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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 I² 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 OVID), Cochrane Google Scholar and ClinicalTrials.gov (via Library, (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 (\leq 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 I² statistic, which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I²<25% was considered as low in heterogeneity and I²>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, t=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 (\leq 24 weeks). The meta-regression showed a significant time-dependent effect on the follow-up durations with R²=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 (\leq 24 weeks) to -1.92kg (\geq 24weeks), which implied the efficacy was time-dependent. The result from meta-regression showed significant time-dependence on the follow-up durations with R²=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

Not commissioned; external peer reviewed.

Data sharing statement

There are no additional data available.

Published protocol of the study

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

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Tables

Table 1 Baseline characteristics of the included RCT

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

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	7/2					_	
	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,	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
2012 [26]	2.5mgDAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)		glycaemic control, stabilized insulin dosing
	5mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)	_'	and lowered weight.
	10mgDAPA + INS	194	59.3(8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)	-	
Wilding,	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
2013 [27]	2.5mgDAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0(5.0)	10.0(3.3)	-	glycaemic control, stabilized insulin dosing
	5/10mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0(5.3)	10.3(3.3)	-	and lowered weight, but elevated rates of
	10mgDAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4(5.1)	9.6(3.0)	-	genital infection and of UTI
§Jabbour	PLA+ MET/SIT	224	55.0 (10.20)	7.97 (0.79)	89.23 (20.89)*	162.97 (34.45) **	24	
2013 [28]	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. , pioglitazone; GLI, BLI

[†] 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)	No of Participants	Quality of the evidence	
Outcomes	Assumed risk	Corresponding risk	(studies)	(GRADE)
	Placebo combined with anti-diabetic drugs	10mg dapagliflozin combined with anti-diabetic drugs		
HbA1c (%)	The mean hba1c ranged across control groups from	The mean hba1c in the intervention groups was	3986	$\oplus \oplus \oplus \oplus$
Follow-up: 12 to 104 weeks	-1.44 to 0.09 %	0.52 lower (0.6 to 0.45 lower)	(14 studies)	high
FPG (mmol/L)	The mean fpg ranged across control groups from	The mean fpg in the intervention groups was	3620	$\oplus \oplus \oplus \oplus$
Follow-up: 12 to 104 weeks	-1.93 to 0.99 mmol/L	1.13 lower (1.33 to 0.93 lower)	(12 studies)	high
Body weight (kg)	The mean body weight ranged across control groups from	The mean body weight in the intervention groups was	4008	$\oplus \oplus \ominus \ominus$
Follow-up: 12 to 104 weeks	-2.12 to 2.99 kg	2.10 lower (2.32 to 1.88 lower)	(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)

	HbA	A1c	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



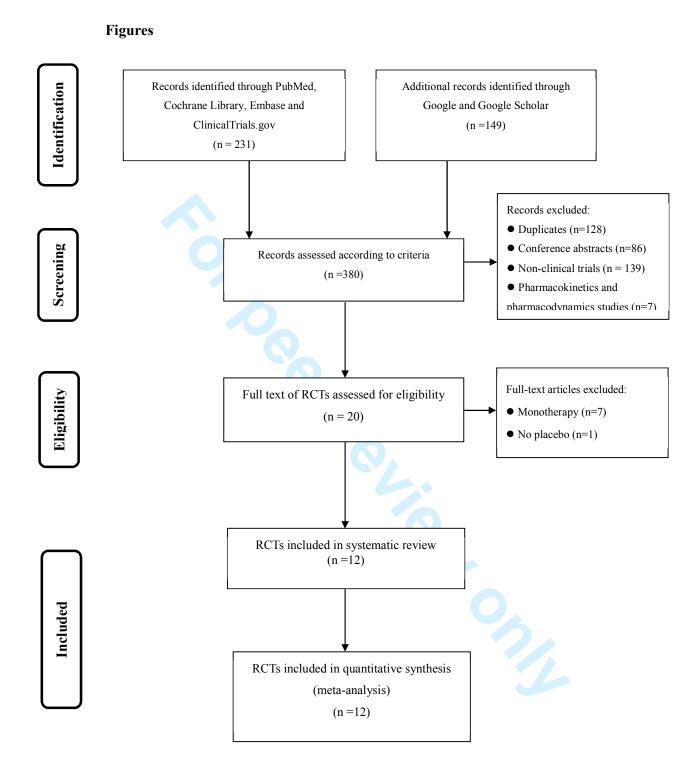


Figure 1 Flow diagram of study selection

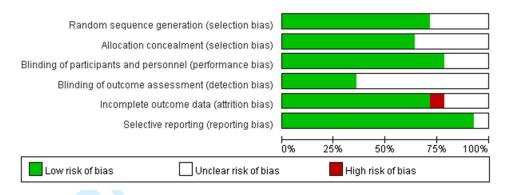


Figure 2a Cochrane risk of bias graph

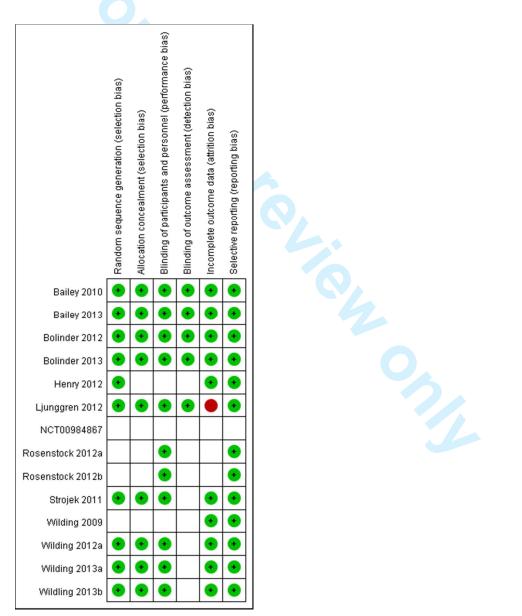


Figure 2b Cochrane risk of bias summary

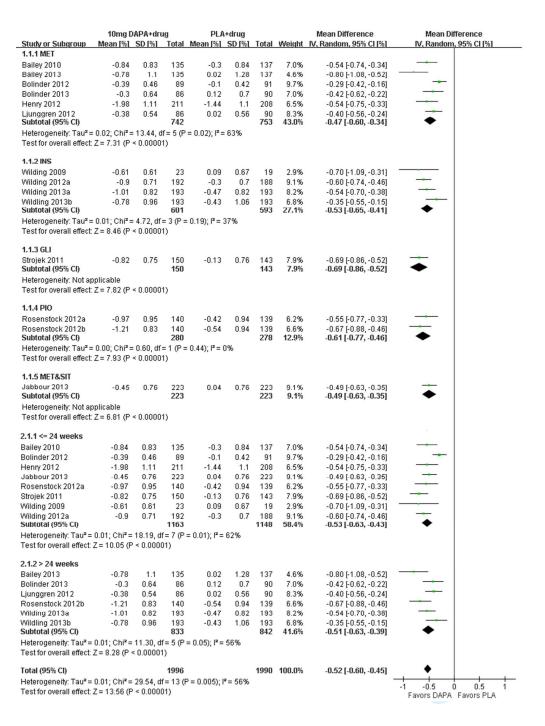


Figure 3a Forest plots of total effect size of HbA1c (%) and subgroup meta-analysis according to combined drugs and follow-up durations

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

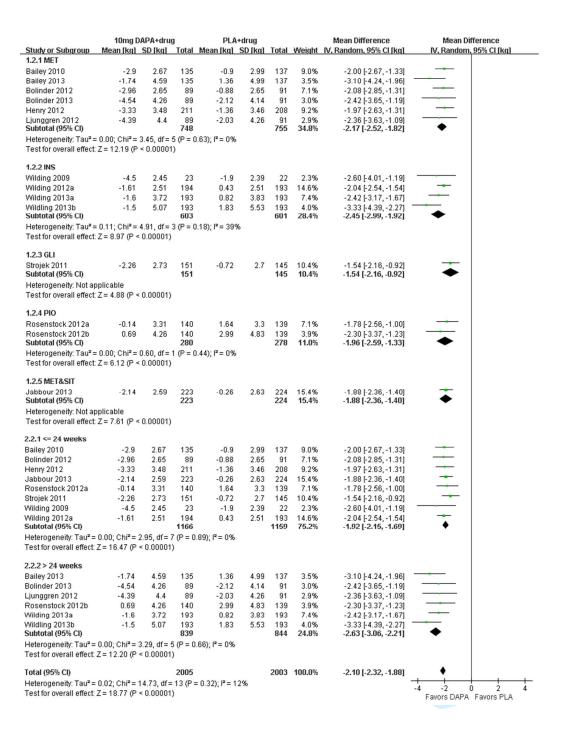


Figure 3c Forest plots of total effect size on body weight (kg) and subgroup meta-analysis according to combined drugs and follow-up durations

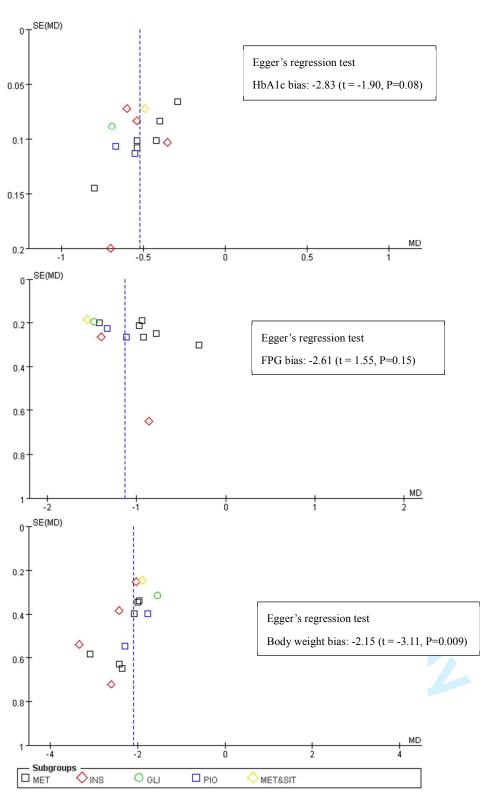
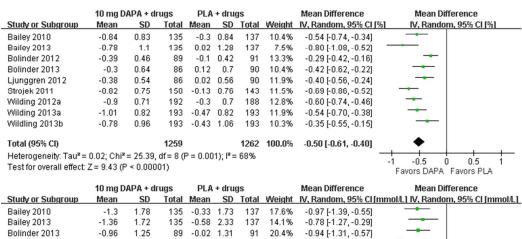


Figure 4 Funnel plots and the Egger's regression test results on HbA1c, FPG, and body weight



Stroiek 2011 -1.58 -0.11 19.5% -1.47 [-1.86, -1.08] 1.7 1.69 Wilding 2012a 0.13 0.99 2.18 2.6% -0.86 (-2.13, 0.41) 2.17 Wilding 2013a 0.18 2.49 12.9% -1.39 (-1.90 -0.88) -1.212.49 Wildling 2013b -1.422.56 -0.5 2.62 12.9% -0.92 [-1.44, -0.40] 902 100.0% -1.08 [-1.29, -0.87] Total (95% CI) Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.05$, df = 6 (P = 0.23); $I^2 = 25\%$ Test for overall effect: Z = 10.06 (P < 0.00001) Favors DAPA Favors PLA

	10 mg D	APA + di	rugs	PLA	+ dru	gs		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI [k	gl IV, Fixed, 95% CI
Bailey 2013	-2.9	2.67	135	-0.9	2.99	137	15.4%	-2.00 [-2.67, -1.33]	
Bolinder 2012	-1.74	4.59	135	1.36	4.99	137	5.4%	-3.10 [-4.24, -1.96]	
Bolinder 2013	-2.96	2.65	89	-0.88	2.65	91	11.7%	-2.08 [-2.85, -1.31]	
Ljunggren 2012	-4.54	4.26	89	-2.12	4.14	91	4.6%	-2.42 [-3.65, -1.19]	
Strojek 2011	-4.39	4.4	89	-2.03	4.26	91	4.4%	-2.36 [-3.63, -1.09]	
Wilding 2012a	-2.26	2.73	151	-0.72	2.7	145	18.3%	-1.54 [-2.16, -0.92]	-
Wilding 2013a	-1.61	2.51	194	0.43	2.51	193	27.9%	-2.04 [-2.54, -1.54]	-
Wildling 2013b	-1.6	3.72	193	0.82	3.83	193	12.3%	-2.42 [-3.17, -1.67]	-
Total (95% CI)			1075			1078	100.0%	-2.08 [-2.35, -1.82]	•
Heterogeneity: Chi ² =		•		5%				-	-4 -2 0 2 4
Test for overall effect:	∠=15.44 ((P < 0.00	001)						Favors DAPA Favors PLA

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

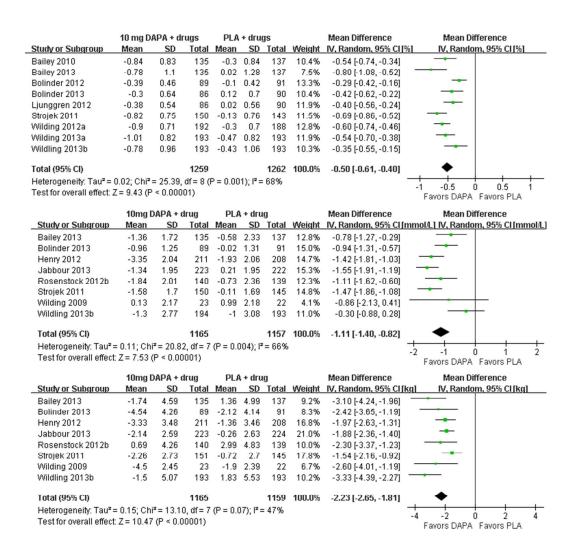


Figure 5b Forest plots of total effect size on HbA1c (%), FPG (mmol/L), and body weight (kg) in RCTs at endpoint



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-http://bmjopen.bmj.com/site/about/guidelines.xhtml	5-6



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PRISMA 2009 Checklist

		Page 1 of 2	
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			
5 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
3 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	•		
9 Funding 0	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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Secondary Subject Heading:	Diabetes and endocrinology, Evidence based practice
Keywords:	DIABETES & ENDOCRINOLOGY, STATISTICS & RESEARCH METHODS, INTERNAL MEDICINE

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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

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

BMJ Open

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 I² 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

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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,

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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 I² statistic [19], which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I²<25% was considered as low in heterogeneity and I²>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, t=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, t=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 (\leq 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 R²=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 (\leq 24 weeks) to -1.92 kg (\geq 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 R²=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 R² 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.

Provenance and peer review

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Data sharing statement

There are no additional data available.

Published protocol of the study

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



TablesTable 1 Basic characteristics of the included RCTs

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

Henry	Study1						24	Dapagliflozin + metformin was effective in
2012 [24]	5 mg DAPA + PLA	203	52.3 (10.2)	9.1 (1.4) 9.2 (1.3)	86.2 (21.1)*	10.59 (3.14)	_	reducing HbA1c, FPG and weight.
	MET +PLA	201	51.8 (9.8)		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,	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	48	Dapagliflozin + insulin enhanced glycaemic
2012 [29]	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)	=	control, stabilized insulin dosing and lowered
	5 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)	_	body weight.
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)	_	
Wilding,	PLA+INS	193	58.8 (8.6)	8.47 (0.77)	33.1 (5.9)	9.5 (3.2)	104	Dapagliflozin + insulin enhanced glycaemic
2013 [30]	2.5 mg DAPA + INS	202	59.8 (7.6)	8.46 (0.78)	33.0 (5.0)	10.0 (3.3)	_	control, stabilized insulin dosing and lowered
	5/10 mg DAPA + INS	211	59.3 (7.9)	8.62 (0.89)	33.0 (5.3)	10.3 (3.3)	_	body weight, but elevated rates of genital
	10 mg DAPA + INS	194	59.3 (8.8)	8.57 (0.82)	33.4 (5.1)	9.6 (3.0)	_	infection and of UTI
§Jabbour	PLA+ MET/SIT	224	55.0 (10.20)	7.97 (0.79)	89.23 (20.89)*	162.97 (34.45) **	24	
2013 [31]	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. ort.

[†] 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)	No of Participants	Quality of the evidence		
Outcomes	Assumed risk	Corresponding risk	(studies)	(GRADE)	
	Placebo combined with anti-diabetic drugs	10 mg dapagliflozin combined with anti-diabetic drugs			
HbA1c (%)	The mean HbA1c ranged across control groups from	The mean HbA1c in the intervention groups was	3986	$\oplus \oplus \oplus \oplus$	
Follow-up: 12 to 104 weeks	-1.44 to 0.09 %	0.52 lower (0.6 to 0.45 lower)	(14 studies)	high	
FPG (mmol/L)	The mean FPG ranged across control groups from	The mean FPG in the intervention groups was	3620	$\oplus \oplus \oplus \oplus$	
Follow-up: 12 to 104 weeks	-1.93 to 0.99 mmol/L	1.13 lower (1.33 to 0.93 lower)	(12 studies)	high	
Body weight (kg)	The mean body weight ranged across control groups from	The mean body weight in the intervention groups was	4008	$\oplus \oplus \oplus \ominus$	
Follow-up: 12 to 104 weeks	-2.12 to 2.99 kg	2.10 lower (2.32 to 1.88 lower)	(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)

	HbA	A1c	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 I² 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

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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

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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 Clinical Trials 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://www.metafor-project.org/)

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 I² statistic [19], which is the proportion of total variance observed between the trials attributed to the differences between trials rather than to sampling error. I²<25% was considered as low in heterogeneity and I²>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, t=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 (\leq 24 weeks, \geq 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% (\leq 24 weeks) and -0.52% (\geq 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 (\leq 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 R²=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 I² = 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, t=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 (\leq 24 weeks) to -1.92 kg (\geq 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 R²=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 R² 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.

Acknowledgements

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 checking data for a pilot study.

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.

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

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- Appendix 3 Forest plots of overall effect size of body weight and subgroup meta-analysis of different follow-up durations
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- Appendix 5 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs at the endpoint

TablesTable 1 Basic characteristics of the included RCTs

			Participants' characteristics†					
Study	Treatments	N	Age	HbA1c	BMI or weight	FPG (mmol/L or	Weeks (max)	Findings
-				(%)	(kg/m² or kg*)	mg/dL**)		
Bailey	PLA	137	53.7 (10.3)	8.11 (0.96)	31.8(5.3)	9.19 (2.57)	24	Dapagliflozin + metformin enhanced
2010 [20]	2.5 mg DAPA	137	55.0 (9.3)	7.99 (0.90)	31.6(4.8)	8.96 (2.39)		glycaemic control and lowered body weight.
	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	PLA+MET	137	NA	8.12 (0.96)	87.74(19.24) *	9.19 (2.58)	102	Dapagliflozin + metformin for 102 weeks
2013 [21]	2.5 mg DAPA + MET	137	NA	7.99 (0.90)	84.90(17.77) *	8.96 (2.39)	-	enhanced glycaemic control and lowered body
	5 mg DAPA + MET	137	NA	8.17 (0.96)	84.73(16.26) *	9.39 (2.72)	-	weight.
	10 mg DAPA + MET	135	NA	7.92 (0.82)	86.28(17.53) *	8.66 (2.15)	-	
Bolinder,	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
2012 [22]	10 mg DAPA + MET	89	60.6 (8.2)	7.99 (0.90)	32.1(3.9)	8.2 (1.4)		weight.
Bolinder,	PLA + MET	91	NA	7.16	90.9*	8.21	102	Dapagliflozin + metformin enhanced
2013 [23]	10 mg DAPA + MET	91	NA	7.19	92.1*	8.3		glycaemic control and reduced body weight.

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

0	Illustrative comparative risks* (95% CI)		No of Participants	Quality of the evidence
Outcomes	Assumed risk	Corresponding risk	(studies)	(GRADE)
	Placebo combined with anti-diabetic drugs	10 mg dapagliflozin combined with anti-diabetic drugs		
HbA1c (%)	The mean HbA1c ranged across control groups from	The mean HbA1c in the intervention groups was	3986	$\oplus \oplus \oplus \oplus$
Follow-up: 12 to 104 weeks	-1.44 to 0.09 %	0.52 lower (0.6 to 0.45 lower)	(14 studies)	high
FPG (mmol/L)	The mean FPG ranged across control groups from	The mean FPG in the intervention groups was	3620	$\oplus \oplus \oplus \oplus$
Follow-up: 12 to 104 weeks	-1.93 to 0.99 mmol/L	1.13 lower (1.33 to 0.93 lower)	(12 studies)	high
Body weight (kg)	The mean body weight ranged across control groups from	The mean body weight in the intervention groups was	4008	$\oplus \oplus \oplus \Theta$
Follow-up: 12 to 104 weeks	-2.12 to 2.99 kg	2.10 lower (2.32 to 1.88 lower)	(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)

	HbA	A1c	FPG		Body v	veight
	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			
2 Structured summary 3 I	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., 1² for each meta-analysis-http://bmjopen.bmj.com/site/about/guidelines.xhtml	5-6



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PRISMA 2009 Checklist

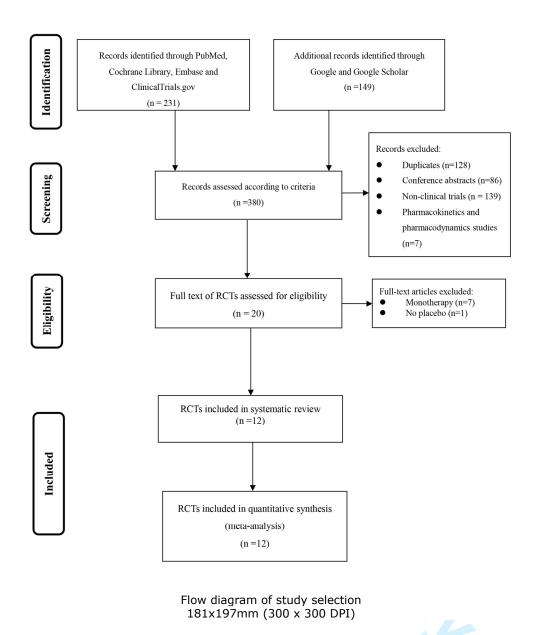
		Page 1 of 2	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., 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	1		
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

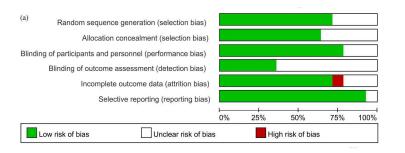
42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

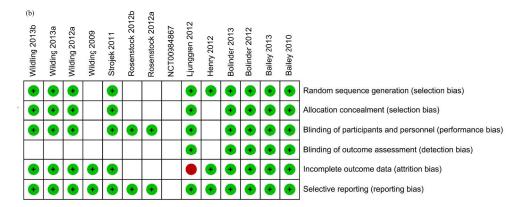
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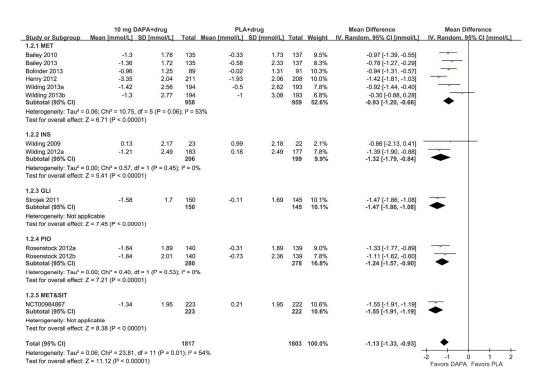




Cochrane risk of bias: (a) graph and (b) summary 264x191mm (300 x 300 DPI)

	10 mg [DAPA+dr	ıg	PLA	+drug			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV. Random, 95% CI [%]	IV. Random. 95% CI [%]
1.1.1 MET									
Bailey 2010	-0.84	0.83	135	-0.3	0.84	137	7.0%	-0.54 [-0.74, -0.34]	
Bailey 2013	-0.78	1.1	135	0.02	1.28	137	4.6%	-0.80 [-1.08, -0.52]	
Bolinder 2012	-0.39	0.46	89	-0.1	0.42	91	9.7%	-0.29 [-0.42, -0.16]	-
Bolinder 2013	-0.3	0.64	86	0.12	0.7	90	7.0%	-0.42 [-0.62, -0.22]	
Henry 2012	-1.98	1.11	211	-1.44	1.1	208	6.5%	-0.54 [-0.75, -0.33]	
Ljunggren 2012 Subtotal (95% CI)	-0.38	0.54	86 742	0.02	0.56	90 753	8.3% 43.0 %	-0.40 [-0.56, -0.24] -0.47 [-0.60, -0.34]	•
Heterogeneity: Tau ² = 0	0.02; Chi ² =	13.44, df	= 5 (P =	0.02); $I^2 = 6$	3%				
Test for overall effect: Z	Z = 7.31 (P <	< 0.00001)						
1.1.2 INS									
Wilding 2009	-0.61	0.61	23	0.09	0.67	19	2.9%	-0.70 [-1.09, -0.31]	
Wilding 2012a	-0.9	0.71	192	-0.3	0.7	188	9.1%	-0.60 [-0.74, -0.46]	
Wilding 2013a	-1.01	0.82	193	-0.47	0.82	193	8.2%	-0.54 [-0.70, -0.38]	
Wildling 2013b Subtotal (95% CI)	-0.78	0.96	193 601	-0.43	1.06	193 593	6.8% 27.1%	-0.35 [-0.55, -0.15] -0.53 [-0.65, -0.41]	•
Heterogeneity: Tau ² = 0 Test for overall effect: Z).19); I² = 37	7%				
1.1.3 GLI									
Strojek 2011 Subtotal (95% CI)	-0.82	0.75	150 150	-0.13	0.76	143 143	7.9% 7.9%	-0.69 [-0.86, -0.52] -0.69 [-0.86, -0.52]	•
Heterogeneity: Not app Test for overall effect: 2		< 0.00001)						
1.1.4 PIO									
Rosenstock 2012a	-0.97	0.95	140	-0.42	0.94	139	6.2%	-0.55 [-0.77, -0.33]	
Rosenstock 2012b Subtotal (95% CI)	-1.21	0.83	140 280	-0.54	0.94	139 278	6.6% 12.9%	-0.67 [-0.88, -0.46] -0.61 [-0.77, -0.46]	•
Heterogeneity: Tau ² = 0 Test for overall effect: 2).44); I ² = 0%	%				
1.1.5 MET&SIT									
NCT00984867 Subtotal (95% CI)	-0.45	0.76	223 223	0.04	0.76	223 223	9.1% 9.1%	-0.49 [-0.63, -0.35] -0.49 [-0.63, -0.35]	→
Heterogeneity: Not app Test for overall effect: 2		< 0.00001)						
Total (95% CI)			1996			1990	100.0%	-0.52 [-0.60, -0.45]	•
Heterogeneity: Tau ² = 0 Test for overall effect: Z	,	,	,	= 0.005); I ²	= 56%				-1 -0.5 0 0.5 1 Favors DAPA Favors PLA

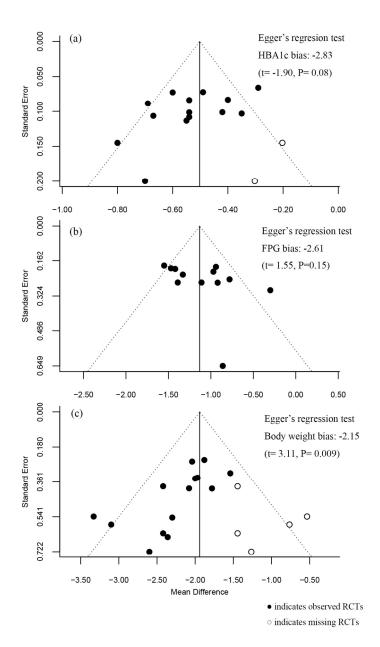
Forest plots of overall effect size of HbA1c and subgroup meta-analysis of different combined drugs 195x170mm (300 x 300 DPI)



Forest plots of overall effect size of FPG and subgroup meta-analysis of different combined drugs $195 \times 135 \text{mm} (300 \times 300 \text{ DPI})$

	10 mg	DAPA+dru	ıa	PI /	\+drua			Mean Difference	Mean Difference
Study or Subgroup						Total	Weight	IV. Random, 95% CI [kg]	IV. Random, 95% CI [kg]
1.3.1 MET	wear [kg]	OD [Kg]	Total	wear [kg]	OD [Kg]	Total	weight	IV. Italiaolii, 33/8 Ci [kg]	TV: Kandom: 35% Cr [kg]
Bailey 2010	-2.9	2.67	135	-0.9	2.99	137	9.0%	-2.00 [-2.67, -1.33]	
Bailey 2013	-1.74	4.59	135	1.36	4.99	137	3.5%	-3.10 [-4.24, -1.96]	
Bolinder 2012	-2.96	2.65	89	-0.88	2.65	91	7.1%	-2.08 [-2.85, -1.31]	
Bolinder 2013	-4.54	4.26	89	-2.12	4.14	91	3.0%	-2.42 [-3.65, -1.19]	
Henry 2012	-3.33	3.48	211	-1.36	3.46	208	9.2%	-1.97 [-2.63, -1.31]	-
Ljunggren 2012 Subtotal (95% CI)	-4.39	4.4	89 748	-2.03	4.26	91 755	2.9% 34.8%	-2.36 [-3.63, -1.09] -2.17 [-2.52, -1.82]	•
Heterogeneity: Tau ² = Test for overall effect:				63); I ² = 0%					
1.3.2 INS									
Wilding 2009	-4.5	2.45	23	-1.9	2.39	22	2.3%	-2.60 [-4.01, -1.19]	-
Wilding 2012a	-1.61	2.51	194	0.43	2.51	193	14.6%	-2.04 [-2.54, -1.54]	-
Wilding 2013a	-1.6	3.72	193	0.82	3.83	193	7.4%	-2.42 [-3.17, -1.67]	
Wildling 2013b	-1.5	5.07	193	1.83	5.53	193	4.0%	-3.33 [-4.39, -2.27]	
Subtotal (95% CI)			603			601	28.4%	-2.45 [-2.99, -1.92]	•
Heterogeneity: Tau ² =	0.11; Chi ² = 4	4.91, df = 3	8 (P = 0.	18); I ² = 39%	5				
Test for overall effect:	Z = 8.97 (P <	0.00001)							
1.3.3 GLI									
Stroiek 2011	-2.26	2.73	151	-0.72	2.7	145	10.4%	-1.54 [-2.16, -0.92]	-
Subtotal (95% CI)			151			145	10.4%	-1.54 [-2.16, -0.92]	•
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 4.88 (P <	0.00001)							
1.3.4 PIO									
Rosenstock 2012a	-0.14	3.31	140	1.64	3.3	139	7.1%	-1.78 [-2.56, -1.00]	
Rosenstock 2012b	0.69	4.26	140	2.99	4.83	139	3.9%	-2.30 [-3.37, -1.23]	
Subtotal (95% CI)	0.03	4.20	280	2.33	4.00	278	11.0%	-1.96 [-2.59, -1.33]	•
Heterogeneity: Tau ² =	0.00: Chi ² = 0	0.60. df = 1	(P = 0.	44): I ² = 0%				, , , , , , , ,	
Test for overall effect:				,,					
1.3.5 MET&SIT									
NCT00984867	-2.14	2.59	223	-0.26	2.63	224	15.4%	-1.88 [-2.36, -1.40]	-
Subtotal (95% CI)			223			224	15.4%	-1.88 [-2.36, -1.40]	•
Heterogeneity: Not ap Test for overall effect:		0.00001)							
Total (95% CI)			2005			2003	100.0%	-2.10 [-2.32, -1.88]	♦
Heterogeneity: Tau ² =	0.02; Chi ² =	14.73, df =	13 (P =	0.32); I ² = 1:	2%				+ + + +
Test for overall effect:				,,					-4 -2 0 2 4 Favors DAPA Favors PLA
	(,						FAVOIS DAPA FAVOIS PLA

Forest plots of overall effect size of body weight and subgroup meta-analysis of different combined drugs $195 \times 165 \text{mm}$ (300 x 300 DPI)



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

Appendices

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

	40 B	4D4 : -		DI A				N D'//	M D'	
udy or Subgroup		APA + dr			+ drug SD [%]	Total	Weight	Mean Difference IV. Random, 95% CI [%]	Mean Dit	fference . 95% CI [%]
1.1 <= 24 weeks	AICUIT [70]	JD [/0]	rotal IV		25 [/0]	i Jiai	Troignt	Nundom, 33/0 OI [/0]	IV. Nandon	. 55/0 51[/0]
ailey 2010	-0.84	0.83	135	-0.3	0.84	137	7.0%	-0.54 [-0.74, -0.34]		
olinder 2012	-0.39	0.46	89	-0.3	0.42	91	9.7%	-0.29 [-0.42, -0.16]	-	
enry 2012	-1.98	1.11	211	-1.44	1.1	208	6.5%	-0.54 [-0.75, -0.33]		
CT00984867	-0.45	0.76	223	0.04	0.76	223	9.1%	-0.49 [-0.63, -0.35]	-	
osenstock 2012a	-0.97	0.95	140	-0.42	0.94	139	6.2%	-0.55 [-0.77, -0.33]		
rojek 2011	-0.82	0.75	150	-0.13	0.76	143	7.9%	-0.69 [-0.86, -0.52]		
ilding 2009	-0.61	0.61	23	0.09	0.67	19	2.9%	-0.70 [-1.09, -0.31]		
ilding 2012a	-0.9	0.71	192	-0.3	0.7	188	9.1%	-0.60 [-0.74, -0.46]	-	
ubtotal (95% CI)			1163			1148	58.4%	-0.53 [-0.63, -0.43]	•	
terogeneity: Tau ² =	0.01; Chi ² = 1	18.19, df =	7 (P = 0.	01); I ² = 62	2%					
st for overall effect:	Z = 10.05 (P - 1)	< 0.00001	1)							
1.2 > 24 weeks										
ailey 2013	-0.78	1.1	135	0.02	1.28	137	4.6%	-0.80 [-1.08, -0.52]		
olinder 2013	-0.70	0.64	86	0.12	0.7	90	7.0%	-0.42 [-0.62, -0.22]		
unggren 2012	-0.38	0.54	86	0.12	0.56	90	8.3%	-0.40 [-0.56, -0.24]		
osenstock 2012b	-1.21	0.83	140	-0.54	0.94	139	6.6%	-0.67 [-0.88, -0.46]		
Iding 2013a	-1.01	0.82	193	-0.54	0.82	193	8.2%	-0.54 [-0.70, -0.38]	-	
ldling 2013a	-0.78	0.82	193	-0.47	1.06	193	6.8%	-0.35 [-0.55, -0.15]		
btotal (95% CI)	-0.78	0.90	833	-0.43	1.00	842	41.6%	-0.51 [-0.63, -0.39]	•	
terogeneity: Tau ² =	0.01: Chi ² = 1	11.30 df =		05): I ² = 56	6%	U-12	71.070	0.01 [0.00, -0.03]	-	
st for overall effect:				- 2/1 00						
tal (95% CI)			1996			1990	100.0%	-0.52 [-0.60, -0.45]	•	
terogeneity: Tau ² =	0.01; Chi ² = 2	29.54. df =		0.005): I ² =	56%			_	1 0-	1 1
st for overall effect:				,,					-1 -0.5 0 Favors DAPA	
									1 01010 2711 71	ravolo i Ex

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

	10 mg DAP	A + drug		PLA +	drug			Mean Difference	Mean Difference
Study or Subgroup	Mean [mmol/l] SD	[mmol/l]	Total I			Total	Weight	IV, Random, 95% CI [mmol/I]	
2.2.1 <= 24 weeks									
Bailey 2010	-1.3	1.78	135	-0.33	1.73	137	9.5%	-0.97 [-1.39, -0.55]	
Henry 2012	-3.35	2.04	211	-1.93	2.06	208	10.0%	-1.42 [-1.81, -1.03]	-
NCT00984867 Rosenstock 2012a	-1.34 -1.64	1.95 1.89	223 140	0.21 -0.31	1.95 1.89	222 139	10.6% 9.0%	-1.55 [-1.91, -1.19] -1.33 [-1.77, -0.89]	
Strojek 2011	-1.58	1.7	150	-0.31	1.69	145	10.1%	-1.47 [-1.86, -1.08]	-
Wilding 2009	0.13	2.17	23	0.99	2.18	22	2.1%	-0.86 [-2.13, 0.41]	
Wilding 2012a	-1.21	2.49	183	0.18	2.49	177	7.8%	-1.39 [-1.90, -0.88]	
Subtotal (95% CI)			1065			1050	59.0%	-1.36 [-1.53, -1.19]	•
Heterogeneity: Tau ² = Test for overall effect: 2); I ² = 0%	•					
2.2.2 > 24 weeks									
Bailey 2013	-1.36	1.72	135	-0.58	2.33	137	8.3%	-0.78 [-1.27, -0.29]	
Bolinder 2013	-0.96	1.25	89	-0.02	1.31	91	10.3%	-0.94 [-1.31, -0.57]	-
Rosenstock 2012b	-1.84	2.01	140	-0.73	2.36	139	7.8%	-1.11 [-1.62, -0.60]	
Wilding 2013a Wildling 2013b	-1.42 -1.3	2.56 2.77	194 194	-0.5 -1	2.62 3.08	193 193	7.8% 6.8%	-0.92 [-1.44, -0.40] -0.30 [-0.88, 0.28]	
Subtotal (95% CI)	-1.3	2.11	752	-1	3.08	753	41.0%	-0.84 [-1.08, -0.61]	•
Heterogeneity: Tau ² =	0.01; Chi ² = 4.76, df =	4 (P = 0.31		%					
Test for overall effect:			,,						
Total (95% CI)			1817			1803	100.0%	-1.13 [-1.33, -0.93]	. •
Heterogeneity: Tau ² =			01); I ² =	54%					-2 -1 0 1 2
Test for overall effect: 2	Z = 11.12 (P < 0.0000	01)							Favors DAPA Favors PLA

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

	10 mg DA	APA + dru	ıa	PLA +	- drua			Mean Difference	Mean Dif	ference
						Total	Weight	IV. Random, 95% CI [kg]		95% CI [kg]
2.3.1 <= 24 weeks										
Bailey 2010	-2.9	2.67	135	-0.9	2.99	137	9.0%	-2.00 [-2.67, -1.33]		
Bolinder 2012 Henry 2012	-2.96 -3.33	2.65 3.48	89 211	-0.88 -1.36	2.65 3.46	91 208	7.1% 9.2%	-2.08 [-2.85, -1.31] -1.97 [-2.63, -1.31]	-	
NCT00984867	-3.33 -2.14	2.59	223	-0.26	2.63	224	15.4%	-1.88 [-2.36, -1.40]	-	
Rosenstock 2012a	-0.14	3.31	140	1.64	3.3	139	7.1%	-1.78 [-2.56, -1.00]		
Strojek 2011	-2.26	2.73	151	-0.72	2.7	145	10.4%	-1.54 [-2.16, -0.92]	-	
Wilding 2009	-4.5	2.45	23	-1.9	2.39	22	2.3%	-2.60 [-4.01, -1.19]		
Wilding 2012a	-1.61	2.51	194	0.43	2.51	193	14.6%	-2.04 [-2.54, -1.54]	T	
Subtotal (95% CI)	0.00, Chi2 - 0.	OF 45 - 7	1166). I2 = O0/		1159	75.2%	-1.92 [-2.15, -1.69]	•	
Heterogeneity: Tau ² = Test for overall effect:); 12 = 0%						
2.3.2 > 24 weeks										
Bailey 2013	-1.74	4.59	135	1.36	4.99	137	3.5%	-3.10 [-4.24, -1.96]		
Bolinder 2013	-4.54	4.26	89	-2.12	4.14	91	3.0%	-2.42 [-3.65, -1.19]		
Ljunggren 2012	-4.39	4.4	89	-2.03	4.26	91	2.9%	-2.36 [-3.63, -1.09]		
Rosenstock 2012b	0.69	4.26	140	2.99	4.83	139	3.9%	-2.30 [-3.37, -1.23]		
Wilding 2013a	-1.6	3.72	193	0.82	3.83	193	7.4%	-2.42 [-3.17, -1.67]		
Wildling 2013b	-1.5	5.07	193	1.83	5.53	193	4.0%	-3.33 [-4.39, -2.27]		
Subtotal (95% CI)			839			844	24.8%	-2.63 [-3.06, -2.21]	•	
Heterogeneity: Tau ² = Test for overall effect:); I ² = 0%						
Total (95% CI)			2005			2003	100.0%	-2.10 [-2.32, -1.88]	•	
Heterogeneity: Tau ² =			13 (P = 0.	32); I² = 12%	6				-4 -2 0	2 4
Test for overall effect:	Z = 18.77 (P <	0.00001)							Favors DAPA	

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

	liey 2010	ley 2010
liely 2013		ley 2013
slinder 2012 - 0.39	Inder 2012	nder 2012
Sinder 2013	Index 2013	Index 2013
nggren 2012	nggren 2012	nggren 2012
ojek 2011	ojek 2011	jek 2011
opiex 2011	opiex 2011	jek 2011
lding 2012a	lding 2012a	sing 2012a
Iding 2013a	Iding 2013a	sting 2013a - 1.01 0.82 193 0.47 0.82 193 11.9% 0.54 [c.70, 0.38] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 1259 1262 100.0% 0.55 [c.55, 0.15] at (95% Cl) 10 mg DAPA + drugs
at (98% C)	at (98% C)	at (98% C)
at (95% Cl) 1259 1259 1262 100.0% -0.59 [-0.61, -0.40]	at (95% Cl) 1259 1259 1262 100.0% -0.59 [-0.61, -0.40]	at (95% CI) 1259 1269 1262 1262 1262 1262 1262 1262 1262 1262 1262 1262 1262 1263 1264 1262 1262 1263 1264 1265 1264 1265
erogeneity: Tau" = 0.02; Chi" = 25.39, df = 8 (P = 0.001); P = 68% t for overal effect: Z = 9.43 (P < 0.00001) 10 mg DAPA + drugs	erogeneity: Tau" = 0.02; Chi" = 25.39, df = 8 (P = 0.001); P = 68% t for overal effect: Z = 9.43 (P < 0.00001) 10 mg DAPA + drugs	erogeneity: Tau* = 0.02; Chi* = 25.39, df = 8 (P = 0.001); P = 68% 1 for overall effect: Z = 9.43 (P < 0.00001) 1 mg DAPA - drugs 2 mg DAPA - d
percegonality: Tau" = 0.02; Chi" = 25.39, df = 8 (P = 0.001); P = 68% at for overall effect: Z = 9.43 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs	percegonality: Tau" = 0.02; Chi" = 25.39, df = 8 (P = 0.001); P = 68% at for overall effect: Z = 9.43 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs	erogeneity: Tau* = 0.02; Chi* = 25.39, df = 8 (P = 0.001); P = 68% 1 for overall effect: Z = 9.43 (P < 0.00001) 1 mg DAPA - drugs 2 mg DAPA - d
No subgroup Mean Fund SD Fund Mean Turbal Turb	No subgroup Mean Fund SD Fund Mean Turbal Turb	No subgroup Mean Femolit SD Femolit Total Mean Templit Tem
ey 2010	ey 2010	yy 2010
ey 2013	ey 2013	ny 2013
inder 2013	nder 2013	nder 2013
gek 2011	gek 2011	ek 2011
ng 2012a	ng 2012a	ng 2012a
10 mg DAPA + drugs	10 mg DAPA + drugs	10 mg DAPA + drugs PLA + d
1 95% CI 1 909 909 902 100.0% -1.08 [-1.29, -0.87]	1 95% CI 1 909 909 902 100.0% -1.08 [-1.29, -0.87]	1 95% CI 909 902 100.0% -1.08 [-1.29] -0.87 -1.08 [-
rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); P = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs vey 2013 -2.9 2.67 135 -0.9 2.99 137 15.4% -2.00 [-2.67, -1.33] nder 2012 -1.74 4.59 135 -0.88 2.65 91 11.7% -2.08 [-2.65, -1.19] rigeren 2012 -4.54 4.26 89 -2.12 4.14 91 4.6% -2.42 [-3.65, -1.19] rigeren 2012 -4.54 4.26 89 -2.13 4.26 91 4.4% -2.36 [-3.65, -1.19] rigeren 2012 -2.62 2.65 3.71 rigeren 2013 -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] rigeren 2013 -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] al (95% CI) 1075 1078 100.0% -2.08 [-2.35, -1.82] -4 -2.00 2 4 Favors DAPA Favors PLA	rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); P = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs vey 2013 -2.9 2.67 135 -0.9 2.99 137 15.4% -2.00 [-2.67, -1.33] nder 2012 -1.74 4.59 135 -0.88 2.65 91 11.7% -2.08 [-2.65, -1.19] rigeren 2012 -4.54 4.26 89 -2.12 4.14 91 4.6% -2.42 [-3.65, -1.19] rigeren 2012 -4.54 4.26 89 -2.13 4.26 91 4.4% -2.36 [-3.65, -1.19] rigeren 2012 -2.62 2.65 3.71 rigeren 2013 -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] rigeren 2013 -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] al (95% CI) 1075 1078 100.0% -2.08 [-2.35, -1.82] -4 -2.00 2 4 Favors DAPA Favors PLA	rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); F = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs PLA + drugs Weight V, Fixed, 95% CI [kg] 10 mg DAPA + drugs Weight V, Fixed, 95% CI [kg] PLA + drugs Mean Difference W, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference W, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference N, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference N, Fixed, 95% CI [kg] V, Fixed,
rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); P = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs Wean Ikgl SD [kgl Total Mean [kgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Weig	rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); P = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs Wean Ikgl SD [kgl Total Mean [kgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Wean Ikgl SD [kgl Total Weight IV, Fixed, 95% CI [kgl Weig	rogenelly. Tay" = 0.02; Chi" = 8.05, df = 6 (P = 0.23); F = 25% for overall effect: Z = 10.06 (P < 0.00001) 10 mg DAPA + drugs PLA + drugs PLA + drugs Weight V, Fixed, 95% CI [kg] 10 mg DAPA + drugs Weight V, Fixed, 95% CI [kg] PLA + drugs Mean Difference W, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference W, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference N, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] V, Fixed, 95% CI [kg] PLA + drugs Mean Difference N, Fixed, 95% CI [kg] V, Fixed,
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ey 2013	ey 2013	ey 2013
nder 2012 -1.74 4.59 135 1.36 4.99 137 5.4% -3.10 [-4.24, -1.96] ander 2013 -2.96 2.65 89 -0.88 2.65 91 11.7% -2.08 [-2.85, -1.31] ander 2012 -4.54 4.26 89 -2.12 4.14 91 4.6% -2.42 [-3.65, -1.19] and 2012a -2.26 2.73 151 -0.72 2.7 145 18.3% -1.54 [-2.16, -0.92] and 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] and (95% CI) 1075 and (95% CI) 1075 arogeneity: Chi² = 7.35, df = 7 (P = 0.39); i² = 5% the rowerall effect: Z = 15.44 (P < 0.00001)	nder 2012 -1.74 4.59 135 1.36 4.99 137 5.4% -3.10 [-4.24, -1.96] ander 2013 -2.96 2.65 89 -0.88 2.65 91 11.7% -2.08 [-2.85, -1.31] ander 2012 -4.54 4.26 89 -2.12 4.14 91 4.6% -2.42 [-3.65, -1.19] and 2012a -2.26 2.73 151 -0.72 2.7 145 18.3% -1.54 [-2.16, -0.92] and 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] and (95% CI) 1075 and (95% CI) 1075 arogeneity: Chi² = 7.35, df = 7 (P = 0.39); i² = 5% the rowerall effect: Z = 15.44 (P < 0.00001)	nder 2012 -1.74
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ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] 1ing 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] 1075 1076 1095 1095 1095 1095 1095 1095 1095 1095	ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] 1ing 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] 1075 1076 1095 1095 1095 1095 1095 1095 1095 1095	ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] ling 2013b -1.6 3.72 193 ling 2013b -1.6 3.72 li
Ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] ing 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] I (95% CI) 1075	Ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] ing 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] I (95% CI) 1075	Ing 2013a -1.61 2.51 194 0.43 2.51 193 27.9% -2.04 [-2.54, -1.54] ing 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] I (95% CI) 1075 rogeneity: Chi² = 7.35, df = 7 (P = 0.39); I² = 5% for overall effect: Z = 15.44 (P < 0.00001)
lling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] al (95% CI) 1075 1078 100.0% -2.08 [-2.35, -1.82] rogeneity: Chi² = 7.35, df = 7 (P = 0.39); i² = 5% to roverall effect: Z = 15.44 (P < 0.00001) Favors DAPA Favors PLA	lling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] al (95% CI) 1075 1078 100.0% -2.08 [-2.35, -1.82] rogeneity: Chi² = 7.35, df = 7 (P = 0.39); i² = 5% to roverall effect: Z = 15.44 (P < 0.00001) Favors DAPA Favors PLA	lling 2013b -1.6 3.72 193 0.82 3.83 193 12.3% -2.42 [-3.17, -1.67] al (95% Cl) 1075 1078 100.0% -2.08 [-2.35, -1.82] roogeneity: Chi² = 7.35, df = 7 (P = 0.39); i² = 5% to roverall effect: Z = 15.44 (P < 0.00001) Favors DAPA Favors PLA
al (95% CI) 1075 arogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% for overall effect: Z = 15.44 (P < 0.00001) 1078 100.0% -2.08 [-2.35, -1.82] 4 -2 0 2 4 Favors DAPA Favors PLA	al (95% CI) 1075 arogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% for overall effect: Z = 15.44 (P < 0.00001) 1078 100.0% -2.08 [-2.35, -1.82] 4 -2 0 2 4 Favors DAPA Favors PLA	al (95% CI) 1075 arogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% for overall effect: Z = 15.44 (P < 0.00001) 1078 100.0% -2.08 [-2.35, -1.82] -4 -2 0 2 4 Favors DAPA Favors PLA
erogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 7 (P	erogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 5% erogeneity: Chi² = 7 (P = 0.39); l² = 7 (P	erogeneity: Chi² = 7.35, df = 7 (P = 0.39); l² = 5% If or overall effect: Z = 15.44 (P < 0.00001) Favors DAPA Favors PLA
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Appendix 5 Forest plots of overall effect size on HbA1c, FPG, and body weight in RCTs at the endpoint

	10 mg [DAPA + drug	,	РΙΔ	+ drug				Mean Difference	Mean Difference	
Study or Subgroup				Mean [%]		Total	Weig	ht l'	V. Random, 95% CI [%]		
Bailey 2013	-0.78	1.1	135	0.02	1.28	137	8.9		-0.80 [-1.08, -0.52]	-	
Bolinder 2013	-0.78	0.64	86	0.02	0.7	90	13.5		-0.42 [-0.62, -0.22]	-	
lenry 2012	-1.98	1.11	211	-1.44	1.1	208	12.6		-0.54 [-0.75, -0.33]		
ICT00984867	-0.45	0.76	223	0.04	0.76	223	18.0		-0.49 [-0.63, -0.35]	-	
Rosenstock 2012b	-1.21	0.70	140	-0.54	0.70	139	12.9		-0.67 [-0.88, -0.46]		
Strojek 2011	-0.82	0.75	150	-0.54	0.76	143	15.4		-0.69 [-0.86, -0.52]		
	-0.62	0.75	23	0.09	0.76		5.5				
Vilding 2009						19			-0.70 [-1.09, -0.31]	-	
Vildling 2013b	-0.78	0.96	193	-0.43	1.06	193	13.3	70	-0.35 [-0.55, -0.15]		
otal (95% CI)			1161			1152	100.0)%	-0.56 [-0.66, -0.46]	♦	
Heterogeneity: Tau ² =	0.01; Chi ² =	13.48, df = 7	(P =	0.06); $I^2 = 48$	3%					1 05 0 05	_
est for overall effect:	Z = 10.71 (P	< 0.00001)								-1 -0.5 0 0.5 1 Favors DAPA Favors PLA	
	E223 12.2				50000				oto estade		
tudy or Subgroup M	10 mg D/ ean [mmol/L]	APA + drug	Total	Mean [mmo	PLA + dru		Total	Weigh	Mean Difference t IV, Random, 95% CI [mi	Mean Difference mol/L] IV. Random. 95% CI [mmol/	
ailey 2013	-1.36	1.72	135		.58	2.33		12.89			
olinder 2013	-0.96	1.72	89		.02	1.31	91	15.09			
enry 2012	-3.35	2.04	211		.93	2.06		14.79			
CT00984867	-1.34	1.95	223		.21	1.95		15.39			
osenstock 2012b	-1.84	2.01	140		.73	2.36		12.39	6 -1.11 [-1.62, -	0.60]	
trojek 2011	-1.58	1.7	150		.11	1.69		14.89			
/ilding 2009	0.13 -1.3	2.17 2.77	23 194	0	.99 -1	2.18		4.19			
Vildling 2013b	-1.3	2.77	194		-1	3.08	193	11.09	6 -0.30 [-0.88,	0.28]	
otal (95% CI)			1165				1157	100.09	6 -1.11 [-1.40, -	0.82]	
leterogeneity: Tau ² = 0.1)4); I ² =	66%						-2 -1 0 1	2
est for overall effect: Z =	7.53 (P < 0.000	01)								Favors DAPA Favors PLA	
	10 mg D	APA + drug		PLA	+ drug				Mean Difference	Mean Difference	
tudy or Subgroup	Mean [kg]				-	Total	Weig	ht_I	/. Random, 95% CI [kg]		
ailey 2013	-1.74	4.59	135	1.36	4.99		9.3		-3.10 [-4.24, -1.96]		
olinder 2013	-4.54	4.26	89	-2.12	4.14		8.3		-2.42 [-3.65, -1.19]		
lenry 2012	-3.33	3.48	211	-1.36	3.46		16.8		-1.97 [-2.63, -1.31]	-	
NCT00984867	-2.14	2.59	223	-0.26	2.63		21.0		-1.88 [-2.36, -1.40]	-	
Rosenstock 2012b	0.69	4.26	140	2.99	4.83		10.0		-2.30 [-3.37, -1.23]		
Strojek 2011	-2.26	2.73	151	-0.72	2.7				-1.54 [-2.16, -0.92]	-	
Vilding 2009	-4.5	2.45	23	-1.9	2.39		6.7		-2.60 [-4.01, -1.19]		
Vildling 2013b	-1.5	5.07	193	1.83	5.53		10.2		-3.33 [-4.39, -2.27]		
Total (95% CI)			1165			1159	100.	0%	-2.23 [-2.65, -1.81]	•	_
Heterogeneity: Tau ² =			(P = 0.	07); $I^2 = 47\%$	o o					-4 -2 0 2	4
est for overall effect:	Z = 10.47 (P	< 0.00001)								Favors DAPA Favors PLA	