ERIC PASQUALOTTO

EFFICACY AND SAFETY OF BEXAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Trabalho apresentado à Universidade Federal de Santa Catarina, como requisito para a conclusão do Curso de Graduação em Medicina.

Florianópolis

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"O sucesso nasce do querer, da determinação e persistência em se chegar a um objetivo. Mesmo não atingindo o alvo, quem busca e vence obstáculos, no mínimo fará coisas admiráveis."

José de Alencar

EFFICACY AND SAFETY OF BEXAGLIFLOZIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Aim: To assess the efficacy of bexagliflozin in reducing glycated hemoglobin (HbA1c) and the occurrence of side effects in patients with type 2 diabetes (T2DM).

Methods: We searched PubMed, Embase, Cochrane and ClinicalTrials.gov databases for placebo-controlled, randomized clinical trials until February 15, 2023. The primary outcome was change in HbA1c. We computed weighted mean differences (WMDs) for continuous outcomes and odds ratios (ORs) for binary endpoints, with 95% confidence intervals (CIs).

Results: A total of 6 studies and 3,111 patients were included, of whom 1,951 were prescribed bexagliflozin. Compared to placebo, bexagliflozin significantly reduced HbA1c levels (WMD -0.53%; 95% CI -0.75,-0.31), fasting plasma glucose levels (WMD -1.45 mmol/L; 95% CI -2.32,-0.57), systolic blood pressure (WMD -4.66 mmHg; 95% CI -6.41,-2.92), diastolic blood pressure (WMD -2.12 mmHg; 95% CI -3.94,-0.30), body weight (WMD -1.61 Kg; 95% CI -2.14,-1.07), and body weight in patients with a body mass index > 25 kg/m^2 (WMD -2.05 Kg; 95% CI -2.78,-1.31). The proportion of patients who achieved HbA1c < 7% was higher in patients who received bexagliflozin as compared with placebo (OR 1.94; 95% CI 1.36-2.78). There were no significant differences between groups regarding side effects as hypoglycemia, genital mycotic infection, urinary tract infection, diarrhea, headache, náusea, polyuria, diabetic ketoacidosis, or all-cause mortality.

Conclusions: In this meta-analysis, the use of bexagliflozin was associated with improved clinical and laboratory measures in patients with T2DM compared to placebo, with a similar profile of side effects. These findings support the efficacy of bexagliflozin in the treatment of T2DM.

Keywords: Sodium-Glucose Transporter 2 Inhibitors; Diabetes Mellitus, Type 2; Glycated Hemoglobin.

INTRODUCTION

Glycemic control is a key aspect in the management of patients with type 2 diabetes (T2DM). This effort involves lifestyle changes, blood sugar monitoring, and use of pharmacotherapies.[1] One novel class of drugs for T2DM is the sodium-glucose cotransporter 2 inhibitors (SGLT-2i), which acts directly on the kidneys without requiring insulin secretion. The sodium-glucose cotransporter 2 (SGLT-2) is the primary glucose transporter located in the apical membrane of the proximal convoluted tubule cells and is responsible for 80-97% of renal glucose reabsorption.[2] Thus, SGLT-2i act decreasing the renal glucose reabsorption, leading to glycosuria and consequent glycemia reduction.[1,3,4]

Interestingly, the benefits of SGLT-2i expand well beyond glycemic control, and include a reduction in blood pressure and body mass, irrespective of glycemic status.[1,4,5] In addition, SGLT-2i also improve cardiovascular and renal outcomes in patients with diabetes.[2] Although these benefits are thought to be class-related across the spectrum of different SGLT2i, newer drugs in this class require testing to demonstrate efficacy and safety.

One example of a new highly specific and potent SGLT-2i is bexagliflozin, which has been associated with a significant reduction in hemoglobin A1c (HbA1c) and glycemic levels, according to results from small randomized controlled trials.[6,7] However, given the small sample sizes of prior studies, a pooled analysis of trials examining bexaglifozin may bring additional insights. Therefore, we aimed to perform a meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy and safety of bexagliflozin in patients with T2DM.

MATERIALS AND METHODS

Eligibility criteria

Studies that met the following eligibility criteria were included: (1) RCTs; (2) comparing bexagliflozin with placebo; (3) enrolling patients with T2DM; and (4) reporting at least one

outcome of interest. We excluded (1) overlapping populations, defined as studies with overlapping institutions and recruitment periods; and (2) non-randomized studies.

Search strategy and data extraction

We systematically searched Embase, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and PubMed databases for studies meeting the eligibility criteria and published from inception to February 15, 2023. The search strategy included the terms 'type 2 diabetes' and 'bexagliflozin'. In addition, references of systematic reviews and included studies were analyzed to verify the possibility of any other eligible studies. Two authors (E.P. and R.M.) independently extracted prespecified baseline characteristics and outcome data. Disagreements were resolved by consensus between the two authors and the senior author (E.P., R.M., and C.E.A.P) after checking the reasons of any discrepancies. Data from the longest follow-up time available in the RCTs were extracted for the analysis.

The protocol for this research was submitted to International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42022341122. The systematic review and meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.[8]

Endpoints and subgroup analysis

Outcomes of interest were: (1) HbA1c (%); (2) proportion of subjects achieving HbA1c < 7%; (3) fasting plasma glucose (FPG) (mmol/L); (4) systolic blood pressure (SBP) (mmHg); (5) diastolic blood pressure (DBP); (6) body weight; (7) body weight in subjects with body mass index (BMI) ≥ 25 Kg/m^2; (8) hypoglycemia; (9) genital mycotic infection; (10) urinary tract

infection; (11) nausea; (12) polyuria; (13) headache; (14) diarrhea; (15) gangrene; (16) amputations; (17) diabetic ketoacidosis; (18) major adverse cardiac events (MACE); and (19) all-cause mortality.

We performed two post-hoc subgroup analyses. First, exploring the efficacy of bexagliflozin 20 mg vs. placebo, as this was the most common dose among the included studies. Second, due to heterogeneity in follow-up between studies, we also conducted an analysis restricted to follow-up time of 12 and 24 weeks for HbA1c and FPG. Finally, we also performed leave-one-out sensitivity analyses for all outcomes to ensure stability of the pooled treatment effect.

Quality assessment

Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Rob 2) was used to assess quality of individual RCTs.[9] Two independent authors (E.P. and R.M.) conducted the quality assessment. Each trial received a score of high, low, or unclear risk of bias in five domains: randomization process, deviations from the intended interventions, missing outcomes, measurement of the outcome and selection of reported results. The layout was produced by Robvis.

The overall quality of evidence was analyzed according to the Grading of Recommendation, Assessment, Development and Evaluations (GRADE) guidelines.[10] The RCTs were labeled with very low, low, moderate, or high quality of evidence based on the presence of risk of bias, inconsistency of results, imprecision, publication bias, and magnitude of treatment effects.

Statistical analysis

The treatment effects for binary endpoints were compared using odds-ratio (OR), with 95% confidence intervals (CI). Continuous outcomes were evaluated using weighted mean differences (WMDs). The heterogeneity was assessed with Cochrane Q-test and I^2 statistics; $p > 0.10$ and $I^2 > 25\%$ were considered significant for heterogeneity.[11] We used a fixed-effect model for endpoints considered to have low heterogeneity. DerSimonian and Laird random-effects model were used in outcomes with significant heterogeneity.[12] For data handling and conversion, we used guidelines of the Cochrane Handbook for Systematic Reviews of Interventions.[13] Review Manager 5.4 was used for statistical analysis (Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Study selection and characteristics

The initial search yielded 63 results, as detailed in Figure 1. After removal of duplicate records and ineligible studies, 12 studies remained for full review according to prespecified criteria. Of these, 6 RCTs were included in this systematic review and meta-analysis, comprising 3,111 patients.[14–19] A total of 1,951 (62.7%) patients received bexagliflozin, while 1,160 (37.3%) received placebo. The follow-up period ranged from 12 weeks to 168 weeks. Mean age ranged from 55.4 to 69.9 years and 1,968 (63%) patients were men. Mean BMI ranged from 28.5 to 32.8 kg/m^2 and mean weight ranged from 78.4 to 94.6 kg. Study and participants characteristics are summarized in Table 1.

Table 1. Baseline characteristics of included studies

Study	Follow-up	Treatment doses BG	Sample size BG/PG (%)	Age, years BG/PG (SD)	Male BG/PG (%)	BMI, kg m^{-2} BG/PG (SD)	Weight, kg BG/PG (SD)	SBP, mmHg BG/PG (SD)	Insulin use at baseline (BG/PG)	GLP-1RA use at baseline (BG/PG)
Allegretti (2019)	24 weeks	20 mg	157(50.3)/ 155(49.7)	69.3(8.36)/ 69.9(8.29)	92(58.6)/ 104(67.1)	30.29(5.9)/ 30.10(5.8)	82.90(20.5)/ 82.59(21.2)	135.9(14.2)/ 137.6(14.7)	89/91	17/13
Halvorsen (2020)†	12 weeks	5,10, 20 mg	76(26.0)/ 72(24.7)	59.5(10.8)/ 58.8(10.4)	50(65.8)/ 42(58.3)	28.5(5.0)/ 28.5(5.5)	78.8(16.7)/ 78.7(19.7)	127.9(14.1)/ 128.1(13.6)	NA	NA
Halvorsen (2019)	96 weeks	20 mg	145(51.2)/ 138(48.8)	56.2(10.9)/ 54.9(10.3)	67(46.2)/ 49(35.5)	29.7(5.3)/ 30.6(5.5)	78.4(17.1)/ 79.7(17.4)	127.5(13.3)/ 126.9(13.5)	NA	NA
BEST (2015)	168 weeks	20 mg	1133(66.7)/ 567(33.3)	64.4(7.9)/ 64.6(8.0)	792(69.9)/ 390(68.8)	32.80(6.1)/ 32.24(5.7)	94.59(21.9)/ 92.62(19.9)	134.2(16.2)/ 133.7(16.2)	610/292	NA
Lock (2016)	24 weeks	20 mg	138(66.7)/ 69(33.3)	55.8(10.2)/ 55.4(10.5)	66(47.8)/ 34(49.3)	32.79(5.6)/ 30.48(4.6)	90.5(20.5)/ 84.6(19.7)	131.0(14.3)/ 125.6(13.8)	0/0	0/0
Lock (2017)	24 weeks	20 mg	158(49.8)/ 159(50.2)	56.0(10.0)/ 55.6(11.2)	100(63.3)/ 94(59.1)	29.67(6.4)/ 29.99(6.3)	84.58(21.9)/ 84.44(20.9)	NA/NA	NA	NA

†Characteristics of patients treated with bexagliflozin 20 mg. The sample size of the intervention group is 220 patients. Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GLP-1RA, glucagon-like peptide 1 receptor agonists; SBP, systolic blood pressure; SD, standard deviation; RCT, randomized controlled trial; BG, Bexagliflozin group; PG, placebo group; NA, not available.

Figure 1. PRISMA flow diagram of study screening and selection

Pooled analysis of all studies

The primary endpoint analyzed was the reduction in HbA1c (%), which significantly improved in the bexagliflozin group when compared with placebo (WMD -0.53 %; 95% CI -0.75, -0.31; $p < 0.001$; I^2=84%; Figure 2A). There was a significant increase in proportion of patients who achieved HbA1c < 7% (OR 1.94; 95% CI 1.36-2.78; p<0.001; I^2=0%; Figure 2B) and a significant reduction in FPG in the bexagliflozin group (WMD -1.45 mmol/L; 95% CI -2.32, -0.57; $p = 0.001$; $I^2 = 89\%$; Figure 2C). SBP (WMD -4.66 mmHg; 95% CI -6.41, -2.92; $p < 0.001$; I^2=32%; Figure 2D) and DBP (WMD -2.12 mmHg; 95% CI -3.94, -0.30; p=0.02; $I^2 = 0\%$; Figure 2E) were significantly reduced in the group treated with bexagliflozin. There was also a significant reduction in body weight (WMD -1.61 Kg; 95% CI -2.14, -1.07; $p < 0.001$; $I^2 = 0\%$; Figure 3A) in the bexagliflozin group, as well as significant weight loss in patients with

BMI ≥ 25 kg/m^2 (WMD -2.05 Kg; 95% CI -2.78, -1.31; p < 0.001; I^2=72%; Figure 3B).

In safety-related outcomes, there was no significant difference between groups regarding genital mycotic infections (OR 3.11; 95% CI 0.86-11.29; p=0.08; I^2=7%; Figure 3C), hypoglycemia (OR 0.95; 95% CI 0.80-1.14; p=0.60; I^2=0%; Figure 3D), urinary tract infection (OR 1.04; 95% CI 0.80-1.36; p=0.75; I^2=19%; Figure 3E), diarrhea (OR 0.75; 95% CI 0.30-1.88; p=0.54; I^2=7%; Figure S1A), headache (OR 0.60; 95% CI 0.24-1.63; p=0.34; I^2=0%; Figure S1B), nausea (OR 0.70; 95% CI 0.48-1.01; p=0.06; I^2=0%; Figure S1C), polyuria (OR 1.57; 95% CI 0.83-2.99; p=0.17; I^2=0%; Figure S1D), diabetic ketoacidosis (OR 0.44; 95% CI 0.01-17.59; p=0.66; I^2=65%; Figure S1E), and all-cause mortality (OR 0.76; 95% CI 0.47-1.24; p=0.28; I^2=0%; Figure S1F).

Figure 2. A. HbA1c (%). **B.** Proportion of patients who achieved HbA1c < 7%. **C.** Fasting plasma glucose (mmol/L). **D.** Systolic blood pressure (mmHg). **E.** Diastolic blood pressure (mmHg).

Figure 3. A. Body weight. **B.** Body weight in subjects with a BMI ≥ 25 kg/m^2. **C.** Genital mycotic infection. **D.** Hypoglycemia **E.** Urinary tract infection.

Subanalysis in selected populations

In the subgroup analysis of patients treated with the 20 mg dose of bexagliflozin vs. placebo, there was a reduction in HbA1c levels (WMD -0.55%; 95% CI -0.79, -0.31; p < 0.001; I^2=85%) and a higher proportion of patients achieved HbA1c < 7% (OR 2.13; 95% CI 1.47-3.08; p < 0.001; I^2=0%) in bexagliflozin-treated patients. There was a significant reduction in FPG in the intervention group (WMD -1.47 mmol/L; 95% CI -2.37, -0.57; p=0.001; I^2=88%). SBP was also significantly reduced by bexagliflozin 20 mg (WMD -4.81 mmHg; 95% CI -6.23,

-3.40; $p < 0.001$; I^2=28%), as was DBP (WMD -2.27 mmHg; 95% CI -4.36, -0.18; p=0.03; I^2=0%). There was a significant reduction in body weight in patients treated with bexagliflozin 20 mg (WMD -1.75 Kg; 95% CI -2.38, -1.11; $p < 0.001$; I^2=0%).

There was no significant difference between bexagliflozin 20 mg and placebo regarding hypoglycemia (OR 0.96; 95% CI 0.80-1.15; p=0.68; I^2=0%), urinary tract infection (OR 1.04; 95% CI 0.79-1.36; p=0.78; I^2=18%), diarrhea (OR 0.68; 95% CI 0.26-1.79; p=0.44; I^2=23%), headache (OR 0.59; 95% CI 0.21-1.65; p=0.31; I^2=0%), polyuria (OR 1.71; 95% CI 0.91-3.22; p=0.10; I^2=0%), and nausea (OR 0.72; 95% CI 0.49-1.04; p=0.08; I^2=0%).

In a separate subgroup analysis restricted to 12-week and 24-week follow-up for glycemic control, there was a significant reduction in HbA1c at 12 weeks (WMD -0.59 %; 95% CI -0.65, -0.53; $p < 0.001$; I^2=0%) and 24 weeks (WMD -0.44%; 95% CI -0.55, -0.34; $p <0.001$; I^2=30%). Furthermore, there was also a reduction in FPG both at 12 weeks (WMD -1.31 mmol/L; 95% CI -1.70, -0.92; $p < 0.001$; I^2=47%) and 24 weeks (WMD -1.40 mmol/L; 95% CI -1.60, -1.20; $p < 0.001$; I^2=15%).

Sensitivity analysis

We performed a leave-one-out sensitivity analysis for all outcomes. Overall, there was no change in the statistical significance of outcomes in each of the leave-one-out tests, for all outcomes. This analysis is shown for the primary endpoint of HbA1c in Table S1. There was a significant reduction in the heterogeneity between studies for the outcome of FPG with the removal of Halvorsen et al., with a reduction in I^2=89% to I^2=36%.[16] This is likely due to the follow-up in this study, which was substantially longer than other trials (96 weeks).[16] Otherwise, there was no major shift in heterogeneity in the outcomes with the removal of each individual study in the leave-one-out analyses.

Quality and evidence assessment

Figure 4 outlines individual appraisal of each RCTs included in the meta-analysis. Overall, all studies were deemed at low risk of bias. As shown in Figure 4, the funnel plot presents a symmetrical distribution of similar-weigh studies, indicating no evidence of significant publication bias.

According to the GRADE assessment, three outcomes evaluated in this study were classified as high-quality evidence: SBP, hypoglycemia, and urinary tract infection. Seven outcomes had moderate quality of evidence: HbA1c (%), proportion of patients who achieved HbA1c < 7%, FPG, DBP, body weight, body weight in patients with a BMI ≥ 25 kg/m^2, and genital mycotic infection. Five outcomes were classified as having low quality of evidence: diarrhea, headache, polyuria, nausea, and all-cause mortality. Only one was considered low-quality evidence, due to the reduced number of RCTs with reported events and high heterogeneity. The main domains responsible for reducing the quality of evidence of the outcomes were: inconsistency of results, due to heterogeneity, and imprecision, due to the reduced number of RCTs with reported events. Quality assessment is detailed in Table S2.

Figure 4. A. Critical appraisal of RCTs according to the Cochrane Collaboration's tool for assessing risk of bias in randomized trials. **B.** Funnel plot analysis of the reduction in HbA1c (%) shows no evidence of publication bias.

DISCUSSION

On this systematic review and meta-analysis including 6 studies and 3,111 patients, the SGLT-2i bexagliflozin was compared with placebo in patients with T2DM. The main findings were as follows. Bexagliflozin was associated with (1) a significant reduction in HbA1c and FGP; (2) an approximate 2-fold increase in the chance of patients achieving HbA1c < 7%; (3)

a significant reduction in SBP and DBP; (4) a significant reduction in body weight; and (5) no significant increase in side effects relative to placebo.

Currently, SGLT-2i are indicated as monotherapy or adjunctive therapy in the treatment of T2DM. All SGLT-2i have shown so far similar effects regarding HbA1c reduction in this patient population. A meta-analysis by Shyangdan et al. found that patients receiving SGLT-2i achieved a greater proportion of HbA1c < 7% compared with placebo.[20] Furthermore, another meta-analysis comparing canagliflozin, dapagliflozin, or empagliflozin with placebo also showed a positive effect of all SGLT-2i on the reduction of HbA1c and FPG.[21] The results of our meta-analysis extend these findings to bexagliflozin, which also was demonstrated to have a significant effect in the glycemic control, in concordance with SGLT-2i literature.[22,23]

SGLT-2i have also consistently been shown to reduce body weight and SBP.[22, 24,25] The significant reductions seen in body weight with SGLT-2i may relate to (1) caloric loss from urinary glucose excretion due to SGLT-2i; (2) osmotic diuresis due to glucosuria; and (3) utilization of lipid substrate by SGLT-2, causing fat loss in T2DM.[23] Our meta-analysis confirms that these findings also apply to bexagliflozin, a newer drug in this class.

Diabetes mellitus is an established risk factor for atherosclerotic cardiovascular disease and heart failure.[26] SGLT-2i are effective in reducing cardiovascular outcomes in this patient population, particularly heart failure events.[26] In the EMPA-REG trial, empagliflozin reduced the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, as well as reduced deaths from any cause, as compared with placebo in patients with T2DM at high risk of cardiovascular events.[24] Similar findings were shown with canagliflozin in the CANVAS study.[25] Two MACE were reported in patients treated with bexagliflozin in our meta-analysis. Of note, we did not find a significant difference between bexagliflozin and placebo in terms of all-cause mortality. Similarly, a prior meta-analysis with fewer patients also showed no significant difference in MACE comparing bexagliflozin with

placebo.[27] However, these findings must be interpreted with caution. Although our meta-analysis represents the largest population of bexagliflozin, the pooled number of patients in our study is still far inferior to those of the CANVAS and EMPA-REG trials.[24,25]

Currently, a few adverse effects of this class of drugs are documented, such as hypoglycemia, genital and urinary tract infections, genital mycotic infection, allergic skin reactions, hypovolemia, dysuria, and diabetic ketoacidosis.[28,29] This meta-analysis evaluated some of these adverse effects and the results showed no significant difference in these outcomes between groups. The relative increase in polyuria has already been documented in patients treated with bexagliflozin and is associated with the recognized volume depletion of SGLT-2i.[6,29] The risk of hypoglycemia was not significant in previous meta-analyses with empagliflozin and dapagliflozin, similar to the results of our study, although others have shown an increase in the risk of hypoglycemia with SGLT-2i.[1,21,22,23,25,30]

Genital mycotic infections were described as an important adverse effect of SGLT-2i, although our meta-analysis found no significant difference between bexagliflozin and placebo.[5,31] Amputation was also described as a serious and uncommon adverse effect of SGLT-2i.[29] The CANVAS study showed a significantly increased risk of amputation with canagliflozin.[25] However, a meta-analysis evaluating exclusively amputation risk with SGLT-2i suggested no significant association.[32] Only one amputation was reported in the studies included in our meta-analysis.

This study has limitations. First, there was moderate to high heterogeneity in some of the outcomes analyzed, such as HbA1c. However, we performed leave-one-out sensitivity analyses and found consistent results after removal of each study from the analysis. Second, the absence of patient-level data regarding the use of insulin or glucagon-like peptide 1 receptor agonists (GLP-1RA) precluded a subgroup analysis of patients with concomitant use of these therapies. Moreover, not all studies reported on the use of these medications. And third, albeit

this study represents the largest pooled analysis of patients treated with bexagliflozin, we remain underpowered for clinical cardiovascular endpoints.

CONCLUSION

In this meta-analysis, the use of bexagliflozin was associated with improved glycemic control, a reduction in blood pressure, and weight loss in patients with T2DM, as compared with placebo, with no significant increase in adverse events. These findings support the efficacy and safety of bexagliflozin, similar to other SGLT-2i.

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FIGURES

Figure 1.

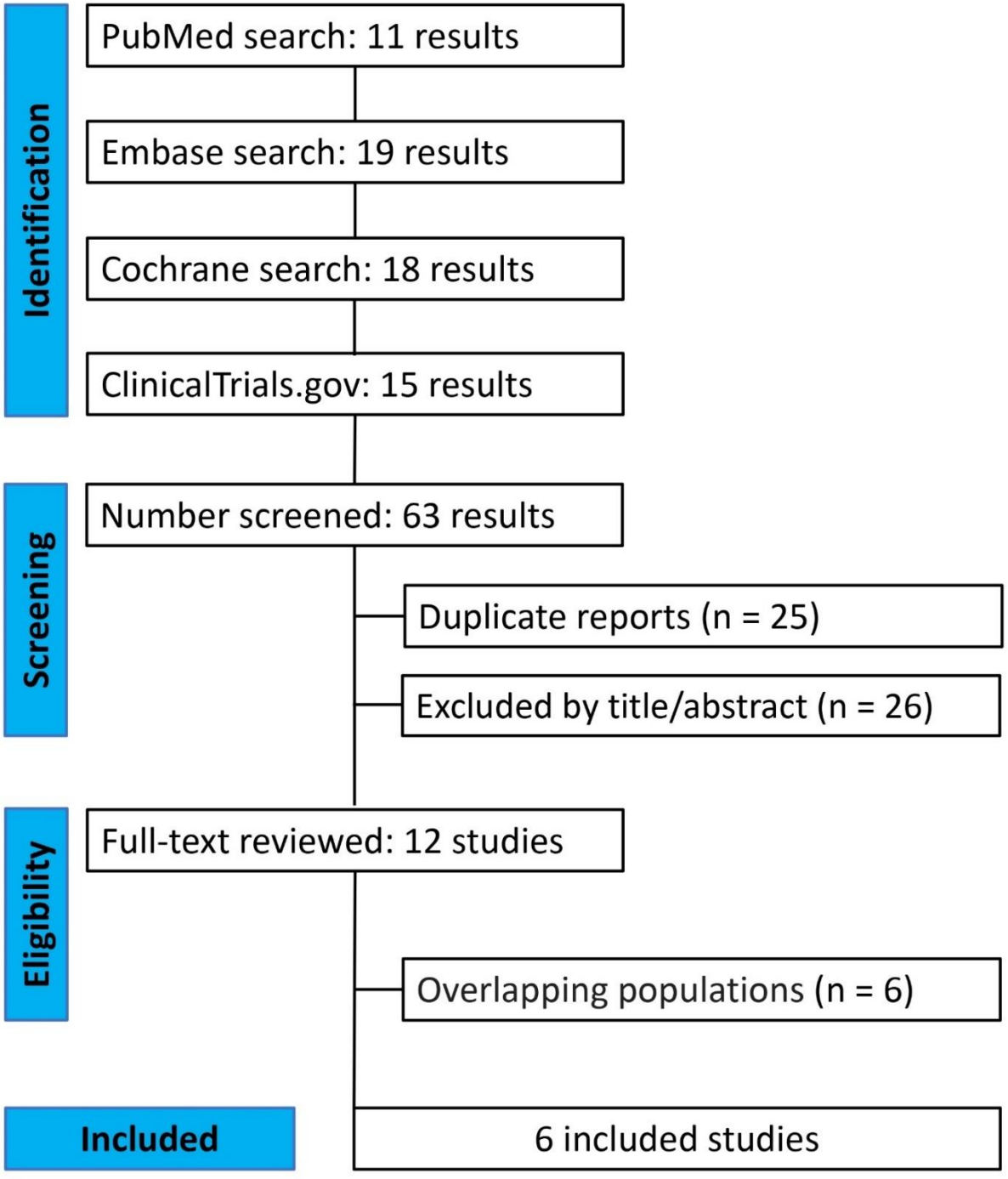
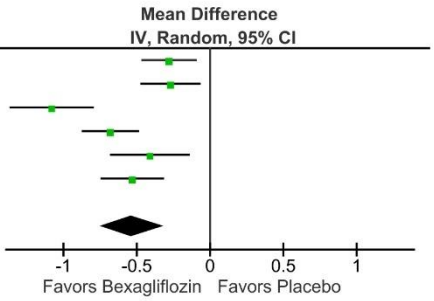


Figure 2.

A. HbA1c (%)

Study or Subgroup	Bexagliflozin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Allegretti 2019	-0.59	0.814	157	-0.31	0.821	155	17.7%	-0.28 [-0.46, -0.10]
BEST 2015	-0.56	0.828	218	-0.29	0.838	99	17.2%	-0.27 [-0.47, -0.07]
Halvorsen 2019	-0.55	1.184	145	0.53	1.22	138	15.1%	-1.08 [-1.36, -0.80]
Halvorsen 2020	-0.44	0.662	201	0.24	0.671	64	17.5%	-0.68 [-0.87, -0.49]
Lock 2016	-0.51	0.946	133	-0.1	0.871	65	15.5%	-0.41 [-0.68, -0.14]
Lock 2017	-1.09	0.906	142	-0.56	0.903	145	17.0%	-0.53 [-0.74, -0.32]
Total (95% CI)			**996**			**666**	**100.0%**	**-0.53 [-0.75, -0.31]**

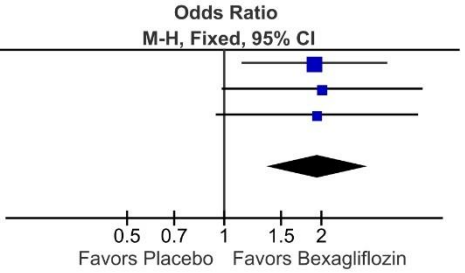
Heterogeneity: Tau² = 0.06; Chi² = 31.28, df = 5 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.75 (P < 0.00001)



B. Proportion of patients who achieved HbA1c < 7%

Study or Subgroup	Bexagliflozin Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Allegretti 2019	52	157	32	155	47.7%	1.90 [1.14, 3.18]
Halvorsen 2020	58	218	11	72	26.9%	2.01 [0.99, 4.08]
Lock 2016	41	124	13	64	25.4%	1.94 [0.95, 3.96]
Total (95% CI)		**499**		**291**	**100.0%**	**1.94 [1.36, 2.78]**
Total events	151		56			

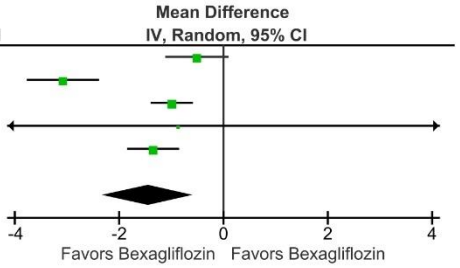
Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 3.62 (P = 0.0003)



C. Fasting plasma glucose (mmol/L)

Study or Subgroup	Bexagliflozin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BEST 2015	-1.06	2.486	218	-0.55	2.487	101	24.1%	-0.51 [-1.10, 0.08]
Halvorsen 2019	-1.58	2.593	145	1.5	3.143	138	23.3%	-3.08 [-3.75, -2.41]
Halvorsen 2020	-1.1	1.415	209	-0.11	1.412	69	25.7%	-0.99 [-1.37, -0.61]
Lock 2016	-1.02	22.506	125	-0.15	19.84	64	1.8%	-0.87 [-7.13, 5.39]
Lock 2017	-2.51	2.073	142	-1.16	2.083	145	25.0%	-1.35 [-1.83, -0.87]
Total (95% CI)			**839**			**517**	**100.0%**	**-1.45 [-2.32, -0.57]**

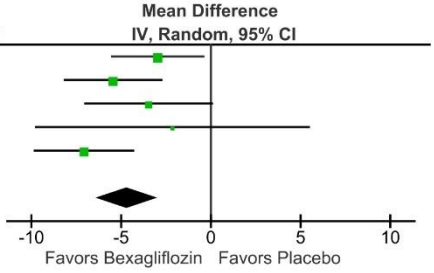
Heterogeneity: Tau² = 0.74; Chi² = 36.37, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.25 (P = 0.001)



D. Systolic blood pressure (mmHg)

Study or Subgroup	Bexagliflozin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
BEST 2015	-9.83	15.107	417	-6.87	15.194	204	27.2%	-2.96 [-5.50, -0.42]
Halvorsen 2019	-4.9	12.51	145	0.55	10.59	138	25.4%	-5.45 [-8.15, -2.75]
Halvorsen 2020	-2.37	12.96	209	1.1	12.958	69	17.7%	-3.47 [-7.00, 0.06]
Lock 2016	-0.6	41.88	138	1.54	12.659	69	4.9%	-2.14 [-9.74, 5.46]
Lock 2017	-5.03	11.874	143	2.04	11.885	145	24.8%	-7.07 [-9.81, -4.33]
Total (95% CI)			**1052**			**625**	**100.0%**	**-4.66 [-6.41, -2.92]**

Heterogeneity: Tau² = 1.23; Chi² = 5.87, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 5.24 (P < 0.00001)



E. Diastolic blood pressure (mmHg)

Study or Subgroup	Bexagliflozin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Halvorsen 2019	-3.07	14.471	140	-0.4	14.593	131	27.7%	-2.67 [-6.13, 0.79]
Halvorsen 2020	-1.1	7.84	209	0.81	7.891	69	72.3%	-1.91 [-4.05, 0.23]
Total (95% CI)			**349**			**200**	**100.0%**	**-2.12 [-3.94, -0.30]**

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)

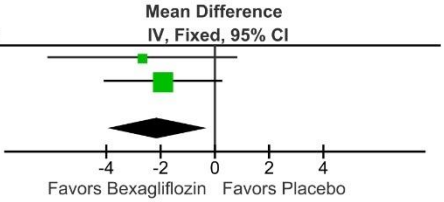


Figure 3.

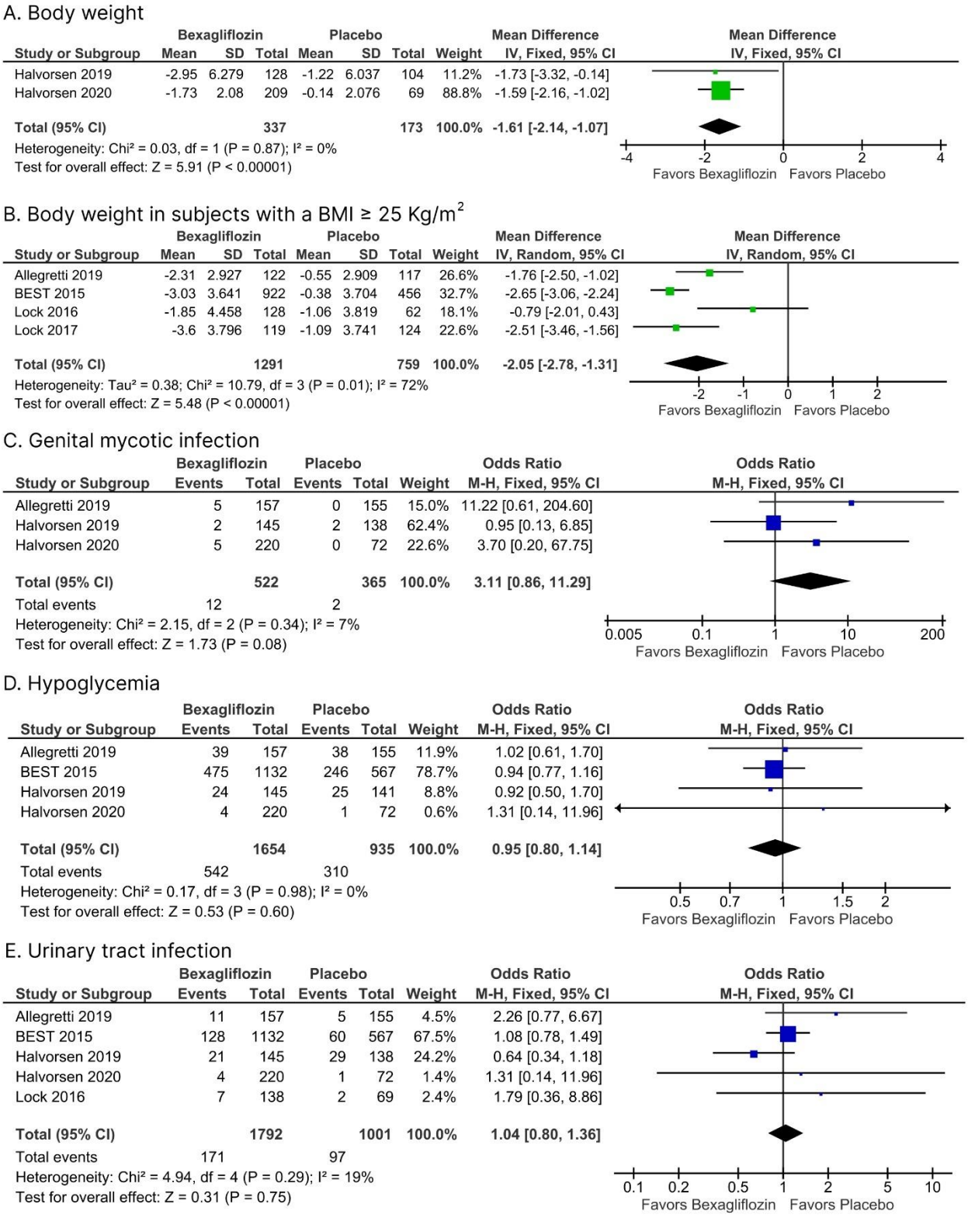
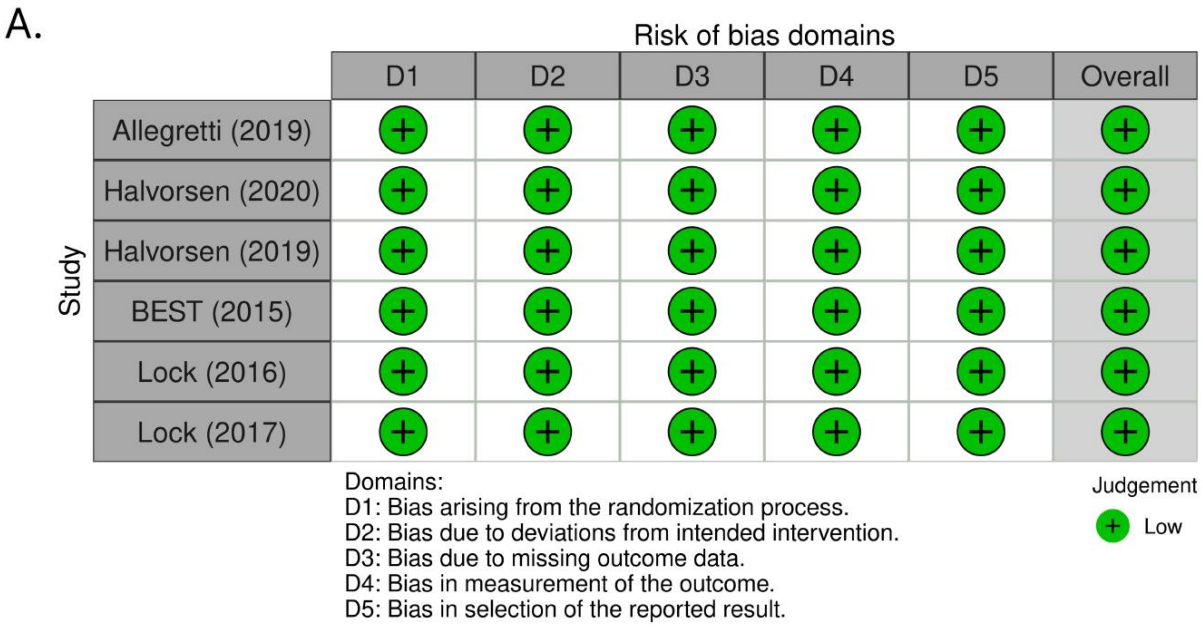
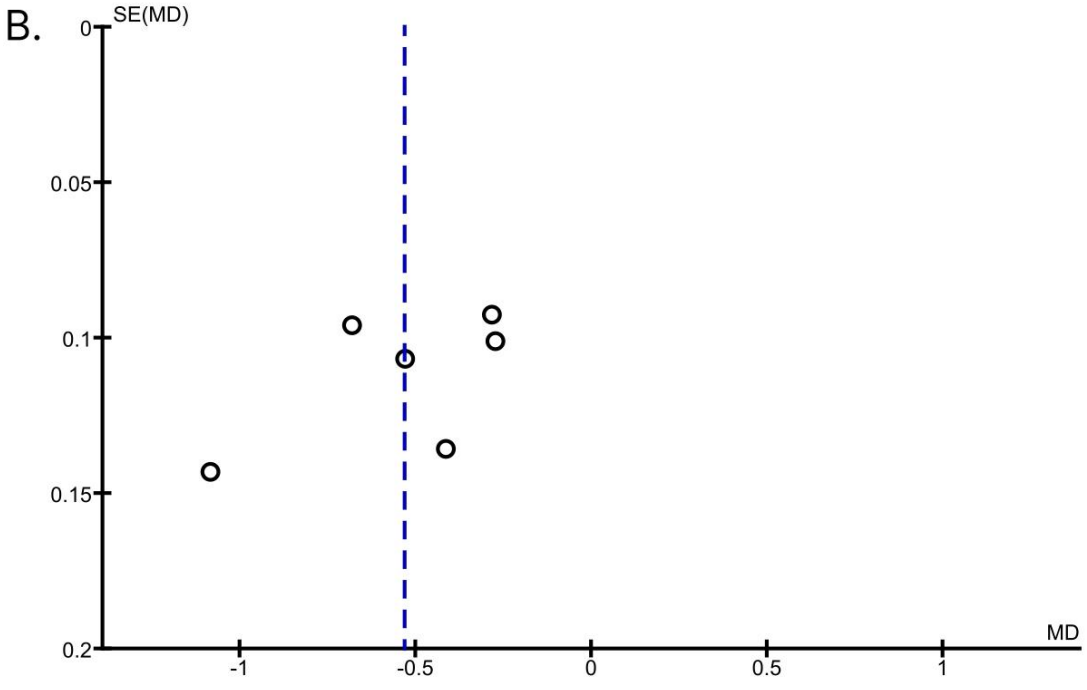

A. Body weight
Bexagliflozin
Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Halvorsen 2019 -2.95 6.279 128 -1.22 6.037 104 11.2% -1.73 [-3.32, -0.14]
Halvorsen 2020 -1.73 2.08 209 -0.14 2.076 69 88.8% -1.59 [-2.16, -1.02]
Total (95% CI) 337 173 100.0% -1.61 [-2.14, -1.07]
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 5.91 (P < 0.00001)
-4 -2 0 2 4
Favors Bexagliflozin Favors Placebo
B. Body weight in subjects with a BMI ≥ 25 Kg/m²
Bexagliflozin
Placebo
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Allegretti 2019 -2.31 2.927 122 -0.55 2.909 117 26.6% -1.76 [-2.50, -1.02]
BEST 2015 -3.03 3.641 922 -0.38 3.704 456 32.7% -2.65 [-3.06, -2.24]
Lock 2016 -1.85 4.458 128 -1.06 3.819 62 18.1% -0.79 [-2.01, 0.43]
Lock 2017 -3.6 3.796 119 -1.09 3.741 124 22.6% -2.51 [-3.46, -1.56]
Total (95% CI) 1291 759 100.0% -2.05 [-2.78, -1.31]
Heterogeneity: Tau² = 0.38; Chi² = 10.79, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 5.48 (P < 0.00001)
-2 -1 0 1 2
Favors Bexagliflozin Favors Placebo
C. Genital mycotic infection
Bexagliflozin
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Allegretti 2019 5 157 0 155 15.0% 11.22 [0.61, 204.60]
Halvorsen 2019 2 145 2 138 62.4% 0.95 [0.13, 6.85]
Halvorsen 2020 5 220 0 72 22.6% 3.70 [0.20, 67.75]
Total (95% CI) 522 365 100.0% 3.11 [0.86, 11.29]
Total events 12 2
Heterogeneity: Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 1.73 (P = 0.08)
0.005 0.1 1 10 200
Favors Bexagliflozin Favors Placebo
D. Hypoglycemia
Bexagliflozin
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Allegretti 2019 39 157 38 155 11.9% 1.02 [0.61, 1.70]
BEST 2015 475 1132 246 567 78.7% 0.94 [0.77, 1.16]
Halvorsen 2019 24 145 25 141 8.8% 0.92 [0.50, 1.70]
Halvorsen 2020 4 220 1 72 0.6% 1.31 [0.14, 11.96]
Total (95% CI) 1654 935 100.0% 0.95 [0.80, 1.14]
Total events 542 310
Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)
0.5 0.7 1 1.5 2
Favors Bexagliflozin Favors Placebo
E. Urinary tract infection
Bexagliflozin
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Allegretti 2019 11 157 5 155 4.5% 2.26 [0.77, 6.67]
BEST 2015 128 1132 60 567 67.5% 1.08 [0.78, 1.49]
Halvorsen 2019 21 145 29 138 24.2% 0.64 [0.34, 1.18]
Halvorsen 2020 4 220 1 72 1.4% 1.31 [0.14, 11.96]
Lock 2016 7 138 2 69 2.4% 1.79 [0.36, 8.86]
Total (95% CI) 1792 1001 100.0% 1.04 [0.80, 1.36]
Total events 171 97
Heterogeneity: Chi² = 4.94, df = 4 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.31 (P = 0.75)
0.1 0.2 0.5 1 2 5 10
Favors Bexagliflozin Favors Placebo

Figure 4.


A.
Risk of bias domains
D1
D2
D3
D4
D5
Overall
Study
Allegretti (2019)
Halvorsen (2020)
Halvorsen (2019)
BEST (2015)
Lock (2016)
Lock (2017)
Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.
Judgement
Low


B.
SE(MD)
0
0.05
0.1
0.15
0.2
MD
-1
-0.5
0
0.5
1

APPENDIX

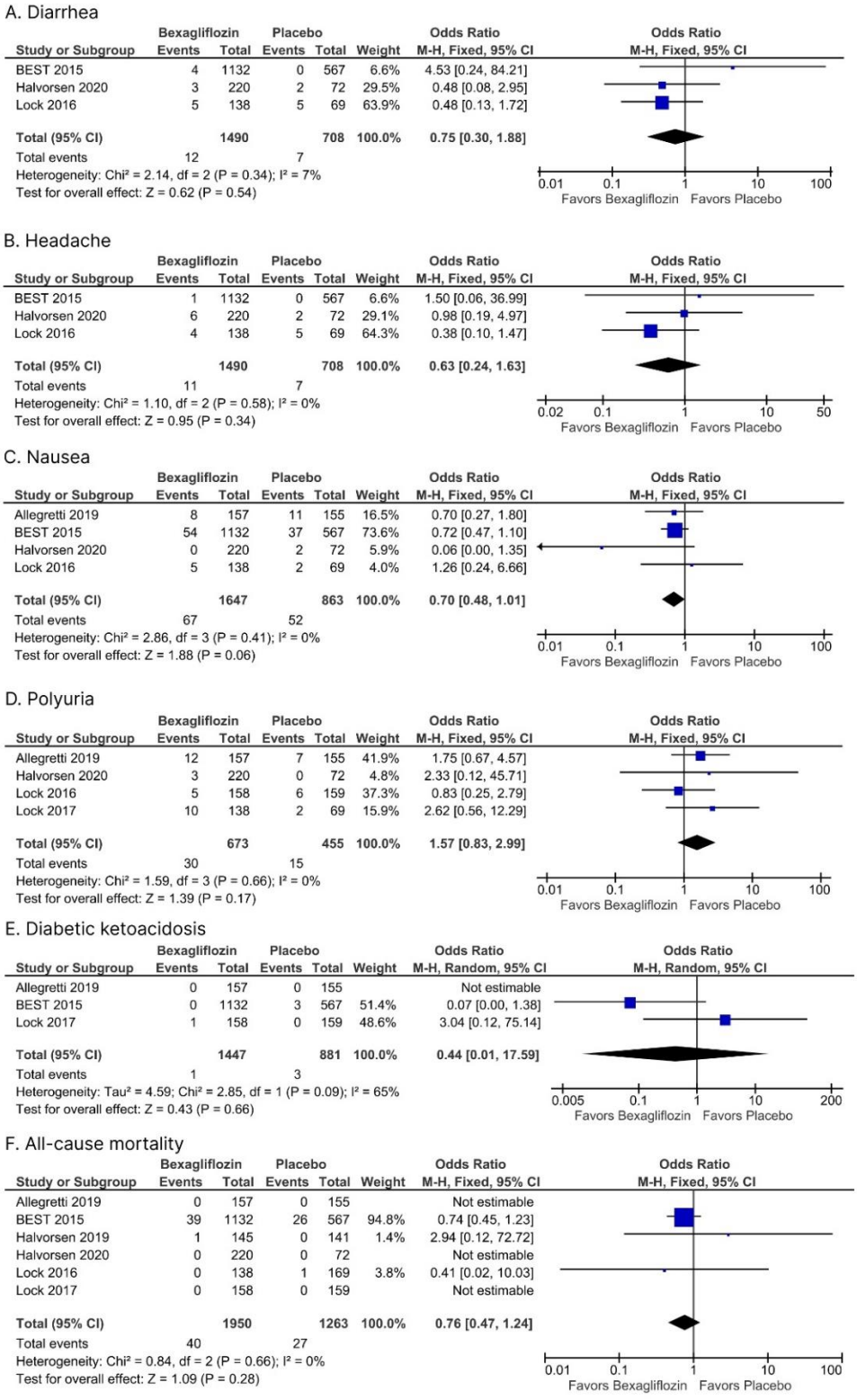


Figure S1. Forest plots outcomes. **A.** Diarrhea. **B.** Headache. **C.** Nausea. **D.** Polyuria. **E.** Diabetic ketoacidosis. **F.** All-cause mortality.

Table S1. Leave-one-out sensitivity analysis for HbA1c (%).

Study removed	OR (CI 95%)	P-Value	I^2
Omitting Allegretti 2019	-0.59 (-0.83, -0.34)	P < 0.00001	84%
Omitting BEST 2015	-0.59 (-0.83, -0.34)	P < 0.00001	84%
Omitting Halvorsen 2019	-0.43 (-0.60, -0.27)	P < 0.00001	69%
Omitting Halvorsen 2020	-0.50 (-0.76, -0.25)	P < 0.00001	85%
Omitting Lock 2016	-0.56 (-0.81, -0.30)	P < 0.00001	87%
Omitting Lock 2017	-0.53 (-0.80, -0.26)	P = 0.0001	87%

Table S2. Results from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Endpoints	**Patients (RCTs)**	**GRADE**	**Rationale for GRADE**
HbA1c (%)	1662 (6)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, there was high heterogeneity (I^2 = 84%).
Proportion of patients who achieved HbA1c < 7%	790 (3)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, we downgraded by one level due to only 3 RCTs reporting this outcome.
FPG (mmol/L)	1356 (5)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, there was high heterogeneity (I^2 = 89%).
SBP (mmHg)	1677 (5)	⊕ ⊕ ⊕ ⊕ Strong	All RCTs had a low risk of bias. However, there was significant heterogeneity (I^2 = 32%), possibly due to the large reduction in SBP found in some studies compared to other RCTs or due to follow-up. Based on this, we consider that this should not reduce the strength of the evidence.
DBP (mmHg)	549 (2)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, only two studies reported this outcome.
Body weight	510 (2)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, only two studies reported this outcome.

Body weight in patients with a BMI ≥ 25 kg/m2	2050 (4)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, there was high heterogeneity (I^2 = 72%).
Genital mycotic infection	887 (3)	⊕ ⊕ ⊕ ⊖ Moderate	All RCTs had a low risk of bias. However, only three studies reported this outcome.
Hypoglycemia	2589 (4)	⊕ ⊕ ⊕ ⊕ Strong	All RCTs had a low risk of bias.
Urinary tract infection	2793 (5)	⊕ ⊕ ⊕ ⊕ Strong	All RCTs had a low risk of bias. Although the confidence intervals include evidence of no effect, the incidence was similar between the bexagliflozin 20 mg and placebo groups across the 5 RCTs. Based on this, we consider that this should not reduce the strength of the evidence.
Diarrhea	2198 (3)	⊕ ⊕ ⊖ ⊖ Low	All RCTs had a low risk of bias. However, we downgraded by two levels due to only 3 RCTs reporting this outcome and given that the confidence intervals include evidence of no effect.
Headache	2198 (3)	⊕ ⊕ ⊖ ⊖ Low	All RCTs had a low risk of bias. However, we downgraded by two levels due to only 3 RCTs reporting this outcome and given that the confidence intervals include evidence of no effect.
Nausea	2510 (4)	⊕ ⊕ ⊖ ⊖ Low	All RCTs had a low risk of bias. However, we downgraded by two levels due to only 4 RCTs reporting this outcome.
Polyuria	1128 (4)	⊕ ⊕ ⊖ ⊖ Low	All RCTs had a low risk of bias. However, we downgraded by two levels due to only 4 RCTs reporting this outcome and given that the confidence intervals include evidence of no effect.
Diabetic ketoacidosis	2328 (3)	⊕ ⊖ ⊖ ⊖ Very Low	All RCTs had a low risk of bias. However, we downgraded by three levels due to only 3 RCTs reporting this outcome and given that the confidence intervals include evidence of no effect. Furthermore, only 2 RCTs that reported events were evaluated with meta-analysis, with high heterogeneity (I^2 = 65%).
All-cause mortality	3213 (6)	⊕ ⊕ ⊖ ⊖ Low	All RCTs had a low risk of bias. However, we downgraded by two levels due to only 3 RCTs reporting events and given that the confidence intervals include evidence of no effect.

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HbA1c, hemoglobin A1c; RCTs, randomized controlled trials; SBP, systolic blood pressure.

ANEXO 1: Normas de publicação da revista Diabetes, Obesity and Metabolism

AIMS AND SCOPE

Authors are reminded that *Diabetes, Obesity and Metabolism* is primarily a journal of pharmacology and therapeutics, focused mainly on human research relevant to patient care. Priority is given to manuscripts that relate to therapeutic interventions.

The scope of the journal includes studies of pharmacokinetics and pharmacodynamics; cost-effectiveness; real world evidence of drug utilisation, safety and effectiveness, as well as conventional randomised controlled trials. High-quality meta-analyses and systematic reviews that provide original information on treatment effects and safety are considered as original research papers.

DOM also welcomes manuscripts which report clinical data relating to novel devices, Apps, glucose sensors and insulin pumps used to improve glycaemic control.

SUBMISSION

Authors should note that submission of a manuscript implies that the content has not been published previously (except in abstract form, e.g as part of conference proceedings), and is not currently under consideration by any other journal.

Once the submission materials have been prepared in accordance with the guidance for authors, manuscripts should be submitted online at: **http://mc.manuscriptcentral.com/dom**

Transparent Peer Review

Diabetes Obesity and Metabolism is participating in a scheme to improve Peer Review Transparency. We encourage all authors to opt in to transparent peer review (TPR) at the time of manuscript submission.

If authors opt into TPR, and their paper is eventually accepted for publication in DOM, the (anonymised) peer review reports, editorial correspondence and author responses during the revision process will be publically accessible via a link to **Publons**, once the article is published in the journal.

Allowing readers access to the peer review process and pre-acceptance clarifications and revisions adds value and invariably reflects positively on the authors, sponsors and the journal. It is pleasing that >90% of authors are currently opting into TPR, but if authors have any concerns they are welcome to raise these with the handling editor.

Data Protection and Privacy

By submitting a manuscript to, or reviewing for, this publication, your name, email address, institutional affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain

the security, integrity, and privacy of the personal data collected and processed. You can learn more at **https://authorservices.wiley.com/statements/data-protection-policy.html**.

Preprint Policy

Diabetes, Obesity and Metabolism will consider for review articles previously available as preprints. Authors may also post the **submitted version** of a manuscript to a preprint server at any time. Authors are requested to update any pre-publication versions with a link to the final published article.

MANUSCRIPT CATEGORIES AND REQUIREMENTS

(i) Original Papers

Original research papers should provide substantial new analyses and be structured as follows:

Title page: Author names, affiliations, and a short running title. The number of co-authors should not exceed 15. The word counts for the abstract and the main body of the text (excluding references and legends) should be clearly stated, along with the number of references, tables and figures. Please conform to the guidance on manuscript size below

Structured abstract: Subheadings - aims, materials and methods, results, and conclusions (maximum 250 words);

Main manuscript: This should be typed double-spaced and structured as follows: introduction; materials and methods (including appropriate subsections, e.g. statistical methods); results; discussion; acknowledgements; references (normally <60); legends to figures; tables; and figures. It is helpful to include line numbering throughout the document.

Original manuscripts should not exceed **3,500 words** (not including references, tables and figures). Manuscripts should include a maximum of 5 Figures and/or tables.

Additional tables or figures and/or extra methodological detail can be included in a separate Supplementary Appendix. The production and handling Editors may relocate large tables or figures into a Supplementary Appendix prior to the production of page proofs if the manuscript exceeds these specifications at the time of final acceptance.

(ii) Research Letters

These are short, focused communications conveying original results from new research which is more limited in scope and depth than what would be expected for an original paper. Nevertheless, Research Letters undergo full peer review; they are fully searchable and citeable items with their own unique DOI number.

Research Letters are ideal to communicate a focused piece of research, e.g a post-hoc or secondary analysis of a large clinical trial, a limited meta-analysis, or a specific new result from real world evidence. Originality and clinical relevance are important.

Research Letters do not have an abstract but they should have a title page (as above).

The main text should be sub-divided into sections, e.g : Background / context, Methods, Results and Conclusions.

The total manuscript length should not exceed **1,200 words**, excluding references.

Research Letters can include a maximum of 12 references (+ any number of references to work published in *Diab. Obes. Metab.*) and 2 figures OR 2 tables (or one of each).

Additional information (e.g text, tables or figures) can be provided as part of a Supplementary Appendix.

Research Letters have now replaced Brief Reports.

(iii) Review Articles & Commentaries

Diabetes, Obesity & Metabolism publishes a limited number of narrative reviews. (Systematic reviews and meta-analyses should be formatted and submitted as original papers).

We consider unsolicited review articles on important topics of therapeutics and pharmacology. Good review articles should provide novel insights, informed discussion and a balanced interpretation of the published literature.

Shorter opinion pieces or those communicating novel hypotheses can be submitted as a Commentary (1,500 words maximum; no abstract; maximum of 20 references).

Review articles should not normally exceed 5000 words and 120 references. They require a non-structured (250 word) Abstract and a Title page (as above). Good quality Figures & Tables enhance the quality and impact of a narrative review.

The sub-structure of a Review Article is left to the discretion of the author. Additional data (e.g Tables or text) can be provided as part of the Supplementary Appendix.

The handling Editor may relocate tables or figures into a supplementary Appendix if the manuscript exceeds these specifications and/or 10 printed pages.

(iv) Letters to the Editor

The editors welcome correspondence relating to work that has recently been published in the journal, and/or other brief comments or observations that may be of wider interest.

Letters to the Editor can include limited amounts of new data, especially if there is direct relevance to, e.g confirmation of, data published in a recent manuscript in *Diab. Obes. Metab*.

Letters to the Editor are peer reviewed. They do not have an abstract. Letters should not exceed 1,200 words. They can include up to 2 small figures OR tables, and a maximum of 12 references (+ any number of references to work published in *Diab. Obes. Metab*.). If Letters raise points of discussion about a recent manuscript published in the journal the editor may invite a response from the authors of the article.

We do not publish case reports.

DIGITAL ENHANCEMENTS

Following the acceptance and online publication of an article in *Diab Obes. Metab*., authors may wish to submit one or more digital enhancements (DE's), e.g a video abstract, infographic or plain language summary (PLS), to augment the communication.

Ideally DE's will be submitted soon after the acceptance of the original manuscript, e.g within 2-3 weeks, in order that DE's (if accepted) can be incorporated into the production of the article, however it is still possible to submit DE's for papers that have already been published in an earlier issue of the journal. (We prefer DE's to be submitted after final acceptance of articles).

DE's are submitted through the journal's online editorial platform (ScholarOne) as new submissions but flagged as 'companion papers' to the main manuscript (quoting the DOM reference number of the original article). Oversight, authorship and responsibility for DE's rests with the authors of the original paper, and DE's should fairly reflect the key results, interpretation and limitations as described in the accepted article.

DE's are peer reviewed, often by the handling editor and/or peer reviewers who evaluated the original submission. There is a fee of USD 1,000 per DE. Further information about specific types of DE's is provided below:

Video abstracts:

Video abstracts (often produced after the original manuscript has been accepted) will be peer reviewed. As with all parts of a manuscript submission, the authors are responsible for the content of the visual abstract to ensure that it fairly summarises the agreed wording in the main manuscript.

The authors have the option to purchase an accompanying video abstract version of their article, following the steps below:

1. Contact corporatesaleseurope@wiley.com for further information on digital enhancement.
2. Once the video abstract has been created, please upload it (as a new submission) as a hyperlink in Scholar One, selecting the article type 'Digital Enhancement'. Please do not try to upload the video file itself. During the submission process there is an opportunity to identify the original DOM manuscript reference number as the 'accompanying article', thereby ensuring that the video abstract is linked to the original (accepted) article.
3. The video abstract will be reviewed by the editorial team but may not be peer reviewed by the original article peer reviewers (this facility is only available for video abstracts submitted by corporate sponsors).
4. If the video abstract is accepted for publication the author will be notified and it will be published alongside the finished article in the online journal.

Plain Language Summaries

These are generally concise word documents which describe in non-technical language the context, purpose of the research, the main results and the clinical relevance and originality of

the study. PLS's should not exceed 500 words. In addition they may include 2 simple Figures or an Infographic. We suggest the following sub-headings for the text of the PLS:

- What is the context and purpose of this research study ?
- What was done ?
- What were the main results ?
- What is the originality and relevance of this study ?

PLS's can be uploaded to ScholarOne after manuscript acceptance. They are uploaded as new submissions but marked as DE's and as companion papers to the original submission. They will then be peer reviewed, and may be subject to revision prior to acceptance. The authorship of the PLS should be the same authorship as the main paper.

PREPARING YOUR SUBMISSION

Authorship

Please refer to the journal's Authorship policy in the Editorial Policies and Ethical Considerations section for details on author listing eligibility.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be disclosed.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the 'Conflict of Interest' section in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

References

All references should be numbered consecutively in order of appearance and should be as complete as possible. In text citations should cite references in consecutive order using Arabic superscript numerals.

For more information about this reference style, please see the AMA Manual of Style.

Reference examples follow:

Journal article

1. King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book

1. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

Please note that journal title abbreviations should conform to the practices of Chemical Abstracts.

Internet Document

1. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf. Accessed March 3, 2003.

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text.

All abbreviations must be defined in the footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. **Click here** for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Figures submitted as a colour original will appear in colour in the Journal's online edition free of charge.

Additional Files

Appendices

Appendices will be published after the references. For submission they should be supplied as separate files but referred to in the text.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

Click here for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

Article Preparation Support

Wiley Editing Services offers expert help with English Language Editing, as well as translation, manuscript formatting, figure illustration, figure formatting, and graphical abstract design – so you can submit your manuscript with confidence.

Also, check out our resources for **Preparing Your Article** for general guidance about writing and preparing your manuscript.

Fast Track Submission

Diabetes Obesity & Metabolism offers a separate fast-track process for important clinical trial papers, usually RCTs of high importance & clinical impact. Authors considering a Fast-Track submission should firstly E-mail the Front page & the Abstract page to the Editorial office (susan.lane@btinternet.com). A journal Editor will advise within 48 hours on whether the full manuscript is suitable for Fast-track consideration.

For manuscripts we agree to evaluate under a Fast-Track pathway, a submission fee of US $2,000 (plus VAT in the UK) is payable. Authors will upload the full submission and select 'fast-track' as the manuscript type. The Editorial office will expedite full peer-review and a decision will be made. There is no guarantee of final acceptance for papers that are reviewed as 'Fast-Track'.

If a 'Fast-Track' manuscript is accepted, usually after revision and re-evaluation, the paper will be prioritised in production with early proofs. The 'Fast-Track' system expedites production and placement into an issue, assuming the paper has been accepted. We aim to publish the final article as an Early View paper (edited, typeset and as corrected final proofs) within 20 to 28 days, and place it into the next monthly issue about one month later.

Authors planning to submit a Fast Track paper are encouraged to contact the Editorial Office in advance of submission, so that peer-review can be planned in advance. An invoice will be issued by Wiley for the submission fee on submission of the manuscript via our "Fast Track" process – please provide full details to whom this invoice should be sent (including an email address).

EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Peer Review and Acceptance

The acceptance criteria for all papers is the quality and originality of the research and its significance to our readership. Papers will only be sent to review if the Editor-in-Chief determines that the paper meets the appropriate quality and relevance requirements. Wiley's policy on confidentiality of the review process is **available here**.

ORCID

As part of our commitment to supporting authors at every step of the publishing process, this journal requires the submitting author to provide an ORCID iD when submitting a manuscript, and prefers that all co-authors also have ORCID iD. This takes around 2 minutes to complete. Find more information. Additionally, the corresponding author is encouraged to use an institutional email address wherever possible.

Data Sharing and Data Accessibility

The journal encourages authors to share the data and other artefacts supporting the results in the paper by archiving it in an appropriate public repository. Authors should include a data accessibility statement, including a link to the repository they have used, in order that this statement can be published alongside their paper.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: **Declaration of Helsinki**; **US Federal Policy for the Protection of Human Subjects**; or **European Medicines Agency Guidelines for Good Clinical Practice**. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study.

Patient anonymity should be preserved. Photographs need to be cropped sufficiently to prevent human subjects being recognized (or an eye bar should be used). Images and information from individual participants will only be published where the authors have obtained the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a **standard patient consent form available** for use.

Clinical Trial Registration

The journal requires that clinical trials are prospectively registered in a publicly accessible database and clinical trial registration numbers should be included in all papers that report their results. Authors are asked to include the name of the trial register and the clinical trial registration number at the end of the abstract. If the trial is not registered, or was registered retrospectively, the reasons for this should be explained.

Research Reporting Guidelines

Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. Authors are expected to adhere to recognised research reporting standards. The EQUATOR Network collects more than 370 reporting guidelines for many study types, including for:

- **Randomised trials**: **CONSORT**
  • **Observational studies**: **STROBE**
  • **Systematic reviews**: **PRISMA**
  • **Case reports**: **CARE**
  • **Qualitative research**: **SRQR**
  • **Diagnostic / prognostic studies**: **STARD**
  • **Quality improvement studies**: **SQUIRE**
  • **Economic evaluations**: **CHEERS**
  • **Animal pre-clinical studies**: **ARRIVE**
  • **Study protocols: SPIRIT**
  • **Clinical practice guidelines: AGREE**

We also encourage authors to refer to and follow guidelines from:

- **Future of Research Communications and e-Scholarship (FORCE11)**
  • **National Research Council's Institute for Laboratory Animal Research guidelines**
  • **The Gold Standard Publication Checklist from Hooijmans and colleagues**
  • **Minimum Information Guidelines from Diverse Bioscience Communities (MIBBI) website**
  • **FAIRsharing website**

Species Names

Upon its first use in the title, abstract, and text, the common name of a species should be followed by the scientific name (genus, species, and authority) in parentheses. For well-known species, however, scientific names may be omitted from article titles. If no common name exists in English, only the scientific name should be used.

Genetic Nomenclature

Sequence variants should be described in the text and tables using both DNA and protein designations whenever appropriate. Sequence variant nomenclature must follow the current HGVS guidelines; see **http://varnomen.hgvs.org/**, where examples of acceptable nomenclature are provided.

Sequence Data

Nucleotide sequence data can be submitted in electronic form to any of the three major collaborative databases: DDBJ, EMBL, or GenBank. It is only necessary to submit to one database as data are exchanged between DDBJ, EMBL, and GenBank on a daily basis. The suggested wording for referring to accession-number information is: ‘These sequence data have been submitted to the DDBJ/EMBL/GenBank databases under accession number U12345’. Addresses are as follows:

- DNA Data Bank of Japan (DDBJ): **http://www.ddbj.nig.ac.jp**
  • EMBL Nucleotide Archive: **ebi.ac.uk/ena**
  • GenBank: **www.ncbi.nlm.nih.gov**

Proteins sequence data should be submitted to either of the following repositories:

- Protein Information Resource (PIR): **pir.georgetown.edu**
  • SWISS-PROT: **expasy.ch/sprot/sprot-top**

Conflict of Interest

The journal requires that all authors disclose any potential sources of conflict of interest. Any interest or relationship, financial or otherwise that might be perceived as influencing an author's objectivity is considered a potential source of conflict of interest. These must be disclosed when directly relevant or directly related to the work that the authors describe in their manuscript. Potential sources of conflict of interest include, but are not limited to: patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, and consultancy for or receipt of speaker's fees from a company. The existence of a conflict of interest does not preclude publication. If the authors have no conflict of interest to declare, they must also state this at submission. It is the responsibility of the corresponding author to review this policy with all authors and collectively to disclose with the submission ALL pertinent commercial and other relationships.

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Authors should list all funding sources in the Acknowledgments section. Authors are responsible for the accuracy of their funder designation. If in doubt, please check the Open Funder Registry for the correct nomenclature: **https://www.crossref.org/services/funder-registry/**

Authorship

The list of authors should accurately illustrate who contributed to the work and how. All those listed as authors should qualify for authorship according to the following criteria:

1. Have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. Been involved in drafting the manuscript or revising it critically for important intellectual content;
3. Given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
4. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section (for example, to recognize contributions from people who provided technical help, collation of data, writing assistance, acquisition of funding, or a department chairperson who provided general support). Prior to submitting the article all authors should agree on the order in which their names will be listed in the manuscript.

Additional Authorship Options

Joint first or senior authorship: In the case of joint first authorship, a footnote should be added to the author listing, e.g. 'X and Y should be considered joint first author' or 'X and Y should be considered joint senior author.'

Correction to authorship

In accordance with Wiley's **Best Practice Guidelines on Research Integrity and Publishing Ethics** and the **Committee on Publication Ethics**' guidance, *Diabetes, Obesity and Metabolism* will allow authors to correct authorship on a submitted, accepted, or published article if a valid reason exists to do so. All authors – including those to be added or removed – must agree to any proposed change. To request a change to the author list, please complete the **Request for Changes to a Journal Article Author List Form** and contact either the journal's editorial or production office, depending on the status of the article. Authorship changes will not be considered without a fully completed Author Change form. Correcting the authorship is different from changing an author's name; the relevant policy for that can be found in **Wiley's Best Practice Guidelines** under "Author name changes after publication."

Publication Ethics

This journal is a member of the **Committee on Publication Ethics (COPE)**. Note this journal uses iThenticate's CrossCheck software to detect instances of overlapping and similar text in submitted manuscripts. Read Wiley's Top 10 Publishing Ethics Tips for Authors **here**. Wiley's Publication Ethics Guidelines can be found **here**.

Transparent Peer Review

Diabetes Obesity and Metabolism is participating in a pilot on Peer Review Transparency, where the reviewer reports, author responses, and the editor's decision letters will be hosted on **Publons** and linked to from the published article in the case that the article is accepted. Authors have the opportunity to opt out during submission, and reviewers can choose to remain anonymous unless they would like to sign their report.

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Once the paper is typeset, the author will receive an email notification with full instructions on how to provide proof corrections.

Please note that the author is responsible for all statements made in their work, including changes made during the editorial process – authors should check proofs carefully. Note that proofs should be returned within 48 hours from receipt of first proof.

POST PUBLICATION

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  • The corresponding author and co-authors can nominate up to ten colleagues to receive a publication alert and free online access to the article.

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Author Guidelines updated 18 July 2023

This is the accepted version of the following article: Pasqualotto E, Watanabe JMF, Gewehr DM, Maintinguer RS, van de Sande-Lee S, Araujo GN, et al. Efficacy and safety of bexagliflozin in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Obes Metab. 2023;25(7):1794-1802. doi:10.1111/dom.15051, which has been published in final form at [https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15051].