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REVIEW

Comparative Effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison

Paul Craddy · Hannah-Jayne Palin · K. Ian Johnson

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ABSTRACT

Objective: To compare the safety and efficacy of the dipeptidylpeptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes and inadequate glycemic control.

Design: Systematic review of randomized controlled trials (RCTs), health economic evaluation studies, systematic reviews, and meta-analyses, followed by primary Bayesian mixed treatment comparison meta-analyses (MTCs), and secondary frequentist direct-comparison meta-analyses using a random-effects model. Outcomes were reported as weighted mean change from baseline, or odds ratio (OR) with 95% credible interval.

Data sources: MEDLINE, MEDLINE In-Process, EMBASE, and BIOSIS via Dialog ProQuest; Cochrane Central Register of Controlled Trials

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P. Craddy
Takeda Pharmaceuticals International GmbH,
Zurich, Switzerland

H.-J. Palin · K. I. Johnson (✉)
McCann Complete Medical, Macclesfield, UK
e-mail: ian.johnson@complete-grp.com

and Cochrane Database of Systematic Reviews via EBSCO; four diabetes and two technical congress abstracts; and health technology assessment organization websites.

Eligibility criteria: Patients with type 2 diabetes and inadequate glycemic control receiving any pharmacological anti-diabetic treatment.

Data extraction and analysis: Title/abstracts were reviewed for eligibility, followed by full-text review of publications remaining after first pass. A three-person team filtered articles and an independent reviewer checked a random selection (10%) of filtered articles. Data extraction and quality assessment of studies were also independently reviewed. Five DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin) were compared via meta-analysis (where data were available) as monotherapy, dual therapy (plus metformin, sulfonylurea, pioglitazone, or insulin), and triple therapy (plus metformin/sulfonylurea).

Results: The review identified 6,601 articles; 163 met inclusion criteria and 85 publications from 83 RCTs contained sufficient or appropriate data for analysis. MTCs demonstrated no differences between DPP-4 inhibitors in mean change from baseline in

glycosylated hemoglobin (HbA_{1c}) or body weight, or the proportions of patients achieving HbA_{1c} <7% or experiencing a hypoglycemic event, apart from in patients on alogliptin plus metformin, who achieved HbA_{1c} <7% more frequently than those treated with saxagliptin plus metformin [OR 6.41 (95% CI 3.15–11.98) versus 2.17 (95% CI 1.56–2.95)].

Conclusions: This systematic review and MTC showed similar efficacy and safety for DPP-4 inhibitors as treatment for type 2 diabetes, either as monotherapy or combination therapy.

Keywords: Alogliptin; DPP-4 inhibitor; Glycosylated hemoglobin; Linagliptin; Mixed treatment comparison; Saxagliptin; Sitagliptin; Type 2 diabetes mellitus; Vildagliptin

INTRODUCTION

Dipeptidylpeptidase-4 (DPP-4) inhibitors have a mechanism of action that is distinct from other oral glucose-lowering agents [1]. The DPP-4 inhibitor class of oral anti-diabetic agents selectively inhibits the DPP-4 enzyme that rapidly degrades two major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide [2].

Scheen [2] reviewed DPP-4 inhibitors in 2011, analyzing the similarities and differences among members of the DPP-4 inhibitor class of oral anti-diabetic agents, including their efficacy and safety profiles as monotherapy or in combination with metformin, a sulfonylurea (SU) and/or a thiazolidinedione, and insulin. The review demonstrated that, although DPP-4 inhibitors produce a similar reduction in glycosylated hemoglobin (HbA_{1c}) levels compared with other existing classes of oral glucose-lowering agents, DPP-4 inhibitors offer several clinical advantages [3]. These include negligible risk of hypoglycemia, much lower than that observed

with SUs, and weight neutrality, compared with the weight gain that is generally associated with SUs and thiazolidinediones [2].

Previous indirect comparisons of the DPP-4 inhibitors in several published meta-analyses [4–8] have reported little or no difference between them with regard to efficacy, both as monotherapy and in combination with other anti-diabetic drugs, and the overall safety profile [2]. However, there are several important differences between the DPP-4 inhibitors with regard to their absorption, distribution, metabolism, and elimination, as well as potency and duration of action [2]. These differences may, potentially, be clinically relevant, particularly in patients with renal or hepatic impairment, and in patients receiving combination therapy, especially those with cardiovascular disease taking multiple drugs [2, 9]. However, there is a lack of head-to-head clinical trials comparing DPP-4 inhibitors: a single clinical trial was identified in the Scheen review [2]. This 18-week trial compared the efficacy of saxagliptin 5 mg and sitagliptin 100 mg in combination with metformin in patients with type 2 diabetes inadequately controlled with metformin alone [10]. The between-group adjusted mean change from baseline in HbA_{1c} demonstrated no difference between saxagliptin and sitagliptin.

Esposito et al. [5] conducted a systematic review and meta-analysis of indirect comparisons of the DPP-4 inhibitors vildagliptin, sitagliptin, saxagliptin, and alogliptin in 2011. The primary outcome of the analysis was the proportion of patients achieving an HbA_{1c} level <7%, with the absolute change from baseline in HbA_{1c}, proportion of patients with hypoglycemic events, and change from baseline in body weight as secondary outcomes. The systematic review of published literature identified no randomized controlled trials (RCTs) with the

DPP-4 inhibitor linagliptin and was limited to trials published up until September 2010. Separate meta-analyses were conducted for each DPP-4 inhibitor compared with placebo and other anti-diabetic agents (including metformin, SUs, pioglitazone, and rosiglitazone) for each of the outcomes.

We have conducted a similar review of DPP-4 inhibitors; as monotherapy compared with placebo, and as dual or triple therapy (where data were available) compared with metformin, SUs, metformin plus SU, pioglitazone, and insulin. Included studies were identified for *all* pharmacologic therapies for type 2 diabetes. Following this wider review, we extracted data from RCTs in patients treated with a DPP-4 inhibitor and conducted mixed treatment comparison meta-analyses (MTCs) to demonstrate the relative treatment effects of each DPP-4 inhibitor compared with a common comparator, assessing the same four outcomes as reported by Esposito et al. [5].

The aim of the MTCs was to test the hypothesis of no difference between the DPP-4 inhibitors with regard to glycemic control [mean HbA_{1c} change from baseline, proportion of patients achieving target HbA_{1c} (<7%)], number of patients with hypoglycemic events, and mean change from baseline in body weight.

METHODS

The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Systematic Literature Search

We conducted a systematic review of published literature to assess the comparative efficacy and

safety of DPP-4 inhibitors compared to other oral and injectable anti-diabetic pharmacologic interventions, including insulin, in the treatment of patients with type 2 diabetes who were receiving monotherapy, dual, or triple therapy. The research question and eligibility criteria for this systematic review conformed to the following PICOS description [11]; studies meeting these criteria were considered for inclusion:

- Population: patients of any age or sex with type 2 diabetes and insufficient glycemic control (including first-, second-, and third-line treatment regimens).
- Intervention: any DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin), GLP-1 or sodium-glucose co-transporter 2 inhibitors, or pioglitazone used in the treatment of type 2 diabetes (as monotherapy, dual or triple therapy).
- Comparator: any pharmacologic anti-diabetic treatment, placebo, or standard of care for diabetes.
- Outcome(s): HbA_{1c} (mean change from baseline and proportion of patients achieving HbA_{1c} target), fasting plasma glucose (FPG), low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, body weight, and hypoglycemia and serious adverse events.
- Study type(s): blinded and open-label RCTs, health economic evaluation studies, systematic reviews, and meta-analyses. Observational studies and retrospective analyses were not included.

Please note that this article focuses on analyses of DPP-4 inhibitors for the following outcomes: mean change in HbA_{1c} from baseline, proportion of patients achieving HbA_{1c} <7%, mean change from baseline in body weight, and number of patients experiencing a hypoglycemic event.

Published RCTs, health economic evaluation studies, systematic reviews, and meta-analyses, were identified from a systematic search of electronic databases with no publication date or language restrictions applied. Databases were searched via Dialog ProQuest [12] [MEDLINE and MEDLINE In-Process; EMBASE and BIOSIS for conference abstracts (limited to the previous 3 years)] and EBSCO [13] (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews), NHS Economic Evaluation Database [14], and Health Economic Evaluations Databases [15] for systematic reviews of health economic outcomes. All electronic databases were searched on November 30, 2012. Reference lists of selected systematic reviews and meta-analyses meeting the inclusion criteria were reviewed to identify further studies, including unpublished studies. ‘Grey literature’ searches were also conducted of relevant congresses (American Diabetes Association [16], European Association for the Study of Diabetes [17], International Diabetes Federation [18], Canadian Diabetes Association [19], Health Technology Assessment (HTA) International [20] and International Society for Pharmacoeconomics and Outcomes Research [21]), limited to the previous 3 years. Other appropriate sources searched included the ClinicalTrials.gov website of the US National Institutes of Health [22], and HTA databases including those from the International Network of Agencies for Health Technology Assessment [23], National Institute for Health and Care Excellence (NICE) [24], National Institute for Health Research [25], and Canadian Agency for Drugs and Technologies in Health [26]. A structured search string was employed, including terms for type 2/non-insulin dependent diabetes mellitus and drug therapy. Specific filters for retrieving RCTs conducted in

humans, meta-analyses, systematic reviews, and health economic evaluation studies were incorporated into the search string. The full search string is presented in Appendix 1 (Electronic Supplementary Material).

Any abstracts associated with full-text articles were identified. If more than one article presented data from the same study population, only data from the most recent full-text publication were included. If a conference abstract superseded a full-text publication, data from outcomes presented in the conference abstract that were not included in the full-text publication were utilized.

Study Selection

Identified articles were screened to ensure they met predetermined inclusion criteria. Each reviewer was provided with a checklist based on the inclusion/exclusion criteria specified in the systematic review protocol (Commercial in confidence), and a structured Microsoft Excel (Microsoft Corp, Redmond, WA, USA) spreadsheet was used to ensure uniformity of appraisal for each study. Initially, titles or abstracts (or both) of all identified citations were reviewed according to a first-pass checklist. Full-text publications of the citations remaining after the first pass were then reviewed according to a second-pass checklist. A three-person team reviewed the articles at first and second pass, and an independent reviewer checked a random selection (10%) of filtered articles for consistency.

A positive exclusion method was used, whereby studies for which there were insufficient information for exclusion remained in the review until a stage where it could be proven that they did not meet the inclusion criteria.

Although the systematic review included all pharmacologic treatments for type 2 diabetes,

in this paper we report only the analyses of DPP-4 inhibitors.

Data Extraction

The Microsoft Excel spreadsheet designed to ensure uniformity of appraisal was subsequently used to capture all relevant data for included studies. All data extracted for meta-analysis were also independently reviewed and reviewers came to a consensus regarding the final data recorded for each study. Data input sheets for the meta-analyses, including data imputations, were also checked for accuracy by a second reviewer prior to conducting the analyses. Extracted data consisted of study characteristics [such as study design, duration, primary and secondary endpoints, study inclusion and exclusion criteria, treatment and dose (including schedule and strategy), and patient baseline characteristics (age, comorbidities, renal impairment, cardiovascular risk, concomitant medications, and disease duration)]. Extracted data were grouped such that information for different treatment regimens could be easily identified.

Assessment of Data for Meta-analysis

Studies were assessed to establish whether sufficient and appropriate data were reported for the relevant outcomes. Studies were excluded based on the following criteria: article reported extension phase of an RCT already included; lack of common comparator (i.e., no connection within treatment network); inappropriate patient population (e.g., patients with adequate glycemic control, mixed population with type 1 diabetes); insufficient data for standard error imputation (i.e., patient numbers not given); cross-over study; and duplicate data.

Quality Assessment

Studies from which data were extracted were assessed for robustness as sources of information for inclusion in subsequent statistical analyses. Quality assessment was conducted according to the methods and assessment instruments recommended by the HTA authorities in France, Germany, Italy, Spain, UK, USA, and Canada. Hierarchical assessment of the risk of bias was conducted as recommended by the Institute for Quality and Efficiency in Health Care (Germany) in their guidelines on methods for conducting systematic reviews [27], checklist criteria recommended by l'Agence nationale d'accréditation et d'évaluation en santé (France) in their guide to the literature and grading of recommendations [28], and quality-assessment criteria recommended by NICE (UK) in their single technology appraisal template [29]. Study quality was also independently reviewed. Clinical trials were also evaluated to assess whether they had been reported according to the Consolidated Standards of Reporting Trials [30] checklist. Study quality was not used as an inclusion/exclusion criterion or to weight individual studies in the meta-analyses.

Data Imputation

Where studies did not explicitly report standard errors, these were derived from available published information. If possible, standard errors were obtained from confidence intervals (CIs) and standard deviations (SDs); if these data were unavailable, they were derived from the *p* value referring to the change from baseline. If none of the above was available, standard errors were imputed using data from other well-reported studies, using methods outlined by

the Cochrane Collaboration [31]. Alternatively, as a final option, if there was no other well-reported study, p values for the difference between treatments were used and the pooled SD applied to both arms. Mean changes from baseline values were derived by subtracting before and after values, if not explicitly stated.

Quantitative Analysis

Direct evidence was assessed by conducting random-effects meta-analyses in a frequentist setting in Stata (Version 12; StataCorp, College Station, TX, USA) for each DPP-4 inhibitor (as monotherapy, dual and triple therapy) against common comparator arms. In studies reporting results for multiple DPP-4 inhibitor doses, only data related to the licensed dose were included in the analysis. Data were presented as the effect estimate and 95% CI. Heterogeneity was assessed using the I^2 statistic, i.e., the percentage of the variability in effect estimates due to heterogeneity rather than sampling error. Interpretation of the I^2 statistic was in accordance with the Cochrane Collaboration recommendations [31]. For direct comparisons that reported I^2 values $>30\%$, sensitivity analyses were considered and were conducted where outliers were identified to assess robustness of the pooled effect estimate.

Mixed treatment comparison meta-analyses were also performed to demonstrate the relative treatment effects of each DPP-4 inhibitor (as monotherapy, dual or triple therapy) using a Bayesian framework and Markov chain Monte Carlo methods, which were fitted using the Bayesian software in WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, UK) [32]. This allowed for direct evidence (within-trial comparisons between treatments) and indirect evidence (treatments

within different trials with a common comparator) to be considered simultaneously.

Typically, models consisted of 100,000 iterations with a 50% burn-in sample. Standard diagnostics tools were used to assess convergence to the stationary distribution. This included observing random walk plots for each node and assessment of the Gelman–Rubin diagnostic statistic. The rejection sampler followed the standard hierarchy of sampling methods in the WinBUGS program [32]. Initial values were generated randomly for different chains to assess the robustness of different starting values. Random-effects models were utilized to account for heterogeneity from varying study populations.

Mean changes from baseline in HbA_{1c} and body weight outcomes are both continuous measures. These were estimated using a vague prior normal distribution, allowing the data to have maximum leverage over the iterative process. Data were presented as a weighted mean difference between treatments. Proportions of patients with HbA_{1c} $<7\%$ and hypoglycemic-event outcome measures are binomial (the outcome is either achieved or not). For this type of data, the probability of the outcome was modeled using a binomial distribution. Each pair of treatments was compared by estimating the odds ratio (OR) of the outcome. Each study within each random-effects meta-analysis had a weight based on the within-study variation. It was assumed that each log OR had been sampled from a normal distribution and that the treatment effects were wholly exchangeable within studies.

Data for all DPP-4 inhibitor and comparator doses were included in the analyses for studies that reported multiple doses. All data were presented as an effect estimate and 95% credible interval, with 95% credible intervals

Table 1 Comparator meta-analysis estimates of treatment effect for input into the calculation of absolute treatment effect

Comparator	Comparator estimate treatment effect mean (standard error)
Placebo	0.18 (0.06)
Metformin	−0.421 (0.02)
Sulfonylurea	−0.065 (0.036)
Metformin plus sulfonylurea	−0.033 (0.038)
Pioglitazone	−0.657 (0.032)
Insulin	−0.155 (0.069)

that did not include zero deemed statistically significant. Overlapping 95% credible intervals were considered as evidence of no difference between treatments.

Mixed treatment comparison meta-analyses were conducted for absolute and relative (vs. comparator) treatment effects. Absolute treatment-effect calculations required an estimate for the efficacy of the comparator arm to be entered into the MTC. Direct-comparison meta-analyses were conducted to obtain more accurate estimates of the comparator treatment effects (see Table 1).

Consistency Between Direct and Indirect Data

The consistency of direct and indirect comparisons was assessed for nodes comparing DPP-4 inhibitors directly. A single study reported direct comparison data of two DPP-4 inhibitors (sitagliptin and saxagliptin) plus metformin. Thus, consistency tests assessing the relationship between sitagliptin plus metformin and saxagliptin plus metformin for mean change from baseline HbA_{1c} and proportion of patients achieving HbA_{1c} <7% were conducted using Bucher's extended

method for multiple loops [33]. Bucher's method for multiple loops combines direct and indirect evidence for multiple pathways and these multiple loops construct a χ^2 test statistic. The p value attained from the calculated χ^2 statistic gives the probability of observing a test statistic at least as extreme as the calculated value, given the null hypothesis of consistency between direct and indirect evidence is true. If this p value is <0.01, typically, this hypothesis is rejected [33].

RESULTS

Data Selection

Figure 1 shows the selection process for articles in the systematic review and meta-analyses. Seventy-eight studies were excluded since they were deemed to contain insufficient or inappropriate data based upon criteria described in the "Methods" [see Appendix 2 for a listing (Electronic Supplementary Material)].

Sixty non-English articles proceeded to second pass, of which only two reported results of an RCT with a DPP-4 inhibitor. Both of these articles included the DPP-4 inhibitor, anagliptin, which is only licensed in Japan and was only reported in these two articles. Thus, it was not eligible for inclusion in the mixed treatment comparison network and was excluded from the analysis.

Characteristics of Included Studies

Appendix 3 (Electronic Supplementary Material) provides details of the 83 RCTs included. Of these, 82 compared DPP-4 inhibitor treatment regimens with placebo, metformin (\pm SU, pioglitazone or insulin), SU, pioglitazone, or insulin, while one directly compared sitagliptin plus metformin with saxagliptin plus

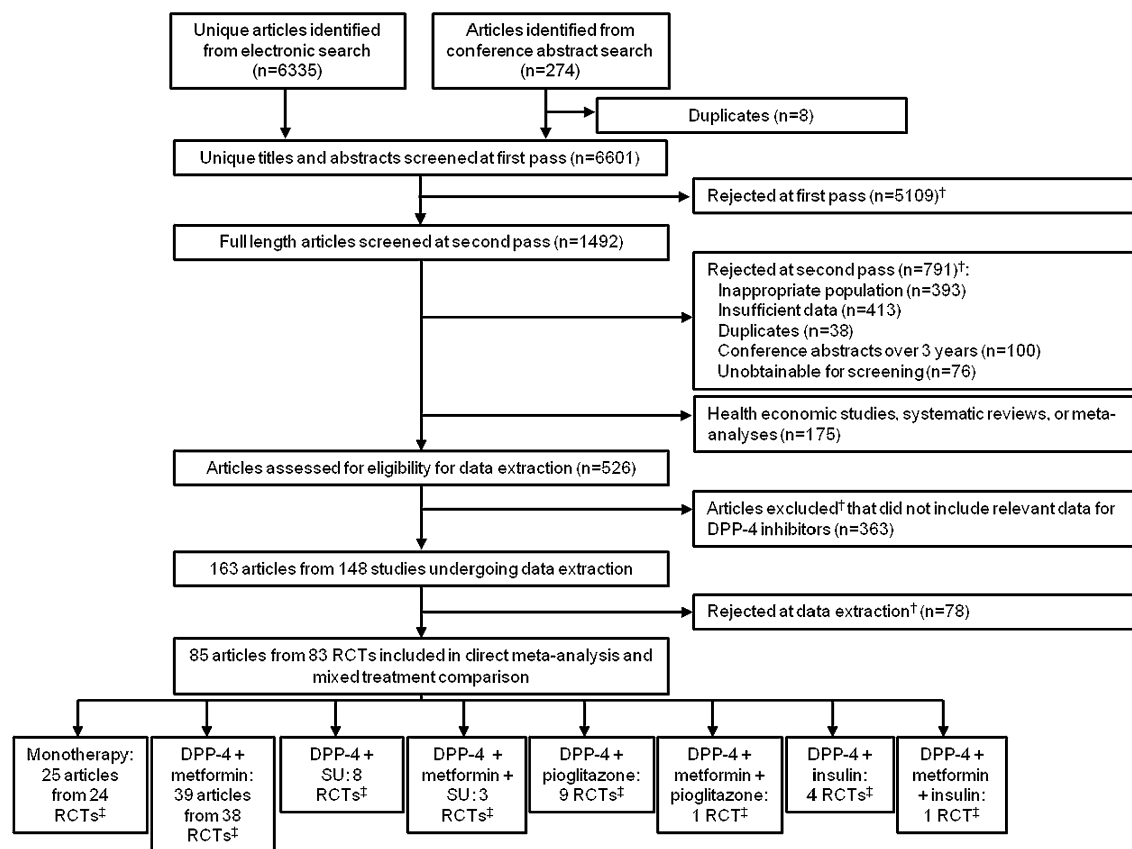


Fig. 1 Number of articles proceeding at each stage of the systematic review. †Articles excluded for more than one reason. ‡Number of RCTs does not add up to 83 as each

RCT could be used in multiple sets of analyses. *DPP-4* dipeptidylpeptidase-4 inhibitor, *RCT* randomized controlled trial, *SU* sulfonylurea

metformin [10]. All RCTs were included in at least one of the analyses; each RCT could be used in multiple sets of analyses.

Quality assessment of studies for which data were extracted (Appendix 4, Electronic Supplementary Material) indicated two studies that represented high-quality or robust sources of information [34, 35], as they were deemed to be of high quality by all quality-assessment criteria. However, it is worth noting that the majority of studies from which data were extracted and subsequently included in the statistical analyses were deemed to have three or fewer ‘unclear’ ratings, which could potentially indicate that the level of reporting was not sufficient to determine an accurate

assessment of robustness. Ten studies were assessed as representing low-quality or non-robust sources of information [36–46]; however, all were deemed to have two or more ‘unclear’ ratings and only a single study [40] was included in the subsequent statistical analysis.

The majority of RCTs were double blind. However, five articles reported data from open-label RCTs [36, 47–50]. Trial durations varied widely—from 4 weeks to 104 weeks. Two studies included an initial 12-week randomization stage followed by a 40-week extension [34, 51].

Inclusion criteria for the majority of trials included baseline HbA_{1c} levels of 6.0–11.0%. However, a number of trials included patients with higher baseline HbA_{1c} levels, which might

have resulted in greater HbA_{1c} reductions during the study. Indeed, baseline HbA_{1c} levels reported by Pfützner et al. [52] were 8.0–12.0%, Derosa et al. [53] >8.0%, Pérez-Monteverde et al. [54] 7.5–12.0%, Wainstein et al. [55] 7.5–12.0%, Jadzinsky et al. [56] 8.0–12.0%, and Yoon et al. [57] 8.0–12.0%. The majority of trials included patients with body mass index (BMI) ≤ 40 kg/m². However, 7 trials included patients with a lower maximum baseline BMI [53, 58–63] and 18 trials included patients with a higher maximum baseline BMI [35, 47, 48, 64–78]. Increased BMI outside the normal range (BMI 18.5–25.0 kg/m²; healthy weight), as classified by the World Health Organization [79], is associated with type 2 diabetes and comorbid conditions including hypertension and dyslipidemia. The mean age of patients was similar between studies, apart from four studies [63, 73, 80, 81], in which the mean age of patients was ≥ 65 years. Elderly patients may have many comorbid conditions or functional disabilities and may take multiple additional medications (polypharmacy).

In the majority of trials, the primary outcome was mean change in HbA_{1c} from baseline to endpoint. However, eight trials reported co-primary outcomes to HbA_{1c} change from baseline [54, 59, 62, 64, 82–85], such as change from baseline in FPG, 2-hour postprandial glucose, BMI, body weight, fasting lipids, fasting plasma insulin, fasting insulin, fasting C-peptide, vital signs, and number/proportion of patients with adverse events, homeostatic model assessment-insulin resistance (β -cell function), and proportion of patients achieving HbA_{1c} <7%. In five trials, HbA_{1c} change from baseline was not the primary outcome [36, 53, 68, 86, 87]. Instead, the primary outcome was another blood glucose measure (e.g., postprandial blood glucose and change from baseline in 24-h weighted mean glucose), postprandial GLP-1 response, change in

insulin secretion at endpoint, or change from baseline in postprandial incremental analytical ultracentrifugation for total plasma triglycerides.

Direct-comparison Meta-analyses and Mixed Treatment Comparisons

The quantitative analyses investigated the difference between treatments in the mean change from baseline HbA_{1c}, OR for proportion of patients achieving HbA_{1c} target (<7%), mean change from baseline in body weight, and OR for the number of patients reporting a hypoglycemic event.

First, the direct evidence was assessed by conducting random-effects meta-analyses for each DPP-4 inhibitor (as monotherapy, dual or triple therapy) against placebo, metformin, SU, metformin plus SU, pioglitazone, metformin plus pioglitazone, insulin, and metformin plus insulin. MTCs were then developed from the network of DPP-4 inhibitor trials identified in the systematic review. Eligible network comparisons for HbA_{1c} mean change from baseline for DPP-4 inhibitors (as monotherapy, dual or triple therapy) are presented in Fig. 2. As an example, we have presented the networks for HbA_{1c} mean change from baseline in this paper as these represent the most complex treatment networks and include the majority of trials (networks for the proportion of patients achieving HbA_{1c} level <7%, mean change from baseline in body weight, and proportion of patients experiencing a hypoglycemic event are available on request).

Individual study data for each of the four outcomes analyzed in the meta-analyses are summarized in Table 2 [10, 34–36, 40, 47–127].

Direct-comparison meta-analysis results are presented in Tables 3 and 4 for continuous and binominal outcomes, respectively. Results of the relative and absolute treatment effects in the MTCs are presented in Tables 5 and 6, respectively.

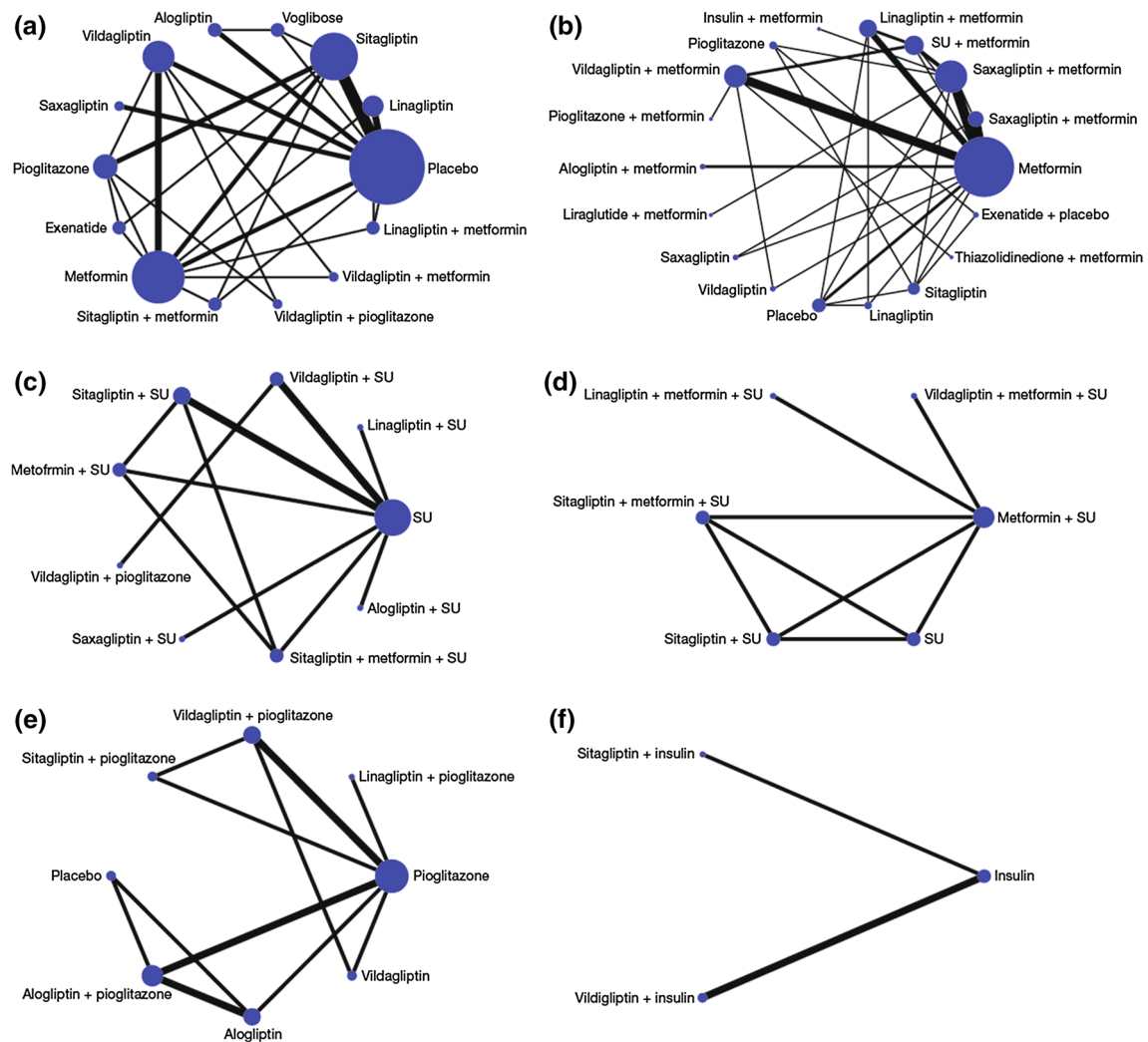


Fig. 2 Networks of eligible comparisons for HbA_{1c} mean change from baseline for **a** DPP-4 monotherapy, **b** DPP-4 plus metformin, **c** DPP-4 plus SU, **d** DPP-4 plus metformin plus SU, **e** DPP-4 plus pioglitazone, and **f** DPP-4 plus insulin. The width of the lines is proportional

to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of trials for each treatment. *DPP-4* dipeptidylpeptidase-4 inhibitor, *HbA_{1c}* glycosylated hemoglobin, *SU* sulfonylurea

DPP-4 Monotherapy

In the direct-comparison analysis, all DPP-4 inhibitors were significantly more effective than placebo in achieving a greater mean reduction from baseline in HbA_{1c} and a greater proportion of patients achieved HbA_{1c} levels <7% (Tables 3, 4). However, the I^2 statistic for linagliptin studies in the HbA_{1c} change from baseline analysis (33.0%) may represent moderate heterogeneity, and the I^2 statistic for

sitagliptin studies in the HbA_{1c} <7% analysis (63.7%) may represent substantial heterogeneity, in the effect estimates.

The relative treatment effects in the MTC analysis showed that DPP-4 inhibitors as monotherapy were significantly more effective than placebo at reducing mean HbA_{1c} from baseline (Table 5). Patients treated with any of the DPP-4 inhibitors, except for saxagliptin, were statistically significantly more likely to

Table 2 Characteristics of included studies and summary of study results

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
<i>Alogliptin (10 RCTs)</i>											
1. NCT00286455											
DeFronzo et al. [66]	64	PLB QD	26	R, DB, P	Naïve	NR	-0.02 (0.020) ^a	NR	0.18 (0.37)	23.4	0
	133	ALO 12.5 mg QD				NR	-0.56 (0.014) ^a	NR	-0.09 (0.26)	47.4	0
	131	ALO 25 mg QD				NR	-0.59 (0.015) ^a	NR	-0.22 (0.26)	44.3	0
2. NCT00328627											
DeFronzo et al. [65]	389	MET + PIO ^b	26	R, DB, P	MET	NR	-0.9 (0.05) ^b	NR	1.5 (0.2) ^b	30.4	8
	390	ALO 12.5 mg QD + MET + PIO ^b				NR	-1.4 (0.05) ^b	NR	1.8 (0.2) ^b	54.6	4
	390	ALO 25 mg QD + MET + PIO ^b				NR	-1.4 (0.05) ^b	NR	1.9 (0.2) ^b	55.8	6
3. NCT00655863											
Eliasson [68]	24	PLB	16	R, DB, P	MET or SU or Glimeide	6.6 (0.7) ^c	0.38 (0.35) ^d	101.8 (12) ^c	NR	NR	0
	25	ALO 25 mg				6.8 (0.8) ^c	-0.39 (0.3) ^d	93.7 (10.8) ^c	NR	NR	0
	22	ALO 25 mg + PIO 30 mg				6.6 (0.6) ^c	-0.95 (0.4) ^d	93.1 (13.2) ^c	NR	NR	3
4. NCT00707993											
Fleck [81]	219	SU 5 mg QD	52	NR	OAD	NR	NR	NR	0.6 (0.012) ^a	NR	NR
	222	ALO 25 mg QD				NR	NR	NR	-0.62 (0.013) ^a	NR	NR
5.											
Kaku [91]	115	PLB + PIO 15/30 mg/day	12	R, DB, P	PIO	7.92 (0.85) ^c	-0.19 (0.051)	69 (14.4) ^c	-0.03 (0.14) ^c	20	0
	111	ALO 12.5 mg QD + PIO 15/30 mg/day				7.91 (0.82) ^c	-0.91 (0.041)	66.5 (12.9) ^c	0.48 (0.12) ^c	49.5	2
	113	ALO 25 mg QD + PIO 15/30 mg/day				7.89 (0.73) ^c	-0.97 (0.048)	68.07 (13) ^c	0.46 (0.13) ^c	49.6	3
6. NCT00286442											
Nauck et al. [74]	104	PLB + MET	26	R, DB, P	MET	8 (0.9) ^c	-0.1 (0.1)	NR	NR	18	3
	213	ALO 12.5 mg QD + MET				7.9 (0.7) ^c	-0.6 (0.1)	NR	NR	52	2
	210	ALO 25 mg QD + MET				7.9 (0.8) ^c	-0.6 (0.1)	NR	NR	44	0
7. NCT00286468											
Pratley et al. [92]	99	PLB + SU	26	R, DB, P	SU	8.15 (0.85) ^c	NR	NR	-0.2 (0.28)	18.2	11
	203	ALO 12.5 mg QD + SU				8.08 (0.83) ^c	NR	NR	0.6 (0.19)	29.6	32
	198	ALO 25 mg QD + SU				8.09 (0.9) ^c	NR	NR	0.68 (0.19)	34.8	19

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
8. NCT00395512											
Rosenstock et al. [77]	164	ALO 25 mg QD + PLB	26	R, DB, P	None	8.8 (0.988) ^c	-1.15 (0.083)	NR	2.19 (0.302)	33.7	NR
	163	PIO 30 mg QD + PLB				8.76 (1.005) ^c	-0.96 (0.081)	NR	-0.29 (0.291)	24.4	NR
	163	ALO 12.5 mg QD + PIO 30 mg QD				8.85 (1.039) ^c	-1.56 (0.081)	NR	2.51 (0.296)	26.4	NR
	164	ALO 25 mg QD + PIO 30 mg QD				8.8 (0.962) ^c	-1.71 (0.081)	NR	3.14 (0.295)	62.8	NR
9.											
Seino et al. [84]	75	PLB QD	12	R, DB, P	None	7.85 (0.89) ^c	0.05 (0.060)	64.57 (12.01) ^c	-0.04 (0.12) ^c	8	1
	79	ALO 6.25 mg QD				7.85 (0.94) ^c	-0.52 (0.059)	65.5 (14.47) ^c	0.12 (0.14) ^c	29.1	1
	84	ALO 12.5 mg QD				7.99 (0.88) ^c	-0.68 (0.057)	67.21 (13.41) ^c	0.45 (0.15) ^c	35.7	0
	80	ALO 25 mg QD				7.88 (0.99) ^c	-0.77 (0.059)	66 (13.34) ^c	0.2 (0.16) ^c	44.3	0
	79	ALO 50 mg QD				8.01 (0.97) ^c	-0.8 (0.059)	63.8 (10) ^c	0.47 (0.14) ^c	38	0
	83	VOG 0.2 mg TID				7.99 (0.82) ^c	-0.16 (0.080)	65.91 (14.92) ^c	-0.46 (0.18) ^c	NR	NR
10. NCT01318109											
Seino et al. [51]	100	PLB + MET 500 or 750 mg/day	12	R, DB, P	MET	8 (0.86) ^c	0.22 (0.055)	NR	-0.23 (0.137)	2	NR
	92	ALO 12.5 mg QD + MET 500 or 750 mg/day				7.89 (0.82) ^c	-0.55 (0.058)	NR	0.17 (0.144)	28.3	NR
	96	ALO 25 mg QD + MET 500 or 750 mg/day				8.02 (0.73) ^c	-0.64 (0.056)	NR	-0.09 (0.132)	27.1	NR
<i>Linagliptin (9 RCTs)</i>											
11.											
Del Prato et al. [93]	167	PLB QD	24	R, DB, P	6-week wash- out or Naïve	8 (0.07)	0.25 (0.07)	NR	NR	11.6	1
	336	LIN 5 mg QD				8 (0.05)	-0.44 (0.05)	NR	NR	25.2	1
12. NCT00309608											
Forst et al. [94]	71	PLB + MET	12	R, DB, P	None	NR	0.24 (0.088)	NR	NR	1.4	0
	65	LIN 1 mg QD + MET				NR	-0.14 (0.115)	NR	NR	15	0
	66	LIN 5 mg QD + MET				NR	-0.5 (0.102)	NR	NR	15	0
	66	LIN 10 mg QD + MET				NR	-0.42 (0.107)	NR	NR	21	0
	65	SU QD + MET				NR	-0.68 (0.029) ^d	NR	NR	NR	3

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
13. NCT00622284											
Gallwitz et al. [95]	775	SU 1 mg QD + MET ≥1,500 mg/day	104	R, DB, P	MET or MET + OAD	7.69 (0.03)	-0.36 (0.03)	86.6 (16.7) ^c	NR	35	280
	776	LIN 5 mg QD + MET ≥1,500 mg/day				7.69 (0.03)	-0.16 (0.03)	86.1 (17.6) ^c	NR	30	58
14. NCT00641043											
Gomis et al. [96]	130	PLB + PIO 30 mg QD	24	R, DB, P	4-week wash- out or Naïve	8.58 (0.08)	-0.56 (0.09)	82.7 (15.8) ^c	1.1 (0.043)	30.5	0
	259	LIN 5 mg QD + PIO 30 mg QD				8.6 (0.05)	-1.06 (0.06)	78.3 (15.6) ^c	2.3 (0.031)	42.9	3
15. NCT00798161											
Haak et al. [97]	72	PLB QD	24	R, DB, P	Naïve or 1 OAD	8.7 (1) ^c	0.1 (0.012) ^c	76.8 (17.5) ^c	-0.7 (0.4)	NR	1
	142	LIN 5 mg QD				8.7 (1) ^c	-0.5 (0.0080) ^c	79.1 (17.3) ^c	0.2 (0.3)	NR	0
	144	MET 500 mg BID				8.7 (0.9) ^c	-0.6 (0.0084) ^c	79.9 (18.4) ^c	-0.7 (0.3)	NR	2
	147	MET 1000 mg BID				8.5 (0.9) ^c	-1.1 (0.0085) ^c	80 (18.5) ^c	-0.5 (0.3)	NR	5
	143	LIN 2.5 mg BID + MET 500 mg BID				8.7 (1) ^c	-1.2 (0.0085) ^c	80.8 (19) ^c	-0.1 (0.3)	NR	5
	143	LIN 2.5 mg BID + MET 1,000 mg BID				8.7 (1) ^c	-1.6 (0.0084) ^c	76.7 (16) ^c	-0.8 (0.3)	NR	0
16. NCT00654381											
Kawamori [98]	80	PLB QD	12	R, DB, P	None or 2-week wash-out	7.95 (0.07)	0.63 (0.08)	NR	-0.39 (0.16)	10	0
	159	LIN 5 mg QD				8.07 (0.05)	-0.24 (0.06)	NR	-0.06 (0.12)	26.4	0
	160	LIN 10 mg QD				7.98 (0.05)	-0.25 (0.06)	NR	-0.04 (0.12)	35.7	0
17. NCT00819091											
Lewin et al. [99]	84	PLB QD + SU	18	R, DB, P	SU or SU + other AD	8.60 (0.08) ^c	-0.07 (0.1)	76.1 (17.0) ^c	-0.01 (0.283) ^c	3.7	4
	161	LIN 5 mg QD + SU				8.61 (0.07) ^c	-0.54 (0.07)	74.5 (17.0) ^c	0.43 (0.283) ^c	15.2	9
18. NCT00602472											
Owens et al. [100]	263	PLB QD + MET + SU	24	R, DB, P	MET and SU	8.14 (0.05)	-0.1 (0.05)	77.4 (1.1)	-0.06 (0.16)	NR	39
	792	LIN 5 mg QD + MET + SU				8.15 (0.03)	-0.72 (0.03)	76.6 (0.6)	0.27 (0.09)	NR	180
19. NCT01012037											
Ross et al. [101]	44	PLB + MET	12	R, DB, P	MET or MT +1 OAD	7.92 (0.74) ^c	0.28 (0.11)	77.7 (19.4) ^c	-1.1 (1.9)	NR	1
	223	LIN 2.5 mg BID + MET				7.96 (0.78) ^c	-0.46 (0.05)	82.2 (17.2) ^c	-0.4 (4.8)	NR	7
	224	LIN 5 mg QD + MET				7.98 (0.82) ^c	-0.52 (0.05)	80.6 (17.5) ^c	-1.0 (2.2)	NR	2

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
20. NCT00601250											
Taskinen et al. [102]	177	PLB QD + MET	24	R, DB, P	MET + 1 OAD	8.02 (0.07)	0.15 (0.06)	83.3 (16.6) ^c	NR	9	NR
	523	LIN 5 mg QD + MET				8.09 (0.04)	-0.49 (0.04)	82.2 (17.2) ^c	NR	26	NR
<i>Saxagliptin (7 RCTs)</i>											
21. NCT00121667											
DeFronzo et al. [89]	179	PLB + MET	24	R, DB, P	MET	8.1 (0.9) ^c	0.13 (0.07)	NR	NR	16.6	9
	192	SAX 2.5 mg + MET				8.1 (1) ^c	-0.59 (0.07)	NR	NR	37.1	15
	191	SAX 5 mg + MET				8.1 (0.8) ^c	-0.69 (0.07)	NR	NR	43.5	10
	181	SAX 10 mg + MET				8 (1) ^c	-0.58 (0.07)	NR	NR	44.4	7
22. NCT00313313											
Chacra et al. [103]	267	PLB + SU 10 mg QD	24	R, DB, P	SU	8.4	0.08 (0.17) ^d	75.6 (17.4) ^c	0.3 (0.196) ^d	9.1	27
	248	SAX 2.5 mg QD + SU 10 mg QD				8.4	-0.54 (0.16) ^d	75.2 (14.4) ^c	0.7 (0.193) ^d	22.4	33
	253	SAX 5 mg QD + SU 10 mg QD				8.4	-0.64 (0.19) ^d	76.2 (17.6) ^c	0.8 (0.199) ^d	22.8	37
23. NCT00960076											
Fonseca et al. [104]	144	MET 2,000 mg QD	18	R, DB, P	MET	8.28 (0.077)	-0.53 (0.081)	NR	NR	26.1	NR
	138	SAX 5 mg + MET 1,500 mg QD				8.41 (0.076)	-0.88 (0.071)	NR	NR	37.2	NR
24.											
Goike et al. [105]	430	SU 5–20 mg QD + MET	52	R, DB, P	MET	7.7 (0.9) ^c	0.8 (0.038)	88.6 (19.64) ^c	1.1 (0.26) ^d	47.8	156
	428	SAX 5 mg QD + MET				7.7 (0.9) ^c	0.74 (0.038)	88.7 (18.61) ^c	-1.1 (0.26) ^d	42.6	13
25. NCT00327015											
Jadzinsky et al. [56]	328	PLB + MET 500 mg BID	24	R, DB, P	Naïve	9.43 (0.07)	-1.79 (0.07) ^f	82.8 ^c (17.5) ^c	NR	41.1 ^g	13
Pfutzner et al. [52]	335	SAX 10 mg QD + PLB	76			9.61 (0.08)	-1.55 (0.08) ^f	83.1 ^c (16.9) ^c	NR	32.2 ^g	5
	320	SAX 5 mg QD + MET 500 mg BID				9.41 (0.07)	-2.31 (0.07) ^f	82.1 ^c (16.3) ^c	NR	60.3 ^g	11
	323	SAX 10 mg QD + MET 500 mg BID				9.53 (0.07)	-2.33 (0.07) ^f	82.5 ^c (16.9) ^c	NR	59.7 ^g	16
26. NCT00698932											
Pan et al. [106]	284	PLB QD	24	R, DB, P	Naïve	8.2 (0.8) ^c	-0.34 (0.007) ^c	NR	NR	NR	2
	284	SAX 5 mg QD				8.1 (0.8) ^c	-0.84 (0.007) ^d	NR	NR	NR	5

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
27. NCT00121641											
Rosenstock et al. [107]	95	PLB QD	24	R, DB, P	Naïve	7.9 (0.9) ^h	0.19 (0.1)	86.56 (16.9) ^h	NR	24	0
	102	SAX 2.5 mg QD				7.9 (0.9) ^h	-0.43 (0.1)	92.1 (18.39) ^h	NR	35	0
	106	SAX 5 mg QD				8 (1.1) ^h	-0.46 (0.1)	90.87 (18.15) ^h	NR	38	0
	98	SAX 10 mg QD				7.9 (0.9) ^h	-0.54 (0.1)	89.3 (17.67) ^h	NR	41	0
28. NCT00661362											
Yang et al. [108]	287	PLB + MET 1,500–2,500 mg/day	24	R, DB, P	MET	7.9 (0.8) ^c	-0.37 (0.107) ^{ld}	69 (11.9) ^c	NR	30.5	4
	283	SAX 5 mg QD + MET 1,500–3,000 mg/day				7.9 (0.8) ^c	-0.78 (0.107) ^{ld}	68.9 (12.5) ^c	NR	46.5	4
<i>Sitagliptin (29 RCTs)</i>											
29. NCT00411411											
Aaboe et al. [86]	12	PLB + MET >1,000 mg/day	12	R, DB, P	MET	7.7 (7.1–9.8) ^j	-0.1 (1.22)	100.3 (85–150) ^j	NR	NR	NR
	12	SIT 100 mg QD + MET >1,000 mg/day				8 (7.3–10.0) ⁱ	-1.0 (0.43)	102 (89–127) ^j	NR	NR	NR
30. NCT00701090											
Arechavaleta et al. [109]	519	SU 1 mg QD + MET	30	R, DB, P	MET	7.49 (0.74) ^c	-0.54 (0.043)	82 (16.7) ^c	1.2 (0.153) ^j	59.6	114
	516	SIT 100 mg QD + MET				7.48 (0.68) ^c	-0.47 (0.0408)	80.6 (15.2) ^c	-0.8 (0.153) ^j	52.4	36
31. NCT00971659											
Arnolds et al. [36]	16	INS 10 units QD + MET	4	R, O	None or MET or SU	7.9 (0.6) ^c	-1.23 (0.316) ^{ld}	96.3 (10.7) ^c	0.4 (0.375) ^e	63	6
	16	EXE 5–10 µg BID + INS ≥10 units QD + MET				8.4 (1) ^c	-1.8 (0.463) ^{ld}	94.2 (17.4) ^c	-0.9 (0.439) ^e	80	5
	16	SIT 100 mg QD + INS ≥10 units QD + MET				7.9 (0.5) ^c	-1.49 (0.383) ^{ld}	97.6 (13.3) ^c	0.1 (0.4) ^e	88	2
32. NCT0087516											
Aschner et al. [110]	253	PLB	24	R, DB	None or ≥1 OAD	8.03 (0.82) ^c	0.18 (0.061) ^j	85 (18.1) ^c	-1.1 (0.2)	17	2
	238	SIT 100 mg QD				8.01 (0.88) ^c	-0.61 (0.063) ^j	85 (18.4) ^c	-0.2 (0.2)	41	1
	250	SIT 200 mg QD				8.08 (0.94) ^c	-0.76 (0.061) ^j	82.7 (19.2) ^c	-0.1 (0.2)	45	0
33. NCT00751114											
Aschner et al. [47]	227	INS Glargine ≥0.2 units/kg + MET	24	R, O, P	None or MET	8.5 (1) ^c	-1.72 (0.06)	83.4 (18.2) ^c	0.44 (0.22)	68	NR
	256	SIT 100 mg QD + MET				8.5 (1.1) ^c	-1.13 (0.06)	84.2 (18.3) ^c	-1.08 (0.20)	42	NR

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
34. NCT00305604											
Barzilai et al. [80]	104	PLB QD	24	R, DB, P	None or OAD washout	7.7 (0.7) ^c	0.2 (0.127) ^j	85.8 (16.5) ^c	-1.7 (0.58) ^d	NR	0
	102	SIT 100 mg QD				7.8 (0.8) ^c	-0.5 (0.127) ^j	85.6 (16.6) ^c	-1.1 (0.58) ^d	NR	0
35. NCT00637273											
Bergstral et al. [35]	160	EXE 2 mg QD + MET + PLB	26	R, DB, P	MET	8.6 (1.2) ^c	-1.5 (0.077) ^j	89 (20) ^c	-2.3 (0.306)	NR	2
	166	SIT 100 mg QD + MET + PLB				8.5 (1.2) ^c	-0.9 (0.102) ^j	87 (20) ^c	-0.8 (0.332)	NR	5
	165	PIO 45 mg QD + MET + PLB				8.5 (1.1) ^c	-1.2 (0.102) ^j	88 (20) ^c	2.8 (0.306)	NR	1
36. NCT0086515											
Charbonnel et al. [111]	224	PLB QD + MET	24	R, DB, P	MET	8.03 (0.82) ^c	-0.02 (0.063)	NR	NR	18.3	5
	454	SIT 100 mg QD + MET				7.96 (0.81) ^c	-0.67 (0.051)	NR	NR	47	6
37.											
Derosa et al. [53]	87	PLB QD + MET 2,500 mg ± 500 mg/day	52	R, DB, P	Naïve	8 (0.7) ^c	-0.7 (0.21) ^d	78.6 (6.7) ^c	-2.3 (1.17) ^d	NR	NR
	91	SIT 100 mg QD + MET 2,500 mg ± 500 mg/day				8.1 (0.8) ^c	-1.4 (0.21) ^d	78.4 (6.6) ^c	-2.5 (1.28) ^d	NR	NR
38.											
Derosa et al. [83]	76	PIO 15 mg BID + MET 850 mg BID	52	R, DB, P	PIO	8.4 (0.8) ^c	-1.4 (0.54) ^d	77.3 (5.4) ^c	-2.8 (0.074) ^d	NR	NR
	75	PIO 30 mg QD + SIT 100 mg QD				8.5 (0.9) ^c	-1.4 (0.54) ^d	78.7 (6.2) ^c	-1.6 (0.073) ^d	NR	NR
39. NCT00103857											
Goldstein et al. [112]	176	PLB QD	24	R, DB, P	Naïve or OAD	8.68 (1) ^k	0.17 (0.084) ^j	NR ^k	NR ^k	9	1
Williams-Herman et al. [113]	179	SIT 100 mg QD	54			8.87 (0.99) ^k	-0.66 (0.084) ^j	NR ^k	0.6 ^k (0.41) ^j	20	1
	182	MET 500 mg BID				8.9 (1) ^k	-0.82 (0.081) ^j	NR ^k	-1 ^k (0.36) ^j	23	1
	182	MET 1,000 mg BID				8.68 (0.91) ^k	-1.13 (0.081) ^j	NR ^k	-1.5 ^k (0.36) ^j	38	2
	190	SIT 50 mg BID + MET 500 mg BID				8.79 (1) ^k	-1.4 (0.081) ^j	NR ^k	-0.7 ^k (0.33) ^j	43	2
	182	SIT 50 mg BID + MET 1,000 mg BID				8.76 (0.95) ^k	-1.9 (0.081) ^j	NR ^k	-1.7 ^k (0.33) ^j	66	4

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
40.											
Hanefeld et al. [114]	111	PLB QD	12	R, DB, P	Naïve or OAD	7.59 (0.89) ^c	0.12 (0.071) ^j	NR	NR	NR	0
	111	SIT 25 mg QD				7.71 (0.91) ^c	-0.28 (0.070) ^j	NR	NR	NR	1
	112	SIT 50 mg QD				7.6 (0.94) ^c	-0.44 (0.071) ^j	NR	NR	NR	1
	110	SIT 100 mg QD				7.78 (0.90) ^c	-0.44 (0.071) ^j	NR	NR	NR	2
	111	SIT 50 mg BID				7.79 (0.85) ^c	-0.43 (0.068) ^j	NR	NR	NR	1
41.											
Hermansen et al. [115]	106	PLB + SU 4–8 mg/day	24	R, DB, P	SU ± MET	8.43 (0.8) ^c	0.27 (0.092) ^j	30.7 (6.4) ^c	0 (0.332) ^j	8.7	3
	116	PLB + SU 4–8 mg/day + MET 1,500–3,000 mg/day				8.26 (0.68) ^c	0.3 (0.076) ^j	30.7 (6.2) ^c	-0.7 (0.332) ^j	1	1
	106	SIT 100 mg QD + SU 4–8 mg/day				8.42 (0.79) ^c	-0.3 (0.092) ^j	31 (6.7) ^c	1.1 (0.382) ^j	10.8	8
	113	SIT 100 mg QD + SU 4–8 mg/day + MET 1,500–3,000 mg/day				8.27 (0.73) ^c	-0.59 (0.076) ^j	31.3 (5.9) ^c	0.4 (0.255) ^j	22.6	19
42. NCT01100125											
Hong et al. [61]	63	INS QD	24	R, P	INS	9.2 (1.1) ^c	-0.22 (0.11) ^j	66.2 (10.6) ^c	1.1 (0.4) ^j	NR	11
	61	SIT 100 mg QD + INS QD				9.2 (1) ^c	-0.63 (0.19) ^j	68.6 (11.6) ^c	-0.7 (0.1) ^j	NR	5
43.											
Iwamoto et al. [116]	156	VOG 0.2 mg TID	12	R, DB, P	≤1 AD	7.8 (0.8) ^c	-0.3 (0.051) ^j	NR	-0.96 (0.094) ^j	NR	NR
	163	SIT 50 mg QD				7.7 (0.9) ^c	-0.7 (0.051) ^j	NR	-0.27 (0.135) ^j	NR	NR
44.											
Kadowaki et al. [40]	137	PLB + INS QD	16	R, DB, P	INS	8.9	NR	NR	NR	NR	17
	129	SIT 50 mg QD + INS QD				8.9	NR	NR	NR	NR	26
45. NCT00094770											
Nauck et al. [117]	584	SU 5 mg QD + MET	52	R, DB, P	MET or OAD or MET + OAD	7.52 (0.85) ^c	-0.67 (0.408) ^j	NR	1.1 (0.281)	58.8	187
	588	SIT 100 mg QD + MET				7.48 (0.76) ^c	-0.67 (0.408) ^j	NR	-1.5 (0.281)	62.8	29
46. NCT00371007											
Nonaka et al. [118]	76	PLB QD	12	R, DB, P	None or 8-week wash out	7.69 (0.86) ^c	0.41 (0.077) ^j	NR	-0.7 (0.153) ^j	14.5	0
	75	SIT 100 mg QD				7.54 (0.85) ^c	-0.65 (0.077) ^j	NR	-0.1 (0.179) ^j	58.1	0

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
47.											
Nonaka et al. [87]	27	PLB	4	R, DB, P	None or 1 OAD	7.9 (1) ^c	NR	NR	NR	NR	1
	24	SIT 50 mg BID				7.5 (0.8) ^c	NR	NR	NR	NR	0
	25	SIT 100 mg QD				7.8 (1.1) ^c	NR	NR	NR	NR	0
48. NCT00541450											
Pérez-Monteverde et al. [54]	248	PIO 15 mg QD	12	R, DB, P	Naïve	NR	-0.9 (0.076) ^j	NR	NR	NR	NR
	244	SIT 100 mg QD				NR	-1.0 (0.076) ^j	NR	NR	NR	NR
49. NCT00700817											
Pratley et al. [50]	219	SIT 100 mg QD + MET	26	R, O, P	MET	8.5 (0.7) ^c	-0.9 (0.066)	93.1 (18.9) ^c	-0.96 (0.276)	NR	10
	225	LIR 1.2 mg QD + MET				8.4 (0.8) ^c	-1.24 (0.066)	93.7 (18.4) ^c	-2.86 (0.273)	NR	13
	221	LIR 1.8 mg QD + MET				8.4 (0.73) ^c	-1.5 (0.066)	94.6 (18.1) ^c	-3.38 (0.273)	NR	11
50. NCT00337610											
Raz et al. [90]	94	PLB QD + MET	30	R, DB, P	MET or OAD or MET + OAD	9.1 (0.8) ^c	0 (0.128) ^j	NR	NR	3.3	NR
	96	SIT 100 mg QD + MET				9.3 (0.9) ^c	-1 (0.102) ^j	NR	NR	13.7	NR
51. NCT00482729											
Reasner [119]	621	MET 500 mg BID	18	R, DB, P	Naïve	9.8 (1.8) ^c	-1.8 (0.076)	NR	NR	34.2	11
	625	SIT 50 mg BID + MET 500 mg BID				9.9 (1.8) ^c	-2.4 (0.076)	NR	NR	49.2	13
52. NCT00676338											
Russell-Jones et al. [78]	248	EXE 2 mg QD	26	R, P	None	NR	-1.53 (0.07)	NR	-2 (0.2)	63	5
	246	MET 2,000 mg QD				NR	-1.48 (0.07)	NR	-2 (0.2)	55	0
	163	PIO 45 mg QD				NR	-1.63 (0.08)	NR	1.5 (0.3)	61	0
	163	SIT 100 mg QD				NR	-1.15 (0.08)	NR	-0.8 (0.3)	43	0
53. NCT00666458 ^f											
Scheen et al. [10]	403	SAX 5 mg QD + MET	18	DB, P	MET	7.68 (0.052)	-0.52 (0.039)	NR	NR	26.3	NR
	398	SIT 100 mg QD + MET				7.69 (0.47)	-0.62 (0.038)	NR	NR	29.1	NR
54. NCT00541775											
Scott et al. [120]	92	PLB QD + MET	18	R, DB, P	MET	7.68 (0.88) ^c	-0.22 (0.071)	84.6 (16.5) ^c	-0.8 (0.204) ^d	38	2
	94	SIT 100 mg QD + MET				7.75 (0.99) ^c	-0.73 (0.068)	83.1 (17.1) ^c	-0.4 (0.204) ^d	55	1

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
55. Srivastava et al. [85]	25	SU 1–2 mg QD + MET	18	R, P	MET	8.248 (0.565)	-1.172 (0.05) ^l	NR	NR	NR	NR
	25	SIT 50–100 mg QD + MET				8.28 (0.418)	-0.636 (0.018) ^l	NR	NR	NR	NR
56. NCT00363519 Tajima et al. [34]	67	PLB + SU 1–6 mg/day	12	R, DB, P	SU or SU + OADs (2 to 8-week wash out)	8.3 (0.8) ^c	0.3 (0.102) ^c	NR	0.03 (0.12) ^l	NR	0
	71	SIT 50 mg QD + SU 1–6 mg/day				8.5 (0.7) ^c	-0.5 (0.102) ^c	NR	0.5 (0.15) ^l	NR	4
57. NCT00532935 Wainstein et al. [55]	256	PIO 30 mg QD	32	R, DB, P	None	8.9 (1.2) ^c	-1.4 (0.051)	81.4 (19.9) ^c	3 (0.383) ^l	43.5	NR
	261	SIT 50 mg BID + MET 500 mg BID				8.9 (1.3) ^c	-1.9 (0.076)	82.8 (21.1) ^c	-1.4 (0.357) ^l	57.3	NR
58. NCT00397631 Yoon et al. [57]	259	PIO 30 mg QD + PLB	24	DB, P	None	9.4 (1.2) ^c	-1.5 (0.102) ^l	80.4 (17.8) ^c	1.9 (0.39) ^d	27.6	2
	261	SIT 100 mg QD + PIO 30 mg QD				9.5 (1.2) ^c	-2.4 (0.102) ^l	80.1 (17.4) ^c	3 (0.39) ^d	60.2	3
<i>Vildagliptin (23 RCTs)</i>											
59. NCT00396627 Blonde et al. [48]	1776	VIL 100 mg QD + MET	12	R, O, P	MET	7.99 (0.02)	-0.68 (0.02)	92.6 (17.7) ^c	NR	NR	NR
	888	TZD + MET				7.97 (0.03)	-0.57 (0.03)	92.9 (18.1) ^c	NR	NR	NR
60. NCT00237237 Bollri et al. [64]	281	PIO 30 mg QD + MET	24	R, DB, P	MET	8.4 (0.9) ^c	-0.98 (0.06)	92 (1.1)	1.9 (0.2)	36	0
	295	VIL 50 mg BID + MET				8.4 (1) ^c	-0.88 (0.5)	91.6 (1.1)	0.3 (0.2)	27	1
61. NCT00099892 Bosi et al. [88]	171	PLB + MET	24	R, DB, P	MET	8.3 (0.1)	0.2 (0.1)	94.8 (1.8)	-1.0 (0.3)	NR	1
	174	VIL 50 mg QD + MET				8.4 (0.1)	-0.5 (0.2)	92.5 (1.6)	-0.4 (0.3)	NR	1
	175	VIL 50 mg BID + MET				8.4 (0.1)	-0.9 (0.2)	95.3 (1.5)	0.2 (0.3)	NR	1
62. NCT00382096 Bosi et al. [58]	294	MET 1,000 mg BID	24	R, DB, P	Naïve	8.62 (0.93) ^c	-1.4 (0.06)	88.43 (17.39) ^c	-1.62 (0.22)	43.5	NR
	300	VIL 50 mg BID				8.68 (1.02) ^c	-1.1 (0.06)	87.84 (17.93) ^c	-0.59 (0.22)	40	NR
	290	VIL 50 mg BID + MET 500 mg BID				8.58 (1.01) ^c	-1.6 (0.06)	86.93 (16.38) ^c	-1.17 (0.23)	55.4	NR
	295	VIL 50 mg BID + MET 1,000 mg BID				8.7 (1.03) ^c	-1.8 (0.06)	89.79 (18.87) ^c	-1.19 (0.22)	65.4	NR

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
63. NCT00099905											
Dejager et al. [67]	149	PLB	24	R, DB, P	Naïve	8.4 (0.1)	-0.3 (0.1)	92.6 (2.5)	-1.4 (0.4)	NR	0
	152	VIL 50 mg QD				8.2 (0.1)	-0.8 (0.1)	90.4 (2.4)	-1.8 (0.4)	NR	2
	143	VIL 50 mg BID				8.6 (0.1)	-0.8 (0.1)	90.4 (2.1)	-0.3 (0.4)	NR	0
	150	VIL 100 mg QD				8.4 (0.1)	-0.9 (0.1)	90.5 (2.1)	-0.8 (0.4)	NR	1
64.											
Derosa et al. [59]	83	PLB BID + MET 2,500 mg ± 500 mg/day	52	R, DB, P	Naïve	8 (0.7) ^c	-0.8 (0.36) ^d	78.6 (6.7) ^c	-5.1 (1.97) ^d	NR	NR
	84	VIL 50 mg BID + MET 2,500 mg ± 500 mg/day				8.1 (0.8) ^c	-1.2 (0.36) ^d	78.4 (6.6) ^c	-5.8 (2.25) ^d	NR	NR
65.											
Derosa et al. [82]	85	SU 2 mg TID + VIL 50 mg BID	52	R, DB, P	PIO or SU	8.3 (0.6) ^c	-1.5 (0.58) ^c	78.4 (6.3) ^c	NR	NR	0
	83	PIO 30 mg QD + VIL 50 mg BID				8.4 (0.7) ^c	-1.5 (0.58) ^c	78 (6.1) ^c	NR	NR	4
66. NCT00106340											
Ferrannini et al. [121]	1396	VIL 50 mg BID + MET	52	R, DB, P	MET	7.31 (0.64) ^c	-0.44 (0.02)	89.01	-0.23 (0.11)	54.1	24
	1393	SU 2 mg QD + MET				7.3 (0.65) ^c	-0.53 (0.02)	88.62	1.56 (0.12)	55.5	224
67.											
Filozof and Gautier [122]	513	VIL 50 mg BID + MET 1,500 mg/day	52	R, DB, P	MET	8.5 (1) ^c	-0.81 (0.06)	85.7 (16.6) ^c	NR	29.6	NR
	494	SU 80–320 mg QD + MET 1,500 mg/day				8.5 (1) ^c	-0.85 (0.06)	84.2 (17.9) ^c	NR	31.9	NR
68. NCT00102388											
Foley and Sreenan [69]	546	SU 80 mg QD	104	R, DB	Naïve	8.7 (0.1)	NR	84.3 (17.6) ^c	1.6 (0.2)	28	14
	546	VIL 50 mg BID				8.5 (0.1)	NR	84.2 (16.3) ^c	0.8 (0.2)	22	4
69. NCT00099931											
Fonseca et al. [70]	152	PLB + INS	24	R, DB, P	INS	8.4 (0.1)	-0.2 (0.1)	95.1 (1.7)	0.6 (0.3)	NR	33
	144	VIL 50 mg BID + INS				8.4 (0.1)	-0.5 (0.1)	94.5 (1.5)	1.3 (0.3)	NR	45
70. NCT00099944											
Garber et al. [72]	144	PLB + SU 4 mg QD	24	R, DB	SU	8.5 (1) ^c	0.07 (0.09)	89.4 (1.6) ^c	-0.4 (0.3)	12	1
	132	VIL 50 mg QD + SU 4 mg QD				8.5 (0.9) ^c	-0.58 (0.1)	91.5 (1.5) ^c	-0.1 (0.3)	21.2	2
	132	VIL 50 mg BID + SU 4 mg QD				8.6 (1) ^c	-0.63 (0.09)	87.3 (1.6) ^c	1.3 (0.3)	24.8	6

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
71. NCT00099853											
Gaerber et al. [71]	138	PLB + PIO QD	24	R, DB, P	TZD	8.7 (0.1)	-0.3 (0.1)	NR	NR	14.8	3
	124	VIL 50 mg QD + PIO				8.6 (0.1)	-0.8 (0.1)	NR	NR	28.7	0
	136	VIL 50 mg BID + PIO				8.7 (0.1)	-1.0 (0.1)	NR	NR	36.4	1
72.											
Goodman et al. [60]	122	PLB QD + MET	24	R, DB, P	MET	8.7 (1.1) ^c	0.17 (0.11)	NR	NR	NR	0
	125	VIL 100 mg QD am + MET				8.5 (1) ^c	-0.66 (0.11)	NR	NR	NR	1
	123	VIL 100 mg QD pm + MET				8.5 (0.9) ^c	-0.53 (0.11)	NR	NR	NR	1
73. NCT00325117											
Kikuchi et al. [62]	100	PLB BID + SU	12	R, DB, P	SU	8 (0.8) ^c	-0.06 (0.06)	63.6 (0.96)	0.06 (0.12)	11.6	1
	102	VIL 50 mg BID + SU				7.8 (0.8) ^c	-1 (0.06)	65 (0.95)	0.97 (0.12)	65.9	2
74.											
Kim et al. [49]	125	MET 1,500 mg/day	24	R, O, P	MET	8.14	-0.9 (0.06)	NR	NR	NR	NR
	132	VIL 50 mg BID + MET 1,500 mg/day				8.16	-1.25 (0.05)	NR	NR	NR	NR
75. NCT01224366											
Koehnly et al. [123]	221	PLB + INS	24	R, DB, P	INS	8.9 (0.11)	0.24 (0.2)	NR	NR	NR	NR
	228	VIL 50 mg + INS				8.84 (0.12)	-0.6 (0.19)	NR	NR	NR	NR
76. NCT01233622											
Lukashevich et al. [124]	160	PLB + MET ≥1,500 mg/day + SU ≥4 mg/day	24	R, DB, P	NR	8.8 (0.07)	-0.25 (0.09)	NR	NR	NR	3
	152	VIL 50 mg BID + MET ≥1,500 mg/day + SU ≥4 mg/day				8.75 (0.07)	-1.01 (0.09)	NR	NR	NR	8
77.											
Matthews et al. [125]	1556	SU 2 mg QD + MET	104	R, DB, P	MET	7.3 (0.7) ^c	-0.1 (0.025)	88.9 (17.8) ^c	1.2 (0.1)	38.3	281
	1562	VIL 50 mg BID + MET				7.3 (0.7) ^c	-0.1 (0.025)	89.5 (18.1) ^c	-0.3 (0.1)	36.9	35
78.											
Pan et al. [126]	144	PLB + MET	24	R, DB, P	MET	8.01 (0.82) ^c	-0.54 (0.08)	NR	NR	34.8	0
	146	VIL 50 mg BID + MET				8.09 (0.85) ^c	-1.05 (0.08)	NR	NR	53.7	1
	148	VIL 50 mg QD + MET				8.05 (0.84) ^c	-0.92 (0.08)	NR	NR	48.9	0

Table 2 continued

Study identifier References	N	Treatment arm and dose	Weeks	Design	ADs	HbA _{1c} baseline % (SE)	HbA _{1c} change from baseline % (SE)	Baseline body weight kg (SE)	Body weight change from baseline kg (SE)	Percentage of patients achieving HbA _{1c} <7%	Number of patients experi- encing hypo- glycemic events
79.											
Pi-Sunyer et al. [75]	92	PLB QD	24	R, DB, P	Naïve	8.5 (0.1)	0.0 (0.1)	92.6 (2.5)	-1.4 (0.4)	13.6	0
	88	VIL 50 mg QD				8.3 (0.1)	-0.5 (0.1)	90.4 (2.4)	-0.4 (0.4)	NR	0
	83	VIL 50 mg BID				8.4 (0.1)	-0.7 (0.1)	90.4 (2.1)	0 (0.4)	30.4	0
	91	VIL 100 mg QD				8.3 (0.1)	-0.8 (0.1)	90.5 (2.1)	-0.4 (0.3)	39.1	0
80. NCT00101803											
Rosenstock et al. [76]	161	PIO 30 mg QD	24	R, DB	None	8.7 (1) ^c	-1.4 (0.1)	81	1.5 (0.3)	42.9	0
	154	VIL 100 mg QD				8.6 (1) ^c	-1.1 (0.1)	82	0.2 (0.3)	42.5	1
	144	VIL 50 mg QD + PIO 15 mg QD				8.8 (0.9) ^f	-1.7 (0.1)	80	1.4 (0.3)	53.6	0
	148	VIL 100 mg QD + PIO 30 mg QD				8.8 (1.1) ^f	-1.9 (0.1)	82	2.1 (0.3)	65	1
81. NCT00099866											
Schweizer et al. [127]	254	MET 2,000 mg/day	52	R, DB, P	None	8.7 (1.1) ^c	-1.4 (0.1)	92.9 (1.2) ^c	-1.9 (0.3)	45	1
	526	VIL 50 mg BID				8.7 (1.1) ^c	-1.0 (0.1)	91.4 (0.9) ^c	0.3 (0.2)	35	3
82. NCT 2006-002466-19											
Schweizer et al. [63]	116	MET 500–1,500 mg/day	24	R, DB, P	None	7.7 (0.6) ^f	-0.75 (0.07)	NR	-1.25 (0.19)	61.1	2
	169	VIL 100 mg QD				7.8 (0.6) ^f	-0.64 (0.07)	NR	-0.45 (0.2)	49	0

AD anti-diabetic drug, ALO alogliptin, DB double-blind, BID twice daily, EXE exenatide, HbA_{1c} glycosylated hemoglobin, INS insulin, LIN linagliptin, LIR liraglutide, MET metformin, NR not reported, O open-label, OAD oral anti-diabetic, P parallel-group, PIO pioglitazone, PLB placebo, QD once daily, R randomized, SMAX saxagliptin, SD standard deviation, SE standard error, STI sitagliptin, SU sulfonlurea, TID three times daily, TZD thiazolidinediones, VIL vildagliptin, VOG voglibose

^a SE derived from *p* value, assuming that change from baseline equals adjusted change from baseline

^b Data pooled according to alogliptin dose

^c SD

^d SE derived from *p* value and adjusted mean change from baseline

^e SE derived from SD

^f Data from week 76

^g Data from week 24

^h Data from week 54

ⁱ HbA_{1c} at baseline range

^j SE derived from 95% confidence interval and adjusted mean change from baseline

^k Week 54

^l Values not specified if SD or SE, assume SD to derive SE

Table 3 Summary of results for the direct comparison of all DPP-4 inhibitors versus comparator (continuous outcome measures)

Endpoint	Alogliptin 25 mg QD		Linagliptin 5 mg QD		Saxagliptin 5 mg QD		Staglipitin 100 mg/day		Vildagliptin 50 mg BID	
	Weighted mean difference (95% CI)	I ² (%)	Weighted mean difference (95% CI)	I ² (%)	Weighted mean difference (95% CI)	I ² (%)	Weighted mean difference (95% CI)	I ² (%)	Weighted mean difference (95% CI)	I ² (%)
HbA _{1c} change from baseline	-0.797* [66, 84] (-0.943 to -0.651)	0.0	-0.734* [93, 97, 98] (-0.888 to -0.588)	33	-0.593* [106, 107] (-0.811 to -0.375)	0.0	-0.788* [80, 110, 112, 114, 118] (-0.954 to -0.622)	3.2	-0.60* [67, 75] (-0.80 to -0.40)	0.0
Weight change from baseline	0.049 [66, 84] (-0.53 to 0.62)	0.0	0.431* [97, 98] (0.004 to 0.86)	11	-	-	0.717* [80, 110, 118] (0.37 to 1.06)	-	1.25* [67, 75] (0.47 to 2.03)	0.0
Endpoint	Alogliptin 25 mg QD + metformin		Linagliptin 5 mg QD + metformin		Saxagliptin 5 mg QD + metformin		Staglipitin 100 mg/day + metformin		Vildagliptin 50 mg BID + metformin	
HbA _{1c} change from baseline	-0.699* [51, 74] (-1.05 to -0.35)	79.8 ^b	-0.679* [94, 101, 102] (-0.79 to -0.57)	0.0	-0.585* [52, 104, 108] (-0.76 to -0.41)	60.5 ^b	0.649* [53, 86, 90, 111, 119, 120] (-0.78 to -0.52)	26.6	0.480* [49, 58-60, 88, 126] (-0.92 to -0.05)	94.9 ^b
Weight change from baseline	0.140 [51] (-0.23 to 0.51)	- ^a	0.100 [101] (-0.56 to 0.58)	- ^a	-	-	0.384 [53, 120] (-0.18 to 0.94)	0.0	0.495* [58, 59, 88] (0.002 to 0.99)	0.0
Endpoint	Alogliptin 25 mg QD + SU		Linagliptin 5 mg QD + SU		Saxagliptin 5 mg QD + SU		Staglipitin 100 mg/day + SU		Vildagliptin 50 mg BID + SU	
HbA _{1c} change from baseline	-0.540* [92] (-0.82 to -0.26)	- ^a	-0.470* [99] (-0.71 to -0.23)	- ^a	-0.720* [103] (-1.22 to -0.22)	- ^a	-0.676* [34, 115] (-0.90 to -0.45)	28.7	-0.839* [62, 72] (-1.07 to -0.61)	59.4 ^b
Weight change from baseline	0.880* [92] (0.22 to 1.54)	- ^a	0.440 [99] (-0.34 to 1.22)	- ^a	-0.700 [103] (-1.62 to 0.22)	- ^a	0.611* [34, 115] (0.10 to 1.13)	26.2	1.209* [62, 72] (0.46 to 1.96)	66.5 ^b
Endpoint	Alogliptin 25 mg QD + metformin + SU		Linagliptin 5 mg QD + metformin + SU		Saxagliptin 5 mg QD + metformin + SU		Staglipitin 100 mg/day + metformin + SU		Vildagliptin 50 mg BID + metformin + SU	
HbA _{1c} change from baseline	-	-	-0.620* [100] (-0.73 to 0.51)	- ^a	-	-	-0.890 [115] (-2.41 to 0.63)	- ^a	-0.760* [124] (-1.01 to 0.51)	- ^a
Weight change from baseline	-	-	0.330 [100] (-0.3 to 0.69)	- ^a	-	-	0.700 [115] (-0.22 to 1.62)	- ^a	-	-
Endpoint	Alogliptin 25 mg QD + pioglitazone		Linagliptin 5 mg QD + pioglitazone		Saxagliptin 5 mg QD + pioglitazone		Staglipitin 100 mg/day + pioglitazone		Vildagliptin 50 mg BID + pioglitazone	
HbA _{1c} change from baseline	-0.606* [77, 91] (-0.97 to -0.25)	86.6 ^b	-0.500* [96] (-0.71 to 0.29)	- ^a	-	-	-0.900* [57] (-1.18 to 0.62)	- ^a	-0.600* [71, 76] (-0.80 to -0.40)	0.1
Weight change from baseline	0.568* [77, 91] (0.23 to 0.91)	0.0	1.200* [96] (1.10 to 1.30)	- ^a	-	-	1.100* [57] (0.019 to 2.181)	- ^a	0.600 [76] (-0.23 to 1.43)	- ^a

Table 3 continued

Endpoint	Alogliptin 25 mg QD + insulin		Linagliptin 5 mg QD + insulin		Saxagliptin 5 mg QD + insulin		Sitagliptin 100 mg/day + insulin		Vildagliptin 50 mg BID + insulin	
	Weighted mean difference (95% CI)	I^2 (%)	Weighted mean difference (95% CI)	I^2 (%)	Weighted mean difference (95% CI)	I^2 (%)	Weighted mean difference (95% CI)	I^2 (%)	Weighted mean difference (95% CI)	I^2 (%)
HbA _{1c} change from baseline	-	-	-	-	-	-	-0.410 [61] (-0.84 to 0.019)	- ^a	-0.518 [70, 123] (-1.04 to 0.001)	67.1 ^b
Weight change from baseline	-	-	-	-	-	-	-1.800 [61] (-2.61 to 0.99)	- ^a	0.700 [70] (-0.13 to 1.53)	- ^a

BID twice daily, CI confidence interval, HbA_{1c} glycosylated hemoglobin, QD once daily, SU sulfonylurea

* Statistically significant versus comparator

^a Only one study eligible

^b I^2 may represent moderate heterogeneity

achieve HbA_{1c} <7% than those treated with placebo (Table 5). Treatment with either sitagliptin or vildagliptin resulted in a statistically significant increase in mean (95% CI) body weight relative to placebo of 0.70 kg (0.33–1.08 kg) and 0.83 kg (0.39–1.27 kg), respectively. There was no significant difference in mean change from baseline in body weight for alogliptin or linagliptin versus placebo. Only linagliptin resulted in statistically significant lower odds of patients having a hypoglycemic event compared with placebo [OR 0.18 (95% CI 0.0074–0.77)].

Absolute mean changes in HbA_{1c} from baseline to study endpoint were all reductions (i.e., improvements; Table 6); however, all reductions were non-significant. There was no significant difference between treatments in absolute mean body weight change from baseline for any DPP-4 inhibitor.

DPP-4 Plus Metformin

In the direct-comparison meta-analysis, all DPP-4 inhibitors as dual therapy with metformin were significantly more effective in achieving a greater mean reduction from baseline in HbA_{1c} and achieving a greater proportion of patients with HbA_{1c} levels <7% compared with metformin alone (Tables 3, 4). However, I^2 statistics >30% may represent heterogeneity in the treatment effect of alogliptin (I^2 79.8%), saxagliptin (I^2 60.5%), and vildagliptin (I^2 94.9%) for the HbA_{1c} mean change from baseline outcome, and of alogliptin (I^2 76.5%), saxagliptin (I^2 53.7%), and sitagliptin (I^2 80.0%) for the proportion of patients achieving HbA_{1c} <7%.

A single head-to-head trial provided data directly comparing two DPP-4 inhibitors: sitagliptin plus metformin versus saxagliptin plus metformin [10]. The HbA_{1c} mean change from baseline between-group difference of

Table 4 Summary of results for the direct comparison of all DPP-4 inhibitors versus comparator (binominal outcome measures)

Endpoint	Alogliptin 25 mg QD		Linagliptin 5 mg QD		Saxagliptin 5 mg QD		Sitagliptin 100 mg/day		Vildagliptin 50 mg BID	
	Odds ratio (95% CI)	I^2 (%)	Odds ratio (95% CI)	I^2 (%)	Odds ratio (95% CI)	I^2 (%)	Odds ratio (95% CI)	I^2 (%)	Odds ratio (95% CI)	I^2 (%)
Patients achieving HbA _{1c} <7	3.157* [66, 84] (1.87–5.49)	0.0	2.772* [93, 98] (1.74–4.41)	0.0	1.909* [107] (1.03–3.56)	– ^a	3.934* [110, 112, 118] (2.20–7.05)	63.7 ^b	4.105* [75] (1.95–8.63)	– ^a
Patients with hypoglycemic event	0.949 [66, 84] (0.06–15.45)	– ^a	0.311 [93, 97, 98] (0.04–2.55)	0.0	0.257 [106, 107] (0.49–13.13)	– ^a	0.924 [80, 87, 110, 112, 114, 118] (0.23–3.77)	0.0	–	–
Endpoint	Alogliptin 25 mg QD + metformin	I^2 (%)	Linagliptin 5 mg QD + metformin	I^2 (%)	Saxagliptin 5 mg QD + metformin	I^2 (%)	Sitagliptin 100 mg/day + metformin	I^2 (%)	Vildagliptin 50 mg BID + metformin	I^2 (%)
Patients achieving HbA _{1c} <7	7.005* [51, 74] (1.41–34.70)	76.5 ^b	4.125* [94, 102] (1.80–9.45)	14.8	2.272* [56, 89, 104, 108] (1.69–3.06)	53.7 ^b	2.869* [90, 111, 112, 119, 120] (1.67–4.92)	80.0 ^b	2.302* [58, 126] (1.75–3.03)	0.0
Patients with hypoglycemic event	0.069 [74] (0.004–1.34)	– ^a	1.394 [94, 101] (0.17–11.62)	– ^a	0.950 [56, 89, 108] (0.54–1.66)	0.0	0.910 [111, 119, 120] (0.48–1.74)	0.0	1.911 [60, 88, 126] (0.33–11.09)	0.0
Endpoint	Alogliptin 25 mg QD + SU	I^2 (%)	Linagliptin 5 mg QD + SU	I^2 (%)	Saxagliptin 5 mg QD + SU	I^2 (%)	Sitagliptin 100 mg/day + SU	I^2 (%)	Vildagliptin 50 mg BID + SU	I^2 (%)
Patients achieving HbA _{1c} <7	2.407* [92] (1.34–4.34)	– ^a	4.716* [99] (1.38–16.17)	– ^a	3.021* [103] (1.81–5.04)	– ^a	1.263 [115] (0.50–3.19)	– ^a	5.536 [62, 72] (0.89–34.36)	92.6 ^b
Patients with hypoglycemic event	0.849 [92] (0.39–1.86)	– ^a	1.184 [99] (0.35–3.97)	– ^a	1.523 [103] (0.90–2.58)	– ^a	3.438* [34, 115] (1.00–11.78)	0.0	3.848 [62, 72] (0.78–19.00)	0.0
Endpoint	Alogliptin 25 mg QD + metformin + SU	I^2 (%)	Linagliptin 5 mg QD + metformin + SU	I^2 (%)	Saxagliptin 5 mg QD + metformin + SU	I^2 (%)	Sitagliptin 100 mg/day + metformin + SU	I^2 (%)	Vildagliptin 50 mg BID + metformin + SU	I^2 (%)
Patients achieving HbA _{1c} <7	–	–	–	–	–	–	–	–	–	–
Patients with hypoglycemic event	–	–	1.689* [100] (1.16–2.47)	– ^a	–	–	8.699* [115] (1.07–70.76)	– ^a	2.791 [124] (0.73–10.72)	– ^a
Endpoint	Alogliptin 25 mg QD + pioglitazone	I^2 (%)	Linagliptin 5 mg QD + pioglitazone	I^2 (%)	Saxagliptin 5 mg QD + pioglitazone	I^2 (%)	Sitagliptin 100 mg/day + pioglitazone	I^2 (%)	Vildagliptin 50 mg BID + pioglitazone	I^2 (%)
Patients achieving HbA _{1c} <7	2.874* [77, 91] (1.67–4.95)	54.6 ^b	1.71* [96] (1.09–2.69)	– ^a	–	–	3.95* [57] (2.71–5.76)	– ^a	2.82* [71, 76] (1.96–4.07)	0.0
Patients with hypoglycemic event	7.32 [91] (0.38–143.28)	– ^a	3.561 [96] (0.18–69.47)	– ^a	–	–	1.494 [57] (0.25–9.02)	– ^a	0.778 [71, 76] (0.09–6.91)	24.0
Endpoint	Alogliptin 25 mg QD + insulin	I^2 (%)	Linagliptin 5 mg QD + insulin	I^2 (%)	Saxagliptin 5 mg QD + insulin	I^2 (%)	Sitagliptin 100 mg/day + insulin	I^2 (%)	Vildagliptin 50 mg BID + insulin	I^2 (%)
Patients achieving HbA _{1c} <7	–	–	–	–	–	–	–	–	–	–
Patients with hypoglycemic event	–	–	–	–	–	–	0.934 [40, 61] (0.23–3.80)	78.7 ^b	1.639 [70] (0.97–2.76)	– ^a

BID twice daily, *CI* confidence interval, *HbA_{1c}* glycosylated hemoglobin, *QD* once daily, *SU* sulfonylurea

* Statistically significant versus comparator

^a Only one study eligible

^b I^2 may represent moderate heterogeneity

Table 5 Relative treatment effect mixed treatment comparisons

	Alogliptin	Linagliptin	Saxagliptin	Stagliptin	Vildagliptin
Monotherapy					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-0.74 (-0.99 to -0.49)*	-0.74 (-0.96 to -0.51)*	-0.61 (-0.91 to -0.31)*	-0.75 (-0.90 to -0.60)*	-0.67 (-0.87 to -0.47)*
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	4.29 (2.10 to 8.00)*	3.33 (1.60 to 6.27)*	2.11 (0.86 to 4.39)	3.64 (2.18 to 5.71)*	4.02 (2.11 to 6.89)*
Mean weight change from baseline, kg (95% CrI)	0.32 (-0.08 to 0.70)	0.37 (-0.11 to 0.86)	-	0.70 (0.33 to 1.08)*	0.83 (0.39 to 1.27)*
Odds ratio of having a hypoglycemic event (95% CrI)	0.27 (0.008 to 1.39)	0.18 (0.0074 to 0.77)*	1.86 (0.169 to 7.39)	0.61 (0.14 to 1.66)	0.78 (0.13 to 2.56)
DPP-4 inhibitor + metformin					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-0.68 (-0.96 to -0.40)*	-0.57 (-0.75 to -0.40)*	-0.61 (-0.79 to -0.44)*	-0.64 (-0.79 to -0.50)*	-0.59 (-0.75 to -0.44)*
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	6.41 (3.15 to 11.98)* [‡]	3.37 (1.91 to 5.72)*	2.17 (1.56 to 2.95)* [‡]	2.87 (2.13 to 3.82)*	2.45 (1.65 to 3.50)*
Mean weight change from baseline, kg (95% CrI)	0.26 (-1.50 to 2.02)	0.17 (-5.58 to 5.80)	-	-0.28 (-1.65 to 1.05)	0.87 (-0.26 to 1.99)
Odds ratio of having a hypoglycemic event (95% CrI)	0.24 (0.02 to 1.00)	0.72 (0.32 to 1.35)	0.81 (0.44 to 1.40)	1.32 (0.72 to 2.23)	0.78 (0.33 to 1.58)
DPP-4 inhibitor + metformin + SU					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-0.47 (-0.87 to -0.08)*	-0.47 (-0.90 to -0.03)*	-0.66 (-1.17 to -0.15)*	-0.68 (-1.00 to -0.37)*	-0.81 (-1.08 to -0.51)*
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	2.82 (0.43 to 9.20)	6.78 (0.56 to 28.07)	3.79 (0.59 to 12.19)	2.00 (0.22 to 7.57)	5.81 (1.35 to 15.11)*
Mean weight change from baseline, kg (95% CrI)	0.83 (-0.60 to 2.26)	0.44 (-1.25 to 2.14)	0.48 (-0.92 to 1.89)	0.68 (-0.42 to 1.91)	0.95 (-0.12 to 2.03)
Odds ratio of having a hypoglycemic event (95% CrI)	1.44 (0.31 to 4.13)	1.71 (0.22 to 6.33)	1.73 (0.42 to 4.67)	4.74 (0.87 to 15.75)	3.69 (0.61 to 13.16)
DPP-4 inhibitor + metformin + SU					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-	-0.62 (-6.84 to 5.63)	-	-0.91 (-7.30 to 5.43)	-0.76 (-6.97 to 5.47)
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	-	-	-	-	-
Mean weight change from baseline, kg (95% CrI)	-	0.32 (-5.93 to 6.58)	-	1.78 (-4.54 to 8.07)	-
Odds ratio of having a hypoglycemic event (95% CrI)	-	7.17 (0.05 to 33.96)	-	12.92 (0.095 to 62.92)	9.89 (0.065 to 49.84)
DPP-4 inhibitor + pioglitazone					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-0.64 (-0.86 to -0.39)*	-0.50 (-0.89 to -0.11)*	-	-0.88 (-1.28 to -0.45)*	-0.51 (-0.77 to -0.26)*
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	3.31 (1.844 to 5.56)*	1.87 (0.72 to 4.00)	-	4.23 (1.66 to 8.67)*	2.40 (1.34 to 4.05)*
Mean weight change from baseline, kg (95% CrI)	0.54 (-0.20 to 1.32)	1.20 (0.06 to 2.34)*	-	1.10 (-0.42 to 2.61)	0.24 (-0.93 to 1.40)
Odds ratio of having a hypoglycemic event (95% CrI)	20.15 (0.68 to 110.3)	13.24 (0.14 to 78.65)	-	3.22 (0.089 to 14.99)	0.49 (0.027 to 2.14)
DPP-4 inhibitor + insulin					
Weighted mean HbA _{1c} change from baseline (95% CrI)	-	-	-	-0.41 (-5.07 to 4.25)	-0.55 (-3.87 to 2.72)
Odds ratio of achieving HbA _{1c} <7% (95% CrI)	-	-	-	-	-
Mean weight change from baseline, kg (95% CrI)	-	-	-	-1.81 (-8.07 to 4.50)	0.78 (-5.63 to 7.02)
Odds ratio of having a hypoglycemic event (95% CrI)	-	-	-	2.74 (0.057 to 13.79)	7.30 (0.045 to 37.12)

CrI credible interval, DPP-4 dipeptidylpeptidase-4, HbA_{1c} glycosylated hemoglobin, SU sulfonylurea

* Statistically significant versus comparator: monotherapy versus placebo, DPP-4 + metformin versus metformin, DPP-4 + SU versus SU, DPP-4 + metformin + SU versus metformin + SU, DPP-4 + pioglitazone versus pioglitazone, DPP-4 + insulin versus insulin

‡ Statistically significant difference between alogliptin + metformin and saxagliptin + metformin

Table 6 Absolute treatment effect mixed treatment comparisons

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Monotherapy					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-0.58 (-0.83 to -0.33)	-0.58 (-0.81 to -0.35)	-0.45 (-0.75 to -0.15)	-0.59 (-0.75 to -0.43)	-0.52 (-0.71 to -0.31)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	0.40 (0.34 to 0.59)	0.34 (0.19 to 0.53)	0.25 (0.11 to 0.44)	0.37 (0.24 to 0.51)	0.39 (0.24 to 0.55)
Absolute mean weight change from baseline, kg (95% CrI)	-0.17 (-0.60 to 0.23)	-0.12 (-0.62 to 0.38)	-	0.20 (-0.18 to 0.60)	0.33 (-0.12 to 0.80)
Absolute probability of having a hypoglycemic event (95% CrI)	0.0013 (0.000032 to 0.0071)	0.008 (0.000028 to 0.0042)	0.0088 (0.00062 to 0.038)	0.0029 (0.00046 to 0.0097)	0.0037 (0.00043 to 0.014)
DPP-4 inhibitor + metformin					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-1.10 (-1.38 to -0.82)	-0.99 (-1.17 to -0.82)	-1.03 (-1.21 to -0.85)	-1.06 (-1.22 to -0.91)	-1.02 (-1.18 to -0.86)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	0.56 (0.32 to 0.78)	0.41 (0.22 to 0.63)	0.31 (0.17 to 0.50)	0.38 (0.22 to 0.57)	0.35 (0.18 to 0.54)
Absolute mean weight change from baseline, kg (95% CrI)	-0.45 (-2.22 to 1.31)	-0.54 (-6.31 to 5.09)	-	-0.99 (-2.38 to 0.35)	0.15 (-0.99 to 1.28)
Absolute probability of having a hypoglycemic event (95% CrI)	0.0039 (0.00028 to 0.017)	0.012 (0.0036 to 0.028)	0.013 (0.0045 to 0.030)	0.021 (0.0074 to 0.047)	0.012 (0.0037 to 0.031)
DPP-4 inhibitor + sulfonylurea					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-0.40 (-0.81 to -0.01)	-0.40 (-0.84 to 0.04)	-0.60 (-1.11 to -0.08)	-0.61 (-0.94 to -0.29)	-0.75 (-1.02 to -0.44)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	0.21 (0.04 to 0.53)	0.34 (0.05 to 0.77)	0.26 (0.06 to 0.60)	0.15 (0.022 to 0.48)	0.36 (0.12 to 0.66)
Absolute mean weight change from baseline, kg (95% CrI)	0.87 (-0.58 to 2.30)	0.47 (-1.22 to 2.18)	-	0.72 (-0.39 to 1.96)	-
Absolute probability of having a hypoglycemic event (95% CrI)	0.043 (0.0035 to 0.18)	0.05 (0.0026 to 0.23)	0.05 (0.0045 to 0.20)	0.11 (0.0096 to 0.44)	0.093 (0.0068 to 0.38)
DPP-4 inhibitor + metformin + sulfonylurea					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-	-0.65 (-6.87 to 5.60)	-	-0.94 (-7.34 to 5.40)	-0.80 (-7.00 to 5.43)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	-	-	-	-	-
Absolute mean weight change from baseline, kg (95% CrI)	-	0.14 (-6.11 to 6.39)	-	1.60 (-4.73 to 7.89)	-
Absolute probability of having a hypoglycemic event (95% CrI)	-	0.13 (0.00057 to 0.76)	-	0.21 (0.0011 to 0.89)	0.17 (0.00071 to 0.84)
DPP-4 inhibitor + pioglitazone					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-1.29 (-1.52 to -1.05)	-1.16 (-1.56 to -0.76)	-	-1.53 (-1.95 to -1.11)	-1.17 (-1.43 to -0.91)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	0.54 (0.34 to 0.73)	0.40 (0.18 to 0.65)	-	0.59 (0.34 to 0.80)	0.47 (0.27 to 0.67)
Absolute mean weight change from baseline, kg (95% CrI)	1.59 (0.84 to 2.37)	2.24 (1.10 to 3.38)	-	2.14 (0.63 to 3.65)	1.28 (0.11 to 2.44)
Absolute probability of having a hypoglycemic event (95% CrI)	0.059 (0.00021 to 0.47)	0.036 (0.00055 to 0.33)	-	0.014 (0.000031 to 0.11)	0.0030 (0.0000084 to 0.021)
DPP-4 inhibitor + insulin					
Weighted absolute HbA _{1c} change from baseline (95% CrI)	-	-	-	-0.56 (-5.22 to 4.09)	-0.70 (-4.03 to 2.56)
Absolute probability of achieving HbA _{1c} <7% (95% CrI)	-	-	-	-	-
Absolute mean weight change from baseline, kg (95% CrI)	-	-	-	-1.03 (-7.31 to 5.32)	1.48 (-4.86 to 7.82)
Absolute probability of having a hypoglycemic event (95% CrI)	-	-	-	0.22 (0.0086 to 0.7903)	0.30 (0.007 to 0.891)

CrI credible interval, DPP-4 dipeptidylpeptidase-4, HbA_{1c} glycosylated hemoglobin

saxagliptin or sitagliptin added to stable metformin therapy was shown to be 0.09% (95% CI -0.01 to 0.20%), which is below the predefined criterion ($<0.3\%$) for non-inferiority.

The relative MTCs showed that all DPP-4 inhibitors plus metformin were significantly more effective than metformin alone in reducing mean HbA_{1c} from baseline and achieving a higher proportion of patients with HbA_{1c} $<7\%$ (Table 5). Patients treated with alogliptin were statistically significantly more likely to achieve HbA_{1c} $<7\%$ than patients treated with saxagliptin; however, it should be noted that the 95% credible interval for alogliptin plus metformin was very wide [OR 6.41 (3.15–11.98)]. The direct and indirect treatment effects for HbA_{1c} change from baseline for saxagliptin plus metformin and sitagliptin plus metformin were shown to be consistent, as assessed by Bucher's method [33], for HbA_{1c} mean change from baseline ($p = 0.16$), but inconsistent for the proportion of patients achieving HbA_{1c} $<7\%$ ($p < 0.05$). There were no significant differences in mean change in body weight reported between DPP-4 plus metformin and metformin alone. No body weight data were available for saxagliptin. Absolute mean changes from baseline to study endpoint in mean HbA_{1c} levels were all reductions (i.e., improvements); however, none was statistically significant. Mean changes from baseline to study endpoint in body weight were also non-significant (Table 6).

DPP-4 Plus Sulfonylurea

In the direct-comparison analysis, linagliptin, saxagliptin, sitagliptin, and vildagliptin as dual therapy with SUs were significantly more effective in achieving a greater reduction in mean HbA_{1c} than SU alone (Tables 3, 4); however, data for linagliptin and saxagliptin were based on only one study and are

inconsistent with the vildagliptin studies (HbA_{1c} mean change from baseline, mean body weight change from baseline, and proportion of patients achieving HbA_{1c} $<7\%$ (I^2 59.4, 66.5, and 92.6%, respectively).

In the MTCs, all DPP-4 inhibitors as dual therapy with SU were significantly more effective relative to SU alone in reducing HbA_{1c} levels (Table 5). No data were available for alogliptin plus SU for HbA_{1c} mean change from baseline. Patients receiving dual therapy were more likely to achieve HbA_{1c} $<7\%$ than those treated with SU alone; however, only the vildagliptin plus SU comparison reached statistical significance, OR 5.81 (95% CI 1.35–15.11).

There was no significant difference between treatments in absolute mean change from baseline to endpoint in HbA_{1c} or body weight for any comparison (Table 6).

DPP-4 Plus Metformin Plus Sulfonylurea

Direct-comparison data were only available for linagliptin, sitagliptin, and vildagliptin, with one study included for each; I^2 analysis was, therefore, not possible. Mean changes from baseline in HbA_{1c} for sitagliptin, linagliptin, and vildagliptin were -0.890% (95% CI -2.41 to 0.63%), -0.20% (95% CI -0.73 to -0.51) and -0.760% (95% CI -1.01 to -0.51%), respectively, and mean changes in body weight for linagliptin and sitagliptin were 0.330 kg (95% CI -0.3 to 0.69 kg) and 0.700 kg (95% CI -0.22 to 1.62 kg), respectively (Tables 3, 4). The proportion of patients experiencing hypoglycemic events was reported for linagliptin [OR 1.689 (95% CI 1.16–2.47)], sitagliptin [OR 8.699 (95% CI 1.07–70.76)], and vildagliptin [OR 2.791 (95% CI 0.73–10.72)].

In the MTC, triple therapy with either sitagliptin, linagliptin or vildagliptin, in

combination with metformin and SU, resulted in a non-significant relative mean reduction in HbA_{1c} compared with metformin plus SU. There were insufficient studies reporting the proportion of patients achieving HbA_{1c} <7% to evaluate this outcome. Neither linagliptin nor sitagliptin as triple therapy, in combination with metformin and SU, resulted in a significant mean change from baseline in body weight (Table 5). Change from baseline in body weight was not reported for vildagliptin triple therapy.

There was no significant difference between sitagliptin, linagliptin, and vildagliptin in absolute mean change from baseline to endpoint in HbA_{1c}. Neither linagliptin nor sitagliptin treatment combination resulted in significant changes in body weight from baseline (Table 6).

DPP-4 Plus Pioglitazone

In the direct-comparison analysis, all DPP-4 inhibitors (except saxagliptin, for which no data were available) plus pioglitazone were significantly more effective than pioglitazone alone in achieving a greater reduction in HbA_{1c} from baseline and achieving a greater proportion of patients with HbA_{1c} levels <7% (Tables 3, 4), although the I^2 statistics for alogliptin (86.6% and 54.6%, respectively) may represent substantial heterogeneity.

In the MTC, all DPP-4 inhibitors as dual therapy with pioglitazone were significantly more effective relative to pioglitazone alone in reducing mean HbA_{1c} levels from baseline. All DPP-4 inhibitors (except linagliptin) achieved a statistically significant greater proportion of patients with HbA_{1c} level <7% (Table 5). Only linagliptin plus pioglitazone resulted in a

statistically significant increase in body weight compared with pioglitazone alone (1.20 kg; 95% CI 0.06–2.34 kg).

There was no statistically significant difference between treatments in absolute mean change from baseline to endpoint in HbA_{1c} or body weight for any comparison (Table 6).

DPP-4 Plus Metformin Plus Pioglitazone

As only a single study reported data for a DPP-4 inhibitor (alogliptin) as triple therapy with metformin plus pioglitazone [65], meta-analyses were not possible. The addition of alogliptin and pioglitazone to metformin therapy was shown to result in statistically significant reductions in mean HbA_{1c} from baseline ($-1.4\% \pm \text{SD } 0.05\%$; $p < 0.001$). When added to metformin, the triple combination therapy of alogliptin (pooled dose; 12.5 or 25 mg) and pioglitazone (pooled dose; 15, 30, or 45 mg) was shown to be statistically significantly more effective than either drug in dual therapy with metformin ($p \leq 0.001$). Compared with pioglitazone plus metformin dual therapy, triple combination therapy with alogliptin was not associated with a statistically significant gain in body weight or increased incidence of hypoglycemic events.

DPP-4 Plus Insulin

Data were only available for sitagliptin and vildagliptin. In the direct-comparison analysis, neither sitagliptin nor vildagliptin was statistically significantly more effective than insulin alone in achieving a greater reduction in mean HbA_{1c} from baseline or achieving a greater proportion of patients with HbA_{1c} levels <7% (Tables 3, 4).

There was no statistically significant difference between sitagliptin or vildagliptin in the MTC of both DPP-4 inhibitors plus insulin in the relative mean change from baseline to endpoint in HbA_{1c}. Neither of the DPP-4 inhibitors plus insulin effected a significant difference in change in mean body weight from baseline compared with insulin alone, nor statistically significant ORs of patients experiencing a hypoglycemic event (Table 5).

There was no statistically significant difference between sitagliptin and vildagliptin in absolute mean change from baseline to endpoint in HbA_{1c} or body weight (Table 6).

DPP-4 Plus Metformin Plus Insulin

Only one study reported data for a DPP-4 inhibitor (sitagliptin) as triple therapy with metformin and insulin [36]; meta-analyses were, therefore, not possible. The addition of sitagliptin to insulin plus metformin resulted in a statistically significantly greater mean reduction in HbA_{1c} from baseline (−1.49%; $p < 0.05$) and a greater proportion of patients achieving HbA_{1c} <7% (88%; $p < 0.05$) versus metformin plus insulin. A statistically non-significant increase in body weight was observed ($0.1 \pm \text{SD } 1.6 \text{ kg}$) with triple combination therapy of sitagliptin plus insulin and metformin versus metformin plus insulin.

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the conclusions drawn from the base-case estimates. As the Cochrane Collaboration considers $I^2 > 30\%$ to represent moderate heterogeneity in the effect estimate, analyses breaching this threshold were examined. Appendix 5 (Electronic Supplementary Material) shows direct-comparison meta-analyses with $I^2 > 30\%$.

Study references highlighted in bold were identified as outliers in the forest plots (data not shown) of these analyses, suggesting that these studies may be a major cause of inconsistency in the effect estimate. Two studies were identified as outliers for HbA_{1c} mean change from baseline [88, 89] and two were identified for proportion of patients achieving HbA_{1c} <7% [89, 90].

Sensitivity analyses were performed by investigating the effect of removing these outliers from the respective direct-comparison analyses. No further action was possible for analyses in which there were only two studies, as it was not possible to identify which study was likely to represent a ‘true’ estimate of the effect. Heterogeneity in the HbA_{1c} mean change from baseline analysis for linagliptin versus placebo was not examined as the I^2 statistic was borderline at 33% and there was no obvious outlier in the forest plot.

Table 7 summarizes the new I^2 values from studies that remained in the direct-comparison meta-analysis for each outcome when outlying studies had been removed. These studies all compared a DPP-4 inhibitor plus metformin versus metformin alone and removing them reduced inconsistency in the treatment effect. The I^2 values for mean HbA_{1c} change from baseline in the saxagliptin plus metformin versus metformin and sitagliptin plus metformin versus metformin comparisons decreased by 60.5% and 30.3%, respectively. For the HbA_{1c} <7% outcome, the I^2 value for the sitagliptin plus metformin versus metformin comparison decreased by 80% when DeFronzo et al. [89] was removed. Raz et al. [90] was also highlighted as a possible outlier responsible for the inflated I^2 value for the direct-comparison meta-analysis of sitagliptin plus metformin versus metformin. However, when this study was removed, the I^2 value increased by 9.2% so

Table 8 Results of the sensitivity analysis for the DPP-4 plus metformin vs. metformin mixed treatment comparison meta-analysis: HbA_{1c} mean change from baseline and patients achieving HbA_{1c} <7%

Treatment	Weighted mean change in HbA _{1c} (95% CrI)	Weighted mean change in HbA _{1c} (95% CrI) with studies DeFronzo et al. [89] and Bosi et al. [88] removed	Odds ratio of patients achieving HbA _{1c} <7% vs. metformin (95% CrI)	Odds ratio of patients achieving HbA _{1c} <7% vs. metformin (95% CrI) with DeFronzo et al. [89] removed
Alogliptin + metformin	-0.68 (-0.96 to -0.40)*	-0.68 (-0.95 to -0.40)*	6.41 (3.15–11.98)*†	6.39 (3.19–11.85)*†
Linagliptin + metformin	-0.57 (-0.75 to -0.40)*	-0.56 (-0.73 to -0.40)*	3.37 (1.91–5.72)*	3.30 (1.89–5.59)*
Saxagliptin + metformin	-0.61 (-0.79 to -0.44)*	-0.57 (-0.76 to -0.37)*	2.17 (1.56–2.95)*†	1.91 (1.32–2.67)*†
Sitagliptin + metformin	-0.64 (-0.79 to -0.50)*	-0.63 (-0.77 to -0.48)*	2.87 (2.13–3.82)*	2.79 (2.08–3.71)*
Vildagliptin + metformin	-0.59 (-0.75 to -0.44)*	-0.54 (-0.71 to -0.40)*	2.45 (1.65–3.50)*	2.40 (1.62–3.43)*

CrI credible interval, DPP-4 dipeptidylpeptidase-4, HbA_{1c} glycosylated hemoglobin

* Statistically significant versus metformin

† Statistically significant between treatment groups

conclusions drawn from the MTC analysis comparing HbA_{1c} mean reduction from baseline and proportion of patients achieving HbA_{1c} target <7% between DPP-4 inhibitors.

DISCUSSION

Principal Findings

The principal finding of this systematic review and MTC of the DPP-4 inhibitors is the demonstration of equivalent effects across the class in terms of key efficacy and safety outcomes (HbA_{1c} mean change from baseline, proportion of patients achieving HbA_{1c} <7%, mean change in body weight from baseline, and number of patients with hypoglycemic events between: alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin as monotherapy or dual therapy (plus metformin or SU); alogliptin, linagliptin, sitagliptin and vildagliptin as dual therapy (plus pioglitazone); sitagliptin and vildagliptin as dual therapy (plus insulin); or linagliptin, sitagliptin and vildagliptin as triple therapy (plus metformin and SU), in patients with type 2 diabetes whose glucose levels were insufficiently controlled. The only treatment comparison for which there was a statistically significant difference in the treatment effect was in patients on alogliptin plus metformin, who achieved HbA_{1c} <7% more frequently than those treated with saxagliptin plus metformin [OR 6.41 (95% CI 3.15–11.98) versus 2.17 (95% CI 1.56–2.95)]; however, it should be noted that the 95% credible interval for alogliptin plus metformin is very wide.

In the direct-comparison meta-analyses, the majority of DPP-4 inhibitors, either as monotherapy or as dual or triple therapy, were significantly more effective than the respective comparator in reducing mean HbA_{1c} (i.e., improving glycemic control). The exceptions were sitagliptin in combination with metformin

plus SU versus metformin plus SU, and sitagliptin or vildagliptin plus insulin versus insulin alone. Although the I^2 statistic indicated moderate to substantial heterogeneity in the effect estimate and subsequent removal of outliers resulted in a reduction in the corresponding I^2 statistic, the average effect sizes and the direction of effect remained largely unchanged. Therefore, the removal of studies with heterogeneity had little or no impact on the overall conclusions drawn from the MTCs comparing mean change from baseline in HbA_{1c} and proportion of patients achieving HbA_{1c} <7% between DPP-4 inhibitors.

The results from the MTC analyses and direct-comparison meta-analyses of the DPP-4 inhibitors in this paper are in line with previously published articles by Scheen [2] and Esposito et al. [5]. Similar to the review of DPP-4 inhibitors by Scheen [2] and the meta-analyses reported by Esposito et al. [5], the results of the MTC indicate no differences between the DPP-4 inhibitors, using predefined criteria of overlapping 95% credible intervals. This was the case for DPP-4 inhibitors that were used either as monotherapy or as dual or triple therapy in combination with other anti-diabetic treatments (including metformin, SU, pioglitazone, or insulin). However, the current analysis expanded on that previously published by Esposito et al. [5]. In addition to individual indirect-comparison meta-analyses of DPP-4 inhibitors, we also conducted MTCs of all DPP-4 inhibitors, including linagliptin (previously not included by Esposito et al. [5]), for the same four outcomes.

Separate MTCs were conducted for DPP-4 inhibitors as monotherapy versus placebo or as dual- or triple-therapy combinations versus the respective monotherapy or dual-therapy comparator, as appropriate. Previous analyses

pooled studies of DPP-4 inhibitors versus placebo and studies of DPP-4 inhibitor combination therapy versus other anti-diabetic combinations [5]. Esposito et al. [5] excluded studies with a randomized duration of <12 weeks; this current review did not exclude studies based upon duration (randomized study durations ranged from 4 weeks to 104 weeks). Despite these differences, the current study reached the same conclusion of no difference between all DPP-4 inhibitors across the four outcomes analyzed.

Strengths and Weaknesses of the Study

The strength of this analysis is its robust and transparent design. We conducted a systematic search and rigorous review of published RCTs of pharmacologic treatments in patients with type 2 diabetes and inadequate glycemic control, according to predefined criteria. Further studies, often unpublished, were identified by reviewing the reference lists of selected published systematic reviews and meta-analyses. Data extracted from included studies of DPP-4 inhibitors were analyzed using robust statistical methodology. Both direct- and indirect-comparison data were combined in an MTC using a Bayesian approach. The Bayesian approach combines data in a robust and more intuitive way than a standard frequentist approach.

The comparison of the DPP-4 inhibitors was limited to four outcomes (HbA_{1c} mean change from baseline, proportion of patients achieving HbA_{1c} <7%, mean change in body weight from baseline, and number of patients experiencing a hypoglycemic event).

Studies from which data were extracted were assessed to establish if they represented a robust source of information. A potential weakness of the studies included in the statistical analyses

was identified: the majority of studies were deemed to have between one and three ‘unclear’ assessments out of the seven assessment criteria. If the assessments were deemed to be ‘unclear’, it was not possible to differentiate between studies that had been poorly reported, and studies that were poorly conducted (i.e., of low quality, making it difficult to assess the quality/level of bias in the majority of the studies included in the analysis). Ten studies eligible for data extraction were deemed to be of low quality and, therefore, at a high risk of bias. However, only one of these was eventually included in the statistical analyses, the remainder being excluded for other reasons.

Further, owing to the addition of a MESH/Embase ‘Drug Therapy’ term restriction in the search string, it is possible that studies not indexed as drug therapy could have been overlooked. However, without this search term, the review would have been unmanageable in terms of the number of titles/abstracts to be filtered. Furthermore, unpublished data were not specifically sought, despite a structured search strategy to identify published articles and unpublished studies from a selection of published systematic reviews and meta-analyses. It thus remains possible that some unpublished studies were not identified.

The MTCs were also limited by a number of factors. In order to have sufficient studies to allow quantitative analysis, assumptions were made regarding the imputation of missing standard errors and to include data for all DPP-4 inhibitor and comparator doses reported in all eligible studies identified. In addition, studies of the various SUs were pooled. Variability in the efficacy of treatment doses and/or different SUs is a possible source of heterogeneity and hence a limitation of the analyses. Furthermore, small study numbers remained in some networks, which may have

resulted in uncertain estimated treatment effects. Extension-phase data were excluded, as most studies were no longer randomized and the study population size was generally limited.

Finally, heterogeneity ($I^2 < 30\%$) in the treatment effect between studies included in the direct-comparison meta-analyses was also identified for a number of treatment comparisons. Although sensitivity analyses were conducted, where appropriate, to confirm the robustness of the base-case analyses, heterogeneity in the effect estimates represents some uncertainty in the overall treatment effect.

Conclusion and Further Research

This systematic review and MTC of DPP-4 inhibitors confirmed no difference between alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin, either as monotherapy, or as dual therapy (plus metformin or SU); alogliptin, linagliptin, sitagliptin, and vildagliptin as dual therapy (plus pioglitazone); sitagliptin and vildagliptin as dual therapy (plus insulin), or linagliptin, sitagliptin, and vildagliptin as triple therapy (plus metformin and SU). The study showed that the DPP-4 inhibitors have similar efficacy in terms of mean reduction (i.e., improvement) in HbA_{1c} from baseline, increased proportion of patients achieving HbA_{1c} <7%, mean change in body weight from baseline, and number of patients experiencing a hypoglycemic event. Further research is required to assess the long-term safety and efficacy of this class of oral anti-diabetic agents. The current MTCs excluded extension-phase data.

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Paul Craddy and K. Ian Johnson were involved in determining the scope and research question for the systematic review and performed critical review of the manuscript. Hannah-Jayne Palin was involved in screening of articles and data-extraction stages of the systematic review and was responsible for all stages of manuscript preparation.

Claire Chadwick and Gillian Sibbring are employees of McCann Complete Medical (Macclesfield, UK), which was commissioned by Takeda Pharmaceuticals International GmbH to conduct the systematic review and meta-analysis. Claire Chadwick undertook project management of the systematic review and meta-analysis and was also involved in finalizing the scope of the analyses, first- and second-pass screening of articles, and data-extraction stages of the systematic review. Gillian Sibbring was involved in data checking for statistical analyses and also undertook project management and critical review of manuscript at all stages of preparation. Daniel Shaw was an employee of McCann Complete Medical at the time the study was undertaken and performed all statistical analyses.

Conflict of interest. Hannah-Jayne Palin was an employee of McCann Complete Medical at the time the study was undertaken, a company sponsored by Takeda Pharmaceuticals International GmbH to conduct this study and prepare the manuscript. K. Ian Johnson was an employee of McCann Complete Medical at the time the study was undertaken, a company sponsored by Takeda Pharmaceuticals

International GmbH to conduct this study and prepare the manuscript. Paul Craddy was an employee of Takeda Pharmaceuticals International GmbH at the time the study was undertaken.

Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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