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ORIGINAL RESEARCH

Efficacy and Safety of Initial Combination Therapy in Treatment-Naïve Type 2 Diabetes Patients: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: The aim of this study was to evaluate the efficacy and safety of initial combination therapy compared with monotherapy in drug-naïve type 2 diabetes patients.

Methods: MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched for randomized clinical trials of initial combination therapy with hypoglycemic agents compared with monotherapy. Those which satisfied the search criteria were included in the meta-analysis. Weighted mean difference and relative risks were calculated.

Results: A total of 36 studies were included in the meta-analysis. Compared with metformin monotherapy, initial combination therapy with metformin plus another anti-diabetes drug exhibited significant reductions in glycated hemoglobin (HbA1c) ($p < 0.001$). Most of the combination therapies had a similar risk of hypoglycemia ($p > 0.05$), with the exception of combinations of sulfonylurea/glinide and metformin or combinations of thiazolidinedione and metformin. Compared with dipeptidyl peptidase-4 (DPP-4) inhibitor monotherapy, initial combination therapy with DPP-4 inhibitor plus another anti-diabetes drug showed a significant decrease in HbA1c ($p < 0.001$) and a similar risk of hypoglycemia ($p > 0.05$). Compared with monotherapy with other anti-diabetes drugs, initial combination therapies also resulted in significant HbA1c reductions, a similar risk of hypoglycemia and similar risks of other adverse events.

Conclusion: Compared with monotherapy, all initial combination therapies resulted in significant HbA1c reductions. Compared with metformin monotherapy, initial combination therapies with DPP-4 inhibitors plus metformin, sodium/glucose cotransporter 2 inhibitors and metformin, respectively, were associated with similar risks of hypoglycemia, but initial combination therapies with sulfonylurea plus metformin, thiazolidinedione and metformin, respectively, were associated with higher risks of hypoglycemia.

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Keywords: DPP-4 inhibitors; Drug-naïve; HbA1c; Hypoglycemia; Initial combination;

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Metformin; Sulfonylurea; Thiazolidinedione; Type 2 diabetes

INTRODUCTION

Initial hypoglycemic monotherapy is usually used in newly diagnosed type 2 diabetes patients, as currently recommended by the guidelines of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [1, 2]. However, initial monotherapy is frequently insufficient to enable patients to achieve or sustain glycemic targets [3, 4]. Thus, initial combination therapy has emerged as an alternative approach. The latest position statement from the ADA/EASD [2] called for an initial combination of two non-insulin agents in patients with a high baseline glycated hemoglobin (HbA1c) level ($\geq$ 9.0%). Additionally, the latest American Association of Clinical Endocrinologists (AACE) treatment algorithm [5] recommended that patients with a HbA1c level of $>$ 7.5% should receive combination therapy with metformin plus an additional drug.

However, we asked the question of whether initial combination therapy is actually more efficacious than monotherapy in terms of glucose control and confirmed safety. To search for the answer, we identified two published systematic reviews and meta-analyses. In one meta-analysis [6] that included 15 randomized controlled trials (RCTs), the authors found that compared to metformin alone, combination therapy with metformin plus another anti-diabetes drug provided statistically significant reductions of 0.43% in HbA1c level and of 14.30 mg/dl in fasting plasma glucose (FPG) level. In another meta-analysis [7] that included eight RCTs, the authors reported that compared with metformin monotherapy, initial combination therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors plus metformin was associated with a higher reduction of 0.49% in HbA1c level, a higher reduction of 0.80 mmol/l in FPG level and a lower weight loss of 0.44 kg. However, the authors of both of these meta-analyses did not present any further analysis with regard to the different types of hypoglycemic agent tested. Therefore, the aims of this study reported here were to comprehensively evaluate the efficacy and safety of initial combination therapies versus monotherapy using updated trial data in type 2 diabetes patients.

METHODS

Literature Search

According to recommendations from the Cochrane Handbook for Systematic Reviews for meta-analysis, two independent investigators (XYG and WJY) conducted systematic searches of MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) for studies published between the date of inception and April 2017. The search terms were: "type 2 diabetes," "initial combination therapy," "early combination therapy," "treatment-naïve," "drug-naïve," "newly diagnosed diabetes" and "randomized controlled trials." Treatment-naïve or drug-naïve patients were defined as those patients diagnosed with type 2 diabetes who have not received treatment with any hypoglycemic agent. "Newly diagnosed diabetes patients" were defined as those patients diagnosed with type 2 diabetes for the first time and who had not received treatment. "Early combination studies" referred to the initial combination therapy for type 2 diabetes patients. This meta-analysis is registered as CRD42017060717 in PROSPERO (International Prospective Register of Systematic Reviews).

Study Selection and Data Extraction

The inclusion criteria for this meta-analysis were: (1) studies of initial combination therapy with hypoglycemic agents compared with monotherapy; (2) efficacy of glucose control was the primary outcome of the study; (3) double-blind RCTs; (4) studies conducted with treatment-naïve type 2 diabetes patients. The exclusion criteria were: (1) studies conducted in type 1 diabetes patients; (2) the study was an extension study and not the original one; (3) study duration of $<$ 12 weeks.

Using the above inclusion and exclusion criteria, XYG and WJY independently evaluated the eligibility of all the studies identified in their search MEDLINE, Embase and CENTRAL. The Cochrane Collaboration tool [8] was used to rate each RCT as having a low, high or unclear risk of bias from the following aspects: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, as well as other sources of bias (Electronic Supplementary Material [ESM] Table S1 and Fig. S1). WJY and XYG then extracted details from each article, including the publication data, study design, baseline characteristics, treatment arms, study duration, changes in glucose and weight control and the hypoglycemic rate. If several doses were used in one trial, the standard doses recommended and approved in the clinical practice were documented (ESM Table S2). The definition of drug-naïve patients and the percentage of drug-naïve patients in each treatment arm were also documented (ESM Table S3).

Statistical Analyses

The primary endpoint of this meta-analysis was the change in HbA1c level from baseline to the study endpoint in patients who received initial combination therapies compared with those receiving monotherapy. The secondary endpoints included changes in FPG, postprandial glucose (PPG) and body weight and the risk of hypoglycemia in patients who received initial combination therapies compared with those receiving monotherapy. Continuous outcomes were evaluated by computing the weighted mean differences (WMDs) and the 95% confidence intervals (CIs). Categorical outcomes were evaluated by computing the relative risks (RRs) and accompanying 95% CIs. Due to between-study heterogeneity, Higgins I^2 statistics were used to evaluate the percentage of variance. Heterogeneity can be quantified as low, moderate and high, with upper limits of 25, 50 and 75% for I^2, respectively [9–11]. The 95% CIs of I^2 were also calculated [11]. Publication bias was assessed using a funnel plot (ESM Fig. S2).

Meta-regression analysis was performed to evaluate whether the pre-specified covariates of baseline age, gender, HbA1c level and baseline body mass index (BMI) were associated with HbA1c changes from baseline corrected by monotherapy. Differences were considered to be statistically significant as $p < 0.05$.

Statistical analyses were primarily performed using the Review Manager statistical software package (version 5.2; Nordic Cochrane Centre, Copenhagen, Denmark). Analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting meta-analyses of RCTs [12]. Meta-regression analyses were performed using the STATA statistical software package (version 11.0; StataCorp, College Station, TX, USA).

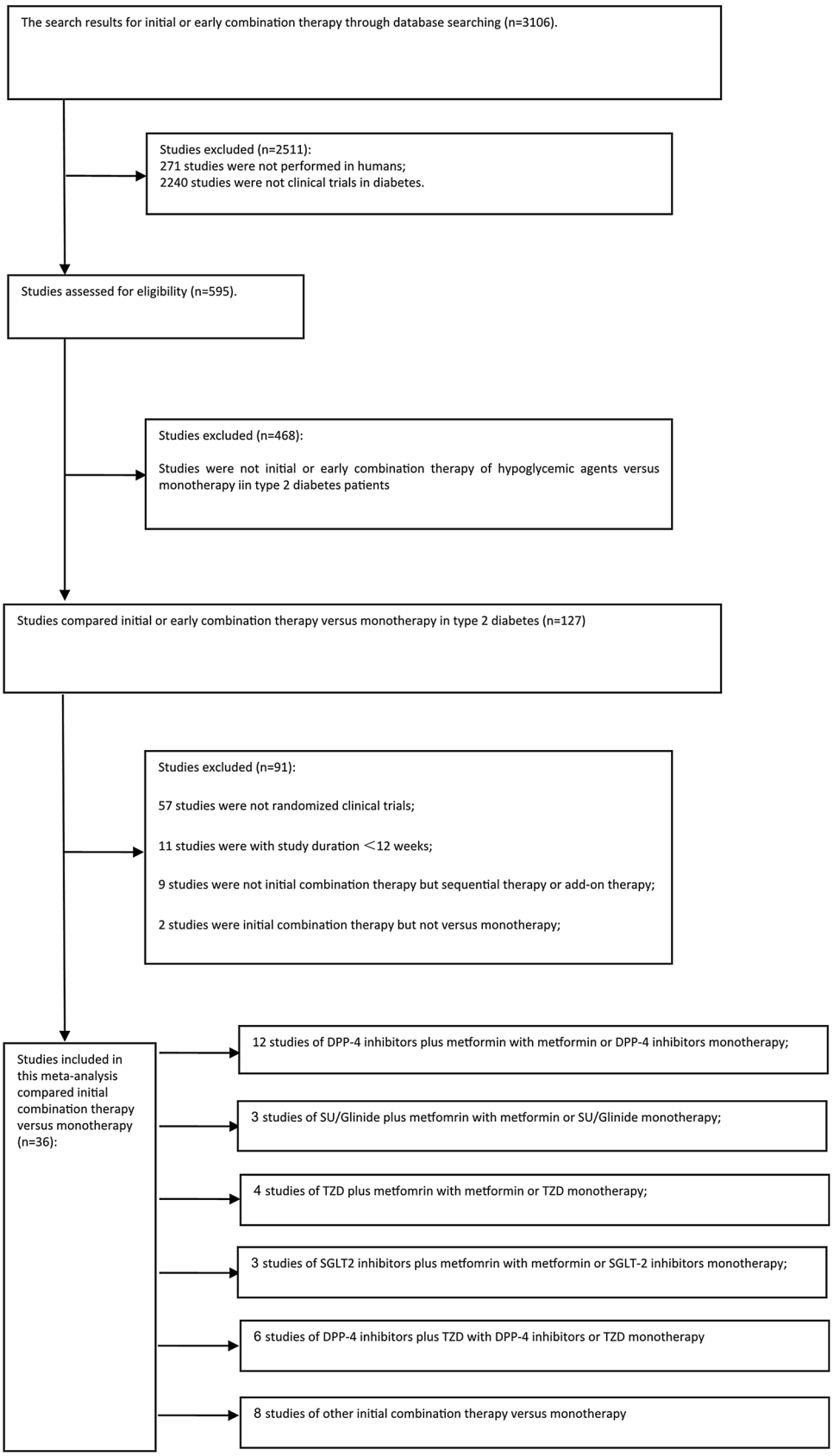
This article does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Characteristics and Methodological Quality of Included Studies

A total of 36 studies were included in the meta-analysis (Fig. 1; Table 1). Of these, 12 were studies [13–24] with initial combination therapies of DPP-4 inhibitors plus metformin, three were studies [25–27] in which the initial combination therapy was sulfonylurea (SU) or glinide plus metformin, four were studies [28–31] in which the initial combination therapy was thiazolidinedione (TZD) plus metformin, three were studies [32–34] in which the initial combination therapy was sodium glucose cotransporter 2 (SGLT2) inhibitor plus metformin and six studies [35–40] utilized an initial combination therapy of DPP-4 inhibitor plus TZD. There were also eight trials with other initial combination therapies [41–48].

Our meta-analysis included studies that were randomized, placebo-controlled, with double-blind treatment. The eligibility criteria were clearly reported in all of the trials. Most studies


The search results for initial or early combination therapy through database searching (n=3106).
Studies excluded (n=2511):
271 studies were not performed in humans;
2240 studies were not clinical trials in diabetes.
Studies assessed for eligibility (n=595).
Studies excluded (n=468):
Studies were not initial or early combination therapy of hypoglycemic agents versus monotherapy iin type 2 diabetes patients
Studies compared initial or early combination therapy versus monotherapy in type 2 diabetes (n=127)
Studies excluded (n=91):
57 studies were not randomized clinical trials;
11 studies were with study duration ＜12 weeks;
9 studies were not initial combination therapy but sequential therapy or add-on therapy;
2 studies were initial combination therapy but not versus monotherapy;
Studies included in this meta-analysis compared initial combination therapy versus monotherapy (n=36):
12 studies of DPP-4 inhibitors plus metformin with metformin or DPP-4 inhibitors monotherapy;
3 studies of SU/Glinide plus metfomrin with metformin or SU/Glinide monotherapy;
4 studies of TZD plus metfomrin with metformin or TZD monotherapy;
3 studies of SGLT2 inhibitors plus metfomrin with metformin or SGLT-2 inhibitors monotherapy;
6 studies of DPP-4 inhibitors plus TZD with DPP-4 inhibitors or TZD monotherapy
8 studies of other initial combination therapy versus monotherapy

◀**Fig. 1** Flow chart of included studies. *DDT-4* Dipeptidyl peptidase-4, *SGLT2* sodium glucose cotransporter 2, *SU* sulfonylurea, *TZD* thiazolidinedione

reported baseline age, BMI, HbA1c level and duration of diabetes between the comparison groups. The risk of bias as evaluated by the Cochrane instrument was low (ESM Fig. S1). The visual inspection of the funnel plots indicated low risks of publication bias (ESM Fig. S2). For some treatment groups included only one trial, no further meta-analysis was done in each group [41–48]. Those extension studies were excluded from this meta-analysis.

Efficacy of Initial Combination Therapy

Compared with metformin monotherapy, initial combinations of DPP-4 inhibitors and metformin exhibited significant decreases in HbA1c (WMD, − 0.44%, $p < 0.001$), FPG (WMD, − 0.77 mmol/l, $p < 0.001$) and PPG (WMD, − 1.65 mmol/l, $p < 0.001$), but increased body weight significantly (WMD, 0.38 kg, $p < 0.001$). Compared with DPP-4 inhibitors monotherapy, initial combinations of DPP-4 inhibitors and metformin caused significant decreases in HbA1c (WMD, − 0.88%, $p < 0.001$), FPG (WMD, − 1.61 mmol/l, $p < 0.001$), PPG (WMD, − 2.69 mmol/l, $p < 0.001$) and body weight (WMD, − 1.00 kg, $p < 0.001$) (Table 2; Figure S3).

Compared with metformin monotherapy, initial treatment combinations of SU/glinides plus metformin resulted in significant decreases in the levels of HbA1c (WMD − 0.68%; $p < 0.001$), FPG (WMD,− 0.87 mmol/l; $p < 0.001$) and PPG (WMD − 0.70 mmol/l; $p < 0.001$), but significant increases in body weight (WMD 2.60 kg; $p < 0.001$). Compared with SU/glinide monotherapy, initial combinations of SU/glinides plus metformin exhibited significant decreases in the levels of HbA1c (WMD − 0.49%; $p < 0.001$), FPG (WMD − 0.66 mmol/l; $p = 0.005$) and PPG (WMD − 0.87 mmol/l; $p < 0.001$) and similar changes in weight (WMD − 0.10 kg; $p = 0.74$) (Table 2; ESM Fig. S3).

Compared with metformin monotherapy, initial combinations of TZDs plus metformin led to significant decreases in HbA1c (WMD − 0.44%; $p < 0.001$) and FPG levels (WMD, − 0.88 mmol/l; $p < 0.001$) but increased body weight significantly (WMD 1.93 kg; $p < 0.001$). Compared with TZD monotherapy, initial combinations of TZDs plus metformin led to significant decreases in the levels of HbA1c (WMD − 0.83%; $p < 0.001$) and FPG (WMD − 1.25 mmol/l; $p < 0.001$) and body weight (WMD − 1.22 kg; $p < 0.001$) (Table 2; ESM Fig. S3).

Initial combinations of SGLT2 inhibitors plus metformin led to significant decreases in HbA1c (WMD, − 0.47%, $p < 0.001$), FPG (WMD, − 1.38 mmol/l, $p < 0.001$) and body weight (WMD, − 2.00 kg, $p < 0.001$) when compared with metformin monotherapy. Initial combinations of SGLT2 inhibitors plus metformin also led to significant decreases in HbA1c (WMD − 0.64%; $p < 0.001$) and FPG (WMD − 0.83 mmol/l; $p < 0.001$) levels and body weight (WMD − 0.66 kg; $p < 0.001$) when compared to SGLT2 inhibitor monotherapy (Table 2; ESM Fig. S3).

Compared with TZD monotherapy, initial combinations of DPP-4 inhibitors plus TZD exhibited significant decreases in the levels of HbA1c (WMD − 0.54%; $p < 0.001$), FPG (WMD − 0.89 mmol/l; $p < 0.001$) and PPG (WMD − 1.97 mmol/l; $p < 0.001$) but increased body weight significantly (WMD 0.96 kg; $p < 0.001$). Compared with DPP-4 inhibitor monotherapy, initial combinations of DPP-4 inhibitors plus TZD resulted in significant decreases in HbA1c (WMD − 0.62%; $p < 0.001$) and FPG (WMD − 1.41 mmol/l; $p < 0.001$) levels but significant increases in body weight (WMD 3.51 kg; $p < 0.001$) (Table 2; ESM Fig. S3).

Meta-regression analysis indicated that compared with monotherapy, the decrease in HbA1c level from baseline at initial combination therapy in each treatment group was not associated with the baseline HbA1c level adjusted by age, gender, and baseline BMI. However, when all data were pooled together, adjusted by age, gender and baseline BMI, HbA1c changes from baseline in the total combination therapy corrected by monotherapy was associated with

Table 1 Characteristics of randomized controlled trials in initial combination therapy in type 2 diabetes

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
DPP-4 inhibitors + metformin initial combination therapy vs. metformin monotherapy									
Goldstein, 2007 [13]	24 weeks	Sitagliptin 50 mg + metformin 1000 mg bid	182	53.3 ± 9.6	42.3	32.4 ± 6.6	4.4 ± 4.2	8.7 ± 0.9	–
		Metformin 1000 mg bid	182	53.2 ± 9.6	45.1	32.2 ± 7.1	4.4 ± 4.4	8.7 ± 0.9	–
Goldstein, 2007-2 [13]	24 weeks	Sitagliptin 50 mg + metformin 500 mg bid	190	54.1 ± 10.0	55.3	32.1 ± 6.7	4.5 ± 4.7	8.8 ± 1.0	–
		Metformmin 500 mg bid	182	53.2 ± 10.2	48.9	32.1 ± 6.8	4.5 ± 3.9	8.9 ± 1.0	–
Bosi, 2009 [14]	24 weeks	Vildagliptin 50 mg + metformin 1000 mg bid	295	52.8 ± 10.64	58	31.37 ± 4.75	1.87 ± 2.60	8.70 ± 1.03	89.79 ± 18.87
		Metformin 1000 mg bid	294	52.4 ± 10.71	58.2	31.31 ± 4.58	2.19 ± 3.33	8.62 ± 0.93	88.43 ± 17.39
Jadzinsky, 2009 [15]	24 weeks	Saxagliptin 10 mg + metformin	323	52.1 ± 11.6	45.2	30.3 ± 5.0	1.4 ± 2.5	9.5 ± 1.2	82.5 ± 16.9
		Metformin	328	51.8 ± 10.7	49.7	30.2 ± 4.9	1.7 ± 3.1	9.4 ± 1.3	82.8 ± 17.5
Reasner, 2011 [16]	18 weeks	Sitagliptin/metformin FDC	625	49.4 ± 10.5	56	32.9 ± 7.2	3.5 ± 4.5	9.9 ± 1.8	94.7 ± 23.4
		Metformmin	621	50.0 ± 10.5	57	33.7 ± 7.8	3.2 ± 4.3	9.8 ± 1.8	97.2 ± 25.5
Haak, 2012 [17]	24 weeks	Linagliptin 2.5 mg + metformin 1000 mg bid	143	56.4 ± 10.7	53.8	28.6 ± 4.8	–	8.7 ± 1.0	76.7 ± 16.0
		Metformin 1000 mg bid	147	55.2 ± 10.6	53.1	29.5 ± 5.3	–	8.5 ± 0.9	80.0 ± 18.5
Haak, 2012-2 [17]	24 weeks	Linagliptin 2.5 mg + metformin 500 mg bid	143	55.6 ± 11.2	51.0	29.7 ± 5.3	–	8.7 ± 1.0	80.8 ± 19.0
		Metformin 500 mg bid	144	52.9 ± 10.4	56.9	28.9 ± 4.8	–	8.7 ± 0.9	79.9 ± 18.4
Pratley, 2014 [18]	26 weeks	Alogliptin/metformin 12.5/1000 mg bid	114	54.6 ± 10.42	54.4	31.0 ± 5.38	4.2 ± 4.97	–	–
		Metformin 1000 mg bid	111	52.6 ± 11.30	45.9	30.5 ± 5.0	4.1 ± 4.59	–	–
Pratley, 2014-2 [18]	26 weeks	Alogliptin/metformin 12.5/500 mg bid	111	53.7 ± 11.59	43.2	30.9 ± 5.35	4.1 ± 4.78	–	–
		Metformin 500 mg bid	114	54.6 ± 10.20	41.2	30.2 ± 4.84	3.8 ± 3.90	–	–
Ji, 2015 [19]	24 weeks	Linagliptin 5 mg + metformin 1000 mg	344	53.1 ± 10.7	49.1	29 ± 5.7	–	8 ± 1.0	76.7 ± 18.8
		Metformin 2000 mg	345	52.9 ± 10.7	45.8	29 ± 5.6	–	8 ± 0.8	76.0 ± 18.8
Ji, 2016 [20]	24 weeks	Sitagliptin 50 mg/metformin 850 mg bid	125	52.4 ± 9.3	53.6	25.4 ± 3.1	1.1 ± 0.3	8.6 ± 0.9	69.4 ± 10.8
		Metformin 850 mg bid	124	53.0 ± 10.3	60.5	25.8 ± 3.5	1.1 ± 0.2	8.7 ± 1.1	71.1 ± 11.8
Ji, 2016-2 [20]	24 weeks	Sitagliptin 50 mg/metformin 500 mg bid	122	52.6 ± 11.3	69.7	26.1 ± 3.4	1.1 ± 0.3	8.5 ± 1.0	72.4 ± 12.1
		Metformin 500 mg bid	126	52.6 ± 9.5	54.8	26.0 ± 3.7	1.0 ± 0.2	8.7 ± 1.0	71.1 ± 13.7
Mu, 2016 [21]	24 weeks	Linagliptin 2.5 mg/metformin 1000 mg bid	147	50.7 ± 9.4	59.2	26.0 ± 3.7	–	8.7 ± 1.0	70.5 ± 12
		Metformin 1000 mg bid	144	51.4 ± 10.4	63.2	26.1 ± 3.3	–	8.6 ± 1.0	71.0 ± 12

Table 1 continued

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
Mu, 2016-2 [21]	24 weeks	Linagliptin 2.5 mg/metformin 500 mg bid	147	51.4 ± 10.2	62.6	26.0 ± 3.6	–	8.7 ± 0.9	70.8 ± 12
		Metformin 500 mg bid	145	52.1 ± 9.6	62.8	25.8 ± 3.3	–	8.7 ± 1.1	69.1 ± 10.7
Dou, 2017 [22]	24 weeks	Saxagliptin 5 mg + metformin 500 mg	210	50.8 ± 10.4	64.8	26.7 ± 3.7	0.97 ± 2.1	9.4 ± 1.1	–
		Metformin 500 mg + placebo	207	50.1 ± 11.0	63.8	26.5 ± 3.6	0.72 ± 2.1	9.5 ± 1.0	–
JI, 2017 [23]	26 weeks	Alogliptin 12.5 mg + metformin 500 mg FDC bid	159	53.4 ± 10.46	57.2	26.16 ± 3.51	–	8.39 ± 0.81	–
		Metformin 500 mg bid	162	53.6 ± 9.91	50.6	26.30 ± 3.57	–	8.40 ± 0.78	–
DPP-4 inhibitors + metformin initial combination therapy vs. DPP-4 inhibitor monotherapy									
Goldstein, 2007 [13]	24 weeks	Sitagliptin 50 mg + metformin 1000 mg bid	182	53.3 ± 9.6	42.3	32.4 ± 6.6	4.4 ± 4.2	8.7 ± 0.9	–
		Sitagliptin 100 mg qd	179	53.3 ± 10.2	52.0	31.2 ± 5.9	4.4 ± 4.6	8.9 ± 1.0	–
Bosi, 2009 [14]	24 weeks	Vildagliptin 50 mg + metformin 1000 mg bid	295	52.8 ± 10.64	58	31.37 ± 4.75	1.87 ± 2.60	8.70 ± 1.03	89.79 ± 18.87
		Vildagliptin 50 mg bid	300	53.5 ± 10.95	60	31.26 ± 4.82	2.12 ± 3.32	8.68 ± 1.02	87.84 ± 17.93
Jadzinsky, 2009 [15]	24 weeks	Saxagliptin 10 mg + metformin	323	52.1 ± 11.6	45.2	30.3 ± 5.0	1.4 ± 2.5	9.5 ± 1.2	82.5 ± 16.9
		Saxagliptin 10 mg	335	52.1 ± 10.2	50.4	30.2 ± 4.9	1.7 ± 2.8	9.6 ± 1.3	83.1 ± 16.9
Haak, 2012 [17]	24 weeks	Linagliptin 2.5 mg + metformin 1000 mg bid	143	56.4 ± 10.7	53.8	28.6 ± 4.8	–	8.7 ± 1.0	76.7 ± 16.0
		Linagliptin 5 mg qd	142	56.2 ± 10.8	56.3	29.0 ± 4.7	–	8.7 ± 1.0	79.1 ± 17.3
Pratley, 2014 [18]	26 weeks	Alogliptin/metformin 12.5/1000 mg bid	114	54.6 ± 10.42	54.4	31.0 ± 5.38	4.2 ± 4.97	–	–
		Alogliptin 25 mg qd	112	52.6 ± 9.38	42.9	30.8 ± 5.22	3.6 ± 4.12	–	–
Ross, 2015 [24]	24 weeks	Linagliptin 5 mg + metformin	159	49 ± 10.9	43.4	29.84 ± 5.82	–	9.79 ± 1.19	–
		Linagliptin 5 mg	157	48.6 ± 11.2	49	29.63 ± 5.43	–	9.88 ± 1.10	–
Ji, 2016 [20]	24 weeks	Sitagliptin 50 mg/metformin 850 mg bid	125	52.4 ± 9.3	53.6	25.4 ± 3.1	1.1 ± 0.3	8.6 ± 0.9	69.4 ± 10.8
		Sitagliptin 50 mg bid	120	51.7 ± 10.2	61.7	26.0 ± 3.5	1.1 ± 0.2	8.7 ± 1.1	71.8 ± 12.1
Mu, 2016 [21]	24 weeks	Linagliptin 2.5 mg/metformin 1000 mg bid	147	50.7 ± 9.4	59.2	26.0 ± 3.7	–	8.7 ± 1.0	70.5 ± 12
		Linagliptin 5 mg qd	147	50.8 ± 10.5	51.7	26.2 ± 3.9	–	8.7 ± 0.9	70.2 ± 13.5
Dou, 2017 [22]	24 weeks	Saxagliptin 5 mg + metformin 500 mg	210	50.8 ± 10.4	64.8	26.7 ± 3.7	0.97 ± 2.1	9.4 ± 1.1	–
		Saxagliptin 5 mg + placebo	213	49.5 ± 10.9	70.9	26.5 ± 3.2	0.73 ± 1.6	9.4 ± 1.0	–
JI, 2017 [23]	26 weeks	Alogliptin 12.5 mg + metformin 500 mg FDC bid	159	53.4 ± 10.46	57.2	26.16 ± 3.51	–	8.39 ± 0.81	–
		Alogliptin 12.5 mg bid	163	55.4 ± 9.62	60.1	26.16 ± 3.92	–	8.48 ± 0.71	–

Table 1 continued

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
SU + metformin initial combination therapy vs. metformin monotherapy									
Garber, 2002 [25]	20 weeks	Glyburide/metformin 2.5/500 mg	165	58.1 ± 9.8	58.2	29.6 ± 4.5	3.30 ± 3.18	8.18 ± 1.14	86.7 ± 17.5
		Metformin 500 mg	161	56.0 ± 11.0	57.8	30.4 ± 4.3	2.98 ± 2.74	8.26 ± 1.08	88.6 ± 14.9
Garber, 2003 [26]	16 weeks	Glyburide/metformin 1.25/500 mg	171	55.6 ± 11.2	44.4	31.4 ± 4.6	3.0 ± 3.0	8.8 ± 1.5	91.9 ± 17.4
		Metformin 500 mg	164	54.7 ± 11.8	43.3	31.4 ± 4.0	2.6 ± 2.3	8.5 ± 1.4	92.8 ± 15.6
Horton, 2004 [27]	24 weeks	Nateglinide 120 mg + metformin 500 mg tid	89	57.7 ± 1.2	65.2	30.6 ± 0.4	3.4 ± 0.4	8.2 ± 0.1	–
		Metformin 500 mg tid	104	55.4 ± 1.1	67.3	29.9 ± 0.4	3.7 ± 0.4	8.3 ± 0.1	–
SU/glinide + metformin initial combination therapy vs. SU/glinide monotherapy									
Garber, 2002 [25]	20 weeks	Glyburide/metformin 2.5/500 mg	165	58.1 ± 9.8	58.2	29.6 ± 4.5	3.30 ± 3.18	8.18 ± 1.14	86.7 ± 17.5
		Glyburide 2.5 mg	161	56.5 ± 10.5	50.9	30.3 ± 3.9	2.81 ± 3.14	8.21 ± 1.09	87.2 ± 15.3
Garber, 2003 [26]	16 weeks	Glyburide/metformin 1.25/500 mg	171	55.6 ± 11.2	44.4	31.4 ± 4.6	3.0 ± 3.0	8.8 ± 1.5	91.9 ± 17.4
		Glyburide 2.5 mg	151	55.3 ± 12.2	43.7	31.1 ± 4.3	3.0 ± 2.6	8.7 ± 1.4	91.0 ± 16.0
Horton, 2004 [27]	24 weeks	Nateglinide 120 mg +Metformin 500 mg tid	89	57.7 ± 1.2	65.2	30.6 ± 0.4	3.4 ± 0.4	8.2 ± 0.1	–
		Nateglinide 120 mg	104	57.9 ± 1.0	56.7	29.9 ± 0.4	4.7 ± 0.6	8.1 ± 0.1	–
TZD + metformin initial combination therapy vs. metformin monotherapy									
Rosenstock, 2006 [28]	32 weeks	Rosiglitazone/Metformmin	155	50.1 ± 10.7	57	33.2 ± 7.7	2.3 ± 2.7	8.9 ± 1.1	–
		Metformin	154	51.5 ± 10.4	56	32.5 ± 7.0	2.9 ± 3.7	8.8 ± 1.0	–
Stewart, 2006 [29]	32 weeks	Roziglitazone + metformin	254	58.9 ± 8.4	55	30.9 ± 5.4	3.7 ± 3.6	7.2 ± 0.6	88.1 ± 16.3
		metformin	272	59.0 ± 7.9	56	30.6 ± 5.5	3.7 ± 3.6	7.2 ± 0.6	87.2 ± 16.5
Perez, 2009 [30]	24 weeks	Pioglitazone 15 mg + metformin 850 mg bid	201	54.7 ± 12.2	44.8	30.8 ± 5.7	–	8.89 ± 0.07	–
		Metformin 850 mg bid	210	53.7 ± 12.0	46.7	30.8 ± 5.7	–	8.65 ± 0.07	–
Borges, 2011 [31]	80 weeks	Rosiglitazone/metformin	344	51.5 ± 10.5	53	32.2 ± 6.8	2.3 ± 3.1	8.6 ± 0.9	87.1 ± 21.3
		Metformin	334	50.7 ± 10.5	53	33.1 ± 7.1	2.6 ± 3.3	8.6 ± 0.9	90.6 ± 22.8
TZD + metformin initial combination therapy vs. TZD monotherapy									
Rosenstock, 2006 [28]	32 weeks	Rosiglitazone/Metformmin	155	50.1 ± 10.7	57	33.2 ± 7.7	2.3 ± 2.7	8.9 ± 1.1	–
		Rosiglitazone	159	50.6 ± 10.2	58	32.8 ± 7.1	2.7 ± 3.0	8.8 ± 1.0	–
Perez, 2009 [30]	24 weeks	Pioglitazone 15 mg + metformin 850 mg bid	201	54.7 ± 12.2	44.8	30.8 ± 5.7	–	8.89 ± 0.07	–
		Pioglitazone 15 mg bid	189	54.0 ± 12.1	34.9	31.2 ± 5.5	–	8.69 ± 0.07	–
SGLT2 inhibitors + metformin initial combination therapy vs. metformin monotherapy									
Henry, 2012–2 [32]	24 weeks	Dapagliflozin 10 mg + metformin 2000 mg	211	51.0 ± 10.1	50.2	–	2.2 ± 3.3	9.1 ± 1.3	88.4 ± 19.7
		Metformin 2000 mg + placebo	208	52.7 ± 10.4	46.6	–	1.9 ± 4.0	9.1 ± 1.3	87.2 ± 19.4

Table 1 continued

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
Hadjadj, 2016 [33]	24 weeks	Empagliflozin 25 mg + metformin 2000 mg	169	53.6 ± 10.7	52.1	30.4 ± 5.3	–	8.66 ± 1.14	83.8 ± 19.8
		Metformin 2000 mg	164	51.6 ± 10.8	56.1	30.5 ± 5.9	–	8.58 ± 1.13	83.7 ± 20.1
Rosenstock, 2016 [34]	26 weeks	Canagliflozin 300/Metformin 2000 mg	237	55.4 ± 9.8	48.5	32.8 ± 6.5	3.3 ± 3.9	8.9 ± 1.2	91.4 ± 21.4
		Metformin 2000 mg	237	55.2 ± 9.8	48.9	33.0 ± 6.0	3.3 ± 4.5	8.8 ± 1.2	92.1 ± 20.1
SGLT2 inhibitors + metformin initial combination therapy vs. SGLT2 inhibitor monotherapy									
Henry, 2012–1 [32]	24 weeks	Dapagliflozin 5 mg + metformin	194	51.7 ± 9.3	40.2	–	1.6 ± 2.4	9.2 ± 1.3	84.1 ± 19.5
		Dapagliflozin 5 mg + placebo	203	52.3 ± 10.2	45.3	–	1.6 ± 3.1	9.1 ± 1.4	86.2 ± 21.1
Henry, 2012–2 [32]	24 weeks	Dapagliflozin 10 mg + metformin	211	51.0 ± 10.1	50.2	–	2.2 ± 3.3	9.1 ± 1.3	88.4 ± 19.7
		Dapaglifozin 10 mg + placebo	219	51.1 ± 11.5	47.9	–	2.1 ± 3.8	9.1 ± 1.3	88.5 ± 19.3
Hadjadj, 2016 [33]	24 weeks	Empagliflozin 25 mg + metformin 2000 mg	169	53.6 ± 10.7	52.1	30.4 ± 5.3	–	8.66 ± 1.14	83.8 ± 19.8
		Empagliflozin 25 mg	164	53.3 ± 10.7	50.6	30.6 ± 5.9	–	8.86 ± 1.29	83.1 ± 20.3
Hadjadj, 2016-2 [33]	24 weeks	Empagliflozin 10 mg + metformin 2000 mg	167	52.3 ± 11.3	59.3	30.5 ± 5.0	–	8.65 ± 1.23	83.0 ± 19.1
		Empagliflozin 10 mg	169	53.1 ± 10.7	57.4	30.3 ± 5.2	–	8.62 ± 1.24	83.8 ± 19.8
Rosenstock, 2016 [34]	26 weeks	Canagliflozin 100 mg/Metformin	237	54.2 ± 9.6	45.6	31.9 ± 5.3	2.9 ± 3.3	8.8 ± 1.1	88.3 ± 17.6
		Canagliflozin 100 mg	237	54.0 ± 10.7	44.3	32.4 ± 5.4	3.5 ± 4.4	8.8 ± 1.2	90.2 ± 18.6
Rosenstock, 2016-2 [34]	26 weeks	Canagliflozin 300/Metformin	237	55.4 ± 9.8	48.5	32.8 ± 6.5	3.3 ± 3.9	8.9 ± 1.2	91.4 ± 21.4
		Canagliflozin 300 mg	238	55.8 ± 9.6	52.5	32.6 ± 5.8	3.3 ± 4.4	8.8 ± 1.2	93.0 ± 19.9
DPP-4 inhibitors + TZD initial combination therapy vs. TZD monotherapy									
Rosenstock, 2007 [35]	24 weeks	Vildagliptin + piogglitazone 100/30 mg qd	148	51.0 ± 11.3	58.1	29.6 ± 5.8	2.0 ± 3.1	8.8 ± 1.1	–
		Piogglitazone 30 mg qd	161	52.4 ± 10.3	64.0	28.9 ± 5.5	2.2 ± 3.3	8.7 ± 1.0	–
Rosenstock, 2010 [36]	26 weeks	Alogliptin 25 mg + piogglitazone 30 mg	164	–	–	–	–	8.80 ± 0.962	–
		Pioglitazone 30 mg	163	–	–	–	–	8.76 ± 1.005	–
Yoon, 2011 [37]	24 weeks	Sitagliptin 100 mg + piogglitazone 30 mg	261	50.2 ± 10.2	52.5	29.7 ± 5.1	2.6 ± 4.3	9.5 ± 1.2	80.1 ± 17.4
		Piogglitazone 30 mg	259	51.7 ± 11.2	56.0	29.6 ± 5.2	2.1 ± 3.9	9.5 ± 1.2	80.4 ± 17.8
Yoon, 2012 [38]	54 weeks	Sitagliptin 100 mg + piogglitazone 45 mg	164	51.4 ± 10.0	52.4	29.7 ± 4.8	2.6 ± 4.0	9.4 ± 1.1	81.6 ± 17.4
		Piogglitazone 45 mg	153	52.3 ± 11.5	58.8	29.9 ± 5.3	1.6 ± 3.7	9.4 ± 1.4	81.9 ± 18.4
Gomis, 2011 [39]	24 weeks	Linagliptin 5 mg + pioglitazone 30 mg	259	57.7 ± 9.6	58.7	28.7 ± 4.8	–	8.60 ± 0.79	78.3 ± 15.6
		Pioglitazone 30 mg + placebo	130	57.1 ± 10.1	65.4	29.7 ± 4.8	–	8.58 ± 0.87	82.7 ± 15.8
Henry, 2014 [40]	54 weeks	Sitagliptin 100 mg + pioglitazone 15 mg	193	52.6	50.8	30.7 ± 5.4	4.1 ± 4	8.9 ± 1.2	–
		Pioglitazone 15 mg	183	50.3	65	30.7 ± 5.2	3.7 ± 4.2	8.9 ± 1.0	–

Table 1 continued

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
Henry, 2014–2 [40]	54 weeks	Sitagliptin 100 mg + pioglitazone 30 mg	190	51.1	58.9	31.1 ± 5.8	3.8 ± 3.8	8.7 ± 1.1	–
		Pioglitazone 30 mg	194	51.8	54.1	30.9 ± 5.6	3.9 ± 4.0	8.9 ± 1.1	–
Henry, 2014–3 [40]	54 weeks	Sitagliptin 100 mg + pioglitazone 45 mg	198	53.5	59.6	30.5 ± 4.9	4.0 ± 4.5	8.9 ± 1.1	–
		Pioglitazone 45 mg	188	52.5	50.5	31.2 ± 5.1	3.7 ± 4.0	8.8 ± 1.1	–
DPP-4 inhibitors + TZD initial combination therapy vs. DPP-4 inhibitor monotherapy									
Henry, 2014 [40]	54 weeks	Sitagliptin 100 mg + pio 30 mg	190	51.1	58.9	31.1 ± 5.8	3.8 ± 3.8	8.7 ± 1.1	–
		Sitagliptin 100 mg	186	51	60.2	31.4 ± 5.7	4.5 ± 6.8	8.7 ± 1.2	–
Rosenstock, 2007 [35]	24 weeks	Vildagliptin + piog 100/30 mg qd	148	51.0 ± 11.3	58.1	29.6 ± 5.8	2.0 ± 3.1	8.8 ± 1.1	–
		Vildagliptin 100 mg qd	154	51.4 ± 10.8	63.6	29.4 ± 5.8	1.9 ± 3.1	8.6 ± 1.0	–
Rosenstock, 2010 [36]	26 weeks	Alogliptin 25 mg + piogglitazone 30 mg	164	–	–	–	–	8.80 ± 0.962	–
		Alogliptin 25 mg	164	–	–	–	–	8.80 ± 0.988	–
SU/glinide + AGI initial combination therapy vs. AGI monotherapy									
Tatsumi, 2013 [41]	12 weeks	Miglitol + mitiglinide	21	63.4 ± 8.9	47.6	24.8 ± 0.9	7.6 ± 5.5	7.19 ± 0.50	62.2 ± 2.9
		Miglitol	22	62.9 ± 11.4	68.2	24.9 ± 1.2	7.3 ± 9.3	7.09 ± 0.82	67.7 ± 3.4
SU/glinide + AGI initial combination therapy vs. SU/glinide monotherapy									
Tatsumi, 2013 [41]	12 weeks	Miglitol + mitiglinide	21	63.4 ± 8.9	47.6	24.8 ± 0.9	7.6 ± 5.5	7.19 ± 0.50	62.2 ± 2.9
		Mitiglinide	21	65.4 ± 10.4	42.9	25.2 ± 0.8	6.1 ± 6.2	7.10 ± 0.48	62.7 ± 2.5
SU/glinide + TZD initial combination therapy vs. TZD monotherapy									
Chou, 2008 [42]	28 weeks	Rosiglitazone + glimepiride (8 mg/4 mg)	218	54.9 ± 11.6	59.6	31.8 ± 6.2	2.0 ± 0.30	9.2 ± 1.3	90.2 ± 19.7
		Rosiglitazone	230	53.6 ± 10.7	60.0	31.3 ± 5.8	2.0 ± 0.21	9.1 ± 1.3	88.9 ± 19.8
SU/glinide + TZD initial combination therapy vs. SU/glinide monotherapy									
Chou, 2008 [42]	28 weeks	Rosiglitazone + glimepiride (8 mg/4 mg)	218	54.9 ± 11.6	59.6	31.8 ± 6.2	2.0 ± 0.30	9.2 ± 1.3	90.2 ± 19.7
		Glimepiride	222	53.0 ± 11.0	57.7	31.8 ± 7.2	1.0 ± 0.18	9.0 ± 1.3	91.6 ± 23.6
DPP-4 inhibitors + metformin initial combination therapy vs. TZD monotherapy									
Wainstein, 2012 [43]	32 weeks	Sitagliptin + metformin	261	52.4 ± 10.7	54.8	30.0 ± 6.1	3.2 ± 4.0	9.0 ± 1.3	82.8 ± 21.1
		Pioglitazone	256	52.2 ± 11.0	52.3	29.6 ± 5.5	3.3 ± 3.5	8.9 ± 1.3	81.4 ± 19.9
DPP-4 inhibitors + metformin initial combination therapy vs SU monotherapy									
Amblee, 2016 [44]	12 weeks	Saxagliptin + metformin FDC	50	45.6 ± 7.3	80	34.3 ± 11.3	–	10.9 ± 1.4	–
		Glipizide	50	43.2 ± 10.6	82	34.3 ± 5.8	–	11.1 ± 1.39	–
Colesvelam + metformin initial combination therapy vs. metformin monotherapy									
Rosenstock, 2010 [45]	16 weeks	Colesvelam + metformin	145	52.7 ± 11.5	48	30.6 ± 4.7	–	7.8 ± 1.0	80.8 ± 15.5
		Metformin	141	53.9 ± 10.1	40	29.8 ± 4.4	–	7.5 ± 0.9	77.3 ± 16.2
DPP-4 inhibitors + AGI initial combination therapy vs AGI monotherapy									
Mikada, 2014 [46]	24 weeks	Miglitol + sitagliptin	13	60.5 ± 11.5	53.8	28.3 ± 2.5	7.4 ± 3.1	7.14 ± 0.76	73.8 ± 10.2
		Miglitol	14	58.7 ± 7.0	78.6	29.5 ± 5.5	9.3 ± 5.8	6.90 ± 0.51	81.4 ± 11.2

Table 1 continued

First author, year	Study duration	Treatment groups	No. of patients	Age (years)	Male (%)	Body mass index (kg/m^2)	Duration of diabetes mellitus (years)	Baseline glycated hemoglobin (HbA1c) (%)	Baseline weight (kg)
DPP-4 inhibitors + AGI initial combination therapy vs. DPP-4 inhibitor monotherapy									
Mikada, 2014 [46]	24 weeks	Miglitol + sitagliptin	13	60.5 ± 11.5	53.8	28.3 ± 2.5	7.4 ± 3.1	7.14 ± 0.76	73.8 ± 10.2
		Sitagliptin	14	59.2 ± 11.8	78.6	28.8 ± 2.5	7.6 ± 8.0	7.45 ± 0.93	76.8 ± 11.4
SGLT2 inhibitors + DPP-4 inhibitors initial combination therapy vs SGLT2 inhibitor monotherapy									
Lewin 2015 [47]	24 weeks	Empagliflozin 25 mg + linagliptin 5 mg	134	54.2 ± 10.0	52.2	31.8 ± 5.3	–	7.99 ± 0.95	87.9 ± 18.2
		Empagliflozin 25 mg	133	56.0 ± 9.3	57.9	31.2 ± 5.7	–	7.99 ± 0.97	86.7 ± 19.7
SGLT2 inhibitors + DPP-4 inhibitors initial combination therapy vs. DPP-4 inhibitor monotherapy									
Lewin 2015 [47]	24 weeks	Empagliflozin 25 mg + linagliptin 5 mg	134	54.2 ± 10.0	52.2	31.8 ± 5.3	–	7.99 ± 0.95	87.9 ± 18.2
		Linagliptin 5 mg	133	53.8 ± 11.5	56.4	31.9 ± 5.9	–	8.05 ± 0.89	89.5 ± 20.1
Triple initial combination therapy vs. conventional therapy									
Abdul-Ghani, 2015 [48]	24 months	Metformin + pioglitazone + exenatide	79	47 ± 1	55	36.4 ± 1	0.42 ± 0.06	8.6 ± 0.2	101.6 ± 2.3
		Conventional therapy	91	46 ± 1	62	36.6 ± 1	0.42 ± 0.05	8.6 ± 0.2	101.0 ± 3.4

AGI Alpha-glucosidase inhibitor, *bid* twice daily, *DDT-4* Dipeptidyl peptidase-4, *FDC* fixed-dose combination, *qd* once daily, *SGLT2* sodium glucose cotransporter 2, *SU* sulfonylurea, *tid* three times daily *TZD* thiazolidinedione

baseline HbA1c level (coefficient − 2.98, 95% CI − 5.32 to − 0.63; $p = 0.014$) (ESM Table S4).

Adverse Effects of Initial Combination Therapy

Compared with metformin monotherapy, initial combinations of DPP-4 inhibitors plus metformin did not increase the risks of hypoglycemia, serious adverse effects (SAEs) or gastrointestinal (GI) side effects or the risk of discontinuation due to adverse effects (AEs) or drug-related AEs. When compared with DPP-4 inhibitor monotherapy, initial combinations of DPP-4 inhibitors plus metformin significantly increased the risks of hypoglycemia (RR 1.84; $p = 0.007$) and GI side effects (RR 2.19; $p < 0.001$) and the risk of drug-related AEs (RR, 1.73, $p < 0.001$).

Compared with metformin monotherapy, initial combinations of SU/glinides plus metformin significantly increased the risk of hypoglycemia (RR 8.91; $p = 0.02$). Compared with SU/glinide monotherapy, initial combinations of SU/glinides plus metformin significantly decreased the risk of hypoglycemia (RR 0.63; $p < 0.001$) but increased the risk of GI side effects (RR 1.42; $p = 0.01$).

Compared with metformin monotherapy, initial combinations of TZDs and metformin significantly increased the risk of hypoglycemia (RR 1.60; $p = 0.03$). Compared with TZD monotherapy, initial combinations of TZDs plus metformin did not increase the risks of any AEs.

Compared with metformin monotherapy, initial combinations of SGLT2 inhibitors and metformin significantly increased the risk of drug-related AEs (RR 1.45; $p = 0.004$). Compared with SGLT2 inhibitor monotherapy, initial combinations of SGLT2 inhibitors plus metformin significantly increased the risks of hypoglycemia (RR 2.23; $p = 0.02$) and GI side effects (RR 1.99; $p = 0.002$).

Compared with DPP-4 inhibitor monotherapy or TZD monotherapy, initial combinations of DPP-4 inhibitors plus TZD did not increase any risk of AEs (Table 3).

Table 2 Comparisons of initial combination therapy versus monotherapy in terms of glycemic control and change in body weight

Comparison group	Included studies	No. of patients	WMD	95% CI	*p* value	I^2 (%)	95% CI of I^2
DPP-4 inhibitors + metformin vs. DPP-4 inhibitors							
HbA1c (%)	10	1967/1951	− 0.88	− 0.99, − 0.78	< 0.001	100	0.76, 1.24
FPG (mmol/l)	9	1824/1823	− 1.61	− 1.84, − 1.37	< 0.001	100	0.75, 1.25
PPG (mmol/l)	6	1065/1020	− 2.69	− 3.27, − 2.12	< 0.001	100	0.65, 1.35
Weight (kg)	8	1627/1624	− 1.00	− 1.28, − 0.77	< 0.001	100	0.73, 1.27
DPP-4 inhibitors + metformin vs. metformin							
HbA1c (%)	11	3379/3375	− 0.44	− 0.57, − 0.31	< 0.001	100	0.81, 1.19
FPG (mmol/l)	10	3085/3086	− 0.77	− 1.02, − 0.51	< 0.001	100	0.80, 1.20
PPG (mmol/l)	5	1377/1374	− 1.65	− 2.09, − 1.21	< 0.001	99	0.70, 1.28
Weight (kg)	8	2505/2505	0.38	0.22, 0.54	< 0.001	99	0.77, 1.21
SU/glinide + metformin vs. metformin							
HbA1c (%)	3	425/429	− 0.68	− 0.86, − 0.50	< 0.001	100	0.32, 1.68
FPG (mmol/l)	3	425/429	− 0.87	− 1.38, − 0.36	< 0.001	100	0.32, 1.68
PPG (mmol/l)	3	425/429	− 0.70	− 1.02, − 0.38	< 0.001	99	0.31, 1.67
Weight (kg)	2	336/325	2.60	2.40, 2.80	< 0.001	95	–
SU/glinide + metformin vs. SU/glinide							
HbA1c (%)	3	425/416	− 0.49	− 0.77, − 0.20	< 0.001	100	0.32, 1.68
FPG (mmol/l)	3	425/416	− 0.66	− 1.12, − 0.20	0.005	100	0.32, 1.68
PPG (mmol/l)	3	425/416	− 0.87	− 1.29, − 0.46	< 0.001	100	0.32, 1.68
Weight (kg)	2	336/312	− 0.10	− 0.69, 0.49	0.74	99	–
TZD + metformin vs. metformin							
HbA1c (%)	4	954/970	− 0.44	− 0.68, − 0.19	< 0.001	99	0.50, 1.48
FPG (mmol/l)	4	954/970	− 0.88	− 1.20, − 0.55	< 0.001	100	0.51, 1.49
PPG (mmol/l)	–	–	–	–	–	–	–
Weight (kg)	4	954/970	1.93	1.88, 1.97	< 0.001	40	− 0.09, 0.89
TZD + metformin vs. TZD							
HbA1c (%)	2	356/348	− 0.83	− 0.97, − 0.68	< 0.001	41	–
FPG (mmol/l)	2	356/348	− 1.25	− 1.75, − 0.75	< 0.001	99	–
PPG (mmol/l)	–	–	–	–	–	–	–
Weight (kg)	2	356/348	− 1.22	− 1.89, − 0.55	< 0.001	76	–
SGLT2 inhibitors + metformin vs. metformin							
HbA1c (%)	3	978/974	− 0.47	− 0.58, − 0.37	< 0.001	98	0.30, 1.66
FPG (mmol/l)	2	642/646	− 1.38	− 1.60, − 1.17	< 0.001	99	–
PPG (mmol/l)	–	–	–	–	–	–	–
Weight (kg)	3	978/974	− 2.00	− 2.29, − 1.71	< 0.001	98	0.30, 1.66
SGLT2 inhibitors + metformin vs, SGLT2 inhibitors							
HbA1c (%)	3	978/989	− 0.64	− 0.84, − 0.43	< 0.001	100	0.32, 1.68
FPG (mmol/l)	2	642/646	− 0.83	− 1.05, − 0.61	< 0.001	99	–
PPG (mmol/l)	–	–	–	–	–	–	–
Weight (kg)	3	978/989	− 0.66	− 1.06, − 0.27	< 0.001	99	0.31, 1.67
DPP-4 inhibitors + TZD vs. TZD							
HbA1c (%)	6	1577/1431	− 0.54	− 0.65, − 0.44	< 0.001	99	0.70, 1.28
FPG (mmol/l)	6	1577/1431	− 0.89	− 1.01, − 0.76	< 0.001	97	0.68, 1.26
PPG (mmol/l)	4	842/824	− 1.97	− 2.37, − 1.58	< 0.001	97	0.48, 1.46
Weight (kg)	6	1577/1431	0.96	0.79, 1.14	< 0.001	96	0.67, 1.25

Table 2 continued

Comparison group	Included studies	No. of patients	WMD	95% CI	*p* value	I^2 (%)	95% CI of I^2
DPP-4 inhibitors + TZD vs. DPP-4 inhibitors							
HbA1c (%)	3	502/504	− 0.62	− 0.75, − 0.48	< 0.001	99	0.31, 1.67
I^2 (mmol/l)	3	502/504	− 1.41	− 1.50, − 1.31	< 0.001	90	0.22, 1.58
PPG (mmol/l)	–	–	–	–	–	–	–
Weight (kg)	3	502/504	3.51	2.13, 4.88	< 0.001	100	0.32, 1.68

CI Confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PPG* postprandial plasma glucose, I^2 Higgins I^2 statistics, *WMD* weighted mean difference

Subgroup Analysis and Sensitivity Analysis

The data were further analyzed by stratification by the study time periods. Since most studies were conducted with a 24-week follow-up, therefore, subgroup analyses were made in those studies which reported on a 24-week period of outcomes. These studies showed similar comparison results between initial combination therapy and monotherapy (ESM Table S5). We also included and excluded the study with the longest study duration of 80 weeks [31] for sensitivity analysis and found the results were all similar with the total ones. Moreover, there were several studies including both drug-naïve patients and patients previously on anti-hyperglycemia agents [13, 17, 20, 27, 29, 39, 40], in which the percentage of drug-naïve patients ranged from 50 to 90% (ESM Table S3). We also conducted a sensitivity analysis and found similar results as those for the efficacy and safety evaluations.

DISCUSSION

Montherapy is unlike to achieve glycemic targets in patients with a high baseline HbA1c level (≥ 9%) [2], and in such cases the guidelines of the ADA/EASD recommend that the patient receive initial combination therapy [2]. In terms of "high" baseline HbA1c level, the AACE recommends initial pharmacologic combination treatment in patients with a HbA1c level of > 7.5% [5], and the Canadian Diabetes Association recommends initial combination therapy in patients with a HbA1c level of > 8.5% [49]. Among all sets of guidelines, the justification for initiating combination therapy is that patient would be unlikely to reach the glycemic target with monotherapy. The results of our meta-analysis supports that rationale, with most initial combination therapies—compared with monotherapy—showing superior glucose control in type 2 diabetes patients with an initial HbA1c level of > 7.5% at a similar risk of hypoglycemia.

As previously indicated [50, 51], there are a number of rationales for initial combination therapy in patients with type 2 diabetes. First, such therapy may lead to early robust lowering of HbA1c levels; as demonstrated by our meta-analysis, most initial combination therapies showed superior glucose control compared to monotherapy. Second, initial combination therapy may avoid the clinical inertia associated with a stepwise approach to therapy. The authors of one study suggested that the time to receive additional anti-hyperglycemic medication exceeded 1 year for patients who failed metformin monotherapy and that this delay was associated with clinical inertia [52]. Consequently, initial combination therapy may one of the best options to directly address the causes of clinical inertia [52]. Third, initial combination therapy may improve ß-cell function [50, 51]. However, this finding was not clearly evident in our meta-analysis due to the lack of data. Fourth, the complementary mechanisms of action provided by initial combination therapy may require comparatively lower doses of individual agents and therefore may cause fewer AEs. This benefit was indicated by the results of our meta-analysis which showed that most initial combination therapies exhibited better glucose control with comparable risks of hypoglycemia, SAEs, discontinuation due to AEs and GI side effects. Fifth, initial combination therapy may avoid the long-term consequences of

Table 3 Comparisons of initial combination therapy versus monotherapy in terms of the risks of hypoglycemia and other adverse effects

Comparison group	No. of patients	Relative risk	95% CI	*p* value	I^2 (%)	95% CI of I^2
DPP-4 inhibitors + metformin vs. DPP-4 inhibitors						
AE	1967/1951	1.07	0.94, 1.22	0.29	0	− 0.24, 0.24
Drug-related AE	1514/1489	1.73	1.39, 2.16	< 0.001	2	− 0.25, 0.29
Hypoglycemia	1824/1823	1.84	1.19, 2.85	0.007	27	0.02, 0.52
GI adverse effects	1584/1591	2.19	1.48, 3.23	< 0.001	62	0.33, 0.91
SAE	1742/1746	0.70	0.45, 1.08	0.11	42	0.15, 0.69
Discontinuation due to AE	1584/1591	0.77	0.48, 1.24	0.29	12	− 0.17, 0.41
DPP-4 inhibitors + metformin vs. metformin						
AE	3379/3375	0.92	0.83, 1.01	0.09	0	− 0.19, 0.19
Drug-related AE	2926/2920	0.97	0.84, 1.11	0.63	0	− 0.20, 0.20
Hypoglycemia	3379/3375	1.15	0.84, 1.55	0.38	17	− 0.02, 0.36
GI adverse effects	2996/2989	0.91	0.80, 1.04	0.17	0	− 0.21, 0.21
SAE	3154/3150	0.71	0.50, 1.01	0.05	0	− 0.20, 0.20
Discontinuation due to AE	2996/2989	0.88	0.63, 1.22	0.44	0	− 0.21, 0.21
SU/glinide + metformin vs.metformin						
AE	425/429	1.26	0.90, 1.76	0.17	0	− 0.68, 0.68
Hypoglycemia	425/429	8.91	1.46, 54.34	0.02	76	0.08, 1.44
GI adverse effects	425/429	0.70	0.48, 1.01	0.06	65	− 0.03, 1.33
SAE	–	–	–	–	–	–
Discontinuation due to AE	–	–	–	–	–	–
SU/glinide + metformin vs. SU/glinide						
AE	425/416	0.98	0.70, 1.37	0.92	0	− 0.68, 0.68
Hypoglycemia	425/416	0.63	0.48, 0.82	< 0.001	93	0.25, 1.61
GI adverse effects	425/416	1.42	1.08,1.88	0.01	25	− 0.43, 0.93
SAE	–	–	–	–	–	–
Discontinuation due to AE	–	–	–	–	–	–
TZD + metformin vs.metformin						
AE	954/970	1.06	0.88, 1.28	0.55	0	− 0.49, 0.49
Hypoglycemia	954/970	1.60	1.05, 2.46	0.03	0	− 0.49, 0.49
GI adverse effects	954/970	0.87	0.75, 1.01	0.07	0	− 0.49, 0.49
SAE	954/970	0.98	0.65, 1.47	0.91	0	− 0.49, 0.49
Discontinuation due to AE	954/970	1.06	0.72, 1.56	0.76	0	− 0.49, 0.49
TZD + metformin vs. TZD						
AE	356/348	1.31	0.97, 1.76	0.08	84	–
Hypoglycemia	356/348	1.53	0.80, 2.91	0.20	0	–
GI adverse effects	–	–	–	–	–	–
SAE	356/348	0.87	0.32, 2.37	0.79	0	–
Discontinuation due to AE	–	–	–	–	–	–
SGLT2 inhibitors + metformin vs. metformin						
AE	978/974	1.19	0.99, 1.43	0.06	3	− 0.37, 0.43
Drug-related AE	978/974	1.45	1.12, 1.87	0.004	0	− 0.40, 0.40
Hypoglycemia	642/646	1.37	0.64, 2.92	0.42	17	− 0.51, 0.85
GI adverse effects	978/974	0.72	0.40, 1.07	0.25	73	0.33, 1.13
SAE	978/974	0.84	0.43, 1.65	0.62	0	− 0.49, 0.49
Discontinuation due to AE	978/974	0.82	0.47, 1.41	0.46	0	− 0.40, 0.40
SGLT2 inhibitors + metformin vs. SGLT2 inhibitors						

Table 3 continued

Comparison group	No. of patients	Relative risk	95% CI	*p* value	I^2 (%)	95% CI of I^2
AE	1220/1236	1.16	0.99, 1.37	0.07	52	0.12, 0.92
Drug-related AE	1220/1236	1.13	0.90, 1.42	0.31	68	0.28, 1.08
Hypoglycemia	642/646	2.23	1.13, 4.41	0.02	27	− 0.41, 0.95
GI adverse effects	978/989	1.99	1.39, 2.86	0.002	0	− 0.40, 0.40
SAE	978/989	0.62	0.33, 1.16	0.13	0	− 0.40, 0.40
Discontinuation due to AE	978/989	0.83	0.48, 1.43	0.50	0	− 0.40, 0.40
DPP-4 inhibitors + TZD vs. TZD						
AE	1154/1138	0.94	0.80, 1.12	0.50	0	− 0.35, 0.35
Drug-related AE	1265/1107	1.06	0.79, 1.41	0.70	0	− 0.35, 0.35
Hypoglycemia	1413/1268	1.08	0.77, 1.53	0.65	0	− 0.31, 0.31
GI adverse effects	1265/1107	0.86	0.56, 1.33	0.50	25	− 0.10, 0.60
SAE	1170/1140	1.31	0.85, .2.01	0.22	0	− 0.35, 0.35
Discontinuation due to AE	1006/977	0.80	0.47, 1.38	0.42	3	− 0.37, 0.43
DPP-4 inhibitors + TZD vs. DPP-4 inhibitors						
AE	502/504	1.09	0.85, 1.40	0.50	45	− 0.68, 0.68
Drug-related AE	350/354	1.40	0.92, 2.15	0.12	17	–
Hypoglycemia	350/354	0.84	0.46, 1.53	0.57	0	–
GI adverse effects	–	–	–	–	–	–
SAE	350/354	1.31	0.66, 2.59	0.44	78	–
Discontinuation due to AE	–	–	–	–	–	–

AE Adverse effect, *GI* gastrointestinal, *SAE* serious adverse effect

metabolic memory, as the initial use of combination therapy could lead to greater HbA1c reduction, enabling more individuals to achieve their glycemic goals while avoiding AEs stemming from multiple metabolic defects [51, 53, 54]. However, this latter potential benefit may not be concluded from the present meta-analysis because most of the studies included were of short-term duration.

The evidence is compelling that type 2 diabetes is a progressive, physiologically and genetically complex heterogeneous disease. Achieving glycemic control is necessary to prevent or delay the progression of vascular complications. As current treatment approaches do not adequately acknowledge the complexity of diabetes, a compelling case may be made for combination treatment [51]. Initial combination therapy may be required to address the complex pathophysiology of type 2 diabetes, which includes improving insulin secretion and insulin sensitivity, inhibiting hepatic glucose production and addressing delayed gastric emptying or glucose absorption, while focusing on satiety and renal glucosuria. Among the mechanisms of hypoglycemic agents [55], metformin inhibits hepatic gluconeogenesis and improves peripheral insulin sensitivity, SUs/glinides stimulate insulin secretion by β-cells, DPP-4 inhibitors stimulate insulin secretion and suppress glucagon secretion, SGLT2 inhibitors reduce renal glucose reabsorption and induce urinary glucose excretion, TZDs activate peroxisome proliferator-activated receptor gamma (PPAR-γ) and increase insulin sensitivity. Therefore, choices for initial combinations of the above agents should also be supported by the pathophysiology of type 2 diabetes.

However, a number of unresolved issues associated with initial combination therapy in type 2 diabetes patients remain. One of these is whether initial combination therapy improve adherence. To date, there is no evidence suggesting that initial combination therapy versus monotherapy or sequential titration therapy would result in a greater adherence of patients to the therapeutic regimen. However, published studies do show that the more complex the

drug regimen, the lower the adherence to that regimen [56]. In our meta-analysis, we did not collect any data on a possible improvement in adherence. Another issue is cost; is initial combination therapy less costly? The relatively high cost of including novel agents, such as DPP-4 inhibitors or SGLT2 inhibitors, in an initial combination with metformin remains a significant barrier to their use in many regions of the world [51]. Several studies have estimated the cost-effectiveness associated with monotherapy compared to combination therapy with oral anti-diabetes agents, but a number of these these were derived from non-RCT data and had multiple confounders [57, 58]. Moreover, the authors of another study indicated that it was difficult to quantify the cost-effectiveness of softer outcomes such as fewer hypoglycemic events or improved quality of life [59]. We did not collect any data on the costs of initial combination therapy in our meta-analysis, but there are other economic models which could be used to answer this question. Moreover, the association between initial combination therapy and cardiovascular risk has not been fully examined in the literature. Gaps still exist in the evidence on treatment paradigms utilizing sequential versus initial combination therapy. Therefore, carefully designed, pragmatic, prospective real-world studies to assess the clinical effectiveness of initial combinations versus sequential treatment in patients with newly diagnosed or poorly controlled type 2 diabetes should be performed to provide more evidence.

There were several limitations to our meta-analysis. First, data from the separate studies covered different durations of the study. As previously indicated, RRs are sensitive to the length of the follow-up; consequently, the pooling of results from studies with different durations of follow-up might lead to an artificial heterogeneity and discrepancy in the meta-analyses [60]. We therefore explored the outcomes in subgroup analyses by pooling all of the studies with a study period of 24 weeks to conduct a sensitivity analysis, which showed similar results with the total results. Second, the definitions of treatment-naïve patients varied depending on the protocols of the trials included in our meta-analysis, and these differences may also be associated with the high heterogeneity of this study and also lower the ability of the authors of this study to propose solid conclusions. Therefore, we also conducted a sensitivity analysis to minimize the bias and found the similar results to the efficacy and safety evaluations. The large differences in the number of studies for several combinations is another limitation. For those treatment groups with only one trial included [41–48], no further meta-analysis was done for evaluation purposes. Another problem may be the variations in dosages used in the different studies. Therefore, the standard doses recommended and approved in the clinical practice were used in this meta-analysis to minimize the bias. Since baseline characteristics were variable across studies, we used the random-effects model for analysis when the level of heterogeneity was high. Given these factors, we suggest that our results be interpreted cautiously.

CONCLUSIONS

In conclusion, compared with monotherapy, all initial combination therapies resulted in significantly reduced HbA1c levels in treatment-naïve type 2 diabetes patients. Compared with metformin monotherapy, the initial combination therapies of DPP-4 inhibitors plus metformin and SGLT2 inhibitors plus metformin exhibited similar risks of hypoglycemia, but the initial combination therapies of SU plus metformin and TZD plus metformin exhibited higher risks of hypoglycemia.

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