ORIGINAL RESEARCH

Efficacy and Safety of DPP-4 Inhibitors and Metformin Combinations in Type 2 Diabetes: A Systematic Literature Review and Network Meta-Analysis

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Objective: Several oral antidiabetic regimens are available for treating type 2 diabetes mellitus (T2DM), dipeptidyl peptidase-4 inhibitors (DPP4i) being one of them. We conducted a network meta-analysis (NMA) comparing DPP4i plus metformin (Met) combination with other Met-based oral antidiabetic drug (OAD) combinations used in treating patients with T2DM.

Methods: We searched PubMed and Embase from inception until 19th April, 2022 for phase II and phase III trials in patients with T2DM on Met-based traditional OADs. The primary outcome was assessed by change in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and 2-hour post-prandial blood glucose (2h-PPG). The secondary safety outcomes assessed were hypoglycemic events, serious adverse events (SAEs), cardiovascular (CV) events, and gastrointestinal (GI) events.

Results: Sixty-two trials were included in the analysis. The combination of DPP4i + Met revealed a comparable mean reduction in HbA1c levels to the glinides (Gli) + Met combination (mean difference [MD]: −0.03%, 95% CI: 0.69, −0.65), although the difference was not statistically significant. The mean HbA1c reduction with DPP4i + Met was greater than with sulfonylureas (SU) + Met (MD: −0.05, 95% CI: −0.29, 0.39), thiazolidinedione (TZD) + Met (MD: −0.69, 95% CI: −1.39, −0.02), and SU + TZD (MD: 0.21; 95% CI: −1.30, 1.71), with no statistical significance. DPP4i + Met demonstrated a non-significant lower incidence of CV events in comparison to TZD + Met (RR: 1.01, 95% CI: 0.46, 2.45) and SU + Met (RR: 1.06, 95% CI: 0.61, 2.06).

Conclusion: DPP4i in combination with Met was efficacious and had a well-tolerated safety profile compared with other traditional OADs. This combination can be considered as a suitable treatment option for patients with T2DM.

Keywords: dipeptidyl peptidase-4 inhibitors, efficacy, safety, metformin, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is an endocrine metabolic disease characterized by the presence of hyperglycemia.[1] About 537 million adults are currently living with the burden of diabetes, and this is expected to rise to 643 million by 2030 and 783 million subsequently.[2] In recent, the incidence of type 2 diabetes mellitus (T2DM) in developing countries has substantially escalated, posing a huge burden on the economy.[3] To reduce long-term complications, most patients are recommended glucose-lowering oral antidiabetic drugs (OADs).

The American Diabetes Association (ADA) states that first-line therapy for diabetes management usually involves metformin (Met), along with comprehensive lifestyle modification. Based upon a patient's glycemic needs, agents such as sodium–glucose co-transporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 receptor agonist (GLP-1RA) with or without Met are recommended as initial therapy in patients with T2DM or who have

a high risk for atherosclerotic cardiovascular (ASCV) disease, heart failure, and/or chronic kidney disease.[4] The efficacy of Met has been extensively studied, often in comparison with other drugs already in use. In short- and medium-term therapies, Met has shown efficacy comparable to sulfonylureas, mitigating the hypoglycemic risks. Moreover, it has demonstrated higher efficacy compared to dipeptidyl peptidase-4 inhibitors (DPP4i), but lower efficacy than that of glucagon-like peptide-1 (GLP-1) receptor agonists. In the context of long-term monotherapy, Met has shown increased efficacy compared to sulfonylureas.[5] Besides, SGLT2 inhibitors or GLP-1RA are also recommended in patients with established ASCV, kidney disease, or heart failure, considering patient-related factors and independent of glycemic levels.[4] However, many patients, particularly those with higher baseline glycated hemoglobin (HbA1c) values, may not achieve their glycemic goals on Met monotherapy and therefore require additional medication.[6] Although multiple classes of OADs are available, there remains a need for agents with different mechanisms of action that offer improved efficacy and/or can be used either as monotherapy or in combination with Met.

The US Food and Drug Administration (FDA) has approved several medications, such as the sulfonylureas (SU), meglitinides, biguanides, thiazolidinediones (TZDs), and alpha-glucosidase inhibitors (AGIs), for the treatment of adult patients with T2DM.[7] Dipeptidyl peptidase-4 inhibitors (DPP4i) are a class of OADs with a unique mechanism of action from other hypoglycemic agents, as they exert antihyperglycemic effects by inhibiting DPP-4 enzyme activity, thereby leading to an increase in the concentration of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) which, in turn, increase insulin secretion from β-cells and reduce blood glucose levels.[8] The foundation for the development of DPP4i relies on the augmentation of the incretin effect. The incretin effect is the increased insulin secretion that occurs after oral glucose delivery compared to intravenous glucose treatment. It is thought that gut hormones increase the amount of insulin secreted in response to glucose.[9] Moreover, DPP4i are weight-gain neutral and are available in combination with Met.[10] Hypoglycemia, weight gain, and edema are generally not associated with DPP4i; however, these adverse events (AEs) have been associated with other antidiabetic drug classes that are often used in conjunction with Met (eg, SUs, glinides, TZDs, and insulin).[11]

The rationale for combining DPP4i in combination with Met has been outlined earlier. Met works primarily by lowering hepatic glucose production and enhancing muscle and liver insulin sensitivity, whereas DPP4i act by increasing GLP-1 levels, thus stimulating insulin secretion and inhibiting glucagon secretion. Met also increases GLP-1 expression and stimulates GLP-1 secretion from the gut.[12] Another fact to be noted is that the pharmacokinetics of Met and a DPP4i in combination therapy remains unaffected, which further indicates the feasibility of the combination.[13] It is therefore evident that the two drugs have the potential to act via different mechanisms in diabetes and provide an additive or synergistic action when used in combination. Also, in terms of AEs, a low propensity for both DPP4i and Met to cause hypoglycemia or weight gain has been observed, thus making this combination a suitable option for patients who fail to meet their glycemic goals.

Although the ADA does not prioritize any specific regimen for a patient's therapy, the American Association of Clinical Endocrinologists recommends the use of SGLT2i, followed by DPP4i, TZD, α-glucosidase inhibitors, and SU among the OADs, mainly based on the weight-reducing effect.[14] To decide on the best treatment approach, clinicians must take into account various patient-centric factors, such as hypoglycemia, glucose-lowering efficacy, drug-to-drug interactions, and the AEs of each OAD. Currently, head-to-head direct comparison studies assessing the Met-based combination therapies are limited. Moreover, the existing studies have examined each drug pair separately, creating a research gap that remains unaddressed in a unified platform. Network meta-analysis (NMA) has become a powerful tool that can evaluate multiple direct or indirect interventions, and quantify and sort the efficacy and safety of each of these measures, so as to screen the most effective and tolerable interventions. Hence, this NMA aimed to comprehensively compare the key efficacy and safety outcomes of DPP4i versus other OADs as add-on therapy to Met in patients with T2DM. The primary objective was to assess the changes in levels of hemoglobin, fasting plasma glucose, and 2-hour post-prandial glucose (2h-PPG) from baseline.

Materials and Methods

Study Design

The NMA was conducted using a prespecified study protocol. The study was planned, conducted, and reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis,[15] and was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42021288932). It is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Sources and Search Strategy

A systematic literature search was performed in databases such as PubMed and Embase from inception until 19th April, 2022, with a predefined search strategy formulated using a population, intervention, comparator, outcome (PICO) framework. The search strategy included terms for the diabetes medications of interest and type 2 diabetes, and consisted of the following keywords: "type 2 diabetes mellitus", "metformin", "dipeptidyl peptidase-4 inhibitors", "saxagliptin", "sitagliptin", "linagliptin", "alogliptin", "vildagliptin", "anagliptin", "gemigliptin", "teneligliptin", "omarigliptin", "dutogliptin", "gosogliptin", "alpha-glucuronidase inhibitors", "acarbose", "migitol", "voglibose", "sulfonylureas", "glimepiride", "glibenclamide", "chlorpropamide", "glipizide", "tolbutamide", "tolazamide", "glinides", "meglitinides", "nateglinide", and "repaglinide".

Study Selection Process

Studies were selected based on following inclusion criteria: 1) participants were adults (≥18 years) with T2DM, and no restrictions on participants' gender, ethnicity, or other demographic characteristics were considered; 2) studies reporting the following key outcomes: change in HbA1c, fasting plasma glucose (FPG), and 2h-PPG from baseline; 3) randomized control studies (RCTs) published in the English language and evaluating the efficacy of various traditional OADs in combination with Met in dual therapy were included. Studies included either patients with uncontrolled T2DM after Met-based therapy or direct comparison between two different OADs in combination with Met. Studies were included irrespective of the duration and line of treatment. Studies focusing on children, participants with type 1 diabetes, gestational diabetes, or prediabetes were excluded. Articles with study designs other than RCTs (eg, case–control studies, cohort studies), reviews, meta-analyses, non-English-language articles, and articles without the desired outcomes of interest were excluded. Studies evaluating different doses and those evaluating the pharmacokinetics and pharmacodynamics (PK/PD) of Met-based combination therapy were not included in this meta-analysis. Also, studies on Met-based combination therapy that could not be accommodated in a completed network were excluded.

Data Extraction

The reviewers extracted data from each included study into a standardized MS Office Excel-based data extraction sheet, regarding author, trial ID/name, title, intervention, intervention drug class, comparator, comparator drug class, efficacy, and safety outcomes. In the first step, the relevant articles were independently screened based on their title and abstract by two researchers to identify potential trials. The reasons for exclusion of studies were documented as well. For secondary screening, full-text versions of selected papers were examined and assessed according to the inclusion criteria. Any differences in opinion were resolved through discussion until a consensus was reached. To minimize bias, a third reviewer was consulted, who double-checked the articles and confirmed their eligibility.

Methodological Assessment and Network Construction

The network was constructed at the level of study drug class for Met in combination with AGI, SUs, glinides (Gli), TZD, and DPP4i. Only Met in combination with DPP4i was considered at the level of the study drug, based on the purpose of the study.

Outcomes

The primary endpoint of the study was to assess change in HbA1c, FPG, and 2h-PPG from baseline; while the secondary outcomes were assessments of safety in terms of hypoglycemic events, serious adverse events (SAEs), cardiovascular (CV) events, and gastrointestinal (GI) events.

Statistical Analysis

The NMA was performed using the "Gemtc" 4.0.4 package (R Foundation for Statistical Computing, Vienna, Austria) using a Bayesian approach. The "gemtc" package provides a matrix of the treatment rank probabilities, as well as a plot of the rank probabilities.[16] Model fitting performed for data pooling used convergence between prior and posterior values with deviance information criteria (DIC). The I^2 values and DIC assessed the heterogeneity among the studies. Statistically significant heterogeneity was defined as a χ^2 P-value <0.1 or an I^2 statistic >50%.[17] By plotting rankograms, the surface under the cumulative ranking curve (SUCRA) values were calculated. The SUCRA values represented the ranking probability of each treatment regimen. Mean differences with 95% confidence intervals (CIs) were used to represent the efficacy outcomes. For dichotomous scores (eg, AEs), the treatment effect was evaluated using the risk ratio (RR) with 95% CI.

Results

Study Selection

The initial electronic search yielded 2879 consolidated studies from the selected databases. Following the initial screening, 148 distinct studies were further scrutinized, and after careful assessment based on inclusion and exclusion criteria, only 62 studies were considered eligible for our analysis. A study flow diagram is presented in Figure 1. The baseline characteristics of the included studies are provided in Table 1.

Change in HbA1c from Baseline

Forty-five articles reported efficacy outcomes related to change in HbA1c levels from baseline. The combination of DPP4i + Met revealed a comparable mean reduction in HbA1c levels to the Gli + Met combination (mean difference [MD]: −0.03%, 95% CI: 0.69, −0.65). In addition, DPP4i + Met showed a greater mean reduction in HbA1c than SU + Met (MD: 0.05, 95% CI: −0.30, 0.40), TZD + Met (MD: 0.69, 95% CI: −0.016, 1.4), and SU + TZD (MD: 0.21, 95% CI: −1.30, 1.71), and monotherapies of Met (MD: 0.33, 95% CI: −0.12, 0.78), AGI (MD: 1.21, 95% CI: −0.40, 2.85), and SU (MD: 0.79, 95% CI: −0.75, 2.35) (Figure 2, Table 2, Table S1 and Figure S1).

Change in FPG

Evidence was available from 41 articles for mean changes in FPG reduction. The mean FPG reductions with DPP4i + Met and Gli + Met (MD: −1.09, 95% CI: −9.31, 11.77) were comparable, while the DPP4i + Met combination showed a greater reduction in FPG levels compared with AGI + Met (MD: 8.82, 95% CI: −4.97, 22.25), and monotherapies of Met (MD: 16.47, 95% CI: 8.24, 24.91) and AGI (MD: 38.48, 95% CI: 8.62, 67.98) (Figure 2, Table 2, Table S2 and Figure S2).

Change in 2h-PPG

A total of 12 articles were considered for this analysis. Pairwise comparisons revealed that DPP4i + Met showed a greater mean reduction of 2h-PPG levels than SU + Met (MD: 10.1, 95% CI: −5.55, 27.66), Met (MD: 23.84, 95% CI: 10.34, 40.39), and AGI alone (MD: 33.79, 95% CI: −8.62, 73.86). Although AGI + Met (MD: −7.97, 95% CI: −33.17, 15.64) and Gli + Met (MD: −7.02, 95% CI: −32.26, 20.55) had better mean FPG reduction compared with DPP4i + Met, these differences were not significant (Figure 2, Table 2, Table S3 and Figure S3).

Serious Adverse Events (SAEs)

The network was constructed with 47 included articles. The incidence of SAEs with DPP4i + Met was lower and comparable to that of TZD + Met (RR: 1.02, 95% CI: 0.72, 1.36) and SU + Met (RR: 1.02, 95% CI: 0.87, 1.16). There were lower
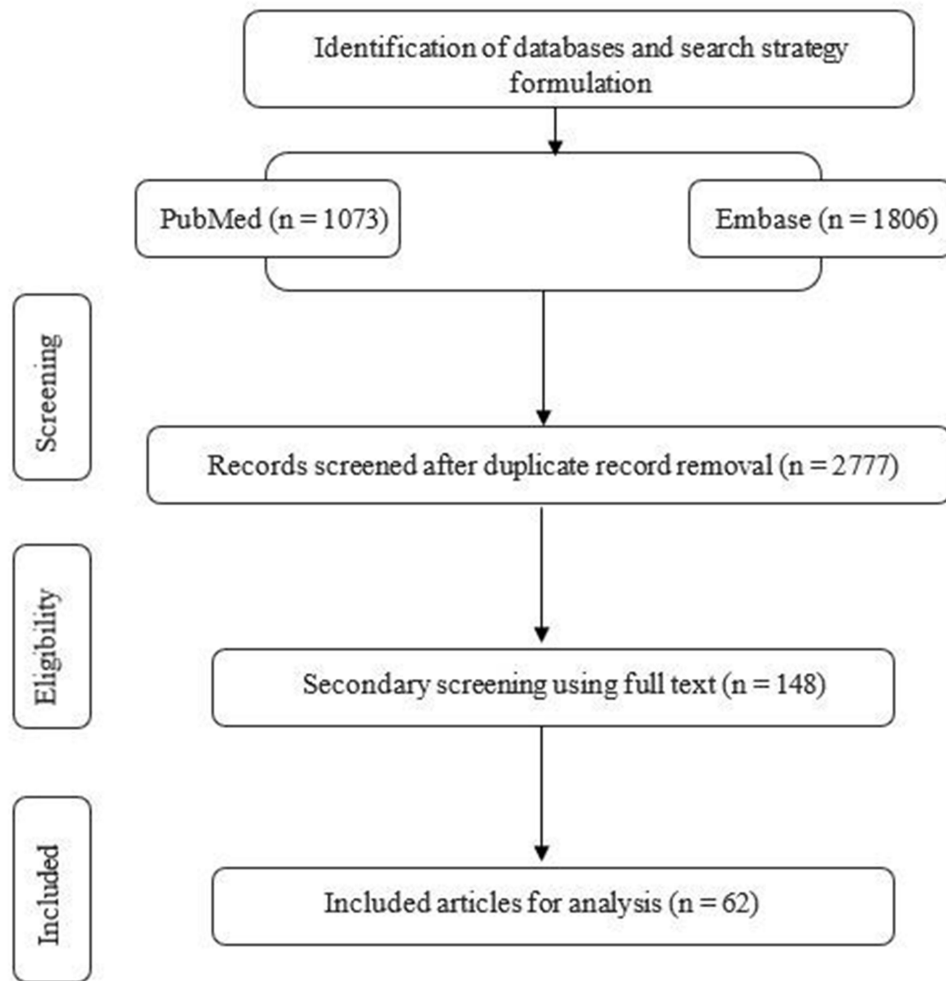
Figure 1 Study flowchart diagram.

incidences of SAEs with SU + TZD (RR: 0.69, 95% CI: 0.36, 1.29), Met (RR: 0.81, 95% CI: 0.55, 1.16), AGI + Met (RR: 0.78 95% CI: 0.35, 1.70), Gli + Met (RR: 0.83, 95% CI: 0.54, 1.26), and AGI (RR: 1.11, 95% CI: 0.20, 6.91) when compared to DPP4i + Met, although these differences were not statistically different (Figure 3, Table 3, Table S4 and Figure S4).

Hypoglycemia

Forty-six articles were included in the analysis. The risk of hypoglycemia was lower with DPP4i + Met compared with Gli (RR: 1.47, 95% CI: 0.03, 30) and SU (RR: 2.54, 95% CI: 0.41, 15.31), while it was statistically significant compared with Gli + Met (RR: 3.61, 95% CI: 1.73, 7.20), SU + Met (RR: 6.21, 95% CI: 4.13, 9.37), and SU + TZD (RR: 8.29, 95% CI: 1.70, 40.64). DPP4i + Met showed comparable hypoglycemic risks when compared with AGI + Met (RR: 0.99, 95% CI: 0.27, 3.42) and Met (RR: 0.99, 95% CI: 0.53, 1.733) (Figure 3, Table 3, Table S5 and Figure S5).

GI Events

The network was constructed with 33 included articles. The incidence of GI events was found to be lower for TZD + Met and SUs compared with DPP4i + Met (RR: 0.76, 95% CI: 0.40, 1.412) and (RR: 0.59, 95% CI: 0.17, 1.92), respectively. Further, GI events with DPP4i + Met were comparable to those for SU + Met (RR: 1.03, 95% CI: 0.72, 1.46), Gli + Met (RR: 1.04, 95% CI: 0.53, 2.00), and Met (RR: 1.08, 95% CI: 0.71, 1.65) while they were observed to be lower compared

Table 1 Baseline Characteristics of the Included Studies

Study no.	Author(s) and year	No. of Arms	Intervention	Comparator	I (n)	C (n)	N (study)	Median follow-up	Age (years)		Gender			
									Mean (SD) or median (range)		Male		Female	
									I	C	I	C	I	C
1	Yang et al,[18] 2011	2	Saxagliptin + Met	Met	283	287	570	Week 24 study	53.8 (10.4)	54.4 (10.1)	136 (48.1)	139 (48.4)	147 (51.9)	148 (51.6)
2	Pfützner et al,[19] 2011	4	Arm 1: saxagliptin 5 mg + 500 mg Met; Arm 2: saxagliptin 10 mg + 500 mg Met	Arm 3: saxagliptin 10 mg + placebo; Arm 4: 500 mg Met + placebo	Arm 1: 320; Arm 2: 323	Arm 3: 335; Arm 4: 328	1306	76 week study	Arm 1: 52.0 (10.4); Arm 2: 52.1 (11.6)	Arm 3: 52.1 (10.2); Arm 4: 51.8 (10.7)	Arm 1: 165 (51.6); Arm 2: 146 (45.2)	Arm 3: 169 (50.4); Arm 4: 163 (49.7)		
3	Phillips et al,[20] 2003	2	Met + acarbose	Met	40	43	83	169 days	58.37 (10.7)	62.39 (8.02)	65%	76.70%	35%	23.30%
4	Chiasson et al,[21] 2001	4	Arm 1: Met alone; Arm 2: miglitol + Met	Arm 3: placebo; Arm 4: miglitol alone	Arm 1: 83; Arm 2: 76	Arm 3: 83; Arm 4: 82	324		Arm 1: 57.9 (8.6); Arm 2: 58.9 (7.9)	Arm 3: 57.7 (9.9); Arm 4: 57.3 (9.0)	Arm 1: 61; Arm 2: 59	Arm 3: 56; Arm 4: 64	Arm 1: 22; Arm 2: 17	Arm 3: 27; Arm 4: 18
5	Gu et al,[22] 2019	2	Met + saxagliptin	Met + glimepiride	187	186	388	48 weeks	54.2 (9.4)	52.8 (9.5)	119 (63.6%)	109 (58.6%)		
6	Du et al,[23] 2017	2	Met + saxagliptin	Met + acarbose	238	243	488	24 weeks	54.7 (10.51)	56.5 (10.81)			91 (38.2)	105 (43.2)
7	Van Gaal et al,[24] 2001	2	Met + miglitol	Met	77	75	153	32 weeks	57.9 (10.0)	57.9 (8.5)	32	37	45	38
8	Dou et al,[25] 2018	3	Arm 1: saxa 5 mg + Met	Arm 2: saxa 5 mg + pbo; Arm 3: Met + pbo	Arm 1: 210	Arm 2: 213; Arm 3: 207	630	24 weeks	Arm 1: 50.8 (10.4)	Arm 2: 49.5 (10.9); Arm 3: 50.1 (11.0)	136 (64.8)	Arm 2: 151 (70.9); Arm 3: 132 (63.8)	74 (35.2)	Arm 2: 62 (29.1); Arm 3: 75 (36.2)
9	Hanefeld et al,[26] 2004	–	Sulfonylurea + pioglitazone 15 mg	Sulfonylurea + Met 850 mg	319	320	639	11 months	60 (8.8) (36–75)	60 (8.0) (36–75)	171 (53.6)	175 (54.7)	148 (46.4)	145 (45.3)
10	Wang et al,[27] 2013	2	Acarbose + Met	Acarbose 50 mg tablet	117	116	233		55.9 (9.5)	55.6 (9.5)	60 (51.3)	51 (44.0)		
11	Cai et al,[28] 2015	2	Rosiglitazone + Met	Met	198	200	398	48 weeks	51.38 (9.57)	51.25 (8.84)	57.70%	59.80%		

12	Rosenstock et al,[29] 2006	3	Arm 1: rsg/Met fixed-dose combination [rosiglitazone maleate/Met hydrochloride (avandamet)]	Arm 2: Met (Met hydrochloride); Arm 3: rsg [rosiglitazone maleate (avandia)]	155	Arm 2: 154; Arm 3: 159	468		Arm 1: 50.1 (10.7)	Arm 2: 51.5 (10.4); Arm 3: 50.6 (10.26)	Arm 1: 66 (43)	Arm 2: 67 (44); Arm 3: 66 (42)	Arm 1: 89 (57)	Arm 2: 87 (56); Arm 3: 93 (58)
13	Oh et al,[30] 2019	2	Voglibose + Met	Met	88	84	187	24 weeks	51.9±8.8	53.4±8.8	55 (62.5)	44 (52.4)		
14	Moses et al,[31] 1999	3	Arm 1: Met repaglinide	Arm 2: repaglinide + placebo; Arm 3: Met + placebo	Arm 1: 27	Arm 2: 28; Arm 3: 27	83		Arm 1: 57.2 ±8.3	Arm 2: 60.3 ±7.7; Arm 3: 57.8±9.5	Arm 1: 18	Arm 2: 15; Arm 3: 17	Arm 1: 9	Arm 2: 13; Arm 3: 10
15	Marre et al,[32] 2002	3	Arm 1: 60 mg nateglinide + Met; Arm 2: 120 mg nateglinide + Met	Placebo + Met	Arm 1: 155; Arm 2: 160	152	467	24 weeks	Arm 1: 57.9 (9.9); Arm 2: 57.3 (10.5)	56.4 (10.3)	Arm 1: 95 (61.3); Arm 2: 98 (61.3)	84 (55.3)	Arm 1: 60 (38.7); Arm 2: 62 (38.8)	68 (44.7)
16	Horton et al,[33] 2000	4	Arm 1: nateglinide; Arm 2: Met; Arm 3: nateglinide + Met	Placebo	Arm 1: 179; Arm 2: 178; Arm 3: 172	172	701	24 weeks	Arm 1: 58.6 (10.7); Arm 2: 56.8 (10.9); Arm 3: 58.4 (10.9)	59.6 (10.9)	Arm 1: 110; Arm 2: 121; Arm 3: 101	104	Arm 1: 69; Arm 2: 57; Arm 3: 71	68
17	Raskin et al,[34] 2009	3	Arm 1: repaglinide/Met fdc, bid; Arm 2: repaglinide/Met fdc, tid	Arm 3: rosiglitazone/Met fdc tablet bid	Arm 1: 187 Arm 2: 187	Arm 3: 187	561	26 weeks	Arm 1: 54.8 (11.5); Arm 2: 54.5 (10.5)	Arm 3: 55.5 (10.3)	Arm 1: 108 (57.8); Arm 2: 110 (58.8)	Arm 3: 95 (50.8)	Arm 1: 79 (42.2); Arm 2: 77 (41.2)	Arm 3: 92 (49.2)
18	Lewin et al,[35] 2007	4	Arm 1: mer 1500 mg qd + sulfonylurea; Arm 2: mer 1000 mg bid + sulfonylurea; Arm 3: mer 2000 mg qd + sulfonylurea	Arm 4: sulfonylurea monotherapy	Arm 1: 144; Arm 2: 141; Arm 3: 146	Arm 4: 144	607	24 weeks	Arm 1: 54.0 (10.3); Arm 2: 53.0 (10.5); Arm 3: 53.0 (10.9)	Arm 4: 53.0 (10.7)	Arm 1: 77 (53.5); Arm 2: 83 (58.9); Arm 3: 75 (51.4)	Arm 4: 79 (54.9)	Arm 1: 67 (46.5); Arm 2: 58 (41.1); Arm 3: 71 (48.6)	Arm 4: 65 (45.1)
19	Jin et al,[36] 2015	2	Lobeglitazone + Met	Pioglitazone + Met	128	125			1.4%					

(*Continued*)

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Table 1 (Continued).

Study no.	Author(s) and year	No. of Arms	Intervention	Comparator	I (n)	C (n)	N (study)	Median follow-up	Age (years) Mean (SD) or median (range)		Gender Male		Female	
									I	C	I	C	I	C
20	Wang et al,[37] 2016	2	Met + glibenclamide	Met + acarbose	23	27	50		54.7 (8.3)	52.5 (8.2)	10 (43.5)	14 (51.9)		
21	Perez et al,[38] 2009		Arm 1: pioglitazone 15 mg/Met 850 mg bid; Arm 2: pioglitazone 15 mg bid	Arm 3: Met 850 mg bid	Arm 1: 201; Arm 2: 190	Arm 3: 209	600		Arm 1: 54.7 (12.2); Arm 2: 54.0 (12.1)	Arm 3: 53.7 (12.0)			Arm 1: 111 (55.2); Arm 2: 123 (65.1)	Arm 3: 112 (53.3)
22	Kawamori et al,[39] 2014	2	Met + repaglinide	Met + placebo	Repaglinide (n =94)	Placebo (n =36)	133	Phase III study: 16 weeks; long-term study: 52 weeks	55.1±11.1	Placebo: 53.6 ±12.1	61	21	31	15
23	Wang et al,[40] 2011	2	Repaglinide + Met	Repaglinide	218	214	588	6-week dose titration period and 10-week dose maintenance period	50.4±9.6	49.4±10	158 (72.5%)	155 (72.4%)	60 (27.5%)	59 (27.6%)
24	Raskin et al,[41] 2003	2	Repaglinide + Met	Nateglinide + Met	96	96	192	16 weeks	55.8±10.7	55.0±10.6	50	60	46	36
25	Moses,[42] 1999	3	Arm 1: Met + repaglinide	Arm 2: repaglinide + placebo; Arm 3: Met + placebo	Arm 1: 27	Arm 2: 28; Arm 3: 27	83	Baseline period: 4–5 weeks; treatment period: 4–5 months	Arm 1: 57.2	Arm 2: 60.3; Arm 3: 57.8	Arm 1: 18	Arm 2: 15; Arm 3: 17	Arm 1: 9	Arm 2: 13; Arm 3: 10
26	Vaccaro et al,[43] 2017	2	Met + pioglitazone	Met + sulfonylurea	1535	1493	4956	Follow-up visits were scheduled at 1, 3, and 6 months after randomization and every 6 months thereafter until study end	62.4 (6.4)	62.2 (6.5)	909 (59%)	865 (58%)	626 (41%)	628 (42%)
27	Handelsman et al,[44] 2017	2	Omarigliptin + Met	Glimepiride + Met	376	375	1197	Study duration up to 57 weeks	58±10	58±9	203 (54.0%)	211 (56.3%)		

28	Derosa et al,[45] 2014	2	Vildagliptin + Met	Glimepiride + Met	86	81	178	6 months	59.8±9.9	57.2±9.0	42	40	44	41
29	Kim et al,[46] 2017	2	Vildagliptin + Met	Glimepiride + Met	17	17	39	12 weeks	55.6±8.4	56.3±5.7			7 (41.2)	7 (41.2)
30	Derosa et al,[47] 2007	2	Nateglinide + Met	Glibenclamide + Met	119	114	248	12 months	55±5	56±4	58	58	61	56
31	González-Ortiz et al,[48] 2009	2	Glimepiride/Met	Glibenclamide/Met	76	76	152	12 months	52.3±7.6	52.9±7.6	28	31	48	45
32	Chien et al,[49] 2007	4	Arm 1: glyburide + Met (2.5 mg/500 mg); Arm 2: glyburide + Met (5 mg/500)	Arm 3: glyburide; Arm 4: Met	Arm 1: 21; Arm 2: 21	Arm 3: 17; Arm 4: 17	100	16 weeks	Arm 1: 60±7; Arm 2: 57±8	Arm 3: 63 ±7; Arm 4: 59±9	Arm 1: 15; Arm 2: 13	Arm 3: 9; Arm 4: 7	Arm 1: 6; Arm 2: 8	Arm 3: 8; Arm 4: 10
33	Garber et al,[50] 2006	2	Met + glibenclamide	Met + rosiglitazone	160	158	356	24 weeks	56 (31–78)	56 (24–78)	90 (56%)	102 (65%)	70 (44%)	56 (35%)
34	Kim et al,[51] 2013	2	Met + sitagliptin	Met + glimepiride	16	17	34	4 weeks	59.6±6.7	55.8±6.6	12	7	4	10
35	Schernthaner et al,[52] 2015	2	Saxagliptin + Met	Glimepiride + Met	360	360	720	52 weeks	72.5 (5.7)	72.7 (5.4)	217 (60.3)	228 (63.3)		
36	Garber et al,[53] 2003	3	Arm 1: glyburide/Met	Arm 2: Met; Arm 3: glyburide	Arm 1: 171	Arm 2: 164; Arm 3: 151	513	16 weeks	Arm 1: 55.6 (11.2)	Arm 2: 54.7 (11.8); Arm 3: 55.3 (12.2)	Arm 1: 76 (44.4)	Arm 2: 71 (43.3); Arm 3: 66 (43.7)	Arm 1: 95 (55.6)	Arm 2: 93 (56.7); Arm 3: 85 (56.3)
37	Del Prato et al,[54] 2014	3	Arm 1: alogliptin 12.5 mg + Met	Arm 2: alogliptin 25 mg + Met; Arm 3: glipizide 5 mg + Met	Arm 1: 880	Arm 2: 885; Arm 3: 874	5789	104 weeks	Arm 1: 55.2 (9.60)	Arm 2: 55.5 (9.81); Arm 3: 55.4 (9.60)	Arm 1: 419 (47.6)	Arm 2: 452 (51.1); Arm 3: 441 (50.5)	Arm 1: 461 (52.4)	Arm 2: 433 (48.9); Arm 3: 433 (49.5)
38	Schwarz et al,[55] 2008	2	Nateglinide + Met	Glyburide + Met	35	40	75	104 weeks	70.1±2.9	70.4±3.8	17 (51.5)	18 (50.0)	16 (48.5)	18 (50.0)
39	Umpierrez et al,[56] 2006	2	Glimepiride + Met	Pioglitazone + Met	96	107	203	28 weeks	51.6±11.8	55.7±9.7	53±55.2	56±52.3	43±44.8	51±47.7

(Continued)

Table 1 (Continued).

Study no.	Author(s) and year	No. of Arms	Intervention	Comparator	I (n)	C (n)	N (study)	Median follow-up	Age (years) Mean (SD) or median (range)		Gender Male		Female	
									I	C	I	C	I	C
40	Göke et al,[57] 2013	2	Saxagliptin + Met	Glipizide + Met	428	430	858	52 weeks	57.5 (27–83)	57.6 (25–80)	212 (49.5)	232 (54.0)	216 (50.5)	198 (46.0)
41	Gerich et al,[58] 2005	2	Nateglinide/Met	Glyburide/Met	219	209	428	104 weeks	52.6±11.6	53.5±11.6	106 (51.0)	95 (48.0)	102 (49.0)	103 (52.0)
42	Forst et al,[59] 2014	2	Linagliptin + Met	Glimepiride + Met	19	20	39	12 weeks	65±8	63±7	13	14	6	6
43	Seck et al,[60] 2010	2	Sitagliptin + Met	Glipizide + Met	248	256	504	2 years	57.6 (8.5)	57.0 (9.1)	142 (57.3)	161 (62.9)	106 (42.7)	95 (37.1)
44	Ristic et al,[61] 2006	2	Nateglinide + Met	Gliclazide + Met	133	129	262	24 weeks	62.0±11.0	61.6±10.1	72 (54.1)	65 (50.4)	61 (45.9)	64 (49.6)
45	Göke et al,[62] 2010	2	Saxagliptin + Met	Glipizide + Met	428	430	891	52 weeks	57.5 (10.26)	57.6 (10.37)	212 (49.5)	232 (54.0)	216 (50.5)	198 (46.0)
46	Matthews et al,[63] 2010	2	Vildagliptin + Met	Glimepiride + Met	1562	1556	3118	2	57.5±9.07	57.5±9.19	829 (53.1%)	838 (53.9%)	733 (46.9%)	718 (46.1%)
47	Arechavaleta et al,[64] 2011	2	Sitagliptin + Met	Glimepiride + Met	516	519	1035	30 weeks	56.3±9.7	56.2±10.1	284 (55.0)	279 (53.8)		
48	Nauck et al,[65] 2007	2	Sitagliptin + Met	Glipizide + Met	588	584	1172	52 weeks	56.8 (9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	252 (42.9)	226 (38.7)
49	Ferrannini et al,[66] 2009	2	Vildagliptin + Met	Glimepiride + Met	1396	1393	2789	52 weeks	57.50±9.06	57.46±9.28	737 (52.8%)	753 (54.1%)	659 (47.2%)	640 (45.9%)
50	Ristic et al,[67] 2007	2	Nateglinide + Met	Gliclazide + Met	133	129	262	52 weeks	61.9 (11.1)	61.5 (10.2)	63 (56.3)	51 (50.5)	49 (43.8)	50 (49.5)
51	Derosa et al,[68] 2014	2	Vildagliptin + Met	Glimepiride + Met	81	86	167	6 months	59.8±9.9	56.8±8.9	42	36	44	34
52	Charpentier et al,[69] 2001	3	Arm 1: Met + glimepiride	Arm 2: glimepiride; Arm 3: Met	Arm 1: 147	Arm 2: 150; Arm 3: 75	379	20 weeks	Arm 1: 56.8 (36–70)	Arm 2: 55.4 (35–70); Arm 3: 56.7 (36–69)	Arm 1: 87 (59)	Arm 2: 87 (58); Arm 3: 45 (60)		

53	Feinglos et al,[70] 2005	2	Met + glipizide	Met + placebo	61	61	122	16 weeks	57.7±10.7	58.8±10.0	28	25	33	36
54	Lin et al,[71] 2011	2	Acarbose	Glibenclamide	20	20	51	16 weeks	51.5 (8.0)	53.9 (8.5)	13	10	7	10
55	Garber et al,[72] 2002	5	Glyburide/Met (1.25 mg/250 mg), glyburide/Met (2.5 mg/500 mg)	Placebo, glyburide, Met	Glyburide/Met (1.25/250): 158; glyburide/Met (2.5/500): 165	Placebo: 161; glyburide: 161; Met: 161	847	20 weeks	Gly/Met (1.25/250): 56.9 (12.0); gly/Met (2.5/500): 58.1 (9.8)	Placebo: 55.4 (10.5); glyburide: 56.5 (10.5); Met: 56.0 (11.0)	Glyburide/Met (1.25/250): 91 (57.6%); glyburide/Met (2.5/500): 96 (58.2%)	Placebo: 76 (47.2%); glyburide: 82 (50.9%); Met: 93 (57.8%)	Glyburide/Met (1.25/250): 67 (42.4%); glyburide/Met (2.5/500): 69 (41.8%)	Placebo: 85 (52.8%); glyburide: 79 (49.1%); Met: 68 (42.2%)
56	Home et al,[73] 2007	2	Met + rosiglitazone	Met + sulfonylurea	259	311	1122	18 months	57 (8)	57 (8)	141 (54)	139 (52)		
57	Wang et al,[74] 2015	2	Saxagliptin + Met	Acarbose + Met	41	40	90	12 months	64.3 (2.6)	65.1 (3.1)	18	19	23	21
58	Rosenstock et al,[75] 2011	3	Gosogliptin 20 mg + Met, gosogliptin 30 mg + Met	Placebo + Met	Pf-734,200: 116; pf-734,200: 116	57	289	12 weeks						
59	Shankar et al,[76] 2017	2	Omarigliptin + Met	Placebo + Met	201	201	659	24 weeks	57.5 (8.1)	56.8 (9.1)	101 (50.2)	102 (50.7)		
60	Filozof and Gautier,[77] 2010	2	Vildagliptin + Met	Gliclazide + Met	513	494	1007	52 weeks	59.2 (9.9)	59.7 (10.2)	268 (52.2%)	256 (51.8%)		
61	Forst et al,[78] 2010	5	Linagliptin (1 mg, 5 mg, 10 mg)	Placebo	Linagliptin 1 mg: 65; 5 mg: 66; 10 mg: 66	Placebo: 71	333	12 weeks	Linagliptin 1 mg: 59.2 (8.4); 5 mg: 59.6 (9.8); 10 mg: 61.8 (8.8)	Placebo: 60.1 (8.1)	Linagliptin 1 mg: 36 (55.4); 5 mg: 37 (56.1); 10 mg: 35 (53.0)	Placebo: 44 (62.0)		
62	Scheen et al,[6] 2010	2	Saxagliptin + Met	Sitagliptin + Met	403	398	822	18 weeks	58.8 (10.1)	58.1 (10.5)	190 (47.1)	202 (50.8)	213 (52.9)	196 (49.2)

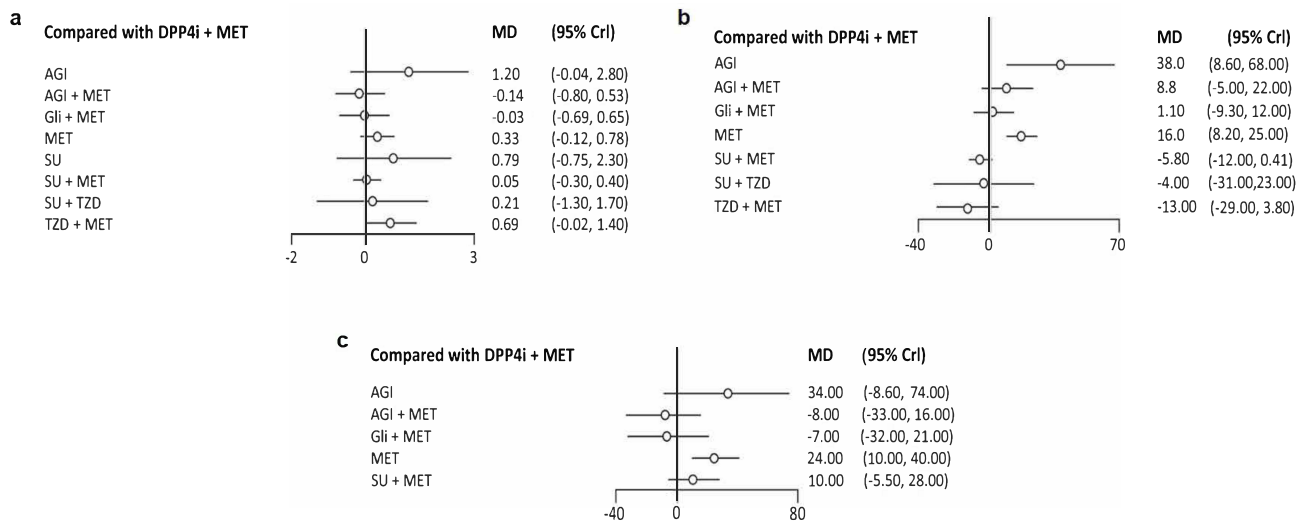**Abbreviations**: n, number; I, intervention; C, comparator; Met, metformin.

Figure 2 Forest plot of efficacy outcomes: (a) change in HbA1c levels from baseline; (b) change in FPG levels from baseline; (c) change in 2h-PPG levels from baseline.

with SU + TZD (RR: 2.00, 95% CI: 0.66, 6.00), AGI + Met (RR: 2.04, 95% CI: 1.06, 4.33), AGI (RR: 1.64, 95% CI: 0.47, 6.29), and Gli (RR: 2.06, 95% CI: 0.51, 8.49) (Figure 3, Table 3, Table S6 and Figure S6).

Cardiovascular Events

Eight articles were considered for the analysis. The incidence of CV events was lower with SU + TZD (RR: 0.82, 95% CI: 0.23, 3.03) and AGI + Met (RR: 0.01, 95% CI: 5.80×10^{-12}, 3.57), although this difference was not statistically significant. DPP4i + Met showed lower incidences of CV events in comparison to TZD + Met (RR: 1.01, 95% CI: 0.46, 2.45), SU + Met (RR: 1.06, 95% CI: 0.61, 2.06), and Met monotherapy (RR: 1.23, 95% CI: 0.52, 3.69), although these differences were not significant (Figure 3, Table 3, Table S7 and Figure S7).

Discussion

Despite advances in pharmacological management for T2DM, glycemic control remains frequently suboptimal, and hypoglycemia associated with uncontrolled or inadequate Met administration remains the most important concern. Clinicians often encounter challenges in comprehending the advantages and potential risks of emerging treatments. NMA offers a systematic means to visualize and comprehend a more comprehensive scope of evidence, enhancing the understanding of the real-world effectiveness and relative merits of these treatment regimens. Using the NMA tool, a recently published study considering a broader range of antidiabetic drugs discovered that SGLT-2i and GLP-1 RA medications were effective in reducing all-cause death, cardiovascular death, non-fatal myocardial infarction, hospitalization for heart failure, and end-stage kidney disease.[79]

AACE/ACE guidelines have reported that DDP4i can reduce both FPG and 2h-PPG levels, both as monotherapy and in combination with Met. Especially in patients with HbA1c between 7.6% and 9.0%, DDP4i are recommended as part of double-combination therapy with Met and as a triple-combination therapy with Met and TZD for patients with HbA1c >9.0%.[80] We found that DPP4i in combination with Met effectively reduced the HbA1c and 2h-PPG levels, and improved various safety outcomes compared with SU and Met combinations. This combination was equally effective and well-tolerated in comparison to other Met-based OADs (Table 4).

DPP4i in combination with Met was effective in reducing HbA1c levels compared with Met-based combinations with SU and TZD, while similar reductions were observed with glinides. This is in accordance with the findings observed in a previous meta-analysis that reported a greater reduction in HbA1c with DPP4i in comparison with SU and TZD.[81] Although both SU and DPP4i exert endogenous insulin secretion, DPP4i provide a more physiological meal-dependent action and help to improve beta- and alpha-cell function, which is speculated to be the reason behind the greater reduction. In an observational study evaluating sitagliptin and Met in combination, patients with T2DM had

Table 2 Effect Estimates for Efficacy Outcomes (Mean Difference and 95% CI)

(A) Change in HbA1c from Baseline

AGI	−1.35 (−2.85, 0.1273)	−1.214 (−2.849, 0.404)	−1.239 (−2.957, 0.4606)	−0.884 (−2.506, 0.721)	−0.4199 (−2.675, 1.799)	−1.163 (−2.814, 0.4661)	−1.005 (−3.225, 1.224)	−0.5204 (−2.26, 1.205)
1.35 (−0.1273, 2.85)	**AGI + Met**	0.1363 (−0.5322, 0.7954)	0.111 (−0.7439, 0.9393)	0.4673 (−0.1594, 1.089)	0.9184 (−0.75, 2.602)	0.1865 (−0.5233, 0.8783)	0.3482 (−1.301, 1.965)	0.8292 (−0.04071, 1.701)
1.214 (−0.404, 2.849)	−0.1363 (−0.7954, 0.5322)	**DPP4i + Met**	−0.02803 (−0.6915, 0.654)	0.3303 (−0.1174, 0.781)	0.7871 (−0.7532, 2.347)	0.0502 (−0.2966, 0.3965)	0.2134 (−1.303, 1.711)	0.6903 (0.01619, 1.39)
1.239 (−0.4606, 2.957)	−0.111 (−0.9393, 0.7439)	0.02803 (−0.654, 0.6915)	**Gli + Met**	0.3572 (−0.2428, 0.951)	0.8076 (−0.8225, 2.476)	0.07739 (−0.579, 0.7264)	0.2379 (−1.374, 1.836)	0.7193 (−0.06438, 1.506)
0.884 (−0.721, 2.506)	−0.4673 (−1.089, 0.1594)	−0.3303 (−0.781, 0.1174)	−0.3572 (−0.951, 0.2428)	**Met**	0.4531 (−1.117, 2.059)	−0.2789 (−0.767, 0.1972)	−0.1168 (−1.683, 1.421)	0.3616 (−0.3024, 1.037)
0.4199 (−1.799, 2.675)	−0.9184 (−2.602, 0.75)	−0.7871 (−2.347, 0.7532)	−0.8076 (−2.476, 0.8225)	−0.4531 (−2.059, 1.117)	**SU**	−0.7379 (−2.262, 0.7718)	−0.5745 (−2.711, 1.518)	−0.09394 (−1.744, 1.536)
1.163 (−0.4661, 2.814)	−0.1865 (−0.8783, 0.5233)	−0.0502 (−0.3965, 0.2966)	−0.07739 (−0.7264, 0.579)	0.2789 (−0.1972, 0.767)	0.7379 (−0.7718, 2.262)	**SU + Met**	0.1611 (−1.313, 1.628)	0.6411 (−0.001001, 1.299)
1.005 (−1.224, 3.225)	−0.3482 (−1.965, 1.301)	−0.2134 (−1.711, 1.303)	−0.2379 (−1.836, 1.374)	0.1168 (−1.421, 1.683)	0.5745 (−1.518, 2.711)	−0.1611 (−1.628, 1.313)	**SU + TZD**	0.4784 (−1.105, 2.099)
0.5204 (−1.205, 2.26)	−0.8292 (−1.701, 0.04071)	−0.6903 (−1.39, −0.01619)	−0.7193 (−1.506, 0.06438)	−0.3616 (−1.037, 0.3024)	0.09394 (−1.536, 1.744)	−0.6411 (−1.299, 0.001001)	−0.4784 (−2.099, 1.105)	**TZD + Met**

(B) Change in FPG from Baseline

AGI	−29.61 (−56, −3.235)	−38.48 (−67.98, −8.616)	−37.32 (−67.97, −6.168)	−22.02 (−51.38, 8.132)	−44.18 (−74.16, −14.06)	−42.43 (−82.6, −1.973)	−51.18 (−84.74, −17.6)
29.61 (3.235, 56)	**AGI + Met**	−8.82 (−22.25, 4.974)	−7.764 (−23.37, 8.417)	7.615 (−5.875, 21.77)	−14.61 (−28.68, −0.1557)	−12.82 (−42.79, 17.58)	−21.6 (−42.4, −0.6941)
38.48 (8.616, 67.98)	8.82 (−4.974, 22.25)	**DPP4i + Met**	1.089 (−9.305, 11.77)	16.47 (8.243, 24.91)	−5.78 (−11.96, 0.4052)	−4.011 (−31.17, 23.34)	−12.84 (−29.42, 3.808)
37.32 (6.168, 67.97)	7.764 (−8.417, 23.37)	−1.089 (−11.77, 9.305)	**Gli + Met**	15.37 (5.854, 25.09)	−6.924 (−16.71, 2.852)	−5.155 (−33.25, 22.87)	−13.95 (−30.82, 2.683)
22.02 (−8.132, 51.38)	−7.615 (−21.77, 5.875)	−16.47 (−24.91, −8.243)	−15.37 (−25.09, −5.854)	**Met**	−22.26 (−31.12, −13.82)	−20.45 (−48.46, 7.209)	−29.34 (−46.71, −12.23)
44.18 (14.06, 74.16)	14.61 (0.1557, 28.68)	5.78 (−0.4052, 11.96)	6.924 (−2.852, 16.71)	22.26 (13.82, 31.12)	**SU + Met**	1.778 (−24.78, 28.35)	−7.02 (−22.66, 8.568)
42.43 (1.973, 82.6)	12.82 (−17.58, 42.79)	4.011 (−23.34, 31.17)	5.155 (−22.87, 33.25)	20.45 (−7.209, 48.46)	−1.778 (−28.35, 24.78)	**SU + TZD**	−8.778 (−39.47, 21.82)
51.18 (17.6, 84.74)	21.6 (0.6941, 42.4)	12.84 (−3.808, 29.42)	13.95 (−2.683, 30.82)	29.34 (12.23, 46.71)	7.02 (−8.568, 22.66)	8.778 (−21.82, 39.47)	**TZD + Met**

(Continued)

Table 2 (Continued).

(C) Change in 2h-PPG from Baseline								
AGI	−41.77 (−74.87, −7.878)	−33.79 (−73.86, 8.621)	−40.81 (−86.22, 9.382)	−9.858 (−49.73, 35.21)	−23.58 (−65.64, 22.76)			
41.77 (7.878, 74.87)	**AGI + Met**	7.966 (−15.64, 33.17)	0.9272 (−31.27, 36.62)	31.78 (7.794, 59.75)	18.12 (−9.178, 48.8)			
33.79 (−8.621, 73.86)	−7.966 (−33.17, 15.64)	**DPP4i + Met**	−7.015 (−32.26, 20.55)	23.84 (10.34, 40.49)	10.1 (−5.548, 27.66)			
40.81 (−9.382, 86.22)	−0.9272 (−36.62, 31.27)	−7.015 (−20.55, 32.26)	**Gli + Met**	30.85 (9.246, 53.05)	17.27 (−12.08, 45.61)			
9.858 (−35.21, 49.73)	−31.78 (−59.75, −7.794)	−23.84 (−40.49, −10.34)	−30.85 (−53.05, −9.246)	**Met**	−13.61 (−33.31, 4.934)			
23.58 (−22.76, 65.64)	−18.12 (−48.8, 9.178)	−10.1 (−27.66, 5.548)	−17.27 (−45.61, 12.08)	13.61 (−4.934, 33.31)	**SU + Met**			
33.79 (−8.621, 73.86)	−7.966 (−33.17, 15.64)	**DPP4i + Met**	−7.015 (−32.26, 20.55)	23.84 (10.34, 40.49)	10.1 (−5.548, 27.66)			

Abbreviations: AGI, α-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitors; Gli, glinides; Met, metformin; SU, sulfonylurea; TZD, thiazolidinedione.
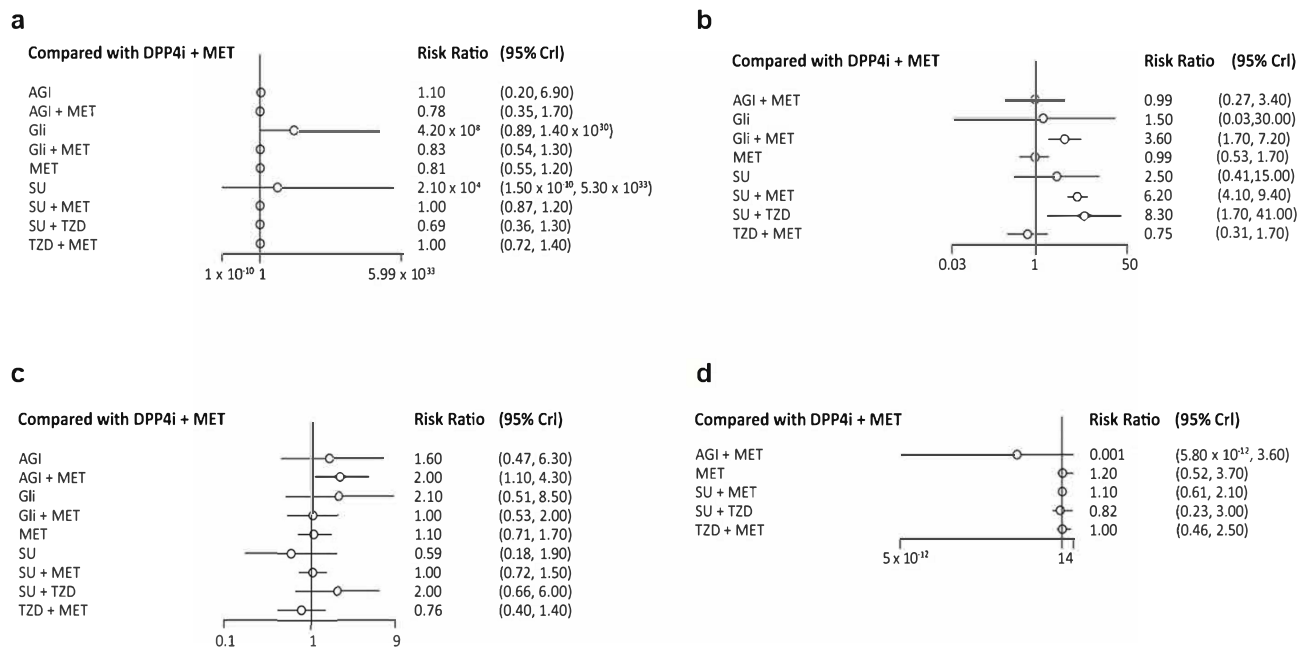
a

Compared with DPP4i + MET | Risk Ratio (95% Crl)

	Risk Ratio	(95% Crl)
AGI	1.10	(0.20, 6.90)
AGI + MET	0.78	(0.35, 1.70)
Gli	4.20×10^8	(0.89, 1.40×10^{30})
Gli + MET	0.83	(0.54, 1.30)
MET	0.81	(0.55, 1.20)
SU	2.10×10^4	(1.50×10^{30}, 5.30×10^{33})
SU + MET	1.00	(0.87, 1.20)
SU + TZD	0.69	(0.36, 1.30)
TZD + MET	1.00	(0.72, 1.40)

1×10^{-10} 1 5.99×10^{33}

b

Compared with DPP4i + MET | Risk Ratio (95% Crl)

	Risk Ratio	(95% Crl)
AGI + MET	0.99	(0.27, 3.40)
Gli	1.50	(0.03, 30.00)
Gli + MET	3.60	(1.70, 7.20)
MET	0.99	(0.53, 1.70)
SU	2.50	(0.41, 15.00)
SU + MET	6.20	(4.10, 9.40)
SU + TZD	8.30	(1.70, 41.00)
TZD + MET	0.75	(0.31, 1.70)

0.03 1 50

c

Compared with DPP4i + MET | Risk Ratio (95% Crl)

	Risk Ratio	(95% Crl)
AGI	1.60	(0.47, 6.30)
AGI + MET	2.00	(1.10, 4.30)
Gli	2.10	(0.51, 8.50)
Gli + MET	1.00	(0.53, 2.00)
MET	1.10	(0.71, 1.70)
SU	0.59	(0.18, 1.90)
SU + MET	1.00	(0.72, 1.50)
SU + TZD	2.00	(0.66, 6.00)
TZD + MET	0.76	(0.40, 1.40)

0.1 1 9

d

Compared with DPP4i + MET | Risk Ratio (95% Crl)

	Risk Ratio	(95% Crl)
AGI + MET	0.001	(5.80×10^{-12}, 3.60)
MET	1.20	(0.52, 3.70)
SU + MET	1.10	(0.61, 2.10)
SU + TZD	0.82	(0.23, 3.00)
TZD + MET	1.00	(0.46, 2.50)

5×10^{-12} 14

Figure 3 Forest plot of safety outcomes: (**a**) serious adverse events; (**b**) hypoglycemia; (**c**) gastrointestinal events; (**d**) cardiovascular events.

a significantly longer duration of treatment compared with an SU and Met combination owing to a comparable HbA1c reduction but a lower incidence of hypoglycemic events.[82]

The ability of a therapy to maintain glycemic control must be weighed against its tendency to cause hypoglycemia. Prevention of hypoglycemia, even in a milder form, has a special place in the guidelines.[83] The common adverse reactions for DPP4i include hypoglycemia, GI problems, pancreatitis, upper respiratory tract infection, and urinary tract infection, while the symptoms of the side effects are mild.[84] In our analysis, the DPP4i and Met combination showed lower incidences of hypoglycemia compared with the SU and glinide-based Met combination, while the risk ratios were similar to the AGI and Met-based combination. The results were consistent with other published literature.[85] Further, a meta-analysis also reported that although there was no significant difference between DPP4i and SUs, when either was added to Met monotherapy, the safety analysis showed a significant decrease in the risk of hypoglycemic events in patients using DPP4i.[86,87] Jeon et al also showed that SUs are especially associated with a higher rate of hypoglycemic events in comparison to DPP4i, indicating the good feasibility of DPP4i as an add-on therapy to Met.[88]

The occurrence of GI events with the DPP4i and Met combination was comparable with that of OADs such as SU and Met, glinides and Met, and Met alone, whereas the incidence of GI events was lower with DPP4i plus Met compared with SU and TZD, glinides monotherapy, and especially AGI in monotherapy as well as in combination with Met. This was consistent with a previous meta-analysis that revealed a lower risk for DPP4i in combination with Met in comparison to AGI and Met.[89,90] In that study, it was observed that the incidence of GI events after treatment with alogliptin, sitagliptin, and vildagliptin was significantly decreased, by 65%, 66%, and 62%, respectively, in comparison to AGI.[89] The combination of DPP4i and Met did not produce a statistically significant increase in the incidence of GI adverse events compared with Met alone.[91] A meta-analysis by Qian et al also revealed that no significant differences in the odds of diarrhea were observed when DPP4i or any other drug class was added to Met.[92] Also, in terms of SAEs, DPP4i were associated with lower SAEs compared with the SU-based Met combination but similar to the TZD-based Met combination.

Patients with T2DM usually have a very high risk for major adverse CV events. Previous studies have questioned the safety of traditional OADs in improving CV outcomes despite their ability to lower blood glucose levels. An NMA with 2967 patients consisting of 10 trials found no significant differences between patients taking DPP4i and those on placebo with regard to CV events.[93] Another observational study comparing DPP4i and Met combination with SU and Met

Table 3 Effect Estimates for Safety Outcomes (Risk Ratio and 95% CI)

(A) Serious Adverse Events									
AGI	0.9052 (0.1448, 5.016)	4.046e+08 (0.6909, 5.051e+29)	0.752 (0.1157, 4.357)	0.7327 (0.1204, 4.003)	1.635e+04 (1.034e-10, 3.948e+33)	0.9198 (0.146, 5.117)	0.6192 (0.09142, 3.899)	0.916 (0.146, 5.169)	
1.406 (0.3047, 7.499)	**AGI + Met**	1.275 (0.5901, 2.856)	5.486e+08 (1.118, 7.769e+29)	1.059 (0.4522, 2.539)	1.034 (0.5018, 2.174)	2.364e+04 (1.762e-10, 6.107e+33)	1.295 (0.5958, 2.91)	0.8727 (0.3264, 2.466)	1.287 (0.5708, 2.989)
1.105 (0.1994, 6.906)	0.7844 (0.3502, 1.695)	**DPP4i + Met**	4.168e+08 (0.8913, 1.37e+30)	0.8323 (0.5387, 1.263)	0.8145 (0.5533, 1.162)	2.054e+04 (1.533e-10, 5.328e+33)	1.02 (0.8749, 1.162)	0.6914 (0.357, 1.289)	1.018 (0.7173, 1.364)
2.471e-09 (1.98e-30, 1.447)	1.823e-09 (1.287e-30, 0.8944)	2.399e-09 (7.298e-31, 1.122)	**Gli**	1.943e-09 (6.001e-31, 0.9284)	1.977e-09 (6.046e-31, 0.8974)	0.0014 (3.552e-36, 2.364e+24)	2.448e-09 (7.668e-31, 1.143)	1.588e-09 (5.897e-31, 0.7828)	2.443e-09 (8.165e-31, 1.148)
1.33 (0.2295, 8.641)	0.9439 (0.3938, 2.211)	1.201 (0.7919, 1.856)	5.147e+08 (1.077, 1.666e+30)	**Gli + Met**	0.9787 (0.5875, 1.626)	2.353e+04 (1.824e-10, 5.993e+33)	1.225 (0.8183, 1.847)	0.8277 (0.3912, 1.754)	1.217 (0.762, 1.947)
1.365 (0.2498, 8.305)	0.967 (0.46, 1.993)	1.228 (0.8603, 1.807)	5.059e+08 (1.114, 1.654e+30)	1.022 (0.6152, 1.702)	**Met**	2.504e+04 (1.913e-10, 6.615e+33)	1.249 (0.8634, 1.863)	0.8477 (0.4114, 1.758)	1.242 (0.8012, 1.961)
6.115e-05 (2.533e-34, 9.671e+09)	4.23e-05 (1.637e-34, 5.676e+09)	4.868e-05 (1.877e-34, 6.522e+09)	714.1 (4.23e-25, 2.815e+35)	4.25e-05 (1.669e-34, 5.483e+09)	3.994e-05 (1.512e-34, 5.227e+09)	**SU**	4.986e-05 (1.921e-34, 6.648e+09)	3.388e-05 (1.263e-34, 4.592e+09)	4.969e-05 (2.063e-34, 6.658e+09)
1.087 (0.1954, 6.847)	0.7723 (0.3436, 1.679)	0.9808 (0.8604, 1.143)	4.086e+08 (0.8752, 1.304e+30)	0.8164 (0.5415, 1.222)	0.8007 (0.5369, 1.158)	2.006e+04 (1.504e-10, 5.205e+33)	**SU + Met**	0.6785 (0.3577, 1.252)	0.9976 (0.7285, 1.313)
1.615 (0.2564, 10.94)	1.146 (0.4055, 3.064)	1.446 (0.776, 2.801)	6.297e+08 (1.277, 1.696e+30)	1.208 (0.5702, 2.556)	1.18 (0.5689, 2.431)	2.952e+04 (2.178e-10, 7.917e+33)	1.474 (0.7988, 2.796)	**SU + TZD**	1.471 (0.73, 2.917)
1.092 (0.1935, 6.847)	0.7767 (0.3346, 1.752)	0.9823 (0.733, 1.394)	4.093e+08 (0.8713, 1.225e+30)	0.8215 (0.5137, 1.312)	0.8051 (0.5099, 1.248)	2.012e+04 (1.502e-10, 4.847e+33)	1.002 (0.7615, 1.373)	0.6799 (0.3428, 1.37)	**TZD + Met**
(B) Hypoglycemia									
AGI + Met	1.013 (0.2922, 3.656)	1.463 (0.02851, 38.73)	3.64 (0.9584, 14.1)	0.9943 (0.2983, 3.335)	2.573 (0.2998, 22.66)	6.263 (1.794, 22.86)	8.38 (1.173, 62.49)	0.7622 (0.1824, 3.035)	
0.9867 (0.2735, 3.422)	**DPP4i + Met**	1.473 (0.03253, 30)	3.608 (1.732, 7.197)	0.9858 (0.5337, 1.733)	2.538 (0.4132, 15.31)	6.206 (4.127, 9.371)	8.293 (1.704, 40.64)	0.7535 (0.3086, 1.656)	
0.6835 (0.02582, 35.07)	0.6791 (0.03333, 30.74)	**Gli**	2.432 (0.1286, 103.4)	0.6716 (0.03234, 28.85)	1.738 (0.05017, 115.4)	4.212 (0.2075, 186.5)	5.721 (0.1951, 325.1)	0.5123 (0.02303, 22.25)	

0.2748 (0.07094, 1.043)	0.2771 (0.1389, 0.5773)	0.4112 (0.009673, 7.773)	**Gli + Met**	0.2735 (0.1418, 0.5121)	0.7061 (0.1095, 4.619)	1.721 (0.9324, 3.278)	2.292 (0.4546, 12.37)	0.2094 (0.08592, 0.4676)
1.006 (0.2999, 3.352)	1.014 (0.577, 1.874)	1.489 (0.03466, 30.92)	3.656 (1.953, 7.051)	**Met**	2.587 (0.4176, 16.61)	6.289 (3.769, 11.15)	8.411 (1.695, 44.33)	0.7654 (0.3465, 1.608)
0.3887 (0.04414, 3.335)	0.394 (0.06534, 2.42)	0.5755 (0.008665, 19.93)	1.416 (0.2165, 9.128)	0.3866 (0.06022, 2.394)	**SU**	2.443 (0.4262, 14.5)	3.258 (0.315, 34.9)	0.2959 (0.04134, 1.976)
0.1597 (0.04375, 0.5573)	0.1611 (0.1067, 0.2423)	0.2374 (0.005362, 4.819)	0.5811 (0.3051, 1.073)	0.159 (0.08972, 0.2653)	0.4093 (0.06895, 2.346)	**SU + Met**	1.339 (0.29, 6.168)	0.1216 (0.05351, 0.2471)
0.1193 (0.016, 0.8529)	0.1206 (0.02461, 0.5868)	0.1748 (0.003076, 5.125)	0.4363 (0.08085, 2.2)	0.1189 (0.02256, 0.59)	0.307 (0.02865, 3.174)	0.7469 (0.1621, 3.449)	**SU + TZD**	0.09142 (0.01549, 0.4745)
1.312 (0.3295, 5.482)	1.327 (0.6039, 3.241)	1.952 (0.04495, 43.42)	4.775 (2.139, 11.64)	1.306 (0.6218, 2.886)	3.38 (0.5061, 24.19)	8.225 (4.047, 18.69)	10.94 (2.108, 64.56)	**TZD + Met**

(C) Gastrointestinal Events									
AGI	1.251 (0.4181, 3.674)	0.6112 (0.1591, 2.133)	1.268 (0.1899, 7.579)	0.6391 (0.1526, 2.389)	0.6571 (0.1778, 2.22)	0.3591 (0.05929, 1.909)	0.629 (0.1605, 2.241)	1.227 (0.2183, 6.161)	0.4638 (0.1129, 1.724)
0.7996 (0.2722, 2.392)	**AGI + Met**	0.4906 (0.2312, 0.9448)	1.012 (0.2149, 4.322)	0.512 (0.2064, 1.127)	0.528 (0.2651, 0.9552)	0.2887 (0.07173, 1.044)	0.5053 (0.2308, 0.9922)	0.9864 (0.2607, 3.349)	0.3722 (0.1564, 0.7972)
1.636 (0.4688, 6.285)	2.038 (1.058, 4.325)	**DPP4i + Met**	2.064 (0.5078, 8.491)	1.043 (0.5325, 2.003)	1.075 (0.707, 1.65)	0.5866 (0.1774, 1.917)	1.028 (0.7163, 1.46)	2.003 (0.6597, 6.001)	0.7579 (0.4041, 1.412)
0.7885 (0.1319, 5.267)	0.9881 (0.2314, 4.654)	0.4846 (0.1178, 1.969)	**Gli**	0.5052 (0.1454, 1.72)	0.5207 (0.1337, 2.038)	0.2838 (0.04688, 1.712)	0.4965 (0.1228, 1.994)	0.9655 (0.1707, 5.601)	0.3669 (0.08578, 1.564)
1.565 (0.4187, 6.552)	1.953 (0.887, 4.845)	0.9587 (0.4993, 1.878)	1.979 (0.5814, 6.879)	**Gli + Met**	1.03 (0.6001, 1.832)	0.563 (0.1548, 2.073)	0.9855 (0.522, 1.881)	1.914 (0.5668, 6.529)	0.7264 (0.3465, 1.553)
1.522 (0.4504, 5.625)	1.894 (1.047, 3.773)	0.9301 (0.606, 1.414)	1.921 (0.4907, 7.479)	0.9712 (0.5459, 1.666)	**Met**	0.5458 (0.1607, 1.818)	0.956 (0.6164, 1.463)	1.864 (0.5925, 5.635)	0.7059 (0.4152, 1.177)
2.785 (0.5237, 16.87)	3.464 (0.9582, 13.94)	1.705 (0.5215, 5.637)	3.523 (0.5842, 21.33)	1.776 (0.4824, 6.459)	1.832 (0.55, 6.223)	**SU**	1.753 (0.566, 5.452)	3.412 (0.7295, 16.17)	1.286 (0.3578, 4.677)
1.59 (0.4462, 6.229)	1.979 (1.008, 4.332)	0.9724 (0.6851, 1.396)	2.014 (0.5014, 8.143)	1.015 (0.5316, 1.916)	1.046 (0.6833, 1.622)	0.5704 (0.1834, 1.767)	**SU + Met**	1.95 (0.6835, 5.579)	0.738 (0.4056, 1.337)

(Continued)

Table 3 (Continued).

0.815 (0.1623, 4.58)	1.014 (0.2986, 3.836)	0.4992 (0.1666, 1.516)	1.036 (0.1785, 5.857)	0.5225 (0.1532, 1.764)	0.5366 (0.1775, 1.688)	0.2931 (0.06186, 1.371)	0.5129 (0.1793, 1.463)	**SU + TZD**	0.3788 (0.1143, 1.267)
2.156 (0.58, 8.857)	2.687 (1.254, 6.396)	1.319 (0.7082, 2.475)	2.726 (0.6394, 11.66)	1.377 (0.6438, 2.886)	1.417 (0.8499, 2.409)	0.7777 (0.2138, 2.795)	1.355 (0.7481, 2.466)	2.64 (0.7895, 8.746)	**TZD + Met**
(D) Cardiovascular Events									
AGI + Met	1325 (0.2804, 1.724e+11)	1683 (0.3257, 2.068e+11)	1421 (0.3059, 1.725e+11)	1112 (0.2083, 1.328e+11)	1359 (0.2775, 1.68e+11)				
0.000755 (5.802e-12, 3.566)	**DPP4i + Met**	1.229 (0.5189, 3.693)	1.06 (0.6103, 2.06)	0.8201 (0.2301, 3.029)	1.014 (0.4583, 2.454)				
0.0005943 (4.836e-12, 3.07)	0.8136 (0.2708, 1.927)	**Met**	0.8669 (0.3152, 2.062)	0.6619 (0.1393, 2.662)	0.8289 (0.3379, 1.713)				
0.0007038 (5.798e-12, 3.269)	0.9438 (0.4854, 1.638)	1.154 (0.4851, 3.173)	**SU + Met**	0.7702 (0.2421, 2.35)	0.9597 (0.4743, 1.892)				
0.0008996 (7.531e-12, 4.802)	1.219 (0.3301, 4.345)	1.511 (0.3757, 7.178)	1.298 (0.4255, 4.13)	**SU + TZD**	1.249 (0.334, 4.762)				
0.0007359 (5.952e-12, 3.603)	0.9862 (0.4075, 2.182)	1.206 (0.5838, 2.959)	1.042 (0.5286, 2.108)	0.8005 (0.21, 2.994)	**TZD + Met**				

Abbreviations: AGI, α-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitors; Gli, glinides; Met, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

Table 4 Summary Table of the Efficacy and Safety Outcomes of DPP4i + Met Combination with Other OAD-Based Met Combination Drug Classes

Drug Class / Outcomes	SU + Met	TZD + Met	Gli + Met	AGI + Met
HbA1c	*	*	X	
FPG			X	*
2h-PPG	*			
SAE	*	X		
Hypoglycemia	*		*	X
GI events	*		*	*
CV events	*	X		

Notes: X: DPP4i + Met combination is comparable to other OAD-based metformin combinations. *: DPP4i + Met combination is better than other OAD-based metformin combinations.
Abbreviations: DPP4i dipeptidyl peptidase-4 inhibitors; Met, metformin; OADs, oral antidiabetic drugs; SU, sulfonylurea; TZD, thiazolidinedione; Gli, glinides; AGI, α-glucosidase inhibitor; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; 2h-PPG, 2-hour post-prandial blood glucose; SAE, serious adverse event; GI, gastrointestinal; CV, cardiovascular.

combination reported lower risk of CV events with DPP4i. Moreover, DPP4i did not reduce myocardial infarction or admission for heart failure compared with SU.[87] In two meta-analyses,[94,95] DPP4i reduced the risk for adverse CV effects and non-fatal myocardial infarction compared with placebo and other oral hypoglycemic agents. In a subgroup analysis, Engel et al[95] found that DPP4i were associated with a lower rate of CV events than SUs. In our study, DPP4i and Met was found to be better than SU in reducing CV events, and comparable to TZD-based Met combinations. A recent meta-analysis found no significant differences in CV events between SUs and DPP4i as add-on therapies to Met in adults diagnosed with T2DM.[88]

The strengths of this NMA include the large sample size and the use of stringent inclusion and exclusion criteria. However, there were some limitations. The analyses were limited by the amount of data in the included studies. Also, moderate to substantial heterogeneity was observed in the studies included for the analysis. The RCTs included in this analysis involved a variety of study designs, including different patient populations and treatment durations. Also, our findings may have been impacted by variations in statistical analysis techniques and data quality between the RCTs. Further studies are needed to observe these results in a real-world clinical practice. Hence, observational studies are a prerequisite to address this evidence gap in effective patient management. Treatment for T2DM requires continuous management, which is often accompanied by adverse events. Although our findings suggest better safety outcomes in terms of hypoglycemia, GI events, and CV events from SU plus Met and a few other Met-based combinations, long-term safety assessments are needed to understand the chronic nature of diseases and uncover delayed adverse events. Finally, we did not distinguish among diverse drug doses or distinct medications within the same therapeutic class. As a consequence, our ability to ascertain whether observed outcomes were attributable to a class-wide effect or the specific impact of an individual drug was limited. Various medications in the same class or different doses of the same drug may have varying efficacy and safety. Owing to the significant level of inconsistency when the analysis was stratified by dosage, the impact of OAD dose variations on the therapeutic effect was not taken into consideration. So, when these drugs are used in clinical settings, it is important to consider the unique circumstances of each patient. Nevertheless, the results of the meta-analysis will assist in clinical decision making in treating patients with T2DM. The study will also assist in benchmarking the efficacies of OADs in T2DM and will provide insights for physicians to consider DPP4i-based Met combination as one of the suitable treatment options for their patients with T2DM. Future research should focus on implementing well-designed observational studies that could complement the findings of this meta-analysis and provide

insights into the real-world effectiveness of these treatment regimens, including long-term evaluation of the outcomes and dose optimization.

Conclusion
Treatment with a combination of DPP4i and Met revealed comparable efficacy and safety compared to other traditional OADs, and thus can be considered as a viable option in treating patients with T2DM.

Data Sharing Statement
The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Informed Consent
Not applicable: no ethical approval was required as this study is a meta-analysis and involves the collection of data from published literature.

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Author Contributions
All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure
The authors declare that they have no conflicts of interest in this work.

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