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ORIGINAL ARTICLE

Comparison between sodium–glucose cotransporter 2 inhibitors and pioglitazone as additions to insulin therapy in type 2 diabetes patients: A systematic review with an indirect comparison meta-analysis

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ABSTRACT

Aims/Introduction: We aimed to evaluate the efficacy and safety of pioglitazone (PIO) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) as additions to insulin therapy for the management of type 2 diabetes mellitus.

Materials and Methods: We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov through December 2016. Randomized controlled trials published in English that compared SGLT2i plus insulin (SGLT2i/INS) or PIO plus insulin (PIO/INS) with placebo plus insulin (PCB/INS) in type 2 diabetes mellitus patients were included. We compared the efficacy and safety between SGLT2i/INS and PIO/INS indirectly.

Results: A total of 14 randomized controlled trials comparing 7,226 participants were included (8 SGLT2i and 6 PIO studies). SGLT2i/INS achieved similar reductions in hemoglobin A1c (weighted mean difference [WMD] −0.01% [−0.1 mmol/mol], 95% confidence interval [CI] −0.25 to 0.22% [−2.7 to −2.4 mmol/mol]; $P = 0.896$) and fasting plasma glucose (WMD −0.90 mg/dL, 95% CI: −15.50 to 13.71 mg/dL; $P = 0.904$), and a similar proportion of participants achieved hemoglobin A1c <7.0% (<53.0 mmol/mol; relative risk 0.98, 95% CI: 0.73 to 1.33; $P = 0.917$) as compared with the PIO/INS group, with greater weight reduction (WMD −4.54 kg, 95% CI: −5.67 to −3.41 kg; $P < 0.001$). PIO/INS showed non-significant trends toward a higher risk of hypoglycemia (relative risk 1.15, 95% CI: 0.97 to 1.35; $P = 0.102$) and higher reduction of total daily insulin doses (WMD −2.45 IU/day, 95% CI: −7.30 to 2.40 IU/day; $P = 0.438$).

Conclusions: Both PIO and SGLT2i are feasible adjunctive oral agents to pre-existing insulin therapy in individuals with inadequately controlled type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus is characterized by peripheral insulin resistance with progressive impairment in pancreatic β-cell function, leading to hyperglycemia[1]. Due to the progressive deterioration in insulin secretion and failure of oral antidiabetic drugs (OADs; including metformin and sulfonylureas) in maintaining optimal glycemic targets, many individuals with type 2 diabetes mellitus eventually require insulin therapy[2].

Although various insulin formulations are available and the dose of insulin can be uptitrated to maintain glycemic targets, several OADs need to be administered to individuals with poorly controlled type 2 diabetes mellitus, despite the use of insulin therapy[3,4]. This combined use of OADs with concurrent insulin treatment minimizes the risk of hypoglycemia associated

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with insulin use, and might help reduce the insulin dose, while simultaneously facilitating further improvement in glycemic control[4]. However, despite these advantages of combined OADs and insulin treatment, there is no clear guideline on which OADs – beyond insulin itself – are the most appropriate agents.

Thiazolidinediones (TZDs) improve insulin resistance to peripheral tissues by increasing insulin-dependent glucose disposal and decreasing hepatic glucose output[1]. Pioglitazone (PIO) – a currently clinically available TZD – in combination with insulin might improve glycemic control at a reduced insulin dose in individuals with type 2 diabetes mellitus that was poorly controlled with previous insulin therapy[5].

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are a novel class of OADs that exert insulin-independent hypoglycemic effects by increasing urinary glucose excretion[6]. Evidence from randomized controlled trials (RCTs) and systematic reviews suggests that SGLT2i can improve glycemic control, while also resulting in weight loss and reduced risk of hypoglycemia[7,8]. The addition of SGLT2i to insulin treatment improves glycemic control and reduces bodyweight, and is associated with a similar risk of hypoglycemia, as compared with placebo treatment[9–14]. Hence, SGLT2i are feasible adjunctive agents to insulin therapy for type 2 diabetes mellitus.

Thus, the adjunctive use of either TZD (usually PIO) or SGLT2i might help improve glycemic control and reduce the amount of insulin needed, particularly in those requiring large insulin doses[3]. However, no head-to-head trial has compared SGLT2i and PIO in individuals with type 2 diabetes mellitus that is inadequately controlled with insulin.

In the present systematic review and meta-analysis, we aimed to evaluate the efficacy and safety of the addition of PIO and SGLT2i to insulin therapy for the management of type 2 diabetes mellitus by carrying out an indirect comparison using studies with either the addition of PIO or SGLT2i to pre-existing insulin therapy in individuals with type 2 diabetes mellitus.

METHODS

Search strategy and Study selection

Before this meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was assessed[15]. We comprehensively searched PubMed, EMBASE and the Cochrane Library from inception to 31 December 2016 to identify eligible RCTs involving PIO or SGLT2i. Additional searches of ClinicalTrials.gov and the references of the included trials and relevant meta-analyses were also carried out. The search terms for PIO and SGLT2i are shown in Tables S1 and S2, respectively.

We included RCTs that compared SGLT2i plus insulin (SGLT2i/INS) or PIO plus insulin (PIO/INS) treatment with a placebo plus insulin (PCB/INS) treatment. English-language RCTs with a follow-up period of ≥12 weeks that included information on the change in hemoglobin A1c (HbA1c) levels from baseline were eligible for inclusion. Studies in the extended phase were excluded. We assessed the study titles, abstracts and full texts to confirm whether the studies met the inclusion criteria. Any disagreements between the authors (YKC and CHJ) were resolved by consensus. Flow charts of the study selection process are described in Figure S1.

Data extraction

The primary outcome was the change in HbA1c from baseline to the final end-point of each study. The secondary outcomes included a change in fasting plasma glucose (FPG) levels, bodyweight and insulin dose from baseline; the proportion of patients achieving the therapeutic goal of HbA1c <7.0% (<53.0 mmol/mol); and the risk of hypoglycemia at the final end-point of each study. For studies wherein the change from baseline was not reported, this change was estimated as the difference in the value at baseline and that at the end of treatment. The FPG value in mmol/L was converted to mg/dL by using the following formula: 1 mmol/L = 18 mg/dL. The definitions of hypoglycemia are shown in Tables S3 and S4. In addition to the outcome measures, the two authors (YKC and CHJ) also extracted data on the author and publication year of each study, antidiabetic medications besides insulin, duration of treatment, number of randomized participants, age, percentage of men, duration of diabetes, body mass index (BMI), baseline HbA1c levels and baseline total daily insulin dose. For continuous outcomes, the mean differences between the baseline and final measures were extracted in each group, along with its variability (standard deviation, standard error or confidence interval). For dichotomous outcomes, the numbers of events and randomized participants for the treatment and placebo groups were extracted. For dose-ranging studies, we selected only the approved doses of each drug. Two authors (YKC and CHJ) independently carried out data extraction according to the pre-specified protocol. Any discrepancy was resolved by consensus.

Assessment of methodological quality

We evaluated the quality of the included RCTs according to the Cochrane Collaboration's tool for assessing the risk of bias[16]. Two independent reviewers (YKC and CHJ) carried out assessments of the risk of bias, and any disagreement was discussed until consensus was reached. The risks of bias were categorized as high, low and unclear. Summaries of the risk of bias assessment are presented in Table S4 and Figure S2.

Statistical analysis

We calculated the pooled estimates of the weighted mean differences (WMDs) and 95% confidence intervals (CIs) for continuous outcomes, including the changes in HbA1c, FPG, bodyweight and insulin doses, as well as the pooled risk ratios (RRs) and their 95% CIs for dichotomous outcomes, including the proportion of participants achieving target HbA1c values and the risk of hypoglycemia. We evaluated the validity of the methods for the analysis of indirect comparisons and

determined an indirect estimate of the treatment effect of PIO/INS vs SGLT2i/INS[17,18]. We first assessed the homogeneity of the results from the PCB/INS groups among the included studies as a common comparator for the indirect comparison, and then evaluated whether the results of the treatment efficacy were sufficiently homogeneous to be pooled for the comparison of SGLT2i/INS vs PCB/INS and PIO/INS vs PCB/INS. We also qualitatively evaluated the participants' characteristics and treatment details in terms of comparability. We assumed that the study participants' age, sex, BMI, baseline HbA1c, duration of diabetes and insulin dose at baseline could be putative confounders influencing the treatment effect. Therefore, we assessed the relationship between each possible confounder and outcome. We used the covariates as confounders at a significance level of 0.2.

First, the crude estimate of the treatment effect was determined between SGLT2i/INS and PIO/INS by simply synthesizing the pooled treatment effect estimate of each treatment, compared with the placebo indirectly. We then carried out multiple meta-regression analyses adjusted for covariates. The RR was log-transformed in the calculation. We used a random-effects model to account for the variability across the included studies, by using a restricted maximum likelihood estimate of the between-studies variance. The I^2 statistic was used to assess the magnitude of the heterogeneity between studies. The potential risk of publication bias was evaluated by constructing funnel plots of the primary outcome separately for the SGLT2i and PIO studies, and the asymmetry was assessed by using Egger's test. We used STATA version 11 (StataCorp, College Station, Texas, USA) for all analyses.

RESULTS

Search results and characteristics

A total of 998 and 260 citations for PIO and SGLT2i, respectively, were identified through our electronic literature search, of which six eligible RCTs involving 2,938 participants with type 2 diabetes mellitus who were randomized into PIO or placebo groups, and eight eligible RCTs involving 4,288 participants with type 2 diabetes mellitus randomized into SGLT2i or placebo groups were finally enrolled in our meta-analysis. Flow charts of the study selection process are shown in Figure S1, and the characteristics of the included studies are presented in Tables 1 and 2.

Efficacy

Meta-analysis of the six PIO studies and eight SGLT2i studies showed that both the PIO/INS (WMD −0.71% [−7.7 mmol/mol], 95% CI: −0.96 to −0.46% [−10.5 to 5.0 mmol/mol]; $P < 0.001$) and SGLT2i/INS groups (WMD −0.66% [−7.2 mmol/mol], 95% CI: −0.80 to −0.52% [−8.7 to −5.7 mmol/mol]; $P < 0.001$) were associated with a greater reduction of HbA1c than the respective PCB/INS group (Figure 1a)[5,9,11–14,19–26]. The result of the unadjusted indirect comparison showed that the PIO/INS and SGLT2i/INS groups did not significantly differ in terms of

Table 1 | Baseline characteristics of the included pioglitazone studies

Author (year)	Background therapy	Regimen of insulin therapy	Interventions	Duration (weeks)	*n*	Age (years)	Male (%)	BMI (kg/m^2)	HbA1c (%)	HbA1c (mmol/mol)	FPG (mg/dL)	Insulin dose (units/day)
Rosenstock (2002)	Insulin (OADs wash out)	Not reported	Placebo	16	187	56.7	45.5	33.2	9.75	83.1	220.5	70.7
			PIO 15 mg		191	56.9	46.1	33.2	9.75	83.1	221.7	70.2
			PIO 30 mg		188	57.5	50.5	34.3	9.84	84.0	229.3	72.3
Mattoo (2005)	Insulin ± OADs	Not reported	Placebo	24	147	58.9	42.9	31.8	8.79	72.6	203.1	0.96‡
			PIO 30 mg		142	58.8	43.7	32.5	8.85	73.2	204.7	0.92‡
Berhanu (2007)	Insulin ± Met	Various insulin regimen†	Placebo	20	110	52.5	41.1	31.8	8.6	70.5	109.7	57.7
			PIO 45 mg		112	52.9	43.6	30.7	8.4	68.3	111.1	55.8
Charbonnel (2010)	Insulin ± OADs	Various insulin regimen†	Placebo	149	896	61.2	61.0	31.9	8.5	69.4	NA	46.7
			PIO 45 mg		864	61.7	58.2	31.6	8.4	68.3	NA	46.5
Galle (2012)	Insulin	Basal and prandial insulin	Placebo	24	19	69.6	68.4	30.3	7.7	60.7	160.5	55.37
			PIO 30 mg		20	68.9	70.0	31.5	7.4	57.4	159.9	63.96
Kharazm-kia (2014)	Insulin	Insulin NPH	Placebo	16	31	54.8	51.6	NA	7.8	61.7	145.5	34.1
			PIO 30 mg		31	50.2	77.4	NA	8.6	70.5	136.0	38.2

Data are expressed as the mean (continuous variables) or percentage (dichotomous variables), unless otherwise indicated. †Various insulin regimen includes non-intensified (1–2 injections/day) and intensified insulin regimens (>3 injections/day). ‡U/day/kg. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; Met, metformin; NA, not available; NPH, neutral protamine Hagedorn; OADs, oral antidiabetic agents; PIO, pioglitazone.

Table 2 | Baseline characteristics of the included sodium–glucose cotransporter 2 inhibitor studies

Author (year)	Background therapy	Regimen of insulin therapy	Interventions	Duration (weeks)	*n*	Age (years)	Male (%)	BMI (kg/m^2)	HbA1c (%)	HbA1c (mmol/mol)	FPG (mg/dL)	Insulin dose (units/day)
Wilding (2009)	Insulin ± Met ± TZD	Not reported	Placebo	12	23	58.4	69.6	34.8	8.4	68.3	165.9	90[§]
			Dapagliflozin 10 mg		24	55.7	54.2	35.5	8.4	68.3	156.0	93[§]
Wilding (2012)	Insulin ± OADs	Not reported	Placebo	48	193	58.8	49.2	33.1	8.47	69.1	170.6	73.7
			Dapagliflozin 5 mg		211	59.3	47.4	33.0	8.62	70.7	185.4	77.0
			Dapagliflozin 10 mg		194	59.3	44.8	33.4	8.57	70.2	173.1	78.0
Rosenstock (2014)	Insulin ± Met	MDI	Placebo	52	188	55.3	40	34.7	8.33	67.5	151.5	93.1
			Empagliflozin 10 mg		186	56.7	52	34.7	8.39	68.2	159.1	89.9
			Empagliflozin 25 mg		189	58.0	44	35.0	8.29	67.1	150.3	92.9
Neal (2015)	Insulin ± Met ± SU	Various insulin regimen[†]	Placebo	52	690	63[†]	66	33.1	8.3	67.2	165.8	58[§]
			Canagliflozin 100 mg		692	62[†]	67	33.0	8.3	67.2	165.8	60[§]
			Canagliflozin 300 mg		690	63[†]	65	33.3	8.3	67.2	165.8	60[§]
Rosenstock (2015)	Insulin ± Met ± SU	Basal insulin[‡]	Placebo	78	170	58.1	53	31.8	8.2	66.1	142.3	47.8
			Empagliflozin 10 mg		169	58.6	55	32.1	8.3	67.2	138.7	45.1
			Empagliflozin 25 mg		155	59.9	60	32.7	8.3	67.2	145.9	48.4
Inagaki (2016)	Insulin	Various insulin regimen[†]	Placebo	16	70	56.1	70.0	25.99	8.85	73.2	169.1	28.1
			Canagliflozin 100 mg		76	59.7	57.9	26.88	8.89	73.7	169.9	31.1
Araki (2016)	Insulin ± DPP4i	Not reported	Placebo	16	60	57.6	66.7	26.1	8.52	69.6	159.7	40.58
			Dapagliflozin 5 mg		122	58.3	73.0	26.9	8.26	66.8	160.7	37.87
Ishihara (2016)	Insulin ± OADs	Various insulin regimen[†]	Placebo	16	87	59.2	58.6	26.4	8.6	70.5	160.5	Range[¶]
			Ipragliflozin 50 mg		175	58.7	62.5	25.6	8.7	71.6	159.9	

Data are expressed as the mean (continuous variables) or percentage (dichotomous variables), unless otherwise indicated. [†]Various insulin regimen includes non-intensified (1–2 injections/day) and intensified insulin regimens (>3 injections/day). [‡]Basal insulin includes glargine, detemir and NPH (Neutral protamine Hagedorn). [§]Median value. [¶]Total insulin dose (units/day) in the placebo group (*n* [%]) and ipragliflozin group (*n* [%]): <15: 30 (34.5) and 59 (35.1); ≥15 to <30: 41 (47.1) and 71 (42.3): ≥30, 16 (18.4) and 38 (22.6). BMI, body mass index; DPP4i, dipeptidyl peptidase-4 inhibitors; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; MDI, multiple daily injections; Met, metformin; NA, not available; OADs, oral antidiabetic agents; SGLT2i, sodium–glucose cotransporter 2 inhibitors; SU, sulfonylurea; TZD, thiazolidinedione.

HbA1c reduction (WMD −0.05% [−0.5 mmol/mol], 95% CI: −0.32 to 0.23% [−3.5 to 2.5 mmol/mol]; $P = 0.745$). We identified sex and BMI as confounding covariates to be included in the model ($P = 0.076$ and $P = 0.015$, respectively). The HbA1c reduction still showed no difference between the PIO/INS and SGLT2i/INS groups after adjusting for those variables (WMD −0.01% [−0.1 mmol/mol]. 95% CI: −0.25 to 0.22% [−2.7 to −2.4 mmol/mol]; $P = 0.896$). Evaluation with the funnel plot and Egger's regression test did not detect any obvious asymmetric distribution or small study effect (Figure S3). However, this result did not clearly show the absence of publication bias, owing to the small number of studies included and the large heterogeneity.

Figure 1b shows the changes in FPG levels from baseline, which were assessed in four PIO studies ($n = 1{,}116$)[5,19,20,22] and six SGLT2i studies ($n = 1{,}683$)[9,11–14,26]. Both the PIO/INS and SGLT2i/INS groups showed significantly reduced FPG levels compared with the respective PCB/INS group ($P < 0.001$ for both). No significant difference in FPG level reduction was observed when comparing the PIO/INS and SGLT2i/INS groups through unadjusted indirect comparisons (WMD −12.53 mg/dL, 95% CI: −26.34 to 1.28 mg/dL; $P = 0.075$), and after adjusting for age, sex, BMI and baseline HbA1c (WMD −0.90 mg/dL, 95% CI: −15.50 to 13.71 mg/dL; $P = 0.904$).

Two PIO studies ($n = 2{,}049$)[20,21] and three SGLT2i studies ($n = 1{,}093$)[9,11,12] reported the proportion of participants attaining the target HbA1c level of <7.0% (<53.0 mmol/mol; Figure 1c). Both the PIO/INS and SGLT2i/INS groups showed greater proportions of participants who attained this target compared with the PCB/INS group ($P = 0.041$ and $P < 0.001$, respectively). The difference in the proportion of participants attaining the HbA1c target in the SGLT2i/INS and PIO/INS groups was not significant, as determined through indirect comparison (RR 0.98, 95% CI: 0.73–1.33; $P = 0.917$). We did not adjust for any covariates, as there was no suitable covariate to be adjusted for.

Five PIO studies ($n = 2{,}217$)[5,19–21,23] and seven SGLT2i studies ($n = 2{,}292$)[9,11–14,24,26] assessed the change in bodyweight from baseline (Figure 2a). The SGLT2i/INS group associated with significant weight loss compared with the PCB/INS group (WMD −2.11 kg, 95% CI: −2.58 to −1.64 kg; $P < 0.001$), whereas the bodyweight was significantly increased in the PIO/INS group compared with in the PCB/INS group (WMD 2.76 kg, 95% CI: 1.57–3.95 kg; $P < 0.001$). The difference in bodyweight change between the PIO/INS and SGLT2i/INS groups was significant when indirectly estimated in both the unadjusted analysis (WMD 5.03 kg, 95% CI: 3.88–6.19 kg; $P < 0.001$), and when adjusted for age and sex (WMD 4.54 kg, 95% CI: 3.41–5.67 kg; $P < 0.001$).

For the change in insulin doses from baseline, five PIO studies ($n = 2{,}650$)[5,19–23] and five SGLT2i studies ($n = 1{,}809$)[9,11,12,14,24] were included (Figure 2b). Both the PIO/INS (WMD −8.45 IU/day, 95% CI: −12.69 to −4.21 IU/day; $P < 0.001$) and SGLT2i/INS groups (WMD −6.75 IU/day, 95% CI: −10.71 to −2.79 IU/day; $P = 0.001$) showed significant decreases in insulin requirement compared with the respective PCB/INS group. The difference in the insulin dose reduction between the PIO/INS and SGLT2i/INS groups was not significant, as determined through indirect comparison analysis before (WMD −1.93 IU/day, 95% CI: −6.96 to 3.11 IU/day; $P = 0.453$) and after adjusting for BMI as a covariate (WMD −2.45 IU/day, 95% CI: −7.30 to 2.40 IU/day; $P = 0.323$), although there was a trend towards a greater reduction of insulin doses in the PIO/INS group than in the SGLT2i/INS group. The study by Kharazmkia *et al.*[23] was excluded from the adjusted indirect comparison, as it did not report the BMI of the participants, which was a covariate for adjustment.

Safety

Five PIO studies ($n = 2{,}876$)[5,19–22] and eight SGLT2i studies ($n = 4{,}239$)[9,11–14,24–26] were analyzed for the risk of hypoglycemia (Figure 2c). The unadjusted indirect comparison showed that the risk for hypoglycemia was higher in the PIO/INS group than in the SGLT2i/INS group (RR 1.24, 95% CI: 1.06–1.44; $P = 0.006$). After adjusting for age, sex, BMI and baseline HbA1c, the risk of hypoglycemia was not significantly different between the two groups (RR 1.15, 95% CI: 0.97–1.35; $P = 0.102$).

DISCUSSION

Most individuals with type 2 diabetes mellitus treated with OADs eventually require insulin therapy to manage the progressive deterioration in glycemic control over time[2]. However, therapies that depend on insulin supplementation are also associated with risks of hypoglycemia, weight gain and loss of effectiveness[11,27]. This complicated clinical situation is commonly exemplified by individuals with advanced type 2 diabetes mellitus who require high doses of insulin or require a novel strategy for better glycemic control[11,28]. The present meta-analysis is the first to evaluate the comparative efficacy and safety of PIO or SGLT2i add-on therapy to insulin. In general, PIO and SGLT2i treatment showed comparable improvements in glycemic control, with similar hypoglycemic risks and insulin-sparing effects in individuals with type 2 diabetes mellitus inadequately controlled with insulin. However, SGLT2i treatment achieved a greater reduction in bodyweight compared with PIO.

As adjunctive agents to insulin therapy, both PIO and SGLT2i were superior to the placebo in terms of improving glycemic control, as shown by the significant decreases in HbA1c and FPG levels, and higher proportion of participants who reached the HbA1c target. Indirect comparison analysis with or without adjustment for confounding variables showed that there were non-significant differences between the PIO/INS and SGLT2i/INS groups in terms of the reductions in HbA1c (Figure 1a) and FPG (Figure 1b). Furthermore, the proportion of participants who reached the HbA1c target did not show a significant difference (Figure 1c). These results imply

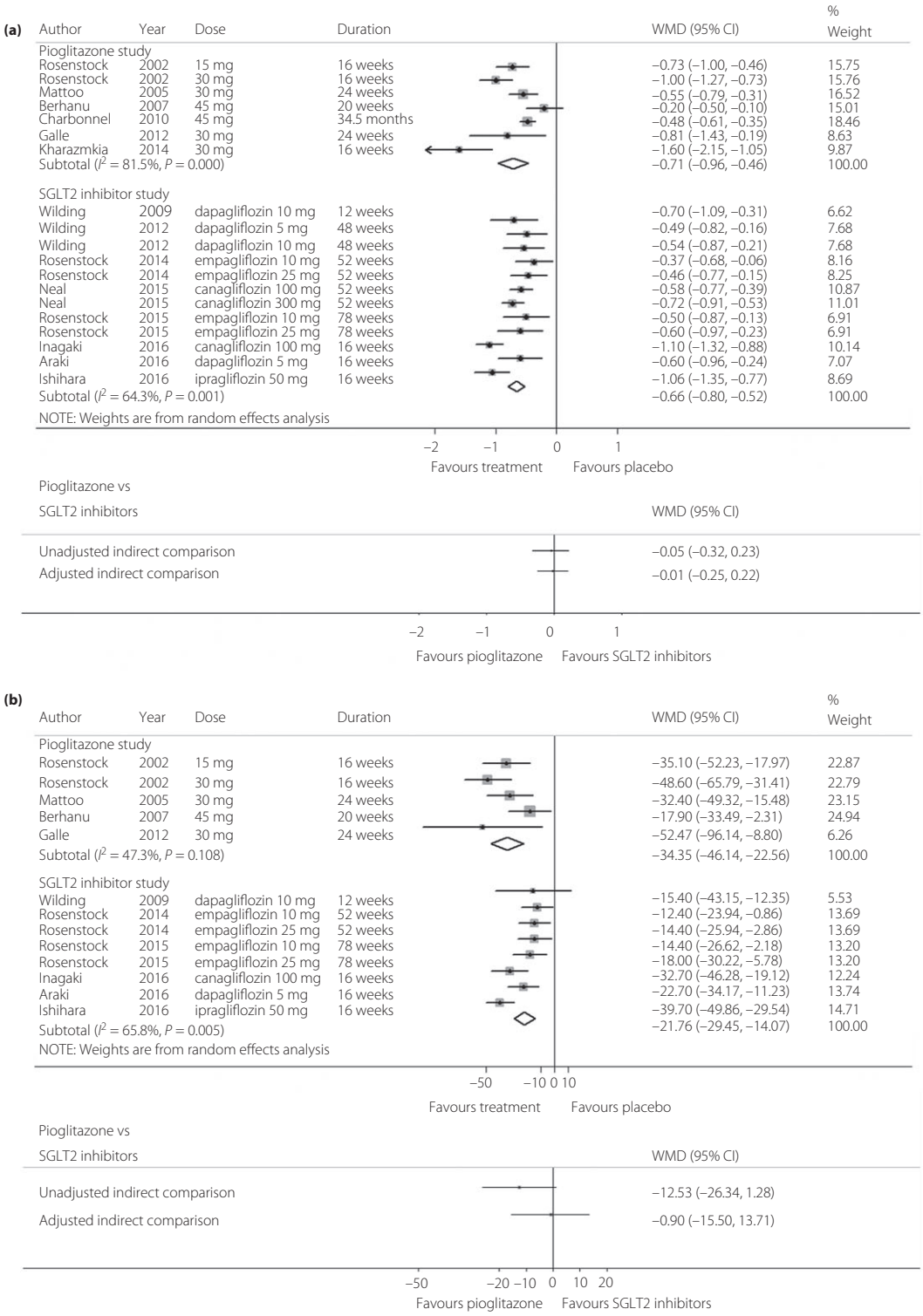

Figure 1 | Efficacy of pioglitazone (PIO) or sodium–glucose cotransporter 2 inhibitors (SGLT2i) added to insulin (INS) therapy. (a) Weighted mean differences (WMDs) in the changes in hemoglobin A1c (HbA1c) from baseline. (b) Weighted mean differences (WMDs) in the changes in fasting plasma glucose levels from baseline. (c) Relative risks (RRs) of attaining the target HbA1c level of <7.0% (53.0 mmol/mol). The tops of each figure represent the comparison of treatment (PIO/INS or SGLT2i/INS) vs PCB/INS, and the bottoms of each figure show the results by indirect comparison with adjustment of covariates when needed. The squares indicate each individual study's effects, and the size of the squares reflects the study's weight, with the horizontal lines extending from the symbols representing 95% confidence intervals (CIs). The diamonds indicate the pooled estimates. PCB, placebo.

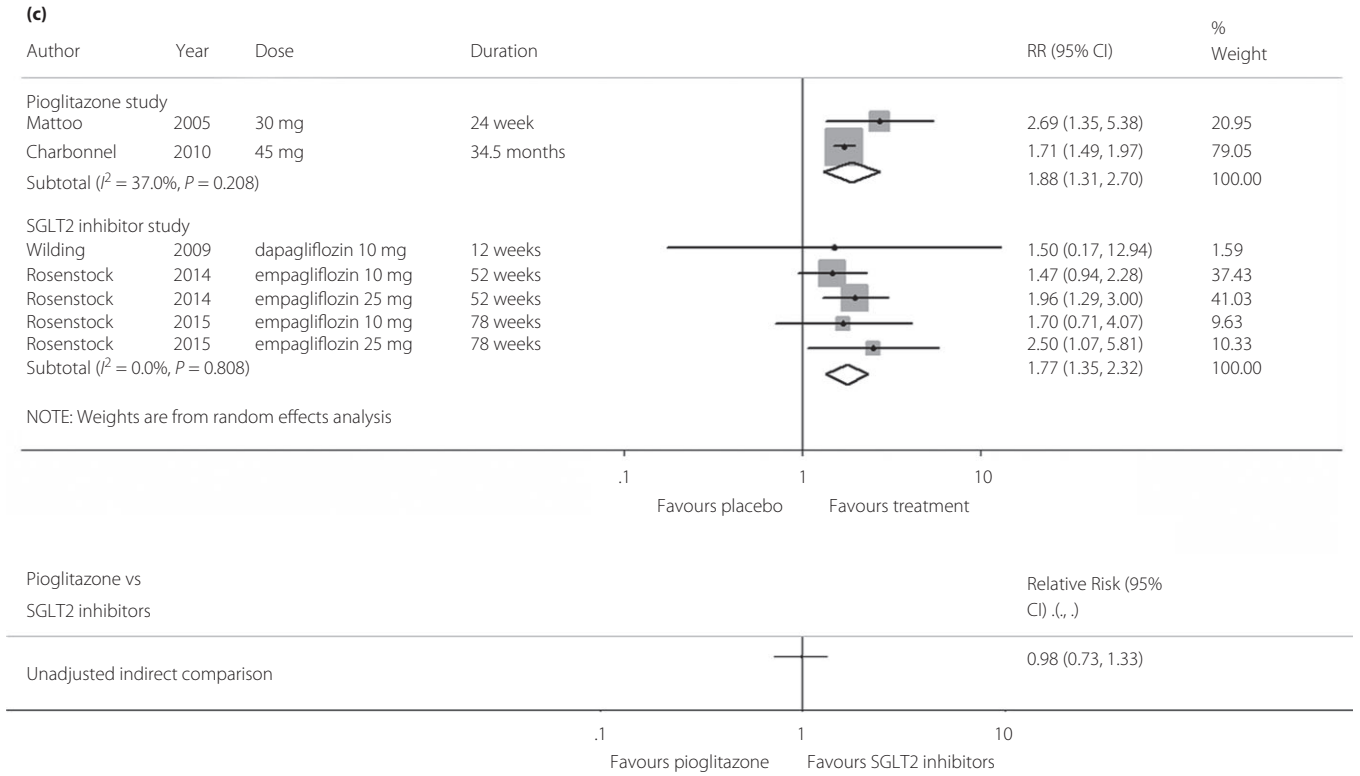

Figure 1 | Continued.

that both PIO and SGLT2i treatments confer comparable efficacy in glycemic control when added to insulin therapy in individuals with poorly controlled type 2 diabetes mellitus.

Most individuals with type 2 diabetes mellitus are obese or overweight[29], which might aggravate insulin resistance and result in dose escalation or intensification of the insulin regimen, thus leading to further weight gain and a vicious cycle[30]. Therefore, insulin-induced weight gain is an important issue in the management of individuals with type 2 diabetes mellitus, particularly in cases poorly controlled with insulin therapy[30]. In the present meta-analysis, SGLT2i/INS treatment led to a significant weight reduction compared with that in the PIO/INS group when adjusted for age and sex (WMD 4.54 kg, 95% CI: 3.41–5.67 kg; $P < 0.001$; Figure 2a), consistent with the known weight loss properties of SGLT2i[31]. As weight loss by SGLT2i treatment can mitigate the insulin-associated weight gain, SGLT2i might serve as a better option for obese or overweight individuals with type 2 diabetes mellitus, particularly those regarding the bodyweight gain accompanying insulin therapy.

Intensification of the insulin regimen occasionally has limited ability to maintain the desired glucose levels, as an aggressive insulin regimen might lead to complications, such as weight gain, edema and hypoglycemia[2,10]. Therefore, there is a need for other OADs as add-on therapy with an insulin-sparing effect. Herein, we showed reduced total daily doses of insulin in both the PIO/INS and SGLT2i/INS groups compared with the respective PCB/INS groups (Figure 2b). These findings are compatible with the known effect of PIO to decrease the insulin requirement by enhancing the peripheral and hepatic insulin sensitivity[32]. Furthermore, the insulin requirement was also reduced in the SGLT2i/INS group, which reflects the improvement in insulin sensitivity and β-cell function with SGLT2i, as previously reported[33]. The difference in the insulin-sparing effects between the PIO/INS and SGLT2i/INS groups was not significant, as determined by an indirect comparison analysis before and after adjusting for BMI as a covariate; however, a trend was observed towards a greater reduction in the insulin doses in the PIO/INS group compared with in the SGLT2i/INS group (Figure 2b).

In addition to the efficacy of a treatment, the risk of hypoglycemia should also be carefully considered during treatment selection in individuals with type 2 diabetes mellitus, and most guidelines highlight the importance of minimizing this risk[34]. Hence, the selection of a treatment that is less likely to cause hypoglycemia is vital. SGLT2i and TZDs both carry a lower risk of hypoglycemia compared with other add-on treatments, such as sulfonylureas, while offering similar glycemic control[8,35]. However, we found that hypoglycemia was more common in the PIO/INS and SGLT2i/INS groups than in the respective PCB/INS group (Figure 2c), although the hypoglycemic events in both groups were mostly mild in severity. Previous studies have reported that although PIO is related to a low incidence of hypoglycemia, concomitant therapy with insulin could increase the risk of hypoglycemia[36,37]. Similarly, hypoglycemia

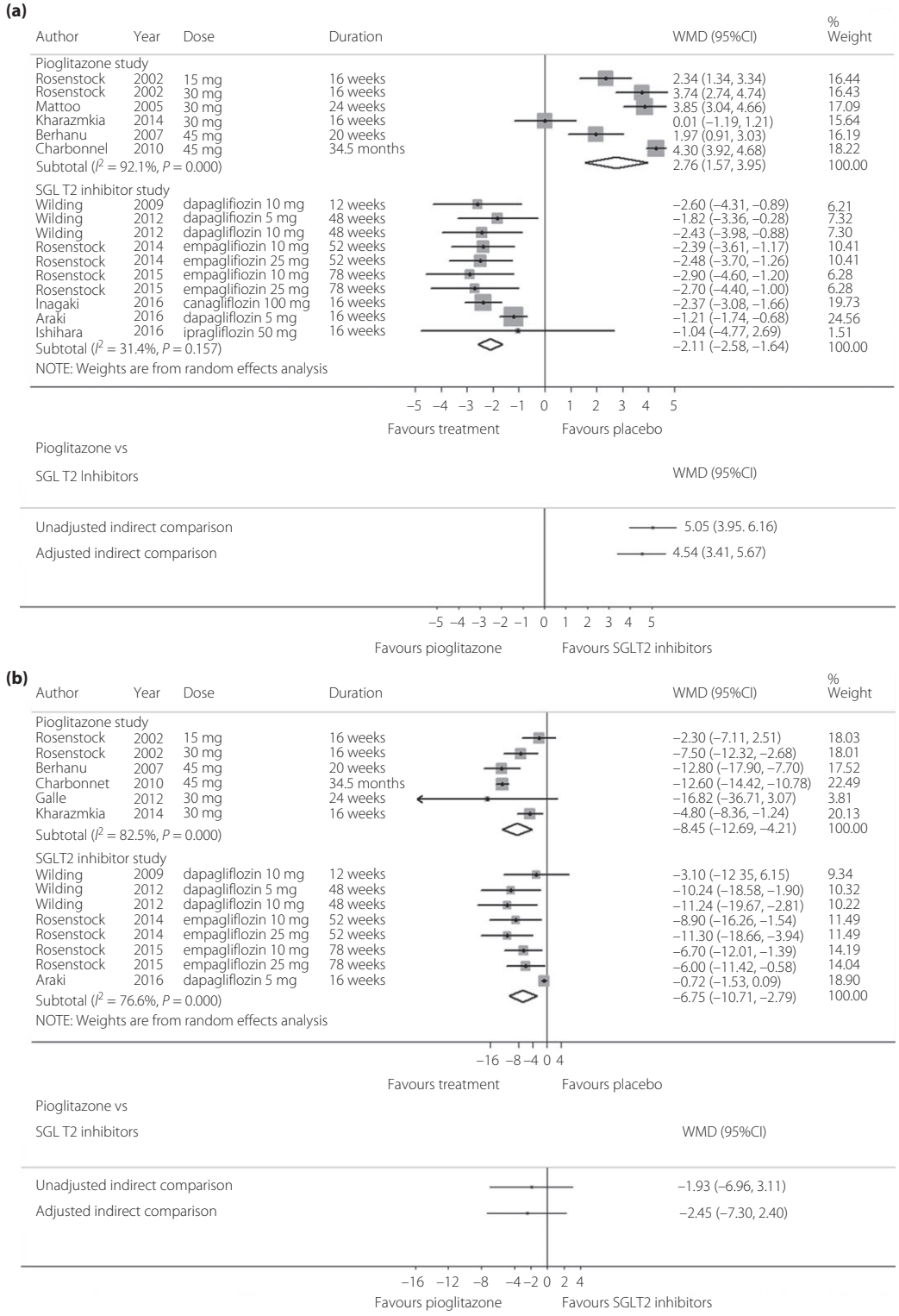

Figure 2 | Effect of pioglitazone (PIO) or sodium–glucose cotransporter 2 inhibitors (SGLT2i) on bodyweight, insulin (INS) requirement and hypoglycemia risk. (a) Weighted mean differences (WMDs) in changes in bodyweight from baseline. (b) Weighted mean differences (WMDs) in changes in insulin dose from baseline. (c) Relative risks (RRs) of hypoglycemia. The tops of each figure represent the comparison of treatment (PIO/INS or SGLT2i/INS) vs PCB/INS, and the bottoms of each figure show the results by indirect comparison with adjustment of covariates when required. The squares indicate each individual study's effects, and the size of the squares reflects the study's weight, with the horizontal lines extending from the symbols representing 95% confidence intervals (CIs). The diamonds indicate the pooled estimates. PCB, placebo.

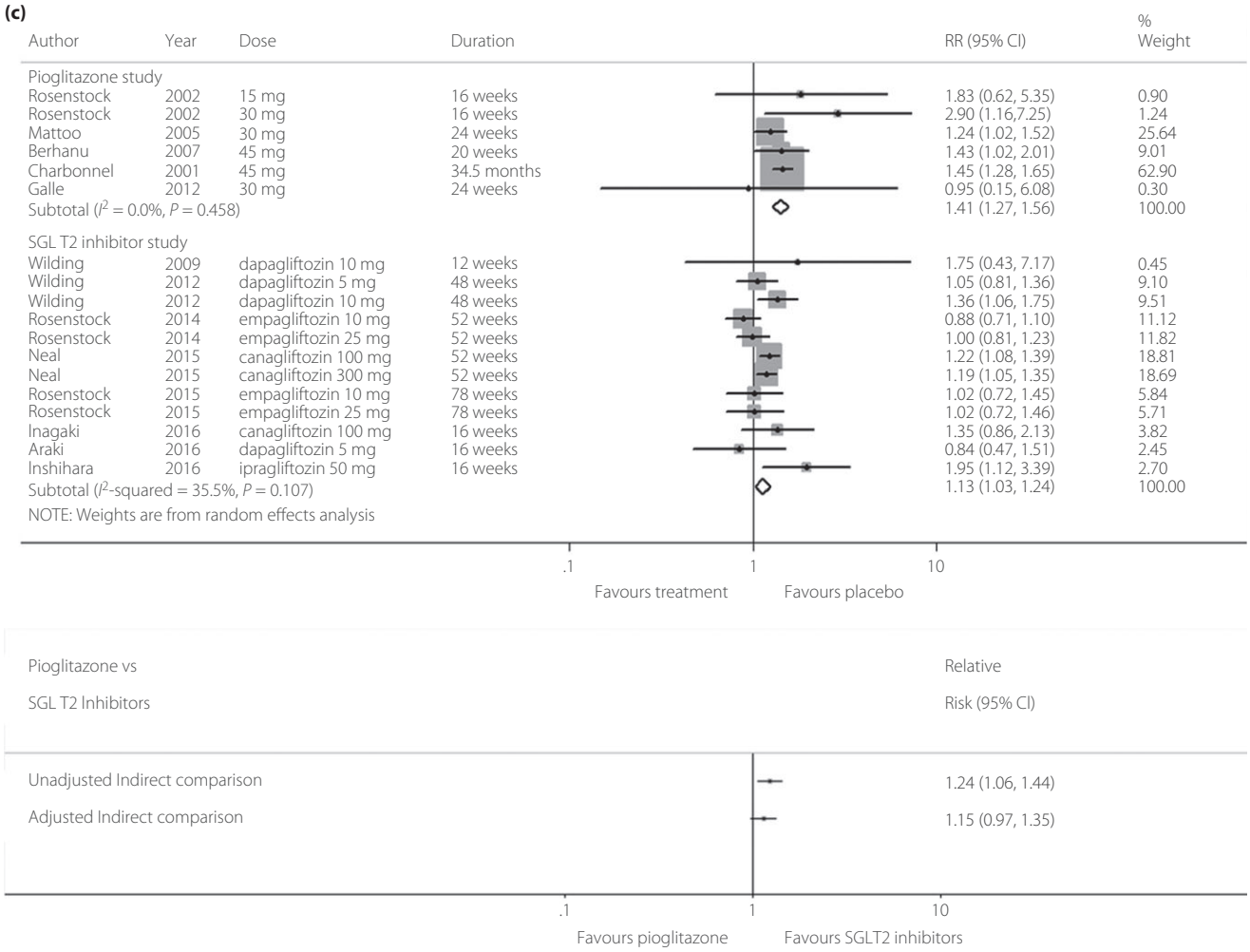

Figure 2 | Continued.

often occurs when individuals receive SGLT2i as an add-on to background therapy with insulin[7,38], whereas the incidence of hypoglycemia during SGLT2i treatment is generally low[38]. Furthermore, in this meta-analysis, there was a non-significant trend towards a higher risk of hypoglycemia in the PIO/INS group compared with the SGLT2i/INS group (Figure 2c). This result is consistent with the non-significant trend of PIO achieving a greater insulin dose reduction compared with SGLT2i (Figure 2b). Thus, these findings suggest that clinicians and caregivers should carefully adjust the insulin dose in individuals who receive combination therapy with PIO and insulin.

The present study had certain limitations. First, the results were based on indirect comparisons. Second, the regimen of insulin treatment, the methods used for insulin dose titration (Tables 1, 2 and S5) and the definition of hypoglycemia (Table S3) were inconsistent among the included studies. Third, although the cardiovascular benefit of OADs is of great importance, and although both agents (i.e., PIO and SGLT2i) showed improved cardiovascular outcomes in patients with type 2 diabetes mellitus at high cardiovascular risk in their corresponding CVD outcome trials (PROactive study for PIO, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose [EMPA-REG OUTCOME] trial for empagliflozin, and Canagliflozin Cardiovascular Assessment Study [CANVAS] for canagliflozin)[39–42], we could not compare the cardiovascular effects of PIO and SGLT2i in the present study. Furthermore, we could not compare the effect of PIO and SGLT2i on the cardiovascular risk factors including blood pressure and lipid profiles because of the limited data or inconsistent reporting systems among studies. Fourth, the characteristics of the participants, especially BMI, in some clinical trials were not comparable, although we adjusted BMI as confounding covariates according to the result of meta-regression analysis. Fifth, the long-term complications of type 2 diabetes mellitus and some major safety concerns, including genital infection, euglycemic ketoacidosis and edema, were not assessed. Finally, we did not carry out additional analysis based on the dose of each agent.

In conclusion, both PIO and SGLT2i offer feasible treatment options as adjunctive OADs to pre-existing insulin therapy in

individuals with inadequately controlled type 2 diabetes mellitus. PIO and SGLT2i treatment both led to a significant reduction in HbA1c and FPG levels, and increased proportions of individuals who achieved HbA1c <7.0% (53.0 mmol/mol). Indirect comparison analyses showed that PIO and SGLT2i treatments confer comparable efficacy, with similar insulin dose reduction and hypoglycemia risk. Thus, in the absence of a head-to-head comparison, the results of the present study provide important evidence for selecting OADs to improve glycemic control in individuals with type 2 diabetes mellitus receiving insulin treatment.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | Search strategy for pioglitazone-related studies.
Table S2 | Search strategy for sodium–glucose cotransporter 2 inhibitor-related studies.
Table S3 | The definitions of hypoglycemia in the included studies.
Table S4 | Methodological quality assessment.
Table S5 | The insulin titration methods used in the included studies.
Figure S1 | Flow chart of the identification of eligible trials.
Figure S2 | Risk of bias in the included studies.
Figure S3 | Funnel plot for absolute glycated hemoglobin change in the included studies.