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Ipragliflozin as an add-on therapy in type 2 diabetes mellitus patients: An evidence-based pharmacoeconomics evaluation

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ABSTRACT

Aim: To evaluate the efficacy, safety and cost-effectiveness of ipragliflozin as an add-on therapy in patients with type 2 diabetes mellitus (T2DM).
Methods: PubMed, EMBASE, the Cochrane Library, Web of Science and four Chinese databases, as well as the ClinicalTrials.gov website were searched from their inception through Jan 2019. Methodological quality was assessed using the Cochrane risk of bias, and meta-analysis was performed using RevMan5.3.
Results: A total of 11 randomized controlled trials with 1766 patients were included. Ipragliflozin administered (50 mg) once daily as an add-on therapy to other glucose-lowering medications (metformin, pioglitazone, sulfonylurea, α-glucosidase inhibitor, sitagliptin, insulin) was associated with reductions in hemoglobin A1c (HbA1c) of −0.74% (95% confidence interval (CI) −1.00 to −0.48), fasting plasma glucose (WMD −25.03 mg/dL; 95% CI −32.89 to −17.16), weight, waist circumference, blood pressure, and triglycerides levels. Neither the incidence of treatment-emergent adverse events (TEAEs) (RR 1.08; 95% CI 1.00 to 1.16) nor drug-related TEAEs (RR 1.19; 95% CI 0.93 to 1.54) was significantly increased. However, it was associated with an increased risk of hypoglycemia when added to insulin (RR 1.71; 95% CI 1.13 to 2.61). Compared with the pioglitazone group and the sitagliptin + metformin group, the incremental cost-effectiveness ratio of ipragliflozin add-on therapy group was $4976.89, $2089.76 per percentage of qualified HbA1c, respectively.
Conclusion: Ipragliflozin as an add-on therapy is well tolerated and effective. Ipragliflozin as an add-on therapy do not appear cost-effective compared with metformin alone, but may be competitive against pioglitazone group and the sitagliptin + metformin group.
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1. Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were recommended to use as monotherapy in patients who are unable to use metformin and as a second- or third-line adjunctive treatment to diet and exercise or other glucose-lowering agents by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE)

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[1]. Ipragliflozin is one such SGLT2 inhibitor that was first globally approved in Japan on 17 January 2014 for the treatment of type 2 diabetes mellitus (T2DM) in adults [2]. Ipragliflozin shows a high level of selectivity (254-fold versus SGLT1), and its bioavailability is approximately 90%. Ipragliflozin is rapidly absorbed, with maximum the plasma concentration occurring within one hour, and the mean half-life after oral administration of 50 mg is 15–16 h [2]. In one clinical pharmacokinetics and pharmacodynamics study, the pharmacokinetics of ipragliflozin and other oral antidiabetic drugs (metformin, sitagliptin, pioglitazone, glimepiride, miglitol and mitiglinide) were not significantly affected by coadministration. With regard to efficacy and safety, some studies have reported tolerability for the use of ipragliflozin as an adjuvant treatment, with beneficial effects [3,4]. However, clinicians should consider not only the glucose-lowering efficacy, safety profile, drug-drug interaction, but also the cost of combination therapy when selecting this approach for patients with T2DM.

Previous meta-analysis and network meta-analysis found that SGLT2 inhibitors were effective glucose-lowering agents with benefits that included reductions in hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), body weight, blood pressure, and hypoglycemic risk [5,6]. However, these studies primarily focused on dapagliflozin, empagliflozin and canagliflozin or evaluated SGLT2 inhibitors used in combination with metformin alone. Conversely, there are few articles addressing ipragliflozin as an add-on therapy to oral glucose-lowering medications other than metformin. What's important, there is no study assessing the economic evaluation of these interventions.

Thus, our objective was to perform a meta-analysis summarizing and evaluating the available evidence from randomized controlled trials (RCTs) with regard to the effect of ipragliflozin as an add-on therapy in T2DM patients who are not able to achieve standard glycemic targets. Then based on the results of meta-analysis, we also performed an economic evaluation by using the cost-effectiveness analysis.

2. Materials and methods

This meta-analysis was written according to the preferred reporting items for systematic reviews and PRISMA statement (Table S1) and a drafted study protocol was also made which was consistent with the Cochrane Collaboration format.

2.1. Search strategy

PubMed, EMBASE, the Cochrane Library, Web of Science and four Chinese databases (WanFang Data, China Biology Medicine disc, VIP database and China National Knowledge Infrastructure) were searched for relevant studies from their date of inception through Jan 2019; ClinicalTrials.gov as also was searched. The search was not restricted to RCTs or humans. All articles about ipragliflozin were searched and the terms "ipragliflozin" or "ASP1941" were used. References cited in the articles were reviewed to identify additional studies.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following conditions: (1) RCTs; (2) investigating T2DM patients older than 18 years old; (3) comparing ipragliflozin as an add-on therapy with other drugs; (4) evaluating ipragliflozin at the typical clinical dosages of 25 mg or 50 mg; (5) the duration of intervention was at least 12 weeks. Studies were excluded if (1) ipragliflozin was used as a monotherapy, (2) patients with type 1 diabetes were involved and (3) published as conference abstracts.

2.3. Study selection data extraction and quality assessment

Two investigators independently performed assessments and screens according to the title and abstract in the initial study selected. They then reviewed and retrieved the paper based on the full-text copy of the article. If agreement could not be reached or if there were any uncertainties, a third reviewer discussed the study with the two investigators to reach a final decision. Two reviewers extracted study information: study characteristics, participant baseline characteristics and efficacy and safety outcomes. The primary outcome was HbA1c, and the main safety outcomes were treatment-emergent adverse events (TEAEs). Other outcomes were as follows: the proportion of participants achieving an HbA1c level $\leq$ 7%; body weight; waist circumference; fasting plasma glucose (FPG), systolic blood pressure (SBP), diastolic blood pressure (DBP), and plasma lipids (total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein–cholesterol (LDL-C) values; estimated glomerular filtration rate (eGFR); incidence of urinary and genital tract infections; and incidence of drug-related TEAEs, hypoglycemia and cardiovascular outcomes.

Two reviewers also discussed and assessed the quality of the included studies using the Cochrane risk of bias tool. The following items were assessed: (1) sequence generation, (2) allocation concealment, (3) blinding of the outcome assessor, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other bias [7]. The items were graded as having an unclear, high or low risk of bias. Funnel plots were used to assess the potential existence of publication bias.

2.4. Data synthesis and analysis

The investigators performed a meta-analysis of the studies using Review Manager (RevMan) Version 5.3 according to the Cochrane Handbook for Systematic Review of Interventions [8]. In the case of dichotomous data, the relative risk (RR) was calculated for each trial with 95% confidence intervals (CIs). The data were then analyzed by calculating the weighted mean difference (WMD) and associated 95% CIs if the data were continuous. Heterogeneity was assessed using the χ^2 test of heterogeneity and the I^2 measure of inconsistency [9]. We used random-effects models in cases of considerable heterogeneity ($p < 0.05$ or $I^2 > 50\%$); otherwise, a fixed-effects model was used. We performed subgroup analyses for the different interventions or study length, and sensitivity analyses were performed to assess the stability of the results.

2.5. Economic evaluation

Effectiveness was measured in terms of the proportion of participants achieving an HbA1c level ≤ 7%. The parameters about costs were derived from the database of yaozh in China(https://db.yaozh.com). After removing the deduplication data, we took the median price of different manufacturers. Then all costs were converted into US dollars using average exchange rate in 2017 (1 USD = 6.7518 RMB) [10]. The study perspective was from the healthcare providers; thus, nonmedical direct costs were excluded. The costs in this study were calculated only based on the medicine costs. The costs were calculated as follows: Costs = average daily treatment cost × days. The cost data were shown in Table S2. In order to eliminate the difference of baseline data from studies as much as possible, this cost-effectiveness analysis used the weighted efficiency $P_B = \sum_{i=1}^{n} WiPi / \sum_{i=1}^{n} Wi$, Wi is the weight, and Pi is the efficiency of each study, then P (A + B) was calculated based on P(B): P(A + B) = PB × RR(A + B), (PB represents total effective rate of the therapy without ipragliflozin; P(A + B) indicates total effective rate of the ipragliflozin added-on therapy). RR(A + B) was calculated by the meta-analysis.

In our study, cost-effectiveness ratio (CER) which means the cost is based on effectiveness per unit, and incremental cost-effectiveness ratio (ICER) were calculated which means the incremental cost is based on incremental effectiveness per unit. The willingness-to-pay (WTP) threshold was three times of the gross domestic product (GDP) per capita. Because the per-capita GDP of China is 8 836.16 US dollars in 2017 [11], the cost-effectiveness threshold in this study is 12 201.16 US dollars after being converted to a 24-week period.

As the RCT included in the study was up to 24 weeks, discounting was not considered. The parameters used in this study have substantial uncertainty. One-way sensitivity analysis was conducted by a 10% reduction in cost as a factor, as the global trend is that drugs are getting cheaper, and the range between the upper limit and the lower limit of 95% CI was used for the effectiveness.

3. Results

3.1. Search results and study characteristics

We initially identified 1016 articles, and 457 duplicates were automatically removed in Endnote X6. A total of 531 articles were excluded after scanning the titles and/or abstracts. The full texts of the 28 remaining articles were then searched and read. Ultimately, 11 articles (n = 1766 patients) met our eligibility criteria. The article search and screening process was depicted in a flowchart in Fig. S1.

The characteristics of the included studies were presented in Table 1. The publication years ranged from 2013 to 2018. Nine RCTs were from Asian countries [12–20], and one from UK [21], another from Russia [22]. Five RCTs evaluated the efficacy and safety of ipragliflozin in patients being treated with metformin [16,19–22], one trial included patients receiving pioglitazone therapy [17], one included patients receiving sulfonylurea [15], one included patients receiving pioglitazone, sulfonylurea or α-glucosidase inhibitor therapy [18], one included patients receiving sitagliptin and metformin [12] and two trials included patients receiving insulin [13,14]. All RCTs reported a dosage of ipragliflozin of 50 mg once daily. The sample sizes in these studies ranged from 39 to 168 patients. The study length was ranged from 12 weeks to 24 weeks.

3.2. Methodological quality of the included studies

The quality of the RCTs was evaluated using the Cochrane risk of bias assessment tool. All RCTs were double-blind, placebo-controlled trials. Most of the included studies were high of quality and had a low risk of bias. The majority of the trials included presented a low risk of bias for sequence generation and allocation concealment. Only two RCTs did not describe the random component in the sequence generation process [16,21] and five RCTs did not report the method of concealed allocation [12,16,18,20,21]. All the studies had low risks of performance, detection, attrition, and reporting biases. In ILLUMINATE study, ipragliflozin group had lower FPG and less frequency of using hypoglycaemic agents other than metformin than patients in the placebo group before the start of the study [16]. In EMIT study, the body weight and body mass index were significantly greater in the ipragliflozin group than in the placebo group in baseline [15]. Other two RCTs included patients treated with different oral hypoglycaemic agents (an α-glucosidase inhibitor, a sulfonylurea, pioglitazone, or a dipeptidyl peptidase-4 (DPP-4) inhibitor), and did not perform subgroup analysis [14,18]. So, we judged these four RCTs as having a high risk of 'other' bias [14–16,18].

The details of the methodological quality of the studies were depicted in the supporting information in Fig. S5 and Fig. S6. The funnel plots for the main outcomes assessed in the meta-analyses were depicted in Fig. S7 and Fig. S8. The generated funnel plot was considered to be moderately asymmetrical in shape, and it was suggested that there was publication bias in the related published studies.

3.3. Efficacy outcomes

Eleven RCTs evaluated the effect of ipragliflozin as an add-on therapy (Table 2). The results of the meta-analysis demonstrated that ipragliflozin significantly decreased HbA1c levels (WMD −0.74%; 95% CI −1.00 to −0.48; $I^2 = 94\%$) (Fig. 1). High heterogeneity ($I^2 > 50\%$) was detected, even though a random-effects model was used. So, subgroup analysis and sensitivity analysis were performed. In subgroup analysis based on study length, pooled analysis of eight RCTs [12,13,15–20] showed that ipragliflozin decreased HbA1c levels (WMD −0.79%; 95% CI −1.11 to −0.46; $I^2 = 95\%$) at 24 weeks, two RCTs [21,22] showed that ipragliflozin decreased HbA1c levels at 12 weeks (WMD −0.39%; 95% CI −0.60 to −0.17; $I^2 = 19\%$), and one RCT also showed reduction in HbA1c levels at 16 weeks (WMD −1.06%; 95% CI −1.23 to −0.89). We performed another subgroup analysis based on different interventions. As shown in Fig. S2, ipragliflozin added to metformin decreased HbA1c [WMD −0.69%; 95% CI −1.27 to −0.10; $I^2 = 96\%$]. After we deleted one RCT [16], no significant

Table 1 – Characteristics of RCTs of ipragliflozin that were included in the meta-analysis.

Study	Country	Study duration (week)	Study ID	Background antidiabetic threapy	Treatment group (once daily dosing)	No. of Patients	Duration of diabetes (years)	Age (years)	Men (%)	Baseline HbA1c (%)	BMI (kg/m2)	Baseline Weight (kg)
Lu2016[19]	China	24	NCT01505426	Metformin	Ipr50 mg	87	6.49 ± 5.67	53.9 ± 11.3	50.6	7.74 ± 0.78	26.57 ± 4.30	70.36 ± 14.75
					Placebo	83	5.8 ± 4.24	53.4 ± 11.3	39.8	7.75 ± 0.71	27.04 ± 4.06	70.45 ± 12.44
Kashiwagi2015[16]	Japan	24	NCT01135433	Metformin	Ipr50mg	112	7.49 ± 6.81	56.2 ± 10.67	58.9	8.25 ± 0.72	25.96 ± 4.41	/
					Placebo	56	8.05 ± 5.16	57.7 ± 9.24	58.9	8.38 ± 0.74	25.47 ± 3.09	/
Min2017[20]	Korea	24	NCT01505426	Metformin	Ipr 50 mg	43	7.83 ± 6.74	55.7 ± 11.25	53.5	7.67 ± 0.85	25.50 ± 3.0	68.12 ± 13.
					Placebo	39	7.21 ± 4.75	56.5 ± 9.79	38.5	7.62 ± 0.78	26.15 ± 3.46	68.96 ± 12.24
Wilding2013[21]	UK	12	NCT01117584	Metformin	Ipr50mg	68	6.0 ± 5.3	58.6 ± 7.6	47.1	7.76 ± 0.66	31.1 ± 4.9	86.7 ± 13.7
					Placebo	66	5.7 ± 3.2	57.3 ± 8.6	54.5	7.68 ± 0.6	32.0 ± 4.8	89.0 ± 14.5
Kashiwagi2015[17]	Japan	24	NCT01225081	Pioglitazone	Ipr50mg	97	6.33 ± 4.71	56.2 ± 10.22	77.3	8.24 ± 0.67	27.11 ± 3.85	73.01 ± 13.17
					Placebo	54	7.71 ± 5.32	56.1 ± 11.91	68.5	8.39 ± 0.64	27.13 ± 4.31	72.80 ± 15.83
Kashiwagi2015[15]	Japan	24	NCT01242215	Sulfonylurea	Ipr50mg	166	10.32 ± 7.08	59.6 ± 10.02	67.3	8.38 ± 0.64	25.81 ± 3.60	68.81 ± 12.43
					Placebo	76	10.75 ± 6.24	59.8 ± 8.58	62.7	8.34 ± 0.73	24.18 ± 2.97	63.96 ± 11.40
Kashiwagi2015[18]	Japan	24	NCT01316094	Pioglitazone, sulfonylurea, α-glucosidase inhibitor	Ipr50mg	119	9.53 ± 7.69	63.9 ± 6.59	78.0	7.53 ± 0.54	25.84 ± 3.45	69.16 ± 11.57
					Placebo	46	9.42 ± 8.31	65.7 ± 6.93	78.3	7.55 ± 0.53	24.96 ± 3.36	66.70 ± 10.94
Han 2018[12]	Korea	24	NCT0245263	Sitagliptin and metformin	Ipr50mg	74	11.62 ± 5.89	57.62 ± 8.26	50.7	7.90 ± 0.69	25.50 ± 3.07	67.50 ± 12.50
					Placebo	68	11.33 ± 6.63	57.62 ± 8.26	48.5	7.92 ± 0.79	26.05 ± 3.79	67.90 ± 10.98
Inoue2018[13]	Japan	24	UMIN000018839	Insulin	Ipr50mg	24	15.9 ± 7.7	60.5 ± 9.8	54.2	8.12 ± 0.93	27.9 ± 4.0	73.6 ± 14.7
					Placebo	24	19.1 ± 10.7	60.8 ± 12.1	58.3	8.30 ± 0.65	27.7 ± 4.5	74.6 ± 13.3
Shestakova2018[22]	Russia	12	NCT02794792	Metformin	Ipr50mg	110	6.65 ± 5.22	58.9 ± 9.3	43.6	8.39 ± 0.93	32.80 ± 4.76	92.74 ± 16.24
					Placebo	55	6.56 ± 4.66	58.0 ± 9.5	40	8.46 ± 0.96	31.95 ± 4.18	89.54 ± 15.60
Ishihara2016[14]	Japan	16	NCT02175784	Insulin with/ without DPP-4	Ipr50mg	168	12.59 ± 7.79	58.7 ± 11.1	62.5	8.67 ± 0.77	25.61 ± 3.5	69.05 ± 11.61
					Placebo	87	14.28 ± 8.54	59.2 ± 9.3	58.6	8.62 ± 0.86	26.42 ± 3.8	70.32 ± 12.17

†HbA1c = hemoglobin A1c; Ipr = ipragliflozin.

Table 2 – Summary of findings for the secondary efficacy and safety outcomes.

Outcome	Number of studies	Patients	Effect estimate (95% CI); I^2, P-value
Patients achieving HbA1c < 7%	9	1413	2.16 [1.57, 2.97]; 57%, P < 0.00001
WC (cm)	9	1516	−0.96 [−1.29, −0.62]; 10%, P < 0.00001
SBP (mmHg)	10	1671	−3.31 [−4.49, −2.13]; 27% , P < 0.00001
DBP (mmHg)	9	1506	−2.14 [−3.02, −1.27]; 34%, P < 0.00001
TC (mg/dL)	9	1300	−3.31 [−8.30, 1.68]; 80%, P = 0.19
TG (mg/dL)	9	1300	−32.19[−52.78, −11.59]; 82%, P = 0.002
HDL-C (mg/dL)	10	1300	2.27 [1.18, 3.36]; 54%, P = 0.002
LDL-C (mg/dL)	8	1300	−1.08 [−3.57, 1.40]; 0%, P = 0.39
eGFR (mL/min/1.73 m^2)	7	1204	−1.33 [−2.40, −0.27]; 0%, P = 0.01
Incidence of TEAEs	11	1729	1.08 [1.00, 1.16]; 0%, P = 0.05
Incidence of drug-related TEAEs	10	1678	1.19 [0.93, 1.54]; 70%, P = 0.17
Incidence of hypoglycaemia	11	1729	1.48 [1.04, 2.12]; 0% P = 0.03
Incidence of urinary tract infections	11	1729	0.95 [0.54, 1.69];2%, P = 0.86
Incidence of genital tract infections	11	1729	1.81 [0.86, 3.81]; 12%, P = 0.12

†WC = waist circumference; SBP = Systolic blood Pressure; DBP = Diastolic blood Pressure; TC = Total cholesterol; TG = Triglycerides; HDL-C = high-density lipoprotein -cholesterol; LDL-C = low-density lipoprotein –cholesterol; TEAEs = treatment-emergent adverse events; HbA1c = hemoglobin A1c; FPG = fasting Plasma glucose; eGFR = estimated glomerular filtration rate.

Study or Subgroup	Ipragliflozin Mean	Ipragliflozin SD	Ipragliflozin Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Han2018[12]	-0.79	0.59	53	0.03	0.84	40	8.7%	-0.82 [-1.12, -0.52]
Inoue2018[13]	-0.69	0.18	24	-0.15	0.17	24	9.8%	-0.54 [-0.64, -0.44]
Ishihara2016[14]	-0.79	0.66	168	0.27	0.65	87	9.5%	-1.06 [-1.23, -0.89]
Kashiwagi2015[15]	-0.83	0.72	165	0.32	0.96	75	9.1%	-1.15 [-1.39, -0.91]
Kashiwagi2015[16]	-0.87	0.66	112	0.83	0.7	56	9.2%	-1.70 [-1.92, -1.48]
Kashiwagi2015[17]	-0.64	0.61	97	0.22	0.81	54	9.1%	-0.86 [-1.11, -0.61]
Kashiwagi2015[18]	-0.42	0.51	118	-0.17	0.52	46	9.5%	-0.25 [-0.43, -0.07]
Lu2016[19]	-0.97	0.81	41	-0.31	0.79	39	8.4%	-0.66 [-1.01, -0.31]
Min2017[20]	-0.65	0.73	66	-0.31	0.73	65	9.1%	-0.34 [-0.59, -0.09]
Shestakova2018[22]	-1.01	0.85	110	-0.77	1.1	55	8.5%	-0.24 [-0.57, 0.09]
Wilding2013[21]	-0.94	0.75	85	-0.47	0.81	83	9.2%	-0.47 [-0.71, -0.23]
Total (95% CI)			**1039**			**624**	**100.0%**	**-0.74 [-1.00, -0.48]**

Heterogeneity: Tau² = 0.17; Chi² = 165.97, df = 10 (P < 0.00001); I² = 94%
Test for overall effect: Z = 5.63 (P < 0.00001)

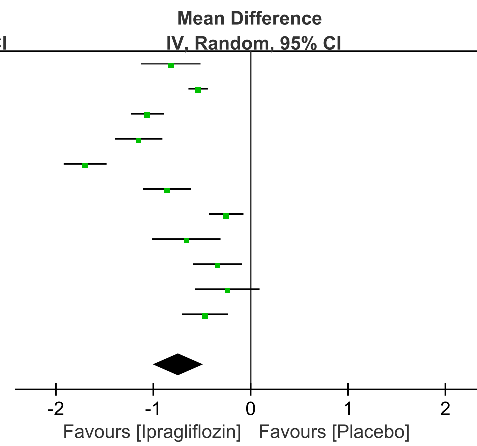

Fig. 1 – Forest plots of ipragliflozin on HbA1c.

heterogeneity was observed, and the overall effect estimates still favoured ipragliflozin + metformin group [WMD −0.42%; 95% CI −0.57 to −0.27; I^2 = 14%]. Ipragliflozin also significantly decreased HbA1c levels from −0.25% to −1.15% when used as an add-on therapy in combination with other drugs (Fig. S2). Moreover, patients treated with ipragliflozin as an add-on therapy were more likely to achieve target HbA1c levels < 7% (RR 2.16; 95% CI 1.57 to 2.97; I^2 = 57%) than were those not treated with ipragliflozin as an add-on (Table 2).

As an add-on therapy, ipragliflozin also led to a significant reduction in FPG (WMD −25.03 mg/dL; 95% CI −32.89 to −17.16; I^2 = 87%). The results of subgroup analysis also showed that ipragliflozin combined with metformin was associated with a significant reduction in FPG versus metformin alone (WMD −20.68 mg/dL; 95% CI −29.75 to −11.60; I^2 = 68%). After one RCT [16] which was high risk of bias was excluded, no significant heterogeneity was observed, and the overall effect estimates still favoured ipragliflozin + metformin group in FPG (WMD −16.43 mg/dL; 95% CI −22.55 to −10.31; I^2 = 2%). When used as an add-on treatment in combination with other medicines, such as insulin, ipragliflozin also significantly decreased FPG (WMD −26.78 mg/dL; 95% CI −51.27 to −2.30; I^2 = 95%) (Fig. S3). Ipragliflozin also led to weight loss (WMD −1.72 kg; 95% CI −2.14 to −1.30; I^2 = 57.3%) (Fig. S4). Indeed, subgroup analysis showed that the effect estimates on weight loss were similar when ipragliflozin was added to different glucose-lowering medications, except for pioglitazone (WMD −2.80 kg; 95% CI −3.51 to −2.09) (Fig. S4).

The other findings of the meta-analysis were presented in Table 2. As an add-on therapy, ipragliflozin was also associated with decreased waist circumference (WMD −0.96 cm; 95% CI −1.29 to −0.62; I^2 = 10%). In particular, waist circumference decreased significantly when used in combination with pioglitazone (WMD −1.96 cm; 95% CI −3.26 to −0.66), and waist circumference also decreased when added to metformin (WMD −0.96 cm, 95% CI −1.45 to −0.47; I^2 = 43%). Furthermore, ipragliflozin significantly decreased both SBP and DBP, with favorable effects [(SBP: WMD −4.31 mmHg; 95% CI −6.09 to −2.54; I^2 = 52%) (DBP: WMD −2.56 mmHg; 95% CI −4.02 to −1.11; I^2 = 33%)] when added to metformin compared with metformin alone. The results of meta-analysis showed that ipragliflozin as an add-on therapy also increased HDL-C levels and significantly decreased TG levels, although it mildly decreased TC and LDL-C levels, the differences were not statistically significant(Table 2). Whereas, two studies found there were no changes in TC, HDL-C, LDL-C, TG or free fatty acid levels from baseline to the end of treatment in ipragliflozin or placebo group [14,22].

Only seven trials reported the outcome of eGFR, with the meta-analysis results showing mild changes in eGFR (WMD −1.33(mL/min/1.73 m^2) 95% CI −2.40 to −0.27; I^2 = 0%). Notably, one trial indicated that ipragliflozin did not significantly change eGFR in patients with mild or moderate renal impairment at 24 weeks , and another trial also indicated no significant change in eGFR at 12 weeks [22].

3.4. *Safety outcomes*

The incidences of TEAEs (RR 1.08; 95% CI 1.00 to 1.16; I^2 = 0%) (Fig. 2) and drug-related TEAEs (RR 1.19; 95% CI 0.93 to 1.54; I^2 = 70%) were not significantly different between the treatment and control groups. Most TEAEs were either mild or moderate in severity. Eleven articles reported hypoglycemia, the total incidences of TEAEs related to hypoglycemia were higher in the ipragliflozin group (RR 1.48; 95% CI 1.04 to 2.12; I^2 = 0%]. Whereas the subgroup analysis showed that ipragliflozin combined with insulin was associated with a higher incidences in hypoglycemia versus insulin alone (RR 1.71; 95% CI 1.13 to 2.61; I^2 = 2%), and similar incidences in hypoglycemia when ipragliflozin combined with other drugs (RR 1.06; 95% CI 0.54 to 2.10; I^2 = 0%). Ipragliflozin as an add-on therapy did not increase the incidence of urinary tract infections (P = 0.86) or genital infections (P = 0.12). None of the included trials reported data on all-cause mortality or cardiovascular outcomes. However, other adverse events, such as skin complications, nasopharyngitis, fatigue, osteoarthritis, dysuria, nocturia, and gastrointestinal disorders, were reported.

3.5. *Economic evaluation*

Only seven RCTs were included in economic evaluation. In terms of 12 or 24 weeks treatment, the cost of the metformin + ipragliflozin group amounted to \$367.39, \$734.78, respectively, whereas that of the metformin alone group amounted to \$59.57, \$119.14, respectively. CER showed that no matter the treatment period was 12 or 24 weeks, the cost of effect per unit for the ipragliflozin + metformin group was higher than that of metformin alone. Compared with metformin alone, ICER showed that an increase in each unit of effect for ipragliflozin + metformin group needed an additional cost of \$1112.47, \$2461.58, for 12 or 24 weeks, respectively. Notably, the proportion of participants achieving an HbA1c level ≤ 7% in pioglitazone group was zero, which is obviously lower than that of the ipragliflozin + pioglitazone group, and ICER showed an increase in each unit of effect for combination therapy of the ipragliflozin + pioglitazone group needed an additional cost of \$4976.89, which was lower than the WTP. When ipragliflozin was added to the sitagliptin + metformin group, CER showed that the cost of effect per unit for three drugs combination therapy was lower than that of the sitagliptin + metformin therapy, and the cost-effectiveness was much better. The ICER was \$2089.76 which was also lower than the WTP.

One-way sensitivity analysis results showed the cost-effectiveness analysis was not mainly affected by fluctuations in costs and effects, except the combination therapy of ipragliflozin + sitagliptin + metformin, when its effectiveness took the lower limit of 95% CI, it was not economical.

4. Discussion

Associations with significant reductions in HbA1c, FPG and body weight were recently reported for some SGLT2 inhibitors when added to other oral glucose-lowering medications, such as canagliflozin, empagliflozin [23,24]. Our meta-analysis showed that a dosage of ipragliflozin of 50 mg once daily added to other glucose-lowering medications (metformin, pioglitazone, sulfonylurea, α-glucosidase inhibitor, sitagliptin, insulin) significantly reduced HbA1c levels (WMD −0.74%; 95% CI −1.00 to −0.48%) compared with the medication alone. In addition, significant effects on body weight (−1.72 kg), FPG (−25.03 mg/dL) and blood pressure (−3.31 mmHg in SBP and −2.14 mmHg in DBP) were found. However, high heterogeneity was detected in the meta-analysis of outcomes such as

	Ipragliflozin		placebo			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Kashiwagi2015[18]	97	119	34	46	10.5%	1.10 [0.91, 1.34]	
Wilding2013[21]	27	68	26	66	5.6%	1.01 [0.66, 1.53]	2013
Kashiwagi2015[15]	126	166	47	76	13.7%	1.23 [1.01, 1.49]	2015
Kashiwagi2015[16]	97	112	49	56	13.9%	0.99 [0.88, 1.12]	2015
Kashiwagi2015[17]	70	97	37	54	10.1%	1.05 [0.85, 1.31]	2015
Ishihara2016[14]	130	175	49	87	14.0%	1.32 [1.07, 1.62]	2016
Lu2016[19]	50	87	51	83	11.1%	0.94 [0.73, 1.20]	2016
Min2017[20]	19	43	17	39	3.8%	1.01 [0.62, 1.66]	2017
Han2018[12]	38	74	34	68	7.6%	1.03 [0.74, 1.42]	2018
Inoue2018[13]	21	24	20	24	4.3%	1.05 [0.83, 1.33]	2018
Shestakova2018[22]	32	110	19	55	5.4%	0.84 [0.53, 1.34]	2018
Total (95% CI)		**1075**		**654**	**100.0%**	**1.08 [1.00, 1.16]**	
Total events	707		383				

Heterogeneity: Chi² = 10.03, df = 10 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

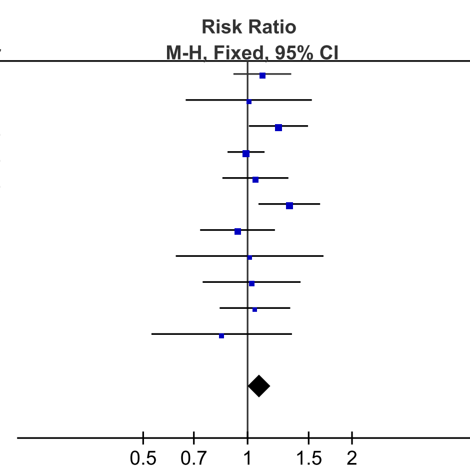

Fig. 2 – Forest plots of ipragliflozin on treatment-emergent adverse events.

HbA1c change, FPG and weight. The heterogeneity may be of clinical, methodological or statistical origin [25]. In our study, the high heterogeneity among studies possibly was mainly due to the different interventions of ipragliflozin added to different glucose-lowering medications. Additionally, three RCTs [15,16,18] had a high risk of bias in the assessment of quality of RCTs (Fig. S6). Considering these factors, we did a subgroup analysis according to the different interventions, and also performed sensitivity analysis by excluding the study which was in high risk of bias. In summary, despite of the high heterogeneity among studies, the results of subgroup and sensitivity analysis indicated that our analysis was reliable. It is important to note that, a publication bias was detected in our study. Four RCTs were reported by Astellas Pharma Inc in Japan, this may be the potential reason, because that studies with significant results were published. To the best of our knowledge, the most efficacious outcomes among our findings were similar to those of a previous study [26]. Nonetheless, we only included studies in which the duration of the intervention was greater than 12 weeks, which was a stricter criterion than applied the previous study in which the duration ranged from 2 to 24 weeks. Most of the trials included in our study were 24 weeks, and except for two, subgroup analysis showed that ipragliflozin add-on therapy reduced HbA1c levels to a greater extent (WMD −0.73%; 95% CI −0.98 to −0.48%) at 24 weeks than at 12 weeks (WMD −0.39%; 95% CI −0.60 to −0.17%). This finding may suggest that the longer the study length, the greater reduction in HbA1c level. Regardless, because of limited data, this result should be further verified by clinical trials with different study lengths.

Obesity and an overweight status are associated with the risk of multiple comorbidities, such as T2DM, cancer and cardiovascular disease [27]. Thus, it is important to consider glucose-lowering treatments are not associated with weight gain when choosing antidiabetic regimens. In our study, ipragliflozin add-on therapy was associated with significant decreases in body weight, in accordance with the findings of a previous study [5]. And we another study found that ipragliflozin alone therapy also reduced weight [28]. The pharmacological action of SGLT2 inhibitors occurs through increasing urinary glucose excretion by reducing renal glucose reabsorption; this leads to an increase in urinary glucose excretion (UGE), and greater UGE results in a loss of 200 kcal/d to 300 kcal/d, which may contribute to modest weight loss [29]. This may explain the finding that ipragliflozin combination therapy was more effective in reducing body weight compared to other therapies alone. A prospective observational study showed that ipragliflozin significantly decreased visceral adipose tissue and improved parameters of metabolic dysfunction in T2DM patients being managed with adequate diet therapy [30]. However, another article reported no statistically significant differences in weight between healthy obese subjects treated with SGLT2 inhibitors and those treated with placebo [31]. Therefore, the effects of SGLT2 inhibitors on body weight, waist circumference and body composition should be verified both in T2DM patients and healthy obese subjects in future trials.

Our study also revealed mild changes in eGFR, however, due to insufficient data, we did not perform a subgroup analysis in patients with diabetic kidney disease. Nonetheless, two trial reported no clinically significant changes [18,22]. Additionally, a previous meta-analysis showed that SGLT2 inhibition was not associated with significant changes in eGFR, likely resulting from a mixture of an initial reduction in eGFR and long-term renal function preservation; however, SGLT2 inhibition was associated with significant albuminuria reduction in T2DM patients with chronic kidney disease [32]. In another meta-analysis, SGLT2 inhibitors were found to be useful for improving early renal damage associated with diabetic disease, though their impact on renal function remains clinically controversial [33]. Despite of these controversial findings, results to date suggest a potential benefit of ipragliflozin in T2DM patients with renal impairment. Overall, any controversy should be resolved in future studies.

Based on our results, ipragliflozin led to decreases in both SBP and DBP and improved patient plasma profiles. We found that ipragliflozin add-on therapy significantly decreased TG levels, which was consistent with a post-marketing surveillance study [3]. Regardless, our study did reveal no significant changes in LDL-C and TC in the ipragliflozin add-on therapy group, which was not completely consistent with a previous study but may be beneficial for T2DM patients and decrease the rate of adverse cardiovascular events [34].

Ipragliflozin add-on therapy appeared to be well tolerated, as neither TEAE nor drug-related TEAE incidence was significantly increased. In addition, we found that ipragliflozin significantly increased the incidence of hypoglycemia when ipragliflozin combined with insulin (RR 1.71; 95% CI 1.13 to 2.61; $I^2 = 2\%$), which is similar to the previous study (RR 1.89, 95% CI [1.15, 3.10], P = 0.01) [26]. Whereas, similar incidences in hypoglycemia were found when ipragliflozin combined with other drugs (RR 1.06; 95% CI 0.54 to 2.10; $I^2 = 0\%$). The reason for this discrepancy may be the increased risk of hypoglycemia was attributed to the glucose-lowering effect of insulin. For example, one trial reported that the incidence of hypoglycemia in the ipragliflozin plus insulin group was 29.1% compared with the non-insulin group (14.9%). Moreover, we found that the incidence of urinary tract infections and genital infections were not significantly increased in the group receiving ipragliflozin add-on therapy, which was not consistent with a previous study reporting that SGLT2 inhibitors were associated with a higher risk of genital infections [35]. As most of the included studies were from Asian countries, it is unclear whether the safety profile of ipragliflozin in other countries will be different. Therefore, further studies on different ethnicities and regions are needed.

To the best of our knowledge, this is the first economic evaluation of ipragliflozin in China. There were no head-to-head comparisons amongst the flozins, it was regrettable that we only compared the ipragliflozin as add-on therapy to other glucose-lowering agents. No economic evaluation was reported in the eleven RCTs, so we performed the cost-effectiveness analysis based on our meta-analysis. Concerning other flozins including dapagliflozin, canagliflozin, and empagliflozin, many studies have been reported. Whalen

Table 3 – The results of cost-effectiveness analysis (the percentage of qualified HbA1c as effective index)

Cost-effectiveness analysis	the percentage of qualified HbA1c		cost		CER (C/E)		ICER(ΔC/ΔE)
	T	C	T	C	T	C	
Combined with metformin [21,22] 12 weeks							
Baseline value	0.4998	0.2231	367.39	59.57	735.07	267.00	1112.47
Upper limit of 95% CI	1.2407	0.2231	367.39	59.57	296.11	267.00	302.50
Lower limit of 95% CI	0.4648	0.2231	367.39	59.57	790.42	267.00	1273.57
10% lower cost	0.4998	0.2231	330.65	59.57	661.56	267.00	979.70
Combined with metformin [16,19,20] 24 weeks							
Baseline value	0.5479	0.2978	734.78	119.14	1341.08	400.05	2461.58
Upper limit of 95% CI	0.9141	0.2978	734.78	119.14	803.83	400.05	998.93
Lower limit of 95% CI	0.3275	0.2978	734.78	119.14	2243.60	400.05	20728.68
10% lower cost	0.5479	0.2978	661.30	119.14	1206.97	400.05	2167.79
Combined with pioglitazone [17] 24 weeks							
Baseline value	0.1237	0	741.58	125.94	5994.97	/	4976.89
Upper limit of 95% CI	0.1944	0	741.58	125.94	3814.70	/	3166.88
Lower limit of 95% CI	0.0531	0	741.58	125.94	13965.69	/	11594.01
10% lower cost	0.1237	0	667.42	125.94	5395.48	/	4377.40
Combined with sitagliptin and metformin [12] 24 weeks							
Baseline value	0.4158	0.1212	1019.05	403.41	2450.81	3328.43	2089.76
Upper limit of 95% CI	0.8376	0.1212	1019.05	403.41	1216.63	3328.43	859.35
Lower limit of 95% CI	0.2060	0.1212	1019.05	403.41	4946.83	3328.43	7259.93
10% lower cost	0.4158	0.1212	917.14	403.41	2205.73	3328.43	1743.85

HbA1c = hemoglobin A1c; T = Test group; C = control group; CER = cost-effectiveness ratio; ICER = incremental cost-effectiveness ratio.

et al. [29] reviewed these three flozins comprehensively, they are efficacious as monotherapy and add-on therapy for patients with T2DM uncontrolled on metformin, sulfonylureas, insulin and other antihyperglycemic combinations. They are associated with modest reduction in weight and systolic blood pressure. Genital mycotic infections and increased urination are the most common adverse effects. Only one study was conducted comparing the cost-effectiveness of dapagliflozin, canagliflozin and empagliflozinin monotherapy [36]. In this study, it was found that these three kinds of flozins were shown to be effective in improving glycaemic control, promoting weight loss and controlling BP, these results were similar with ours. But it evaluated the three drugs' monotherapy economic analysis, which is different from our study, as we evaluated the economic effect of ipragliflozin as add-on therapy. Actually, it was meaningful to assess the economic effect of ipragliflozin as add-on therapy within the limited financial resources of health care systems. Because healthcare decision makers should regard not only the efficacy, hypoglycemia risk, other adverse events, but also the costs associated with each drug class, when choosing two or more agents as combination therapy. In addition, the American Diabetes Association (ADA) also recommend that a second agent can be added to metformin monotherapy within 3 months if the maximum tolerated dose of metformin fails to achieve or sustain the glycemic goals [37], and ipragliflozin as an SGLT-2 inhibitor is one of the options. In our health economic evaluation, we didn't take discount rate into consideration, and we only captured differences in direct costs and effectiveness associated with glucose-lowering medications and did not take into consideration other differences such as cost of the adverse reactions, because the meta-analysis showed ipragliflozin as add-on therapy was well tolerated, and neither TEAE nor drug-related TEAE incidence rate was statistically different between groups. So, the total costs of each treatment regimen in our study may be lower. However, it is necessary to include the costs of diabetes complications, adverse events and discount rate in the long-term economic evaluation. Additionally, the prices of medicines may be different from other countries and the cost-effectiveness thresholds also are various. In our study, we used three times the local GDP per capita as the WTP, actually the WTP may be different in countries and regions. It would be an interesting and meaningful work to investigate the WTP of patients in combination of glucose-lowering medications. Four RCTs were excluded in the cost-effectiveness analysis because the following different reasons: the RCTs did not describe the insulin types and dosage [13,14], or the study reported insufficient data of effectiveness in patients with different sulfonylureas [15] or other glucose-lowering medications such as pioglitazone or sulfonylurea or α-glucosidase inhibitor [18]. Notably, only one RCT assessed the quality of life by European Quality of Life-5 (EQ-5D) Dimensions and Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaires. But the results showed that changes from baseline to 12 weeks in EQ-5D domains and ADDQoL scores were small and there was a non-statistically significant trend for improvement in the ipragliflozin treatment groups. Regrettably, we were unable to perform cost-effectiveness analysis in terms of changes in quality of life. The quality of life of ipragliflozin as add-on therapy in the long-term treatment also needs to be studied in original RCTs. In our study, we chose the proportion of patients who achieved a target goal of HbA1c (<7.0) as the effectiveness indicator. Actually, we also performed another cost-effectiveness analysis with the decrease value of HbA1c as the effective index (Table S3). The results showed that the therapy of ipragliflozin added to metformin was not economical, it was consistent with the results of Table 3. When ipragliflozin was added to pioglitazone, or sitagliptin + metformin, the combination therapies including ipragliflozin were more economical than the corresponding control group, because the control group did not decrease the value of HbA1c, and compared with pioglitazone group and sitagliptin + metformin group, their ICER of ipragliflozin add-on therapy were $715.86, $750.78, respectively, this was also lower than WTP and consistent with the previous results in Table 3. So, our results of cost-effectiveness analysis were also reliable and stable.

We should acknowledge some limitations of our study and the results of this analysis should be interpreted carefully. First, we included only eleven studies. Because there was limited number of patients included in the meta-analysis, our results need to be verified in additional high-quality studies with large samples. Second, ipragliflozin is an SGLT2 inhibitor associated with reductions in weight and other outcomes; however, there was a lack of trials comparing ipragliflozin with other SGLT2 inhibitors or other glucose-lowering medications, such as glucagon-like peptide-1 analogs and DPP-4 inhibitors. Third, in the current analyses, because of the absence of relevant studies in China, most of the parameter values were derived from RCTs in other countries, thus it may not reflect Chinese data. Fourth, the efficacy and safety of dapagliflozin, canagliflozin and empagliflozin as monotherapy and add-on therapy for patients with T2DM were proved in previous meta-analysis [5,38]. But the economic effect of these treatments was not clear. In our study, we only assessed ipragliflozin, it would be meaningful to conduct a comprehensive economic evaluation of all SGLT2 inhibitors combination therapy with other glucose-lowering agents. So future studies on all SGLT2 inhibitors in patients with T2DM are expected.

5. Conclusion

In conclusion, ipragliflozin add-on therapy is effective in lowering blood glucose in T2DM patients and provides additional clinical benefits, such as weight loss, blood pressure reduction, and reduction in TG levels. In addition, limited data suggest that ipragliflozin add-on therapy does not increase the risk of urinary tract infections or genital infections, but increases the risk of hypoglycemia when added to insulin. The cost-effectiveness analysis showed that ipragliflozin as an add-on therapy did not appear cost-effective compared with metformin alone, but may be more competitive against pioglitazone group and the sitagliptin + metformin group. However, these results need to be verified in additional high-quality studies with large samples.

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Declaration of Competing Interest

Hongmei Wang, Gaoqiong Yao, Xi Chen, Jing Ouyang, and Jiadan Yang declare no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107867.

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