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Review Article

Combined use of dipeptidyl peptidase-4 inhibitors and metformin reduces blood sugar level and improves pancreatic islet β cell function in the treatment of type 2 diabetes mellitus: a meta-analysis

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Abstract: Aims: The present study is to use meta-analysis to evaluate the efficacy and safety of the combined use of dipeptidyl peptidase-4 (DPP-4) inhibitors and metformin (MET) in the treatment of type 2 diabetes mellitus (T2DM). Methods: Literatures were carefully searched in databases including PubMed, Embase, Medline, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database, Chinese VIP Journal Database, and Chinese Biomedical Database from the construction date of the databases to August 2014. The experimental (DPPI + MET) group orally took DPP-4 inhibitors and MET, while control (MET) group only orally took MET or MET + placebo. Glycosylated hemoglobin (HbA1c) and pancreatic islet cell function were the main outcome indices. Hypoglycemia and other adverse reactions were secondary outcome indices. Methodology quality evaluation of included randomized controlled trials (RCTs) was performed using the "bias risk assessment tool" in Cochrane Review Manager version 5.2. The heterogeneity among the included studies was examined using χ^2 test. Results: A total of 22 RCTs and 13,987 subjects were finally included in the meta-analysis. Meta-analysis showed that the efficacy of combined use of DPP-4 inhibitors and MET was better than that of MET alone in reducing HbA1c. Similarly, combined use of DPP-4 inhibitors and MET had better efficacy than MET alone in improving pancreatic islet β cell function. These results were not altered by changes in duration of treatments. Combined use of DPP-4 inhibitors and MET or MET alone had low risks for total adverse events or hypoglycemia. Conclusions: The present study demonstrates that the combination of DPP-4 inhibitors and MET has better efficacy than MET alone in controlling blood sugar level and improving pancreatic islet β cell function during the treatment of T2DM. However, the incidence for hypoglycemia and total adverse reactions is the same for the combination of DPP-4 inhibitors and MET and MET alone.

Keywords: Dipeptidyl peptidase-4 inhibitors, metformin, type 2 diabetes mellitus, systematic evaluation, meta-analysis

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that is characterized by fat and protein metabolic disorder caused by absolute or relative lack of insulin [1]. There are 347 million diabetes patients all over the world at present. According to the prediction by World Health Organization, diabetes will become the 7th leading cause of death in 2030 [2]. About 90% diabetes cases are T2DM. There are a variety of oral drugs used clinically for the treatment of T2DM. As a preferred oral hypoglycemic agent for T2DM, metformin (MET) take effects by increasing the uptake and utilization of glucose by peripheral tissues. It inhibits gluconeogenesis and glycogenolysis, reduces hepatic glucose output, improves insulin sensitivity, and alleviates insulin resistance [3-5]. The efficacy and safety of MET have already been confirmed by clinical practice. However, single drug is often difficult to continuously reduce blood sugar due to the complex pathogenesis of T2DM. It is reported that combined

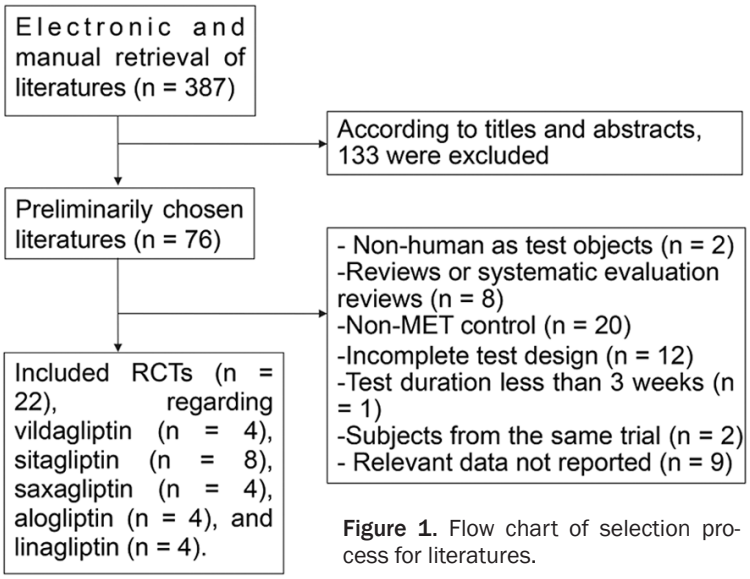

Figure 1. Flow chart of selection process for literatures.

use of different drugs at early stage can persistently control blood sugar on a basis of life style intervention [6].

Dipeptidyl peptidase-4 (DPP-4) inhibitors, a kind of oral hypoglycemic agent that exerts its effect by inhibiting in vivo decomposition and metabolism of glucagon like peptide-1 (GLP-1), have become important measures in the treatment of T2DM. GLP-1 is a kind of hormone secreted by L cells in intestinal tract. It exerts its hypoglycemic effect by promoting the insulin secretion, inhibiting glucagon secretion, and slowing down gastric emptying [7]. Under physiological conditions, GLP-1 is rapidly degraded by DPP-4, while DPP-4 inhibitors can slow down the degradation of GLP-1. The hypoglycemic effect of DPP-4 inhibitors is similar to that of traditional hypoglycemic drugs. In addition, DPP-4 inhibitors reduce the risk of hypoglycemia in patients, repair pancreatic islets, and protect heart and blood vessels without increasing the weight of patients [8, 9].

Commercial DPP-4 inhibitors include sitagliptin, saxagliptin, vildagliptin, alogliptin and linagliptin. Of note, the combination of DPP-4 inhibitors with MET has attracted much concern as a novel treatment scheme. There have been some literatures on the clinical trials for the combined use of DPP-4 inhibitors with MET in the past years. However, the quality of the literatures is not the same due to different experimental design and sample size. In the present study, we search literatures that have reported randomized controlled trials (RCTs) on the effects of combined DPP-4 inhibitors and MET or MET alone on T2DM. In addition, we evaluate the efficacy and safety of the combined use of DPP-4 inhibitors and MET.

Materials and methods

Literature search

Literatures were carefully searched in databases including PubMed, Embase, Medline, Cochrane Library, China National Knowledge Infrastructure, Wanfang Database, Chinese VIP Journal Database, and Chinese Biomedical Database from the construction date of the databases to August 2014. The search terms (both English and Chinese) included various combinations of “dipeptidyl peptidase-4 inhibitors OR DPP-4 inhibitors”, “sitagliptin”, “alogliptin”, “saxagliptin”, “vildagliptin”, “linagliptin”, “metformin”, “dutogliptin”, “combined use”, “diabetes”, “randomized clinical trial”, “safety”, and “efficacy”.

Inclusion and exclusion criteria

RCTs were included in the analysis, regardless of whether the blind method was used. The included literatures met the following criteria: i) The included patients were T2DM patients; ii) All patients were over 18 years old; iii) The diagnosis of T2DM was in accordance with the standards established by World Health Organization or American Diabetes Association. The exclusion criteria were: i) Severe liver and kidney dysfunction, severe cardiac insufficiency, pregnancy or lactation; ii) Enrollment of other clinical trials within 3 months before the trial; iii) Other situations that are not appropriate for the inclusion into the current clinical trial.

Intervention measures

The experimental (DPPI + MET) group orally took DPP-4 inhibitors and MET, while control (MET) group only orally took MET or MET + pla-

Table 1. General characteristics of included studies

Literatures	Tested drug	No. of cases	Age (years)	T2DM duration (years)	HbA1c (%)	BMI (kg/m^2)	MET (mg)	Duration (weeks)	Jadad scores
Ahren 2004 [5]	Vildagliptin	57	56.7 ± 9.6	5.55 ± 3.98	7.7 ± 0.6	29.55 ± 3.55	1050-3000	52	5
Bosi 2007 [6]	Vildagliptin	544	54.2 ± 9.83	6.3 ± 5.16	8.4 ± 1.0	32.6 ± 5.5	2109 ± 315	24	5
Goodman 2009 [7]	Vildagliptin	370	54.7 ± 10.4	4.46 ± 4.45	8.6 ± 1.1	31.5 ± 4.2	1880 ± 380	24	5
Pan 2012 [8]	Vildagliptin	438	54.1 ± 9.9	5.2 ± 4.65	8.06 ± 0.84	25.5 ± 3.2	> 1500	24	6
Charbonnel 2006 [9]	Sitagliptin	701	54.55 ± 10	6.3 ± 5.25	8 ± 0.8	31.2 ± 5.1	≥1500	24	5
Goldstein 2007* [10]	Sitagliptin	1091	53.3 ± 9.93	4.16 ± 4.45	8.78 ± 0.95	32 ± 6.63	21000	24	5
Raz 2008 [11]	Sitagliptin	190	54.85 ± 9.5	5.02 ± 4.6	8.7 ± 0.84	30.25 ± 3.16	> 1500	30	5
Scott 2008 [12]	Sitagliptin	271	55.1 ± 9.8	4.9 ± 3.6	7.7 ± 0.9	30.2 ± 4.9	> 1500	18	6
Olansky 2011 [13]	Sitagliptin	1250	49.7	3.35	9.1 ± 1.3	33.35	1000-2000	44	6
Bergenstal 2012 [14]	Sitagliptin	636	55.95 ± 9.6	5.8 ± 4.6	7.97 ± 0.86	32.47 ± 5.3	≥1500	51	5
Yang 2012 [15]	Sitagliptin	395	54.6 ± 9.4	-	8.5 ± 0.9	-	1000-1700	24	4
NCT01076088 2014 [16]	Sitagliptin	744	52.7 ± 10.0	-	8.70 ± 1.04	-	500/850	24	4
DeFronzo 2008 [17]	Saxagliptin	743	60 ± 9	6.5 ± 5.2	8 ± 0.5	31.9 ± 4.3	1500-2550	12	4
Jadzinsky 2009 [18]	Saxagliptin	1306	52.1 ± 11.7	1.7 ± 3	9.5 ± 1.2	30.2 ± 4.8	1000-2000	24	6
Yang 2011 [19]	Saxagliptin	570	54.6 ± 10.24	-	-	-	> 1500	24	4
NCT00885378 2014 [20]	Saxagliptin	160	55.4 ± 10.20	6.00 ± 5.30	-	33.05 ± 6.08	1882 ± 352	12	4
Forst 2010 [21]	Linagliptin	333	54.6 ± 10	7 ± 6.3	8.3 ± 0.3	31.4 ± 4.8	≥1500/d	24/54-104	5
Taskinen 2011 [22]	Linagliptin	701	56.5 ± 10.3	-	8.08 ± 0.87	29.9 ± 4.88	-	24	6
Haak 2012 [23]	Linagliptin	791	55.3 ± 10.8	-	8.66 ± 0.97	29.1 ± 5.1	1000-2000	24	6
Ross 2012 [24]	Linagliptin	491	58.6 ± 10.3	4.9 ± 3.6	7.97 ± 0.75	29.6 ± 5.1	-	12	5
Nauck 2009 [25]	Alogliptin	627	55 ± 11	6 ± 5	7.96 ± 6.8	32 ± 5.3	< 1500	26	5
Seino 2012 [26]	Alogliptin	288	52.6 ± 8.28	6.33 ± 4.84	7.97 ± 0.8	25.85 ± 4.14	500-700	12	6
Pratley et al. 2014 [27]	Alogliptin	784	53.5 ± 10.33	4.0 ± 4.56	-	30.7 ± 5.17	1000/2000	26	5
NCT01289119 2014 [28]	Alogliptin	506	52.6 ± 9.71	4.11 ± 4.22	-	25.73 ± 3.04	1427 ± 451	16	5

Note: BMI, body mass index; MET, metformin. *, the literature is about the same trial with Williams-Herman D 2010 [29] and Williams-Herman D 2009 [30].

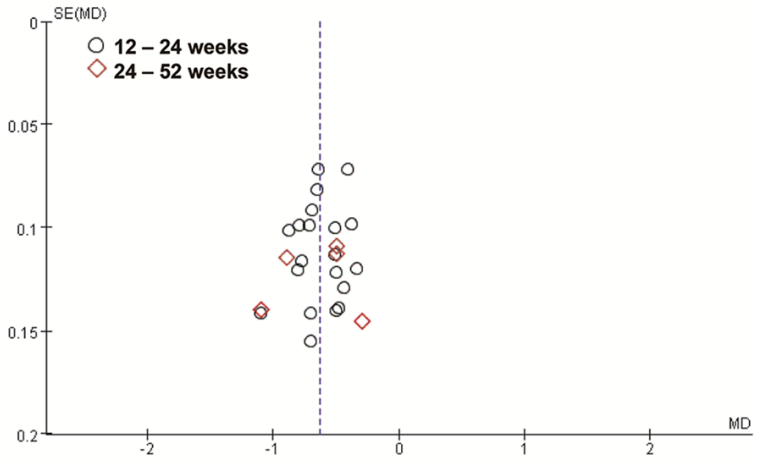

Figure 2. Funnel plot the determination of HbA1c.

cebo. The participants did not take any other drugs that may affect blood sugar during the whole test process.

Outcome indices

Glycosylated hemoglobin (HbA1c) and pancreatic islet cell function were the main outcome indices. Hypoglycemia and other adverse reactions were secondary outcome indices.

Data extraction and quality assessment

Two investigators independently evaluated the quality of the literatures and extracted relevant data. In case of any disagreement between the two investigators, the decision was made after thorough discussion with a third investigator. Methodology quality evaluation of included RCTs was performed using the "bias risk assessment tool" in Cochrane Review Manager (RevMan) version 5.2 [10]. Evaluation content included the following aspects: i) whether the random method was correct; ii) whether allocation concealment was performed; iii) whether blind method was used; iv) whether there were withdrawal or loss of follow-up (if there was any, whether intention-to-treat was adopted); v) whether the baseline

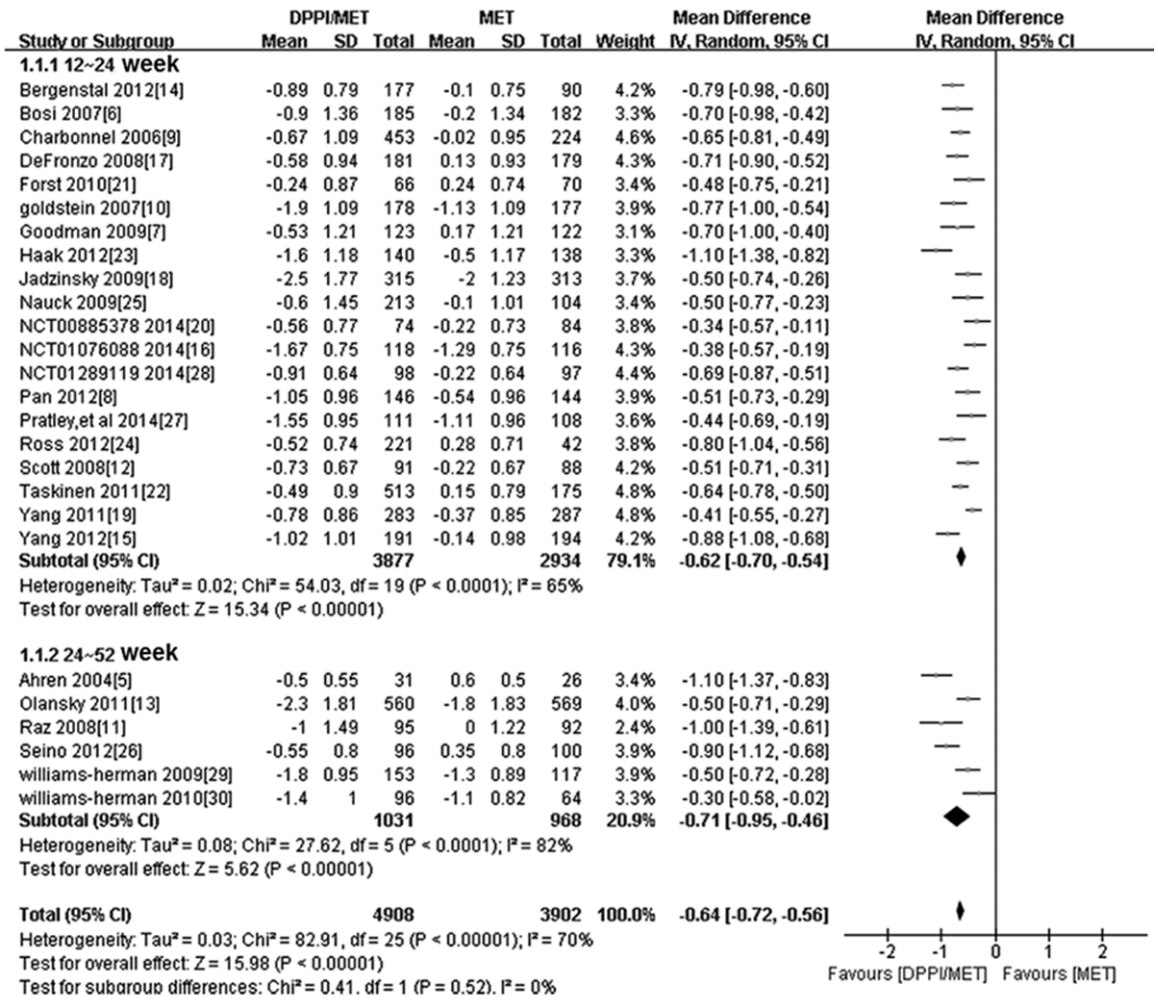

Figure 3. Meta-analysis for changes in HbA1c level after treatment with the combination of DPP-4 and MET or MET alone.

was comparable. In the present study, modified Jadad scale was used to evaluate the quality of literatures. Random method, allocation concealment, or double blind corresponded to 2 points, and withdrawal or loss of follow-up corresponded to 1 point. Literatures with less than 4 points were considered to be of low quality and excluded from the present study. The extracted data included basic information of literatures, subjects, quality, intervention measures and outcome measurements.

Statistical analysis

Meta-analysis was carried out using RevMan 5.2 software (http://www.cochrane.org/). The heterogeneity among the included studies was examined using χ^2 test. If $P > 0.1$ and $I^2 < 50\%$, fixed effect model was used for analysis; If $P < 0.1$ and $I^2 > 50\%$, random effect model was used. Weighted mean difference (WMD) was used as effect size for continuous variables. Interval estimation was expressed as 95% confidence interval (95% CI). If the number of literatures for combined analysis was more than 10, funnel plot made by RevMan 5.2 was used to evaluate publication bias.

Results

Characteristics of the included studies

A total of 387 literatures were acquired by searching. By reviewing titles, abstracts and full texts, 76 literatures on the treatment of T2DM with DPP-4 inhibitors were preliminarily chosen. According to the inclusion and exclusion criteria, 24 literatures [11-33] with a total of 22 RCTs and 13,987 subjects were finally included in the meta-analysis (**Figure 1**). All included lit-

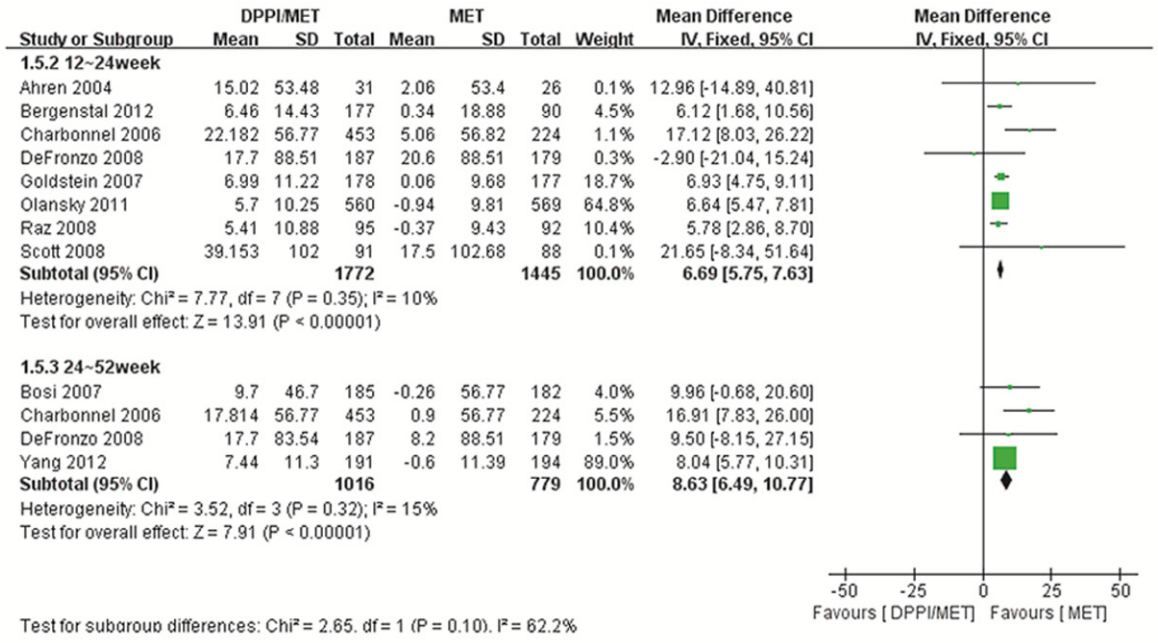

Figure 4. Meta-analysis for changes in pancreatic islet β cell function after treatment with the combination of DPP-4 and MET or MET alone.

eratures were published in English. The subjects in three literatures [16, 32, 33] were from the same RCT. Vildagliptin, saxagliptin, linagliptin and alogliptin were investigated in 4 RCTs each, while sitagliptin was studied in 8 RCTs. Of note, the results of three clinical trials from ClinicalTrials.gov website were not published yet, and these trials could be included as grey literatures. The durations of trials were between 12 weeks and 52 weeks, including 18 literatures of 12-24 weeks (including 24 weeks), and 6 literatures of 24-52 weeks (**Table 1**).

Risk assessment of publication bias

To assess the risk of publication bias, funnel plot of studies using HbA1c as outcome index was made. The plot showed good bilateral symmetry (**Figure 2**). This result suggests that the risk of publication bias is small.

Analysis of efficacy

According to the duration of included studies, the studies were divided into two subgroups with 12-24 weeks and 24-52 weeks of durations. The analysis showed that MET alone or the combination of DPP-4 inhibitor and MET reduced the levels of HbA1c. Combined analysis showed that the effect of combined use of DPP-4 inhibitor and MET was stronger than MET alone in reducing the levels of HbA1c, with a combined effect value of -0.64% (95% CI: -0.72, -0.56; $P < 0.00001$) (**Figure 3**). Subgroup analysis showed that the effect of combined use of DPP-4 inhibitor and MET was significantly stronger than MET alone in both subgroups (for subgroup with 12-24 weeks of duration, WMD = -0.62%, 95% CI (-0.70, -0.54), and $P < 0.00001$; for subgroup with 24-52 weeks of duration, WMD = -0.71%, 95% CI (-0.95, -0.46), and $P < 0.00001$). The result suggests that the efficacy of combined use of DPP-4 inhibitors and MET is better than that of MET alone in reducing HbA1c.

Furthermore, the combined use of DPP-4 inhibitors and MET in both subgroups showed significantly different effect in improving pancreatic islet β cell function than MET alone. For the subgroup with 12 - 24 weeks of duration, the combined effect value was 6.69 [95% CI: 5.75-7.63, $P < 0.00001$]. For the subgroup with 24-52 weeks of duration, the combined effect value was 8.63 [95% CI: 6.49-10.77, $P < 0.00001$] (**Figure 4**). The result indicates that combined use of DPP-4 inhibitors and MET has better efficacy than MET alone in improving pancreatic islet β cell function.

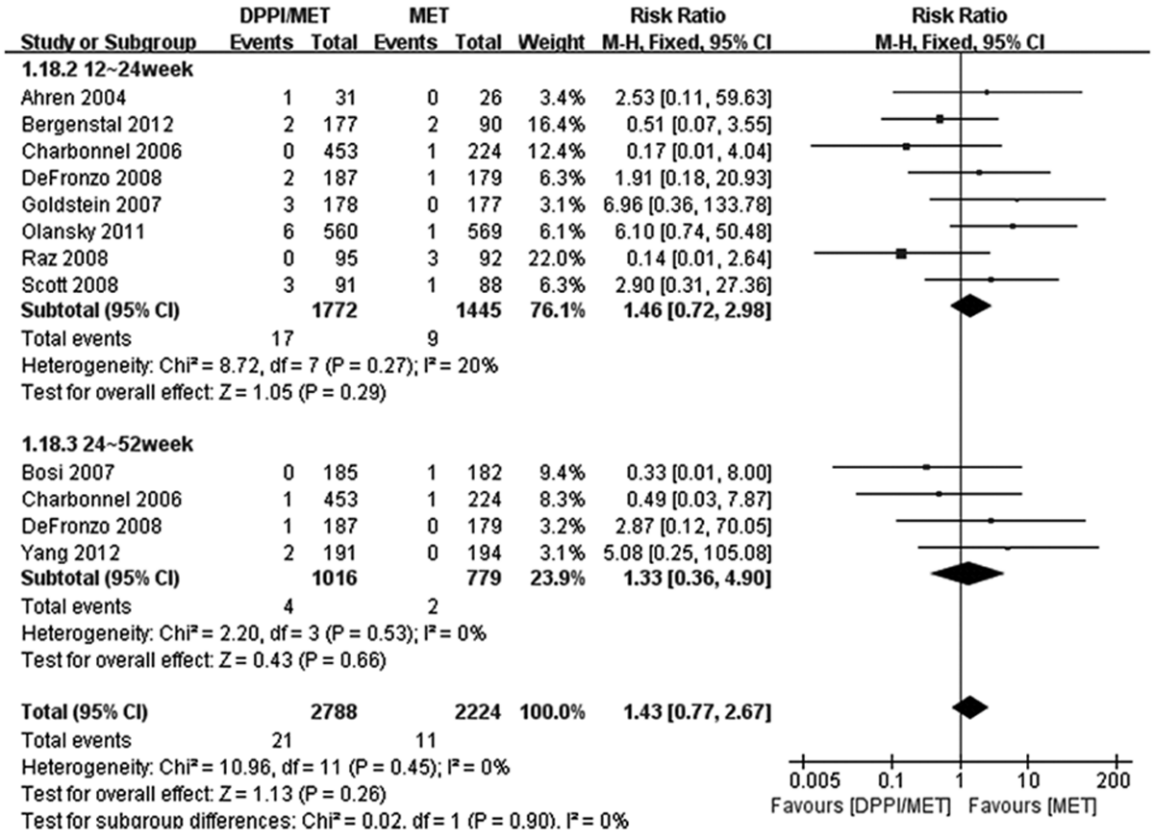

Figure 5. Meta-analysis for the incidence of hypoglycemia after treatment with the combination of DPP-4 and MET or MET alone.

Table 2. Prevalence of adverse events

Adverse reactions	DPPI/MET	MET
Total adverse events	37.1	38.9
Cardiovascular adverse events	10.5	11.9
Severe adverse events	2.6	2.8
Withdrawal due to adverse reactions	4.0	4.2
Nausea	3.8	3.2
Vomiting	4.6	4.6
Constipation	6.2	7.7
Urinary-tract infection	4.7	4.6
Hypertension	3.3	3.7

Analysis of safety

The safety of the combined use of DPP-4 inhibitors and MET was examined in nearly all clinical trials. Meta-analysis of hypoglycemia incidence rate showed that the heterogeneity was $I^2 = 0\%$ and P = 0.45, and fixed effect model was used to combine data. Combined meta-analysis showed RR = 1.43, 95% CI (0.77, 2.67), and P = 0.26 (**Figure 5**), suggesting that combined use of DPP-4 inhibitors and MET did not increase the incidence of hypoglycemia. In addition, the patients were well tolerated after using MET alone or combination of DPP-4 inhibitors and MET, and the incidence of severe adverse reactions or withdrawal was very low. The incidence of total and cardiovascular adverse events in the two groups was close to each other, and the incidence of gastrointestinal adverse reactions was not significantly different between the two groups (**Table 2**).

Discussion

DPP-4 inhibitors reduce the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting the activity of DPP-4, and achieve the goal of blood sugar control by elevating the levels of GLP-1 and GIP [34]. Due to the complex pathogenesis of T2DM, single drug is often difficult to continuously lower the levels of blood sugar. As the progression of the disease, multiple drug com-

binations, especially the combinations of drugs with complementary mechanisms, are often required. DPP-4 inhibitors and MET have complementary mechanisms, and their combination can be an important choice in the treatment of T2DM [35]. American Association of Clinical Endocrinologists recommends using DPP-4 inhibitors in single drug therapy for T2DM patients with HbA1c levels between 6.5% and 7.5%. For patients with HbA1c levels between 7.5% and 9.0%, the combined use of DPP-4 inhibitors and MET is suggested [36].

In the present study, we have evaluated the efficacy and safety of the combination of DPP-4 inhibitors and MET in the treatment of T2DM. Our results show that the combined use of both drugs more significantly reduces HbA1c levels compared with MET alone, suggesting that the combination has good efficacy in lowering blood sugar in T2DM patients. In addition, the combination of both drugs has better efficacy than MET alone in improving pancreatic islet cell function. Regarding the duration of treatment, patients with 12-24 weeks of treatment have similar level of decrease in HbA1c levels compared with patients with 24-52 weeks of treatment after combined use of DPP-4 inhibitors and MET. By contrast, the improvement of pancreatic islet β cell function in patients with 24-52 weeks of treatment is greater than that in patients with 12-24 weeks of treatment. This result suggests that combined use of DPP-4 inhibitors and MET has significant blood sugar reduction effect at the initial stage of drug use, but its effect is reduced as the duration of treatment is prolonged. By contrast, pancreatic islet β cell function is improved. Of note, the number of literatures and patients with 24-52 weeks of treatment is smaller, and the above-mentioned effect should be further verified in a longer medication period. Regarding safety, the present study shows that the combined use of DPP-4 inhibitors and MET cannot increase the incidence of hypoglycemia, or the rates of total adverse reactions, adverse cardiovascular events, and gastrointestinal adverse reactions. It is reported that DPP-4 inhibitors can control blood sugar, decrease vascular oxidative stress reaction, and reduce myocardial ischemia/reperfusion injury [37, 38]. Wu et al. show that DPP-4 inhibitors have no risk in increasing or reducing cardiovascular events such as acute coronary syndrome, being consistent with the results in the present study [39].

The present study has evaluated 22 RCTs, and the results of three RCTs among them have not been published. The literatures by Goldstein [39] and Williams-Herman D [32, 33] are originated from the same RCT, and the latter literature mainly reports the long-term efficacy and safety of sitagliptin. The included literatures have some problems in methodology. The literatures haven't clearly reported random method, only mentioning randomization without elaboration. The JADAD scores of all studies are higher than 4 points, and the overall quality of the studies is high. However, there are still some limitations in the present systematic evaluation. First, the present study hasn't analyzed single DPP-4 inhibitor by subgroups, and only studied the effect of the maximal dose when multiple doses are used. In addition, the number of included literatures for 24-52 weeks of treatment is small, and these literatures have obvious heterogeneity. Of note, differences in years of disease, body mass index, and MET dosages will also affect the efficacy of drugs. In the present study, we haven't carried out sensitivity analysis according to the baselines of patients. This may also affect the combined analysis result. In conclusion, the combined use of DPP-4 inhibitors and MET reduces blood sugar and the incidence of adverse reactions. However, the long-term efficacy and safety of this combination still need further research.

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Disclosure of conflict of interest

None.

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