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Research article

The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomized controlled trials

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Abstract

Background Dapagliflozin is a first-in-class oral sodium glucose co-transporter 2 (SGLT2) inhibitor and is often used in combination with conventional anti-diabetic drugs in treating type 2 diabetes mellitus (T2DM).

Objectives This meta-analysis aimed to evaluate whether dapagliflozin is synergistic with other anti-diabetic drugs without risk of weight gain.

Data sources Information of relevant RCTs was retrieved from PubMed, Cochrane Library, Embase, ClinicalTrials.gov, Google Scholar and Google according to a pre-specified search strategy.

Methods This meta-analysis was based on the random effects model and compared the changes of HbA1c (%), FPG (mmol/L) and body weight (kg) between dapagliflozin arm and placebo arm of randomized controlled trials (RCT) on patients with T2DM. The Cochrane risk of bias tool was used to assess the quality of the eligible RCTs. Publication bias was evaluated with a funnel plot and the Egger's regression test. Heterogeneity was assessed with the I^2 statistics. Sensitivity analysis was conducted by excluding low quality and interim RCTs, respectively. Meta-regression was conducted on follow-up durations. The evidential quality of the findings was assessed by the GRADE profiler.

Results Twelve RCTs were eligible for quantitative synthesis and meta-analysis. The overall effect size of HbA1c calculated from mean difference was -0.52% (Z= -13.56, P<0.001) with 95%CI [-0.60, -0.45]. The effect size of FPG was -1.13mmol/L (Z=-11.12, P<0.001) with 95%CI [-1.33, -0.93]. The effect size of body weight was -2.10kg (Z=-18.77, P<0.001) with 95%CI [-2.32, -1.88]. After excluding low quality and interim RCTs respectively, the overall mean difference was changed to -0.56%, -1.11mmol/L, 2.23kg and -0.50%, -1.08mmol/L, -2.08kg. The sensitivity analysis indicated good stability of the meta-analysis on HbA1c, FPG, and body weight.

Conclusions The meta-analysis showed that dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved the glycemic control in T2DM patients without the risk of weight gain.

PROSPERO registration number CRD42013005034

ARTICLE SUMMARY

Article focus

- To explore the efficacy of dapagliflozin as an add-on drug for anti-diabetic treatment.

Key messages

- Dapagliflozin as an add-on drug improves the control of HbA1c and FPG levels in type 2 diabetes mellitus (T2DM) patients with little risk of weight gain.
- Dapagliflozin have significant effects on glycemic control and body weight of T2DM patients.

Strengths and limitations of this study

- This study is the first meta-analysis to focus on the weight gain issue of dapagliflozin.
- The protocol of this study was properly registered with the PROSPERO database and published.
- The conduct of this study is in accordance with the PRISMA statement to ensure high study quality.
- Subgroup meta-analysis, sensitivity analysis and publication bias analysis were performed to evaluate the robustness of the evidence.
- A meta-regression was conducted to determine the time-dependence of the dapagliflozin efficacy.
- There is a potential limitation of the study that all eligible RCTs were sponsored by Bristol-Myers Squibb or AstraZeneca.

INTRODUCTION

The efficacy of common anti-diabetic drugs (including metformin, sulfonylureas, nonsulfonylurea secretagogues, alpha glycosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 analog, and dipeptidyl peptidase-4 inhibitors) is insulin-dependent [1]. Their efficacy diminishes when the function of pancreatic islet β-cells declines during the progression of type 2 diabetes mellitus (T2DM) [2]. Sulphonylureas and thiazolidinediones cause weight gain, which further worsens insulin resistance [3]. It came as no surprise that approximately two-thirds of the patients with diabetes in Europe [4] and the United States [5] under conventional treatment could not meet the goal of glucose control. By contrast, as a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT2), dapagliflozin is distinctive in its insulin-independent action on reducing reabsorption of glucose particularly by the proximal tubule in the kidney to eliminate more glucose from plasma into urine [6-8]. Dapagliflozin would enhance glucose control, as claimed in recent studies, without adverse effects on body weight, blood pressures and lipids like conventional anti-diabetic drugs, making dapagliflozin desirable to combine conventional anti-diabetic drugs with dapagliflozin in treating T2DM [9-10]. However, these claims were made by individual clinical studies, not well-established by the systematic reviews and meta-analysis. Three existing meta-analysis reports did not focus on dapagliflozin but addressed the efficacy issues of SGLT2 inhibitors in general [3, 11-12]. The latest meta-analysis [13] on dapagliflozin in particular still lacked analysis of publication bias and sensitivity to various possible factors as required by the PRISMA guideline for meta-analysis reporting. Although a subgroup analysis on dapagliflozin monotherapy was available in the meta-analysis [13], it did not provide a specific analysis of the efficacy of dapagliflozin combined with other anti-diabetic drugs. All these four meta-analysis studies were not registered before conduct. The present meta-analysis aims to evaluate the efficacy of dapagliflozin in combination with conventional anti-diabetic drugs for glucose control as measured by the changes of glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG). The body weight data were analyzed to test whether the claim that dapagliflozin does not affect body weight (that is, no weight gain).

METHODS

This study of systematic review and meta-analysis is in compliance with the guideline Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The protocol of this study [14] was registered with the PROSPERO database and assigned an identifier CRD42013005034.

Data sources

Bibliographical databases for literature search included MEDLINE (via PubMed), Embase (via OVID), Cochrane Library, Google Scholar and ClinicalTrials.gov (http://www.clinicaltrials.gov). The initial search was performed on 9 July 2013 and was last updated on 21 October 2013. Our search strategy included keywords "dapagliflozin" and "diabetes". We searched all fields in PubMed, all text in Cochrane Library, but restricted to the fields of abstracts, titles, and keywords in Embase. When searching ClinicalTrials.gov, we used the term "dapagliflozin". Google search was conducted to find the RCT information unavailable from bibliographical databases. In addition, manual search of journals was conducted to track relevant RCTs that were not indexed by normal keywords.

Inclusion and exclusion criteria

The identified studies were selected according to the following inclusion and exclusion criteria:

Study design Only RCTs were included. Observational, cohort, case-control, case series, and laboratory studies were excluded.

Durations For observing changes in HbA1c levels, only the RCTs with follow-up durations longer than 8 weeks were included.

Participants Only the RCTs on adult T2DM patients (age≥18) were included.

Interventions This meta-analysis included only the RCTs on the efficacy of dapagliflozin combined with conventional anti-diabetic drugs. The RCTs on dapagliflozin monotherapy were excluded.

Comparators This meta-analysis included the RCTs employing placebo combined with conventional anti-diabetic drugs as the controls. The RCTs employing only placebo as the control group were excluded.

Outcomes This meta-analysis included the RCTs measuring HbA1c, FPG, and body weight as the outcomes. The RCTs without all these three outcomes were excluded.

Study selection and data extraction

The studies were evaluated by at least two reviewers according to the inclusion and exclusion criteria. Disagreement in evaluation was resolved by discussion among the reviewers.

Data from each included RCT were extracted by one reviewer and verified by another reviewer. In addition to the outcome measures, the following characteristics of the RCTs were extracted: (1) first author and publication year, (2) interventions (doses of dapagliflozin and the drugs used in combination), (3) characteristics of participants, (4) follow-up durations, and (5) findings.

Quality assessment

We assessed the design, execution and reporting of the included RCTs according to the Cochrane risk of bias tool [15]. The quality of each RCT was assessed by one reviewer and verified by another reviewer. Disagreement was resolved by discussion. The evidential level of each outcome was determined in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [16]. The analysis was conducted with GRADE profiler 3.2.

Data synthesis and analysis

The meta-analysis of effect sizes was performed using Review Manager 5.2 (http: http://ims.cochrane.org/revman/). Other statistical tests and regression analysis were conducted using R3.0.1 (http://www.r-project.org/). P values<0.05 were considered statistically significant. Meta-analysis based on the random effects model was conducted for comparing the changes of HbA1c (%), FPG (mmol/L), and body weight (kg) between 10mg dapagliflozin arm and placebo arm. The continuous variables extracted from the included RCTs were adjusted mean differences (AMD) with 95% confidential interval (CI). Subgroup analysis was conducted according to drug combinations (selected from metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) and the durations of follow-up (≤24 weeks or not). The effects of follow-up durations were also assessed by meta-regression. Publication bias was evaluated using the Egger's regression test and a funnel plot of the effect sizes against the stand errors (SE). Heterogeneity was assessed with the I^2 statistic, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I^2<25% was considered as low in heterogeneity and I^2>75% was of high heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. The RCTs with high risk of bias were excluded for sensitivity analysis. The sensitivity analysis evaluated the differences between overall results and the results from the studies with low risk of bias. In addition, we excluded the interim results, that is, only using endpoint results of trials, to re-evaluate the robustness of the meta-analysis results.

RESULTS

Study selection

A total of 380 citations were assessed in the initial searching, of which 231 were identified via bibliographical databases and 149 were identified by supplementary search via the Google and Google Scholar (Fig 1). By screening the abstracts, we excluded 139 non-RCTs and seven

pharmacokinetics and pharmacodynamics studies. Of the remaining 20 RCTs, eight RCTs did not meet the inclusion criteria on interventions and comparators. Finally, a total number of 12 RCTs were included for quantitative synthesis and meta-analysis.

Study characteristics

The characteristics of the included 12 RCTs [17-28] were summarized in Table 1. The RCTs contained interventions of 2.5mg, 5mg, and 10mg add-on dapagliflozin. The eligible RCTs were also summarized according to their combined drugs: (1) 10mg dapdgliflozin plus metformin *vs.* placebo plus metformin; (2) 10mg dapdgliflozin plus insulin *vs.* placebo plus insulin; (3) 10mg dapdgliflozin plus glimepiride *vs.* placebo plus glimepiride; (4) 10mg dapdgliflozin plus pioglitazone *vs.* placebo plus pioglitazone; (5) 10mg dapdgliflozin plus metformin/sitagliptin *vs.* placebo plus metformin/sitagliptin. The participants in all RCTs were T2DM patients (≥18 years old). The outcomes measuring the effects of dapagliflozin were HbA1c (%), FPG (mmol/L), and body weight (kg).

The data extracted from the included RCTs for meta-analysis were sample size and changes from baselines, such as adjusted mean differences (AMD) and standard deviations/standard errors (SD/SE). The mean differences were adjusted according to the last observation carried forward (LOCF) was adopted in most RCTS, thus the changes extracted from the RCTs were AMD using analysis of covariance (ANCOVA) model.

Risk of bias within studies

According to the Cochrane risk of bias tool, four RCTs had more than one unclear risks of bias [21, 23, 25, 28]. The common bias was the detection bias due to no report of blinding (Figure 2). The average quality of the RCTs was acceptable. The GRADE evaluation indicated that the outcomes of both HbA1c and FPG had high quality of the evidence. However, the quality of the evidence on body weight was moderate due to publication bias (Table 2).

Synthesis of results from individual studies

HbA1c

Twelve RCTs with 3986 participants were included in the meta-analysis on the effect of dapagliflozin on changing the patients' HbA1c levels. There were 1996 participants in the intervention groups (10mg dapagliflozin combined with five drugs) and 1990 participants in the control groups (placebo combined with corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot of HbA1c was presented in Figure 3a.

The differences of AMD between the intervention groups and the control groups ranged from -0.8% to -0.29%. HbA1c levels decreased after supplement of dapagliflozin. The overall

effect size in terms of mean difference was -0.52% (Z= -13.56, P<0.001) with 95% CI [-0.60, -0.45]. The heterogeneity among the RCTs was moderate with I^2=56 % (Q=29.54, P=0.0055) and 95%CI [19.9%, 75.8%]. A funnel plot showed no publication bias (Figure 4) and the Egger's regression test was not significant in asymmetry (t= -1.90, P=0.08).

Subgroup meta-analyses were conducted by stratifying the five anti-diabetic drugs (metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) combined with dapagliflozin and the follow-up durations (≤24 weeks, >24 weeks). The effect sizes ranged from -0.69% to -0.47%. The metformin plus metformin subgroup had the smallest effect size with a mean difference of -0.47% (Z=-7.31, P<0.001). The two duration subgroups on two durations did not differ much, with a mean difference -0.53% (≤24 weeks) and -0.52% (>24 weeks). The meta-regression on the follow-up durations did not give any statistically significant results (Table 3).

FPG

All 12 included RCTs with 3620 participants reported the effect sizes of dapagliflozin on FPG. There were 1817 participants in the intervention groups (10mg dapagliflozin combined with the five types of drugs) and 1803 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. As depicted in a forest plot of FPG (Figure 4), all the RCTs showed the decreases in FPG after the add-on of dapagliflozin. The overall mean difference between the intervention groups and the control groups was -1.13mmol/L (Z=-11.12, P<0.001) with 95%CI [-1.33, -0.93]. The heterogeneity among these RCTs was moderate with I^2 = 53.8% (Q=23.81, P=0.0135). A funnel plot also showed no publication bias (Figure 4) and the Egger's regression test was not significant in asymmetry (t=1.55, P=0.15).

Subgroup meta-analyses were conducted on five different combined drugs and follow-up durations. The effect sizes of the drug subgroups ranged from -1.47mmol/L (pioglitazone group) to -0.93mmol/L (metformin group). In the follow-up duration subgroups, the mean differences were -1.13mmol/L (>24 weeks) and -1.36mmol/L (≤ 24 weeks). The meta-regression showed a significant time-dependent effect on the follow-up durations with R^2=0.9704 and P<0.001 (Table 3).

Body weight

Twelve RCTs with a total of 4008 participants reported the effect sizes of dapagliflozin on body weight changes. The RCTs included 2005 participants in the intervention groups (10mg dapagliflozin combined with the five types of drugs) and 2003 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot showed decreases in body weight after the intervention of

dapagliflozin (Figure 3c). The decreases ranged from -3.33kg to -1.54kg. The overall mean difference between the intervention groups and the control groups was -2.10kg (Z=-18.77, P<0.001) with 95%CI [-2.32, -1.88]. The heterogeneity among RCTs was not significant with I^2 = 12% (Q=14.73, P=0.32). A funnel plot revealed some publication bias (Figure 4) and the Egger's regression test was significant in asymmetry (t= -3.11, P=0.009).

The subgroup meta-analyses were conducted on five different combinations of drugs and two follow-up durations. The effect sizes of the drug subgroups ranged from -2.45kg to -1.54kg with insulin the most effective and glimepiride the least. The results of follow-up duration subgroups showed that the differences of effect sizes ranged from -2.63kg (≤ 24 weeks) to -1.92kg (> 24weeks), which implied the efficacy was time-dependent. The result from meta-regression showed significant time-dependence on the follow-up durations with R^2=1 and P<0.01(Table 3).

Risk of bias across studies

The funnel plots of HbA1c, FPG and body weight checked the existence of publication bias (Figure 4). The results from the Egger's regression test indicated that there was significant publication bias in the outcome of body weight (t=-3.11, P=0.0091). There was no significant publication bias in the result of HbA1c (t=-1.90, P=0.08) and FPG (t=1.55, P=0.152).

Sensitivity analysis

By the Cochrane risk of bias tool, we found that four RCTs had more than one unclear risk of bias [21, 23, 25, 28]. When we excluded those RCTs, the overall effect size of HbA1c changed to -0.50% with 95% CI [-0.61, -0.40]. The effect size of FPG became -1.08mmol/L with 95% CI [-1.29, -0.87] and the result of body weight -2.08kg with 95% CI [-2.36, -1.82]. The new results did not differ much from the previous ones, that is -0.52% in HbA1c, -1.13mmol/L in FPG and -2.10kg in body weight (Figure 5a).

In addition, we found that four RCTs published only interim results [17, 19, 22, 26]. Hence, we excluded the interim RCTs to re-examine the robustness of our meta-analysis. The data from eight RCTs were kept for sensitivity analysis [18, 20, 21, 23-25, 27-28]. The overall mean differences were changed to -0.56% in HbA1c, -1.11mmol/L in FPG, and -2.23kg in body weight (Figure 5b).

DISCUSSION

This study of systematic review and meta-analysis on the efficacy of dapagliflozin in combination with anti-diabetic drugs followed the PRISMA guideline and was registered with the PROSPERO database before the conduct. Subgroup meta-analyses and sensitivity

analyses were also conducted to ensure the robustness of the evidence.

In agreement with another meta-analysis on monotherapy of T2DM with dapagliflozin [13] and three other meta-analyses on SGLT2 inhibitors in general [3, 11-12], we found dapagliflozin beneficial in glucose control of T2DM. In contrast to these meta-analyses, we did a PRISMA-compliant meta-analysis, including additional sensitivity analyses and publication bias analyses, on the efficacy of dapagliflozin combined with another anti-diabetic drug.

This meta-analysis indicated that dapagliflozin as an add-on drug to conventional anti-diabetic drugs did improve the control of the HbA1c and FPG levels in T2DM patients. Individual RCTs indicated that insulin and pioglitazone increased the risk of weight gain [23, 26, 27], which would be deemed harmful to T2DM patients. Our meta-analysis confirmed a consensus that the body weight of T2DM patients was well controlled under treatment of dapagliflozin.

Even though the Egger's regression test showed publication bias in the outcome of body weight, dapagliflozin as an add-on drug still reduced body weight after a trim-and-fill procedure on the funnel plot. Subgroup meta-analyses showed that dapagliflozin enhanced the effects of conventional anti-diabetic drugs on controlling the HbA1c, FPG, and body weight. A meta-regression further discovered that dapagliflozin had significant time-dependent effects on controlling FPG and body weight of T2DM patients.

There were limitations in this meta-analysis to be overcome in later studies. Four RCTs published only short follow-up periods [17, 19, 22, 26]. Considering the consistency in dosage, we used 10mg dapagliflozin data only. In this meta-analysis, most RCTs [17, 19, 20, 21, 23, 24, 25, 26, 28] used LOCF methods to impute missing data. The combination of LOCF imputation with exclusion of post rescue data could lead to overstated results [29] and cause low estimates of standard errors and P values [30]. All the included RCTs were sponsored by Bristol-Myers Squibb [17, 18, 21, 23, 25] or AstraZeneca [19, 20, 22, 24, 26-28] which might introduce some potential bias, due to a concern that industry funding was strongly associated with favorable outcomes [31]. We will update our meta-analysis with further RCTs with proper registration and less potential biases.

CONCLUSION

Dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved glucose control and reduced weight gain in T2DM patients, especially those who had inadequate glucose control with conventional drugs.

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Competing interests

The authors declare that they have no competing interests

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Contributors

YNS conceived the study, developed the selection criteria, searched the literature, selected the studies, extracted the data, and wrote the manuscript. YZ assisted in the study design, managed the literature, selected the studies, extracted the data, performed data analysis, and wrote the manuscript. XC and WSC evaluated the Cochrane risk of bias for each study. SWL proposed the methods, decided the study design and wrote the manuscript. All authors read and approved the final manuscript.

Provenance and peer review

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Data sharing statement

There are no additional data available.

Published protocol of the study

http://www.systematicreviewsjournal.com/content/2/1/103

REFERENCES

1 Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician 2009;**79(1)**:29-36.

2 Pretki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006;**116(7)**:1802-1812.

3 Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012;**2(5)**:e001007.

4 Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications in type II diabetes in Europe. Diabetologia 2002;**45(7)**:S23-S28.

5 Saydah SH, Frafin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;**291**:335-342.

6 Dapagliflozin. http://www.nyrdtc.org/GMMMG/Groups/Publications/GM_NDE/NDE_121_Dapagliflozin.pdf.

7 Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010;**9(7)**:551-559.

8 Hu L, Zhou ZY. Research progress of sodium-glucose co-transporter-2 inhibitor drugs. Medical Recapitulate 2011;**12(24)**:3782-3785.

9 Tahrani AA, Barnett AH. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Ther 2010;**1(2)**:45-56.

10 Freeannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. Diabetes Care 2010;**33(10)**:2217-2224.

11 Musso G, Gambino R, Cassader M, et al. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and

meta-analysis of randomized trials. Ann Med 2012;**44(4)**:375-393.

12 Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;**159(4)**:262-274.

13 Zhang M, Zhang L, Wu B, et al. Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev Published Online First: 2 October 2013. doi: 10.1002/dmrr.2479

14 Sun YN, Zhou Y, Chen X, et al. The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes: protocol for meta-analysis of randomized controlled trials. Syst Rev 2013;**2(1)**:103. http://www.systematicreviewsjournal.com/content/2/1/103 (accessed 18 November 2013)

15 Higgins J, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of boas in randomized trials. BMJ 2011;**343**:d5928.

16 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;**336(7650)**:924-926.

17 Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010;**375(9733)**:2223–2233.

18 Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med 2013;**11**:43.

19 Bolinder J, Ljunggren Ö, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012;**97(3)**:1020–1031.

20 Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2013 Published Online First: 1 August 2013. doi: 10.1111/dom.12189

21 Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012;**66(5)**:446–456.

22 Ljunggren Ö, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2012;**14(11)**:990–999.

23 Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, a sodium- glucose cotransporter-2 Inhibitor, on hemoglobin A1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;**35(7)**:1473-1478.

24 Strojek K, Yoon KH, Hruba V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011;**13(10)**:928–938.

25 Wilding JP, Norwood P, Tjoen C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009;**32(9)**: 1656-1662.

26 Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012;**156(6)**:405–415.

27 Wilding JP, Woo V, Soler NG, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab Published Online First: 1 August 2013. doi: 10.1111/dom.12187

28 Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled studys. Diabetes Care Published Online First: 21 October 2013. doi: 10.2337/dc13-0467

29 U.S. Food and Drug Administration. FDA Briefing Document. NDA 202293.

Dapagliflozin tablets, 5 and 10 mg. Rockville, MD: U.S. Food and Drug Administration, 2011.

30 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;**367(14)**:1355-1360.

31 Khan SN, Mermer MJ, Myers E, et al. The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. Am J Orthop (Belle Mead NJ) 2008;**37(12)**:E205-E212.

Tables

Table 1 Baseline characteristics of the included RCT

First author year	Treatments	N	Participants baseline characteristic †				weeks (max)	Findings
			Age	HbA1c (%)	BMI or weight (kg/m^2 or kg*)	FPG (mmol/L or mg/dL**)		
Bailey 2010 [17]	PLA	137	53.7 (10.3)	8.11 (0.96)	31.8(5.3)	9.19 (2.57)	24	Dapagliflozin added to metformin enhanced glycaemic control and lowered weight.
	2.5mgDAPA	137	55.0 (9.3)	7.99 (0.90)	31.6(4.8)	8.96 (2.39)		
	5mgDAPA	137	54.3 (9.4)	8.17 (0.96)	31.4(5.0)	9.39 (2.72)		
	10mgDAPA	135	52.7 (9.9)	7.92 (0.82)	31.2(5.1)	8.66 (2.15)		
Bailey 2013 [18]	PLA+MET	137	NA	8.12 (0.96)	87.74(19.24) *	9.19 (2.58)	102	Dapagliflozin added to metformin for 102 weeks enhanced glycaemic control and lowered weight.
	2.5mgDAPA + MET	137	NA	7.99 (0.90)	84.90(17.77) *	8.96 (2.39)		
	5mgDAPA + MET	137	NA	8.17 (0.96)	84.73(16.26) *	9.39 (2.72)		
	10mgDAPA + MET	135	NA	7.92 (0.82)	86.28(17.53) *	8.66 (2.15)		
Bolinder, 2012 [19]	PLA + MET	91	60.8 (6.9)	8.11 (0.96)	31.7(3.9)	8.3 (1.4)	24	Dapagliflozin added to metformin reduced total body weight.
	10mgDAPA + MET	89	60.6 (8.2)	7.99 (0.90)	32.1(3.9)	8.2 (1.4)		
Bolinder, 2013 [20]	PLA + MET	91	NA	7.16	90.9*	8.21	102	Dapagliflozin added to metformin enhanced glycaemic control and reduced weight.
	10mgDAPA + MET	91	NA	7.19	92.1*	8.3		

Henry	Study1						24	Dapagliflozin added to metformin was
2012 [21]	5mgDAPA + PLA	203	52.3 (10.2)	9.1 (1.4)	86.2 (21.1)*	10.59 (3.14)		effective in reducing HbA1c, FPG and weight.
	MET +PLA	201	51.8 (9.8)	9.2 (1.3)	85.6 (20.0)*	10.94 (3.53)		
	5mgDAPA + MET	194	51.7 (9.3)	9.2 (1.3)	84.1 (19.5)*	10.76 (3.12)		
	Study 2							
	10mgDAPA + PLA	219	51.1 (11. 5)	9.1 (1.3)	88.5 (19.3)*	10.99 (3.43)		
	MET+PLA	208	52.7 (10.4)	9.1 (1.3)	87.2 (19.4)*	10.57 (3.00)		
	10mgDAPA + MET	211	51.0 (10.1)	9.1 (1.3)	88.4 (19.7)*	10.52 (3.22)		
Ljunggren	PLA + MET	91	60.8 (6.9)	7.16 (0.53)	31.7(3.9)	8.3 (1.4)	50	Dapagliflozin added to metformin didn't affect
2012 [22]	10mgDAPA + MET	89	60.6 (8.2)	7.19 (0.44)	32.1(3.9)	8.2 (1.4)		markers of bone formation and resorption.
Roenstock	≥30mg PIO + PLA	139	53.5 (11.4)	8.34 (1.00)	NA	8.92 (2.61)	48	Dapagliflozin added to pioglitazone further
2012 [23]	≥30mg PIO + 5mgDAPA	141	53.2 (10.9)	8.40 (1.03)	NA	9.36 (2.98)		enhanced glycaemic control without
	≥30mgPIO +10mgDAPA	140	53.8 (10.4)	8.37 (0.96)	NA	9.15 (2.57)		pioglitazone-related weight gain.
Strojek	PLA + GLI	145	60.3(10.16)	8.15 (0.74)	NA	9.58 (2.07)	24	Dapagliflozin added to glimepiride
2010 [24]	2.5mgDAPA + GLI	154	59.9 (10.14)	8.11 (0.75)	NA	9.56 (2.13)		significantly enhanced glycaemic control and
	5mgDAPA + GLI	142	60.2 (9.73)	8.12 (0.78)	NA	9.68 (2.12)		reduced weight.
	10mgDAPA + GLI	151	58.9 (8.32)	8.07 (0.79)	NA	9.55 (2.04)		
Wilding,	PLA+INS	23	58.4 (6.5)	8.4 (0.9)	34.8 (4.6)	165.9 (51.5) **	12	Dapagliflozin added to insulin improved
2009 [25]	10mg DAPA + INS	24	55.7 (9.2)	8.4 (0.7)	35.5 (3.6)	156.0 (39.0) **		glycaemic control and lowered weight.
	20mg DAPA + INS	24	56.1 (10.6)	8.5 (0.9)	36.2 (4.6)	161.6 (55.0) **		

Wilding, 2012 [26]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	48	Dapagliflozin added to insulin enhanced glycaemic control, stabilized insulin dosing and lowered weight.
	2.5mgDAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		
	5mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)		
	10mgDAPA + INS	194	59.3(8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)		
Wilding, 2013 [27]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1(5.9)	9.5(3.2)	104	Dapagliflozin added to insulin enhanced glycaemic control, stabilized insulin dosing and lowered weight, but elevated rates of genital infection and of UTI
	2.5mgDAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0(5.0)	10.0(3.3)		
	5/10mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0(5.3)	10.3(3.3)		
	10mgDAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4(5.1)	9.6(3.0)		
[§]**Jabbour 2013 [28]**	PLA+ MET/SIT	224	55.0 (10.20)	7.97 (0.79)	89.23 (20.89)*	162.97 (34.45) **	24	
	10mgDAPA + MET/SIT	223	54.8 (10.42)	7.90 (0.81)	91.0 2(21.64)*	162.19 (36.83) **		

Abbreviations: PLA, placebo; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; GLI, glimepiride; INS, insulin; SIT, sitagliptin. FPG, fasting plasma glucose.

† measured by mean (SD)

*meansured by weight (kg); ** meansured by mg/dL

[§]The data was from ClinicalTrial.gov due to no full-text available.

Table 2 GRADE assessment for the outcomes (HbA1c, FPG, body weight)

10mg dapagliflozin arm compared to PLA arm for GRADE				
Patient or population: patients with type 2 diabetes **Intervention:** 10mg dapagliflozin combined with anti-diabetic drugs **Comparison:** placebo combined with anti-diabetic drugs				
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Placebo combined with anti-diabetic drugs**	 Corresponding risk **10mg dapagliflozin combined with anti-diabetic drugs**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
HbA1c (%) Follow-up: 12 to 104 weeks	The mean hba1c ranged across control groups from **-1.44 to 0.09 %**	The mean hba1c in the intervention groups was **0.52 lower** (0.6 to 0.45 lower)	3986 (14 studies)	⊕⊕⊕⊕ **high**
FPG (mmol/L) Follow-up: 12 to 104 weeks	The mean fpg ranged across control groups from **-1.93 to 0.99 mmol/L**	The mean fpg in the intervention groups was **1.13 lower** (1.33 to 0.93 lower)	3620 (12 studies)	⊕⊕⊕⊕ **high**
Body weight (kg) Follow-up: 12 to 104 weeks	The mean body weight ranged across control groups from **-2.12 to 2.99 kg**	The mean body weight in the intervention groups was **2.10 lower** (2.32 to 1.88 lower)	4008 (14 studies)	⊕⊕⊕⊖ **moderate**
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;				
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

Table 3 Meta-regression results of the time-dependent outcomes (HbA1c, FPG, body weight)

	HbA1c		FPG		Body weight	
	Estimate (SE)	**95% CI**	**Estimate (SE)**	**95% CI**	**Estimate (SE)**	**95% CI**
Intercept	-0.55 (0.07)*	[-0.68, -0.41]	-1.52 (0.12)*	[-1.75, -1.29]	-1.61 (0.18)*	[-1.97,-1.26]
Week	0.001 (0.001)	[-0.002, 0.003]	-0.01 (0.002)*	[0.004, 0.012]	-0.01 (0.004)*	[-0.02, 0.01]

* P value < 0.001

Figures

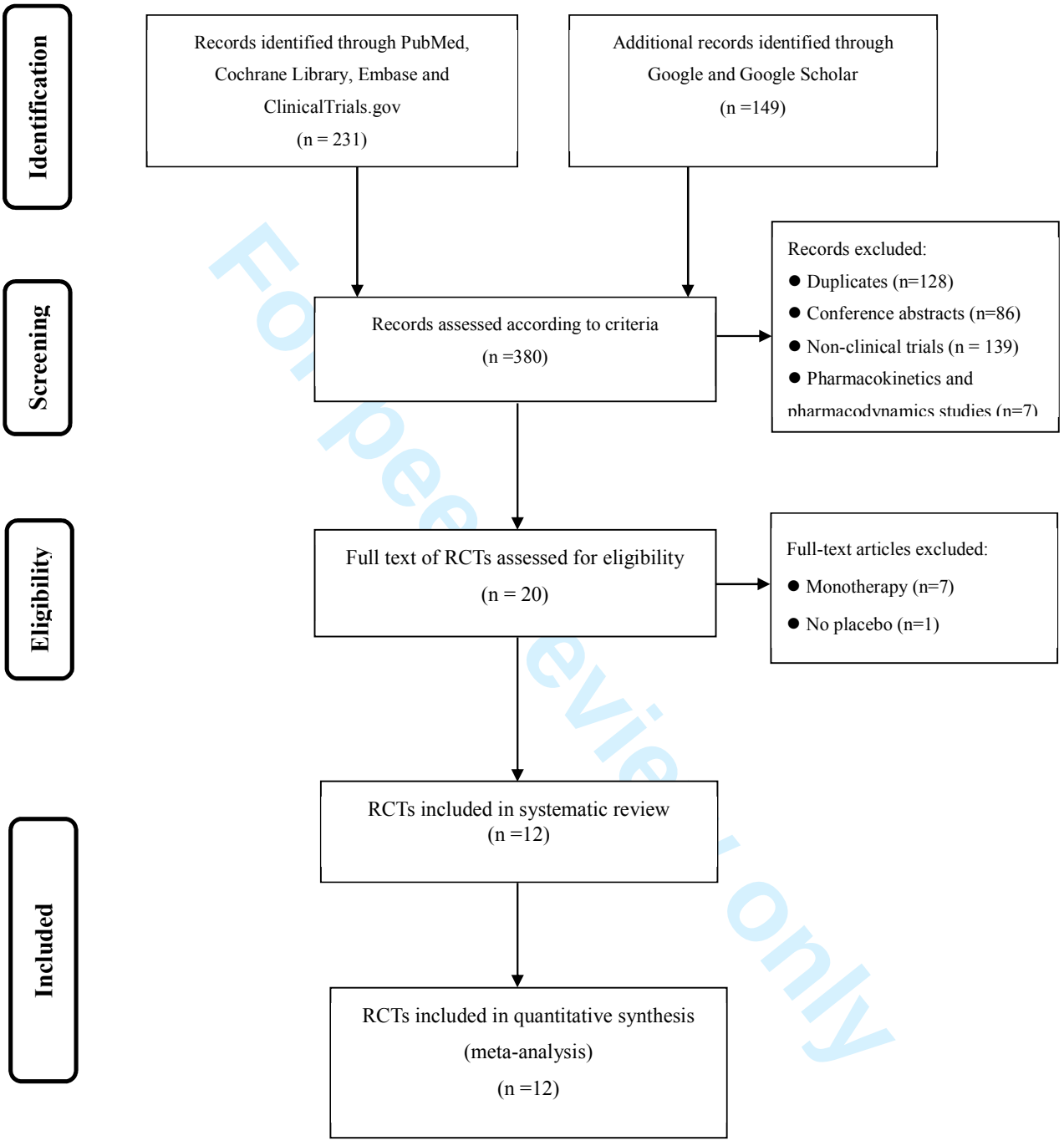

Figure 1 Flow diagram of study selection

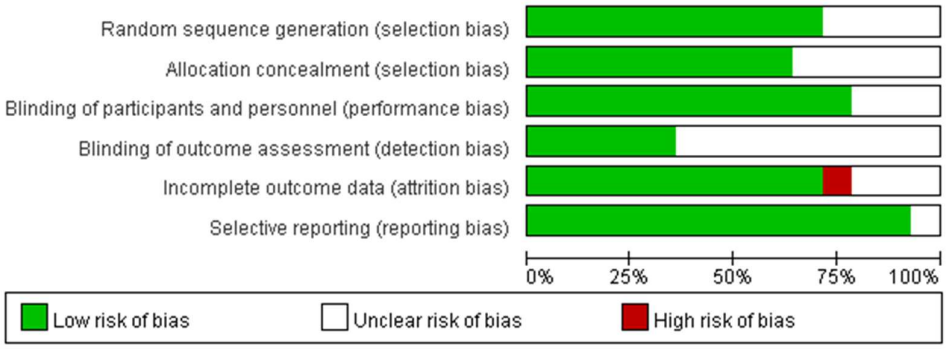

Figure 2a Cochrane risk of bias graph

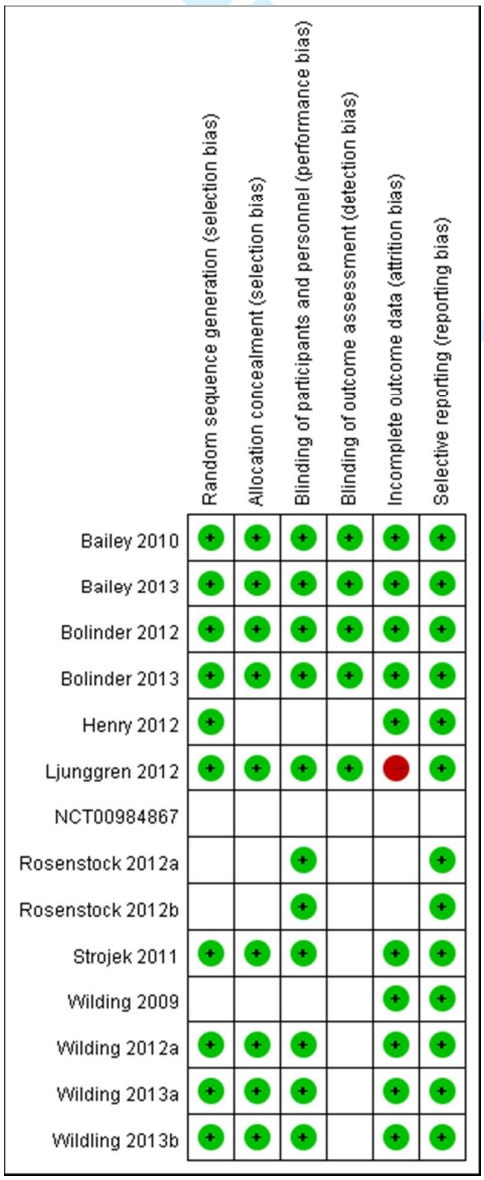

Figure 2b Cochrane risk of bias summary

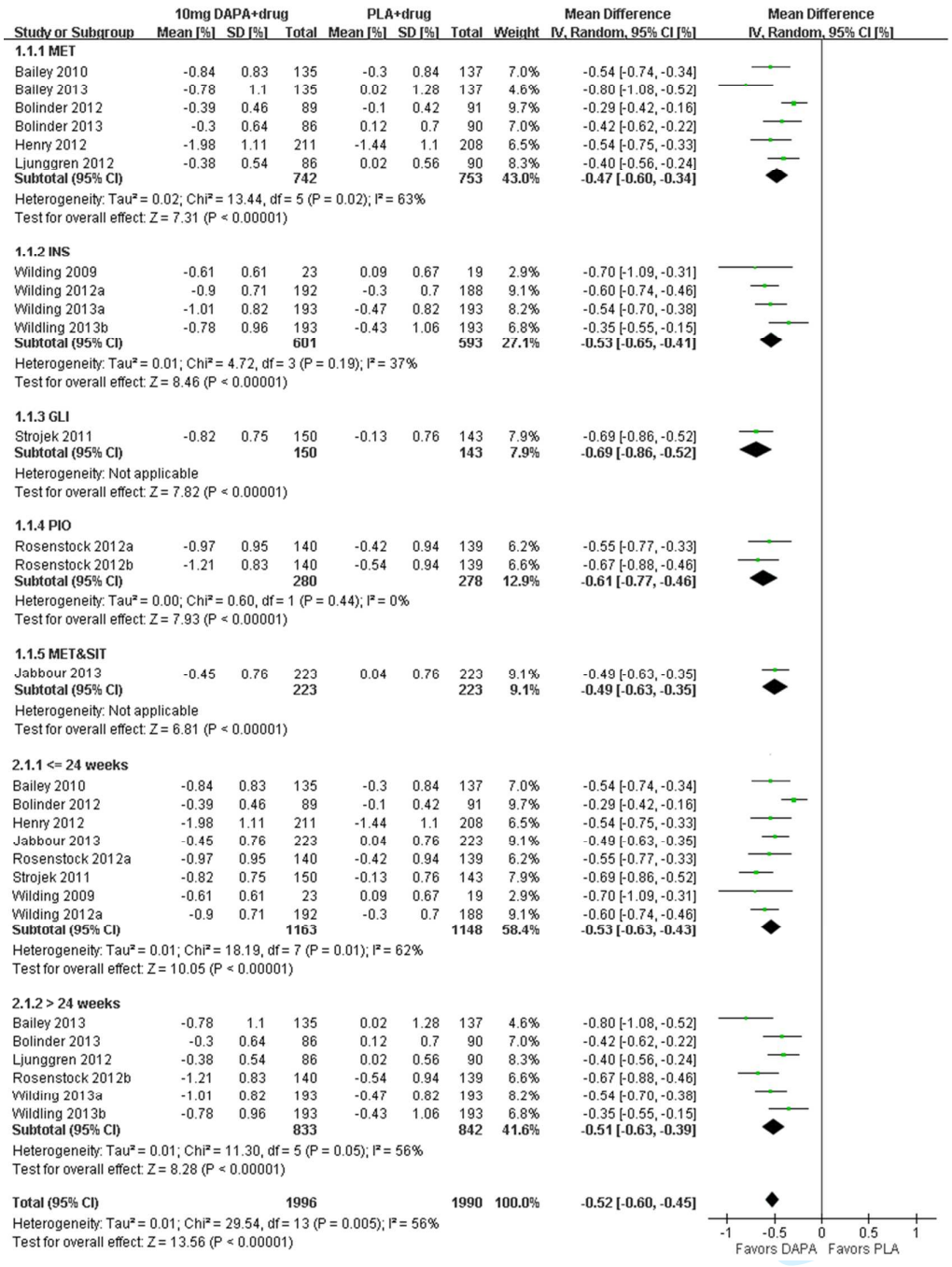

Figure 3a Forest plots of total effect size of HbA1c (%) and subgroup meta-analysis according to combined drugs and follow-up durations

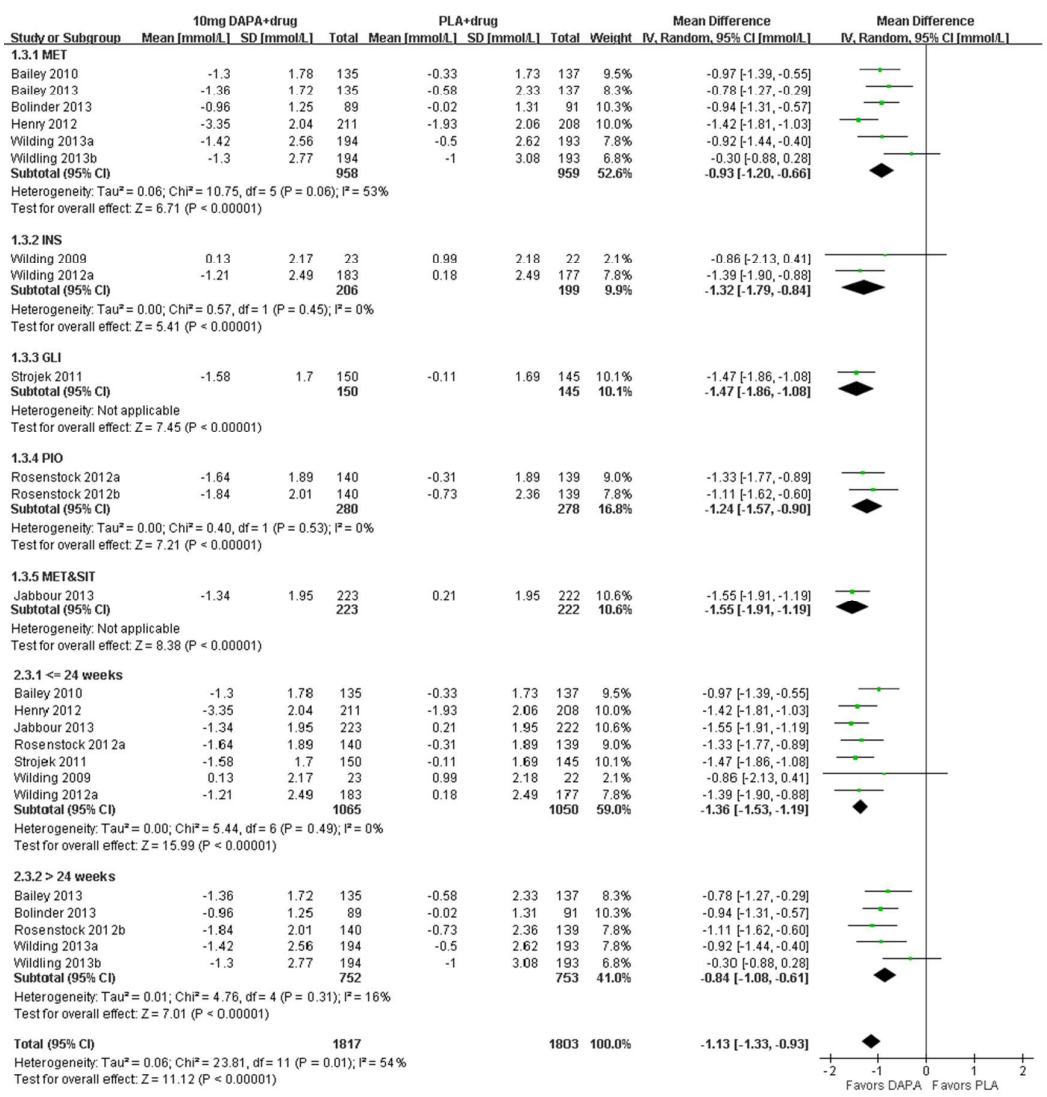

Figure 3b Forest plots of total effect size on FPG (mmol/L) and subgroup meta-analysis according to combined drugs and follow-up durations

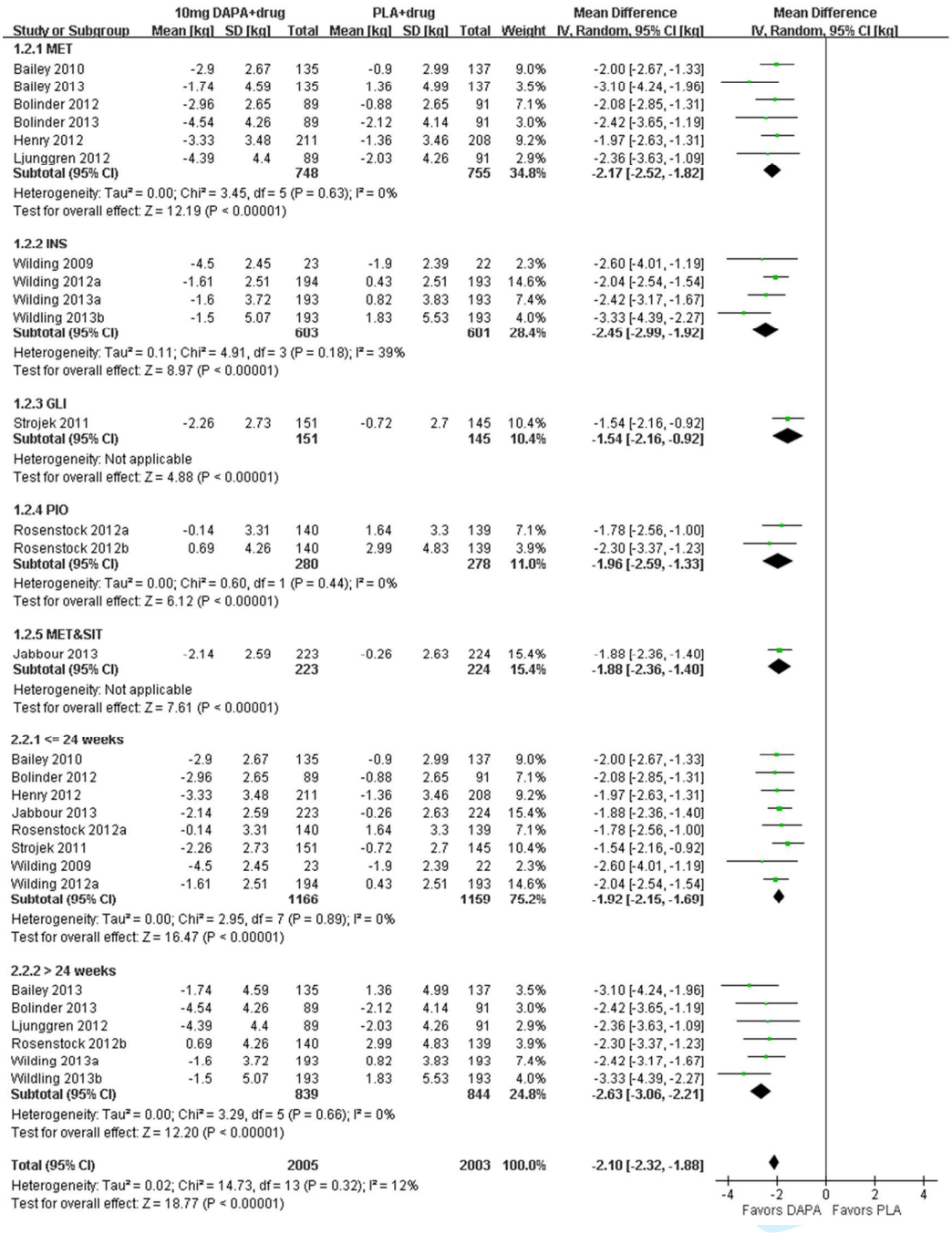

Figure 3c Forest plots of total effect size on body weight (kg) and subgroup meta-analysis according to combined drugs and follow-up durations

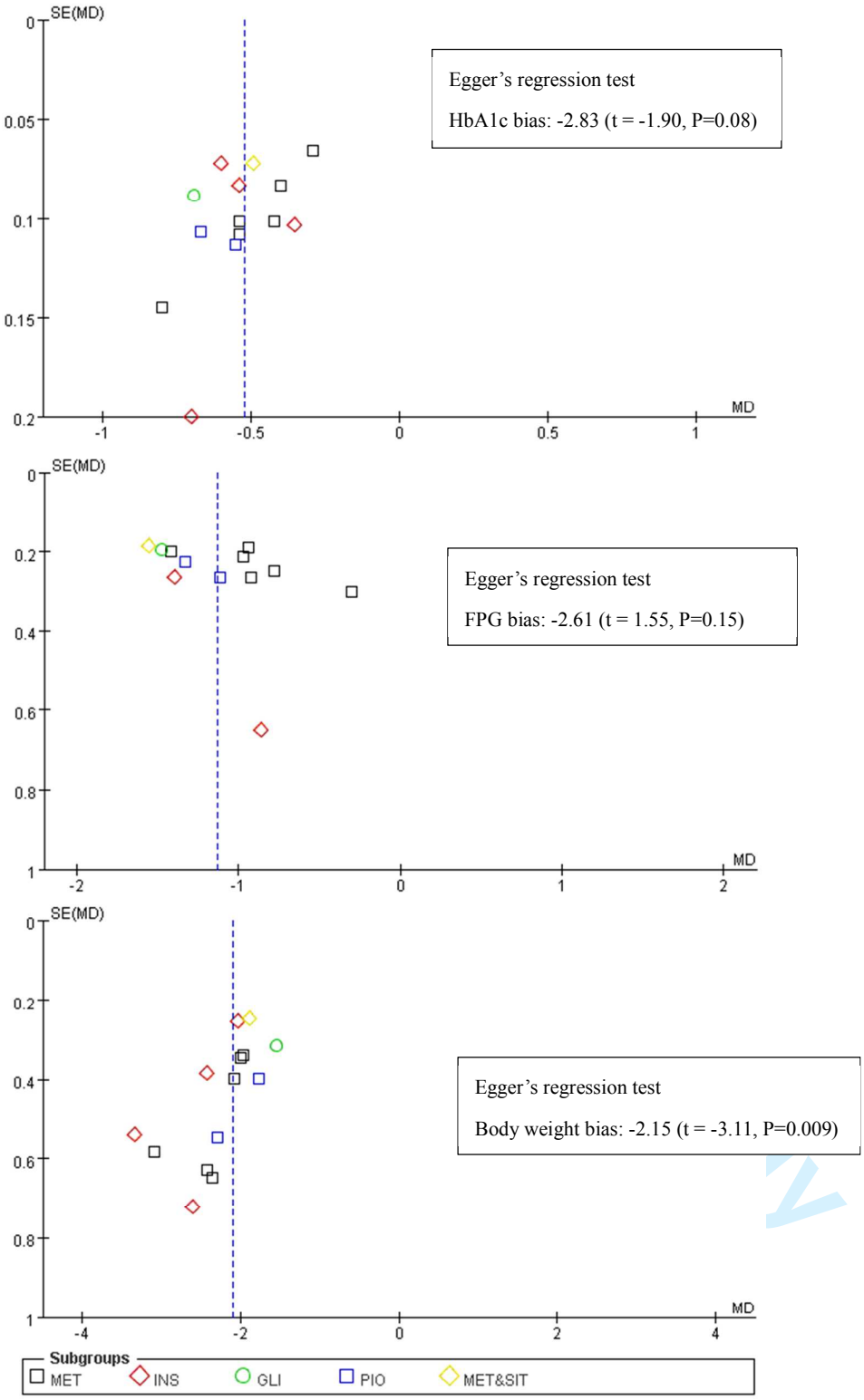

Figure 4 Funnel plots and the Egger's regression test results on HbA1c, FPG, and body weight

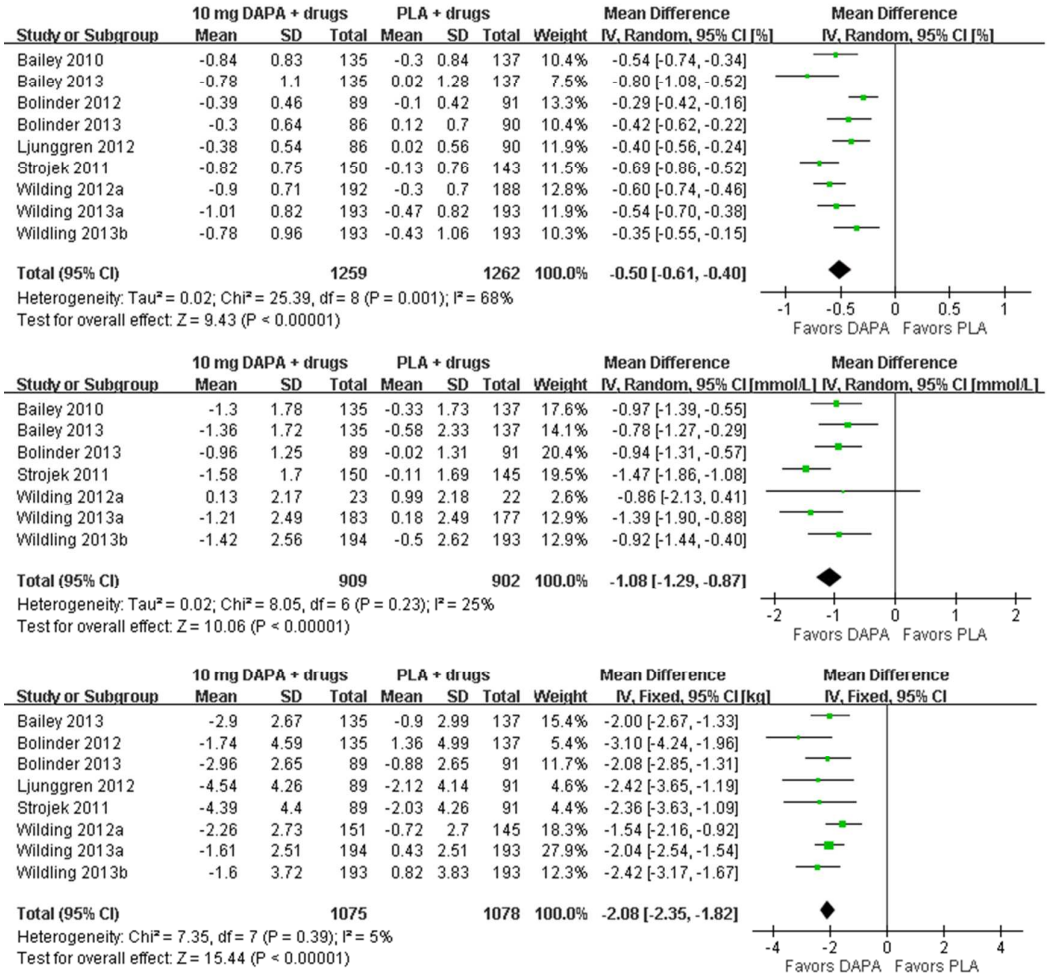

Figure 5a Forest plots of total effect size on HbA1c (%), FPG (mmol/L), and body weight (kg) in RCTs with high quality

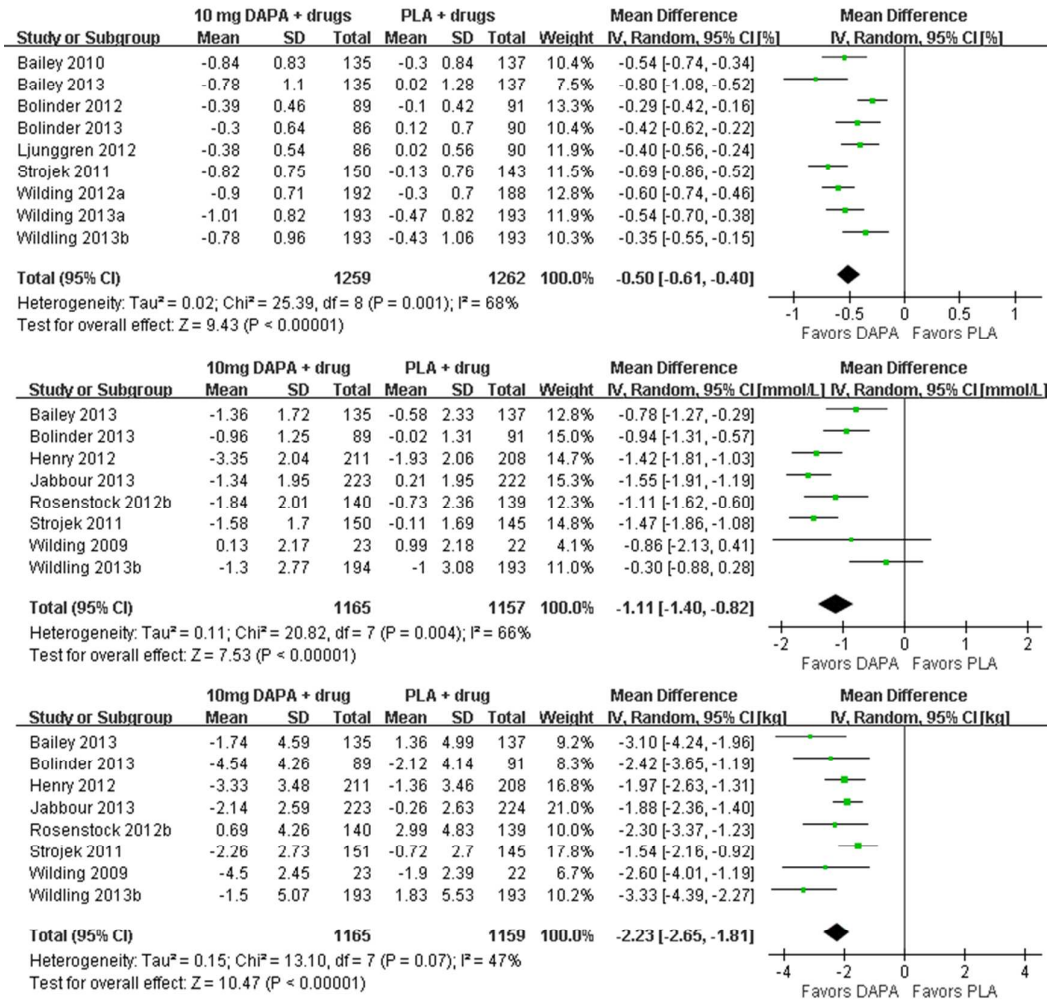

Figure 5b Forest plots of total effect size on HbA1c (%), FPG (mmol/L), and body weight (kg) in RCTs at endpoint

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6,20
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7,15-17
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,18,21
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8,22,23,24
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8,25
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9,19,26,27
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomized controlled trials

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice
Keywords:	DIABETES & ENDOCRINOLOGY, STATISTICS & RESEARCH METHODS, INTERNAL MEDICINE

Research article

The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomized controlled trials

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Keywords: Dapagliflozin, type 2 diabetes mellitus, meta-analysis

Word count: 2904 words

ABSTRACT

Objectives This meta-analysis aimed to evaluate whether dapagliflozin is synergistic with other anti-diabetic drugs without body weight gain.

Setting RCT reports were retrieved from PubMed, Cochrane Library, Embase, ClinicalTrials.gov, Google Scholar and Google. Eligible RCTs were selected according to the criteria (including types of participants, intervention, outcomes) and assessed by the Cochrane risk of bias tool and GRADEpro software for evidential quality. Meta-analysis on the eligible RCTs was performed with the random effects model. The RCTs of low quality and interim stages were excluded for further sensitivity analysis. Meta-regression was conducted on the follow-up durations. Publication bias was evaluated with funnel plots and the Egger's regression test and adjusted using the trim-and-fill procedure. Heterogeneity was assessed with the I^2 statistics.

Participants Adult type 2 diabetes mellitus (T2DM) patients.

Interventions Dapagliflozin combined with conventional anti-diabetic drugs.

Primary and secondary outcome measures Glycaemic level (measured by HbA1c and FPG) and body weight.

Results Twelve RCTs were eligible for quantitative synthesis and meta-analysis. The overall effect size of HbA1c calculated from mean difference was -0.52% (Z= -13.56, P<0.001) with 95%CI [-0.60, -0.45]. The effect size of FPG was -1.13 mmol/L (Z= -11.12, P<0.001) with 95%CI [-1.33, -0.93]. The effect size of body weight was -2.10 kg (Z= -18.77, P<0.001) with 95%CI [-2.32, -1.88]. Exclusions of low quality and interim RCTs changed the overall mean differences respectively to -0.56%, -1.11 mmol/L, 2.23kg and -0.50%, -1.08 mmol/L, -2.08 kg. The sensitivity analysis indicated good robustness of the meta-analysis on HbA1c, FPG, and body weight.

Conclusions The meta-analysis showed that dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved the glycaemic control in T2DM participants without significant body weight gain.

PROSPERO registration number CRD42013005034

ARTICLE SUMMARY

Article focus

- To explore the efficacy of dapagliflozin as an add-on drug for anti-diabetic treatment.

Key messages

- Dapagliflozin as an add-on drug improves the control of HbA1c and FPG levels in type 2 diabetes mellitus (T2DM) participants without body weight gain.
- Dapagliflozin have significant effects on glycaemic control and body weight of T2DM participants.

Strengths and limitations of this study

- This study is the first meta-analysis to focus on both the efficacy and body weight gain issue of dapagliflozin versus placebo in synergy with anti-diabetic drugs (not only metformin).
- The protocol of this study was properly registered with the PROSPERO database and published.
- The conduct and reporting of this study is in accordance with the PRISMA statement to ensure high study quality.
- Subgroup meta-analysis, sensitivity analysis and publication bias analysis were performed to evaluate the robustness of the evidence.
- A meta-regression was conducted to determine dapagliflozin had long-term (>24 weeks) effects on controlling FPG and body weight of T2DM participants.
- There is a potential limitation of the study that all eligible RCTs were sponsored by Bristol-Myers Squibb or AstraZeneca.

INTRODUCTION

The efficacy of common anti-diabetic drugs (including metformin, sulfonylureas, nonsulfonylurea secretagogues, alpha glycosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 analog, and dipeptidyl peptidase-4 inhibitors) is insulin-dependent [1]. Their efficacy diminishes when the function of pancreatic islet β-cells declines during the progression of type 2 diabetes mellitus (T2DM) [2]. Sulphonylureas and thiazolidinediones cause body weight gain, which further worsens insulin resistance [3]. It came as no surprise that approximately two-thirds of the patients with diabetes in Europe [4] and the United States [5] under conventional treatment could not meet the goal of glycaemic control. By contrast, as a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT2), dapagliflozin is distinctive in its insulin-independent action on reducing reabsorption of glucose particularly by the proximal tubule in the kidney to eliminate more glucose from plasma into urine [6-8]. Dapagliflozin would enhance glycaemic control, as claimed in recent studies, without adverse effects on body weight, blood pressures and lipids like conventional anti-diabetic drugs, making dapagliflozin desirable to combine conventional anti-diabetic drugs with dapagliflozin in treating T2DM [9-10]. However, these claims were made by individual clinical studies, not well-established by the systematic reviews and meta-analysis. Three existing meta-analysis reports did not focus on dapagliflozin but addressed the efficacy issues of SGLT2 inhibitors in general [3, 11-12]. The meta-analysis [13] on dapagliflozin in particular still lacked analysis of publication bias, that is available publications do not fully represent the research that have been done, and sensitivity to various possible factors as required by the PRISMA guideline for meta-analysis reporting. Although a subgroup analysis on dapagliflozin monotherapy was available in the meta-analysis [13], it did not provide specific analysis of the efficacy of dapagliflozin combined with other anti-diabetic drugs. The latest meta-analysis used the Bayesian method to estimate the relative effect of dapagliflozin versus other anti-diabetes treatments (not placebo) added to metformin therapy [14]. All these five meta-analysis studies were not registered before conduct. The present meta-analysis aims to evaluate the synergistic efficacy of dapagliflozin versus placebo in combination with conventional anti-diabetic drugs for glycaemic control as measured by the changes of glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG). The body weight data were analyzed to test whether the claim that dapagliflozin does not affect body weight (that is, no weight gain).

METHODS

This study of systematic review and meta-analysis is in compliance with the guideline Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The

protocol of this study [15] was registered with the PROSPERO database and assigned an identifier CRD42013005034.

Data sources

Bibliographical databases for literature search included MEDLINE (via PubMed), Embase (via OVID), Cochrane Library, Google Scholar and ClinicalTrials.gov (http://www.clinicaltrials.gov). The initial search was performed on 9 July 2013 and was last updated on 21 October 2013. Our search strategy included keywords "dapagliflozin" and "diabetes". We searched all fields in PubMed, all text in Cochrane Library, but restricted to the fields of abstracts, titles, and keywords in Embase. When searching ClinicalTrials.gov, we used the term "dapagliflozin". Google search was conducted to find the RCT information unavailable from bibliographical databases. In addition, manual search of journals was conducted to track relevant RCTs that were not indexed by normal keywords.

Inclusion and exclusion criteria

The identified studies were selected according to the following inclusion and exclusion criteria:

Study design Only RCTs were included. Observational, cohort, case-control, case series, and laboratory studies were excluded.

Durations For observing changes in HbA1c levels, only the RCTs with follow-up durations longer than 8 weeks were included.

Participants Only the RCTs on adult T2DM patients (age≥18) were included.

Interventions This meta-analysis included only the RCTs on the efficacy of dapagliflozin combined with conventional anti-diabetic drugs. The RCTs on dapagliflozin monotherapy were excluded.

Comparators This meta-analysis included the RCTs employing placebo combined with conventional anti-diabetic drugs as the controls. The RCTs employing only placebo as the control group were excluded.

Outcomes This meta-analysis included the RCTs measuring HbA1c, FPG, and body weight as the outcomes. The RCTs without all these three outcomes were excluded.

Study selection and data extraction

The studies were evaluated by at least two reviewers according to the inclusion and exclusion criteria. Disagreement in evaluation was resolved by discussion among the reviewers.

Data from each included RCT were extracted by one reviewer and verified by another reviewer. In addition to the outcome measures, the following characteristics of the RCTs were extracted: (1) first author and publication year, (2) interventions (doses of dapagliflozin and the drugs used in combination), (3) characteristics of participants, (4) follow-up durations,

and (5) findings.

Quality assessment

We assessed the design, execution and reporting of the included RCTs according to the Cochrane risk of bias tool [16]. The quality of each RCT was assessed by one reviewer and verified by another reviewer. Disagreement was resolved by discussion. The evidential level of each outcome was determined in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [17] and conducted with GRADE profiler 3.2 (http://tech.cochrane.org/revman/gradepro).

Data synthesis and analysis

The meta-analysis of effect sizes was performed using both R 3.0.1 (http://www.r-project.org/) with the metaphor package (http://www.metafor-project.org/) and Review Manager 5.2 (http: http://ims.cochrane.org/revman/). Other statistical tests and regression analysis were conducted using R 3.0.1. P values<0.05 were considered statistically significant. Meta-analysis based on the random effects model was conducted for comparing the changes of HbA1c (%), FPG (mmol/L), and body weight (kg) between 10mg dapagliflozin arm and placebo arm. The continuous variables extracted from the included RCTs were adjusted mean differences (AMD) with 95% confidential interval (CI).The overall effect size was calculated as mean difference of AMD, thus the mean differences in results stood for AMD. Subgroup analysis was conducted according to drug combinations (selected from metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) and the durations of follow-up (≤24 weeks or not). The effects of different follow-up durations were also assessed by meta-regression. Publication bias was evaluated using the Egger's regression test and a funnel plot of the effect sizes against the standard errors (SE). Publication bias was adjusted using the trim-and-fill procedure [18]. Heterogeneity was assessed with the I^2 statistic [19], which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I^2<25% was considered as low in heterogeneity and I^2>75% was of high heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. The RCTs with high risk of bias were excluded for sensitivity analysis. The sensitivity analysis evaluated the differences between overall results and the results from the studies with low risk of bias. In addition, we excluded the interim results, that is, only using endpoint results of trials, to evaluate the robustness of the meta-analysis results.

RESULTS

Study selection

A total of 380 citations were assessed in the initial searching, of which 231 were identified via bibliographical databases and 149 were identified by supplementary search via the Google and Google Scholar (Figure 1). By screening the abstracts, we excluded 139 non-RCTs and seven pharmacokinetics and pharmacodynamics studies. Of the remaining 20 RCTs, eight RCTs did not meet the inclusion criteria on interventions and comparators. Finally, a total number of 12 RCTs were included for quantitative synthesis and meta-analysis.

Study characteristics

The characteristics of the included 12 RCTs [20-31] were summarized in Table 1. The RCTs contained interventions of 2.5 mg, 5 mg, and 10 mg add-on dapagliflozin. The eligible RCTs were also summarized according to their combined drugs: (1) 10 mg dapdgliflozin plus metformin *vs.* placebo plus metformin; (2) 10 mg dapdgliflozin plus insulin *vs.* placebo plus insulin; (3) 10 mg dapdgliflozin plus glimepiride *vs.* placebo plus glimepiride; (4) 10 mg dapdgliflozin plus pioglitazone *vs.* placebo plus pioglitazone; (5) 10 mg dapdgliflozin plus metformin/sitagliptin *vs.* placebo plus metformin/sitagliptin. The participants in all RCTs were T2DM patients (≥18 years old). The outcomes measuring the effects of dapagliflozin were HbA1c (%), FPG (mmol/L), and body weight (kg).

The data extracted from the included RCTs for meta-analysis were sample sizes and changes from baselines, such as adjusted mean differences (AMD) and standard deviations/standard errors (SD/SE). The mean differences were adjusted according to the last observation carried forward (LOCF) which was adopted in most RCTS. Hence the AMD extracted from the RCTs were subject to analysis of covariance (ANCOVA) model.

Risk of bias within studies

According to the Cochrane risk of bias tool, four RCTs had more than one items with unclear risk of bias [24, 26, 28, 31]. The common bias was the detection bias due to no report of blinding (Figure 2). The average quality of the RCTs was acceptable. The GRADE evaluation indicated that the outcomes of both HbA1c and FPG had high quality of the evidence. However, the quality of the evidence on body weight was moderate due to publication bias (Table 2).

Synthesis of results from individual studies

HbA1c

Twelve RCTs with 3986 participants were included in the meta-analysis on the effect of dapagliflozin on changing the participants' HbA1c levels. There were 1996 participants in the

intervention groups (10 mg dapagliflozin combined with five drugs) and 1990 participants in the control groups (placebo combined with corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot of HbA1c was presented in Figure 3.

The differences of AMD between the intervention groups and the control groups ranged from -0.8% to -0.29%. HbA1c levels decreased after supplement of dapagliflozin. The overall effect size in terms of mean difference was -0.52% (Z= -13.56, P<0.001) with 95% CI [-0.60, -0.45]. The heterogeneity among the RCTs was moderate with I^2=56 % (Q=29.54, P=0.0055) and 95%CI [19.9%, 75.8%]. The funnel plot analysis showed no publication bias (Figure 6) and the Egger's regression test was not significant in asymmetry (t= -1.90, P=0.08).

Subgroup meta-analyses were conducted by stratifying the five anti-diabetic drugs (metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) combined with dapagliflozin and the follow-up durations (≤24 weeks, >24 weeks). The effect sizes ranged from -0.69% to -0.47%. The metformin plus metformin subgroup had the smallest effect size with a mean difference of -0.47% (Z=-7.31, P<0.001). The two duration subgroups did not differ much, with a mean difference -0.53% (≤24 weeks) and -0.52% (>24 weeks) (Appendix 1). The meta-regression on the overall follow-up durations (12th, 24th, 48th, 50th, 102nd, 104th weeks) did not give any statistically significant results (Table 3).

FPG

All 12 included RCTs with 3620 participants reported the effect sizes of dapagliflozin on FPG. There were 1817 participants in the intervention groups (10 mg dapagliflozin combined with the five types of drugs) and 1803 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. As depicted in a forest plot of FPG (Figure 4), all the RCTs showed the decreases in FPG after the add-on of dapagliflozin. The overall mean difference between the intervention groups and the control groups was -1.13 mmol/L (Z=-11.12, P<0.001) with 95%CI [-1.33, -0.93]. The heterogeneity among these RCTs was moderate with I^2 = 53.8% (Q=23.81, P=0.0135). The funnel plot analysis also showed no publication bias (Figure 6) and the Egger's regression test was not significant in asymmetry (t=1.55, P=0.15).

Subgroup meta-analyses were conducted on five different combined drugs and follow-up durations. The effect sizes of the drug subgroups ranged from -1.47 mmol/L (pioglitazone group) to -0.93 mmol/L (metformin group). In the follow-up duration subgroups, the mean differences were -1.13 mmol/L (>24 weeks) and -1.36 mmol/L (≤ 24 weeks) (Appendix 2). The meta-regression showed a significant effect of the overall follow-up durations (12th, 24th, 48th, 50th, 102nd, 104th weeks) with R^2=0.9704 and P<0.001. The estimated coefficient on follow-up duration was -1.52 with SE 0.12 and 95%CI [-1.75, -1.29] (Table 3).

Body weight

Twelve RCTs with a total of 4008 participants reported the effect sizes of dapagliflozin on body weight changes. The RCTs included 2005 participants in the intervention groups (10mg dapagliflozin combined with the five types of drugs) and 2003 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot showed decreases in body weight after the intervention of dapagliflozin (Figure 5). The decreases ranged from -3.33 kg to -1.54 kg. The overall mean difference between the intervention groups and the control groups was -2.10 kg (Z=-18.77, P<0.001) with 95%CI [-2.32, -1.88]. The heterogeneity among RCTs was not significant with I^2 = 12% (Q=14.73, P=0.32). The funnel plot analysis revealed some publication bias (Figure 6) and the Egger's regression test was significant in asymmetry (t= -3.11, P=0.009).

The subgroup meta-analyses were conducted on five different combinations of drugs and two follow-up durations. The effect sizes of the drug subgroups ranged from -2.45 kg to -1.54 kg with insulin the most effective and glimepiride the least. The results of follow-up duration subgroups showed that the differences of effect sizes ranged from -2.63 kg (≤ 24 weeks) to -1.92 kg (> 24 weeks) (Appendix 3), which implied dapagliflozin has the efficacy of long-term clinical outcome. The result from meta-regression showed significant effect of the follow-up durations (12th, 24th, 48th, 102nd, 104th weeks) with R^2=1 and P<0.01. The estimated coefficient was -1.61 with SE 0.18 and 95%CI [-1.97, -1.26] (Table 3).

Risk of bias across studies

The funnel plots of HbA1c, FPG and body weight checked the possible of publication bias (Figure 6). The results from the Egger's regression found a significant publication bias in the outcome of body weight (t=-3.11, P=0.0091). After the trim-and-fill adjustment on the funnel plot, the estimated mean difference is -1.94 kg with 95%CI [-2.18,-1.70]. However, There was no significant publication bias in the result of HbA1c (t=-1.90, P=0.08) and FPG (t=1.55, P=0.152).

Sensitivity analysis

By the Cochrane risk of bias tool, we found that four RCTs had more than one items with unclear risk of bias [24, 26, 28, 31]. When we excluded those RCTs, the overall effect size of HbA1c changed to -0.50% with 95% CI [-0.61, -0.40]. The effect size of FPG became -1.08 mmol/L with 95% CI [-1.29, -0.87] and the result of body weight -2.08 kg with 95% CI [-2.36, -1.82] (Appendix 4). The new results did not differ much from the previous ones, that is -0.52% in HbA1c, -1.13 mmol/L in FPG and -2.10 kg in body weight (Figure 3-5).

In addition, we found that four RCTs published only interim results [20, 22, 25, 29]. Hence, we excluded the interim RCTs to re-examine the robustness of our meta-analysis. The

data from eight RCTs [21, 23, 24, 26-28, 30-31] with final results were kept for sensitivity analysis. The overall mean differences became to -0.56% in HbA1c, -1.11 mmol/L in FPG, and -2.23 kg in body weight, which did not change too much (Appendix 5).

DISCUSSION

This study of systematic review and meta-analysis on the efficacy of dapagliflozin in combination with anti-diabetic drugs followed the PRISMA guideline and was registered with the PROSPERO database before the conduct. Subgroup meta-analyses and sensitivity analyses were also conducted to ensure the robustness of the evidence.

In agreement with another meta-analysis on monotherapy of T2DM with dapagliflozin [13], one network meta-analysis on dapaliflozin in combination with metformin[14] and three other meta-analyses on SGLT2 inhibitors in general [3, 11-12], we found dapagliflozin beneficial in glycaemic control of T2DM. In contrast to these meta-analyses, we did a PRISMA-compliant meta-analysis, including additional sensitivity analyses and publication bias analyses, on the efficacy of dapagliflozin combined with another anti-diabetic drug.

This meta-analysis indicated that dapagliflozin as an add-on drug to conventional anti-diabetic drugs did improve the control of the HbA1c and FPG levels in T2DM participants. Individual RCTs indicated that insulin and pioglitazone increased body weight [26, 29, 30], which would be deemed harmful to T2DM participants. Our meta-analysis confirmed a consensus that the body weight of T2DM participants was well controlled under treatment of dapagliflozin in combination with other anti-diabetic drugs.

Even though the Egger's regression test showed publication bias in the outcome of body weight, dapagliflozin as an add-on drug still reduced body weight after a trim-and-fill procedure on the funnel plot. Although the publication bias on body weight was statistically significant, it might not indicate a strong clinical significance because body weight was not the primary outcome in the RCTs. Subgroup meta-analyses showed that dapagliflozin enhanced the effects of conventional anti-diabetic drugs on controlling the HbA1c, FPG, and body weight. A meta-regression further suggested that dapagliflozin had long-term effects on controlling FPG and body weight of T2DM participants.

There were limitations in this meta-analysis to be overcome in later studies. Four RCTs published only short follow-up periods [20, 22, 25, 29]. Considering the consistency in dosage, we used 10 mg dapagliflozin data only. The limited number of RCTs might overestimate the R^2 in meta-regression. In this meta-analysis, most RCTs [20, 22, 23, 24, 26, 27, 28, 29, 31] used LOCF methods to impute missing data. The combination of LOCF imputation with exclusion of post-rescue data could lead to overstated results [32] and cause low estimates of standard errors and P values [33]. All the included RCTs were sponsored by Bristol-Myers Squibb [20, 21, 24, 26, 28] or AstraZeneca [22, 23, 25, 27, 29-31] which might

introduce some potential bias, due to a concern that industry funding was strongly associated with favorable outcomes [34]. We will update our meta-analysis with further RCTs that have proper registration and less potential biases.

CONCLUSION

Dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved glycaemic control and reduced weight gain in T2DM, especially with inadequate glycaemic control by conventional drugs.

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Competing interests

None declared.

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Contributors

YNS conceived the study, developed the selection criteria, searched the literature, selected the studies, extracted the data, and wrote the manuscript. YZ assisted in the study design, managed the literature, selected the studies, extracted the data, performed data analysis, and wrote the manuscript. XC and WSC evaluated the Cochrane risk of bias for each study. SWL proposed the methods, decided the study design and wrote the manuscript. All authors read and approved the final manuscript.

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There are no additional data available.

Published protocol of the study

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REFERENCES

1 Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician 2009; **79(1)**:29-36.

2 Pretki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; **116(7)**:1802-1812.

3 Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012; **2(5)**:e001007.

4 Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications in type II diabetes in Europe. Diabetologia 2002; **45(7)**:S23-S28.

5 Saydah SH, Frafin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004; **291**:335-342.

6 Dapagliflozin. http://www.nyrdtc.org/GMMMG/Groups/Publications/GM_NDE/NDE_121_Dapagliflozin.pdf.

7 Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; **9(7)**:551-559.

8 Hu L, Zhou ZY. Research progress of sodium-glucose co-transporter-2 inhibitor drugs. Medical Recapitulate 2011; **12(24)**:3782-3785.

9 Tahrani AA, Barnett AH. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Ther 2010; **1(2)**:45-56.

10 Freeannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. Diabetes Care 2010; **33(10)**:2217-2224.

11 Musso G, Gambino R, Cassader M, et al. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012; **44(4)**:375-393.

12 Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; **159(4)**:262-274.

13 Zhang M, Zhang L, Wu B, et al. Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev Published Online First: 2 October 2013. doi: 10.1002/dmrr.2479

14 Goring S, Hawkins N, Wygant G, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. Diabetes Obes Metab Published Online First: 14 November 2013. doi: 10.1111/dom.12239

15 Sun YN, Zhou Y, Chen X, et al. The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes: protocol for meta-analysis of randomized controlled trials. Syst Rev 2013; **2(1)**:103. http://www.systematicreviewsjournal.com/content/2/1/103 (accessed 18 November 2013)

16 Higgins J, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of boas in randomized trials. BMJ 2011; **343**:d5928.

17 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; **336(7650)**:924-926.

18 Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; **56(2):**455-463.

19 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; **327:**557–560.

20 Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010; **375(9733)**:2223–2233.

21 Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind,

placebo-controlled 102-week trial. BMC Med 2013; **11**:43.

22 Bolinder J, Ljunggren Ö, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. J Clin Endocrinol Metab 2012; **97(3)**:1020–1031.

23 Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2013 Published Online First: 1 August 2013. doi: 10.1111/dom.12189

24 Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012; **66(5)**:446–456.

25 Ljunggren Ö, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2012; **14(11)**:990–999.

26 Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, a sodium- glucose cotransporter-2 Inhibitor, on hemoglobin A1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012; **35(7)**:1473-1478.

27 Strojek K, Yoon KH, Hruba V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011; **13(10)**:928–938.

28 Wilding JP, Norwood P, Tjoen C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009; **32(9)**: 1656-1662.

29 Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012; **156(6)**:405–415.

30 Wilding JP, Woo V, Soler NG, et al. Dapagliflozin in patients with type 2 diabetes

receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab Published Online First: 1 August 2013. doi: 10.1111/dom.12187

31 Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled studys. Diabetes Care Published Online First: 21 October 2013. doi: 10.2337/dc13-0467

32 U.S. Food and Drug Administration. FDA Briefing Document. NDA 202293. Dapagliflozin tablets, 5 and 10 mg. Rockville, MD: U.S. Food and Drug Administration, 2011.

33 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012; **367(14)**:1355-1360.

34 Khan SN, Mermer MJ, Myers E, et al. The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. Am J Orthop (Belle Mead NJ) 2008; **37(12)**:E205-E212.

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Abbreviations: PLA, placebo; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; GLI, glimepiride; INS, insulin; SIT, sitagliptin. FPG, fasting plasma glucose

Appendices

Appendix 4 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs with least risk of biases

Appendix 5 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs at the endpoint

Tables

Table 1 Basic characteristics of the included RCTs

Study	Treatments	N	Participants' characteristics†				Weeks (max)	Findings
			Age	HbA1c (%)	BMI or weight (kg/m^2 or kg*)	FPG (mmol/L or mg/dL**)		
Bailey 2010 [20]	PLA	137	53.7 (10.3)	8.11 (0.96)	31.8(5.3)	9.19 (2.57)	24	Dapagliflozin + metformin enhanced glycaemic control and lowered body weight.
	2.5 mg DAPA	137	55.0 (9.3)	7.99 (0.90)	31.6(4.8)	8.96 (2.39)		
	5 mg DAPA	137	54.3 (9.4)	8.17 (0.96)	31.4(5.0)	9.39 (2.72)		
	10 mg DAPA	135	52.7 (9.9)	7.92 (0.82)	31.2(5.1)	8.66 (2.15)		
Bailey 2013 [21]	PLA+MET	137	NA	8.12 (0.96)	87.74(19.24) *	9.19 (2.58)	102	Dapagliflozin + metformin for 102 weeks enhanced glycaemic control and lowered body weight.
	2.5 mg DAPA + MET	137	NA	7.99 (0.90)	84.90(17.77) *	8.96 (2.39)		
	5 mg DAPA + MET	137	NA	8.17 (0.96)	84.73(16.26) *	9.39 (2.72)		
	10 mg DAPA + MET	135	NA	7.92 (0.82)	86.28(17.53) *	8.66 (2.15)		
Bolinder, 2012 [22]	PLA + MET	91	60.8 (6.9)	8.11 (0.96)	31.7(3.9)	8.3 (1.4)	24	Dapagliflozin + metformin reduced total body weight.
	10 mg DAPA + MET	89	60.6 (8.2)	7.99 (0.90)	32.1(3.9)	8.2 (1.4)		
Bolinder, 2013 [23]	PLA + MET	91	NA	7.16	90.9*	8.21	102	Dapagliflozin + metformin enhanced glycaemic control and reduced body weight.
	10 mg DAPA + MET	91	NA	7.19	92.1*	8.3		

Henry	Study1						24	Dapagliflozin + metformin was effective in
2012 [24]	5 mg DAPA + PLA	203	52.3 (10.2)	9.1 (1.4)	86.2 (21.1)*	10.59 (3.14)		reducing HbA1c, FPG and weight.
	MET +PLA	201	51.8 (9.8)	9.2 (1.3)	85.6 (20.0)*	10.94 (3.53)		
	5 mg DAPA + MET	194	51.7 (9.3)	9.2 (1.3)	84.1 (19.5)*	10.76 (3.12)		
	Study 2							
	10 mg DAPA + PLA	219	51.1 (11. 5)	9.1 (1.3)	88.5 (19.3)*	10.99 (3.43)		
	MET+PLA	208	52.7 (10.4)	9.1 (1.3)	87.2 (19.4)*	10.57 (3.00)		
	10 mg DAPA + MET	211	51.0 (10.1)	9.1 (1.3)	88.4 (19.7)*	10.52 (3.22)		
Ljunggren	PLA + MET	91	60.8 (6.9)	7.16 (0.53)	31.7(3.9)	8.3 (1.4)	50	Dapagliflozin + metformin did not affect
2012 [25]	10 mg DAPA + MET	89	60.6 (8.2)	7.19 (0.44)	32.1(3.9)	8.2 (1.4)		markers of bone formation and resorption.
Roenstock	≥30 mg PIO + PLA	139	53.5 (11.4)	8.34 (1.00)	NA	8.92 (2.61)	48	Dapagliflozin + pioglitazone further enhanced
2012 [26]	≥30 mg PIO + 5 mgDAPA	141	53.2 (10.9)	8.40 (1.03)	NA	9.36 (2.98)		glycaemic control without pioglitazone-related
	≥30 mg PIO +10 mgDAPA	140	53.8 (10.4)	8.37 (0.96)	NA	9.15 (2.57)		body weight gain.
Strojek	PLA + GLI	145	60.3(10.16)	8.15 (0.74)	NA	9.58 (2.07)	24	Dapagliflozin + glimepiride significantly
2010 [27]	2.5 mg DAPA + GLI	154	59.9 (10.14)	8.11 (0.75)	NA	9.56 (2.13)		enhanced glycaemic control and reduced body
	5 mg DAPA + GLI	142	60.2 (9.73)	8.12 (0.78)	NA	9.68 (2.12)		weight.
	10 mg DAPA + GLI	151	58.9 (8.32)	8.07 (0.79)	NA	9.55 (2.04)		
Wilding,	PLA+INS	23	58.4 (6.5)	8.4 (0.9)	34.8 (4.6)	165.9 (51.5) **	12	Dapagliflozin + insulin improved glycaemic
2009 [28]	10 mg DAPA + INS	24	55.7 (9.2)	8.4 (0.7)	35.5 (3.6)	156.0 (39.0) **		control and lowered body weight.
	20 mg DAPA + INS	24	56.1 (10.6)	8.5 (0.9)	36.2 (4.6)	161.6 (55.0) **		

Wilding, 2012 [29]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	48	Dapagliflozin + insulin enhanced glycaemic control, stabilized insulin dosing and lowered body weight.
	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		
	5 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)		
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)		
Wilding, 2013 [30]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	104	Dapagliflozin + insulin enhanced glycaemic control, stabilized insulin dosing and lowered body weight, but elevated rates of genital infection and of UTI
	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		
	5/10 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)		
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)		
[§]**Jabbour 2013 [31]**	PLA+ MET/SIT	224	55.0 (10.20)	7.97 (0.79)	89.23 (20.89)*	162.97 (34.45) **	24	
	10 mg DAPA + MET/SIT	223	54.8 (10.42)	7.90 (0.81)	91.02 (21.64)*	162.19 (36.83) **		

Abbreviations: PLA, placebo; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; GLI, glimepiride; INS, insulin; SIT, sitagliptin. FPG, fasting plasma glucose.

† measured by mean (SD)

*meansured by weight (kg); ** meansured by mg/dL

[§]The data was extracted from ClinicalTrial.gov due to unavailability of final report.

Table 2 GRADE assessment of the outcomes (HbA1c, FPG, and body weight)

10 mg dapagliflozin arm compared to PLA arm for GRADE				
Patient or population: patients with type 2 diabetes mellitus **Intervention:** 10 mg dapagliflozin combined with anti-diabetic drugs **Comparison:** placebo combined with anti-diabetic drugs				
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Placebo combined with anti-diabetic drugs**	Corresponding risk **10 mg dapagliflozin combined with anti-diabetic drugs**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
HbA1c (%) Follow-up: 12 to 104 weeks	The mean HbA1c ranged across control groups from **-1.44 to 0.09 %**	The mean HbA1c in the intervention groups was **0.52 lower** (0.6 to 0.45 lower)	3986 (14 studies)	⊕⊕⊕⊕ **high**
FPG (mmol/L) Follow-up: 12 to 104 weeks	The mean FPG ranged across control groups from **-1.93 to 0.99 mmol/L**	The mean FPG in the intervention groups was **1.13 lower** (1.33 to 0.93 lower)	3620 (12 studies)	⊕⊕⊕⊕ **high**
Body weight (kg) Follow-up: 12 to 104 weeks	The mean body weight ranged across control groups from **-2.12 to 2.99 kg**	The mean body weight in the intervention groups was **2.10 lower** (2.32 to 1.88 lower)	4008 (14 studies)	⊕⊕⊕⊖ **moderate**
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;				
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

Table 3 Meta-regression results of the long-term outcomes (HbA1c, FPG, body weight)

	HbA1c		FPG		Body weight	
	Estimate (SE)	**95% CI**	**Estimate (SE)**	**95% CI**	**Estimate (SE)**	**95% CI**
Intercept	-0.55 (0.07)*	[-0.68, -0.41]	-1.52 (0.12)*	[-1.75, -1.29]	-1.61 (0.18)*	[-1.97, -1.26]
Week	0.001 (0.001)	[-0.002, 0.003]	-0.01 (0.002)*	[0.004, 0.012]	-0.01 (0.004)*	[-0.02, 0.01]

* $P < 0.001$

Research article

The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomized controlled trials

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ABSTRACT

Objectives This meta-analysis aimed to evaluate whether dapagliflozin is synergistic with other anti-diabetic drugs without body weight gain.

Setting RCT reports were retrieved from PubMed, Cochrane Library, Embase, ClinicalTrials.gov, Google Scholar and Google. Eligible RCTs were selected according to the criteria (including types of participants, intervention, outcomes) and assessed by the Cochrane risk of bias tool and GRADEpro software for evidential quality. Meta-analysis on the eligible RCTs was performed with the random effects model. The RCTs of low quality and interim stages were excluded for further sensitivity analysis. Meta-regression was conducted on the follow-up durations. Publication bias was evaluated with funnel plots and the Egger's regression test and adjusted using the trim-and-fill procedure. Heterogeneity was assessed with the I^2 statistics.

Participants Adult type 2 diabetes mellitus (T2DM) patients.

Interventions Dapagliflozin combined with conventional anti-diabetic drugs.

Primary and secondary outcome measures Glycaemic level (measured by HbA1c and FPG) and body weight.

Results Twelve RCTs were eligible for quantitative synthesis and meta-analysis. The overall effect size of HbA1c calculated from mean difference was -0.52% (Z= -13.56, P<0.001) with 95%CI [-0.60, -0.45]. The effect size of FPG was -1.13 mmol/L (Z= -11.12, P<0.001) with 95%CI [-1.33, -0.93]. The effect size of body weight was -2.10 kg (Z= -18.77, P<0.001) with 95%CI [-2.32, -1.88]. Exclusions of low quality and interim RCTs changed the overall mean differences respectively to -0.56%, -1.11 mmol/L, 2.23kg and -0.50%, -1.08 mmol/L, -2.08 kg. The sensitivity analysis indicated good robustness of the meta-analysis on HbA1c, FPG, and body weight.

Conclusions The meta-analysis showed that dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved the glycaemic control in T2DM participants without significant body weight gain.

PROSPERO registration number CRD42013005034

ARTICLE SUMMARY

Article focus

- To explore the efficacy of dapagliflozin as an add-on drug for anti-diabetic treatment.

Key messages

- Dapagliflozin as an add-on drug improves the control of HbA1c and FPG levels in type 2 diabetes mellitus (T2DM) participants without body weight gain.
- Dapagliflozin have significant effects on glycaemic control and body weight of T2DM participants.

Strengths and limitations of this study

- This study is the first meta-analysis to focus on both the efficacy and body weight gain issue of dapagliflozin versus placebo in synergy with anti-diabetic drugs (not only metformin).
- The protocol of this study was properly registered with the PROSPERO database and published.
- The conduct and reporting of this study is in accordance with the PRISMA statement to ensure high study quality.
- Subgroup meta-analysis, sensitivity analysis and publication bias analysis were performed to evaluate the robustness of the evidence.
- A meta-regression was conducted to determine dapagliflozin had long-term (>24 weeks) effects on controlling FPG and body weight of T2DM participants.
- There is a potential limitation of the study that all eligible RCTs were sponsored by Bristol-Myers Squibb or AstraZeneca.

INTRODUCTION

The efficacy of common anti-diabetic drugs (including metformin, sulfonylureas, nonsulfonylurea secretagogues, alpha glycosidase inhibitors, thiazolidinediones, glucagon-like peptide-1 analog, and dipeptidyl peptidase-4 inhibitors) is insulin-dependent [1]. Their efficacy diminishes when the function of pancreatic islet β-cells declines during the progression of type 2 diabetes mellitus (T2DM) [2]. Sulphonylureas and thiazolidinediones cause body weight gain, which further worsens insulin resistance [3]. It came as no surprise that approximately two-thirds of the patients with diabetes in Europe [4] and the United States [5] under conventional treatment could not meet the goal of glycaemic control. By contrast, as a highly selective inhibitor of sodium glucose co-transporter 2 (SGLT2), dapagliflozin is distinctive in its insulin-independent action on reducing reabsorption of glucose particularly by the proximal tubule in the kidney to eliminate more glucose from plasma into urine [6-8]. Dapagliflozin would enhance glycaemic control, as claimed in recent studies, without adverse

effects on body weight, blood pressures and lipids like conventional anti-diabetic drugs, making dapagliflozin desirable to combine conventional anti-diabetic drugs with dapagliflozin in treating T2DM [9-10]. However, these claims were made by individual clinical studies, not well-established by the systematic reviews and meta-analysis. Three existing meta-analysis reports did not focus on dapagliflozin but addressed the efficacy issues of SGLT2 inhibitors in general [3, 11-12]. The meta-analysis [13] on dapagliflozin in particular still lacked analysis of publication bias, that is available publications do not fully represent the research that have been done, and sensitivity to various possible factors as required by the PRISMA guideline for meta-analysis reporting. Although a subgroup analysis on dapagliflozin monotherapy was available in the meta-analysis [13], it did not provide specific analysis of the efficacy of dapagliflozin combined with other anti-diabetic drugs. The latest meta-analysis used the Bayesian method to estimate the relative effect of dapagliflozin versus other anti-diabetes treatments (not placebo) added to metformin therapy [14]. All these five meta-analysis studies were not registered before conduct. The present meta-analysis aims to evaluate the synergistic efficacy of dapagliflozin versus placebo in combination with conventional anti-diabetic drugs for glycaemic control as measured by the changes of glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG). The body weight data were analyzed to test whether the claim that dapagliflozin does not affect body weight (that is, no weight gain).

METHODS

This study of systematic review and meta-analysis is in compliance with the guideline Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The protocol of this study [15] was registered with the PROSPERO database and assigned an identifier CRD42013005034.

Data sources

Bibliographical databases for literature search included MEDLINE (via PubMed), Embase (via OVID), Cochrane Library, Google Scholar and ClinicalTrials.gov (http://www.clinicaltrials.gov). The initial search was performed on 9 July 2013 and was last updated on 21 October 2013. Our search strategy included keywords “dapagliflozin” and “diabetes”. We searched all fields in PubMed, all text in Cochrane Library, but restricted to the fields of abstracts, titles, and keywords in Embase. When searching ClinicalTrials.gov, we used the term “dapagliflozin”. Google search was conducted to find the RCT information unavailable from bibliographical databases. In addition, manual search of journals was conducted to track relevant RCTs that were not indexed by normal keywords.

Inclusion and exclusion criteria

The identified studies were selected according to the following inclusion and exclusion criteria:

Study design Only RCTs were included. Observational, cohort, case-control, case series, and laboratory studies were excluded.

Durations For observing changes in HbA1c levels, only the RCTs with follow-up durations longer than 8 weeks were included.

Participants Only the RCTs on adult T2DM patients (age≥18) were included.

Interventions This meta-analysis included only the RCTs on the efficacy of dapagliflozin combined with conventional anti-diabetic drugs. The RCTs on dapagliflozin monotherapy were excluded.

Comparators This meta-analysis included the RCTs employing placebo combined with conventional anti-diabetic drugs as the controls. The RCTs employing only placebo as the control group were excluded.

Outcomes This meta-analysis included the RCTs measuring HbA1c, FPG, and body weight as the outcomes. The RCTs without all these three outcomes were excluded.

Study selection and data extraction

The studies were evaluated by at least two reviewers according to the inclusion and exclusion criteria. Disagreement in evaluation was resolved by discussion among the reviewers.

Data from each included RCT were extracted by one reviewer and verified by another reviewer. In addition to the outcome measures, the following characteristics of the RCTs were extracted: (1) first author and publication year, (2) interventions (doses of dapagliflozin and the drugs used in combination), (3) characteristics of participants, (4) follow-up durations, and (5) findings.

Quality assessment

We assessed the design, execution and reporting of the included RCTs according to the Cochrane risk of bias tool [16]. The quality of each RCT was assessed by one reviewer and verified by another reviewer. Disagreement was resolved by discussion. The evidential level of each outcome was determined in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [17] and conducted with GRADE profiler 3.2 (http://tech.cochrane.org/revman/gradepro).

Data synthesis and analysis

The meta-analysis of effect sizes was performed using both R 3.0.1 (http://www.r-project.org/) with the metaphor package (http://www.metafor-project.org/) and Review Manager 5.2 (http:

http://ims.cochrane.org/revman/). Other statistical tests and regression analysis were conducted using R 3.0.1. P values<0.05 were considered statistically significant. Meta-analysis based on the random effects model was conducted for comparing the changes of HbA1c (%), FPG (mmol/L), and body weight (kg) between 10mg dapagliflozin arm and placebo arm. The continuous variables extracted from the included RCTs were adjusted mean differences (AMD) with 95% confidential interval (CI).The overall effect size was calculated as mean difference of AMD, thus the mean differences in results stood for AMD. Subgroup analysis was conducted according to drug combinations (selected from metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) and the durations of follow-up (≤24 weeks or not). The effects of different follow-up durations were also assessed by meta-regression. Publication bias was evaluated using the Egger's regression test and a funnel plot of the effect sizes against the standard errors (SE). Publication bias was adjusted using the trim-and-fill procedure [18]. Heterogeneity was assessed with the I^2 statistic [19], which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I^2<25% was considered as low in heterogeneity and I^2>75% was of high heterogeneity.

Sensitivity analysis

Sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. The RCTs with high risk of bias were excluded for sensitivity analysis. The sensitivity analysis evaluated the differences between overall results and the results from the studies with low risk of bias. In addition, we excluded the interim results, that is, only using endpoint results of trials, to evaluate the robustness of the meta-analysis results.

RESULTS

Study selection

A total of 380 citations were assessed in the initial searching, of which 231 were identified via bibliographical databases and 149 were identified by supplementary search via the Google and Google Scholar (Figure 1). By screening the abstracts, we excluded 139 non-RCTs and seven pharmacokinetics and pharmacodynamics studies. Of the remaining 20 RCTs, eight RCTs did not meet the inclusion criteria on interventions and comparators. Finally, a total number of 12 RCTs were included for quantitative synthesis and meta-analysis.

Study characteristics

The characteristics of the included 12 RCTs [20-31] were summarized in Table 1. The RCTs contained interventions of 2.5 mg, 5 mg, and 10 mg add-on dapagliflozin. The eligible RCTs

were also summarized according to their combined drugs: (1) 10 mg dapdgliflozin plus metformin *vs.* placebo plus metformin; (2) 10 mg dapdgliflozin plus insulin *vs.* placebo plus insulin; (3) 10 mg dapdgliflozin plus glimepiride *vs.* placebo plus glimepiride; (4) 10 mg dapdgliflozin plus pioglitazone *vs.* placebo plus pioglitazone; (5) 10 mg dapdgliflozin plus metformin/sitagliptin *vs.* placebo plus metformin/sitagliptin. The participants in all RCTs were T2DM patients (≥18 years old). The outcomes measuring the effects of dapagliflozin were HbA1c (%), FPG (mmol/L), and body weight (kg).

The data extracted from the included RCTs for meta-analysis were sample sizes and changes from baselines, such as adjusted mean differences (AMD) and standard deviations/standard errors (SD/SE). The mean differences were adjusted according to the last observation carried forward (LOCF) which was adopted in most RCTS. Hence the AMD extracted from the RCTs were subject to analysis of covariance (ANCOVA) model.

Risk of bias within studies

According to the Cochrane risk of bias tool, four RCTs had more than one items with unclear risk of bias [24, 26, 28, 31]. The common bias was the detection bias due to no report of blinding (Figure 2). The average quality of the RCTs was acceptable. The GRADE evaluation indicated that the outcomes of both HbA1c and FPG had high quality of the evidence. However, the quality of the evidence on body weight was moderate due to publication bias (Table 2).

Synthesis of results from individual studies

HbA1c

Twelve RCTs with 3986 participants were included in the meta-analysis on the effect of dapagliflozin on changing the participants' HbA1c levels. There were 1996 participants in the intervention groups (10 mg dapagliflozin combined with five drugs) and 1990 participants in the control groups (placebo combined with corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot of HbA1c was presented in Figure 3.

The differences of AMD between the intervention groups and the control groups ranged from -0.8% to -0.29%. HbA1c levels decreased after supplement of dapagliflozin. The overall effect size in terms of mean difference was -0.52% (Z= -13.56, P<0.001) with 95% CI [-0.60, -0.45]. The heterogeneity among the RCTs was moderate with I^2=56 % (Q=29.54, P=0.0055) and 95%CI [19.9%, 75.8%]. The funnel plot analysis showed no publication bias (Figure 6) and the Egger's regression test was not significant in asymmetry (t= -1.90, P=0.08).

Subgroup meta-analyses were conducted by stratifying the five anti-diabetic drugs (metformin, insulin, glimepiride, pioglitazone, and metformin/sitagliptin) combined with dapagliflozin and the follow-up durations (≤24 weeks, >24 weeks). The effect sizes ranged

from -0.69% to -0.47%. The metformin plus metformin subgroup had the smallest effect size with a mean difference of -0.47% (Z=-7.31, P<0.001). The two duration subgroups did not differ much, with a mean difference -0.53% (≤24 weeks) and -0.52% (>24 weeks) (Appendix 1). The meta-regression on the overall follow-up durations (12th, 24th, 48th, 50th, 102nd, 104th weeks) did not give any statistically significant results (Table 3).

FPG

All 12 included RCTs with 3620 participants reported the effect sizes of dapagliflozin on FPG. There were 1817 participants in the intervention groups (10 mg dapagliflozin combined with the five types of drugs) and 1803 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. As depicted in a forest plot of FPG (Figure 4), all the RCTs showed the decreases in FPG after the add-on of dapagliflozin. The overall mean difference between the intervention groups and the control groups was -1.13 mmol/L (Z=-11.12, P<0.001) with 95%CI [-1.33, -0.93]. The heterogeneity among these RCTs was moderate with I^2 = 53.8% (Q=23.81, P=0.0135). The funnel plot analysis also showed no publication bias (Figure 6) and the Egger's regression test was not significant in asymmetry (t=1.55, P=0.15).

Subgroup meta-analyses were conducted on five different combined drugs and follow-up durations. The effect sizes of the drug subgroups ranged from -1.47 mmol/L (pioglitazone group) to -0.93 mmol/L (metformin group). In the follow-up duration subgroups, the mean differences were -1.13 mmol/L (>24 weeks) and -1.36 mmol/L (≤ 24 weeks) (Appendix 2). The meta-regression showed a significant effect of the overall follow-up durations (12th, 24th, 48th, 50th, 102nd, 104th weeks) with R^2=0.9704 and P<0.001. The estimated coefficient on follow-up duration was -1.52 with SE 0.12 and 95%CI [-1.75, -1.29] (Table 3).

Body weight

Twelve RCTs with a total of 4008 participants reported the effect sizes of dapagliflozin on body weight changes. The RCTs included 2005 participants in the intervention groups (10mg dapagliflozin combined with the five types of drugs) and 2003 participants in the control groups (placebo combined with the corresponding drugs). The follow-up durations ranged from 12 to 104 weeks. A forest plot showed decreases in body weight after the intervention of dapagliflozin (Figure 5). The decreases ranged from -3.33 kg to -1.54 kg. The overall mean difference between the intervention groups and the control groups was -2.10 kg (Z=-18.77, P<0.001) with 95%CI [-2.32, -1.88]. The heterogeneity among RCTs was not significant with I^2 = 12% (Q=14.73, P=0.32). The funnel plot analysis revealed some publication bias (Figure 6) and the Egger's regression test was significant in asymmetry (t= -3.11, P=0.009).

The subgroup meta-analyses were conducted on five different combinations of drugs and

two follow-up durations. The effect sizes of the drug subgroups ranged from -2.45 kg to -1.54 kg with insulin the most effective and glimepiride the least. The results of follow-up duration subgroups showed that the differences of effect sizes ranged from -2.63 kg (≤ 24 weeks) to -1.92 kg (> 24 weeks) (Appendix 3), which implied dapagliflozin has the efficacy of long-term clinical outcome. The result from meta-regression showed significant effect of the follow-up durations (12th, 24th, 48th, 102nd, 104th weeks) with R^2=1 and P<0.01. The estimated coefficient was -1.61 with SE 0.18 and 95%CI [-1.97, -1.26] (Table 3).

Risk of bias across studies

The funnel plots of HbA1c, FPG and body weight checked the possible of publication bias (Figure 6). The results from the Egger's regression found a significant publication bias in the outcome of body weight (t=-3.11, P=0.0091). After the trim-and-fill adjustment on the funnel plot, the estimated mean difference is -1.94 kg with 95%CI [-2.18,-1.70]. However, There was no significant publication bias in the result of HbA1c (t=-1.90, P=0.08) and FPG (t=1.55, P=0.152).

Sensitivity analysis

By the Cochrane risk of bias tool, we found that four RCTs had more than one items with unclear risk of bias [24, 26, 28, 31]. When we excluded those RCTs, the overall effect size of HbA1c changed to -0.50% with 95% CI [-0.61, -0.40]. The effect size of FPG became -1.08 mmol/L with 95% CI [-1.29, -0.87] and the result of body weight -2.08 kg with 95% CI [-2.36, -1.82] (Appendix 4). The new results did not differ much from the previous ones, that is -0.52% in HbA1c, -1.13 mmol/L in FPG and -2.10 kg in body weight (Figure 3-5).

In addition, we found that four RCTs published only interim results [20, 22, 25, 29]. Hence, we excluded the interim RCTs to re-examine the robustness of our meta-analysis. The data from eight RCTs [21, 23, 24, 26-28, 30-31] with final results were kept for sensitivity analysis. The overall mean differences became to -0.56% in HbA1c, -1.11 mmol/L in FPG, and -2.23 kg in body weight, which did not change too much (Appendix 5).

DISCUSSION

This study of systematic review and meta-analysis on the efficacy of dapagliflozin in combination with anti-diabetic drugs followed the PRISMA guideline and was registered with the PROSPERO database before the conduct. Subgroup meta-analyses and sensitivity analyses were also conducted to ensure the robustness of the evidence.

In agreement with another meta-analysis on monotherapy of T2DM with dapagliflozin [13], one network meta-analysis on dapaliflozin in combination with metformin[14] and three other meta-analyses on SGLT2 inhibitors in general [3, 11-12], we found dapagliflozin

beneficial in glycaemic control of T2DM. In contrast to these meta-analyses, we did a PRISMA-compliant meta-analysis, including additional sensitivity analyses and publication bias analyses, on the efficacy of dapagliflozin combined with another anti-diabetic drug.

This meta-analysis indicated that dapagliflozin as an add-on drug to conventional anti-diabetic drugs did improve the control of the HbA1c and FPG levels in T2DM participants. Individual RCTs indicated that insulin and pioglitazone increased body weight [26, 29, 30], which would be deemed harmful to T2DM participants. Our meta-analysis confirmed a consensus that the body weight of T2DM participants was well controlled under treatment of dapagliflozin in combination with other anti-diabetic drugs.

Even though the Egger's regression test showed publication bias in the outcome of body weight, dapagliflozin as an add-on drug still reduced body weight after a trim-and-fill procedure on the funnel plot. Although the publication bias on body weight was statistically significant, it might not indicate a strong clinical significance because body weight was not the primary outcome in the RCTs. Subgroup meta-analyses showed that dapagliflozin enhanced the effects of conventional anti-diabetic drugs on controlling the HbA1c, FPG, and body weight. A meta-regression further suggested that dapagliflozin had long-term effects on controlling FPG and body weight of T2DM participants.

There were limitations in this meta-analysis to be overcome in later studies. Four RCTs published only short follow-up periods [20, 22, 25, 29]. Considering the consistency in dosage, we used 10 mg dapagliflozin data only. The limited number of RCTs might overestimate the R^2 in meta-regression. In this meta-analysis, most RCTs [20, 22, 23, 24, 26, 27, 28, 29, 31] used LOCF methods to impute missing data. The combination of LOCF imputation with exclusion of post-rescue data could lead to overstated results [32] and cause low estimates of standard errors and P values [33]. All the included RCTs were sponsored by Bristol-Myers Squibb [20, 21, 24, 26, 28] or AstraZeneca [22, 23, 25, 27, 29-31] which might introduce some potential bias, due to a concern that industry funding was strongly associated with favorable outcomes [34]. We will update our meta-analysis with further RCTs that have proper registration and less potential biases.

CONCLUSION

Dapagliflozin as an add-on drug to conventional anti-diabetic drugs improved glycaemic control and reduced weight gain in T2DM, especially with inadequate glycaemic control by conventional drugs.

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Competing interests

None declared.

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Contributors

YNS conceived the study, developed the selection criteria, searched the literature, selected the studies, extracted the data, and wrote the manuscript. YZ assisted in the study design, managed the literature, selected the studies, extracted the data, performed data analysis, and wrote the manuscript. XC and WSC evaluated the Cochrane risk of bias for each study. SWL proposed the methods, decided the study design and wrote the manuscript. All authors read and approved the final manuscript.

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Data sharing statement

There are no additional data available.

Published protocol of the study

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REFERENCES

1 Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician 2009; **79(1)**:29-36.

2 Pretki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. J Clin Invest 2006; **116(7)**:1802-1812.

3 Clar C, Gill JA, Court R, et al. Systematic review of SGLT2 receptor inhibitors in dual or triple therapy in type 2 diabetes. BMJ Open 2012; **2(5)**:e001007.

4 Liebl A, Mata M, Eschwege E. Evaluation of risk factors for development of complications

in type II diabetes in Europe. Diabetologia 2002; **45(7)**:S23-S28.

5 Saydah SH, Frafin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004; **291**:335-342.

6 Dapagliflozin. http://www.nyrdtc.org/GMMMG/Groups/Publications/GM_NDE/NDE_121_Dapagliflozin.pdf.

7 Chao EC, Henry RR. SGLT2 inhibition--a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; **9(7)**:551-559.

8 Hu L, Zhou ZY. Research progress of sodium-glucose co-transporter-2 inhibitor drugs. Medical Recapitulate 2011; **12(24)**:3782-3785.

9 Tahrani AA, Barnett AH. Dapagliflozin: a sodium glucose cotransporter 2 inhibitor in development for type 2 diabetes. Diabetes Ther 2010; **1(2)**:45-56.

10 Freeannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycaemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. Diabetes Care 2010; **33(10)**:2217-2224.

11 Musso G, Gambino R, Cassader M, et al. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. Ann Med 2012; **44(4)**:375-393.

12 Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013; **159(4)**:262-274.

13 Zhang M, Zhang L, Wu B, et al. Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev Published Online First: 2 October 2013. doi: 10.1002/dmrr.2479

14 Goring S, Hawkins N, Wygant G, et al. Dapagliflozin compared with other oral anti-diabetes treatments when added to metformin monotherapy: a systematic review and network meta-analysis. Diabetes Obes Metab Published Online First: 14 November 2013. doi:

10.1111/dom.12239

15 Sun YN, Zhou Y, Chen X, et al. The efficacy of dapagliflozin combined with hypoglycemic drugs in treating type 2 diabetes: protocol for meta-analysis of randomized controlled trials. Syst Rev 2013; **2(1)**:103. http://www.systematicreviewsjournal.com/content/2/1/103 (accessed 18 November 2013)

16 Higgins J, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of boas in randomized trials. BMJ 2011; **343**:d5928.

17 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; **336(7650)**:924-926.

18 Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; **56(2):**455-463.

19 Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003; **327:**557–560.

20 Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010; **375(9733)**:2223–2233.

21 Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med 2013; **11**:43.

22 Bolinder J, Ljunggren Ö, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycaemic control on metformin. J Clin Endocrinol Metab 2012; **97(3)**:1020–1031.

23 Bolinder J, Ljunggren Ö, Johansson L, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab 2013 Published Online First: 1 August 2013. doi: 10.1111/dom.12189

24 Henry RR, Murray AV, Marmolejo MH, et al. Dapagliflozin, metformin XR, or both:

initial pharmacotherapy for type 2 diabetes, a randomised controlled trial. Int J Clin Pract 2012; **66(5)**:446–456.

25 Ljunggren Ö, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2012; **14(11)**:990–999.

26 Rosenstock J, Vico M, Wei L, et al. Effects of dapagliflozin, a sodium- glucose cotransporter-2 Inhibitor, on hemoglobin A1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012; **35(7)**:1473-1478.

27 Strojek K, Yoon KH, Hruba V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011; **13(10)**:928–938.

28 Wilding JP, Norwood P, Tjoen C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care 2009; **32(9)**: 1656-1662.

29 Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med 2012; **156(6)**:405–415.

30 Wilding JP, Woo V, Soler NG, et al. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Diabetes Obes Metab Published Online First: 1 August 2013. doi: 10.1111/dom.12187

31 Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled studys. Diabetes Care Published Online First: 21 October 2013. doi: 10.2337/dc13-0467

32 U.S. Food and Drug Administration. FDA Briefing Document. NDA 202293. Dapagliflozin tablets, 5 and 10 mg. Rockville, MD: U.S. Food and Drug Administration, 2011.

33 Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012; **367(14)**:1355-1360.

34 Khan SN, Mermer MJ, Myers E, et al. The roles of funding source, clinical trial outcome, and quality of reporting in orthopedic surgery literature. Am J Orthop (Belle Mead NJ) 2008; **37(12)**:E205-E212.

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Abbreviations: PLA, placebo; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; GLI, glimepiride; INS, insulin; SIT, sitagliptin. FPG, fasting plasma glucose

Appendices

Tables

Table 1 Basic characteristics of the included RCTs

Study	Treatments	N	Participants' characteristics†				Weeks (max)	Findings
			Age	HbA1c (%)	BMI or weight (kg/m^2 or kg*)	FPG (mmol/L or mg/dL**)		
Bailey 2010 [20]	PLA	137	53.7 (10.3)	8.11 (0.96)	31.8(5.3)	9.19 (2.57)	24	Dapagliflozin + metformin enhanced glycaemic control and lowered body weight.
	2.5 mg DAPA	137	55.0 (9.3)	7.99 (0.90)	31.6(4.8)	8.96 (2.39)		
	5 mg DAPA	137	54.3 (9.4)	8.17 (0.96)	31.4(5.0)	9.39 (2.72)		
	10 mg DAPA	135	52.7 (9.9)	7.92 (0.82)	31.2(5.1)	8.66 (2.15)		
Bailey 2013 [21]	PLA+MET	137	NA	8.12 (0.96)	87.74(19.24) *	9.19 (2.58)	102	Dapagliflozin + metformin for 102 weeks enhanced glycaemic control and lowered body weight.
	2.5 mg DAPA + MET	137	NA	7.99 (0.90)	84.90(17.77) *	8.96 (2.39)		
	5 mg DAPA + MET	137	NA	8.17 (0.96)	84.73(16.26) *	9.39 (2.72)		
	10 mg DAPA + MET	135	NA	7.92 (0.82)	86.28(17.53) *	8.66 (2.15)		
Bolinder, 2012 [22]	PLA + MET	91	60.8 (6.9)	8.11 (0.96)	31.7(3.9)	8.3 (1.4)	24	Dapagliflozin + metformin reduced total body weight.
	10 mg DAPA + MET	89	60.6 (8.2)	7.99 (0.90)	32.1(3.9)	8.2 (1.4)		
Bolinder, 2013 [23]	PLA + MET	91	NA	7.16	90.9*	8.21	102	Dapagliflozin + metformin enhanced glycaemic control and reduced body weight.
	10 mg DAPA + MET	91	NA	7.19	92.1*	8.3		

Henry	Study1						24	Dapagliflozin + metformin was effective in
2012 [24]	5 mg DAPA + PLA	203	52.3 (10.2)	9.1 (1.4)	86.2 (21.1)*	10.59 (3.14)		reducing HbA1c, FPG and weight.
	MET +PLA	201	51.8 (9.8)	9.2 (1.3)	85.6 (20.0)*	10.94 (3.53)		
	5 mg DAPA + MET	194	51.7 (9.3)	9.2 (1.3)	84.1 (19.5)*	10.76 (3.12)		
	Study 2							
	10 mg DAPA + PLA	219	51.1 (11. 5)	9.1 (1.3)	88.5 (19.3)*	10.99 (3.43)		
	MET+PLA	208	52.7 (10.4)	9.1 (1.3)	87.2 (19.4)*	10.57 (3.00)		
	10 mg DAPA + MET	211	51.0 (10.1)	9.1 (1.3)	88.4 (19.7)*	10.52 (3.22)		
Ljunggren	PLA + MET	91	60.8 (6.9)	7.16 (0.53)	31.7(3.9)	8.3 (1.4)	50	Dapagliflozin + metformin did not affect
2012 [25]	10 mg DAPA + MET	89	60.6 (8.2)	7.19 (0.44)	32.1(3.9)	8.2 (1.4)		markers of bone formation and resorption.
Roenstock	≥30 mg PIO + PLA	139	53.5 (11.4)	8.34 (1.00)	NA	8.92 (2.61)	48	Dapagliflozin + pioglitazone further enhanced
2012 [26]	≥30 mg PIO + 5 mgDAPA	141	53.2 (10.9)	8.40 (1.03)	NA	9.36 (2.98)		glycaemic control without pioglitazone-related
	≥30 mg PIO +10 mgDAPA	140	53.8 (10.4)	8.37 (0.96)	NA	9.15 (2.57)		body weight gain.
Strojek	PLA + GLI	145	60.3(10.16)	8.15 (0.74)	NA	9.58 (2.07)	24	Dapagliflozin + glimepiride significantly
2010 [27]	2.5 mg DAPA + GLI	154	59.9 (10.14)	8.11 (0.75)	NA	9.56 (2.13)		enhanced glycaemic control and reduced body
	5 mg DAPA + GLI	142	60.2 (9.73)	8.12 (0.78)	NA	9.68 (2.12)		weight.
	10 mg DAPA + GLI	151	58.9 (8.32)	8.07 (0.79)	NA	9.55 (2.04)		
Wilding,	PLA+INS	23	58.4 (6.5)	8.4 (0.9)	34.8 (4.6)	165.9 (51.5) **	12	Dapagliflozin + insulin improved glycaemic
2009 [28]	10 mg DAPA + INS	24	55.7 (9.2)	8.4 (0.7)	35.5 (3.6)	156.0 (39.0) **		control and lowered body weight.
	20 mg DAPA + INS	24	56.1 (10.6)	8.5 (0.9)	36.2 (4.6)	161.6 (55.0) **		

Wilding, 2012 [29]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	48	Dapagliflozin + insulin enhanced glycaemic control, stabilized insulin dosing and lowered body weight.
	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		
	5 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)		
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)		
Wilding, 2013 [30]	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	104	Dapagliflozin + insulin enhanced glycaemic control, stabilized insulin dosing and lowered body weight, but elevated rates of genital infection and of UTI
	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		
	5/10 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)		
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)		
[§]**Jabbour 2013 [31]**	PLA+ MET/SIT	224	55.0 (10.20)	7.97 (0.79)	89.23 (20.89)*	162.97 (34.45) **	24	
	10 mg DAPA + MET/SIT	223	54.8 (10.42)	7.90 (0.81)	91.02 (21.64)*	162.19 (36.83) **		

Abbreviations: PLA, placebo; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; GLI, glimepiride; INS, insulin; SIT, sitagliptin. FPG, fasting plasma glucose.

† measured by mean (SD)

*meansured by weight (kg); ** meansured by mg/dL

[§]The data was extracted from ClinicalTrial.gov due to unavailability of final report.

Table 2 GRADE assessment of the outcomes (HbA1c, FPG, and body weight)

10 mg dapagliflozin arm compared to PLA arm for GRADE				
Patient or population: patients with type 2 diabetes mellitus **Intervention:** 10 mg dapagliflozin combined with anti-diabetic drugs **Comparison:** placebo combined with anti-diabetic drugs				
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Placebo combined with anti-diabetic drugs**	 Corresponding risk **10 mg dapagliflozin combined with anti-diabetic drugs**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
HbA1c (%) Follow-up: 12 to 104 weeks	The mean HbA1c ranged across control groups from **-1.44 to 0.09 %**	The mean HbA1c in the intervention groups was **0.52 lower** (0.6 to 0.45 lower)	3986 (14 studies)	⊕⊕⊕⊕ **high**
FPG (mmol/L) Follow-up: 12 to 104 weeks	The mean FPG ranged across control groups from **-1.93 to 0.99 mmol/L**	The mean FPG in the intervention groups was **1.13 lower** (1.33 to 0.93 lower)	3620 (12 studies)	⊕⊕⊕⊕ **high**
Body weight (kg) Follow-up: 12 to 104 weeks	The mean body weight ranged across control groups from **-2.12 to 2.99 kg**	The mean body weight in the intervention groups was **2.10 lower** (2.32 to 1.88 lower)	4008 (14 studies)	⊕⊕⊕⊖ **moderate**
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval;				
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				

Table 3 Meta-regression results of the long-term outcomes (HbA1c, FPG, body weight)

	HbA1c		FPG		Body weight	
	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI
Intercept	-0.55 (0.07)*	[-0.68, -0.41]	-1.52 (0.12)*	[-1.75, -1.29]	-1.61 (0.18)*	[-1.97, -1.26]
Week	0.001 (0.001)	[-0.002, 0.003]	-0.01 (0.002)*	[0.004, 0.012]	-0.01 (0.004)*	[-0.02, 0.01]

* $P < 0.001$

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	5-6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6,
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7,17-19
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7,20
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9,21,
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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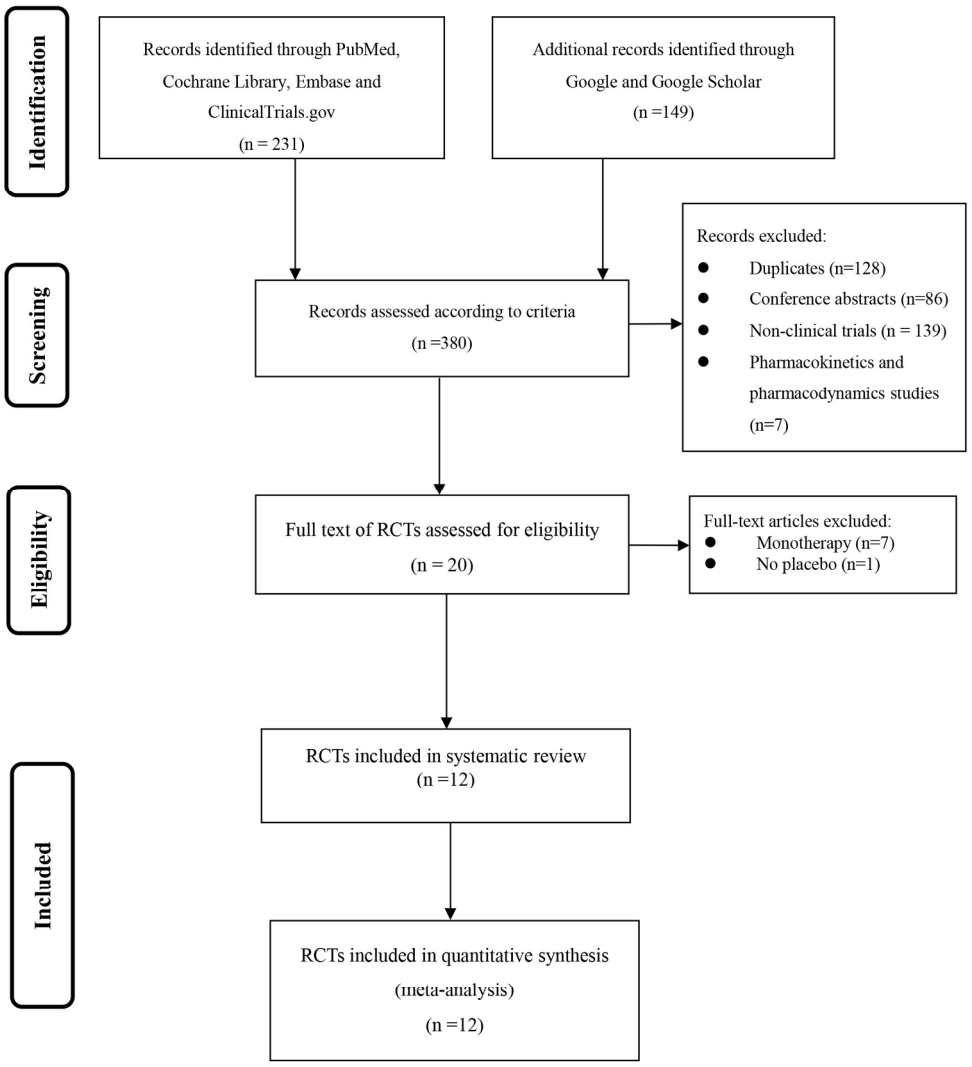

Flow diagram of study selection
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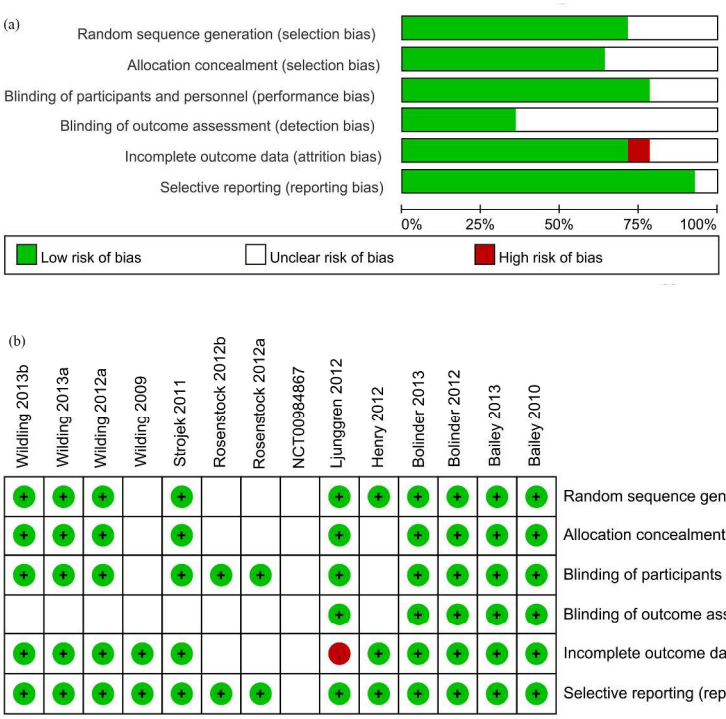

Cochrane risk of bias: (a) graph and (b) summary
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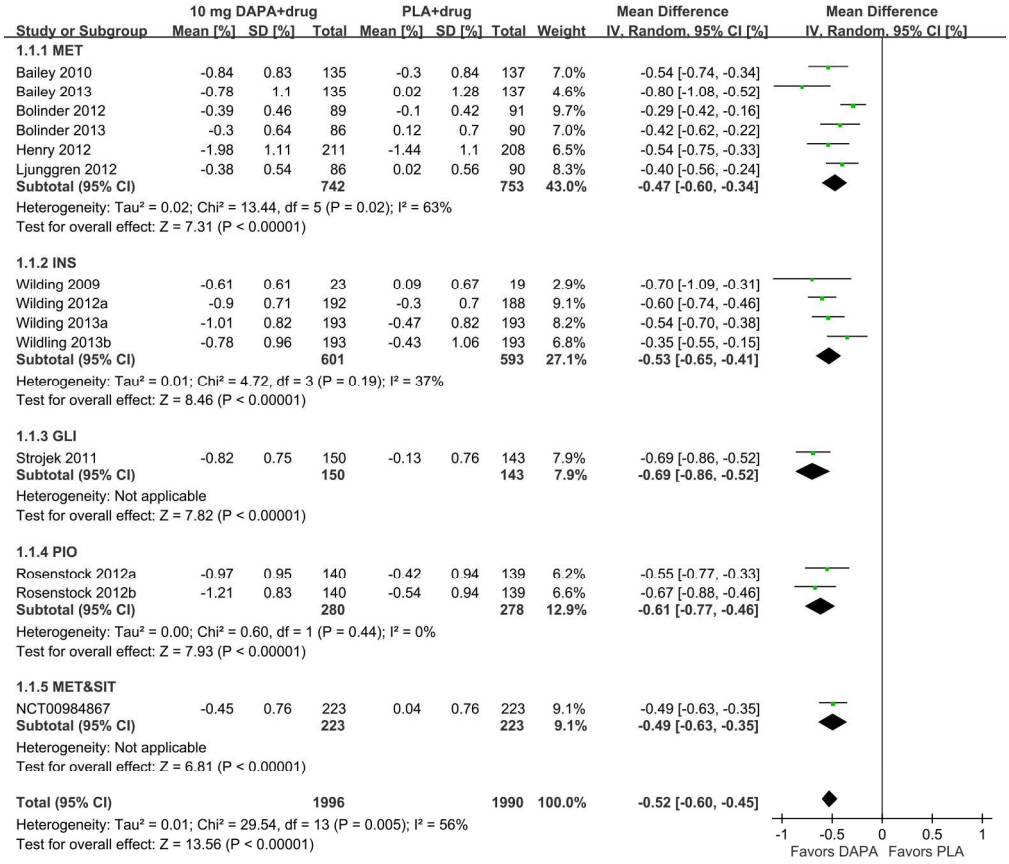

Forest plots of overall effect size of HbA1c and subgroup meta-analysis of different combined drugs
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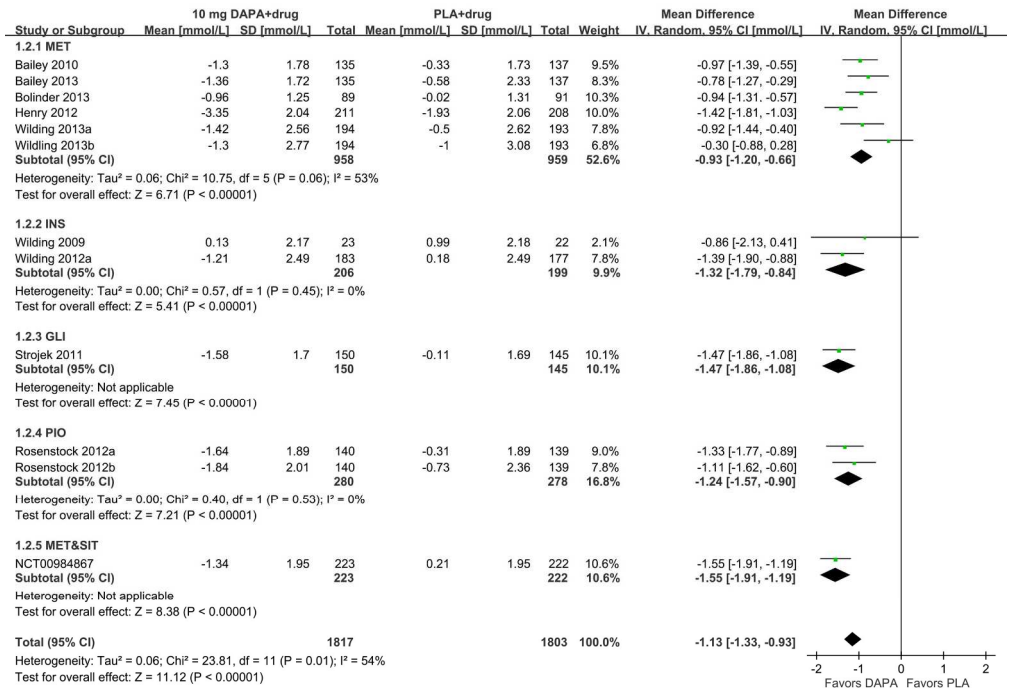

Forest plots of overall effect size of FPG and subgroup meta-analysis of different combined drugs
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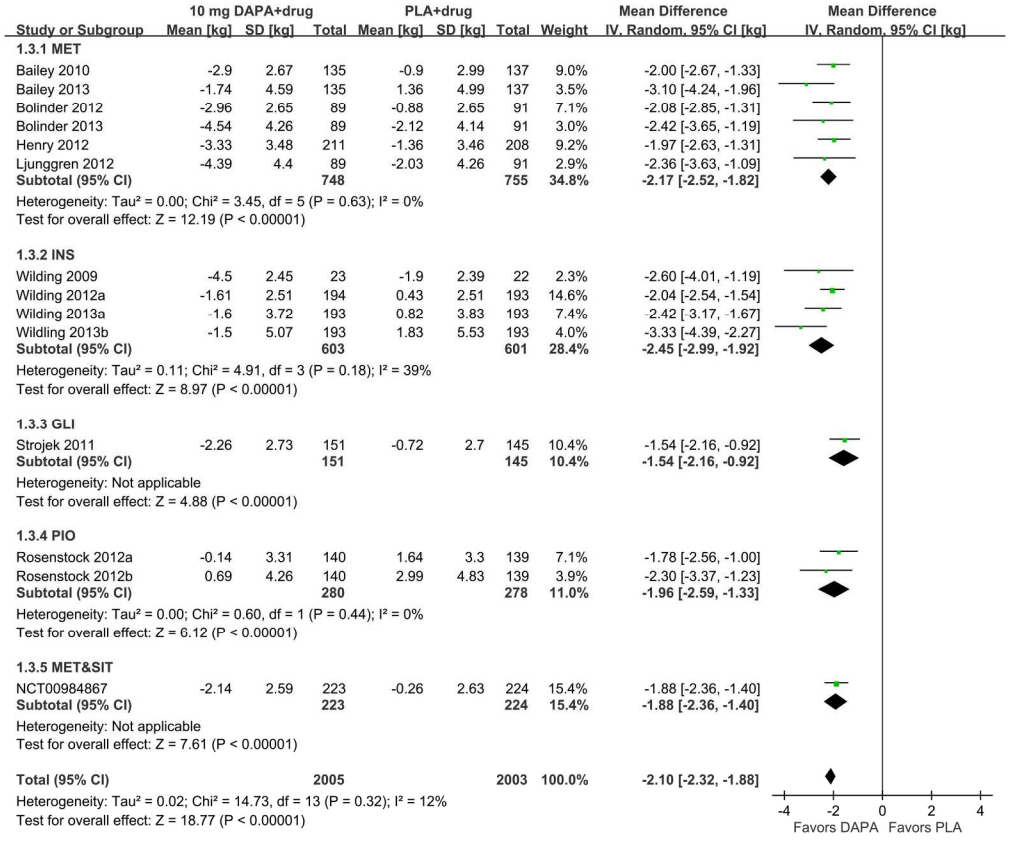

Forest plots of overall effect size of body weight and subgroup meta-analysis of different combined drugs
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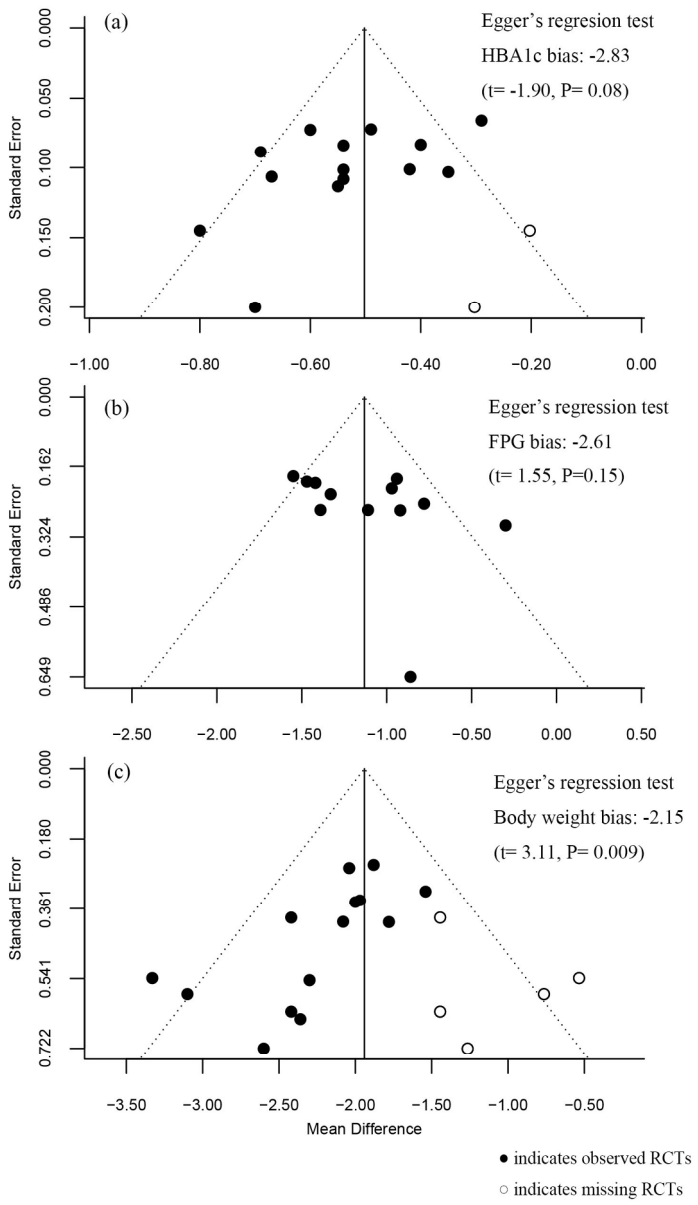
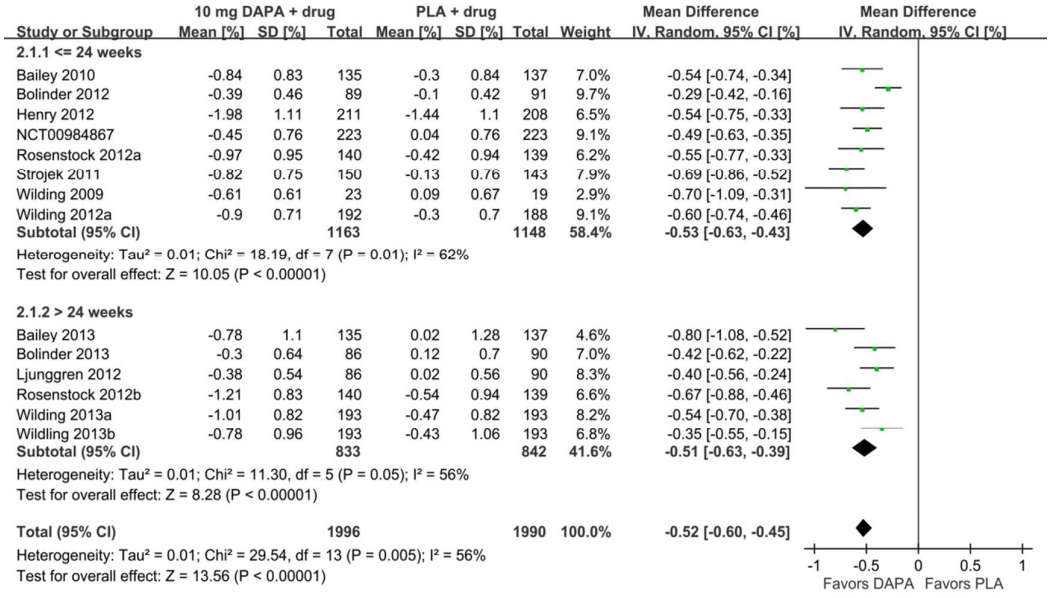


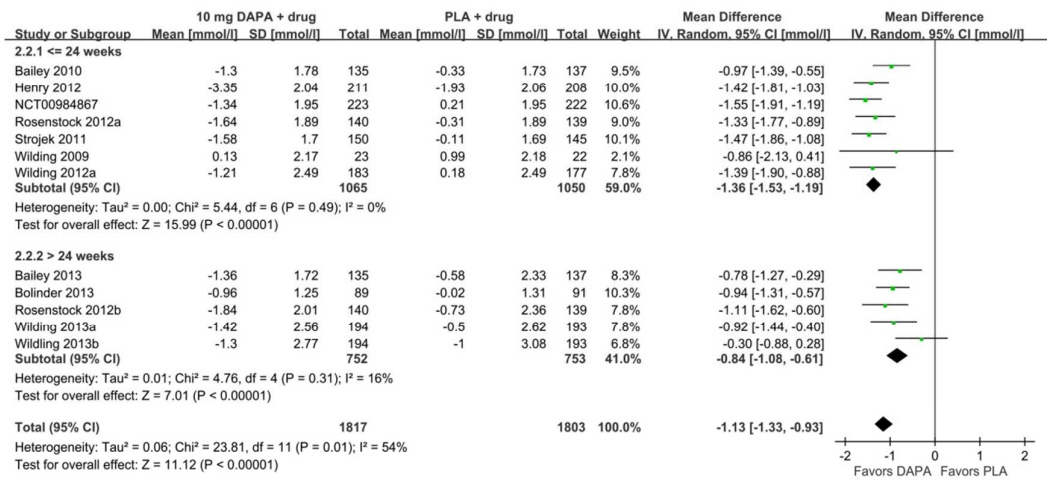
Funnel plots after trim-and-fill adjustment and the Egger's regression test results on (a) HbA1c, (b) FPG, and (c) body weight
124x214mm (300 x 300 DPI)

Appendices

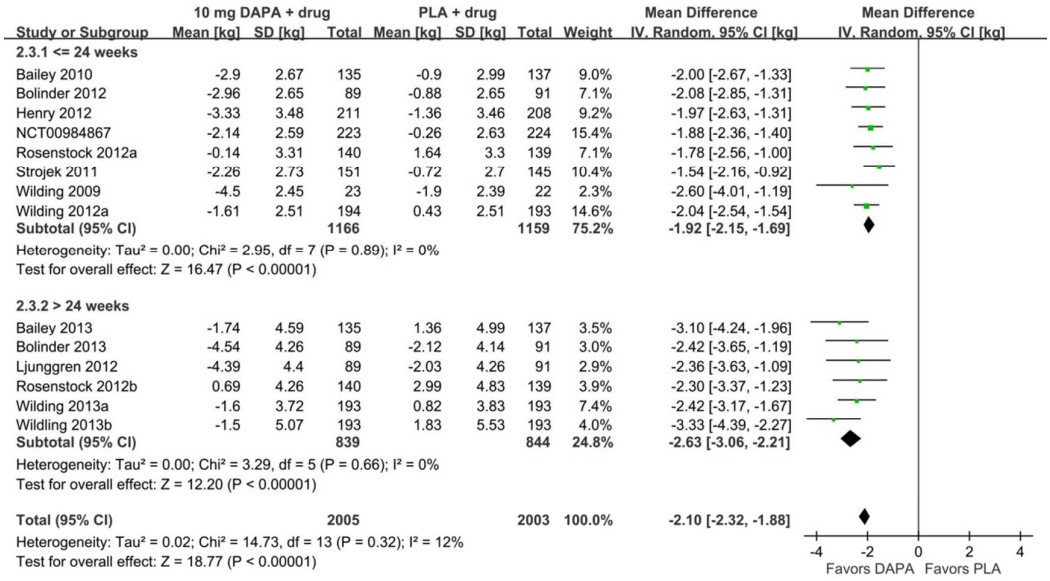
Appendix 1 Forest plots of overall effect size of HbA1c and subgroup meta-analysis of different follow-up durations



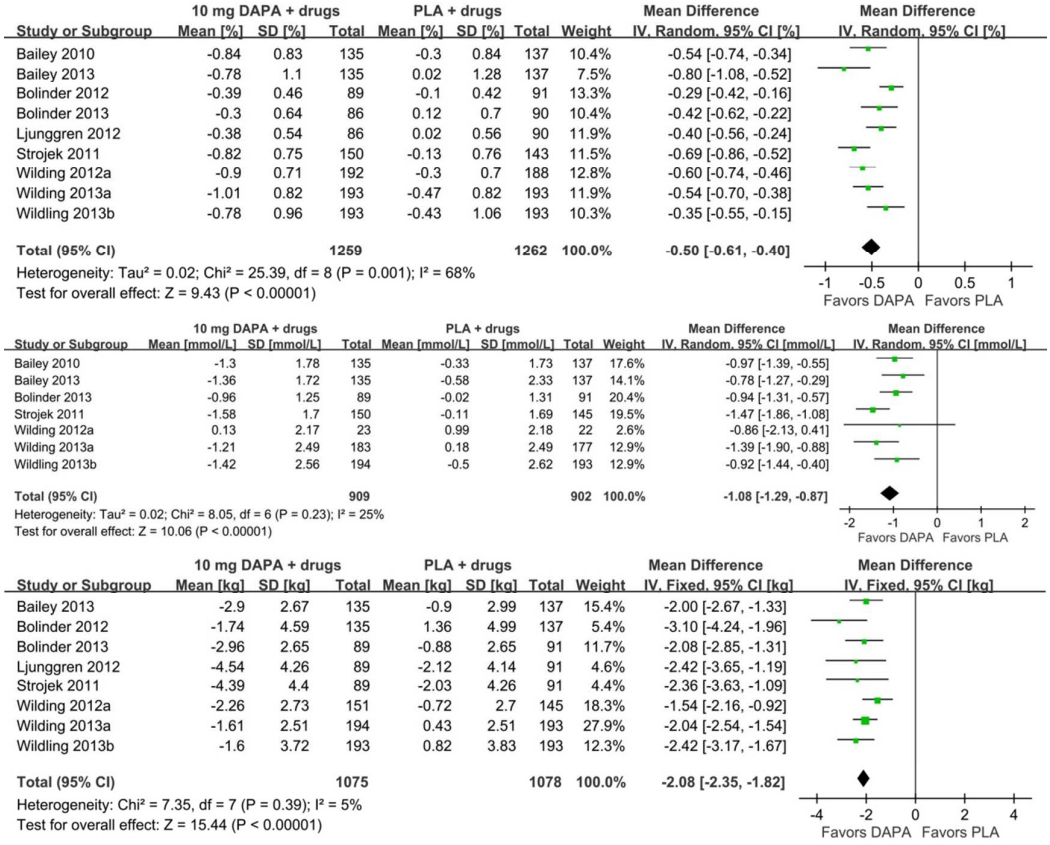
Appendix 2 Forest plots of overall effect size of FPG and subgroup meta-analysis of different follow-up durations



Appendix 3 Forest plots of overall effect size of body weight and subgroup meta-analysis of different follow-up durations



Appendix 4 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs with least risk of biases



Appendix 5 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs at the endpoint