 RCTs involving 24 371 patients (12 208 received high-dose and 12 163 received low-dose SGLT2 inhibitors) were included. Overall, the heterogeneity among included studies was relatively low (I^2 < 50% for each outcome). No significant differences between high-dose and low-dose SGLT2 inhibitors were observed for overall safety (including any AEs, serious AEs, AEs leading to discontinuation, and death) and specified safety (including infections and infestations, musculoskeletal disorders, gastrointestinal disorders, osmotic diuresis-related AEs, volume-related AEs, renal-related AEs, and metabolism and nutrition), except for a mild increase in risk for AEs related to study drugs (RR: 1.08; 95% CI, 1.01–1.16) that mainly derived from canagliflozin (RR: 1.17; 95% CI, 1.05–1.30). Subgroup analyses were consistent with the primary outcomes.

Conclusions: This study provided substantial evidence that AEs of SGLT2 inhibitors were not dose related.

Introduction

Diabetes mellitus is estimated to affect more than 415 million people worldwide, and type 2 diabetes mellitus accounts for more than 90%.[1] American Diabetes Association guidelines in 2020 recommended metformin as the first-line therapy for type 2 diabetic patients.[2] Recently, for type 2 diabetic patients with cardiovascular diseases, sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have been regarded as the initial treatment according to the guidelines of the European Society of Cardiology and the European Association for the Study of Diabetes.[3]

SGLT2 inhibitors, as a novel class of antidiabetic drugs, can reduce the reabsorption of renal tubular glucose and subsequently cause the excretion of urine glucose.[4] SGLT2 inhibitors have favorable effects on blood glucose control as well as cardiovascular and renal benefits;[5] however, certain safety issues, such as infection-related[6–8] and renal-related adverse events (AEs),[9–11] have been raised with the extensive clinical application of SGLT2 inhibitors. The US Food and Drug Administration (FDA) has published a series of safety communications, including the risk of necrotizing fasciitis with all SGLT2 inhibitors; risk of serious urinary tract infections, ketoacidosis, and acute kidney injury related to canagliflozin and dapagliflozin; risk of leg/foot amputations; and bone fractures associated with canagliflozin.[12–16] Our previous meta-analysis has given a comprehensive picture of the overall noncardiovascular safety of SGLT2 inhibitors. It validated the FDA safety alerts and detected additional safety issues including osmotic diuresis-related AEs, volume-related AEs, and hypoglycemia,[17] but we did not assess the association of AEs with different dosages of SGLT2 inhibitors. To date only 2 meta-analyses have evaluated certain AEs on low- and high-dose of canagliflozin and empagliflozin.[18,19] But these studies did not concern the overall safety of all approved SGLT2 inhibitors. Therefore, we aimed to summarize all approved SGLT2 inhibitors from randomized clinical trials (RCTs) for a comprehensive AEs evaluation of SGLT2 inhibitors at high and low doses.

Materials and Methods

This systematic review and meta-analysis was established according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) Statement and Cochrane Collaboration[17,20,21] and a prior protocol (PROSPERO: CRD42020172149).

Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane library from January 1, 2006 to March 10, 2020, with a language restriction of English, using Medical Subject Heading search and free-text terms related to SGLT2 inhibitors and terms related to RCTs. References of included studies, review articles, and meta-analysis were also checked to identify additional trials. Details of study selection are provided in Table S1.[22]

Study Selection and Outcomes

Studies were eligible for inclusion criteria if they were RCTs; included patients with type 2 diabetes mellitus; received SGLT2 inhibitors with monotherapy or multidrug therapy; divided SGLT2 inhibitors according to approved high dosage and low dosage; reported AEs; and had more than 12 weeks of follow-up duration. Observational studies, pooled-analyses, and abstracts or letters were excluded. Two authors (F.S. and H.L.) independently reviewed each title and abstract, and assessed full texts of retrieved studies, with any disagreements being resolved via consultation with the corresponding author (Z.G.). The outcomes of this study were overall safety outcomes (including any AEs, serious AEs, AEs leading to discontinuation, AEs related to study drugs, and death associated with AEs), specified safety outcomes (including infections and infestations, musculoskeletal disorders, gastrointestinal disorders, osmotic diuresis-related AEs, volume-related AEs, renal-related adverse events, metabolism and nutrition, and other AEs), and clinically related AEs (for example, urinary tract infection, genital mycotic infection, and hypoglycemia). AEs related to study drugs were determined to be possibly, probably, or very likely related to the study drug, as assessed by investigators. Infections and infestations included urinary tract infection, genital mycotic infection, respiratory tract infection, bronchitis, nasopharyngitis, influenza, and gastroenteritis. Musculoskeletal disorders encompassed back pain, arthralgia, and pain in extremity. Gastrointestinal disorders included nausea, diarrhea, constipation, and vomiting. Osmotic diuresis-related disorders included pollakiuria, polyuria, nocturia, dry mouth, dry throat, micturition urgency, polydipsia, thirst, and increased urine output. Volume-related AEs included dehydration, dizziness postural or dizziness, hypotension, orthostatic hypotension, orthostatic intolerance, presyncope, and syncope. Renal-related AEs included increased blood creatinine, renal impairment, renal failure (chronic or acute), glomerular filtration and urine β2 macroglobulin increase, and microalbuminuria. Metabolism and nutrition included dyslipidemia and hyperuricemia.

Data Extraction

Data were independently extracted by 2 authors (F.S. and H.L.) using an a priori designed form that included study characteristics, patient demographics, and clinical characteristics. The overall main safety outcomes of SGLT2 inhibitors have been reported in our previous study;[17] we therefore extracted only the outcome data related to individual SGLT2 inhibitors at high and low dosages. If multiple publications existed in a particular RCT, we extracted only data from the publication with the longest duration of follow-up.

Quality Assessment and Bias Assessment

The methodological quality of included RCTs was assessed according to the Cochrane Collaboration Risk of Bias Tool,[23] which included random sequence generation, allocation concealment, masking, incomplete outcome data, selective reporting, and other bias.

Data Analysis

We used forest plots to measure the outcomes, and relative risks (RRs) and associated 95% CI were calculated using random-effects models. Heterogeneity among the studies was explored using the I^2 statistic (significance for I^2 > 50%).[24] Prespecified subgroup analyses were conducted according to individual SGLT2 inhibitors (dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and luseogliflozin) and duration of follow-up (> 26 weeks and < 26 weeks). Interaction analysis was performed to assess the comparability of outcomes across individual SGLT2 inhibitors and different follow-up duration. Leave-one-out sensitivity analysis was applied to detect the robustness of the results. Potential publication bias was evaluated by visually inspecting funnel plots as well as quantitative analysis of the Begg test and Egger test.[25] Statistics were performed using STATA software (version 12.0, STATA Corporation), with a *P* value of less than .05 considered statistically significant.

Results

Search Results and Study Evaluation

Our initial search identified 12 587 recorded from databases; 11 720 records were excluded by screening titles and abstracts. Ultimately, 51 RCTs (overall: 24 371 patients; high-dose: 12 208 patients; low-dose: 12 163 patients) fulfilled the inclusion criteria, including 6 SGLT2 inhibitors individuals (17 RCTs for empagliflozin: 10 mg vs 25 mg; 13 for canagliflozin: 100 mg vs 300 mg; 12 for dapagliflozin: 5 mg vs 10 mg; 6 for ertugliflozin: 5 mg vs 15mg; 2 for luseogliflozin: 2.5 mg vs 5 mg; and 1 for ipragliflozin: 50 mg vs 100 mg) (Figure 1). The characteristics of the included trials are presented in Table S2.[22] Among 51 trials, 34 enrolled mainly Caucasian individuals, 14 Asians, and the remaining 3 were unclear. The durations of follow-up ranged from 12 weeks to 161 weeks, with a mean follow-up time of 43.9 weeks. Across all study groups, the mean age of the participants was 57.8 years, mean baseline glycated hemoglobin (HbA_{1c} %) was 8.1%, mean baseline body mass index was 30.5 kg/m^2, and mean diabetic duration was 7.9 years.

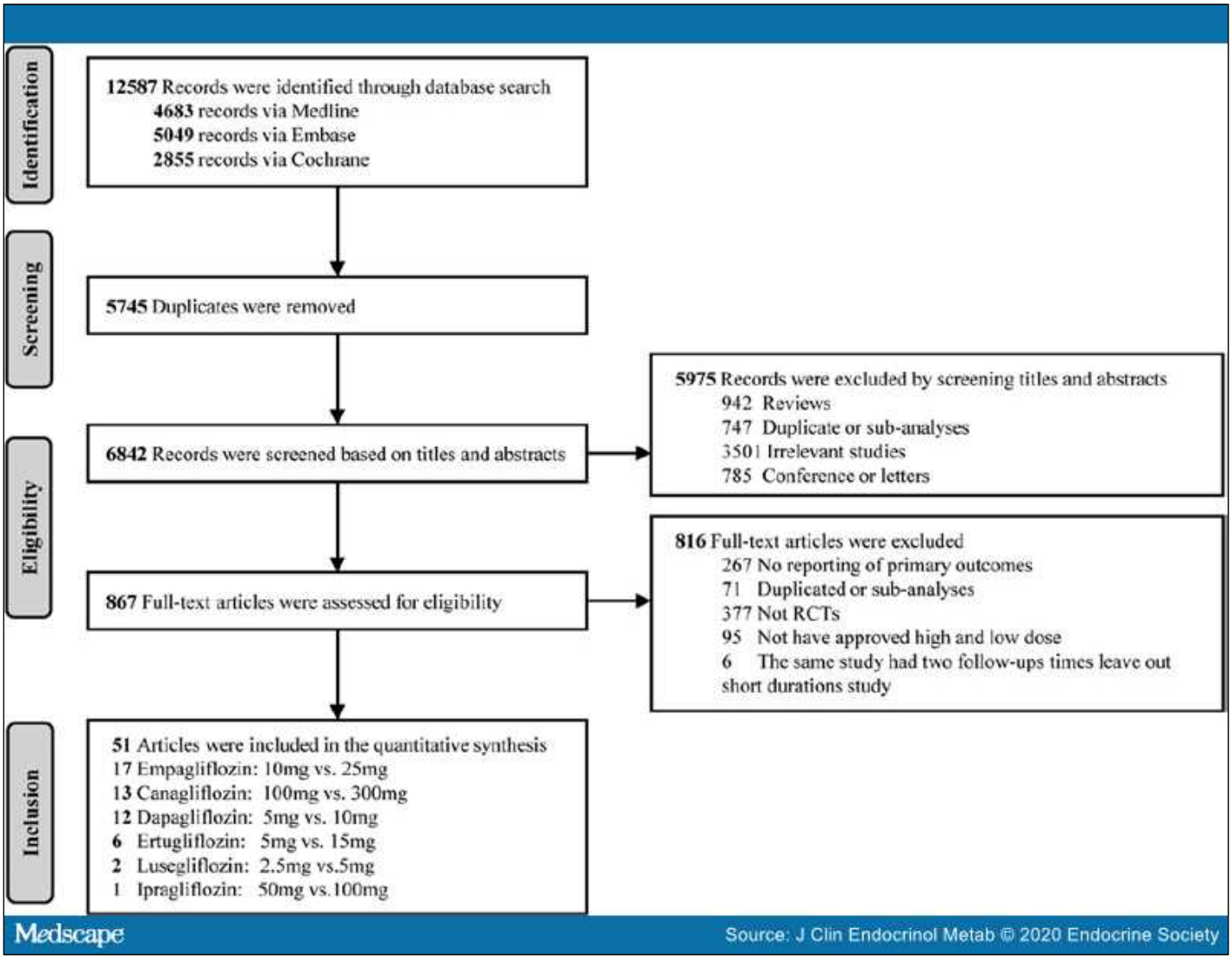


Figure 1.

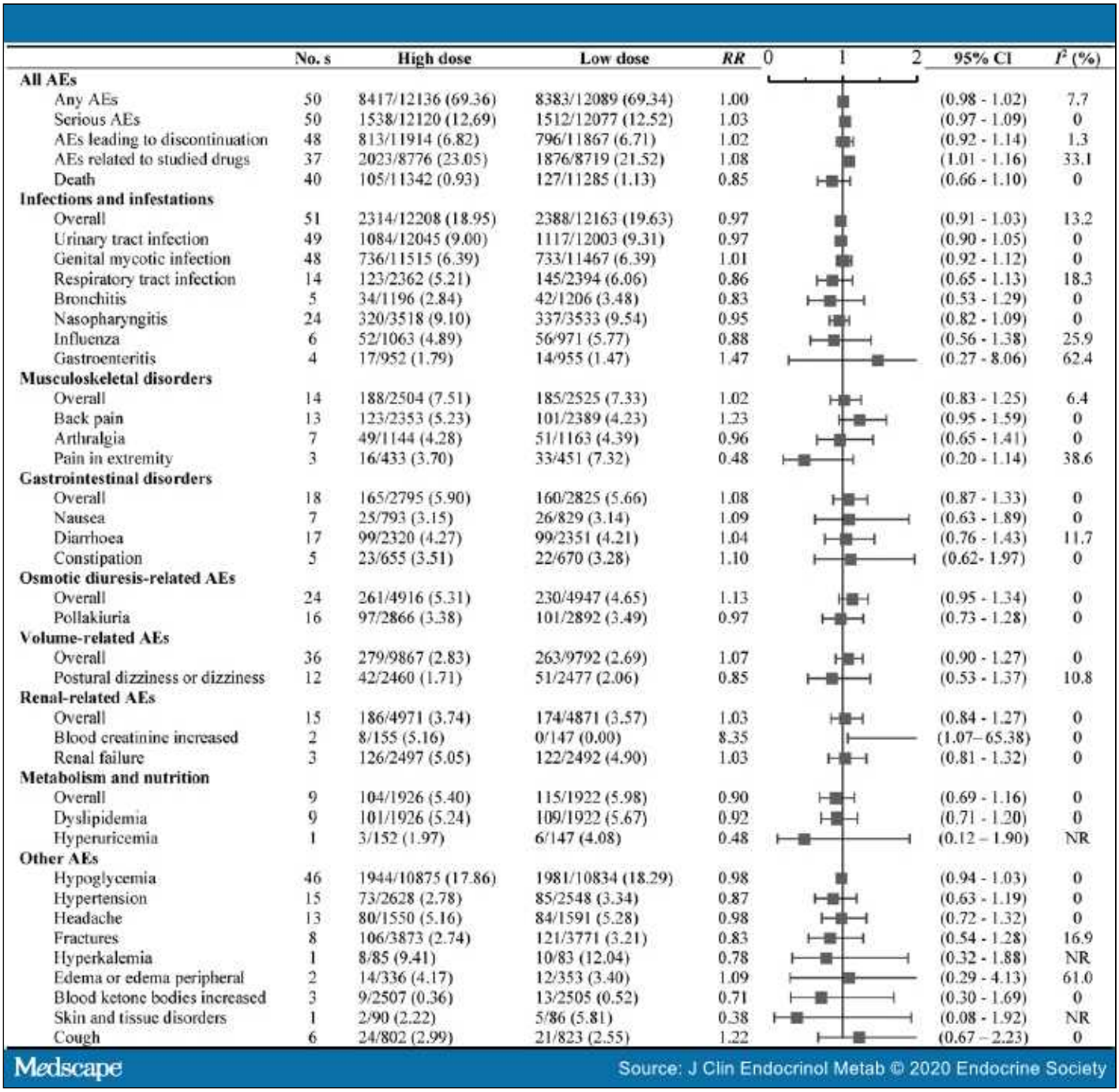
Flow diagram for the selection of eligible randomized clinical trials (RCTs).

Risk of Bias

Assessment of study quality is presented in Table S3.[22] All 51 studies had low risk in terms of randomized sequence generation, blinding of outcome assessment, incomplete outcome data, and selective reporting. Seven studies contained double-blinded data and open-label data, and only data within double-blinded periods were included in this study. Therefore, most of the included studies were judged to have a low risk of bias.

Safety Outcomes

Overall Safety. The results of overall safety outcomes are summarized in Figure 2. Overall, the heterogeneity among included studies was relatively low (I^2 < 50% for each outcome). The incidence of any AEs was 69.4% (8417/12 136) in high-dose SGLT2 inhibitors compared with 69.3% (8383/12 089) in low-dose SGLT2 inhibitors, indicating a similar risk between 2 dosage groups. Also, no significant differences between high-dose and low-dose SGLT2 inhibitors were observed in terms of serious AEs, AEs leading to discontinuation, or death associated AEs. AEs related to studied drugs were slightly higher in patients taking high-dose SGLT2 inhibitors than in those receiving low-dose SGLT2 inhibitors (RR, 1.08; 95% CI, 1.01–1.16; I^2, 33.1%). As for individual SGLT2 inhibitors, the overall results were consistent with the primary analyses, without finding a significant difference across individual SGLT2 inhibitors ($P_{interaction}$ > .05 for each outcome; Figures 3–6). Notably, the increased risk of AEs related to studied high-dose vs low-dose drugs was mainly derived from canagliflozin (RR, 1.17; 95% CI, 1.05–1.30; I^2, 31.6%). As for follow-up duration, the overall results were also in line with the primary analyses ($P_{interaction}$ > .05 for each outcome; Table S4[22]). A higher risk for AEs related to the studied drugs was observed in groups with follow-up of greater than 26 weeks (RR, 1.10; 95% CI, 1.02–1.19; I^2, 31.2%).



	No. s	High dose	Low dose	RR	95% CI	I^2 (%)
All AEs						
Any AEs	50	8417/12136 (69.36)	8383/12089 (69.34)	1.00	(0.98 - 1.02)	7.7
Serious AEs	50	1538/12120 (12.69)	1512/12077 (12.52)	1.03	(0.97 - 1.09)	0
AEs leading to discontinuation	48	813/11914 (6.82)	796/11867 (6.71)	1.02	(0.92 - 1.14)	1.3
AEs related to studied drugs	37	2023/8776 (23.05)	1876/8719 (21.52)	1.08	(1.01 - 1.16)	33.1
Death	40	105/11342 (0.93)	127/11285 (1.13)	0.85	(0.66 - 1.10)	0
Infections and infestations						
Overall	51	2314/12208 (18.95)	2388/12163 (19.63)	0.97	(0.91 - 1.03)	13.2
Urinary tract infection	49	1084/12045 (9.00)	1117/12003 (9.31)	0.97	(0.90 - 1.05)	0
Genital mycotic infection	48	736/11515 (6.39)	733/11467 (6.39)	1.01	(0.92 - 1.12)	0
Respiratory tract infection	14	123/2362 (5.21)	145/2394 (6.06)	0.86	(0.65 - 1.13)	18.3
Bronchitis	5	34/1196 (2.84)	42/1206 (3.48)	0.83	(0.53 - 1.29)	0
Nasopharyngitis	24	320/3518 (9.10)	337/3533 (9.54)	0.95	(0.82 - 1.09)	0
Influenza	6	52/1063 (4.89)	56/971 (5.77)	0.88	(0.56 - 1.38)	25.9
Gastroenteritis	4	17/952 (1.79)	14/955 (1.47)	1.47	(0.27 - 8.06)	62.4
Musculoskeletal disorders						
Overall	14	188/2504 (7.51)	185/2525 (7.33)	1.02	(0.83 - 1.25)	6.4
Back pain	13	123/2353 (5.23)	101/2389 (4.23)	1.23	(0.95 - 1.59)	0
Arthralgia	7	49/1144 (4.28)	51/1163 (4.39)	0.96	(0.65 - 1.41)	0
Pain in extremity	3	16/433 (3.70)	33/451 (7.32)	0.48	(0.20 - 1.14)	38.6
Gastrointestinal disorders						
Overall	18	165/2795 (5.90)	160/2825 (5.66)	1.08	(0.87 - 1.33)	0
Nausea	7	25/793 (3.15)	26/829 (3.14)	1.09	(0.63 - 1.89)	0
Diarrhoea	17	99/2320 (4.27)	99/2351 (4.21)	1.04	(0.76 - 1.43)	11.7
Constipation	5	23/655 (3.51)	22/670 (3.28)	1.10	(0.62- 1.97)	0
Osmotic diuresis-related AEs						
Overall	24	261/4916 (5.31)	230/4947 (4.65)	1.13	(0.95 - 1.34)	0
Pollakiuria	16	97/2866 (3.38)	101/2892 (3.49)	0.97	(0.73 - 1.28)	0
Volume-related AEs						
Overall	36	279/9867 (2.83)	263/9792 (2.69)	1.07	(0.90 - 1.27)	0
Postural dizziness or dizziness	12	42/2460 (1.71)	51/2477 (2.06)	0.85	(0.53 - 1.37)	10.8
Renal-related AEs						
Overall	15	186/4971 (3.74)	174/4871 (3.57)	1.03	(0.84 - 1.27)	0
Blood creatinine increased	2	8/155 (5.16)	0/147 (0.00)	8.35	(1.07– 65.38)	0
Renal failure	3	126/2497 (5.05)	122/2492 (4.90)	1.03	(0.81 - 1.32)	0
Metabolism and nutrition						
Overall	9	104/1926 (5.40)	115/1922 (5.98)	0.90	(0.69 - 1.16)	0
Dyslipidemia	9	101/1926 (5.24)	109/1922 (5.67)	0.92	(0.71 - 1.20)	0
Hyperuricemia	1	3/152 (1.97)	6/147 (4.08)	0.48	(0.12 – 1.90)	NR
Other AEs						
Hypoglycemia	46	1944/10875 (17.86)	1981/10834 (18.29)	0.98	(0.94 - 1.03)	0
Hypertension	15	73/2628 (2.78)	85/2548 (3.34)	0.87	(0.63 - 1.19)	0
Headache	13	80/1550 (5.16)	84/1591 (5.28)	0.98	(0.72 - 1.32)	0
Fractures	8	106/3873 (2.74)	121/3771 (3.21)	0.83	(0.54 - 1.28)	16.9
Hyperkalemia	1	8/85 (9.41)	10/83 (12.04)	0.78	(0.32 - 1.88)	NR
Edema or edema peripheral	2	14/336 (4.17)	12/353 (3.40)	1.09	(0.29 - 4.13)	61.0
Blood ketone bodies increased	3	9/2507 (0.36)	13/2505 (0.52)	0.71	(0.30 - 1.69)	0
Skin and tissue disorders	1	2/90 (2.22)	5/86 (5.81)	0.38	(0.08 - 1.92)	NR
Cough	6	24/802 (2.99)	21/823 (2.55)	1.22	(0.67 – 2.23)	0

Figure 2.

Main adverse events of high-dose vs low-dose SGLT2 inhibitors. AEs, adverse events; I^2, heterogeneity; No. s, numbers of studies; RR, relative risk; SGLT2, sodium–glucose cotransporter 2.

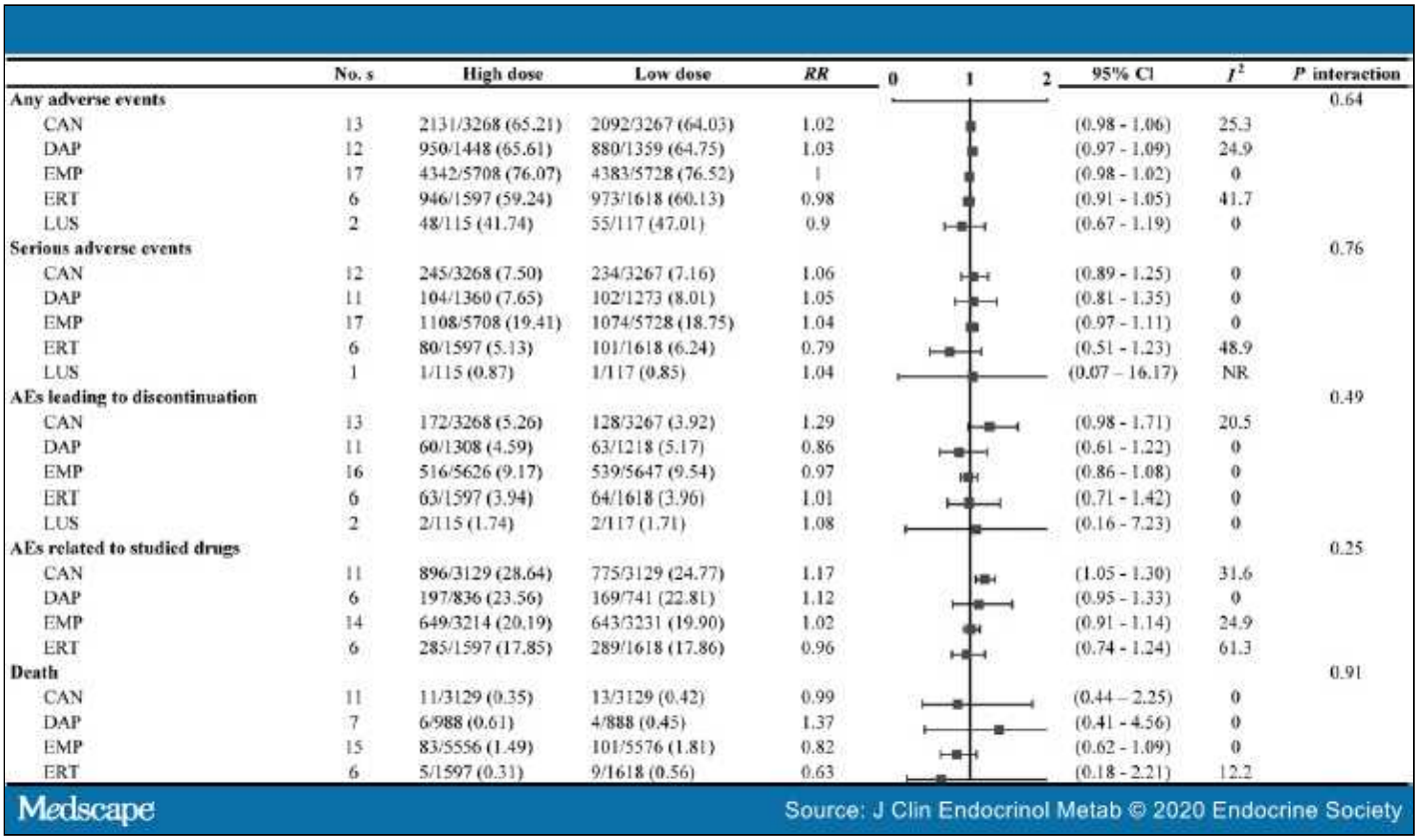


Figure 3.

Subgroup analysis of overall adverse events of different SGLT2 inhibitors. AEs, adverse events; CAN, canagliflozin; DAP, dapagliflozin; EMP, empagliflozin; ERT, ertugliflozin; I^2, heterogeneity; LUS, luseogliflozin; No. s, numbers of studies; NR, not reported; RR, relative risk; SGLT2, sodium–glucose cotransporter 2.

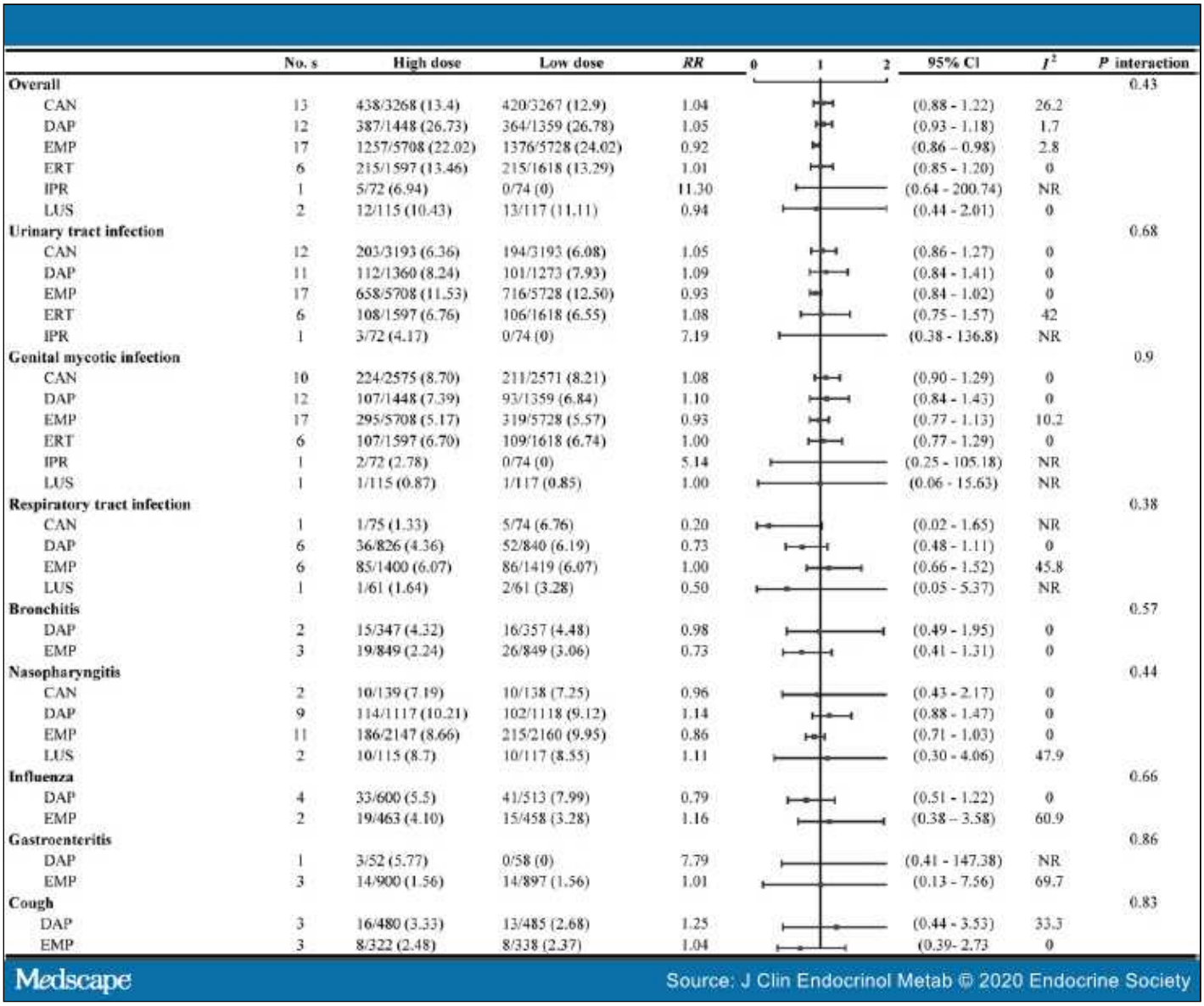
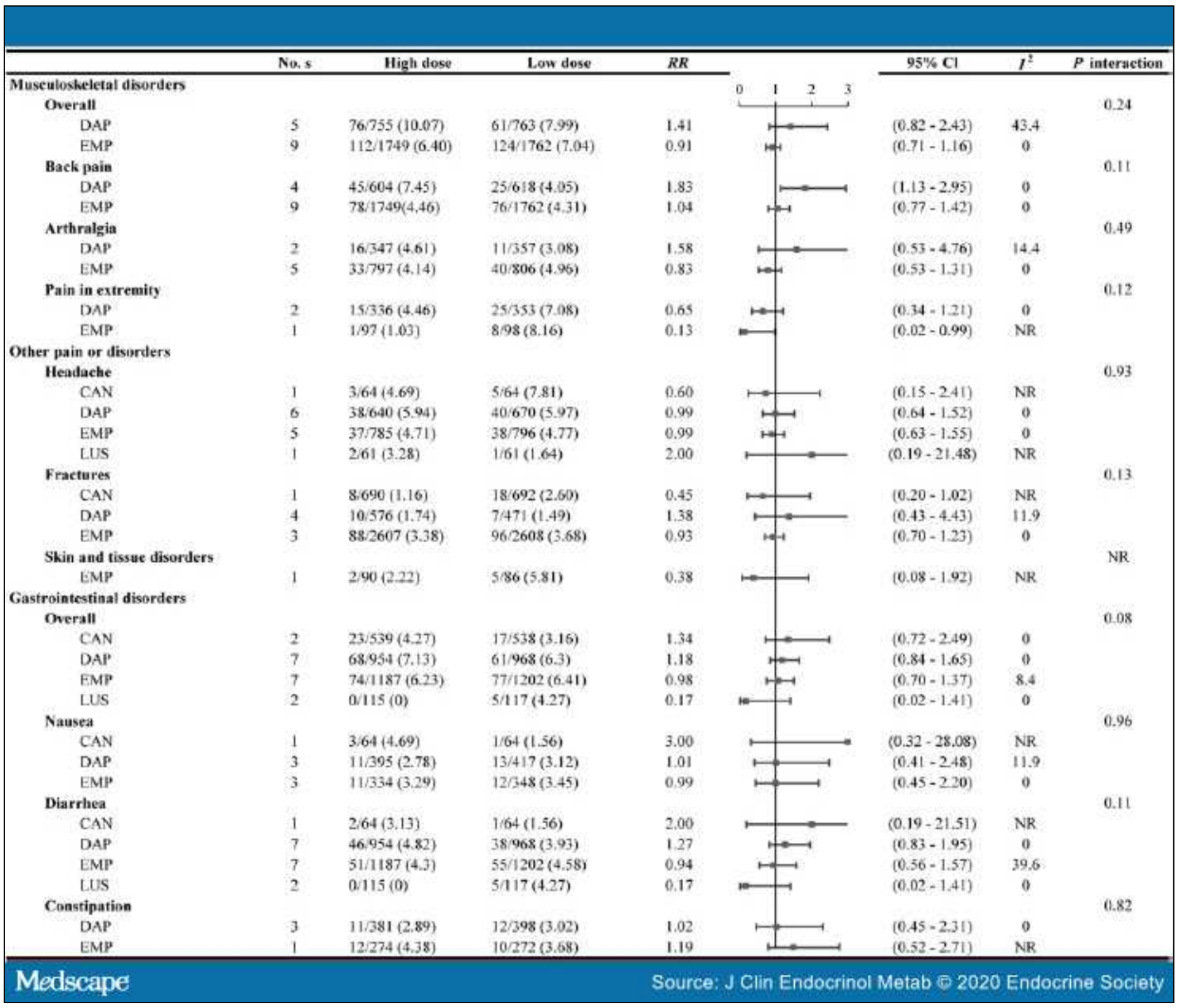


Figure 4.

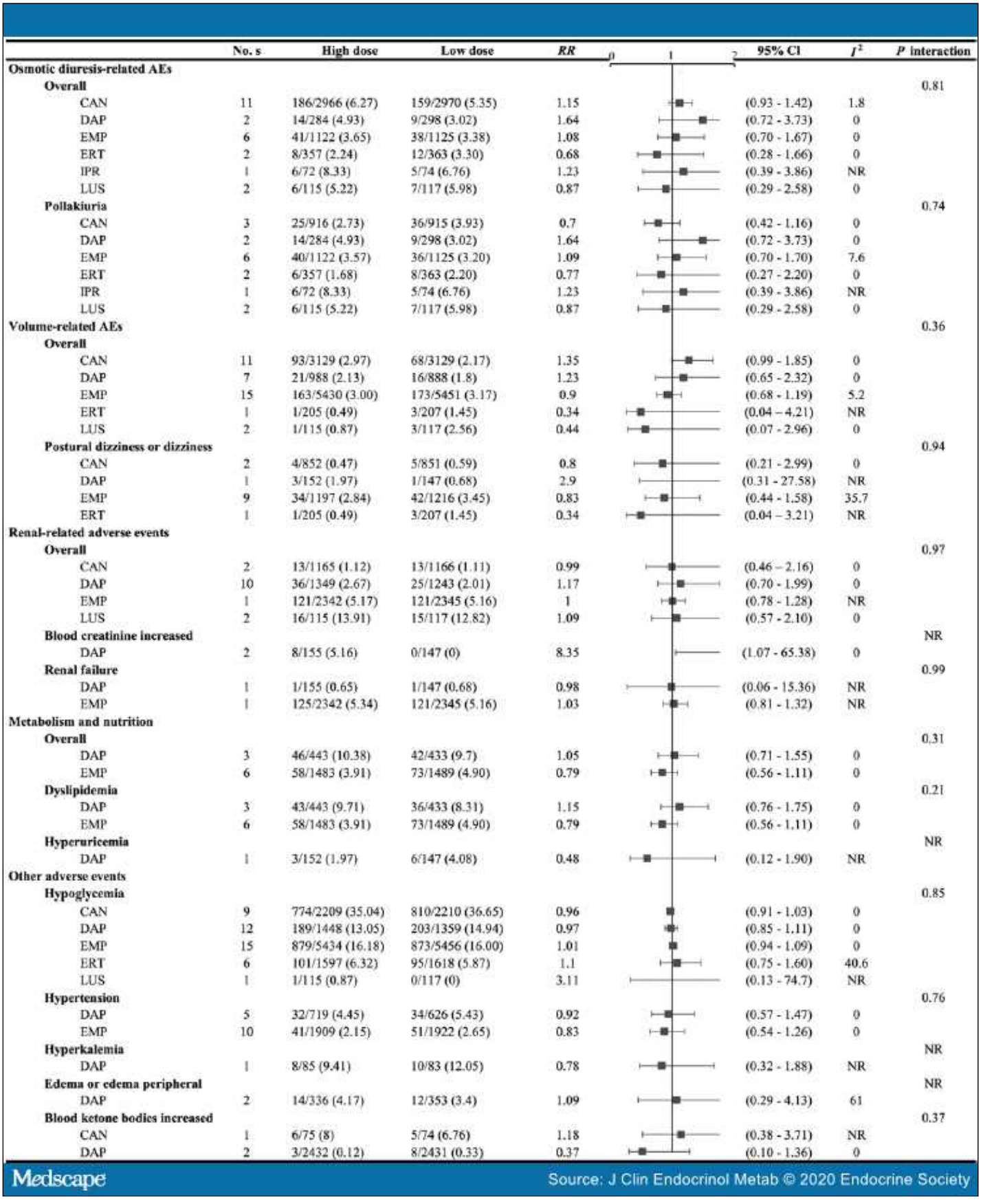
Subgroup analysis of infections and infestations of different SGLT2 inhibitors. AEs, adverse events; CAN, canagliflozin; DAP, dapagliflozin; EMP, empagliflozin; ERT, ertugliflozin; I^2, heterogeneity; IPR, ipragliflozin; LUS, luseogliflozin; No. s, numbers of studies; NR, not reported; RR, relative risk; SGLT2, sodium–glucose cotransporter 2.



	No. s	High dose	Low dose	RR	95% CI	I^2	P interaction
Musculoskeletal disorders							
Overall							0.24
DAP	5	76/755 (10.07)	61/763 (7.99)	1.41	(0.82 - 2.43)	43.4	
EMP	9	112/1749 (6.40)	124/1762 (7.04)	0.91	(0.71 - 1.16)	0	
Back pain							0.11
DAP	4	45/604 (7.45)	25/618 (4.05)	1.83	(1.13 - 2.95)	0	
EMP	9	78/1749(4.46)	76/1762 (4.31)	1.04	(0.77 - 1.42)	0	
Arthralgia							0.49
DAP	2	16/347 (4.61)	11/357 (3.08)	1.58	(0.53 - 4.76)	14.4	
EMP	5	33/797 (4.14)	40/806 (4.96)	0.83	(0.53 - 1.31)	0	
Pain in extremity							0.12
DAP	2	15/336 (4.46)	25/353 (7.08)	0.65	(0.34 - 1.21)	0	
EMP	1	1/97 (1.03)	8/98 (8.16)	0.13	(0.02 - 0.99)	NR	
Other pain or disorders							
Headache							0.93
CAN	1	3/64 (4.69)	5/64 (7.81)	0.60	(0.15 - 2.41)	NR	
DAP	6	38/640 (5.94)	40/670 (5.97)	0.99	(0.64 - 1.52)	0	
EMP	5	37/785 (4.71)	38/796 (4.77)	0.99	(0.63 - 1.55)	0	
LUS	1	2/61 (3.28)	1/61 (1.64)	2.00	(0.19 - 21.48)	NR	
Fractures							0.13
CAN	1	8/690 (1.16)	18/692 (2.60)	0.45	(0.20 - 1.02)	NR	
DAP	4	10/576 (1.74)	7/471 (1.49)	1.38	(0.43 - 4.43)	11.9	
EMP	3	88/2607 (3.38)	96/2608 (3.68)	0.93	(0.70 - 1.23)	0	
Skin and tissue disorders							NR
EMP	1	2/90 (2.22)	5/86 (5.81)	0.38	(0.08 - 1.92)	NR	
Gastrointestinal disorders							
Overall							0.08
CAN	2	23/539 (4.27)	17/538 (3.16)	1.34	(0.72 - 2.49)	0	
DAP	7	68/954 (7.13)	61/968 (6.3)	1.18	(0.84 - 1.65)	0	
EMP	7	74/1187 (6.23)	77/1202 (6.41)	0.98	(0.70 - 1.37)	8.4	
LUS	2	0/115 (0)	5/117 (4.27)	0.17	(0.02 - 1.41)	0	
Nausea							0.96
CAN	1	3/64 (4.69)	1/64 (1.56)	3.00	(0.32 - 28.08)	NR	
DAP	3	11/395 (2.78)	13/417 (3.12)	1.01	(0.41 - 2.48)	11.9	
EMP	3	11/334 (3.29)	12/348 (3.45)	0.99	(0.45 - 2.20)	0	
Diarrhea							0.11
CAN	1	2/64 (3.13)	1/64 (1.56)	2.00	(0.19 - 21.51)	NR	
DAP	7	46/954 (4.82)	38/968 (3.93)	1.27	(0.83 - 1.95)	0	
EMP	7	51/1187 (4.3)	55/1202 (4.58)	0.94	(0.56 - 1.57)	39.6	
LUS	2	0/115 (0)	5/117 (4.27)	0.17	(0.02 - 1.41)	0	
Constipation							0.82
DAP	3	11/381 (2.89)	12/398 (3.02)	1.02	(0.45 - 2.31)	0	
EMP	1	12/274 (4.38)	10/272 (3.68)	1.19	(0.52 - 2.71)	NR	

Figure 5.

Subgroup analysis of musculoskeletal disorders, pain, and gastrointestinal disorders of different SGLT2 inhibitors. AEs, adverse events; CAN, canagliflozin; DAP, dapagliflozin; EMP, empagliflozin; I^2, heterogeneity; LUS, luseogliflozin; No. s, numbers of studies; NR, not reported; RR, relative risk; SGLT2, sodium–glucose cotransporter 2.



	No. s	High dose	Low dose	RR	95% CI	I^2	P interaction
Osmotic diuresis-related AEs							
Overall							0.81
CAN	11	186/2966 (6.27)	159/2970 (5.35)	1.15	(0.93 - 1.42)	1.8	
DAP	2	14/284 (4.93)	9/298 (3.02)	1.64	(0.72 - 3.73)	0	
EMP	6	41/1122 (3.65)	38/1125 (3.38)	1.08	(0.70 - 1.67)	0	
ERT	2	8/357 (2.24)	12/363 (3.30)	0.68	(0.28 - 1.66)	0	
IPR	1	6/72 (8.33)	5/74 (6.76)	1.23	(0.39 - 3.86)	NR	
LUS	2	6/115 (5.22)	7/117 (5.98)	0.87	(0.29 - 2.58)	0	
Pollakiuria							0.74
CAN	3	25/916 (2.73)	36/915 (3.93)	0.7	(0.42 - 1.16)	0	
DAP	2	14/284 (4.93)	9/298 (3.02)	1.64	(0.72 - 3.73)	0	
EMP	6	40/1122 (3.57)	36/1125 (3.20)	1.09	(0.70 - 1.70)	7.6	
ERT	2	6/357 (1.68)	8/363 (2.20)	0.77	(0.27 - 2.20)	0	
IPR	1	6/72 (8.33)	5/74 (6.76)	1.23	(0.39 - 3.86)	NR	
LUS	2	6/115 (5.22)	7/117 (5.98)	0.87	(0.29 - 2.58)	0	
Volume-related AEs							0.36
Overall							
CAN	11	93/3129 (2.97)	68/3129 (2.17)	1.35	(0.99 - 1.85)	0	
DAP	7	21/988 (2.13)	16/888 (1.8)	1.23	(0.65 - 2.32)	0	
EMP	15	163/5430 (3.00)	173/5451 (3.17)	0.9	(0.68 - 1.19)	5.2	
ERT	1	1/205 (0.49)	3/207 (1.45)	0.34	(0.04 – 4.21)	NR	
LUS	2	1/115 (0.87)	3/117 (2.56)	0.44	(0.07 - 2.96)	0	
Postural dizziness or dizziness							0.94
CAN	2	4/852 (0.47)	5/851 (0.59)	0.8	(0.21 - 2.99)	0	
DAP	1	3/152 (1.97)	1/147 (0.68)	2.9	(0.31 - 27.58)	NR	
EMP	9	34/1197 (2.84)	42/1216 (3.45)	0.83	(0.44 - 1.58)	35.7	
ERT	1	1/205 (0.49)	3/207 (1.45)	0.34	(0.04 – 3.21)	NR	
Renal-related adverse events							
Overall							0.97
CAN	2	13/1165 (1.12)	13/1166 (1.11)	0.99	(0.46 – 2.16)	0	
DAP	10	36/1349 (2.67)	25/1243 (2.01)	1.17	(0.70 - 1.99)	0	
EMP	1	121/2342 (5.17)	121/2345 (5.16)	1	(0.78 - 1.28)	NR	
LUS	2	16/115 (13.91)	15/117 (12.82)	1.09	(0.57 - 2.10)	0	
Blood creatinine increased							NR
DAP	2	8/155 (5.16)	0/147 (0)	8.35	(1.07 - 65.38)	0	
Renal failure							0.99
DAP	1	1/155 (0.65)	1/147 (0.68)	0.98	(0.06 - 15.36)	NR	
EMP	1	125/2342 (5.34)	121/2345 (5.16)	1.03	(0.81 - 1.32)	NR	
Metabolism and nutrition							
Overall							0.31
DAP	3	46/443 (10.38)	42/433 (9.7)	1.05	(0.71 - 1.55)	0	
EMP	6	58/1483 (3.91)	73/1489 (4.90)	0.79	(0.56 - 1.11)	0	
Dyslipidemia							0.21
DAP	3	43/443 (9.71)	36/433 (8.31)	1.15	(0.76 - 1.75)	0	
EMP	6	58/1483 (3.91)	73/1489 (4.90)	0.79	(0.56 - 1.11)	0	
Hyperuricemia							NR
DAP	1	3/152 (1.97)	6/147 (4.08)	0.48	(0.12 - 1.90)	NR	
Other adverse events							
Hypoglycemia							0.85
CAN	9	774/2209 (35.04)	810/2210 (36.65)	0.96	(0.91 - 1.03)	0	
DAP	12	189/1448 (13.05)	203/1359 (14.94)	0.97	(0.85 - 1.11)	0	
EMP	15	879/5434 (16.18)	873/5456 (16.00)	1.01	(0.94 - 1.09)	0	
ERT	6	101/1597 (6.32)	95/1618 (5.87)	1.1	(0.75 - 1.60)	40.6	
LUS	1	1/115 (0.87)	0/117 (0)	3.11	(0.13 - 74.7)	NR	
Hypertension							0.76
DAP	5	32/719 (4.45)	34/626 (5.43)	0.92	(0.57 - 1.47)	0	
EMP	10	41/1909 (2.15)	51/1922 (2.65)	0.83	(0.54 - 1.26)	0	
Hyperkalemia							NR
DAP	1	8/85 (9.41)	10/83 (12.05)	0.78	(0.32 - 1.88)	NR	
Edema or edema peripheral							NR
DAP	2	14/336 (4.17)	12/353 (3.4)	1.09	(0.29 - 4.13)	61	
Blood ketone bodies increased							0.37
CAN	1	6/75 (8)	5/74 (6.76)	1.18	(0.38 - 3.71)	NR	
DAP	2	3/2432 (0.12)	8/2431 (0.33)	0.37	(0.10 - 1.36)	0	

Figure 6.

Subgroup analysis of osmotic diuresis, volume, renal, and other clinical adverse events. AEs, adverse events; CAN, canagliflozin; DAP, dapagliflozin; EMP, empagliflozin; I^2, heterogeneity; LUS, luseogliflozin; No. s, numbers of studies; NR, not reported; RR, relative risk.

Specified Safety. Specified safety that included 7 categories of AEs and other clinical interested AEs are also outlined in Figure 2. All the outcomes presented low heterogeneity except for those with small sample size outcomes (I^2 = 62.4% for gastroenteritis and I^2 = 61.0% for edema). In accordance with the overall safety outcomes, no significant differences between high-dose and low-dose SGLT2 inhibitors were detected when regarding all categories of AEs (infections and infestations, musculoskeletal disorders,

gastrointestinal disorders, osmotic diuresis-related AEs, volume-related AEs, renal-related AEs, and metabolism and nutrition) and clinically related AEs (urinary tract infection, genital mycotic infection, and hypoglycemia, etc). As for different SGLT2 inhibitors, the overall results were consistent with the key findings, with the exception of a reduced tendency for infections and infestations risk observed with empagliflozin (RR, 0.92; 95% CI, 0.86–0.98; I^2, 2.8%) and a higher risk for back pain found with dapagliflozin (RR, 1.83; 95% CI, 1.13–2.95; I^2, 0%). As for follow-up duration, the overall results were also in accordance with the primary analyses ($P_{interaction} > .05$ for each outcome; Table S4[22]).

Sensitivity Analysis and Publication Bias

Sensitivity analyses failed to identify any individual trial as having influenced the primary outcomes and thus confirmed the robustness of the results (Table S5[22]). No potential publication bias was observed by qualitative funnel plots and Begg test and Egger test (Figure S1[22]).

Discussion

Main Findings

This study presented clinical AEs of high-dose vs low-dose SGLT2 inhibitors based on 51 RCTs involving 24 371 patients. We did not find significant differences in overall AEs, 7 categories of AEs, and other clinically related AEs between high-dose and low-dose SGLT2 inhibitors. It remained consistent among various SGLT2 inhibitors and different follow-up durations. This study confirmed that the clinical AEs of SGLT2 inhibitors was not dose related.

Comparison to Previous Studies

To date only 2 meta-analyses have addressed clinical AEs associated with different dosages of SGLT2 inhibitors. Bundhun et al[18] concluded that 300 mg canagliflozin did not increase the risk for AEs compared with 100 mg canagliflozin after evaluating 5394 type 2 diabetic patients in 10 RCTs. A Chinese study,[19] including 8 trials and 8514 patients, failed to detect a significant difference in the comparisons of 25 mg with 10 mg empagliflozin regardless of monotherapy or add-on other antidiabetic medications. These studies had small population sizes and failed to evaluate overall safety outcomes. Our study not only included all previous studies of dapagliflozin and canagliflozin but also updated new studies from the years 2012 to 2020. In addition, our study observed 6 types of SGLT2 inhibitors and reported comprehensive safety end points (overall safety, 7 categories of AEs, and other clinically related AEs) among 24 371 type 2 diabetic patients.

Overall Efficacy of High-dose vs Low-dose Sodium–Glucose Cotransporter 2 Inhibitors

Regarding hypoglycemic effects, administration of SGLT2 inhibitors showed a dose-dependent reduction of HbA_{1c} levels (from 0.5% to 1.5%).[26] In addition, effects of dapagliflozin on decreased serum uric acid also showed a dose-dependent manner (from 5 mg to 50 mg).[27] Although high-dose SGLT2 inhibitors may bring about better control of blood glucose and uric acid metabolism, their dose-dependent protective effects for renal and cardiovascular system remain unclear.

Overall Safety of High-dose vs Low-dose Sodium–Glucose Cotransporter 2 Inhibitors

In the present study, we found SGLT2 inhibitors at high dosages did not cause more overall safety issues compared to low dosages of SGLT2 inhibitors. It has been established that SGLT2 inhibitors decreased deaths.[17] Results from Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetic Patients (EMPA-REG OUTCOME)[28] indicated that there was no difference between 25 mg empagliflozin and 10 mg empagliflozin either in deaths (3.4% vs 4.1%, $P_{interaction} = .398$) or serious AEs (39.0% vs 37.4%, $P_{interaction} = .296$). Our findings remain in line with the previous meta-analysis.[18,19] Moreover, the incidence of death and serious AEs was not dose related, which was a class effect. However, in our study, AEs related to drugs occurred more frequently in patients taking high-dose SGLT2 inhibitors than in those receiving low-dose SGLT2 inhibitors. Further analyses indicated that the increased risks of AEs were found mainly in patients taking canagliflozin. Although a prior meta-analysis evaluated the dose-dependent effect of canagliflozin,[18] it did not assess AEs related to study drugs. It appears that the increased risk may be at least partly driven by a possible tendency of volume-related AEs in patients taking 300 mg canagliflozin (RR: 1.35; 95% CI, 0.99–1.85, $P = .059$). Other main results regarding AEs and canagliflozin originated primarily from 3 trials, accounting for 69.7% weight.[29–31] They are characterized by longer follow-ups (52 weeks for 2 studies and 104 weeks for 1 study), older patients (age 55–80 years),[29] and drug combinations with insulin[30] or metformin.[31] Importantly, we confirmed a higher risk of AEs related to studied drugs observed in SGLT2 inhibitors when patients were followed up over 26 weeks. The possible reasons remain unclear and need further investigation.

Specified Safety With High-dose vs Low-dose Sodium–Glucose Cotransporter 2 Inhibitors

Our previous meta-analysis indicated that treatment with SGLT2 inhibitors was associated with a higher risk of infections, osmotic diuresis-related AEs, volume-related AEs, renal-related AEs, and hypoglycemia.[17]

The infection-related safety profile of SGLT2 inhibitors, including genital mycotic infection and urinary tract infections,[17] is always a concern for clinicians. We failed to show that high-dose SGLT2 inhibitors increased the risk of genital mycotic infection compared with low-dose SGLT2 inhibitors. Stratified analysis of different drugs and follow-ups presented similar results. Several meta-analyses reported the association between SGLT2 inhibitors and genital mycotic infection with consistent results, indicating an increased risk of SGLT2 inhibitors, but there were no apparent differences between the lower and higher dosages of SGLT2 inhibitors.[8,32] However, a study focused on infection risks of SGLT2 inhibitors[32] found dapagliflozin dose-dependently increased risk of genital infections. Compared to 2.5 mg dapagliflozin, 10 mg dapagliflozin resulted in a higher risk of genital infections (odds ratio, 1.55; 95% CI, 1.08–2.23). The possible reasons for the contradictory results regarding dapagliflozin might be the assessment of clinically approved high (10 mg) and low doses (5 mg) in our study. With respect to urinary tract infections, 2 prior meta-analyses showed no evidence of dose dependence. Canagliflozin at 300 mg did not increase the risk of urinary tract infections compared to 100 mg canagliflozin (RR, 0.93; 95% CI, 0.70–1.23), nor did 25 mg empagliflozin in comparison with 10

mg empagliflozin (RR, 0.97; 95% CI, 0.85–1.11).[18,19] Our findings supported that SGLT2 inhibitors did not have dose dependence with respect to urinary tract infections. Although one meta-analysis[8] found an increased risk of urinary tract infections with 10 mg dapagliflozin (RR, 1.33; 95% CI, 1.10–1.60), but not with 5 mg dapagliflozin (RR, 1.07; 95% CI, 0.78–1.48), it did not analyze *P* values for interaction between 10 mg and 5 mg dapagliflozin. Thus, results about dose dependence and risk of urinary tract infections need to be further verified.

Other than antidiabetic effects, SGLT2 inhibitors promoted natriuresis and osmotic diuresis to lower blood pressure and improve subendocardial blood flow in patients with heart failure.[33] Our prior study already found[17] that SGLT2 inhibitors were closely associated with the risk for osmotic diuresis-related AEs and volume-related AEs. In the present study, we first found that the effects of SGLT2 inhibitors on osmotic diuresis, volume-related AEs, and hypertension were not dose dependent. Many diuretics such as furosemide[34] and hydrochlorothiazide[35] have shown a dose-dependent effect on blood potassium, glucose, and uric acid levels. Unlike other osmotic diuretic agents, SGLT2 inhibitors are restricted to the renal tubules and stimulate vasopressin-induced water reabsorption to maintain body fluid volume.[36] It appears that the specific diuretic effect of SGLT2 inhibitors might be different from those of classic diuretics, which might, at least partly, be beneficial in type 2 diabetic patients with heart failure.[28,37]

In terms of hypoglycemia, we did not show any differences between high and low doses of SGLT2 inhibitors in all circumstances. It has been well established that monotherapy with SGLT2 inhibitors does not cause hypoglycemia, whereas the incidence of hypoglycemia increases in type 2 diabetic patients when used as add-on therapy.[17] Two previous meta-analyses[18,19] showed similar results. An earlier study has observed that an increase in empagliflozin exposure was positively related to urinary glucose excretion (UGE); however, it did not enhance risk of hypoglycemia.[38]

A safety and tolerability study of empagliflozin based on 48 healthy individuals.[39] found that there were no increased adverse effect at 5 different dosages (1 mg, 5 mg, 10 mg, 25 mg, and 100 mg), and all AEs were mild in intensity. Empagliflozin dose-dependently increased UGE; however, increased UGE may be not correlated to AEs. In addition, rates of renal clearance and cumulative fractions of different empagliflozin doses (1 mg-100 mg) excreted in the urine over 72 hours were similar.[39] Timely elimination of drugs and no obvious accumulative effects may partly explain why dose increases did not significantly increase AEs. This is possible speculation on the basis of current studies, however, and explicit mechanisms require further scientific verification.

Clinical Implications

No evidence of dose-dependent overall safety was observed in clinical usage of SGLT2 inhibitors. Among poorly controlled diabetic patients, the doses may be maximized to reach ideal glycemic control. Our study extrapolated that it is probably safe to adjust to high doses if patients do not experience serious clinical AEs with low doses of SGLT2 inhibitors.

Strengths and Limitations

The main strength of this study was to comprehensively assess the clinical AEs of approved high-dose SGLT2 inhibitors compared with low-dose SGLT2 inhibitors based on 24 371 patients from 51 RCTs. Certainly, there were some limitations in this study. First, we did not evaluate very low incidences of AEs such as amputation, cancer, and necrotizing fasciitis. Second, only studies with 2 clinically approved doses were included, and some RCTs (eg, DECLARE-TIMI 58[40] and CREDENCE[41]) as well as real-world studies (eg, CVD-REAL Nordic[42] and CVD-REAL 3[43]) with only one dose or without detailed doses were excluded. Third, we do not know whether AEs might be dose dependent after long-term treatment of SGLT2 inhibitors because all included RCTs were of relatively short follow-up duration. Fourth, tofogliflozin is approved in Japan for use in patients with type 2 diabetes at a dose of 20 mg orally once daily,[44] thus we did not include tofogliflozin in this study. Finally, overall AEs for SGLT2 inhibitors other than empagliflozin, dapagliflozin, and canagliflozin remain uncertain because of a lack of data. Accordingly, further long-term RCTs as well as high-quality real-world studies are needed to confirm the safety issues of SGLT2 inhibitors.

Conclusions

In conclusion, there were no differences between low and high doses of SGLT2 inhibitors with respect to overall AEs and specified AEs. Therefore, it is probably safe to increase SGLT2 inhibitors from low to high doses in the clinic if needed.

References

1. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet.* 2017;389(10085):2239–2251.

2. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020. Diabetes Care.* 2020;43(Suppl 1):S98-S110.

3. Cosentino F, Grant PJ, Aboyans V, et al; ESC Scientific Document Group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J.* 2020;41(2):255–323.

4. Fitchett D. A safety update on sodium glucose co-transporter 2 inhibitors. *Diabetes Obes Metab.* 2019;21(Suppl 2):34–42.

5. Wu JH, Foote C, Blomster J, et al. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2016;4(5):411–419.

6. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. Effectiveness and safety of standard-dose nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke risk factor: a nationwide cohort study. *JAMA Cardiol.* 2017;2(8):872–881.

7. Liu J, Li L, Li S, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep.* 2017;7(1):2824.

8. Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol.* 2018;55(5):503–514.

9. Tang H, Li D, Zhang J, et al. Sodium-glucose co-transporter-2 inhibitors and risk of adverse renal outcomes among patients with type 2 diabetes: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2017;19(8):1106–1115.

10. Xu L, Li Y, Lang J, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibition on renal function and albuminuria in patients with type 2 diabetes: a systematic review and meta-analysis. *PeerJ.* 2017;5:e3405.

11. Perlman A, Heyman SN, Matok I, Stokar J, Muszkat M, Szalat A. Acute renal failure with sodium-glucose-cotransporter-2 inhibitors: analysis of the FDA adverse event report system database. *Nutr Metab Cardiovasc Dis.* 2017;27(12):1108–1113.

12. FDA. Food and Drug Administration (2015): FDA drug safety communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections, 2015. http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm. Accessed January 12, 2016.

13. FDA. Food and Drug Administration (2015): FDA Drug Safety Communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density, 2015. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Accessed October 9, 2015.

14. FDA. Food and Drug Administration (2016): FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canaglifozin (Invokana, Invokamet) and dapaglifozin (Farxiga, Xigduo XR), 2016. http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm. Accessed August 6, 2016.

15. FDA. Food and Drug Administration (2017): FDA Drug Safety Communication:FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR), 2017. https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm. Accessed July 7, 2017.

16. FDA. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes, 2018. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrences-serious-infection-genital-area-sglt2-inhibitors-diabetes. Accessed August 29, 2018.

17. Shi FH, Li H, Shen L, et al. Appraisal of non-cardiovascular safety for sodium-glucose co-transporter 2 inhibitors: a systematic review and meta-analysis of placebo-controlled randomized clinical trials. *Front Pharmacol.* 2019;10:1066.

18. Bundhun PK, Janoo G, Huang F. Adverse drug events observed in patients with type 2 diabetes mellitus treated with 100 mg versus 300 mg canagliflozin: a systematic review and meta-analysis of published randomized controlled trials. *BMC Pharmacol Toxicol.* 2017;18(1):19.

19. Dai X, Luo ZC, Zhai L, Zhao WP, Huang F. Adverse drug events associated with low-dose (10 mg) versus high-dose (25 mg) empagliflozin in patients treated for type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Ther.* 2018;9(2):753–770.

20. Shamseer L, Moher D, Clarke M, et al; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ.* 2015;350:g7647.

21. Davlouros PA, Mplani VC, Koniari I, Tsigkas G, Hahalis G. Transcatheter aortic valve replacement and stroke: a comprehensive review. *J Geriatr Cardiol.* 2018;15(1):95–104.

22. Shi FH, Li H, Yue J, et al. Clinical adverse events of high-dose versus low-dose sodium-glucose co-transporter 2 inhibitors in type 2 diabetes: a meta-analysis of 51 randomized clinical trials. *figshare*. Deposited August 3, 2020. Doi:10.6084/m9.figshare.12752033.v1

23. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.

24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539–1558.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629–634.

26. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. *Nat Rev Endocrinol.* 2012;8(8):495–502.

27. Zhao Y, Xu L, Tian D, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2018;20(2):458–462.

28. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117–2128.

29. Bode B, Stenlöf K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55–80 years with type 2 diabetes. *Diabetes Obes Metab.* 2015;17(3):294–303.

30. Neal B, Perkovic V, de Zeeuw D, et al; CANVAS Trial Collaborative Group. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care.* 2015;38(3):403–411.

31. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet.* 2013;382(9896):941–950.

32. Li D, Wang T, Shen S, Fang Z, Dong Y, Tang H. Urinary tract and genital infections in patients with type 2 diabetes treated with sodium-glucose co-transporter 2 inhibitors: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2017;19(3):348–355.

33. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation.* 2017;136(17):1643–1658.

34. Hammarlund MM, Paalzow LK. Dose-dependent pharmacokinetics of furosemide in the rat. *Biopharm Drug Dispos.* 1982;3(4):345–359.

35. Ziegler MG, Lernhardt E, Solt-Buzsaki V. Dose response to hydrochlorothiazide in hypertensives receiving a calcium channel blocker. *Clin Exp Hypertens A.* 1988;10(5):791–800.

36. Masuda T, Muto S, Fukuda K, et al. Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. *Physiol Rep.* 2020;8(2):e14360.

37. Scheen AJ. Reappraisal of the diuretic effect of empagliflozin in the EMPA-REG OUTCOME trial: comparison with classic diuretics. *Diabetes Metab.* 2016;42(4):224–233.

38. Seman L, Macha S, Nehmiz G, et al. Empagliflozin (BI 10773), a potent and selective SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. *Clin Pharmacol Drug Dev.* 2013;2(2):152–161.

39. Sarashina A, Koiwai K, Seman LJ, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in healthy Japanese subjects. *Drug Metab Pharmacokinet.* 2013;28(3):213–219.

40. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347–357.

41. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295–2306.

42. Persson F, Nyström T, Jørgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. *Diabetes Obes Metab.* 2018;20(2):344–351.

43. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol.* 2020;8(1):27–35.

44. Rosenwasser RF, Rosenwasser JN, Sutton D, Choksi R, Epstein B. Tofogliflozin: a highly selective SGLT2 inhibitor for the treatment of type 2 diabetes. *Drugs Today (Barc).* 2014;50(11):739–745.

Abbreviations

AE, adverse event; FDA, Food and Drug Administration; HbA_{1c}, glycated hemoglobin; RCT, randomized clinical trial; RR, relative risk; SGLT2, sodium–glucose cotransporter 2 inhibitors; UGE, urinary glucose excretion.

Acknowledgments

Financial Support

This work was supported by the Research Funds of Shanghai Health and Family Planning Commission (20204Y0011), the Clinical Pharmacy Innovation Research Institute of Shanghai Jiao Tong University School of Medicine (CXYJY2019QN004 and CXYJY2019ZD001), the Fundamental Research Funds for the Central Universities (17JCYB11), the Pharmaceutical Fund of College of Medicine, Shanghai Jiaotong University (JDYX2017QN003), the fund of Shanghai Pharmaceutical Association (2015-YY-01-20), and the Program for Key but Weak Discipline of Shanghai Municipal Commission of Health and Family Planning (2016ZB0304), Shanghai "Rising Stars of Medical Talent" Youth Development Program -Youth Medical Talents - Clinical Pharmacist Program (SHWJRS(2019)_072; SHWRS(2020)_087).

Additional Information

Data Availability

All data generated or analyzed during this study are included in this published article or in the data repositories listed in "References."

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