A Meta-Analysis of Placebo-Controlled Clinical Trials Assessing the Efficacy and Safety of Incretin-Based Medications in Patients with Type 2 Diabetes

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Key Words

Incretin mimetics • Dipeptyl peptidase type 4 inhibitor • Diabetes • Glycemic control • Hypoglycemia • Weight

Abstract

Aims: A systematic review of the literature, in combination with a meta-analysis of randomized controlled trials comparing treatments with placebo, was conducted to provide an update on the clinical efficacy and safety of incretin-based medications in adult patients with type 2 diabetes.

Methods: A literature search (2000–2009) identified 38 placebo-controlled trials (phase II or later – parallel design) comparing exenatide (n = 8), liraglutide (n = 7), vildagliptin (n = 11) and sitagliptin (n = 12) with placebo. Outcomes were change from baseline in HbA_{1c} and in weight, and the number of patient-reported hypoglycemic episodes. HbA_{1c} and weight outcomes were analyzed as weighted mean differences (WMD), and the number of hypoglycemic episodes as relative risks (RR). **Results:** Patients receiving liraglutide showed greater reduction in HbA_{1c} in comparison to placebo (WMD = –1.03, 95% confidence interval, CI = –1.16 to –0.90, p < 0.001) than those on sitagliptin (WMD = –0.79, 95% CI = –0.93 to –0.65, p < 0.001), exenatide (WMD = –0.75, 95% CI = –0.83 to –0.67, p < 0.001) or vildagliptin (WMD = –0.67, 95% CI = –0.83 to –0.52, p < 0.001). Weight was statistically sig-

nificantly negatively associated with exenatide (WMD = –1.10, 95% CI = –1.32 to –0.87, p < 0.001) and positively associated with sitagliptin (WMD = 0.60, 95% CI = 0.33–0.87, p < 0.001) and vildagliptin (WMD = 0.56, 95% CI = 0.27–0.84, p < 0.001). The number of patient-reported hypoglycemic episodes was statistically significantly associated with the use of sitagliptin (RR = 2.56, 95% CI = 1.23–5.33, p = 0.01) and exenatide (RR = 2.40, 95% CI = 1.30–4.11, p = 0.002). **Conclusion:** Incretin-based therapies are effective in glycemic control and also offer other advantages such as weight loss (exenatide and liraglutide). This may have an important impact on patient adherence to medication.

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Introduction

Diabetes is a serious global health issue, with type 2 diabetes mellitus (T2DM) accounting for approximately 90–95% of all cases [1]. The recent rapid increase in the prevalence of T2DM is in part due to an ageing population but may also be attributed to an increase in the number of overweight and obese people. It is estimated that approximately 6.6% of the world's population aged between 20 and 79 years will have diabetes in 2010, with this figure projected to increase to 7.8% by 2030 [2].

In the USA, the prevalence of T2DM among people over 20 years of age is 10.7% (23.5 million people) [3]. The total estimated cost of diabetes in the USA in 2007 was USD 174 billion, including USD 116 billion in excess medical expenditures and USD 58 billion in reduced national productivity [4]. In the UK, the prevalence of T2DM in 2009 within the adult population was 2.6 million, with the current estimated cost of treating diabetes and its related complications estimated to account for 10% of the National Health Service 2007/2008 budget or GBP 9 billion a year [5].

It has been suggested that ineffective drug therapies, poor patient adherence to therapy and inadequate management regimes may all contribute to the increasing incidence of complications linked to the disease [6]. Patients with T2DM are often required to undertake significant lifestyle and dietary changes in addition to prescription antidiabetes drug therapy. There exist a variety of antidiabetes drug therapies including metformin, sulfonylurea, thiazolidinediones, acarbose, prandial glucose regulators and insulin in various forms. A relatively new class of oral antihyperglycemic drugs has recently gained widespread use, namely the dipeptyl peptidase type 4 (DPP-4) inhibitors; these are best classified as incretin enhancers: sitagliptin (Januvia™; Merck & Co. Inc.) and vildagliptin (Galvus™; Novartis).

Sitagliptin [7, 8] is a once daily oral antihyperglycemic agent. It is used in addition to diet and exercise in the following ways:

- monotherapy in patients who are not satisfactorily controlled by diet and exercise and for whom metformin (an antidiabetic medicine) is contraindicated;
- in combination with metformin or a peroxisome proliferator-activated receptor (PPAR) γ agonist such as thiazolidinediones, in patients who are not satisfactorily controlled on metformin or PPAR- γ agonist used alone;
- in combination with a sulfonylurea in patients who are not adequately controlled with a sulfonylurea when used as monotherapy or for whom metformin is contraindicated;
- in combination with both metformin and a sulfonylurea or a PPAR- γ agonist, in patients who are not satisfactorily controlled on the two medicines;
- in combination with insulin, with or without metformin, in patients who are not satisfactorily controlled by a stable dose of insulin [7, 8].

Sitagliptin is often prescribed at a dose of 100 mg once daily and is not currently licensed for use in triple therapy [9].

Vildagliptin [10] is administered as dual oral therapy in combination with:

- metformin, in patients with insufficient glycemic control despite a maximal tolerated dose of monotherapy with metformin;
- a sulfonylurea, in patients with insufficient glycemic control despite a maximal tolerated dose of a sulfonylurea and for whom metformin is inappropriate due to contraindications or intolerance;
- a thiazolidinedione, in patients with insufficient glycemic control and for whom the use of a thiazolidinedione is appropriate;
- when used in dual combination with a sulfonylurea, the recommended dose of vildagliptin is 50 mg once daily.

Another recently marketed class of antidiabetes therapies is the incretin mimetics, consisting of exenatide (Byetta™; Eli Lilly & Co.) and liraglutide (Victoza™; Novo Nordisk). Both are injectable medications.

Exenatide is administered in combination with metformin and/or sulfonylurea in patients who have not achieved adequate glycemic control by maximally tolerated doses of these oral antihyperglycemic drugs; it has also been recently approved as a monotherapy [11]. Exenatide therapy is initiated at a 5- μ g dose administered twice daily for at least 1 month in order to improve tolerability following which the dose can be increased to 10 μ g twice daily to further improve glycemic control [11].

Liraglutide (Victoza) is indicated for treatment in combination with:

- metformin or a sulfonylurea, in patients with insufficient glycemic control despite a maximal tolerated dose of monotherapy with metformin or sulfonylurea;
- metformin and a sulfonylurea or metformin and a thiazolidinedione in patients with insufficient glycemic control despite dual therapy [12].

The starting dose of liraglutide is 0.6 mg daily. After at least 1 week, the dose is increased to 1.2 mg, based on clinical response, and after at least 1 further week the dose can be increased to 1.8 mg [12].

In order to provide an up-to-date comprehensive picture of the clinical efficacy and safety of the main types of incretin mimetics and DPP-4 inhibitors, we conducted a systematic review of the literature including trials of exenatide, liraglutide, sitagliptin and vildagliptin. Furthermore, a meta-analysis of the randomized controlled trials was performed, comparing each of these treatments to placebo. The aims were to: (1) describe the published evidence on the main clinical efficacy and safety outcomes of each of the treatments, and (2) identify a pooled

estimate of the effect of each treatment versus placebo for the main outcomes so that comparative data are available in the literature for use in evidence-based practice and research.

Materials and Methods

The Embase, and Cochrane Library electronic databases were searched through Embase.com for English-language papers from January 2000 to July 2009, using the following search headings: type of diabetes, type of intervention, type of trial, comparators of interest and outcomes of interest. Clinical trials were included if they met the following criteria: (1) published in the English language, (2) primary study comparing either exenatide, liraglutide, vildagliptin or sitagliptin with placebo; (3) included patients with T2DM at least 18 years of age; (4) randomized controlled trial design (phase II, phase III, parallel design); (5) minimum study sample of 100 patients; (6) at least one baseline and posttreatment efficacy and/or safety outcome of interest (see Outcomes section below), and (7) reports of a dispersion measure [standard deviation, standard error of the mean or confidence interval (CI)], for both treatment arms of the study.

In addition, the reference lists and citation sections of recovered articles were searched for further studies, as were abstracts presented at the American Diabetes Association and the European Association Study of Diabetes conferences from August 2008 to July 2009.

The literature search identified 389 potentially relevant articles for screening. Of these, the research team (W.F., C.L., D.W.) excluded 312 articles (303 literature reviews and 9 conference abstracts). Any discrepancies were resolved by consensus between the 3 reviewers. Thus, 77 abstracts were retained for detailed evaluation. Of these, 40 were excluded for various reasons (less than 100 participants, no placebo group, no relevant outcome, no medication of interest), and 37 were retained for full data extraction for meta-analysis. One further study was identified by checking the reference lists of full-text articles, bringing the total to 38. For quality reasons, the team ensured (W.F., C.L., D.W.) that all selected studies were controlled clinical trials with proper randomization of patients and that they reported on all initially included patients according to the intention-to-treat principle and reported blinded outcome assessment.

Of the 38 trials identified, 8 were of exenatide, 7 of liraglutide, 12 of sitagliptin and 11 of vildagliptin (fig. 1).

Outcomes

The outcomes of interest in this analysis were: (1) change from baseline in hemoglobin A_{1c} (HbA_{1c}); (2) change from baseline in weight, and (3) when available, body mass index. For these outcomes 1–3, the weighted mean differences (WMDs) and associated precision for the change from baseline were calculated in each study. Baseline and study endpoint HbA_{1c}, weight and patient-reported hypoglycemic events are presented in table 1.

Data Extraction

Data on the key characteristics of the study sample (e.g. age, gender, study duration, duration of diabetes, study location, sample size, definition of hypoglycemia by study), outcomes mea-

Fig. 1. Decision process for selecting relevant full-text articles for exenatide, liraglutide, sitagliptin and vildagliptin. RCT = Randomized controlled trial.

sured and results reported in each study were tabulated in a data extraction sheet. Data extraction was performed by one reviewer (D.W.), with the completed table checked for accuracy by a second reviewer (W.F.). The data extraction sheet was further reviewed by a statistician (C.L.) to ensure that all data needed for the meta-analysis were captured correctly.

Statistical Analysis

The statistical analysis was divided into 3 steps: (1) direct meta-analyses of each treatment versus placebo and (2) assessment of the impact of adjustment variables on the results of the meta-analyses. The outcome measures reported in each study were meta-analyzed to produce a pooled estimate of the effect of each treatment versus placebo for each outcome. Pooling was done using both fixed-effect and random-effect models. Heterogeneity was assessed using the χ^2 test and the I² statistic. If the I² statistics showed that significant heterogeneity existed between study results, a random-effect model was used, as advocated by Egger and Davey Smith [51].

Table 1. Baseline and study endpoint HbA_{1c} (%) and weight (kg) values

Study reference	Interventions	Baseline HbA _{1c}	HbA _{1c} at study endpoint	Change in HbA _{1c}	Baseline mean weight	Weight at study endpoint	Change in weight	Number of hypoglycemic episodes
<i>Exenatide versus placebo</i>								
Zinman et al. [13], 2007	Exenatide 10 µg twice daily Placebo	7.9 ± 0.9 7.9 ± 0.8	not reported	0.09 ± 0.10 ^a −0.89 ± 0.09 ^a	97.5 ± 18.8 ^a 96.9 ± 19.0 ^a	96.89 ± 0.26 ^a 95.38 ± 0.25 ^a	−1.75 ± 0.25 ^a −0.24 ± 0.26 ^a	13
De Fronzo et al. [14], 2005	Exenatide 5 µg twice daily Exenatide 10 µg twice daily Placebo twice daily	8.3 ± 1.1 8.2 ± 1.0 8.2 ± 1.0	not reported	−0.4 ± 0.1 ^a −0.8 ± 0.1 ^a 0.1 ± 0.1 ^a	100 ± 22 101 ± 20 100 ± 19	not reported	−1.6 ± 0.4 ^a −2.8 ± 0.5 ^a −0.3 ± 0.3 ^a	11
Gao et al. [15], 2009	Exenatide 10 µg twice daily Placebo twice daily	8.3 ± 1.0 8.3 ± 1.0	not reported	−1.2 −0.4	69.6 ± 11.2 67.9 ± 11.1	not reported	−1.2 ± 2.34 −0.1 ± 1.94	41
Kendall et al. [16], 2005	Exenatide 5 µg twice daily Exenatide 10 µg twice daily Placebo	8.5 ± 1.0 8.5 ± 1.1 8.5 ± 1.0	not reported	−0.55 ± 0.07 ^a −0.77 ± 0.08 ^a 0.23 ± 0.07 ^a	97 ± 19 98 ± 21 99 ± 19	not reported	−1.6 ± 0.2 ^a −1.6 ± 0.2 ^a −0.9 ± 0.2 ^a	114
Moretto et al. [17], 2008	Exenatide 5 µg twice daily Exenatide 10 µg twice daily Placebo twice daily	7.9 ± 1.0 7.8 ± 1.0 7.8 ± 0.9	not reported	−0.7 ± 0.1 ^a −0.9 ± 0.1 ^a −0.2 ± 0.1 ^a	85 ± 15 86 ± 16 86 ± 16	not reported	−2.8 ± 0.3 ^a −3.1 ± 0.3 ^a −1.4 ± 0.3 ^a	7
Poon et al. [18], 2005	Exenatide 2.5 µg twice daily Exenatide 5 µg twice daily Exenatide 7.5 µg twice daily Exenatide 10 µg twice daily Placebo twice daily	7.7 ± 0.7 7.5 ± 0.7 7.4 ± 0.7 7.5 ± 0.5 7.5 ± 0.8	not reported	−0.3 ± 0.1 ^a −0.4 ± 0.1 ^a −0.5 ± 0.0 ^a −0.5 ± 0.1 ^a 0.1 ± 0.1 ^a	98.6 ± 22.6 103.6 ± 15.4 99.5 ± 21.0 92.4 ± 15.1 102.6 ± 19.9	not reported	−0.07 ± 0.3 ^a −0.7 ± 0.2 ^a −1.4 ± 0.3 ^a −1.8 ± 0.3 ^a 0.0 ± 0.3 ^a	2
Buse et al. [19], 2004	Exenatide 5 µg b.i.d. Exenatide 10 µg b.i.d. Placebo b.i.d.	8.5 ± 1.1 8.6 ± 1.2 8.7 ± 1.2	not reported	−0.46 ± 0.12 ^a −0.86 ± 0.11 ^a 0.12 ± 0.09 ^a	94.9 ± 1.9 ^a 95.2 ± 1.6 ^a 99.1 ± 1.7 ^a	not reported	−0.9 ± 0.3 ^a −1.6 ± 0.3 ^a −0.6 ± 0.3 ^a	64
Fineman et al. [20], 2003	Exenatide 0.08 µg (breakfast, dinner, bedtime) Exenatide 0.08 µg (breakfast, dinner) Exenatide 0.08 µg (breakfast, bedtime) Placebo 0.08 µg (breakfast, dinner, bedtime)	9.1 ± 1.2 9.3 ± 1.0 9.2 ± 1.1 9.4 ± 1.3	not reported	−1.1 ± 0.07 ^a −0.71 ± 0.12 ^a −1.02 ± 0.11 ^a −0.3 ± 0.11 ^a	97.0 ± 16.7 98.2 ± 16.0 96.8 ± 17.5 97.6 ± 16.7	not reported	not reported	not reported
<i>Liraglutide versus placebo</i>								
Zinman et al. [21], 2009	Liraglutide 1.2 mg once daily Liraglutide 1.8 mg once daily Placebo once daily	8.5 ± 1.2 8.6 ± 1.2 8.4 ± 1.2	7.0 7.1 7.9	−1.5 ± 0.1 ^a −1.5 ± 0.1 ^a −0.5 ± 0.1 ^a	not reported	not reported	−1.75 ± 2.75 −0.24 ± 2.75	
Madsbad et al. [22], 2004	Liraglutide 0.045 mg once daily Liraglutide 0.225 mg once daily Liraglutide 0.45 mg once daily Liraglutide 0.60 mg once daily Liraglutide 0.75 mg once daily Placebo once daily	7.4 ± 0.8 7.9 ± 0.8 7.7 ± 1.0 7.4 ± 1.2 7.4 ± 0.9 7.4 ± 1.2	7.91 7.51 7.31 6.81 6.81 7.31	not reported	not reported	not reported	not reported	1
Marre et al. [23], 2009	Liraglutide 0.6 mg once daily Liraglutide 1.2 mg once daily Liraglutide 1.8 mg once daily Placebo once daily	8.4 ± 1.0 8.5 ± 1.1 8.5 ± 0.9 8.4 ± 1.0	7.8 ± 0.15 ^a 7.4 ± 0.16 ^a 7.4 ± 0.16 ^a 8.6 ± 0.24 ^a	−0.6 ± 0.15 ^a −1.08 ± 0.11 ^a −1.13 ± 0.17 ^a 0.23 ± 0.16 ^a	82.6 ± 17.7 83.0 ± 18.1 81.9 ± 17.1 80.6 ± 17.0	not reported	0.7 ± 0.4 ^a 0.3 ± 0.3 ^a −0.2 ± 0.4 ^a −0.1 ± 0.5 ^a	52
Nauck et al. [24], 2009	Liraglutide 0.6 mg once daily Liraglutide 1.2 mg once daily Liraglutide 1.8 mg once daily Placebo once daily	8.4 ± 0.9 8.3 ± 1.0 8.4 ± 1.0 8.4 ± 1.1	not reported	−0.7 ± 0.1 ^a −1.0 ± 0.1 ^a −1.0 ± 0.1 ^a 0.1 ± 0.1 ^a	not reported	not reported	not reported	21
Seino et al. [25], 2008	Liraglutide 0.1 mg once daily Liraglutide 0.3 mg once daily Liraglutide 0.6 mg once daily Liraglutide 0.9 mg once daily Placebo once daily	8.50 ± 0.84 8.24 ± 0.92 8.21 ± 0.83 8.12 ± 0.98 8.43 ± 1.02	7.78 ± 0.91 7.17 ± 1.01 6.71 ± 0.92 6.45 ± 0.77 8.52 ± 1.23	not reported	64.26 ± 10.46 61.52 ± 9.46 61.54 ± 10.98 61.48 ± 10.55 62.00 ± 10.97	64.21 ± 10.67 61.67 ± 11.39 61.42 ± 9.68 61.00 ± 11.07 61.05 ± 10.89	not reported	0

Table 1 (continued)

Study reference	Interventions	Baseline HbA _{1c}	HbA _{1c} at study endpoint	Change in HbA _{1c}	Baseline mean weight	Weight at study endpoint	Change in weight	Number of hypoglycemic episodes
Vilsboll et al. [26], 2007	Liraglutide 0.65 mg once daily Liraglutide 1.25 mg once daily Liraglutide 1.90 mg once daily Placebo once daily	8.1 ± 0.6 8.3 ± 0.8 8.5 ± 0.9 8.2 ± 0.7	not reported	-0.98 -1.4 -1.45 0.29	not reported	not reported	not reported	0
Russell-Jones et al. [27], 2008 (abstract only)	Liraglutide 1.8 mg once daily Placebo twice daily	8.3 8.2	7.0 ± 1.0 8.1 ± 1.3	-1.3 ± 0.09 ^a -0.2 ± 0.11 ^a	not reported	not reported	-1.80 ± 5.03 -0.42 ± 4.18	not reported
<i>Sitagliptin versus placebo</i>								
Scott et al. [28], 2008	Sitagliptin 100 mg once daily Placebo once daily	7.8 ± 1.0 7.7 ± 0.9	7.01 ± 0.86 7.47 ± 1.05	-0.73 -0.22	83.1 ± 17.1 84.6 ± 16.5	not reported	-0.4 ± 1.98 -0.8 ± 1.96	12
Aschner et al. [29], 2006	Sitagliptin 100 mg once daily Sitagliptin 200 mg once daily Placebo once daily	8.01 ± 0.88 8.08 ± 0.94 8.03 ± 0.82	7.39 ± 1.15 7.31 ± 1.14 8.20 ± 1.37	-0.61 -0.76 0.18	85.0 ± 18. 83.7 ± 19.2 85.0 ± 18.1	not reported	-0.2 ± 0.2 ^a -0.1 ± 0.2 ^a -1.1 ± 0.2 ^a	5
Charbonnel et al. [30], 2006	Sitagliptin 100 mg once daily Placebo once daily	7.96 ± 0.81 8.03 ± 0.82	7.26 ± 0.97 7.95 ± 1.10	-0.67 -0.02	86.7 ± 17.8 89.6 ± 17.5	not reported	not reported	6
Goldstein et al. [31], 2007	Sitagliptin 50 mg twice daily Sitagliptin 50 mg twice daily Sitagliptin 100 mg once daily Placebo	8.79 ± 1.00 8.76 ± 0.95 8.87 ± 0.99 8.68 ± 1.00	7.37 ± 1.20 6.87 ± 1.09 8.18 ± 1.45 8.88 ± 1.47	-1.4 -1.9 -0.66 0.17	not reported	not reported	not reported	7
Hanefeld et al. [32], 2007	Sitagliptin 25 mg once daily Sitagliptin 50 mg once daily Sitagliptin 100 mg once daily Sitagliptin 50 mg twice daily Placebo	7.71 ± 0.91 7.60 ± 0.94 7.78 ± 0.90 7.79 ± 0.85 7.59 ± 0.89	7.47 ± 1.30 7.22 ± 1.02 7.38 ± 1.11 7.41 ± 1.10 7.76 ± 1.11	-0.28 -0.44 -0.44 -0.43 0.12	not reported	not reported	not reported	5
Hermansen et al. [33], 2007	Sitagliptin 100 mg once daily Sitagliptin 100 mg once daily Sitagliptin cohort Placebo once daily Placebo once daily Placebo cohort	8.42 ± 0.79 8.27 ± 0.73 8.34 ± 0.76 8.43 ± 0.80 8.26 ± 0.68 8.34 ± 0.74	not reported	-0.3 -0.59 -0.45 0.27 0.3 0.28	85.8 ± 22.5 87.2 ± 19.7 86.5 ± 21.1 85.1 ± 22.6 86.7 ± 21.1 85.9 ± 21.8	not reported	1.1 not reported 0.8 not reported not reported not reported	27 (sitagliptin 100 mg once daily) 8 (sitagliptin 100 mg once daily) 19 (sitagliptin cohort)
Mohan et al. [34], 2009	Sitagliptin 100 mg once daily Placebo once daily	8.7 ± 1.0 8.7 ± 1.0	8.0 ± 1.3 9.1 ± 1.6	-0.7 0.3	66.8 ± 10.2 66.6 ± 11.4		0.6 ± 0.1 0.0 ± 0.2	0
Nonaka et al. [35], 2008	Sitagliptin 100 mg once daily Placebo once daily	7.54 ± 0.85 7.69 ± 0.86	6.90 ± 1.00 8.09 ± 1.04	-0.65 0.41	not reported	not reported	-0.1 ± 1.56 -0.7 ± 1.33	0
Raz et al. [36], 2008	Sitagliptin 100 mg once daily Placebo once daily	9.3 ± 0.9 9.1 ± 0.8	not reported	-1.0 0.0	81.5 ± 16.8 81.2 ± 19.4	not reported	not reported	5
Scott et al. [37], 2007	Sitagliptin 5 mg twice daily Sitagliptin 12.5 mg twice daily Sitagliptin 25 mg twice daily Sitagliptin 50 mg twice daily Placebo	7.89 ± 0.94 7.85 ± 0.88 7.89 ± 0.94 7.83 ± 0.95 7.88 ± 0.96	7.77 ± 1.22 7.48 ± 0.98 7.50 ± 1.14 7.34 ± 1.01 8.14 ± 1.23	-0.15 -0.41 -0.43 -0.54 0.23	not reported	not reported	not reported	2

Table 1 (continued)

Study reference	Interventions	Baseline HbA _{1c}	HbA _{1c} at study endpoint	Change in HbA _{1c}	Baseline mean weight	Weight at study endpoint	Change in weight	Number of hypoglycemic episodes
Rosenstock et al. [38], 2006	Sitagliptin 5 mg once daily Placebo	8.05 ± 0.81 8.00 ± 0.83	7.17 ± 0.91 7.82 ± 1.10	-0.85 -0.15	90.9 ± 17.0 86.4 ± 17.4	not reported	1.8 1.5	2
Raz et al. [39], 2006	Sitagliptin 100 mg once daily Sitagliptin 200 mg once daily Placebo	8.04 ± 0.82 8.14 ± 0.91 8.05 ± 0.90	7.58 ± 1.35 7.58 ± 1.35 8.21 ± 1.35	-0.48 -0.36 0.12	89.7 ± 19.1 89.6 ± 19.4 92.8 ± 18.8	not reported	not reported	12
<i>Vildagliptin versus placebo</i>								
Ahren et al. [40], 2004	Vildagliptin 50 mg once daily Placebo once daily	7.7 ± 0.1 ^a 7.9 ± 0.1 ^a	not reported	-0.6 ± 0.1 0.1 ± 0.1	not reported	not reported		3
Ristic et al. [41], 2005	Vildagliptin 25 mg once daily Vildagliptin 25 mg twice daily Vildagliptin 50 mg once daily Vildagliptin 100 mg once daily Placebo once daily	7.64 ± 0.69 7.73 ± 0.80 7.70 ± 0.82 7.64 ± 0.75 7.76 ± 0.83	not reported	-0.31 ± 0.11 -0.27 ± 0.10 -0.56 ± 0.10 -0.53 ± 0.10 -0.13 ± 0.10	89.4 ± 2.8 ^a 91.1 ± 2.0 ^a 87.9 ± 2.3 ^a 91.5 ± 2.2 ^a 92.0 ± 2.1 ^a	not reported	0.06 ± 0.33 ^a -0.55 ± 0.32 ^a 0.04 ± 0.33 ^a -0.07 ± 0.31 ^a -0.73 ± 0.33 ^a	14
Bosi et al. [42], 2007	Vildagliptin 50 mg once daily Vildagliptin 100 mg once daily Placebo once daily	8.4 ± 0.9 8.4 ± 1.0 8.3 ± 0.9	not reported	-0.9 ± 0.1 ^a -0.5 ± 0.1 ^a 0.2 ± 0.1 ^a	not reported	not reported	not reported	2
Dejager et al. [43], 2007	Vildagliptin 50 mg once daily Vildagliptin 50 mg twice daily Vildagliptin 100 mg once daily Placebo	8.2 ± 0.1 ^a 8.6 ± 0.1 ^a 8.4 ± 0.1 ^a 8.4 ± 0.1 ^a	not reported	-0.8 ± 0.1 ^a -0.8 ± 0.1 ^a -0.9 ± 0.1 ^a -0.3 ± 0.1 ^a	104 90 92 94	not reported	1.8 ± 0.4 -0.3 ± 0.4 -0.8 ± 0.4 -1.4 ± 0.4	3
Garber et al. [44], 2007	Vildagliptin 50 mg once daily Vildagliptin 100 mg once daily Placebo	8.6 ± 1.0 8.7 ± 1.2 8.7 ± 1.2	7.7 ± 0.1 ^a 7.5 ± 0.1 ^a 8.1 ± 0.1 ^a		not reported	not reported	not reported	1
Garber et al. [45], 2008	Vildagliptin 50 mg once daily Vildagliptin 100 mg once daily Placebo	8.5 ± 0.9 8.6 ± 1.0 8.5 ± 1.0	not reported	-0.58 ± 0.10 -0.63 ± 0.09 -0.07 ± 0.09	91.5 ± 1.6 87.3 ± 1.6 89.4 ± 1.6	not reported	1.3 ± 0.3 -0.1 ± 0.3 -0.4 ± 0.3	8
Goodman et al. [46], 2009	Vildagliptin 100 mg once daily a.m. Vildagliptin 100 mg once daily p.m. Vildagliptin total Placebo once daily	8.5 ± 1 8.5 ± 0.9 8.5 ± 1 8.7 ± 1.1	not reported	-0.66 ± 0.1 ^a -0.53 ± 0.1 ^a not reported 0.17 ± 0.1 ^a	not reported	not reported	not reported	2
Kikuchi et al. [47], 2009	Vildagliptin 10 mg twice daily Vildagliptin 25 mg twice daily Vildagliptin 50 mg twice daily Placebo twice daily	7.4 ± 0.8 7.4 ± 0.9 7.4 ± 0.8 7.4 ± 0.8	6.8 ± 0.1 ^a 6.7 ± 0.1 ^a 6.5 ± 0.1 ^a 7.6 ± 0.1 ^a	-0.53 -0.67 -0.92 0.28	64.2 ± 10.4 63.6 ± 9.7 62.7 ± 9.3 63.8 ± 10.1	not reported	-0.2 ± 1.5 0.2 ± 1.3 0.5 ± 1.4 -0.5 ± 1.1	5
Pi-Sunyer et al. [48], 2007	Vildagliptin 50 mg once daily Vildagliptin 50 mg twice daily Vildagliptin 100 mg once daily Placebo	8.3 ± 0.1 ^a 8.4 ± 0.1 ^a 8.3 ± 0.1 ^a 8.5 ± 0.1 ^a	7.9 ± 0.2 ^a 7.7 ± 0.2 ^a 7.5 ± 0.1 ^a 8.4 ± 0.2 ^a	-0.5 ± 0.1 ^a -0.7 ± 0.1 ^a -0.8 ± 0.1 ^a 0.0 ± 0.1 ^a	90.4 ± 2.4 ^a 90.4 ± 2.1 ^a 90.5 ± 2.1 ^a 92.6 ± 2.5 ^a	90.1 ± 2.4 ^a 90.5 ± 2.1 ^a 90.2 ± 2.2 ^a 91.1 ± 2.4 ^a	-0.4 ± 0.4 ^a -0.0 ± 0.4 ^a -0.4 ± 0.3 ^a -1.4 ± 0.4 ^a	0
Scherbaum et al. [49], 2008	Vildagliptin 50 mg once daily Placebo	6.7 ± 0.4 6.7 ± 0.4	not reported	-0.2 ± 0.1 0.1 ± 0.1	86 ± 1.2 85 ± 1.4	not reported	-0.5 ± 0.3 -0.2 ± 0.3	0
Mimori et al. [50], 2006	Vildagliptin 10 mg twice daily Vildagliptin 25 mg twice daily Vildagliptin 50 mg twice daily Placebo	7.4 ± 0.8 7.4 ± 0.9 7.4 ± 0.8 7.4 ± 0.7	not reported	0.53 ± 0.07 0.67 ± 0.07 0.92 ± 0.07 0.28 ± 0.07	not reported	not reported	not reported	5

^a Means ± SEM, all other results are means ± SD.

The impact of major adjustment variables on these pooled estimates was assessed using meta-regression [51]. These covariates included (1) study duration, (2) mean age, (3) gender, (4) duration of diabetes, (5) mean HbA_{1c} level at baseline, (6) mean weight at baseline and (7) whether the treatment was given as monotherapy or as add-on. However, these adjustments were only performed when data were available to run the model.

The metaregression model relates the treatment effect to the study level covariates, assuming a normal distribution for the residual errors. The estimated between-studies variance is reported for each model and is a measure of the residual heterogeneity once having adjusted for the covariates. An adjusted estimate of the difference between each treatment and placebo is reported for each analysis, alongside p values and 95% two-sided CIs. All analyses were performed in Stata SE version 8.2.

Results

Study/Patient Characteristics

There were 8 trials on exenatide, 7 on liraglutide, 12 on sitagliptin and 11 on vildagliptin. Descriptions of the studies and of the patient characteristics are presented in the Appendix.

Of the 38 studies that were reviewed in depth, 2 had a duration longer than 30 weeks, both of which were vildagliptin trials. Trials on exenatide ranged in duration from 4 to 30 weeks, on liraglutide from 12 to 26 weeks, on sitagliptin from 12 to 30 weeks and on vildagliptin from 12 to 52 weeks. All study arms were directly compared with placebo; 34/38 were double-blind while 4/38 were triple-blind (all were exenatide trials).

In terms of patient characteristics, the mean age of patients across all trials ranged from 50.9 to 62.9 years. For exenatide patients, the mean age was 54.0 ± 1.3 years, for those on liraglutide 56.6 ± 0.8 years, sitagliptin 54.9 ± 1.4 years and vildagliptin 56.4 ± 3.3 years. Gender distribution was also similar across trials. For example, the proportion of male participants in the exenatide trials ranged from 42 to 60%, for liraglutide from 50 to 67%, for sitagliptin from 45 to 62% and for vildagliptin from 47 to 67%. There were also variations in the duration of the diabetes diagnosis: exenatide 1.7–8.9 years; liraglutide 4.5–9.0 years; sitagliptin 2.0–8.8 years; vildagliptin 2.2–7.2 years.

Glycemic Control

The results on glycemic control are presented in table 2. Both DPP-4 inhibitors, sitagliptin and vildagliptin, were shown to produce a statistically significant reduction in HbA_{1c} compared with placebo. The direct random-effect meta-analysis of randomized controlled trials

Table 2. Unadjusted results of HbA_{1c} comparing each study treatment with placebo

Change from baseline in HbA _{1c} levels: metaregression	Number of RCTs	WMD	95% CI	p value
Vildagliptin	11	–0.67	–0.83 to –0.52	<0.001
Sitagliptin	12	–0.79	–0.93 to –0.65	<0.001
Exenatide	8	–0.75	–0.83 to –0.67	<0.001
Liraglutide	7	–1.03	–1.16 to –0.90	<0.001

RCT = Randomized controlled trial.

comparing vildagliptin with placebo showed a statistically significant difference in HbA_{1c} decline from baseline favoring vildagliptin (unadjusted model: WMD = –0.67, 95% CI = –0.83 to –0.52, $p < 0.001$). Controlling for the covariates did not impact on the results.

Similar HbA_{1c} efficacy results were found when sitagliptin was compared with placebo (unadjusted model: WMD = –0.79, 95% CI = –0.93 to –0.65, $p < 0.001$), with a significantly high level of heterogeneity detected in the analysis ($\chi^2 p < 0.001$). In the adjusted analyses, 2 covariates were found to be statistically significant in the models: baseline weight (WMD = –0.74, 95% CI = –0.83 to –0.65, $p < 0.001$) and baseline HbA_{1c} level (WMD = –0.80, 95% CI = –0.92 to –0.68, $p < 0.001$).

When exenatide and liraglutide were compared against placebo, both treatments showed a statistically significant difference in HbA_{1c} decrease from baseline. Two separate direct fixed-effect meta-analyses showed statistically significant differences in HbA_{1c} decrease from baseline favoring exenatide (unadjusted model: WMD = –0.75, 95% CI = –0.83 to –0.67, $p < 0.001$), and favoring liraglutide (unadjusted model: WMD = –1.03, 95% CI = –1.16 to –0.90, $p < 0.001$), compared with placebo. In the adjusted analyses for exenatide, controlling for whether exenatide was given as monotherapy or in combination with another treatment provided the most variability, but even this estimate fell within the boundaries of the unadjusted model CI (WMD = –0.84, 95% CI = –0.95 to –0.73, $p < 0.001$). Two other covariates were found to be statistically significant in the exenatide model: age (WMD = –0.74, 95% CI = –0.82 to –0.67, $p < 0.001$) and duration of diabetes (WMD = –0.74, 95% CI = –0.82 to –0.66, $p < 0.001$). In the adjusted analyses for liraglutide, no covariates were found to be statistically significant.

Table 3. Unadjusted results of weight comparing each study treatment with placebo

Metaregression	WMD	95% CI	p value
Vildagliptin	0.56	0.27 to 0.84	<0.001
Sitagliptin	0.60	0.33 to 0.87	<0.001
Exenatide	-1.10	-1.32 to -0.88	<0.001
Liraglutide	-0.82	-1.92 to 0.27	0.142

Weight

The results for weight are presented in table 3. A direct meta-analysis of studies comparing sitagliptin versus placebo and reporting data on changes in weight indicated that there was a statistically significant weight gain with sitagliptin compared with placebo (unadjusted model: WMD = 0.60, 95% CI = 0.33–0.87, $p < 0.001$). When we controlled for the covariates in the adjusted model, study duration was the only variable that was statistically significant, with a positive correlation between treatments (WMD = 0.67, 95% CI = 0.48–0.87, $p < 0.001$).

The analyses indicated a statistically significant weight gain with vildagliptin (unadjusted model: WMD = 0.56, 95% CI = 0.27–0.84, $p < 0.001$). Exenatide (unadjusted model: WMD = -1.10, 95% CI = -1.32 to -0.88, $p < 0.001$) and liraglutide (unadjusted model: WMD = -0.82, 95% CI = -1.92 to -0.27, $p = 0.142$; table 3) both exhibited reduction in weight. The most remarkable result is the average weight reduction of 1.10 kg observed with exenatide. In the adjusted models for liraglutide, exenatide and vildagliptin, none of the covariates were statistically significant.

Hypoglycemia

The meta-analysis of vildagliptin versus placebo showed a nonstatistically significant increase in the number of patients who reported hypoglycemic episodes in comparison to those who received a placebo [relative risk (RR) = 1.52, 95% CI = 0.80–2.88, $p = 0.196$]. As for sitagliptin, patients under this treatment were 156% more likely to experience some hypoglycemia in comparison to placebo patients (unadjusted model: RR = 2.56, 95% CI = 1.23–5.33, $p = 0.01$). When adjusted for covariates, age was the only variable found to be statistically significant (RR = 1.84, 95% CI = 1.02–3.34, $p = 0.044$).

For the incretin mimetics, the analysis showed that patients treated with exenatide were 140% more likely to experience some hypoglycemia than patients treated with placebo, and this difference was statistically signifi-

cant (RR = 2.40, 95% CI = 1.39–4.11, $p = 0.002$). Patients treated with liraglutide were 69% more likely to experience some hypoglycemia than patients treated with placebo. This difference just reached significance at the 95% probability level (RR = 1.69, 95% CI = 1.00–2.86, $p = 0.050$). No covariates were statistically significant in the adjusted models.

Discussion

This meta-analysis assessed the clinical efficacy and safety of incretin mimetics and DPP-4 inhibitors in T2DM patients compared with placebo. In the analysis, we ran a direct meta-analysis of each treatment versus placebo, and assessed the impact of adjustment variables on the results of the meta-analyses. When there was a significant moderate to high level of heterogeneity in this meta-analysis, the random-effect model was used to pool the data, and analyses were conducted controlling for heterogeneity by adjusting for key study covariates (age, study duration, duration of diabetes, gender and treatment as monotherapy or in combination). There were only very few instances where the covariates had a statistically significant impact on the outcomes. The present analysis therefore represents the best synthesis of the current published evidence on the clinical efficacy and safety of each of the treatments in comparison to placebo.

The analysis has indicated that treatment with either incretin mimetics (exenatide, liraglutide) or DPP-4 inhibitors (vildagliptin, sitagliptin) leads to reasonable glycemic control in comparison to placebo. However, there were some differences in changes in patient weight and the risk of experiencing hypoglycemic episodes. In terms of clinical efficacy, as measured by the level of reduction in HbA_{1c}, and in comparison to placebo, liraglutide ranked highest (a reduction of 1% across trials of 12–26 weeks), followed by sitagliptin (a reduction of 0.79% across trials of 20–30 weeks), exenatide (a reduction of 0.75% across trials of 4–30 weeks) and vildagliptin (a reduction of 0.67% across trials of 12–52 weeks). The findings from our analyses contrast with those of Chia and Egan [52], who reported that liraglutide lowered HbA_{1c} by 1.5% in a 14-week study (with no evidence from phase III trials), sitagliptin monotherapy lowered HbA_{1c} by 0.6–0.7% after 54 weeks, and vildagliptin by 0.9–1.4% after 24 weeks. A possible explanation for this difference could be that more trials were included in our review and that in our analyses a pooled estimate of the effect of each treatment versus placebo for HbA_{1c} was obtained from all selected trials on each treatment.

As far as safety outcomes are concerned, our analysis indicated a statistically significant reduction in weight with exenatide and liraglutide as compared with placebo. A statistically significant weight gain was observed with use of sitagliptin and vildagliptin. The analyses also showed that patients on sitagliptin and exenatide were statistically significantly more likely to experience hypoglycemic episodes compared with patients on placebo. One should note the importance of achieving glycemic control while reducing adverse events such as hypoglycemia or weight gain. Evidence in the literature points to fear of hypoglycemia as a major barrier to implementation of intensive therapy and has adversely affected adherence to the prescribed medication regimen [53]. In addition, the specter of weight gain can increase diabetic morbidity and mortality when acting as a psychological barrier to the initiation or intensification of treatment, or affecting adherence to prescribed regimens [54].

A major limitation of our analysis was that the trials included exhibited a wide variation in study duration. Trials on exenatide ranged from 4 to 30 weeks, those on liraglutide from 12 to 26 weeks, on sitagliptin from 12 to 30 weeks and on vildagliptin from 12 to 52 weeks. To con-

trol for this, we ran adjusted models with study duration as a covariate for the HbA_{1c}, weight and hypoglycemia outcomes. Study duration was found to have a statistically significant impact only on weight gain for patients on sitagliptin (WMD = 0.67, 95% CI = 0.48–0.87, $p < 0.001$). In addition, longer study duration does not seem to be associated with a cumulatively greater number of patient-reported hypoglycemic episodes for any of the treatments under investigation and appears to have no statistically significant impact on reporting hypoglycemic episodes. The data also suggest that the relationship between study duration and the number of hypoglycemic episodes may be nonlinear. For example, while Ristic et al. [41] reported the total number of hypoglycemic episodes reported by vildagliptin patients to be 14 in a 12-week trial, Garber et al. [44] reported it to be 1 in a 24-week trial. Raz et al. [36] reported the total number of hypoglycemic episodes in patients on sitagliptin to be 5 in a 30-week trial, while Goldstein et al. [31] reported 7 in a 24-week trial. One may therefore presume that the difference in study duration does not account for the wide variation in hypoglycemia event rates and/or variations in reduction of HbA_{1c} and weight changes.

Appendix 1

Study Description and Patient Characteristics

Vildagliptin

Study reference	Aim	Study design	Participants	Intervention
Ahren et al. [40], 2004	To assess 12- and 52-week efficacy of vildagliptin versus placebo in patients with T2DM continuing metformin treatment	Double-blind RCT	107 patients, mean age 56.9 years, 62% male, mean duration of diabetes 5.6 years; study duration 12 weeks	Vildagliptin 50 mg q.d.
Ristic et al. [41], 2005	To establish a dose of vildagliptin that was effective in reducing HbA _{1c} levels and was well tolerated in patients with T2DM	Double-blind RCT	279 patients, mean age 56.1 years, 54% male, mean duration of diabetes 2.9 years; study duration 12 weeks	Vildagliptin 25 mg b.i.d., 25 mg q.d., 50 mg q.d. or 100 mg q.d.
Bosi et al. [42], 2007	To evaluate the efficacy and safety of vildagliptin added to metformin	Double-blind RCT	544 patients, mean age 54.2 years, 57% male, mean duration of diabetes 6.3 years; study duration 24 weeks	Vildagliptin 50 mg q.d. or 100 mg q.d.
Dejager et al. [43], 2007	To assess the efficacy and tolerability of vildagliptin	Double-blind RCT	632 patients, mean age 53.5 years, 47% male, mean duration of diabetes 2.90 years; study duration 24 weeks	Vildagliptin 50 mg q.d., 50 mg b.i.d. or 100 mg q.d.
Garber et al. [44], 2007	To assess the efficacy and tolerability of vildagliptin in combination with pioglitazone in patients with T2DM	Double-blind RCT	463 patients, mean age 54.3 years, 50% male, mean duration of diabetes 4.7 years; study duration 24 weeks	Vildagliptin 50 or 100 mg q.d.
Garber et al. [45], 2008	To compare the efficacy and tolerability of vildagliptin versus placebo in patients with T2DM who are inadequately controlled with prior sulfonylurea monotherapy	Double-blind RCT	515 patients, mean age 58.2 years, 59% male, mean duration of diabetes 7.2 years; study duration 24 weeks	Vildagliptin 50 mg q.d. or b.i.d.

Goodman et al. [46], 2009	To demonstrate that HbA _{1c} reduction with vildagliptin 100 mg q.d. a.m. dosing is superior to placebo	Double-blind RCT	370 patients, mean age 54.8 years, 58% male; study duration 24 weeks	Vildagliptin 100 mg a.m. and 100 mg p.m.
Kikuchi et al. [47], 2009	To assess the efficacy and tolerability of vildagliptin (10, 25 or 50 mg b.i.d.) in Japanese patients with T2DM	Double-blind RCT	291 patients, mean age 59.0 years, 67% male, mean duration of diabetes 5.2 years; study duration 12 weeks	Vildagliptin 10, 25 or 50 mg b.i.d.
Pi-Sunyer et al. [48], 2007	To assess the efficacy and tolerability of vildagliptin	Double-blind RCT	354 patients, mean age 51.2 years, 55% male, mean duration of diabetes 2.2 years; study duration 24 weeks	Vildagliptin 50 mg q.d., 50 mg b.i.d. or 100 mg q.d.
Scherbaum et al. [49], 2008	To assess the efficacy and tolerability of vildagliptin in drug-naïve patients with T2DM and mild hyperglycemia	Double-blind RCT	306 patients, mean age 62.9 years, 57% male, mean duration of diabetes 2.6 years; study duration 52 weeks	Vildagliptin 50 mg q.d.
Mimori et al. [50], 2006	To assess the efficacy and tolerability of vildagliptin	Double-blind RCT	219 patients, mean age 59 years	Vildagliptin 10 mg twice daily, 25 mg twice daily or 50 mg twice daily, placebo

Sitagliptin

Study reference	Aim	Study design	Participants
Scott et al. [28], 2008	To assess the addition of sitagliptin to ongoing metformin therapy in patients with T2DM who were inadequately controlled with HbA _{1c} 7–11% on metformin monotherapy	Double-blind RCT	273 patients, mean age 55.2 years, 57% male, mean duration of diabetes 5.2 years; study duration 18 weeks
Aschner et al. [29], 2006	To examine the efficacy and safety of sitagliptin as monotherapy in patients with T2DM	Double-blind RCT	741 patients, mean age 54.2 years, 51.7% male, mean duration of diabetes 4.4 years; study duration 24 weeks
Charbonnel et al. [30], 2006	To assess the efficacy and safety of sitagliptin, added to ongoing metformin therapy, in patients with T2DM who had inadequate glycemic control with metformin alone	Double-blind RCT	701 patients, mean age 54.5 years, 57.1% male, mean duration of diabetes 6.2 years; study duration 24 weeks
Goldstein et al. [31], 2007	To assess the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with T2DM and inadequate glycemic control by diet and exercise	Double-blind RCT	1,091 patients, mean age 53.6 years, 51% male; study duration 24 weeks
Hanefeld et al. [32], 2007	To evaluate sitagliptin once daily monotherapy in a dose-ranging study	Double-blind RCT	555 patients, mean age 55.1 years, 54.3% male, mean duration of diabetes 4.5 years; study duration 18 weeks
Hermansen et al. [33], 2007	To assess the efficacy and safety of sitagliptin in patients with T2DM who had inadequate glycemic control while on glimepiride alone or in combination with metformin	Double-blind RCT	441 patients, mean age 56.0 years, 53.1% male, mean duration of diabetes 8.8 years; study duration 24 weeks
Mohan et al. [34], 2009	To evaluate the efficacy and safety of sitagliptin as monotherapy in Chinese, Indian and Korean patients with T2DM inadequately controlled by diet and exercise	Double-blind RCT	530 patients, mean age 50.9 years, 57.7% male, mean duration of diabetes 2.0 years; study duration 18 weeks
Nonaka et al. [35], 2008	Efficacy and tolerability of sitagliptin was assessed in Japanese patients with T2DM	Double-blind RCT	151 patients, mean age 55.3 years, 62.5% male, mean duration of diabetes 4.1 years; study duration 12 weeks
Raz et al. [36], 2008	To evaluate the efficacy and safety of sitagliptin as an add-on to metformin therapy in patients with moderately severe T2DM	Double-blind RCT	190 patients, mean age 54.8 years, 45.3% male, mean duration of diabetes 7.9 years; study duration 30 weeks
Scott et al. [37], 2007	To assess the efficacy and tolerability of sitagliptin, in patients with T2DM who had inadequate glycemic control by diet and exercise	Double-blind RCT	743 patients, mean age 55.5 years, 54% male, mean duration of diabetes 4.6 years; study duration 12 weeks
Rosenstock et al. [38], 2006	To assess the efficacy and tolerability of sitagliptin added to ongoing pioglitazone therapy in patients with T2DM and inadequate glycemic control	Double-blind RCT	535 patients, mean age 56.3 years, 55.5% male, mean duration of diabetes 6.1 years; study duration 24 weeks

Exenatide

Study reference	Aim	Study design	Participants	Intervention	Treatment add-on
Zinman et al. [13], 2007	To compare the effects of exenatide versus placebo on glycemic control	Double-blind RCT	233 patients, mean age 56 years, 55% male, mean duration of diabetes 7.7 years; study duration 16 weeks	Subcutaneous abdominal injections of 10 µg of exenatide b.i.d.	Thiazolidinediones (with or without metformin)
De Fronzo et al. [14], 2005	To evaluate the ability of exenatide to improve glycemic control in patients with T2DM failing to achieve glycemic control with maximally effective metformin doses	Triple-blind RCT	336 patients, mean age 53 years, 57% male, mean duration of diabetes 5.9 years; study duration 30 weeks	5 µg s.c. exenatide b.i.d. for 4 weeks followed by 5 µg or 10 µg s.c. exenatide b.i.d. for 26 weeks	Metformin
Gao et al. [15], 2009	To evaluate the efficacy of exenatide in Asian patients with T2DM inadequately controlled with oral agents	Double-blind RCT	465 patients, mean age 55 years, 44% male, mean duration of diabetes 8 years; study duration 16 weeks	5 µg, then 10 µg b.i.d. for 4 and 12 weeks	Metformin alone or with a sulfonylurea
Kendall et al. [16], 2005	To evaluate the effects of exenatide in hyperglycemic patients with T2DM unable to achieve glycemic control with metformin/sulfonylurea combination therapy	Double-blind RCT	733 patients, mean age 55 years, 52% male, mean duration of diabetes 8.9 years; study duration 30 weeks	5 µg s.c. exenatide b.i.d. (arms A and B) for 4 weeks; thereafter, arm A remained at 5 µg b.i.d. and arm B escalated to 10 µg b.i.d.	Metformin
Moretto et al. [17], 2008	To evaluate the efficacy and tolerability of exenatide monotherapy in patients with T2DM naive to anti-diabetic agents and whose disease was inadequately controlled with diet and exercise alone	Double-blind RCT	232 patients, mean age 54 years, 56% male, mean duration of diabetes 1.7 years; study duration 24 weeks	5 or 10 µg s.c. exenatide b.i.d.	None
Poon et al. [18], 2005	To assess the dose dependencies of the glucoregulatory effects and tolerability of exenatide when added to diet and exercise or metformin monotherapy in patients with T2DM	Triple-blind RCT	156 patients, mean age 53 years, 43% male, mean duration of diabetes 3.9 years; study duration 4 weeks	2.5, 5.0, 7.5 or 10 µg b.i.d.	Metformin
Buse et al. [19], 2004	To evaluate the ability of exenatide to improve glycemic control in patients with T2DM failing maximally effective doses of a sulfonylurea as monotherapy	Triple-blind RCT	377 patients, mean age 55 years, 60% male, mean duration of diabetes 6.2 years; study duration 30 weeks	4 weeks at 5 µg s.c. exenatide b.i.d. (arms A and B) or placebo; subsequently, subjects in arm B were escalated to 10 µg b.i.d. exenatide	Sulfonylurea therapy
Fineman et al. [20], 2003	To examine the activity and safety of subcutaneously injected AC2993 (exenatide) in patients with T2DM currently treated with diet and/or oral antidiabetic agents	Triple-blind RCT	109 patients, mean age 52 years, 54% male; study duration 4 weeks	Exenatide 0.08 µg/kg s.c.; three treatment groups: b.i.d. (breakfast and dinner); b.i.d. (breakfast and bedtime); t.i.d. (breakfast, dinner and bedtime)	Regimen of sulfonylurea or metformin (alone or in combination)

Liraglutide

Study reference	Aim	Study design	Participants	Intervention
Zinman et al. [21], 2009	To determine the efficacy and safety of liraglutide when added to metformin and rosiglitazone in T2DM	Double-blind RCT	533 patients, mean age 55.1 years, 66% male, mean duration of diabetes 9 years; study duration 26 weeks	Liraglutide 1.2 or 1.8 mg
Madsbad et al. [22], 2004	To assess the efficacy and safety of liraglutide after 12 weeks of treatment in T2DM patients	Double-blind RCT	193 patients, mean age 56.7 years, 67% male, mean duration of diabetes 4.5 years; study duration 12 weeks	Liraglutide 0.045, 0.225, 0.45, 0.60 or 0.75 mg or open-label glimepiride 1–4 mg
Marre et al. [23], 2009	To compare the effects of combining liraglutide (0.6, 1.2 or 1.8 mg/day) or rosiglitazone 4 mg/day or placebo with glimepiride (2–4 mg/day) on glycemic control, body weight and safety in T2DM	Double-blind RCT	1,041 patients, mean age 56.2 years, 50% male; study duration 26 weeks	Liraglutide 0.6, 1.2 or 1.8 mg and rosiglitazone placebo; or liraglutide placebo and rosiglitazone placebo; or liraglutide placebo and rosiglitazone 4 mg/day
Nauck et al. [24], 2009	To compare the efficacy and safety of liraglutide added to metformin with addition of placebo or glimepiride to metformin in patients previously treated with oral antidiabetes therapy	Double-blind RCT	1,091 patients, mean age 56.6 years, 59% male, mean duration of diabetes 7.4 years; study duration 26 weeks	Liraglutide 0.6, 1.2 or 1.8 mg q.d.; glimepiride 4 mg q.d.
Seino et al. [25], 2008	To evaluate the dose-response efficacy and safety of liraglutide in Japanese subjects with T2DM	Double-blind RCT	226 patients, mean age 57.3 years, 57% male, mean duration of diabetes 7.6 years; study duration 14 weeks	Liraglutide 0.1, 0.3, 0.6 or 0.9 mg q.d.
Vilsboll et al. [26], 2007	To evaluate the efficacy and safety of liraglutide in patients with T2DM	Double-blind RCT	165 patients, mean age 55.8 years, 61% male, mean duration of diabetes 5.5 years; study duration 14 weeks	Liraglutide 0.65, 1.25 or 1.90 mg
Russell-Jones et al. [27], 2008 (abstract only)	To compare the efficacy and safety of liraglutide, liraglutide placebo and open-label insulin glargine	Double-blind, 26-week trial	581 subjects	Liraglutide 1.8 mg

RCT = Randomized controlled trial.

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