UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:

ENDOCRINOLOGIA

EFICÁCIA E SEGURANÇA DOS INIBIDORES DO SGLT2 NO TRATAMENTO DO DIABETES MÉLITO TIPO 2: REVISÃO SISTEMÁTICA COM METANÁLISE

DISSERTAÇÃO DE MESTRADO

LANA CATANI FERREIRA PINTO

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Orientadora: Profa. Dra. Cristiane Bauermann Leitão

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Esta dissertação de mestrado será apresentada no formato exigido pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia. Ela será constituída de uma introdução em português e um artigo em inglês, este formatado conforme as exigências da respectiva revista médica à qual será submetido para avaliação e posterior publicação. O artigo em inglês desta tese é um artigo do tipo Revisão Sistemática e Metanálise.

DEDICATÓRIA

“Feliz aquele que transfere o

que sabe e aprende o que ensina.”

Cora Carolina

A minha irmã, companheira de todas as horas.

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À Luciana Reck Remonti, cuja ajuda foi essencial nas análises mais complexas e quando eu errava algo nas configurações do computador.

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Ao Maycon, que no último ano aguentou com muita paciência, as negativas aos convites para sair, ser trocado pelo computador e ir para a cama com o Pé de Pano, tudo

por causa do mestrado. Apesar de tudo isso, até conseguia me ajudar quando eu brigava com o computador e me consolava quando eu chorava.

A Deus.

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LISTA DE ABREVIATURAS

SGLT2 *Sodium-Glucose Cotransporter 2*

BP *Blood Pressure*

SBP *Systolic Blood Pressure*

DBP *Diastolic Blood Pressure*

DPP-IV *Dipeptidyl Peptidase-IV*

PRISMA *Preferred Reporting Items in Systematic Reviews and Meta-analysis*

GRADE *Grading of Recommendations, Assessment, Development and Evaluation*

RCT *Randomized Clinical Trial*

SD *Standard Deviation*

CI *Confidence Interval*

WMD *Weighted Mean Difference*

NMA *Network Meta-analysis*

CrI *Credibility Interval*

FDA *Food and Drug Administration*

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

Capítulo 1- Introdução

Nos últimos 50 anos diversas opções terapêuticas para o tratamento do diabetes mélito (DM) tipo 2 foram desenvolvidas (1). Desde os ensaios clínicos clássicos que comprovaram benefícios em complicações macrovasculares e microvasculares da metformina (2) e sulfoniluréias (3), diversas drogas surgiram, algumas já foram retiradas do mercado pelos potenciais danos causados e, atualmente, temos nove classes de medicamentos para o tratamento dos pacientes com DM tipo 2, sendo os inibidores do cotransportador sódio-glicose 2 (SGLT2) a mais nova delas.

O SGLT2 é expressado na porção proximal do túbulo contorcido proximal (segmento S1) (4, 5) onde cotransporta sódio e glucose. Sua inibição leva a 70-80 g de glicosúria por dia (6), acompanhada de natriurese e diurese osmótica (4). A longo prazo, a perda calórica de cerca de 300 kcal/dia na forma de glucose resulta em perda de peso, efeito demonstrado em estudos com os representantes da classe canagliflozina (7), dapagliflozina (8) e empagliflozina (9).

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Capítulo 2 – Artigo Original

Efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes: a systematic review and meta-analysis

Running title: SGLT2 inhibitors and treatment of type 2 diabetes

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ABSTRACT

Background: Sodium–glucose cotransporter2 (SGLT2) inhibitors have different selectivity of SGLT2 over SGLT1 transporter and this may influence their potency and safety. SGLT2 inhibitors use is associated with adaptive mechanisms that may affect the efficacy of their combination with other antihyperglycemic medications.

Purpose: to compare individual SGLT2 inhibitors and as a class versus other antihyperglycemic agents and the combination of SGLT2 inhibitors plus metformin versus SGLT2 inhibitors plus DPP-IV inhibitors. Outcomes: HbA_{1c}, body weight, blood pressure (BP), and adverse events.

Data sources: MEDLINE, Cochrane, EMBASE databases.

Study selection: Randomized control trials of SGLT2 inhibitors in type 2 diabetes patients, lasting at least 12 weeks.

Data extraction: 2 authors independently extracted the articles**.**

Data synthesis: Thirty-nine studies were included (25,505 patients). Canagliflozin 300 mg induced greater HbA_{1c} reduction than dapagliflozin 10 mg (-0.26%) and empagliflozin 25 mg (-0.22%). SGLT2 inhibitors produced a similar HbA_{1c} reduction as metformin and sulphonylureas, but superior to DPP-IV inhibitors (-0.16%), and caused more weight loss and decrease in BP than metformin (-1.04 kg, -5.86 mmHg), sulphonylureas (-4.76 kg, -5.44 mmHg) and DPP-IV inhibitors (-2.45 kg, -4.34 mmHg). Initial combination of SGLT2 inhibitor plus metformin resulted in greater HbA_{1c} reduction (-0.53%) than SGLT2 plus DPP-IV inhibitors (-0.19%).

Limitations: Risk for publication bias.

Conclusions: SGLT2 inhibitors were associated with clinically significant HbA_{1c} reductions, similar to metformin and sulphonylureas, but superior to DPP-IV inhibitors. They also were superior in terms of weight and BP reductions. SGLT2 inhibitors plus metformin may represent a beneficial option to start diabetes treatment.

Introduction

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a novel class of antihyperglycemic medications that inhibit renal glucose reabsorption leading to glucosuria (1). They inhibit SGLT2 in the proximal convoluted renal tubule producing glucosuria of about 80 g/day (2, 3). These medications may also inhibit the SGLT1 transporter in the more distal portion of the proximal tubules and intestinal lumen. Members of this class may differ in efficacy and safety depending on their selectivity profiles for SGLT2 over SGLT1 inhibition. They also have a beneficial effect on blood pressure and body weight (4-6). Weight loss is related to caloric waste in the form of glucosuria, but it is limited to only 2 to 3 kg (7-9) in spite of persistent and unchanged glucosuria (10). This is probably related to increased intake of the same amount of calories lost as glucosuria (11). Other adaptive mechanism observed in patients using SGLT2 inhibitors is increased endogenous glucose production and fasting plasma glucagon concentration (10). Although they are effective as monotherapy and in association with other antihyperglycemic agents, including insulin these adaptive mechanisms may influence the clinical response of combinations of SGLT2 inhibitors with other antihyperglycemic agents.

Previous systematic reviews and meta-analyses have already analyzed the efficacy and safety of SGLT2 inhibitors (12,13). Since then, data from new studies were presented or published allowing a more comprehensive analysis that may provide evidence for a better clinical use of this novel class of antihyperglycemic agents.

The aims of this study were to analyze the efficacy and safety of each SGLT2 inhibitor and the SGLT2 inhibitors as a class versus other antihyperglycemic

medications.in patients with type 2 diabetes regarding HbA_{1c}, body weight and blood pressure variation Finally, we also compared the effect of the initial treatment of patients with type 2 diabetes of the combination of SGLT2 inhibitors plus metformin versus SGLT2 inhibitors versus DPP-IV inhibitors on HbA_{1c} and body weight change.

Methods

Protocol and registration

This systematic review and meta-analysis follows Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (14) and was registered at PROSPERO (15) (*CRD42015006975).*

Information sources and search strategy

We performed a systematic literature search for all randomized clinical trials (RCTs) that compared SGLT-2 inhibitors either to placebo or to an active control. We searched Medline (via PubMed), EMBASE, Cochrane CENTRAL, clinicaltrials.gov until September 2014 and abstracts published in American Diabetes Association and the European Association for the Study of Diabetes. The search strategy combined the Medical Subject Heading (MeSH) terms “2-(3-(4-ethoxybenzyl)-4-chlorophenyl)-6-hydroxymethyltetrahydro-2H-pyran-3,4,5-triol" OR "dapagliflozin" OR "canagliflozin" OR "ipragliflozin" OR "6-((4-ethylphenyl)methyl)-3',4',5',6'-tetrahydro-6'-(hydroxymethyl)spiro(isobenzofuran-1(3H),2'-(2H)pyran)-3',4',5'-triol" OR "empagliflozin" OR "sergliflozin" OR "sergliflozin etabonate” OR "remogliflozin etabonate" AND “diabetes mellitus, type 2” AND a validated filter (16) to identify randomized, controlled trials. All eligible trials were considered for review, regardless of language. Manual search of references lists of key articles was also done.

Eligibility criteria

The inclusion criteria were [1] RCTs, [2] SGLT2 inhibitors as one of the interventions compared with either placebo or active comparator, [3] treatment for at least 12 weeks, [4] description of variation in HbA_{1c}, [5] inclusion of adult patients (18 years old or above), and [6] diagnosis of type 2 diabetes according to American Diabetes Association (17).

Study selection and data collection

Two independent investigators (LCP and DVR) selected studies based on titles and abstracts. Studies satisfying inclusion criteria or those which abstracts lacked crucial information to decide upon its exclusion were retrieved for full-text evaluation. Both investigators (LCP and DVR) also analyzed the trials selected for detailed analysis, extracted data and disagreements were resolved by consensus. We extracted the following information: first author's name, year of trial publication, participant number and dropouts, age, gender, mean diabetes duration, trial duration, treatment in use previously to randomization, change in HbA_{1c} (mean [SD]), change in body weight (mean [SD]), change in systolic (SBP) and diastolic blood pressure (DBP) (mean [SD]), as well as the main adverse effects of interest: number of patients with hypoglycemic episodes, urinary tract infections, genital tract infections, and ketoacidosis.

Risk of bias in individual studies and meta-analysis quality

The studies quality was assessed according to Cochrane Collaboration's tool (18,19) for risk of bias, including the six domains: random sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting; and source of funding. The quality of each meta-analysis was evaluated by the GRADE

approach (20), considering factors that may decrease (limitations of design or implementation, indirectness of evidence, inexplicable heterogeneity, inconsistent results and presence of significant publication bias) or increase the quality of evidence (large magnitude of effect, presence of a dose-response gradient and plausible confounding that increased confidence in an estimate). As recommended, each meta-analysis was rated as high, moderate, low or very low.

Synthesis of results

Initially, we performed a direct meta-analysis comparing each individual SGLT2 inhibitor with placebo. Absolute changes in HbA_{1c}, body weight and both SBP and DBP in SGLT2 inhibitors and control groups were reported as differences between arithmetic means before and after interventions. The Cochran's $_2 x$ test (Q test) was used to evaluate heterogeneity between studies and a threshold p value 0.1 was considered statistically significant; the I^2 test was also conducted to evaluate the magnitude of the heterogeneity between studies. The adverse effects were assessed by direct meta-analysis of individual SGLT2 inhibitors compared to placebo: proportion of events of hypoglycemia (any reported event), urinary tract infections (symptoms and/or confirmed), and genital tract infection (symptoms). We calculated pooled estimates of the mean differences in HbA_{1c}, body weight, and BP between intervention groups by using a fixed-effects model as no heterogeneity was found in the analysis. Results of direct meta-analysis were described as weight mean difference (WMD), which represents the difference from baseline to the end of the study in SGLT-2 inhibitors versus placebo or active comparator arms (95% Confidence interval [95%CI]). Thereafter, Network Meta-analysis (NMA) models were constructed including the three SGLT2 inhibitors and placebo using Bayesian Markov

Chain Monte Carlo simulation. Results are shown as mean of the difference of HbA_{1c} and body weight from baseline to the end of the treatment and its credibility intervals (95%CrI).

In the case of NMA showing similar HbA_{1c} reductions among the three SGLT2 inhibitors medications, we planned to deal with them as a group and compare their effect on HbA_{1c}, body weight and both SBP and DBP with other classes of antidiabetic agents through a direct meta-analysis. We also performed a direct meta-analysis to evaluate the effect of SGLT2 inhibitors in combination with other antihyperglycemic agents as initial therapy.

We assessed the possibility of publication bias by a funnel plot of each trial's effect size against the standard error. Funnel plot asymmetry was evaluated by Begg's and Egger's tests, and a significant publication bias was considered if the *p* value was <0.1 The trim-and-fill computation was used to estimate if the publication bias would influence the interpretation of results (21,22).

The analyses were made using Stata version 12.0 (Stata Inc., College Station, Texas, USA). The NMA was performed with Winbugs 14 (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom; www.mrc-bsu.cam.ac.uk/bugs). Risk of bias was analyzed with RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark).

Results

Literature search

Our search retrieved 567 articles and we included 11 additional RCTs through manual search. After removal of duplicated papers and reading titles and abstracts, 69

articles remained for whole text evaluation. Subsequently, 39 RCTs were included for analysis (Figure 1). The reviewers had an excellent agreement rate (κ=0.874). From the selected articles, only two manuscripts analysed efficacy and safety of ipragliflozin. So we decided not to include this agent in the comparative analysis of each drug in the class. As well, the main analysis presented includes only the data of arms with maximum recommended doses because these are the most frequently doses employed and this class of medications seems not to have a consistent dose-effect relation. The results of other doses are presented in Supplemental material.

Study characteristics and risk of bias

The included trials were published from 2009 to 2015. Mean trial duration was 31 weeks (range 12 to 102 weeks). The studies included 25,505 patients, of which 14,089 were men (55.2%), with a mean age of 57 years (range 51.6 to 63.8), a mean duration of type 2 diabetes of 4.3 years, a baseline HbA_{1c} of 7.88% (63 mmol/mol), and the mean body weight was 74.8 kg. Individual articles description is presented in Table 1. We present details regarding the assessment of quality for individual studies and across studies in the additional material (supplemental material table 1). Random sequence generation, allocation concealment and blinding of outcome assessment were clear in most studies; blinding of participants and personnel, incomplete outcome data and selective reporting were considered as having a low chance of bias in most studies.

The funnel plot (supplemental figure 1) suggested no publication bias, but the Begg's and Egger's tests show a significant publication bias for HbA_{1c} outcome. We performed a trim-and-fill computation and the results did not change.

Data synthesis

1. Efficacy versus placebo: 15,552 patients were included in this analysis, 8,847 were men (56.9%). At baseline, mean HbA_{1c} was 8.04% (64 mmol/mol) and mean body weight was 79.8 kg.

1.1. HbA_{1c}. All SGLT2 inhibitors reduced significantly the HbA_{1c}. Numerically the HbA_{1c} mean reduction with canagliflozin 300 mg (-0.92%; 95%CI -1.10 to -0.73) was higher than dapagliflozin 10 mg (-0.52%; 95%CI -0.59 to -0.46) and empagliflozin 25 mg (-0.70%; 95%CI -0.87 to -0.54) (Figure 2). Considering that head-to-head studies comparing SGLT2 inhibitors among each other are not available, we compared the efficacy of different compounds at maximum doses by using a NMA method. For this analysis, we included data from placebo and SGLT2 inhibitors arms of all trials available. NMA showed that canagliflozin 300 mg was associated with greater reduction in HbA_{1c} than dapagliflozin 10 mg (-0.26%; 95% credibility interval [CrI] -0.42 to -0.09) and empagliflozin 25 mg (-0.22%; 95%CrI -0.42 to -0.01).

1.2. Body Weight. When compared to placebo, all three SGLT2 inhibitors were able to produce significant reductions in body weight, but canagliflozin 300 mg was associated with a numerically higher weight loss (-2.66 kg; 95%CI -3.02 to -2.29) than with dapagliflozin 10 mg (-1.50kg; 95%CI -1.66 to -1.34) and empagliflozin 25 mg (-1.51 kg; 95%CI -1.77 to -1.26). These results were confirmed by NMA method. According to this analysis, canagliflozin 300 mg caused a reduction of 0.84 kg (95%CrI -1.38 to -0.26) higher than dapagliflozin 10 mg and 1.06 kg (95%CrI -1.71 to -0.37) higher than empagliflozin.

1.3. Blood pressure. Both canagliflozin and dapagliflozin were able to reduce significantly SBP (canagliflozin 300 mg: -4.77 mmHg; 95%CI -6.17 to -3.37;

dapagliflozin 10 mg -2.66 mmHg; 95%CI -3.82 to -1.49) but only canagliflozin lowered significantly DBP when compared to placebo (-1.99 mmHg; 95% CI -3.12 to -0.86). It was not possible to perform a NMA for BP variation because some studies did not present these data.

2. **Efficacy versus active comparator.** For this analysis, we decided to pool the data of all members of SGLT2 inhibitor class because there was no difference in terms of HbA_{1c} between dapagliflozin and empagliflozin and the mean difference in HbA_{1c} favoring canagliflozin was only 0.2%, lower than the non-inferiority margin of 0.4% recommended by F.D.A. (23). This analysis included 10,775 patients, 5,419 were men (50.3%). Their mean baseline HbA_{1c} was 7.98% (64 mmol/mol) and mean body weight was 86.78 kg.

2.1. **Metformin**. When compared with metformin (3 studies, n = 1,207), SGLT-2 inhibitors showed no statistically difference in HbA_{1c} and DBP variation, but there was a statistical difference favoring lower body weight (-1.04 kg; 95%CI -1.64 to -0.43) and SBP (-5.86 mmHg; 95%CI -9.49 to -2.24) in SGLT2 inhibitors groups.

2.2. **Sulphonylureas**. A total of three studies (n = 3,796) compared SGLT2 inhibitors with sulphonylureas. There was no significant difference in HbA_{1c} variation between SGLT-2 inhibitors and sulphonylureas arms, but SGLT2 inhibitors were associated with a significantly greater change in body weight (-4.76 kg; 95%CI -4.98 to -4.53) and blood pressure (SBP: -5.44 mmHg; 95%CI -6.44 to -4.45 DBP: -2.59 mmHg; 95%CI -3.26 to -1.93).

2.3. **DPP-IV Inhibitors**. In pooled analysis of 7 studies (n = 5,772) comparing SGLT2 inhibitors to DPP-IV inhibitors, SGLT2 inhibitors were significantly superior to DPP-IV

inhibitors regarding HbA_{1c} reduction (-0.16%; 95% CI -0.22 to -0.10), body weight reduction (-2.45 kg; 95%CI -2.71 to -2.19) and decrease of SBP (-4.34 mmHg; 95% CI -5.22 to -3.46) and DBP (-1.77 mmHg; 95% CI -2.51 to -1.03).

3. **Efficacy of initial combination of SGLT2 inhibitors with metformin or SGLT-2 inhibitors with DPP-IV inhibitors**. We analyzed the variation of HbA_{1c} and body weight in drug-naïve patients with type 2 diabetes treated initially with the combination of SGLT2 inhibitors plus metformin or the combination of SGLT2 inhibitors plus DPP-IV inhibitors. A total of 4 studies were identified: three studies compared the combination of SGLT2 inhibitors plus metformin versus SGLT2 inhibitors (3,191 patients) and only one study compared the association of SGLT2 inhibitors plus DPP-IV inhibitors versus SGLT2 inhibitors (677 patients). So we pooled the data of the three studies analyzing the combination of SGLT2 inhibitors plus metformin. At baseline, mean HbA_{1c} was 8.87% (73 mmol/mol) and mean body weight was 85.59 kg. The HbA_{1c} reduction was numerically greater with the initial combination of SGLT2 inhibitor plus metformin (-0.51%; 95%CI -0.62 to -0.39) than with SGLT2 inhibitor plus DPP-IV inhibitor (-0.14%; 95%CI -0.33 to -0.06). Moreover, the variation of body weight was also more beneficial in patients treated initially with SGLT2 inhibitors plus metformin (-0.9 kg; 95%CI -1.42 to -0.39) than in patients treated with SGLT2 inhibitors plus DPP-IV inhibitors (0.1 kg; 95%CI -0.9 to 1.1).

4. Adverse effects. A direct meta-analysis was conducted to evaluate the adverse effects of the individual medications compared to placebo. The adverse events evaluated were number of patients with any hypoglycemic episodes, urinary tract infection, and

genital tract infection. Bone mineral density and rate of ketoacidosis episodes were also assessed.

There was no association with hypoglycemia for both dapagliflozin (0.88 95%CI 0.75 to 1.05) and for empagliflozin (2.11 95%CI 0.45 to 9.91), while canagliflozin increased the risk for hypoglicemia (1.56 95% 1.19 to 2.03). This observation was mainly due to the results of two studies where metformin and sulphonylurea (24) or insulin (25) were used as background therapy. Only dapagliflozin increased the risk for urinary tract infection when compared to placebo (1.34 95%CI 1.07 to 1.69), and the three drugs were associated with an increased risk of genital tract infection (dapagliflozin: 2.68 95%CI 1.99 to 3.60; canagliflozin: 5.17 95%CI 3.48 to 7.67; empagliflozin: 7.60 95%CI 3.20 to 18.02). It was not possible to perform meta-analysis regarding bone mineral density because only two studies evaluated this variable (26, 27) and no significant change in bone mineral density was observed. Only two cases of ketoacidosis were reported in patients using canagliflozin as add-on to either oral agents or insulin (24, 27).

Meta-analysis quality evaluation

The GRADE quality of evidence for glycemic control through HbA_{1c} was high. The identified publication bias does not appear to have skewed the results of the meta-analysis.

Discussion

The present study shows that SGLT2 inhibitors were associated with a clinical significant reduction in HbA_{1c} when compared to placebo. The decrease in HbA_{1c} was similar to metformin and sulphonylurea, but greater than DPP-IV inhibitors. We also observed that the combination of SGLT2 inhibitors and metformin is numerically superior to the

combination of SGLT2 inhibitors and DPP-IV inhibitors as initial therapy. SGLT2 inhibitors have a beneficial effect on body weight and BP as compared to metformin, sulphonylurea and DPP-IV inhibitors. However, there was an increased frequency of genital tract infections.

Other systematic reviews and meta-analyses have also evaluated this new class of anti-hyperglycemic agents. Our study adds original information about the efficacy and safety of individual SGLT inhibitor agents compared to each other, as well as the comparison of SGLT2 inhibitors with other classes of anti-hyperglycemic agents. Finally, our review analyzes the efficacy of the combination of SGLT2 inhibitors and metformin versus SGLT2 inhibitors and DPP-IV inhibitors as initial therapy.

The efficacy and safety of each SGLT2 inhibitor currently approved for clinical use were compared. The analysis of the data of arms with maximum recommended doses may provide clinical relevant information for every-day practice. The comparative analysis of individual SGLT2 suggested that canagliflozin was numerically superior to empagliflozin and dapagliflozin regarding HbA_{1c}, body weight and BP variation. The greater reduction on HbA_{1c} and body weight with cangliflozin as compared to dapagliflozin and empagliflozin was observed in direct meta-analysis as well in NMA. This observation may be due to the fact that selectivity of SGLT inhibition for SGLT2 over SGLT1 varies among the SGLT2 inhibitors. Canagliflozin has lower selectivity (>250 fold) than dapagliflozin (>1200 fold) and empagliflozin (>3500 fold), leading also to SGLT1 inhibition in the distal part of convoluted proximal tubule (S3 segment) and intestine (28) and this particular characteristic may increase the amount of glucosuria or decrease the intestinal absortion of glucose. However, the difference in reduction of HbA_{1c} among the

agents was only -0.22% and -0.26%, which is below the non-inferiority margin recommended by FDA (23), and may have minor clinical relevancy.

Given this small difference, we grouped the data to analyze the efficacy of SGLT2 inhibitors versus other antihyperglycemic agents. Efficacy was comparable to other oral agents in terms of HbA1c, but a greater reduction on body weight and BP was demonstrated. The observed benefits of SGLT2 inhibitors in body weight are probably related to the 70-80 g of glucosuria per day resulting in a loss of around 300 kcal/day (11,29). The reduction of BP might be due to glucosuria as well, that is accompanied by osmotic diuresis and natriuresis (30). However, we have to take into account that these data refers to type 2 diabetic patients with normal renal function, because SGLT2 inhibitor are not effective in patients with decreased glomerular filtration rate (31).

Interestingly, the initial combination of SGLT2 inhibitors and metformin resulted in higher HbA_{1c} reduction than SGLT2 inhibitors and DPP-IV inhibitors. Theoretically, the combination of SGLT2 inhibitors plus DPP-IV inhibitors would induce a marked reduction in HbA_{1c} (32). An increase in endogenous glucose production and glucagon levels has been associated to the glucosuria produced by SGLT2 inhibitors, which may attenuate the reduction in glycemic control (10). As DPP-IV inhibitors reduce glucagon secretion and endogenous glucose production (33), the addition of DPP-IV inhibitors to SGLT2 inhibitors would have more than an additive effect to reduce HbA_{1c}. However, the observed effect was less than expected. The explanation for this observation is still unknown, but the potential reduction in glucagon levels by DPP-IV inhibitors in patients using SGLT2 inhibitors may influence the effect on HbA_{1c}. Another adaptive response observed in patients treated with SGLT2 inhibitors is an increase in caloric intake, which

is equivalent to the calories lost as glucosuria, thus preventing progressive weight loss (11). It is well known that metformin reduces food consumption (34, 35) and so could increase the effect of SGLT2 inhibitors in weight and HbA_{1c} reduction (11).

Regarding adverse events, only a 3 to 7 fold increase in genital infections was reported with SGLT2 inhibitors in patients with type 2 diabetes. This is a well-recognized adverse event (36) and seems not be associated with severe complications. It usually responds to conventional treatment. Hypoglycemia was only reported in patients using sulphonylureas and insulin and may be attributed to the improved metabolic control with SGLT2 associated to the hypoglycemic action of sulphonylureas and insulin. It was not possible to perform a proper analysis of bone mineral variation because there were only two studies with duration of 24 weeks and 102 weeks. It seems that SGLT2 inhibitors did not have a significant deleterious effect on bone mineral density but long duration studies are needed. A major concern that is being raised lately is the risk of ketoacidosis in patients using SGLT2 inhibitors. We searched specifically for reports of ketosis, acidosis, ketoacidosis in all included trials and we identified only 2 reports of ketoacidosis in the 13,787 patients randomized for SGLT2 inhibitors. Recently (37,38), two studies reported the association of SGLT2 inhibitors and ketoacidosis. In both of them, most of patients had type 1 diabetes (7 out of 9) or had presumed type 2 diabetes on insulin or had ketoacidosis precipitating factors. The reasons for this association of SGLT2 inhibitors with increased ketogenesis are still unknown.

The main strains of this meta-analysis are related to the quality of the individual studies, the large sample size evaluated, and the low statistical heterogeneity. A potential

limitation is the risk for publication bias detected by Begg´s and Egger´s test, but the results did not change after trim-and-fill analysis.

In conclusion, the current study shows that SGLT2 inhibitors are associated with clinical significant HbA_{1c} reduction, similar to metformin and sulphonylureas and superior to DPP-IV inhibitors. Moreover, there was a beneficial effect on body weight and BP. The initial combination of SGLT2 inhibitors with metformin seems to be more potent than SGLT2 inhibitors with DPP-IV inhibitors. They have an acceptable safety profile, with an increased proportion of genital tract infections, but the recent concerns regarding ketoacidosis should be better clarified. Long duration cardiovascular studies will provide more conclusive evidence about its safety and potential benefits on cardiovascular and mortality outcomes.

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Table 1. Baseline characteristics of included studies

Author Year	n	Follow up (weeks)	Men (%)	Mean age (years)	Diabetes duration (years)	Mean HbA1c (%)	Mean weight (kg)	Mean SBP (mmHg)	Mean DBP (mmHg)	Background treatment
Bailey 2013	546	24	53.48	59.9	NR	8.05	85.91	NR	NR	Metformin
Bailey 2012	282	24	50.00	53.0	1.38	7.9	86.97	NR	NR	Naive
Bolinder 2013	180	24	27.22	60.7	5.8	7.17	91.50	NR	NR	Metformin
Ferrannini 2010	559	24	49.37	51.6	0.54	8.55	89.68	NR	NR	Diet + Exercise
Kaku 2013	279	12	77.06	57.3	NR	8.07	68.63	NR	NR	Naïve
Wilding 2012	808	48	47.28	59.3	13.6	8.53	93.82	NR	NR	Insulin and/or OAD
Wilding 2009	71	12	59.15	56.7	12.3	8.43	102.10	NR	NR	Insulin
Jabbour 2012	447	48	54.81	54.9	NR	7.93	90.12	139.85	NR	DPP-IV i and/or Metformin
List 2009	389	12	49.36	54.1	NR	7.80	88.85	126.4	77.1	Naïve
Cefalu 2012	914	24	68.27	62.9	6.8	8.13	93.11	NR	NR	OAD
Rosenstock 2012	420	48	49.52	53.4	NR	8.37	86.30	NR	NR	Pioglitazone
Strojek 2011	592	24	48.14	59.8	NR	8.11	81.09	NR	NR	Sulfonylurea
Matthaei 2015	216	24	49.07	61.0	NR	8.16	89.35	135.45	81.0	Metformin + Sulfonylurea

Leiter 2014	962	52	66.94	63.8	13.25	8.06	93.88	134.7	NR	Insulin or OAD
Ji 2014	393	24	65.39	51.4	1.4	8.25	70.66	NR	NR	Naïve
Wilding 2013	469	52	50.96	56.8	9.6	8.10	92.80	130.4	78.7	Metformin + Sulphonylurea
Yale 2013	269	52	60.59	68.5	16.3	8.00	NR	NR	NR	Insulin
Stenlof 2013	584	26	44.18	55.4	4.3	8.00	86.80	NR	NR	Diet + Exercise
Bode 2013	451	102	52.33	52.9	11.7	7.70	89.50	NR	NR	Naïve or OAD
Rosenstock 2012	451	12	52.33	52.9	6.0	7.75	87.10	127.0	78.0	Metformin
Inagaki 2013	383	12	68.15	57.4	NR	8.09	69.38	NR	NR	Naïve or OAD
Rosenstock 2013	495	12	50.51	58.3	NR	7.97	89.04	133.7	80.0	Metformin
Tikkanen 2015	823	12	60.15	60.2	NR	7.90	NR	142.1	83.9	Naïve
Ferrannini 2013	406	12	51.97	58.0	NR	7.90	81.10	131.1	80.0	Naïve (or 4 week wash-out)
Schernthaner 2013	755	52	55.89	56.7	9.6	8.10	88.30	NR	NR	Metformin + Sulphonylurea
Lavelle - Gonzalez 2013	1284	52	47.12	55.4	6.9	7.90	87.20	NR	NR	Metformin
Neal 2015	1967	52	69.50	62.6	16.0	8.30	NR	NR	NR	Insulin
Roden 2013	986	24	62.37	55.0	NR	NR	NR	NR	NR	Naive

DeFronzo 2015	677	24	53.03	55.4	NR	8.02	87.4	128.3	78.5	Diet + exercise
Ridderstrale 2014	1545	52	55.21	55.9	NR	NR	NR	NR	NR	Diet + Exercise
Nauck 2011	801	52	55.06	58.4	NR	7.72	NR	NR	NR	Metformin
Cefalu 2013	1450	52	52.14	56.2	6.8	7.80	86.60	NR	NR	Metformin
Fonseca 2013	412	12	51.21	53.5	4.5	7.93	85.43	NR	NR	Naive
Wilding 2013	343	12	51.02	57.4	5.9	7.76	89.76	NR	NR	Metformin
Hadjadj 2015	1364	24	54.47	52.5	NR	8.7	83.16	NR	NR	Naïve
Rosenstock 2015	1186	26	47.97	54.9	3.26	8.82	NR	NR	NR	Naïve
Henry 2012	628	24	48.11	51.6	2.06	9.1	88.03	NR	NR	Naïve
Rosenstock 2015	534	24	50.18	54.0	7.60	8.94	NR	NR	NR	Metformin

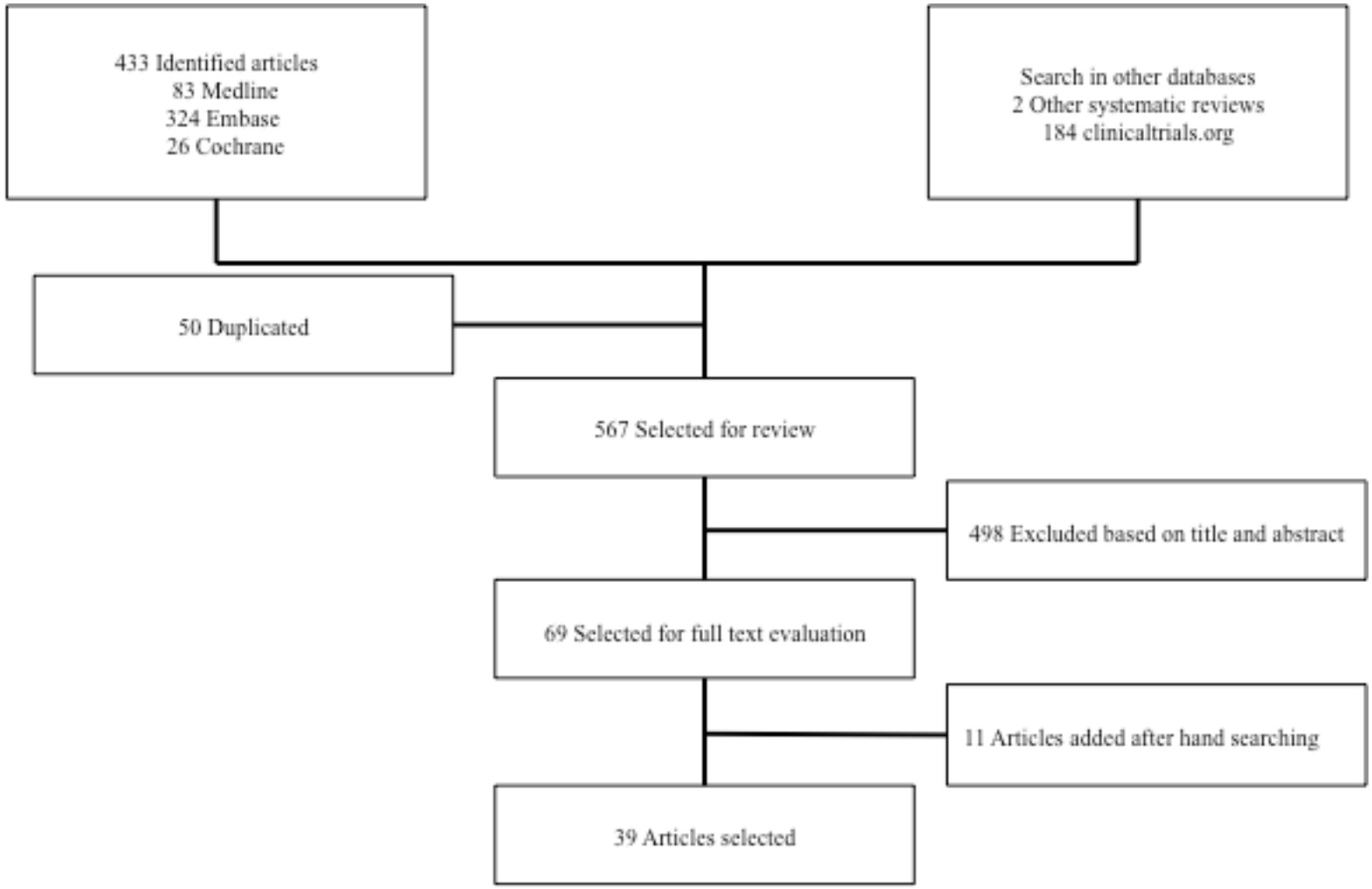


Figure 1. Results of literature search

Table 2. Mean change in $HbA_{1c,}$ body weight, systolic and diastolic blood pressure according to dose and each SGLT2 inhibitor

	HbA_{1c} (%)	Body Weight (kg)	SBP (mmHg)	DBP (mmHg)
Canagliflozin				
50 mg	-0.70 (-0.85 to -0.55)	-0.85 (-2.22 to -0.5)	-4.60 (-7.93 to -1.27)	---
100 mg	-0.75 (-0.85 to -0.58)	-1.81 (-2.22 to -1.41)	-3.47 (-4.86 to -2.09)	-1.48 (-2.32 to -0.63)
200 mg	-0.85 (-1.01 to -0.69)	---	---	---
300 mg	-0.92 (-1.00 to -0.83)	-2.66 (-3.02 to -2.29)	-4.77 (-6.17 to -3.37)	-1.99 (-2.83 to -1.14)
300 mg BID	-0.82 (-0.87 to -0.77)	---	---	---
Dapagliflozin				
1 mg	-0.59 (-0.81 to -0.35)	-1.20 (-1.71 to -0.59)	---	---
2.5 mg	-0.44 (-0.55 to -0.33)	-1.11 (-1.42 to -0.61)	2.20 (-2.23 to 6.63)	0.0 (-2.58 to 2.58)
5 mg	-0.51 (-0.52 to -0.40)	-1.60 (-1.90 to -1.30)	-1.74 (-4.28 to 0.79)	-0.83 (-2.49 to 0.83)
10 mg	-0.51 (-0.57 to -0.45)	-1.80 (-2.08 to -1.53)	-2.66 (-3.82 to -1.49)	-1.76 (-3.49 to -0.03)
20 mg	-0.57 (-0.87 to -0.24)	---	---	---
50 mg	-0.72 (-1.15 to -0.29)	---	---	---
Empagliflozin				
1 mg	-0.24 (-0.46 to -0.02)	-0.39 (-1.25 to -0.47)	---	0.95 (-3.72 to 5.62)
5 mg	-0.50 (-0.75 to -0.25)	-1.08 (-1.54 to -0.53)	---	0.26 (-4.49 to 5.01)
10 mg	-0.57 (-0.62 to -0.52)	-1.56 (-1.82 to -1.30)	-4.00 (-7.71 to -0.29)	-1.71 (-3.69 to 0.27)
25 mg	-0.63 (-0.68 to -0.58)	-1.81 (-2.07 to -1.55)	-2.30 (-5.07 to 0.47)	-2.10 (-4.09 to -0.12)
50 mg	---	-1.59 (-2.55 to -0.83)	---	---

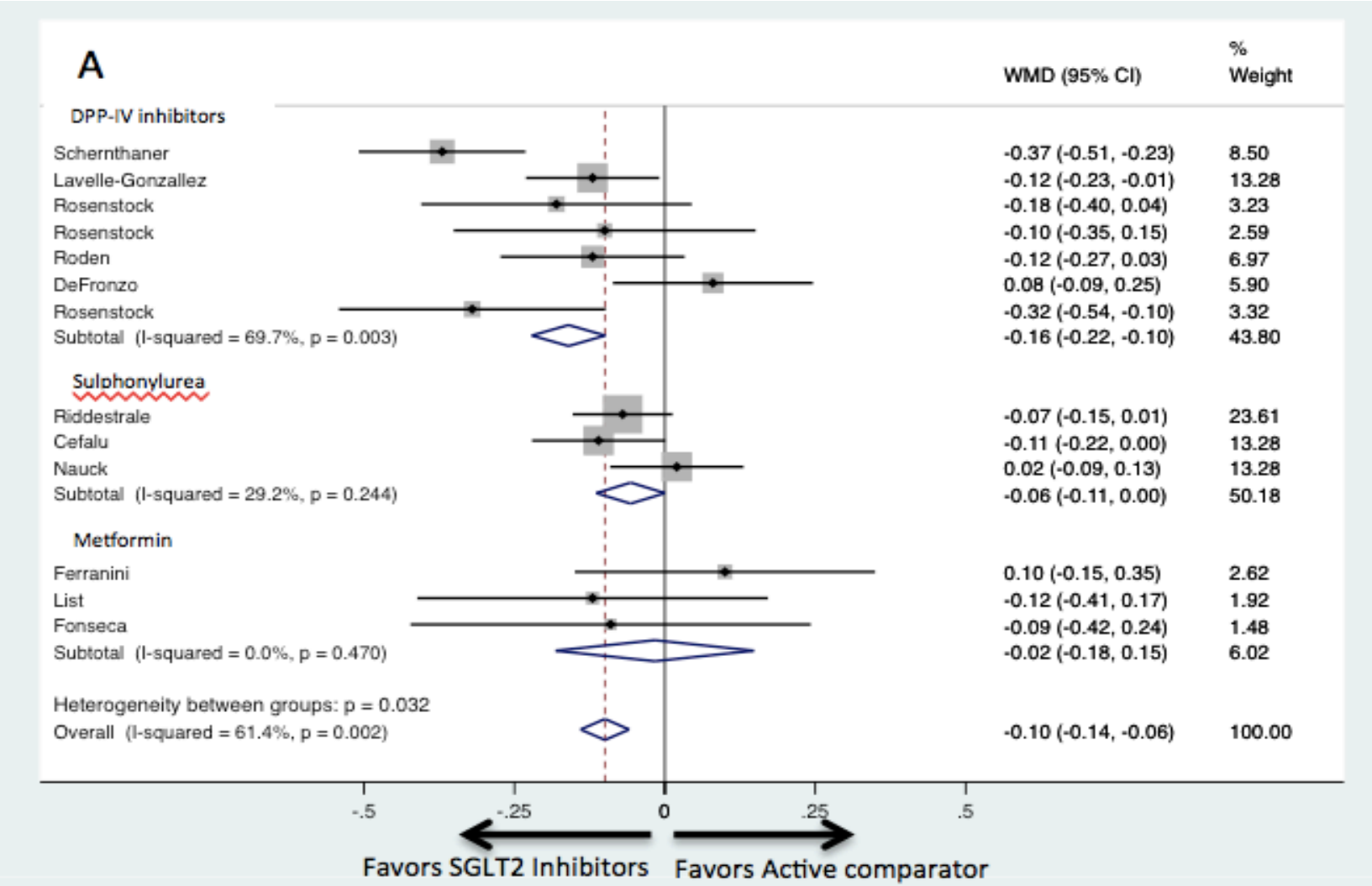


Figure 3 A. Forest plot for SGLT2 inhibitors versus active comparator: mean change in HbA_{1c}

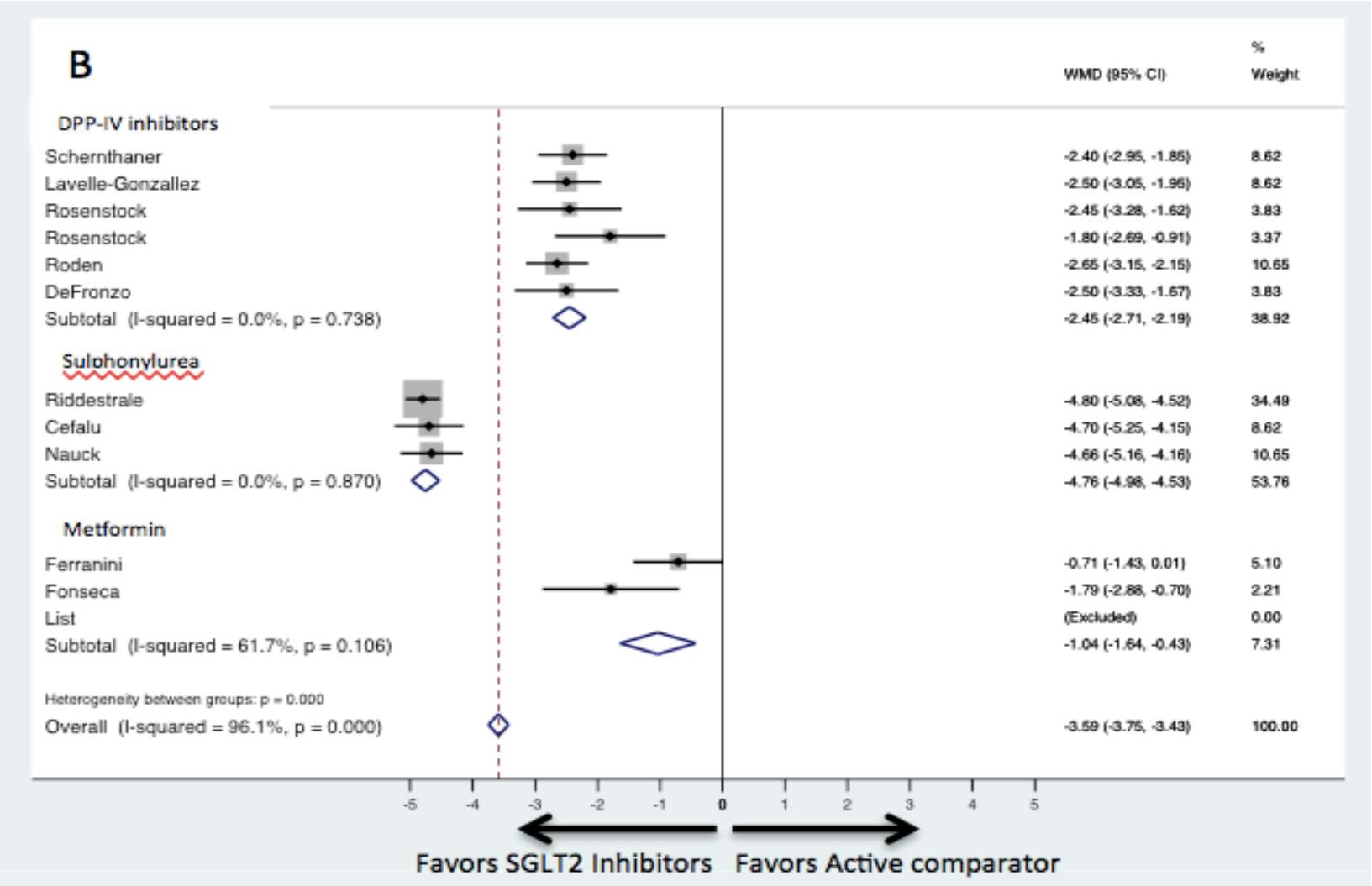


Figure 3 B. Forest plot for SGLT2 inhibitors versus active comparator: mean change in body weight

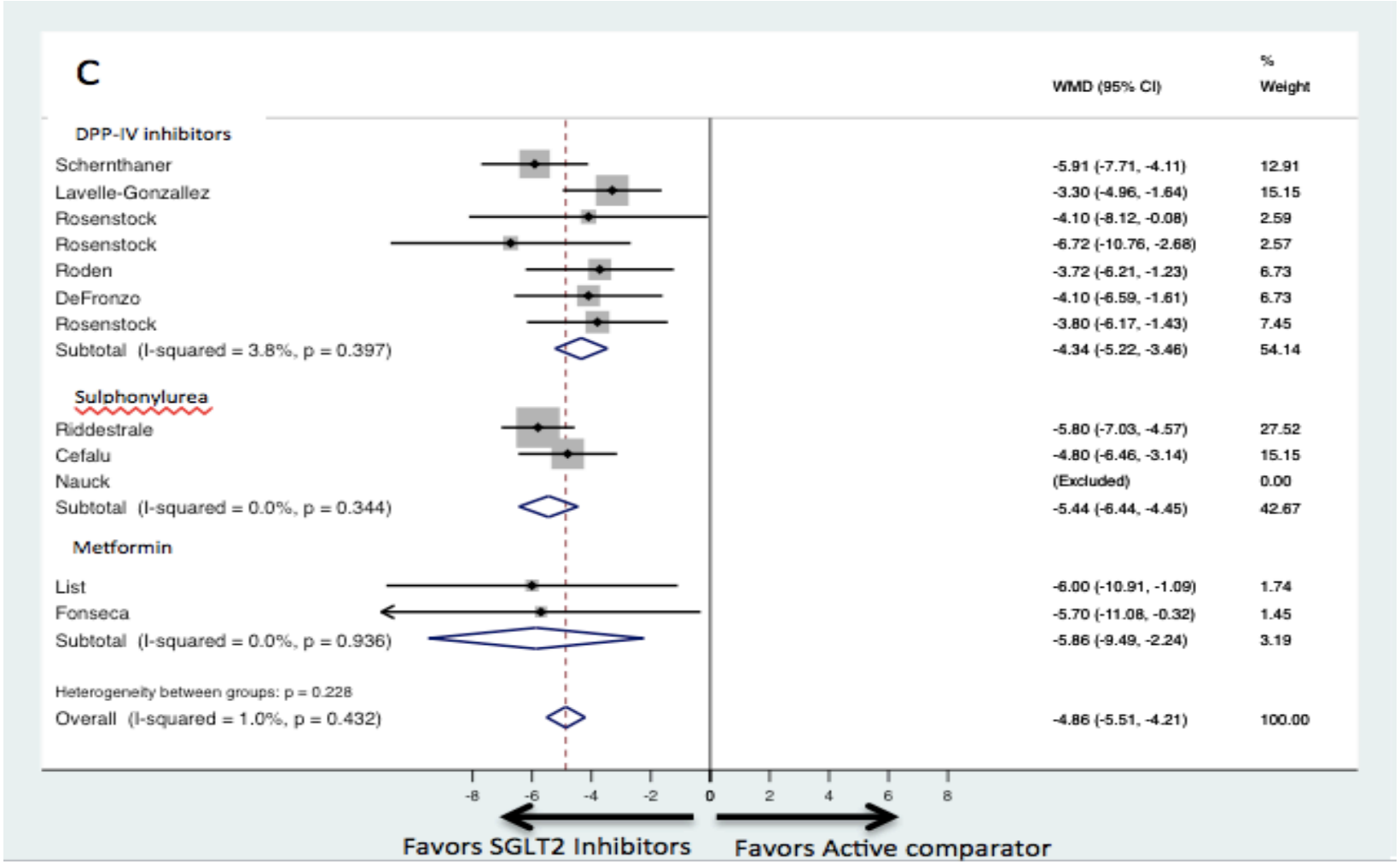


Figure 3 C. Forest plot for SGLT2 inhibitors versus active comparator: mean change in SBP

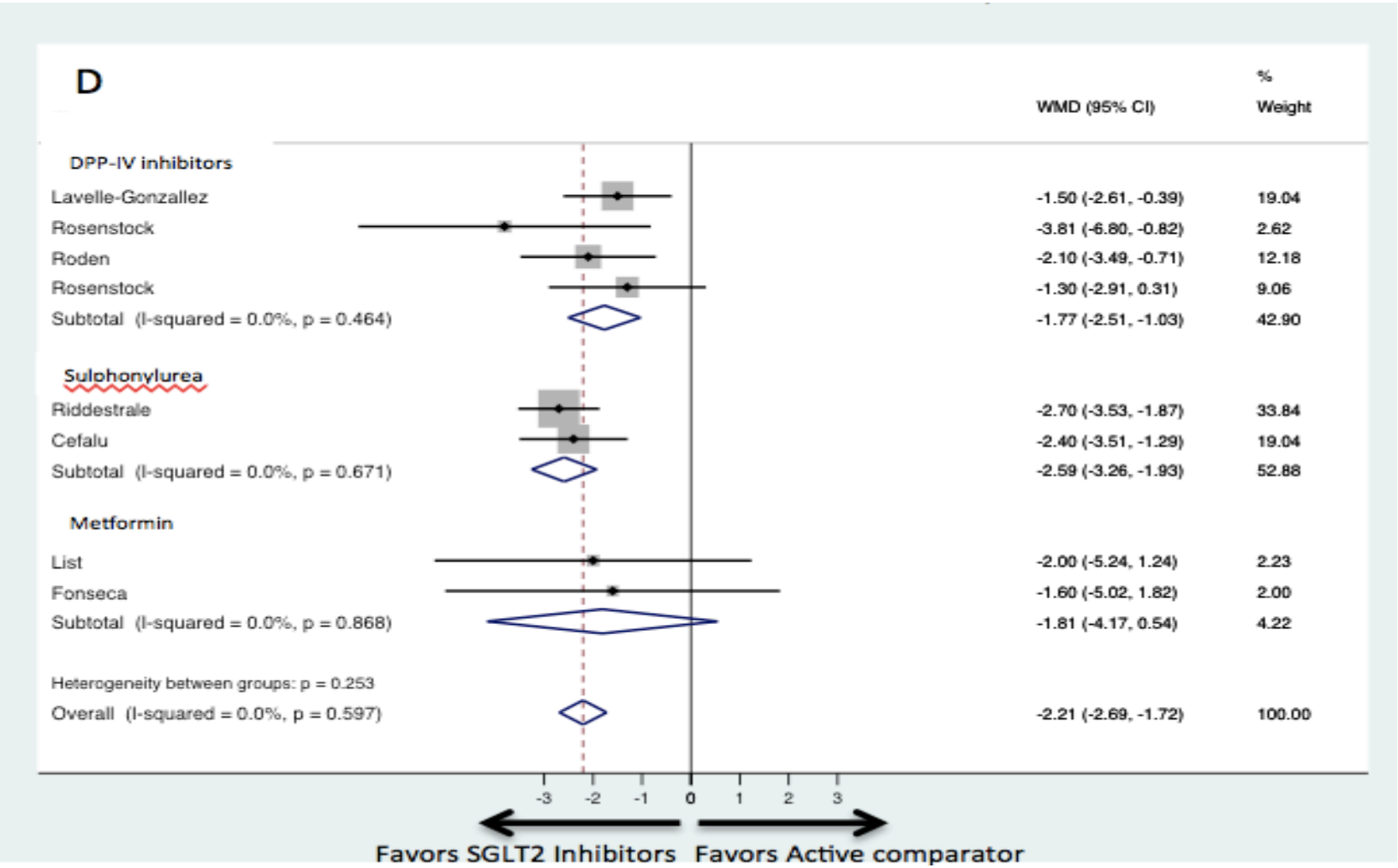


Figure 3 D. Forest plot for SGLT2 inhibitors versus active comparator: mean change in DBP

Supplemental Material

Supplemental Table 1. Outcomes reported in randomized controlled trials according to group of randomization

Author	Arms - patients	Delta HbA1c - % (SE)	Delta Weight - kg (SE)	Delta SBP - mmHg (SE)	Delta DBP - mmHg (SE)
Bailey	Placebo	-0.30 (0.07)	-0.89 (0.24)	1.5 (1.6)	-1.0 (0.93)
	Dapa 2.5 mg	-0.67 (0.07)	-2.21 (0.24)	0.7 (1.8)	-0.1 (0.91)
	Dapa 5 mg	-0.70 (0.07)	-3.04 (0.23)	-1.1 (1.4)	-1.5 (0.86)
	Dapa 10 mg	-0.84 (0.07)	-2.86 (0.24)	-0.3 (1.5)	-1.2 (1.04)
Bailey	Placebo	0.02	-0.96	NR	NR
	Dapa 1 mg	-0.68	-2.69	NR	NR
	Dapa 2.5 mg	-0.72	-2.64	NR	NR
	Dapa 5 mg	-0.82	-2.69	NR	NR
Bolinder	Placebo	-0.10	-0.88 (0.39)	0.1	0.3
	Dapa 10 mg	-0.39	-2.96 (0.39)	-2.7	-0.7
Ferranini	Placebo	-0.23 (0.10)	-2.2 (0.4)	NR	NR
	Dapa 2.5 mg A.M.	-0.58 (0.10)	-3.3 (0.4)		
	Dapa 5 mg A.M.	-0.77 (0.10)	-2.8 (0.5)		
	Dapa 10 mg A.M.	-0.89 (0.10)	-3.2 (0.5)		
	Dapa 2.5 mg P.M.	-0.83 (0.10)	-3.8 (0.5)		
	Dapa 5 mg P.M.	-0.79 (0.10)	-3.6 (0.5)		
	Dapa 10 mg P.M.	-0.79 (0.10)	-3.1 (0.4)		
	Dapa 5 mg (High A1c patients)	-2.88 (1.41)	-2.1 (2.4)		
	Dapa 10 mg (High A1c patients)	-2.66 (1.26)	-1.9 (3.5)		
Kaku	Placebo	0.37 (0.07)	-0.05 (0.19)	NR	NR
	Dapa 1 mg	-0.12 (0.07)	-1.25 (0.18)		
	Dapa 2.5 mg	-0.11 (0.07)	-1.24 (0.18)		
	Dapa 5 mg	-0.37 (0.07)	-2.06 (0.18)		
	Dapa 10 mg	-0.44 (0.07)	-1.91 (0.19)		
Wilding	Placebo	-0.47 (0.07)	0.82	-1.49	-1.31
	Dapa 2.5 mg	-0.79 (0.07)	-0.96	-5.30	-2.96
	Dapa 5 mg	-0.96 (0.07)	-1.00	-4.33	-2.64
	Dapa 10 mg	-1.01 (0.07)	-1.61	-4.09	-2.85

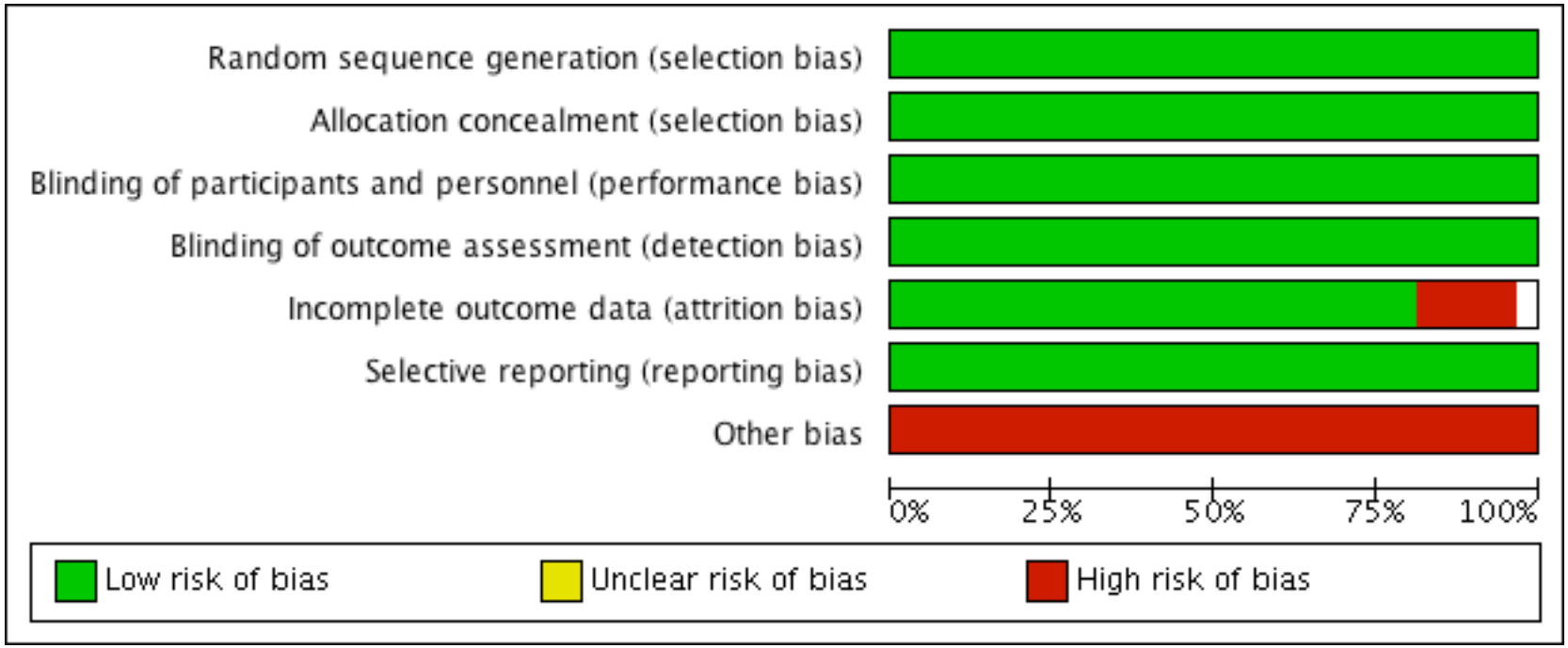
Wilding	Placebo	0.09	-1.9	NR	NR
	Dapa 10 mg	-0.61	-4.5		
	Dapa 20 mg	-0.69	-4.3		
Jabbour	Placebo	0.04 (0.07)	-0.26 (0.24)	NR	NR
	Dapa 10 mg	-0.45 (0.07)	-2.14 (0.24)		
List	Placebo	-0.18 (0.20)	-1.2	2.4 (11.1)	0.3 (5.7)
	Dapa 2.5 mg	-0.71 (0.09)	-2.7	-3.1 (10.7)	0.8 (6.4)
	Dapa 5 mg	-0.72 (0.09)	-2.5	-2.9 (12.7)	-0.3 (7.0)
	Dapa 10 mg	-0.85 (0.11)	-2.7	-6.4 (11.4)	-2.6 (7.7)
	Dapa 20 mg	-0.55 (0.09)	-3.4	-4.3 (12.3)	-0.5 (7.1)
	Dapa 50 mg	-0.90 (0.10)	-3.4	-2.6 (13.1)	0.1 (8.0)
	Metformin XR 750/1500 mg	-0.73 (0.10)	-1.7	-0.4 (12.4)	-0.6 (8.0)
Cefalu	Placebo	0.08 (0.04)		-1.03 (0.82)	NR
	Dapa 10 mg	-0.38 (0.04)		-2.99 (0.82)	NR
Rosenstock	Placebo	-0.54 (0.08)	2.99 (0.41)	2.0 (1.2)	0.4 (0.9)
	Dapa 5 mg	-0.95 (0.08)	1.35 (0.38)	-1.0 (1.1)	-0.7 (0.7)
	Dapa 10 mg	-1.21 (0.07)	0.69 (0.36)	-2.2 (1.2)	-2.4 (0.7)
Strojek	Placebo	-0.13 (0.08)	-0.72 (0.32)	NR	NR
	Dapa 2.5 mg	-0.58 (0.08)	-1.18 (0.32)		
	Dapa 5 mg	-0.63 (0.08)	-1.56 (0.32)		
	Dapa 10 mg	-0.82 (0.08)	-2.26 (0.32)		
Matthaei	Placebo	-0.17 (0.10)	-0.6 (0.36)	-0.27 (1.66)	NR
	Dapa 10 mg	-0.86 (0.10)	-2.7 (0.36)	-4.04 (1.66)	
Leiter	Placebo	0.1 (0.04)	-0.6	0.3 (14)	NR
	Dapa 10 mg	-0.3 (0.04)	-2.5	-2.7 (14.5)	
Ji	Placebo	-0.29 (-0.43, -0.16)*	-0.27 (-0.72, 0.18)*	NR	NR
	Dapa 5 mg	-1.04 (-1.18, -0.90)*	-1.64 (-2.09, -1.18)*		
	Dapa 10 mg	-1.11 (-1.24, -0.98)*	-2.25 (-2.70, -1.80)*		
Wilding	Placebo	-0.13 (0.07)	-0.7 (0.3)	-2.7 (1.0)	-1.7 (0.6)
	Cana 100 mg	-0.85 (0.07)	-2.1 (0.3)	-4.9 (1.0)	-2.9 (0.6)
	Cana 300 mg	-1.06 (0.07)	-2.6 (0.3)	-4.3 (1.0)	-2.3 (0.6)
Yale	Placebo	-0.03	0.2	-0.3 (1.5)	-1.4 (0.9)
	Cana 100 mg	-0.33	-1.2	-6.1 (1.5)	-2.6 (0.9)
	Cana 300 mg	-0.44	-1.4	-6.4 (1.5)	-3.5 (0.9)

Stenlof	Placebo	0.14 (0.06)	-0.5 (0.2)	0.4 (0.8)	-0.1 (0.5)
	Cana 100 mg	-0.77 (0.06)	-2.5 (0.2)	-3.3 (0.8)	-1.7 (0.5)
	Cana 300 mg	-1.03 (0.06)	-3.4 (0.2)	-5.0 (0.8)	-2.1 (0.5)
Bode	Placebo	-0.03 (0.06)	-0.1(0.3)	1.1 (1.0)	0.1 (0.6)
	Cana 100 mg	-0.60 (0.06)	-2.2 (0.3)	-3.5 (1.0)	-1.6 (0.6)
	Cana 300 mg	-0.73 (0.06)	-2.8 (0.3)	-6.8 (1.1)	-3.2 (0.6)
Rosenstock	Placebo	-0.22 (0.70)	-1.1 (2.09)	NR	NR
	Cana 50 mg	-0.79 (0.74)	-2.3 (2.33)		
	Cana 100 mg	-0.76 (0.99)	-2.6 (2.14)		
	Cana 200 mg	-0.70 (0.72)	-2.7 (2.84)		
	Cana 300 mg	-0.92 (0.69)	-3.4 (2.39)		
	Cana 300 mg BID	-0.95 (0.70)	-3.4 (2.34)		
	Sita 100 mg	-0.74 (0.61)	-0.6 (2.69)		
Inagaki	Placebo	0.11 (0.06)	-0.78	-1.2 (1.2)	-0.9 (0.9)
	Cana 50 mg	-0.62 (0.06)	-1.98	-5.8 (1.2)	-2.2 (0.8)
	Cana 100 mg	-0.80 (0.06)	-2.51	-7.1 (1.2)	-3.9 (0.9)
	Cana 200 mg	-0.79 (0.06)	-2.39	-9.3 (1.2)	-5.1 (0.8)
	Cana 300 mg	-0.88 (0.06)	-3.19	-8.7 (1.2)	-4.2 (0.8)
Rosenstock	Placebo	0.15	-1.2	-2.23 (14.84)†	-1.01 (8.27)†
	Empa 1 mg	-0.09	-1.6	-2.17 (12.11)†	-0.06 (7.47)†
	Empa 5 mg	-0.23	-2.3	-3.03 (14.58)†	-0.75 (8.41)†
	Empa 10 mg	-0.56	-2.7	-4.39 (13.09)†	-1.70 (7.50)†
	Empa 25 mg	-0.55	-2.6	-8.51 (12.82)†	-4.16 (8.76)†
	Empa 50 mg	-0.49	-2.9	-3.16 (15.26)†	-1.99 (7.57)†
	Sita 100 mg	-0.45	-0.8	-1.79 (11.65)†	-0.35 (9.35)†
Tikkanen	Placebo	0.03 (0.05)	-0.18 (1.55)	-0.67 (11.92)	-1.13 (6.58)
	Empa 10 mg	-0.62 (0.05)	-1.49 (2.38)	-4.60 (12.54)	3.06 (7.10)
	Empa 25 mg	-0.65 (0.05)	-1.98 (2.38)	-5.47 (12.43)	-3.02 (7.05)
Ferranini	Placebo	0.1 (-0.09, 0.27)*	-0.75 (-1.26, -0.23)*	NR	NR
	Empa 5 mg	-0.4 (-0.61, -0.25)*	-1.81 (-2.32, -1.29)*		
	Empa 10 mg	-0.5 (-0.66, -0.30)*	-2.33 (-2.84, -1.82)*		
	Empa 25 mg	-0.6 (-0.81,-0.45)*	-2.03 (-2.54, -1.52)*		
	Metformin	-0.7 (-0.92, -0.57)*	-1.32 (-1.84, -0.81)*		
Schernthaner	Cana 300 mg	-1.03 (0.05)	-2.5 (0.2)	-5.06 (0.65)	NR
	Sita 100 mg	-0.66 (0.05)	0.3 (0.2)	0.85 (0.66)	

Lavelle - Gonzalez	Placebo	-0.17 (0.06)	-1.2 (0.3)	1.52 (0.83)	NR
	Cana 100 mg	-0.79 (0.04)	-3.7 (0.2)	-3.84 (0.60)	
	Cana 300 mg	-0.94 (0.04)	-4.2 (0.2)	-5.06 (0.60)	
	Sita 100 mg	-0.82 (0.04)	-1.2 (0.2)	-1.83 (0.61)	
Neal	Placebo	0.0	0.0	NR	NR
	Cana 100 mg	-0.58 (-0.68;-0.48)*	-2.8 (-3.3;-2.4)*	-3.1 (-4.6;-1.7)*	-1.2 (-2.0;-0.3)*
	Cana 300 mg	-0.73 (0.83;-0.63)*	-3.5 (-3.9;-3.0)*	-6.2 (-7.7;-4.8)*	-2.4 (-3.2;-1.5)*
Roden	Placebo	0.06 (0.05)	-0.33 (0.15)	0.0 (0.8)	-0.4 (0.5)
	Empa 10 mg	-0.66 (0.05)	-2.26 (0.19)	-3.5 (1.0)	-1.1 (0.6)
	Empa 25 mg	-0.77 (0.05)	-2.48 (0.18)	-3.2 (0.9)	-1.7 (0.5)
	Sita 100 mg	-0.65 (0.05)	0.17 (0.18)	0.2 (0.9)	0.4 (0.5)
	Empa 25 mg OL	-3.10 (0.22)	-1.93 (0.44)	-3.8 (1.2)	-1.5 (0.8)
DeFronzo	Empa 25 mg+Lina 5 mg	-1.08 (0.07)	-2.0 (0.36)	NR	NR
	Empa 10 mg+Lina 5mg	-1.24 (0.07)	-2.7 (0.36)		
	Empa 25 mg	-0.95 (0.07)	-2.1 (0.36)		
	Empa 10 mg	-0.83 (0.07)	-2.3 (0.36)		
	Lina 5 mg	-0.67 (0.07)	-0.8 (0.36)		
Ridderstrale	Empa 25 mg	-0.66 (0.03)	-3.11 (0.13)	-3.1 (0.5)	-1.8 (0.3)
	Glimepiride	-0.55 (0.03)	1.33 (0.13)	2.5 (0.5)	0.9 (0.3)
Nauck	Dapa 10 mg	-0.52 (0.06)	-3.22 (0.25)	NR	NR
	Glipizide	'0.52 (0.06)	1.44 (0.25)		
Cefalu	Cana 100 mg	-0.82 (0.04)	-3.7 (0.2)	-3.3 (0.6)	-1.8 (0.4)
	Cana 300 mg	-0.93 (0.04)	-4.0 (0.2)	-4.6 (0.6)	-2.5 (0.4)
	Glimepiride	-0.81 (0.04)	0.4 (0.2)	0.2 (0.6)	-0.1 (0.4)
Fonseca	Placebo	NR	NR	NR	NR
	Ipra 12.5 mg	-0.49	-0.50	0.5	0.4
	Ipra 50 mg	-0.65	-0.66	-2.6	1.2
	Ipra 150 mg	-0.73	-1.08	-3.0	-1.2
	Ipra 300 mg	-0.81	-1.67	-2.6	-0.1
	Metformin	-0.72	0.12	3.1	1.5
Wilding	Placebo	-0.31	-0.48	-0.5	-0.5
	Ipra 12.5 mg	-0.53	-0.92	-1.9	-2.9
	Ipra 50 mg	-0.65	-2.10	-3.8	-1.9
	Ipra 150 mg	-0.72	-1.99	-2.7	-1.1
	Ipra 300 mg	-0.79	-2.21	-4.8	-4.2

Hadjadj	Empa 12.5 mg bid + Metformin 1000 bid	-2.08	-3.8	NR	NR
	Empa 12.5 mg bid + Metformin 500 mg bid	-1.93	-3.0		
	Empa 5 mg bid + Metformin 1000 mg bid	-2.07	-3.5		
	Empa 5 mg bid + Metformin 500 mg bid	-1.98	-2.8		
	Empa 25 mg	-1.36	-2.4		
	Empa 10 mg	-1.35	-2.4		
	Metformin 1000 mg bid	-1.75	-1.3		
	Metformin 500 mg bid	-1.18	-0.5		
Rosenstock	Metformin XR 2000 mg	-1.30	-1.9	NR	NR
	Cana 100 mg	-1.37	-2.8		
	Cana 300 mg	-1.42	-3.7		
	Cana 100 mg + Metformin XR 2000 mg	-1.77	-3.2		
	Cana 300 mg + Metformin XR 2000 mg	-1.78	-3.9		
Henry	Dapa 10 mg + Metformin	-1.98	-3.33	NR	NR
	Dapa 10 mg + Placebo	-1.45	-2.73		
	Metformin + Placebo	-1.44	-1.76		
Rosenstock	Dapa 10 mg + Saxa 5 mg	-1.47	-2.1	NR	NR
	Saxa 5 mg + Placebo	-0.88	0.0		
	Dapa 10 mg + Placebo	-1.20	-2.4		

Data are shown as mean change from from baseline (Standard error); * 95% Confidence interval † Standard Deviation; NR = Not reported; Dapa = Dapagliflozin; Cana = Canagliflozin; Empa = Empagliflozin; Sita = Sitagliptin; MTF = Metformin;



Supplemental Figure 1. Risk of bias

Supplemental Table 2. Network metanalysis for SGLT2 inhibitors and placebo for HbA1c and body weight

	HbA_{1c} (%)	**Peso (kg)**
Placebo x Dapa	-0.59 (-0.68 to -0.50)	-1.96 (-2.24 to -1.68)
Placebo x Cana	-0.85 (-0.98 to -0.72)	-2.81 (-3.26 to -2.28)
Placebo x Empa	-0.61 (-0.74 to -0.50)	-1.74 (-2.20 to -1.27)
Cana x Dapa	-0.26 (-0.41 to -0.10)	-0.84 (–1.38 to –0.25)
Dapa x Empa	-0.02 (-0.18 to 0.12)	-0.22 (-0.76 to 0.31)
Cana x Empa	-0.23 (-0.05 to -0.40)	-1.06 (–1.71 to –0.36)

Capítulo 3 – Considerações finais e perspectivas futuras

Os dados desta revisão sistemática e metanálise demonstram a eficácia e segurança dos inibidores do SGLT2 para o tratamento do diabetes melito tipo 2. Nesse sentido, seu benefício em desfecho em parâmetros como peso, pressão arterial sistólica e diastólica se torna ainda mais atraente dado o perfil de comorbidades comumente encontrado nos pacientes com DM tipo 2. Além disso, ao comparar os inibidores do SGLT2 a outras classes de antihiperglicemiantes, percebemos que os benefícios sobre peso e pressão arterial se mantem quando os inibidores do SGLT2 são comparados a metformina, sulfoniluréias e inibidores da DPP-IV.

O antihiperglicemiante recomendado pela American Diabetes Association e pela European Association for the Study of Diabetes como primeira linha no tratamento do DM tipo 2 é a metformina (1), porém quando há falha em atingir HbA_{1c} <7%, está indicada a adição de um segundo agente. Uma metanálise recente analisou a adição de segundo antihiperglicemiante a metformina e já demonstrava o potencial benefício dos inibidores do SGLT2 (2). Aliados aos resultados do presente estudo, os inibidores do SGLT2 parecem uma opção ainda mais atrativa e estudos a longo prazo poderão comprovar maiores benefícios.

Um dos desafios no tratamento do DM tipo 2, o tratamento da obesidade, ainda não tem solução, apesar de diferentes manejos propostos. Aliar o efeito antihiperglicemiante dos inibidores do SGLT2 com uma perda de peso de 2-3 kg (3-5) pode ser mais um passo nesse caminho.

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