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Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

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Summary

Aims: To evaluate the efficacy and safety of combined therapy with sodium-glucose cotransporter 2 (SGLT-2) inhibitors plus pioglitazone versus pioglitazone alone in type 2 diabetic patients.

Materials and Methods: Systematic literature searches were performed across PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov from 1966 to September 2018 to identify randomized, controlled trials. Mean difference (MD) or odds ratio (OR) was used to evaluate efficacy and safety end-points (active group vs control group), wherever appropriate. Heterogeneity was assessed by *P* value of χ^2 statistics and I^2.

Results: Four randomized controlled trials with 1411 diabetic patients were included. Pooling data from included trials showed that HbA1c change was significantly larger in both low-dose SGLT-2 inhibitors (MD: −0.59%, 95% CI: −0.77 to −0.41%) and high-dose SGLT-2 inhibitors (MD: −0.65%, 95% CI: −0.78 to −0.53%) plus pioglitazone than pioglitazone alone in 24-26 weeks. Favourable outcomes were also found in fasting blood glucose level reduction and more patients achieving HbA1c <7% in SGLT-2 inhibitor plus pioglitazone (OR: 3.21, 95% CI: 1.99 to 5.16). Also, SGLT-2 inhibitor plus pioglitazone vs pioglitazone, reduced weight and blood pressure. The risks of death, heart failure, hypoglycaemia and urinary tract infection were not different between active and control groups although genital tract infection was more frequently seen in SGLT-2 inhibitor group.

Conclusions: Compared to pioglitazone alone, SGLT-2 inhibitor plus pioglitazone improved glycaemic control, reduced body weight and lowered blood pressure, but increased genital tract infection.

KEYWORDS

add-on treatment, meta-analysis, pioglitazone, sodium-glucose cotransporter 2 inhibitor, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus is a progressive disease characterized by insulin resistance, deterioration of β-cell function and impaired glucose tolerance.[1] In the United Kingdom Prospective Diabetes Study (UKPDS), roughly 50% of newly diagnosed type 2 diabetic patients were adequately controlled with monotherapy after 3 years, which declined to only about 25% after 9 years.[2] Combination therapy of oral anti-hyperglycaemic agents appears to be a more viable strategy for improving glycaemic control.

Multiple classes of oral anti-hyperglycaemic agents are available.[3] Pioglitazone, a thiazolidinedione, increases insulin sensitivity and decreases hepatic gluconeogenesis.[4] Pioglitazone reduces the risk of cardiovascular events,[5,6] which is important because type 2 diabetic patients are greatly burdened by cardiovascular disease.[7] However, pioglitazone has adverse effects of fluid retention, body weight gain and heart failure.[8,9] Sodium-glucose cotransporter 2 (SGLT-2) inhibitor, a new class of oral anti-hyperglycaemic agent, increases urinary glucose excretion by inhibiting renal glucose reabsorption and facilitating net calorie loss.[10] Moreover, the mild osmotic diuresis[10] and caloric loss caused by SGLT-2 inhibitors reduce body weight, oedema and risk of heart failure.[11-13]

Combining pioglitazone with an SGLT-2 inhibitor to balance fluid status and body weight might enhance glycaemic and other vascular risk factor control, while reducing side effects among type 2 diabetics. To better assess this notion, we conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy (eg, glycaemic control) and safety (eg, hypoglycaemia, weight change, urinary/genital tract infection) of combined therapy with pioglitazone plus SGLT-2 inhibitors versus pioglitazone alone, in type 2 diabetic patients.

2 | METHODS

The current study was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: the PRISMA Statement.[14] This study is exempted from IRB approval and contains no patient-level data.

2.1 | Search strategy

A systematic search was performed of PubMed, EMBASE, MEDLINE, the Cochrane Central Register of Controlled Trials, Scopus, and Web of Science and the clinical trial registry maintained at clinicaltrials.gov from 1966 to September 2018 with the terms: *pioglitazone* or *actos* AND *gliflozin* or *sodium-glucose cotransporter 2 inhibitor* or *empagliflozin* or *dapagliflozin* or *canagliflozin* or *ipragliflozin* or *tofogliflozin* or *remogliflozin AND glucose or Hba1c or blood pressure or mortality or death or heart failure or cancer or infection or hypoglycaemia or oedema or weight or side effect*. We restricted the search to studies in humans and clinical trials. There was no language restriction. We retrieved further information by a manual search of references from recent reviews and relevant published original studies. Two investigators (HWL and ML) independently conducted the literature search, screen of abstracts and selection of included trials.

2.2 | Study selection and data abstraction

We selected studies using the following entry criteria: (a) the study was randomized controlled trial; (b) patients had a history of type 2 diabetes mellitus; (c) the comparison treatment was SGLT-2 inhibitor plus pioglitazone (active group) vs pioglitazone (control group); (d) reported at least one measure of the following: mean and standard deviation (SD) or standard error (SE) were reported for change from baseline in HbA1c, fasting glucose, and body weight, in active and control groups; (e) intended follow-up of at least 24 weeks for all participants. All data from eligible studies were abstracted by two independent investigators (HWL and ML) according to standard protocol. Discrepancies were resolved by joint discussion. Recorded data variables were trial name, year of publication, study area, treatment regimens and daily dose for each group, mean age, number of participants, number of events/participants in certain end-points (eg, people who achieved Hba1c <7.0, hypoglycaemia, death, heart failure, urinary tract infection, genital tract infection), percentage of women, duration of follow-up and mean and SD or SE of the interested variables or event of each groups.

2.3 | Quality assessment

All the included studies were randomized controlled trials. Risk of bias (eg, selection bias, performance bias, detection bias, attrition bias and reporting bias) of the included trials was assessed according to the Cochrane risk of bias algorithm (https://www.cochrane.org/training/cochrane-handbook).[15]

2.4 | Data synthesis and analysis

The efficacy end-points were HbA1c change and fasting glucose change from baseline and patients achieving Hba1C <7.0% in active vs control groups. The safety end-points were patients with hypoglycaemia, heart failure, urinary tract infection, genital tract infection and death in active vs control groups. Additional end-points were body weight change, systolic and diastolic blood pressure change from baseline. Study analyses were conducted according to dose of SGLT-2 inhibitors (high-dose and low-dose). All analyses were based on the intention-to-treat principle. Mean difference with standard deviation or odds ratio (OR) with 95% confidence interval (CI) was used to estimate the results between the active group and control group. We used a random effect model to estimate mean difference between active and control group based on an assumption that the different trials were estimating different, yet related, intervention effect.[15] Adverse effects of the treatment were reported as events and total number of participants in each trial. A random effect model based on Mantel-Haenszel method was used when odds ratio was used. Heterogeneity was assessed by *P* value of χ^2

TABLE 1 Baseline characters of included trials

Study	EMPA-REG PIO[16,20]	Forst[17]	Rosenstock[18]	SPOTLIGHT[19]
Year	2014	2014	2012	2014
Location	Canada, China, Greece, India, Philippines, Thailand, Ukraine and USA	74 centres in 11 countries	105 sites in Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan and USA	Japan
Age	≧ 18 y/o and (≦ 65 y/o in India); mean: 54.5 y/o	≧ 18 y/o and ≦ 80 y/o; mean: 57.4 y/o	≧ 18 y/o; mean age: 53.8 y/o	≧ 20 y/o; mean age: 56.2 y/o
Population	HbA1C ≧7 and ≦ 10%; BMI ≦ 45 kg/m2	HbA1C ≧7 and ≦ 10.5%; 6.1 mmol/L (110 mg.dL) ≦ fasting plasma glucose <15 mmol/L (270 mg/dL)	C-peptide≧ 1.0 ng/mL, BMI ≦ 45 kg/m2; Group A: HbA1C ≧7 and ≦ 10.5%; Group B: HbA1C ≧8 and ≦ 11.0% with pioglitazone 15 mg/day or other drug less than half of maximum dose	HbA1c: 7.4%-9.9%, treatment with pioglitazone monotherapy; BMI: 20.0-45.0 kg/m^2
Oral hypoglycaemic agent before randomization	≧ 12 wk prior to randomization, unchanged dose or pioglitazone monotherapy dose or pioglitazone +metformin	Protocol-specified doses of metformin and pioglitazone; other background therapies entered a 12-wk metformin/pioglitazone dose titration-stable period	Group A received ≧12 wk of pioglitazone; Group B was drug naïve or received low dose of pioglitazone or any dose of rosiglitazone or ≧ 8 wk of metformin or sulfonylurea	≧ 4-wk stable dose of pioglitazone monotherapy
SGLT2 inhibitor/control	Empagliflozin 10 mg, 25 mg/placebo	Canagliflozin 100 mg, 300 mg/placebo	Dapagliflozin 5 mg, 10 mg/placebo	Ipragliflozin 50 mg/placebo
Follow times	24 wk	26 wk; a expansion to 52 wk (placebo switch to sitagliptin 100 mg) after 26 wk	24-wk study; extension period to 48 wk	24 wk; extension period to 52 wk (all participants received 50 mg or 100 mg ipragliflozin according to HbA1c)
Participant numbers	498	342	420	151
Woman, n (%)	257 (51.6)	126 (36.8)	212 (50.5)	39 (26)
End-points	Primary point: HbA1c change from baseline at 24 wk; secondary end-points: fasting plasma glucose (FPG) and body weight (BW) change from baseline at 24 wk	Primary end-point: HbA1c change from baseline at 26 wk; secondary end-points: HbA1c change from baseline at 52 wk, proportion of patients reaching HbA1c <7.0%, change from baseline in FPG, systolic BP, fasting index of β-cell function, Homeostasis Model Assessment, BW change, HDL-C and triglycerides	Primary end-point: HbA1c change from baseline at 24 wk; FPG, postprandial glucose, and BW change from baseline	Primary end-point: HbA1c change from baseline at 24 wk; secondary end-points: FPG, fasting serum insulin, leptin, adiponectin, BW and waist circumference change from baseline at 24 wk

Continues

TABLE 1 Continued

Study	EMPA-REG PIO[16,20]	Forst[17]	Rosenstock[18]	SPOTLIGHT[19]
Baseline HbA1c, %	Placebo: 8.2 ± 0.92 Empa (10 mg): 8.1± .89 Empa (25 mg): 8.1± .82	Placebo: 8.0 ± 1.0 Cana (100 mg): 8.0 ± 0.9 Cana (300 mg): 7.9 ± 0.9	Placebo: 8.34 ± 1.00 Dapa (5 mg): 8.4 ± 1.03 Dapa (10 mg): 8.37 ± 0.96	Placebo: 8.39 ± 0.64 Ipra (50 mg): 8.24 ± 0.67
Baseline Fasting blood glucose	Placebo: 8.43 ± 2.24 (mmol/L) Empa (10 mg): 8.44 ± 2.12 Empa (25 mg):8.43 ± 2.05	Placebo: 9.1 ± 2.2 mmol/L (164 ± 39.6 mg/dL) Cana (100 mg): 9.4 ± 2.2 (169.4 ± 39.6) Cana (300): 9.1 ± 2.3 (164.0 ± 41.4)	Placebo: 8.92 ± 2.61 (mmol/L) (160.7 ± 47.0 mg/dL) Dapa (5 mg): 9.36 ± 2.89 (168.6 ± 52.1) Dapa (10 mg): 9.15 ± 2.57 (164.9 ± 46.3)	Placebo: 170.0 ± 29.18 mg/dL Ipra (50 mg): 172.9 ± 36.8 mg/dL

Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Ipra, Ipragliflozin; tx, treatment.

and I^2 statistics. Heterogeneity was considered if either the χ^2 test was significant with the $P = 0.05$ level or the I^2 statistic was >70%. Publication bias was assessed by funnel plot if more than 10 studies were included. Sensitivity analysis was also performed to further explore the robustness of our analysis. We evaluated the quality of evidence for primary and secondary outcomes with the GRADE system.[15] We used the software, Review Manager Software Package (RevMan version 5.3, The Cochrane Collaboration, London, UK), for meta-analysis.

3 | RESULTS

The literature review identified 14 full articles for detailed assessment, of which nine were excluded for comparison between SGLT-2 and pioglitazone ($k = 2$), comparison between SGLT-2 and placebo ($k = 6$) or comparison between GLP-1 receptor agonist plus pioglitazone and insulin ($k = 1$). Our final analysis included five articles derived from four randomized controlled trials (Figure S1).[16-20] The SGLT-2 inhibitors used in the included trials were four different SGLT-2 inhibitors.[16-19] All included studies had run-in period before the experiment started, and finally, a total of 1411 individuals were enrolled. The mean age was 55.2 years old and 44.9% were women. The baseline characteristics of the included studies are summarized in Table 1. About 938 participants were randomly assigned to the active group which received SGLT-2 inhibitor and background treatment with pioglitazone with or without metformin while 473 were randomly assigned to control group which received pioglitazone with or without metformin. The 4 included trials had short-term, core period about half a year (24-26 weeks), and long-term, extension period (48-76 weeks). In core period, the active group received add-on treatment with SGLT-2 inhibitor under the background treatment with pioglitazone with or without metformin and was compared with control group which received only background treatment. Referring to extension period, study designs were different among the included trials. Three trials[17,18,20] maintained comparable groups between SGLT-2 inhibitor plus pioglitazone versus pioglitazone in extension period while one trial[19] allowed ipragliflozin use in a controlled group, and data from this trial were not included for analysis of extension period. Risk of bias for included trials is presented in Table S1.

3.1 | Efficacy end-points

The assessment of the quality of a body of evidence for all end-points is shown in Table S2.

Pooling data from included trials showed that Hba1C reduction was larger in both low-dose SGLT-2 inhibitors plus pioglitazone (mean difference: −0.59%, 95% CI: −0.77 to −0.41%, $P < 0.001$) and high- dose SGLT-2 inhibitors plus pioglitazone (mean difference: −0.65%, 95% CI: −0.78 to −0.53%, $P < 0.001$) than pioglitazone alone in 24-26 weeks (Figure 1A). The quality of a body of evidence was found to be low (low-dose) to moderate (high-dose). We conducted

sensitivity analysis and heterogeneity was not noted after excluding SPOTLIGHT trial, which related to more substantial HbA1c reduction. There was no substantial publication bias on funnel plot (Figure S2). The efficacy of Hba1c reduction was sustained to extension period (48-76 weeks; Figure S2A).

Pooling data from included trials showed that more patients with use of SGLT-2 inhibitor plus pioglitazone than use of pioglitazone in achieving Hba1C <7% (37.5% vs 17.5%; OR: 3.21, 95% CI: 1.99 to 5.16, $P < 0.001$), and there was no heterogeneity among trials ($P = 0.22$; Figure 1B). The quality of a body of evidence was found to be moderate and additional 230 per 1000 diabetic patients treated with SGLT-2 inhibitor plus pioglitazone compared with pioglitazone alone would achieve Hba1c <7%.

Pooling data from included trials showed fasting glucose reduction was larger in both low-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −28.23 mg/dL, 95% CI: −36.57 to −19.89 mg/dL, $P < 0.001$) and high-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −29.46 mg/dL, 95% CI: −35.58 to −23.34 mg/dL, $P < 0.001$) than pioglitazone alone (Figure 1C). The quality of a body of evidence was found to be low. The efficacy of fasting glucose reduction was sustained to extension period (48-76 weeks; Figure S2B).

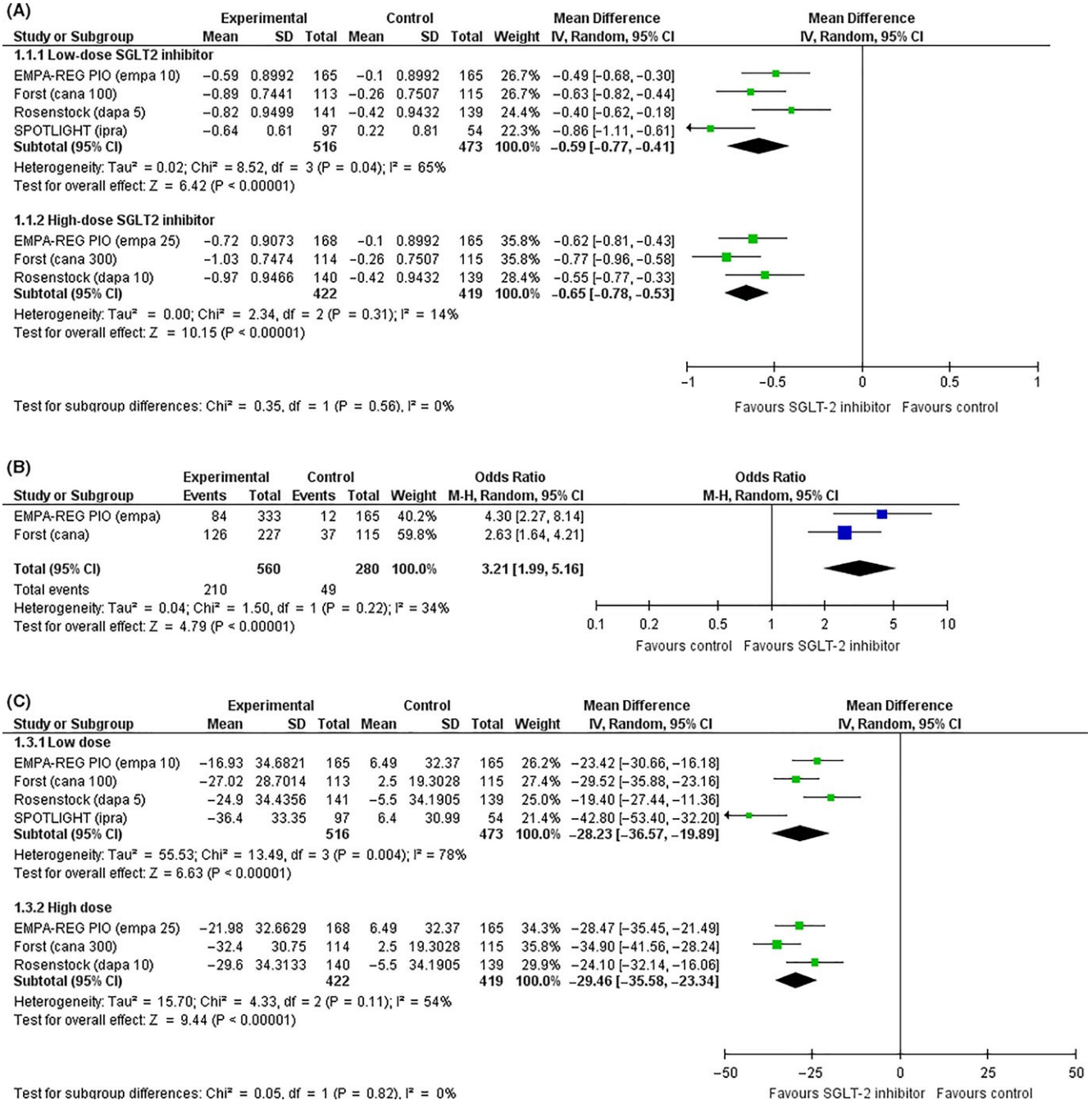

FIGURE 1 Glycaemic control efficacy: A, HbA1c change from baseline; B, participants achieved Hba1c <7%; C, fasting glucose change from baseline in an SGLT-2 inhibitor plus pioglitazone vs pioglitazone at 24-26 weeks

Heterogeneity was observed among low-dose SGLT-2 inhibitor plus pioglitazone vs pioglitazone in end-points of Hba1C change (I^2 = 65%) and fasting glucose change (I^2 = 78%), probably due to stronger glucose reducing effect of ipragliflozin. Heterogeneity disappeared when we excluded SPOTLIGHT study (I^2 = 18% for Hba1c change, I^2 = 50% for fasting glucose change).

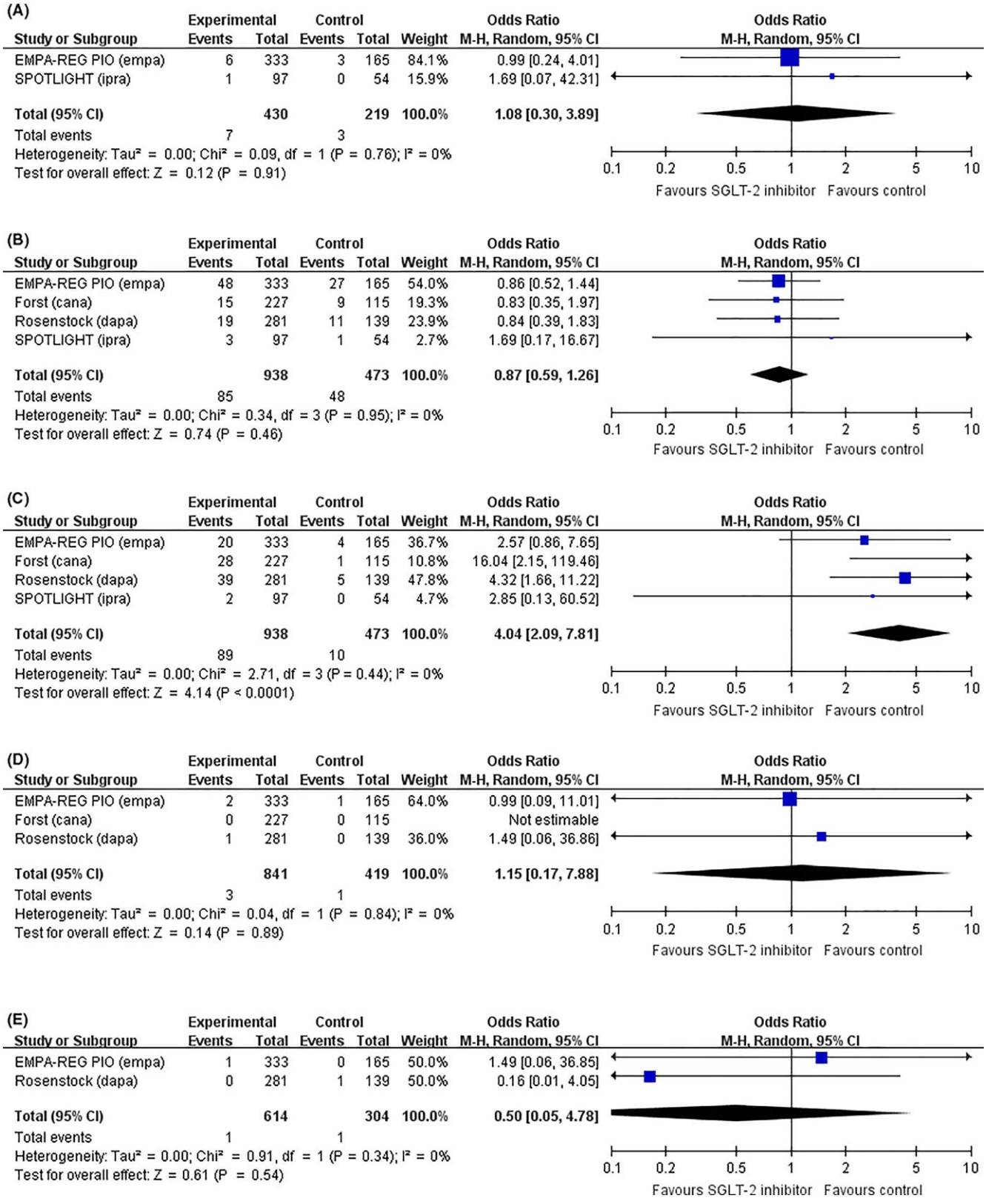

FIGURE 2 Safety assessments: A, risk of hypoglycaemia; B, urinal tract infection; C, genital tract infection; D, death rate; E, heart failure; in an SGLT-2 inhibitor plus pioglitazone vs pioglitazone

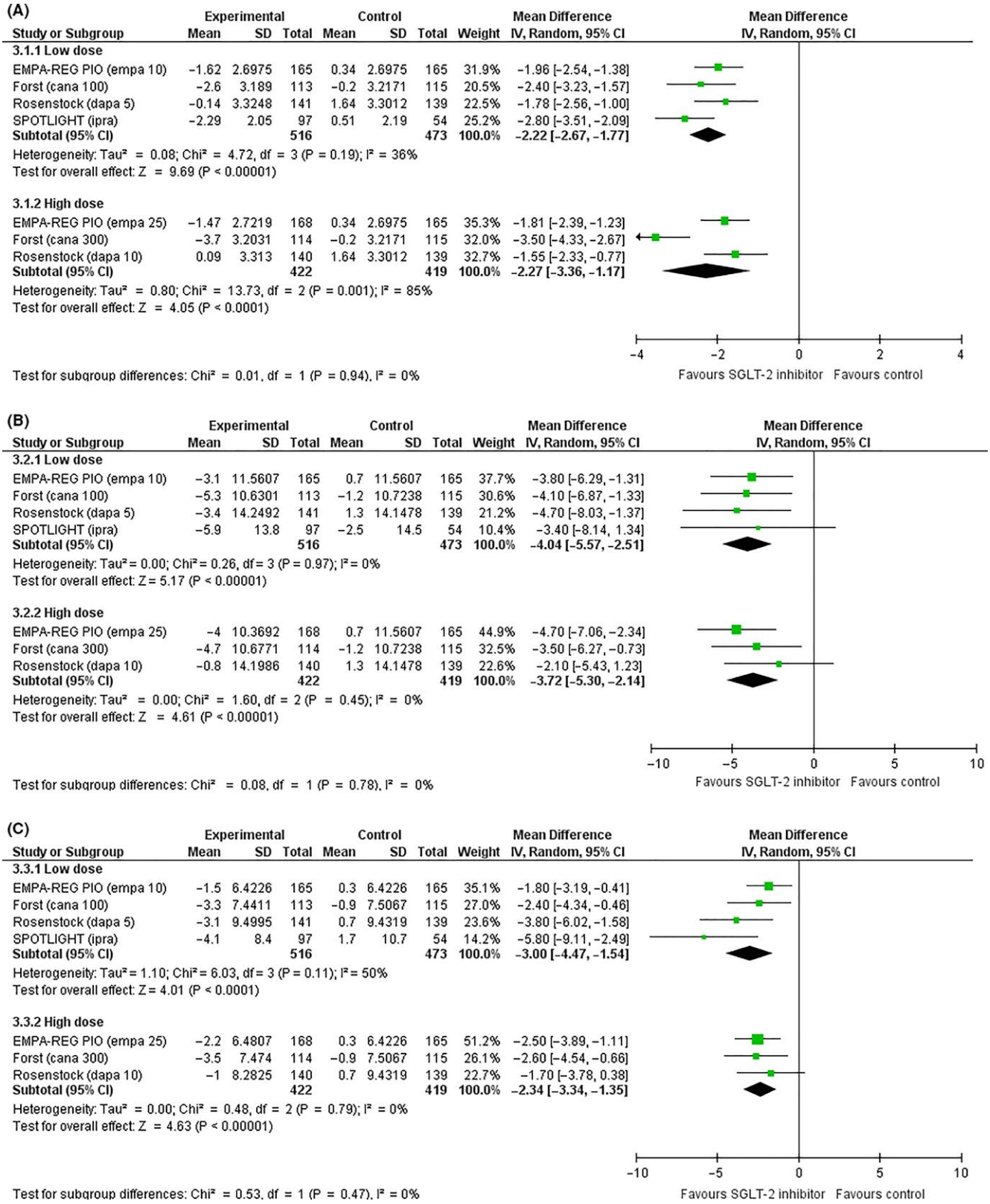

FIGURE 3 Body weight and blood pressure change from baseline: A, body weight change; B, systolic blood pressure change; C, diastolic blood pressure change in an SGLT-2 inhibitor plus pioglitazone vs pioglitazone

3.2 | Safety end-points

Pooling results from the included trials showed that SGLT-2 inhibitor plus pioglitazone compared with pioglitazone did not increase risk of hypoglycaemia (OR: 1.08, 95% CI: 0.30 to 3.89, $P = 0.91$; Figure 2A) or urinal tract infection (OR: 0.87, 95% CI: 0.59 to 1.26, $P = 0.46$; Figure 2B) but did increase genital tract infection (OR: 4.04, 95% CI: 2.09 to 7.81, $P < 0.001$; Figure 2C). The death rate was not

significantly different between active group and control group (OR: 1.15, 95% CI: 0.17 to 7.88, $P = 0.89$; Figure 2D). The heart failure was not significantly different between active group and control group (OR: 0.50, 95% CI: 0.05 to 4.78, $P = 0.54$; Figure 2E). The quality of a body of evidence was found to be low to moderate.

3.3 | Body weight and blood pressure change

At the short-term core period, pooling data from included trials showed that both low-dose and high-dose SGLT-2 inhibitors plus pioglitazone were associated with larger weight change than pioglitazone alone (low-dose: mean difference: −2.22 kg, 95% CI −2.67 to −1.77 kg, $P < 0.001$; high-dose: mean difference: −2.27 kg, 95% CI −3.36 to −1.17 kg, $P < 0.001$; Figure 3A). Heterogeneity was noted in high-dose SGLT-2 inhibitors ($P = 0.001$). The quality of a body of evidence was found to be low. The body weight reduction was sustained to extension period (Figure S3A).

Pooling data from included trials showed that both low-dose (mean difference: −4.04 mm Hg, 95% CI: −5.57 to −2.51 mm Hg, $P < 0.001$) and high-dose (mean difference: −3.72 mm Hg, 95% CI: −5.30 to −2.14 mm Hg, $P < 0.001$) SGLT-2 inhibitors combined with pioglitazone had a better systolic blood pressure control than pioglitazone at the end of core period (Figure 3B). Pooling data from included trials showed that both low-dose (mean difference: −3.00 mm Hg, 95% CI: −4.47 to −1.54 mm Hg, $P < 0.001$) and high-dose (mean difference: −2.34 mm Hg, 95% CI: −3.34 to −1.35 mm Hg, $P < 0.001$) SGLT-2 inhibitors combined with pioglitazone had a better diastolic blood pressure control than pioglitazone at the end of core period (Figure 3C). The quality of a body of evidence was found to be moderate to high. Similar results were found at the end of 48-72 weeks (Figure S3B,C).

4 | DISCUSSION

In this meta-analysis comprising 4 randomized controlled trials with more than 1400 type 2 diabetic patients, we found SGLT-2 inhibitors added on to pioglitazone were more efficacious in controlling blood glucose than pioglitazone alone, as shown with several indices of better glycaemic control such as HbA1c reduction, lower fasting glucose and percentage of participants achieving HbA1c <7%. Also, SGLT-2 inhibitor as add-on therapy to pioglitazone vs pioglitazone, reduced weight and blood pressure. The risks of death, heart failure, hypoglycaemia and urinary tract infection were not different between active and control groups, although genital tract infection was more frequently seen in active group. These results were consistent at 24-26 weeks and 48-72 weeks.

Although metformin is widely accepted as the first line of oral hypoglycaemic drug for type 2 diabetes mellitus,[21] the number of patients who achieve the target glucose level with a single oral anti-hyperglycaemic agent decreases as type 2 diabetes mellitus progresses.[2] Combination therapy of anti-hyperglycaemic drugs is often necessary to achieve glycaemic goal.

Our meta-analysis showed that compared to pioglitazone alone, SGLT-2 inhibitor plus pioglitazone was associated with sustained glycaemic control, without increasing risk of hypoglycaemia. Hypoglycaemia due to anti-hyperglycaemic drugs causes significant morbidity and occasional mortality, limiting maintenance of euglycaemia.[22] A meta-regression analysis suggested that HbA1c reduction was significantly associated with a decreased risk of major cardiovascular events.[23] Furthermore, an anti-hyperglycaemic drug, which improves cardiovascular outcomes, is considered to be the therapeutic agent of choice.[24,25] Both pioglitazone and SGLT-2 are associated with reduction of major cardiovascular events.[6,13,26] Pioglitazone, an insulin sensitizer agent, might slow down, or even reverse, the atherosclerotic process, thus reducing myocardial infarction and stroke,[27-29] and the benefits of pioglitazone are most prominent in diabetic patients with established cardiovascular disease or stroke.[30,31] On the other hand, SGLT-2 inhibitors reduce major cardiovascular events, mainly through reducing cardiovascular death.[13,26] SGLT-2 inhibitors also substantially reduced heart failure.[13,26] Heart failure may play a role in the mortality of patients with coronary artery disease, and reduced risk of death through heart failure may provide at least one mechanism to explain the reduced risk of cardiovascular death with SGLT-2 inhibitors.[29] Also, our meta-analysis showed that SGLT-2 inhibitors plus pioglitazone vs pioglitazone reduced systolic/diastolic blood pressure by 3-4/2-3 mm Hg which might also be beneficial for diabetic patients. Taking all of this together raises the possibility that the combination of metformin, pioglitazone and a SGLT-2 inhibitor might be additive, with regard to reducing, cardiovascular risk in people with diabetes at high cardiovascular risk.[29]

Pioglitazone was found to increase the risk of heart failure, probably due to fluid retention, and increased body weight.[6,32] On the other hand, osmotic diuresis caused by SGLT-2 inhibitors leads to mild volume depletion and total caloric loss related to urinary glucose excretion participates.[11] Our study suggested that combination therapy with SGLT-2 inhibitor and pioglitazone significantly reverses the side effect of body weight gain caused by pioglitazone. Also, moderate weight loss has been shown to help fasting blood glucose control,[33] and such benefits can be achieved through long-term combination therapy with SGLT-2 inhibitor and pioglitazone. Moreover, since main composition of reduced body weight caused by SGLT-2 inhibitor was fat mass, rather than muscle mass,[34] it would not cause additional problem of fragility. Although the current meta-analysis did not assess end-point of heart failure due to such information not provided by included trials, it is plausible that combination of SGLT-2 inhibitor and pioglitazone would have fewer heart failure than pioglitazone since SGLT-2 inhibitors have been shown to substantially reduce heart failure in large clinical trials.[13,26,35] From the perspective of safety, combination therapy with SGLT-2 inhibitor plus pioglitazone might be a better choice than pioglitazone for the treatment of type 2 diabetes mellitus in most clinical scenarios if patients can follow good hygiene to avoid genital tract infection, and there are no contraindications, such as severe chronic kidney disease, for use of SGLT-2 inhibitors.

When the first-line anti-hyperglycaemic drug metformin is inadequate for blood glucose control, we argue that adding pioglitazone and an SGLT-2 inhibitor simultaneously might be an attractive strategy compared with other combination of anti-hyperglycaemic drugs. For example, although combination therapy with an SGLT-2 inhibitor and a glucagon-like peptide-1 receptor agonist may produce additive cardiovascular benefits,[36] cost concerns make some countries, such as Taiwan, not to allow national health insurance to reimburse for doing so. Also, combination therapy with glucagon-like peptide-1 receptor agonist, exenatide and pioglitazone is a very effective and safe therapeutic option in diabetic patients with poorly controlled by metformin plus a sulfonylurea,[37] but some people may hesitate to receive regular injection if they have an option for diabetic control by only through oral anti-hyperglycaemic drugs.

Our study has limitations. First, meta-analysis may be biased when the literature search fails to identify all relevant trials. To minimize these risks, we performed thorough searches across multiple literature and trial databases and used explicit criteria for study selection, data abstraction and data analysis. Second, sample size was moderate in all included trials, and no end-point of major cardiovascular events was assessed. Also, the individuals with previous cardiovascular disease were excluded from included trials. Whether combination of SGLT-2 inhibitor and pioglitazone has beneficial effects on cardiovascular outcomes, especially in patients with high cardiovascular risk, was not known in the current meta-analysis. Third, the quality of a body of evidence was found to be low to moderate in most end-points.

In conclusion, in this meta-analysis of randomized controlled trials comparing an SGLT-2 inhibitor plus pioglitazone vs pioglitazone, we found that an SGLT-2 inhibitor plus pioglitazone was associated with better glycaemic control, and reduced body weight and blood pressure, without any increase in hypoglycaemia, death or urinary tract infection. However, genital tract infection increased with combination therapy. Large randomized controlled trials might be warranted to evaluate whether such combination therapy is beneficial for cardiovascular outcomes in diabetic patients with high cardiovascular risks.

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None.

ETHICAL APPROVAL

Not required.

CONFLICT OF INTEREST

Nothing to declare.

AUTHORS CONTRIBUTION

HWL and ML contributed to the acquisition and interpretation of data and writing of the manuscript. YLW, YMS and BO contributed to the interpretation of data and reviewed/edited the manuscript.

TRANSPARENCY DECLARATION

Hung-Wei Liao, the lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA ACCESSIBILITY

All data are included within the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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