

Original Article

Efficacy and safety of vildagliptin combined with metformin in the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract: Background: Many treatment options are available for type 2 diabetes mellitus (T2DM), but long-term glucose control remains unsatisfactory. Vildagliptin is a highly selective DDP-4 inhibitor, but evidence support its use in combination with metformin is not convincing. Methods: We searched for randomized controlled trials (RCTs) in the Cochrane Library, PubMed, EMBASE, China Knowledge Resource Integrated Database (CNKI), VIP Database for Chinese Technical Periodicals (VIP) and Chinese Biomedical Database (CBM). Trial quality was evaluated using the Cochrane Handbook. Primary efficacy measure was reduction in glycated hemoglobin (HbA1c). Safety assessment included hypoglycemic episodes and overall adverse events. Pre-planned subgroup analysis (and comparison) was conducted for trials lasting for ≤ 52 weeks vs. > 52 weeks. Results: The analysis included 12 studies. One study reported the end points at both ≤ 52 weeks and > 52 weeks. In comparison to metformin alone (or metformin plus placebo), the metformin/vildagliptin combination was superior in efficacy measures and comparable in safety profile. A comparison to metformin plus other oral hypoglycemic agents (OHAs) revealed that the metformin/vildagliptin combination is: 1) comparable in terms of HbA1c reduction regardless of follow-up duration; 2) comparable in terms of hypoglycemic episodes and overall adverse events at ≤ 52 weeks, but superior at > 52 weeks. Conclusions: In comparison to metformin plus other OHAs, the metformin/vildagliptin combination is equally effective in HbA1c reduction. The advantage in safety profile of the metformin/vildagliptin combination over metformin plus other OHAs manifests itself upon longer treatment (> 52 weeks).

Keywords: Meta-analysis, type 2 diabetes mellitus, vildagliptin, metformin, systematic review

Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly health problem worldwide [1, 2]. The primary goal of treatment is to control hyperglycemia (reflected as reduced HbA1c). Towards this end, many pharmacological agents are effective; but choosing the optimal agent or regimen is a challenging task.

Classical oral hypoglycemic agents (OHAs) for the treatment of T2DM mainly include biguanides, sulfonylureas, thiazolidinediones, and α -glucosidase inhibitors. These agents typically act through one of the following mechanisms: promotion of insulin secretion, inhibition of glucose absorption, and increase of insulin sensitivity. Due to the progressive nature of the disease, these agents tend to be limited in efficacy

upon advanced stage of the disease as β -cell failure develops.

Unsatisfactory blood glucose control may result in the development of chronic complications in diabetic patients, including heart disease, stroke, amputation, blindness, nephropathy and peripheral neuropathy [3]. With increasing disease duration, the treatment intensity for T2DM needs to be enhanced. The conventional stepwise escalation of therapy starts from lifestyle modification, followed by single OHA at increasing dosage, simultaneous use of multiple OHAs, and finally insulin.

Dipeptidyl peptidase-4 (DDP-4) inhibitors are a relative new class of agents that indirectly increases insulin secretion and suppresses hepatic glucose production by blocking the deg-

radation of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) [4]. A meta-analysis by Richter in 2008 confirmed the efficacy and safety of DPP-4 [5]. DPP-4 inhibitors target a different set of physiological and molecular targets than metformin: increasing insulin sensitivity via stimulating GLP-1 secretion and reducing endogenous hepatic glucose production [6]. A combination of DPP-4 inhibitors and metformin is believed to produce synergistic effects [7, 8]. Vildagliptin is a DPP-4 inhibitor increasingly used in combination with metformin in patients with T2DM who require combination therapy [9]. A meta-analysis by Cai in 2012 [10] revealed satisfactory glucose control with acceptable risk of hypoglycemic events by vildagliptin, but did not conduct subgroup analysis for the combination of vildagliptin and metformin. A meta-analysis by Wu in 2013 [11] revealed superiority of DPP-4 inhibitors in combination with metformin (relative to metformin alone) in glucose control without increasing major adverse events, but did not discriminate among individual DPP-4 inhibitors. Also, the Wu study did not compare the combination of metformin with DPP-4 inhibitors with metformin plus other OHAs.

The purpose of the current meta-analysis was to assess the efficacy and safety of vildagliptin in combination with metformin for the treatment of T2DM in randomized controlled trials (RCTs).

Materials and methods

Data sources and searches

We searched the Cochrane Library, PubMed, EMBASE, China Knowledge Resource Integrated Database (CNKI), VIP Database for Chinese Technical Periodicals (VIP) and Chinese Biomedical Database (CBM) for RCTs published in English or Chinese between the starting date of the databases and November, 2014. The search strategy is shown in [Supplementary Table 1](#). The abstracts of each screened publication were read carefully. We manually searched additional studies in the reference lists of all identified publications, including relevant meta-analyses and systematic reviews.

Study selection

We included RCTs conducted in adult patients with T2DM diagnosed according to the WHO or

American Diabetes Association (ADA) criteria [12, 13]. Included studies had to have an intervention group receiving the combination regimen with vildagliptin and metformin and a parallel group receiving metformin plus a placebo, a blank or another OHA. We excluded studies conducted in subjects with type 1 diabetes mellitus (T1DM), severe liver or kidney injury, severe cardiac insufficiency, and pregnant or lactating women.

The primary and secondary outcome measures were HbA1c reduction and fasting plasma glucose (FPG) reduction, respectively. The primary and secondary safety outcome was hypoglycemic events and the incidence of adverse events.

Literature screening and data extraction

Two non-blinded reviewers (TX and MZ) independently screened and cross-checked the searched literatures according to the inclusion and exclusion criteria. If required, authors of the original papers were contacted via mail or telephone to confirm the implementation process of the trial. If disagreement occurred, the final decision was made through discussion or by the third reviewer. The extracted data included 1) the title, the first author, time of publication, journal of publication (journal title, volume, issue, and page); 2) demographic and baseline characteristics of the study subjects including sex, ethnicity, and body mass index (BMI, kg/m²); 3) sample size, the number of subjects who were withdrawn from the study and/or lost to follow up, and any complications and their severity; 4) name and dose of drugs for T2DM, the course of treatment, and the route and method of drug administration; 5) the study outcomes, time of measurement and data types captured according to different outcome measures. If different units were employed for the same outcome measure, a uniform unit was used.

Assessment of study quality

The quality of the included studies was evaluated by two reviewers (TX and MZ) in a cross-checking manner. Disagreement was resolved by discussion or by a third reviewer (X-HJ). The risk of bias was evaluated using the quality of included studies was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2, and included the

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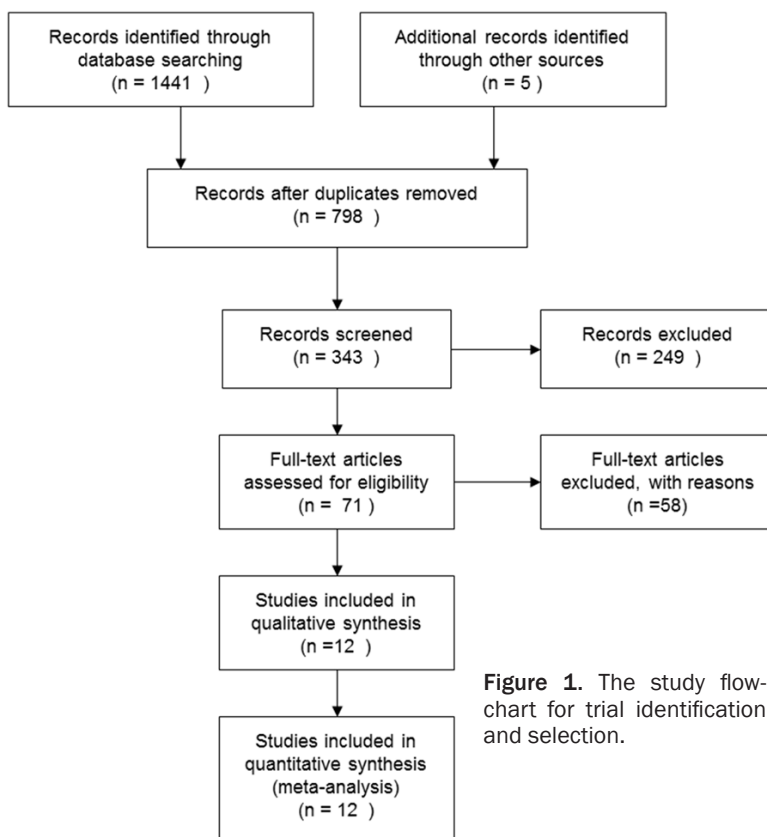


Figure 1. The study flowchart for trial identification and selection.

accuracy of randomization method, the presence of allocation concealment, the use of blinding, the presence of bias due to incomplete data, the presence of bias due to selective reporting, presence of loss of follow-up and withdrawal, the use of intent-to-treatment (ITT) analysis if loss of follow-up or withdrawal occurred, selective reporting of outcomes, and the presence of other biases [14].

Data analysis

Meta-analysis was performed using the software RevMan version 5.0 developed by the Cochrane Collaboration. The homogeneity among studies was tested for statistical significance with chi-square test. Heterogeneity was considered present if the *P*-value was less than 0.1, and a random effects model was used; otherwise, a fixed effects model was employed to combine the effect size. For continuous variables like HbA1c and FPG, mean difference (MD) represented the effect size, while risk ratio (*RR*) indicated effect size for non-continuous variables, such as incidence of adverse events including hypoglycemia. Interval estima-

tion was performed with 95% confidential interval (*CI*).

Results

Outcome of literature search

The study flowchart is shown in **Figure 1**. We retrieved a total of 1441 articles, with 501 articles from PubMed, 188 from the Cochrane Library, 712 from EMBASE, 14 from CNKI, 10 from VIP and 16 from CBM and five additional articles from other sources. After removing duplicate reports, the total number of articles was 798. Of these, 455 were excluded on the basis of title and abstract. Of the 343 that underwent full text evaluation, 12 studies [15-27] met our inclusion criteria. The basic characteristics of the eligible studies are described in **Table 1**. Ferrannini 2009 [15] and Ma-

tthews 2010 [16] reported the results of the same clinical trials, but with distinct follow-up duration. Both articles were included in the analysis.

Study quality assessment

The quality assessment is shown in **Table 2**.

Effects on HbA1c

Five RCTs reported HbA1c reduction between metformin/vildagliptin and metformin/placebo [20, 21, 23, 24, 26]. Bosi 2009 [22] and Pan 2012 [25] compared metformin/vildagliptin combination vs. metformin alone. Derosa 2013 [24] reported HbA1c at 3, 6, 9, 12 months: only the 12-month data were included in the meta-analysis. Five studies [15-19] compared metformin/vildagliptin vs. metformin plus other OHAs. The metformin/vildagliptin combination was superior to metformin alone or metformin plus placebo [MD=-0.66; 95% *CI*, -0.92 to -0.40; *P*<0.00001] (**Supplementary Figure 1**), but comparable to metformin plus other OHAs [MD=0.02; 95% *CI*, -0.02 to 0.06; *P*=0.41] (**Supplementary Figure 2**).

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Table 1. Basic characteristics of twelve randomized controlled trials included in this study

Study	Study type	Country	Sample size (E/C)	Duration of disease (E/C)	Age (Year) (E/C)	Body mass index (kg/m ²) (E/C)	HbA1c (%) (E/C)	Interventions	Follow-up duration
Ferrannini 2009 [15] & Matthews 2010 [16]	RCT	Multinational	1396/1393	5.71 y/5.75 y	57.50/57.46	31.80/31.69	7.31/7.30	E: vildagliptin (50 mg b.i.d) + metformin (1898 mg/d) C: glimepiride (adjusted to 6 mg/d) + metformin (mean dose of 1898 mg/d)	52 w
	RCT	Multinational	1562/1556	5.7 y/5.7 y	57.5/57.5	31.9/31.7	7.3/7.3	E: vildagliptin (50 mg b.i.d) + metformin C: glimepiride (adjusted to 6 mg/day) + metformin	104 w
Filozof 2010 [17]	RCT	France	513/494	6.4 y/6.8 y	59.2/59.7	31.2/30.8	8.5/8.5	E: vildagliptin (50 mg b.i.d) + metformin (≥1500 mg/day) C: gliclazide (adjusted to 320 mg/d) + metformin (≥1500 mg/d)	52 w
Bolli 2008 [18]	RCT	Multinational	295/281	6.4 y/6.4 y	56.3/57.0	32.2/32.1	8.4/8.4	E: vildagliptin (50 mg b.i.d) + metformin (≥1500 mg/d) C: pioglitazone (30 mg/d) + metformin (≥1500 mg/d)	24 w
Blonde 2009 [19]	RCT	USA	1776/888	5.1 y/5.2 y	55.3/56.2	32.4/32.4	7.99/7.97	E: vildagliptin (100 mg/d) + metformin (≥1000 mg/d) C: thiazolidinedione + metformin (≥1000 mg/d)	12 w
Ahren 2004 [20]	RCT	Multinational	56/51	5.6 y/5.5 y	57.9/55.7	29.6/29.9	7.7/7.8	E: vildagliptin (50 mg q.d) + metformin (1500-3000 mg/d) C: placebo + metformin (1500-3000 mg/d)	52 w
Bosi 2007 [21]	RCT	Multinational	177/185/182	6.8 y/5.8 y/6.2 y	54.3/53.9/54.5	32.1/32.9/33.2	8.4/8.4/8.3	E1: vildagliptin (50 mg/d) + metformin (≥1500 mg/d) E2: vildagliptin (100 mg/d) + metformin (≥1500 mg/d) C: placebo + metformin (≥1500 mg/d)	24 w
Bosi 2009 [22]	RCT	Multinational	295/294	22.48 m/26.26 m	52.8/52.4	31.37/31.31	8.70/8.62	E: vildagliptin (50 mg b.i.d) + metformin (1000 mg b.i.d) C: metformin (1000 mg b.i.d)	24 w
Goodman 2009 [23]	RCT	the USA	125/122	\	54.7/54.5	31.7/31.7	8.5/8.7	E: vildagliptin (100 mg q.d) + metformin (1889 mg/d) C: placebo + metformin (1932.2 mg/d)	24 w
Derosa 2013 [24]		Italy	84/83	6.1/6.3	54.2/52.4	27.9/27.8	8.1/8.2	E: vildagliptin (50 mg b.i.d) + metformin C: placebo + metformin	12 m
Pan 2012 [25]	RCT	China	146/148/144	4.92/5.02/5.15	54.2/53.7/54.5	26.01/25.03/25.46	8.09/8.05/8.01	E1: vildagliptin (50 mg b.i.d) + metformin E2: vildagliptin (50 mg qd) + metformin C: metformin	24 w
Odawara 2014 [26]	RCT	Japan	69/70	7.2/7.0	58.7/57.5	25.3/25.9	8.0/8.0	E: vildagliptin (50 mg b.i.d) + metformin (250 mg or 500 mg bid) C: placebo + metformin (250 mg or 500 mg bid)	12 w
Stozik 2015 [27]	RCT	Poland	15/13		45.9/51.4	28.2/29.0	7.8/7.6	E: vildagliptin (100 mg/d) + metformin (1500 mg/d) C: placebo + metformin	12 w

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Table 2. Quality evaluation of twelve randomized controlled trials included in this study

Study	Adequate sequence generation	Allocation concealment	Blinding	Incomplete outcome data addressed	Free of selective reporting	Free of other biases	
Ferrannini 2009 [15] & Matthews 2010 [16]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Filozof 2010 [17]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	6
Bolli 2008 [18]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Blonde 2009 [19]	Low risk	Low risk	High risk	Low risk	Low risk	Unclear risk	5
Ahren 2004 [20]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Bosi 2007 [21]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Bosi 2009 [22]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Goodman 2009 [23]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Derosa 2013 [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	7
Pan 2012 [25]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	5
Odawara 2014 [26]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Strozik 2015 [27]	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	4

Effects on FPG

Seven RCTs [20-24, 26, 27] reported FPG between metformin/vildagliptin vs. metformin alone or plus placebo. Four studies [15-18] compared FPG between metformin/vildagliptin vs. metformin plus other OHAs. Ahren 2004 [20] reported FPG at both 12 and 52 weeks: only the 52-week data were included in the meta-analysis. The metformin/vildagliptin combination was superior to metformin alone or plus placebo [MD=-1.31; 95% CI, -1.74 to -0.89; $P<0.00001$] (Supplementary Figure 3). In comparison to metformin plus other OHAs, the metformin/vildagliptin combination was less effective at ≤ 52 -week follow-up [MD=0.25; 95% CI, 0.13 to 0.38; $P<0.0001$], but comparable at >52 -week follow-up (MD=0.20; 95% CI, -0.08 to 0.48; $P=0.16$) (Supplementary Figure 4).

Adverse events

Hypoglycemic episodes: The rate of glycemic episodes in patients receiving metformin/vildagliptin combination was compared with metformin alone or placebo plus metformin [21-23, 25, 26]. Five studies compared the rate of hypoglycemia between metformin/vildagliptin combination vs. metformin plus other OHAs [15-19]. The metformin/vildagliptin combination was comparable to metformin alone or metformin plus placebo [RR=0.99; 95% CI, 0.27 to 3.65, $P=0.99$] (Supplementary Figure 5). In comparison to metformin plus OHAs, the metformin/vildagliptin combination was comparable at ≤ 52 weeks [RR=0.61; 95% CI, 0.11 to 3.39, $P=0.57$], but caused less frequent glycemic episodes at >52 week follow-up

[RR=0.12; 95% CI, 0.09 to 0.17, $P<0.00001$] (Supplementary Figure 6).

Other AEs: Six RCTs compared adverse events other than hypoglycemic episodes between metformin/vildagliptin combination vs. metformin alone or metformin plus placebo [20-23, 25, 26]. Five studies [15-19] compared metformin/vildagliptin combination vs. metformin plus other OHAs. The included trials revealed that adverse events are generally mild and tolerable. In comparison to metformin alone or metformin plus placebo, the metformin/vildagliptin combination was comparable [RR=1.04; 95% CI, 0.95 to 1.14, $P=0.40$] (Supplementary Figure 7). In comparison to metformin plus other OHAs, the metformin/vildagliptin combination was comparable at ≤ 52 week follow-up [RR=1.01; 95% CI, 0.91 to 1.12, $P=0.86$], and had lower rate of adverse events at >52 week follow-up [RR=0.96; 95% CI, 0.93 to 0.99, $P=0.01$] (Supplementary Figure 8).

All the meta-results were summarized in the **Table 3**.

Sensitivity analysis and subgroup analyses

The sensitivity analysis revealed that the results of the Meta-analysis that compared vildagliptin/metformin vs. metformin alone or plus placebo were stable. The sensitivity analysis indicated that intervention in the control group might affect results. Blonde 2009 [19] was open-label study, comparing vildagliptin plus metformin with thiazolidinediones plus metformin. Pioglitazone is a drug of the thiazolidinedione (TZD) class, Gliclazide and glimepiri-

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Table 3. The results of meta-analysis

Outcomes	Interventions	Subgroup	Studies	Participants	Statistical Method	Statistical Method Effect Estimate
HbA1c	vildagliptin + metformin vs. placebo + metformin	≤52 w	[20-26]	1903	Mean Difference (IV, Random, 95% CI)	-0.66 [-0.92, -0.40]
	vildagliptin + metformin vs. OADs + metformin	≤52 w	[15, 17-19]	5997	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.02, 0.06]
FPG	vildagliptin + metformin vs. placebo + metformin	≤52 w	[20-24, 26, 27]	1607	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.74, -0.89]
		≤52 w	[15, 17, 18]	4101	Mean Difference (IV, Fixed, 95% CI)	0.25 [0.13, 0.38]
	>52 w	[16]	2060	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.08, 0.48]	
Hypoglycemic episodes	vildagliptin + metformin vs. placebo + metformin	≤52 w	[21-23, 25, 26]	1629	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.27, 3.65]
		≤52 w	[15, 17-19]	6978	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.11, 3.39]
	>52 w	[16]	3099	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.09, 0.17]	
Other AEs	vildagliptin + metformin vs. placebo + metformin	≤52 w	[20-23, 25, 26]	1699	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.95, 1.14]
		≤52 w	[15, 17-19]	6977	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.12]
	>52 w	[16]	3099	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.93, 0.99]	

Table 4. The results of meta-analysis (additional subgroup analysis)

Outcomes	Interventions	Subgroup	Studies	Participants	Statistical Method	Statistical Method Effect Estimate
HbA1c	vildagliptin + metformin vs OADs + metformin	vildagliptin + metformin vs sulfonylurea + metformin	[15, 17]	3009	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.03, 0.14]
		vildagliptin + metformin vs thiazolidinedione + metformin	[18, 19]	2988	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.17, -0.03]
FPG	vildagliptin + metformin vs OADs + metformin	vildagliptin + metformin vs sulfonylurea + metformin	[15, 17]	3591	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.00, 0.28]
		vildagliptin + metformin vs thiazolidinedione + metformin	[18]	510	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.42, 0.98]
Hypoglycemic episodes	vildagliptin + metformin vs OADs + metformin	vildagliptin + metformin vs sulfonylurea + metformin	[15, 17]	3775	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.04, 1.10]
		vildagliptin + metformin vs thiazolidinedione + metformin	[18, 19]	3203	Risk Ratio (M-H, Random, 95% CI)	2.38 [0.75, 7.59]
Other AEs	vildagliptin + metformin vs OADs + metformin	vildagliptin + metformin vs sulfonylurea + metformin	[15, 17]	3775	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.04]
		vildagliptin + metformin vs thiazolidinedione + metformin	[18, 19]	3203	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.99, 1.18]

de are classified as a sulfonylurea. Ferrannini 2009 [15] & Matthews 2010 [16], Filozof 2010 [17] compared vildagliptin/metformin with sulfonylurea/metformin, and Blonde 2009 [19] and Bolli 2008 [18] compared vildagliptin/metformin with thiazolidinedione/metformin. An additional subgroup analysis was conducted according to the class of antidiabetic drugs that plus metformin in the control group. The metformin/vildagliptin combination was superior to metformin plus thiazolidinedione [MD=-0.10; 95% CI, -0.17 to -0.03; P=0.005] in reduction of HbA1c, but the metformin/sulfonylurea combination was superior to the metformin/vildagliptin combination [MD=0.09; 95% CI, 0.03 to 0.14; P=0.001]. In comparison to metformin plus sulfonylurea, the metformin/vildagliptin combination was comparable [MD=0.14; 95% CI, 0.00 to 0.28; P=0.05] in reduction of PFG, while the metformin/thiazolidinedione combination was superior to the metformin/vildagliptin combination [MD=0.70; 95% CI, 0.42 to 0.98; P<0.00001]. Subgroup analyses did not affect the safety outcomes (Table 4).

Discussion

The primary purpose of T2DM therapy is reduction of hyperglycemia, but the selection of an optimal agent for treatment of T2DM can pose a challenge given that many therapeutic options are effective in reducing HbA1c. Due to the specific mechanism of action, DPP-4 inhibitor is a viable option for use in combination with metformin for the treatment of T2DM. The currently commercially available DPP-4 inhibitor/metformin compounds include Janumet (sitagliptin/metformin), Eucreas (vildagliptin/metformin) and Kombiglyze XR (saxagliptin/metformin). In the current meta-analysis, we assessed the efficacy and safety of vildagliptin in combination with metformin for the treatment of T2DM in comparison with metformin in combination with other anti-diabetic drugs by analyzing data from eligible RCTs. Our findings showed that the vildagliptin-metformin combination therapy achieved a significantly higher efficacy than metformin monotherapy and comparable efficacy to metformin in combination with other anti-diabetic agents in reducing HbA1c for the treatment of T2DM.

Although the primary goal of T2DM treatment is reduction of hyperglycemia, avoidance of hypoglycemia also remains a critical concern as

severe hypoglycemia is associated with an increased risk of death [28]. We compared the incidence of hypoglycemic events associated with the vildagliptin-metformin combination therapy versus metformin alone or metformin in combination with other OHAs. We found that the incidence of hypoglycemic events caused by the vildagliptin-metformin combination therapy was comparable to metformin alone in the treatment of T2DM. And with long follow-up duration (over one year), combined treatment with vildagliptin and metformin was superior to metformin plus other OHAs in reducing the risk of hypoglycemia. The vildagliptin-insulin combination therapy causes more significant reduction in HbA1c than insulin monotherapy in T2DM patients with high-risk hypoglycemia, and is associated with a lower incidence of severe hypoglycemia [24]. In addition to blood glucose control, vildagliptin improves the function of pancreatic islet α and β cells [25, 26]. These findings suggest that vildagliptin may protect against hypoglycemia. Therefore, the vildagliptin-metformin combination therapy offers an effective and safe alternative treatment for T2DM.

The present study systematically evaluates the efficacy and safety of vildagliptin combined with metformin for the treatment of T2DM, which provides evidence for clinical application of the vildagliptin-metformin combination regimen. The RCTs enrolled in this meta-analysis are of high quality. Although blinding was not employed in the study by Blonde 2009 [19], the major outcome measure of HbA1c is an objective and quantitative parameter with low risk of bias. However, we only retrieved English and Chinese literatures, and therefore cannot rule out the possibility of publication bias. In addition, the participants recruited in the RCTs were followed up for a short period of time. Therefore, the long-term efficacy and safety of vildagliptin in combination with metformin for the treatment of T2DM was not evaluated in this study.

Conclusions

In summary, the vildagliptin-metformin combination therapy is effective in reducing HbA1c, and does not increase the incidence of adverse events and the risk of hypoglycemia in the treatment of T2DM. Further high-quality, long-term clinical trials are required to validate the long-term efficacy and safety of vildagliptin in

combination with metformin for the treatment of T2DM.

Disclosure of conflict of interest

None.

Authors' contribution

Ting Xu and Xuehua Jiang designed the study. Ting Xu and Mei Zhan collected and analyzed the data. All authors approved the final version of the manuscript.

Abbreviations

T2DM, type 2 diabetes mellitus; RCTs, randomized, controlled trials; CNKI, China Knowledge Resource Integrated Database; VIP, VIP Database for Chinese Technical Periodicals; CBM, Chinese Biomedical Database; MD, mean difference; OHAs, other oral hypoglycemic agents; HbA1c, glycated hemoglobin; DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; GIP, gastric inhibitory polypeptide; PPAR α , peroxisome proliferator-activated receptor α ; ADA, American Diabetes Association; T1DM, type 1 diabetes mellitus; FPG, fasting plasma glucose; BMI, body mass index; ITT, intent-to-treatment; OR, odds ratio; RR, risk ratio; CI, confidential interval.

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Supplementary Table 1. Search strategy

PubMed:

- #1 randomized controlled trial [pt]
- #2 controlled clinical trial [pt]
- #3 randomized [tiab]
- #4 placebo [tiab]
- #5 drug therapy [sh]
- #6 randomly [tiab]
- #7 trial [tiab]
- #8 groups [tiab]
- #9 or/#1~#8
- #10 vildagliptin/
- #11 vildagliptin [ab/ti/kw]
- #12 galvus [ab/ti/kw]
- #13 LAF 237 [ab/ti/kw]
- #14 LAF237 [ab/ti/kw]
- #15 LAF-237 [ab/ti/kw]
- #16 or/#10~#15 [ab/ti/kw]
- #17 #9 and #16 [ab/ti/kw]

EMBASE:

- #1 'controlled clinical trial'/exp
- #2 'double blind procedure'/exp
- #3 'single blind procedure'/exp
- #4 'crossover procedure'/exp
- #5 'prospective study'/exp
- #6 'comparative study'/exp
- #8 'randomization'/exp
- #9 'placebo'/exp
- #10 blind*: ab, ti
- #11 random*: ab, ti
- #12 control*: ab, ti
- #13 placebo*: ab, ti
- #14 or/#1~#13
- #15 'vildagliptin'/syn and [embase]/lim
- #16 and #14, #15

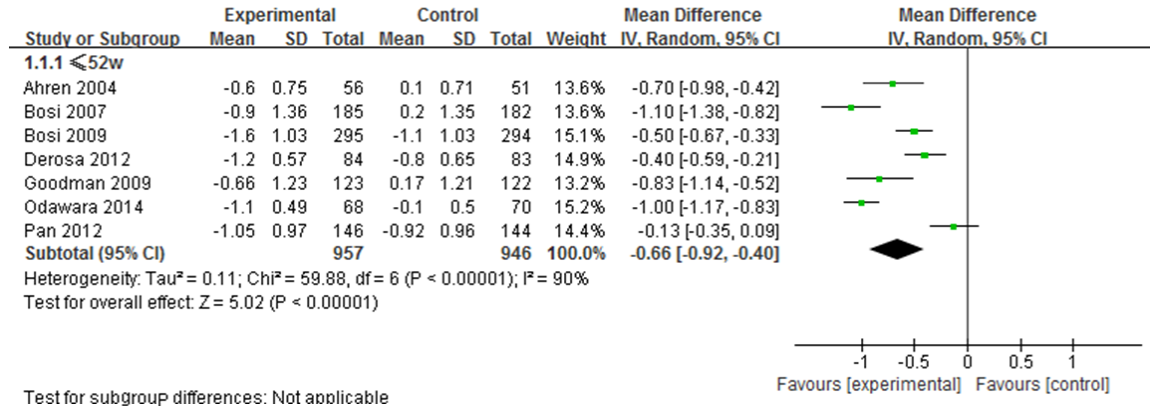
The Cochrane central register of controlled trials:

- #1 vildagliptin [ab/ti/kw]
- #2 galvus [ab/ti/kw]
- #3 LAF 237 [ab/ti/kw]
- #4 LAF237 [ab/ti/kw]
- #5 LAF-237 [ab/ti/kw]
- #6 or/#10~#15 [ab/ti/kw]
- #7 clinical trial [pt]
- #8 #6 and #7

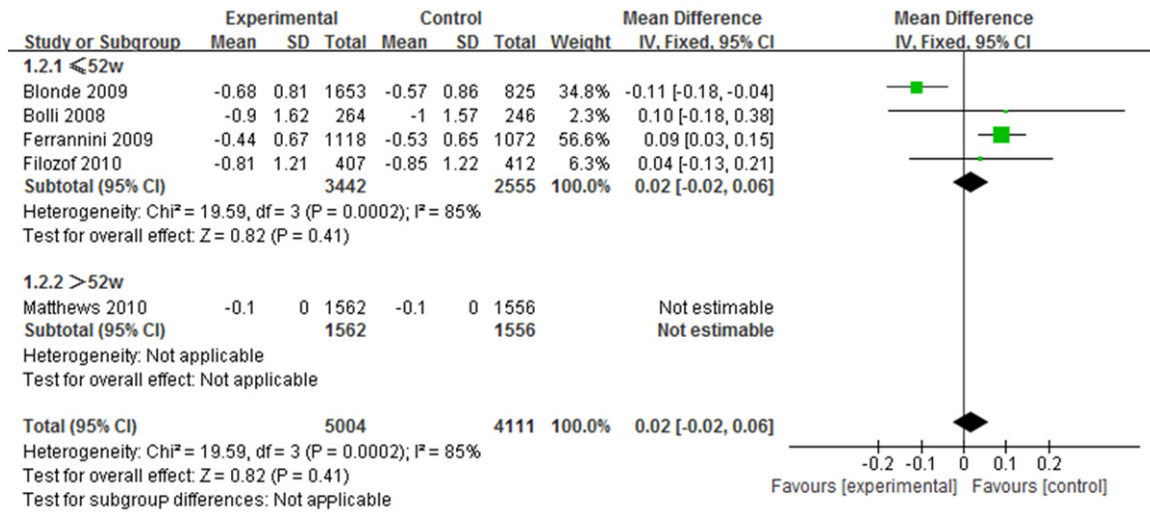
Chinese Literature Database:

- #1 randomization
 - #2 control
 - #3 blind
 - #4 single-blind
 - #5 double-blind
 - #6 three-blind
 - #7 placebo
 - #8 or/#1~#7
 - #9 vildagliptin
 - #10 Galvus
 - #11 or/#9~#10
 - #12 #8 and #11
-

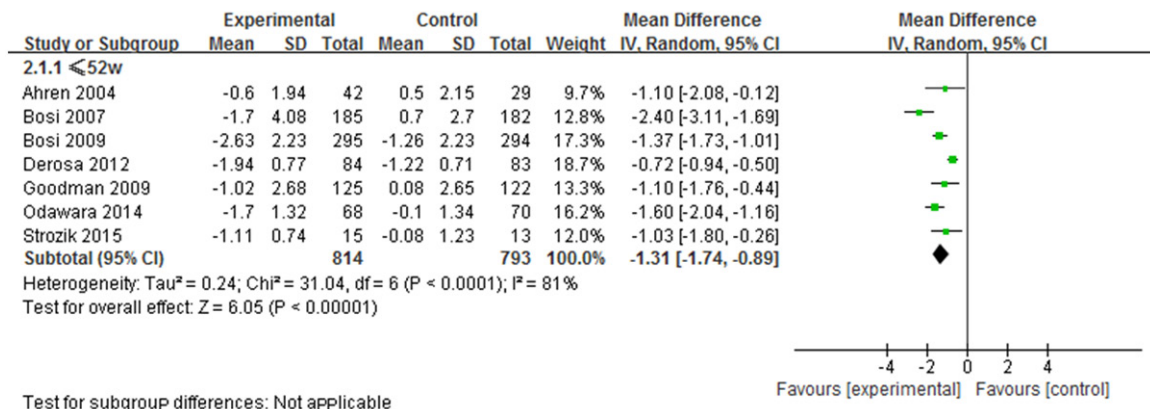
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Supplementary Figure 1. A meta-analysis of the effect of vildagliptin + metformin vs. placebo + metformin or metformin alone on HbA1c in type 2 diabetes mellitus patients.

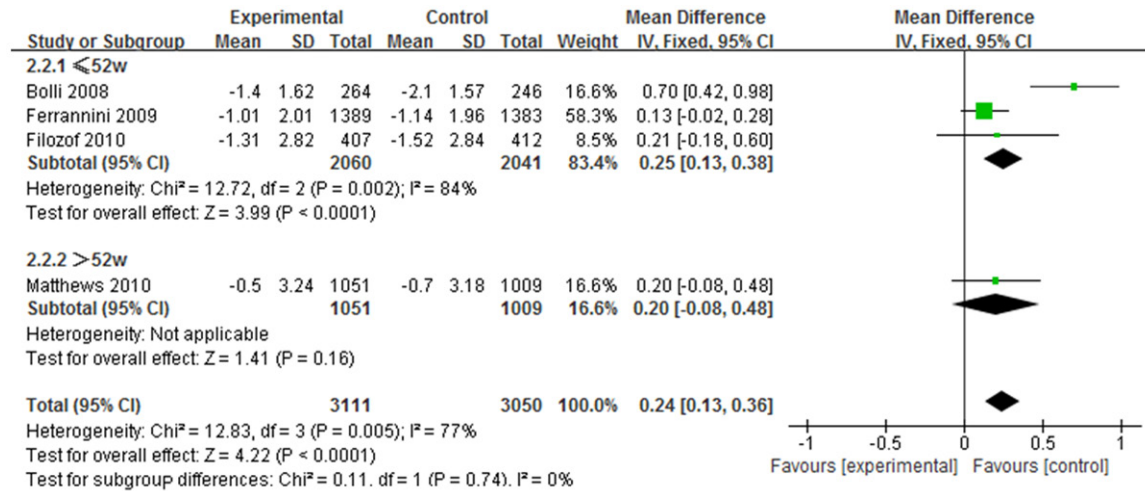


Supplementary Figure 2. A meta-analysis of the effect of vildagliptin + metformin vs. other oral antidiabetic drugs + metformin on HbA1c in type 2 diabetes mellitus patients.

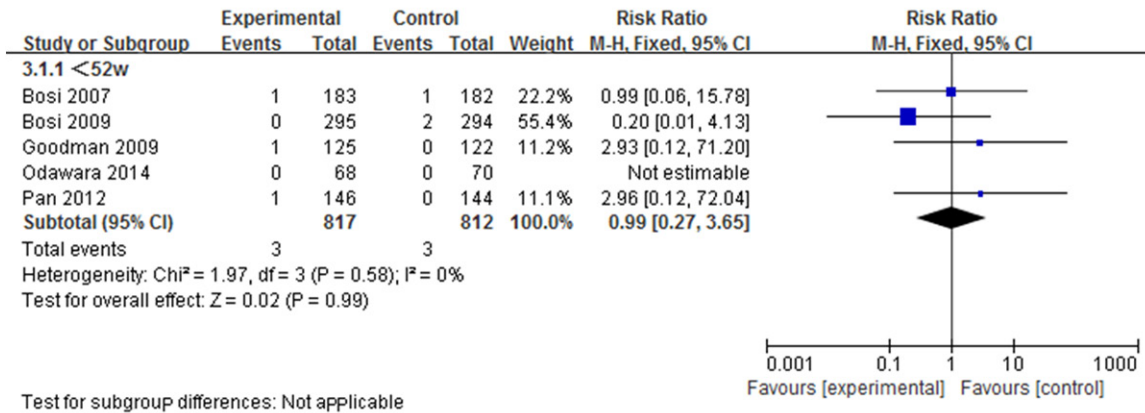


Supplementary Figure 3. A meta-analysis of the effect of vildagliptin + metformin vs. placebo + metformin or metformin alone on FPG in type 2 diabetes mellitus patients.

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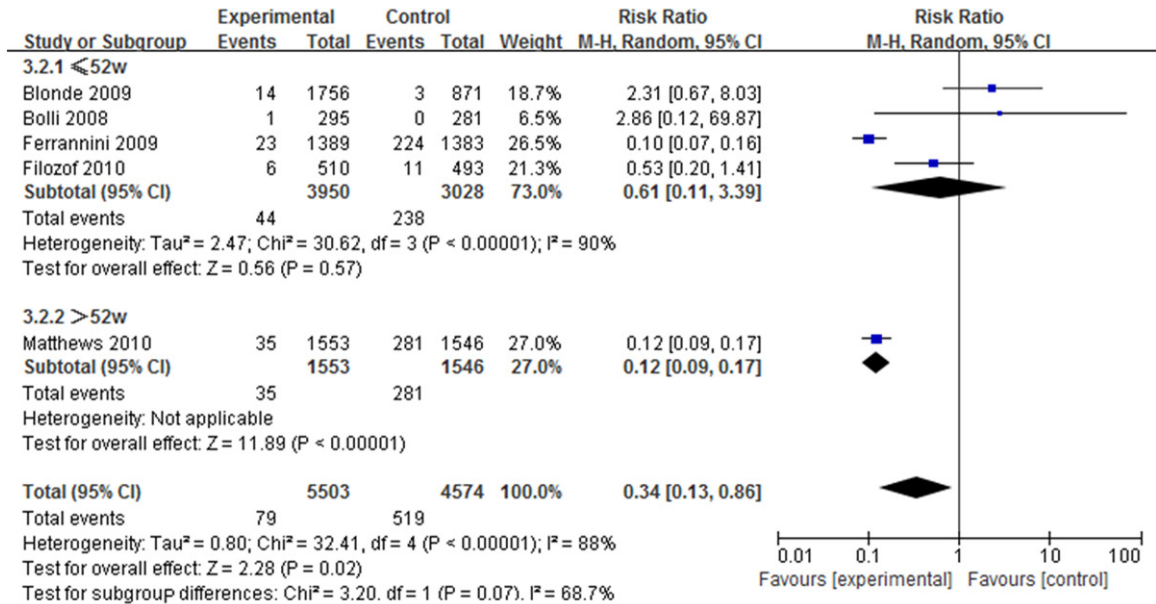


Supplementary Figure 4. A meta-analysis of the effect of vildagliptin + metformin vs. other oral antidiabetic drugs + metformin on FPG in type 2 diabetes mellitus patients.

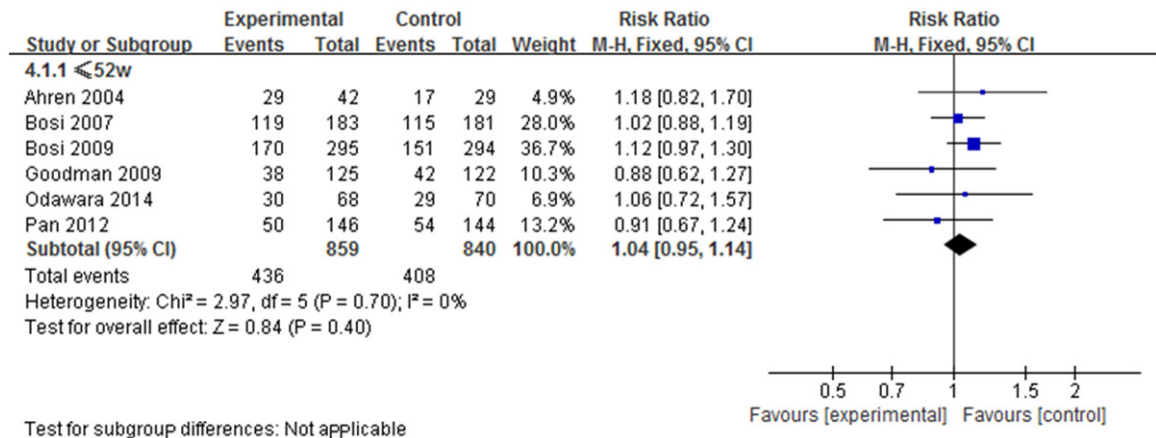


Supplementary Figure 5. A meta-analysis of the effect of vildagliptin + metformin vs. placebo + metformin or metformin alone on the incidence of hypoglycemic events in type 2 diabetes mellitus patients.

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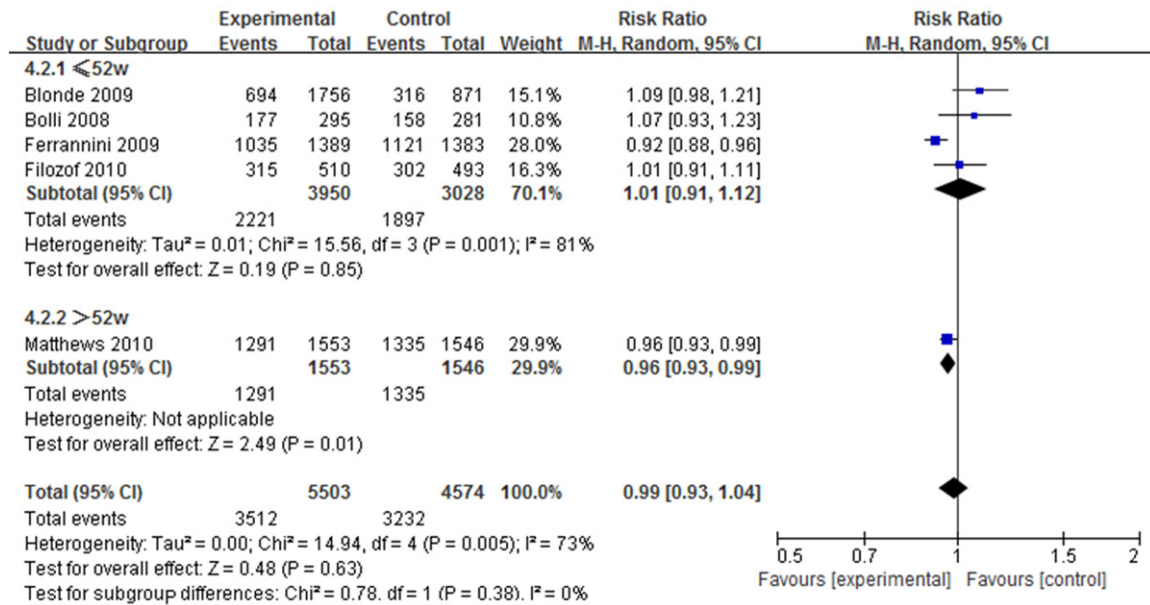


Supplementary Figure 6. A meta-analysis of the effect of vildagliptin + metformin vs. other oral antidiabetic drugs + metformin on the incidence of hypoglycemic events in type 2 diabetes mellitus patients.



Supplementary Figure 7. A meta-analysis of the effect of vildagliptin + metformin vs. placebo + metformin or metformin alone on the incidence of adverse events in type 2 diabetes mellitus patients.

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Supplementary Figure 8. A meta-analysis of the effect of vildagliptin + metformin vs. other oral antidiabetic drugs + metformin on the incidence of adverse events in type 2 diabetes mellitus patients.