CURRENT THERAPEUTIC RESEARCH

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Glucagon-Like Peptide-1 Receptor Agonists Versus Insulin Glargine for Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

BACKGROUND: Glucagon-like peptide-1 (GLP-1) receptor agonists are a new class of hypoglycemic drugs, including exenatide, liraglutide, albiglutide, lixisenatide, and taspoglutide. Insulin glargine is a standard agent used to supplement basal insulin in type 2 diabetes mellitus (T2DM).

OBJECTIVE: The aim of this study was to review the efficacy and safety profiles of GLP-1 receptor agonists versus insulin glargine in type 2 diabetic patients who have not achieved treatment goals with oral hypoglycemic agents.

METHODS: The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and the database of ongoing trials were searched from inception through April 2010. Additional data were sought from relevant Web sites, the American Diabetes Association, reference lists of included trials and related (systematic) reviews, and industry. Randomized controlled trials (RCTs) were selected if they were ≥3 months in duration, compared GLP-1 receptor agonists with insulin glargine in patients with T2DM, and included ≥1 of the following outcomes: mortality, complications of T2DM, glycemic control, weight, lipids, blood pressure, adverse effects, and health-related quality of life. Quasirandomized controlled trials were excluded. The quality of the eligible studies was assessed on the basis of the following aspects: randomization procedure, allocation concealment, blinding, incomplete outcome data (intent-to-treat [ITT] analysis), selective outcome reporting, and publication bias.

RESULTS: A total of 410 citations were retrieved; 5 multicenter RCTs that met the inclusion criteria were identified. They were all open-label designs with an insulin glargine arm, predefined outcomes reported, and ITT analysis. One trial had an unclear randomization procedure and allocation concealment. Publication bias was not able to be determined. No data were found with regard to mortality or diabetes-associated complications, and few data were found on quality of life. The results of the meta-analysis suggest that insulin glargine was significantly better in reducing the fasting

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blood glucose (mean difference [MD] [95% CI], 1.31 [1.04 to 1.58]; $P < 0.001$), but exhibits greater incidence of nocturnal hypoglycemia (risk ratio [RR] [95% CI], 0.40 [0.23 to 0.71]; $P = 0.002$) and influenza (RR [95% CI], 0.56 [0.32 to 0.98]; $P = 0.04$). GLP-1 receptor agonists are more conducive to reducing weight (MD [95% CI], −3.96 [−5.14 to −2.77]; $P < 0.001$), postprandial blood glucose (after breakfast, $P < 0.001$; after dinner, $P < 0.001$), and LDL-C (MD [95% CI], −0.18 [−0.28 to −0.08]; $P < 0.001$), but have significantly more gastrointestinal adverse effects (eg, nausea/vomiting, $P < 0.001$). There were no significant differences between GLP-1 receptor agonists and insulin glargine in reducing glycosylated hemoglobin (HbA_{1c}) levels (MD [95% CI], −0.03 [−0.13 to 0.08]) and the overall incidence of hypoglycemia (RR [95% CI], 0.69 [0.42 to 1.14]).

CONCLUSIONS: Compared with insulin glargine, GLP-1 receptor agonists did not have a significant difference in regard to reducing HbA_{1c} levels and they were significantly associated with decreased weight but increased gastrointestinal adverse events. It remains unclear whether GLP-1 receptor agonists influence mortality or diabetes-associated complications in patients with T2DM. More trials with longer follow-up are needed to determine the exact long-term efficacy and safety profiles of this new class of hypoglycemic drugs. (*Curr Ther Res Clin Exp.* 2010;71:211–238) © 2010 Excerpta Medica Inc.

KEY WORDS: type 2 diabetes, diabetes mellitus, GLP-1, glucagon-like peptide-1, insulin glargine, insulin detemir, meta-analysis.

INTRODUCTION

Diabetes is a major public health problem. In 2000, there were 171 million patients with diabetes mellitus worldwide, and the number is predicted to increase to 366 million by 2030.[1] The World Health Organization (WHO) estimated that almost 3 million deaths per year worldwide are the result of diabetes. Type 2 diabetes mellitus (T2DM) represents ~90% of all cases of diabetes; the main pathogenesis of T2DM includes insulin secretory dysfunction, insulin resistance, and excess glucagon secretion.[2] Pharmacologic treatments are mainly directed against 2 aspects: insulin secretory dysfunction and insulin resistance. Pharmacologic treatments include sulfonylurea and meglitinides to increase insulin secretion, a variety of insulins to supplement the low level of endogenous insulin, and thiazolidinediones and metformin to decrease insulin resistance.[3] These drugs hardly improve the gradual decline in islet β-cell function[4,5] and reduce the secretion of glucagon. Moreover, adverse events (AEs) such as weight gain and hypoglycemia have been found to increase when the dose and frequency of these drugs are increased.[6] In recent years, long-acting insulin analogues and glucagon-like peptide-1 (GLP-1) receptor agonists offer new possibilities for the treatment of hyperglycemia in people with T2DM.[7,8]

Insulin glargine was the first long-acting insulin analogue produced by recombinant DNA technology, approved for treatment of both type 1 diabetes and T2DM by the US Food and Drug Administration (FDA) in April 2000 and by the European Agency for the Evaluation of Medicinal Products in June 2000.[8] Because of its long duration of action

without a pronounced peak, it is primarily used to supplement basal insulin. It has been used in many countries, such as the United States and China, because of its low risk and high compliance rates.[8] Insulin detemir is another type of long-acting insulin analogue, approved by the FDA in 2005.[9] It is also used to supplement basal insulin.

GLP-1 is associated with enhanced glucose-induced insulin secretion, reduced weight, and inhibited glucagon secretion, gastrointestinal motility, appetite, and food intake when it is released into the blood circulation from the gut.[10–13] Preclinical data suggest that GLP-1 also has some important characteristics including enhancement of insulin biosynthesis and insulin-gene transcription, improvement of β-cell function and mass, and reduction of apoptosis of β-cells.[14] GLP-1 receptor agonists are more resistant to degradation and have a longer half-life and similar pharmacokinetic properties[7] compared with native GLP-1; therefore, GLP-1 receptor agonists can better control blood glucose. Exenatide and liraglutide were the 2 earliest developed GLP-1 receptor agonists. Exenatide is the synthetic form of naturally occurring exendin-4, a potent agonist of mammalian GLP-1 receptors, and the amino acid sequence overlap with GLP-1 is 53%.[15,16] Liraglutide is a recombinant, acylated analogue of human GLP-1 and has 97% sequence homology to native GLP-1.[17] Exenatide was approved by the FDA in 2005 as an adjunctive treatment for T2DM in patients unable to achieve adequate glycemic control.[18] Liraglutide[19] was approved by the European Medicines Agency for use in Europe in 2009 and the FDA approved liraglutide as an adjunct to diet and exercise to improve glycemic control in adults with T2DM in 2010. Several other GLP-1 receptor agonists are albiglutide,[20] lixisenatide,[21] and taspoglutide[22]; these 3 drugs are now in Phase II or III clinical trials.

The aim of this review was to assess the efficacy and safety profiles of GLP-1 receptor agonists versus insulin glargine in patients with T2DM who have not achieved treatment goals with oral hypoglycemic agents.

MATERIALS AND METHODS

Study Selection

Randomized controlled trials (RCTs) of GLP-1 receptor agonist (exenatide, liraglutide, albiglutide, lixisenatide, or taspoglutide) injection versus long-acting insulin analogue (insulin glargine or insulin detemir) injection in combination with an oral antidiabetic drug were included for this review. Parallel and crossover designs were eligible; there were no restrictions on publication status or language. Patients were required to be aged ≥18 years with T2DM diagnosed using WHO 1998[23] or American Diabetes Association (ADA) 2009[24] diagnostic criteria. Duration of treatment was to be >12 weeks of basal treatment with stable doses of oral antidiabetic drug. Quasirandomized trials were excluded.

Primary end point outcomes included: (1) mortality—diabetes-related mortality (eg, death from myocardial infarction, stroke, peripheral vascular disease, renal disease, hyper- or hypoglycemia, or sudden death), total mortality; (2) diabetes-related AEs—angina pectoris, neuropathy, retinopathy, nephropathy, erectile dysfunction, and hyperosmolar nonketotic coma; and (3) health-related quality of life (using a validated instrument)—patient-reported health outcomes.

Secondary outcomes included: (1) glycemic control (change in glycosylated hemoglobin [HbA_{1c}] levels from baseline to end point), proportion of subjects achieving $HbA_{1c} \leq 7\%$, and fasting and postprandial blood glucose levels; (2) plasma lipid levels (triglycerides [TG], total cholesterol [TC], HDL-C, and LDL-C); (3) fasting and postprandial insulin and C-peptide levels; (4) weight (or body mass index [BMI]); (5) blood pressure (BP) (systolic BP [SBP]/diastolic BP [DBP]); (6) waist and hip circumference, waist/hip ratio; (7) mild or moderate hypoglycemia; (8) AEs (eg, nausea, vomiting, diarrhea, dyspepsia, constipation, upper abdominal pain, headache, dizziness, nasopharyngitis, influenza, cough, back pain, arthralgia); and (9) costs.

LITERATURE SEARCH

The Cochrane Library (Issue 3, 2010), MEDLINE (January 1965–April 2010), EMBASE (January 1966–April 2010), Science Citation Index Expanded (1900–April 2010), as well as an online database of ongoing trials, Current Controlled Trials, were searched. The following search terms were used: *type 2 diabetes*, *non insulin dependent diabetes mellitus*, *exenatide*, *liraglutide*, *GLP-1*, *albiglutide*, *glucagon-like peptide 1*, *taspoglutide*, *lixisenatide*, *insulin glargine*, and *insulin detemir*. The following additional sources were explored for additional studies: reference lists of the included trials and related (systematic) reviews or meta-analyses; the FDA and International Diabetes Federation (IDF) Web site; and 2 pharmaceutical companies (Eli Lilly and Company, Novo Nordisk). We also searched posters and abstracts presented at the ADA annual meetings from 2004 through 2009.

DATA EXTRACTION AND QUALITY EVALUATION

Two researchers (W.-X.L. and J.-F.G.) independently cross-checked the search results including titles, abstracts, and full texts according to the inclusion and exclusion criteria. During selection of the included trials, in the case of disagreements, a third researcher (J.-H.T.) would decide whether the trial should be included. The main data were extracted into 2 forms and 1 table: baseline characteristics form of the study (eg, authors, year, sponsors, design type, sample size; age, gender, BMI intervention, duration of treatment); quality evaluation form including the following aspects: randomization procedure, allocation concealment, method of blinding, handling losses to follow-up (intent-to-treat [ITT] analysis), and selective outcome reporting. Every aspect of the quality evaluation form is divided according to the method described in the Cochrane Collaboration handbook (version 5.0.2)[25] into 3 classes (yes [low risk of bias], unclear [uncertain risk of bias], and no [high risk of bias]); and outcome indicators table including primary end point outcomes and secondary outcomes.

STATISTICAL ANALYSIS

RevMan 5.0 statistical software provided by the Cochrane Collaboration was used for statistical analysis. Measurement data were reported as mean difference (MD) and count data were reported as relative risk (RR) for statistical analysis; both were expressed as 95% CIs. If there were different drugs, a subanalysis was used; if there were

different design types, a sensitivity analysis was used. The χ^2 test was used to determine statistical heterogeneity; $P < 0.1$ and $I^2 > 50\%$ indicated that there was statistical heterogeneity. To handle heterogeneity, the source was determined and, if possible, the random-effects model was used. If there was no statistical heterogeneity, the fixed-effects model was used for data analysis. $P < 0.05$ was considered statistically significant. The funnel plot of primary end point indicators or important secondary outcomes was used as an assessment of publication bias.

RESULTS

LITERATURE SEARCH RESULTS

The systematic database search resulted in 410 relevant articles; 397 citations were excluded after reading titles and abstracts. After reading the remaining 13 full-text articles, 5 RCTs were included in the meta-analysis (1452 patients) (**Figure 1**)[26–30]; the other 8 articles were found to be secondary analyses of an included RCT.[26] No additional studies were retrieved from the references listed in relevant reviews, included articles, FDA and IDF Web sites, pharmaceutical companies, or the ADA. We found 16 RCTs that met the inclusion criteria that are registered in the Current Controlled Trials database. At the time of publication, 5 registered studies had been completed, which were included in the meta-analysis. The results of 11 ongoing trials were not obtained.

BASELINE CHARACTERISTICS OF THE INCLUDED TRIALS

The GLP-1 receptor agonists experimental data found were only for exenatide and liraglutide. For long-acting insulin analogues, no articles were found on insulin detemir. Four trials[26–28,30] compared exenatide and insulin glargine, and 1 trial[29] compared liraglutide and insulin glargine. Four trials were of a parallel design[26,28–30] and the other was a crossover design.[27] The GLP-1 receptor agonists–treatment groups and insulin glargine–treatment groups in the included trials were not significantly different in regard to baseline data. The baseline BMI of subjects was 30.3 to 34.6 kg/m^2 (within the obesity range) in all of the included trials. The basic characteristics of included studies are shown in **Table I**.

QUALITY OF THE INCLUDED TRIALS

Table II shows the methodologic quality assessment of the 5 included studies. Random sequence generation was adequate (low risk of bias) in 4 of the trials[26–29]; 1 trial[30] reported that it was randomized, but did not elaborate on the specific method used. Allocation concealment of 1 trial was unclear[30]; it was adequate for the other 4 trials.[26–29] ITT analysis was confirmed in all 5 trials.[26–30] The study protocol was available and all of the studies' predefined outcomes were reported in all of the included trials. Blinding was open-label in all 5 trials. Publication bias was assessed using the funnel plot of the change in HbA_{1c} levels. As shown in **Figure 2**, the funnel plot was symmetric (meaning no bias was found), but from a relatively small number (5) of studies; therefore, publication bias was not able to be determined.

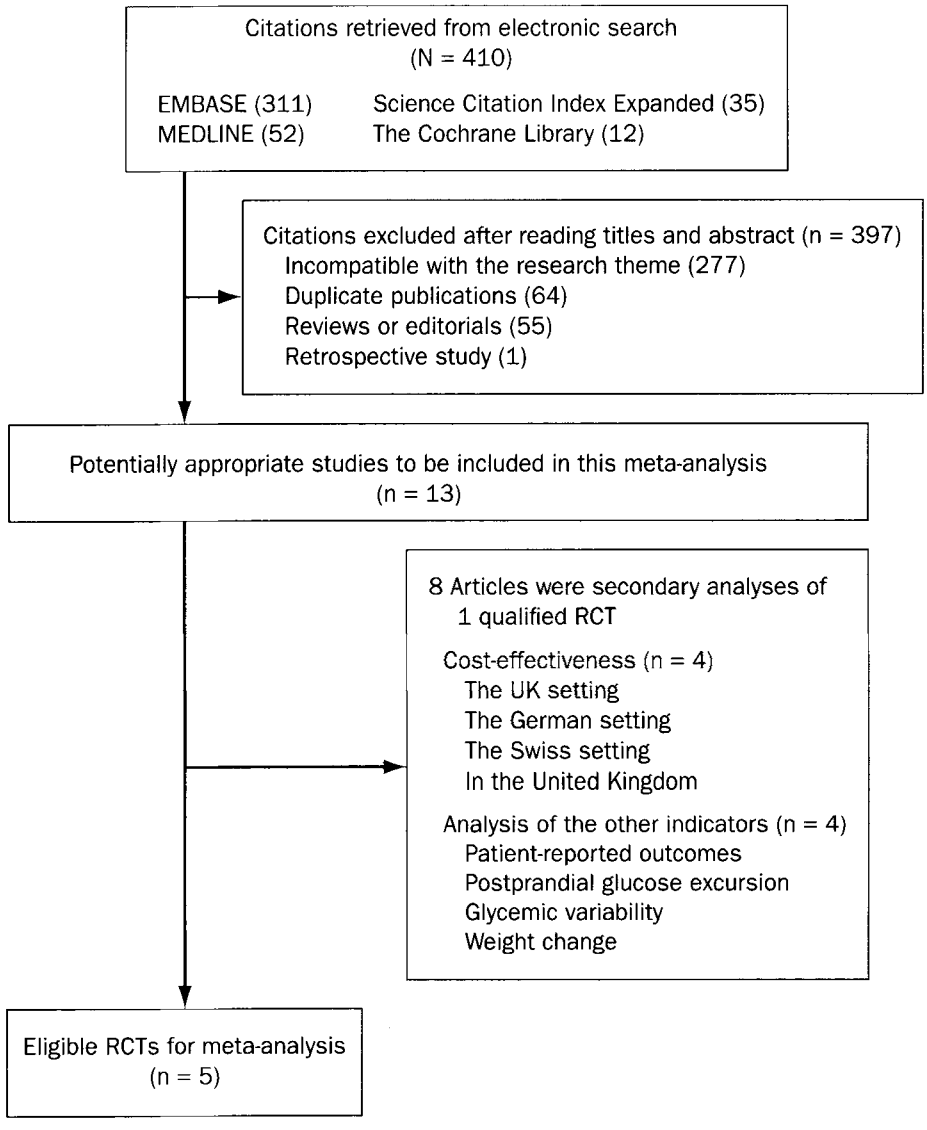

Figure 1. Flow chart of study identification and selection procedure. RCT = randomized controlled trial.

META-ANALYSIS RESULTS

Data were unavailable for mortality and diabetes-related complications. One article[31] assessed patient-reported health outcomes of the trial by Heine et al.[26] In this trial, patients completed 5 health outcomes instruments: Diabetes Symptom Checklist-revised (DSC-R); Diabetes Treatment Flexibility Scale (TFS); Diabetes Treatment Satisfaction Questionnaire (DTSQ); EuroQol EQ-5D; and the Vitality Subscale of the SF-36 (Medical Outcomes Study 36-Item Short Form Health Survey). It reported that

Table I. Basic Characteristics of included trials. Data are mean (SD) unless otherwise indicated.

Study	Design Type	Duration, wks	Participants, n	Age, y	Sex, Male, %	Duration of Diabetes, y	HbA_{1c}, %	FBG, mmol/L	Weight, kg	BMI, kg/m^2	Intervention (Dose and Method)
Heine et al[26]	Randomized, parallel, controlled trial	26	549 (A: 282 B: 267)	A: 59.8 (8.8) B: 58.0 (9.5)	A: 55.0 B: 56.6	A: 9.9 (6.0) B: 9.2 (5.7)	A: 8.2 (1.0) B: 8.3 (1.0)	A: 10.1 (2.6) B: 10.4 (2.9)	A: 87.5 (16.9) B: 88.3 (17.9)	A: 31.4 (4.4) B: 31.3 (4.6)	A: 5 μg twice daily for 4 weeks, 10 μg thereafter; + MET and SU B: Once daily at bedtime, until FBG ≤5.6 mmol/L; + MET and SU
Bunck et al[28]	Randomized, parallel, controlled trial	52	69 (A: 36 B: 33)	A: 58.4 (8.4) B: 58.3 (7.5)	A: 63.9 B: 66.7	A: 5.7 (4.8) B: 4.0 (3.4)	A: 7.6 (0.6) B: 7.4 (0.6)	A: 9.4 (2.4) B: 8.9 (2.3)	A: 90.6 (12.6) B: 92.4 (13.8)	A: 30.9 (4.2) B: 30.1 (3.4)	A: 5 μg twice daily for 4 weeks, 10 μg thereafter, titrated to a maximum dose of 20 μg TID; + MET B: Once daily at bedtime, until FBG ≤4.5–5.5 mmol/L; + MET
Barnett et al[27]	Randomized, crossover, controlled trial	16 (2 Periods)	138 (A/B: 68 B/A: 70)	A/B: 54.5 (9.1) B/A: 55.3 (10.0)	A/B: 33 B/A: 32	A/B: 6.6 (4.9) B/A: 8.3 (5.9)	A/B: 8.89 (1.1) B/A: 9.00 (1.1)	A/B: 11.8 (3.3) B/A: 12.2 (3.3)	A/B: 85.6 (16.5) B/A: 84.0 (16.7)	A/B: 31.3 (4.1) B/A: 30.9 (4.2)	A: 5 μg twice daily for 4 weeks, 10 μg thereafter; + MET or SU B: Once daily at bedtime, until FBG ≤5.6 mmol/L; + MET or SU (16 weeks of A followed by 16 weeks of B or 16 weeks of B followed by 16 weeks of A)
Russell-Jones et al[29]	Randomized, parallel, controlled trial	26	462 (C: 230 B: 232)	C: 57.6 (9.5) B: 57.5 (10.5)	C: 57 B: 60	C: 9.2 (5.8) B: 9.7 (6.4)	C: 8.3 (0.9) B: 8.2 (0.9)	C: 9.1 (2.1) B: 9.1 (2.0)	C: 85.5 (19.4) B: 85.0 (17.9)	C: 30.4 (5.3) B: 30.3 (5.3)	C: 0.6–1.8 mg once daily for 2 weeks, 1.8 mg thereafter for 24 weeks; + MET and/or SU B: Once daily at bedtime, until FBG ≤5.5 mmol/L; + MET and/or SU
Davies et al[30]	Randomized, parallel-arm, comparator	26	234 (A: 118 B: 116)	A: 56.8 (10.2) B: 56.2 (7.9)	A: 70.3 B: 66.4	A: 9.0 (4.6) B: 8.4 (4.4)	A: 8.65 (0.68) B: 8.48 (0.66)	A: 10.84 (2.23) B: 10.12 (2.22)	A: 101.4 (19.8) B: 97.6 (16.4)	A: 34.6 (5.7) B: 33.7 (4.9)	A: 5 μg twice daily for 4 weeks, 10 μg thereafter; + MET and/or SU and/or TZD B: Once daily at bedtime, until FBG ≤5.6 mmol/L; + MET and/or SU and/or TZD

HbA_{1c} = glycosylated hemoglobin; FBG = fasting blood glucose; BMI = body mass index; A = Exenatide; B = insulin glargine; MET = metformin; SU = sulfonylurea; C = liraglutide; TZD = thiazolidinedione.

Table II. Methodologic quality of included trials.

Study	Randomization Procedure	Allocation Concealment	Blinding	Incomplete Outcome Data (ITT Analysis)	Selective Outcome Reporting (Registration Number)
Heine et al[26]	Adequate	Adequate	Open label	Yes	Yes (NCT00082381)
Bunck et al[28]	Adequate	Adequate	Open label	Yes	Yes (ISRCTN87762302)
Barnett et al[27]	Adequate	Adequate	Open label	Yes	Yes (NCT00099619)
Russell-Jones et al[29]	Adequate	Adequate	Open label	Yes	Yes (NCT00331851)
Davies et al[30]	Unclear	Unclear	Open label	Yes	Yes (NCT00360334)

ITT = intent-to-treat.

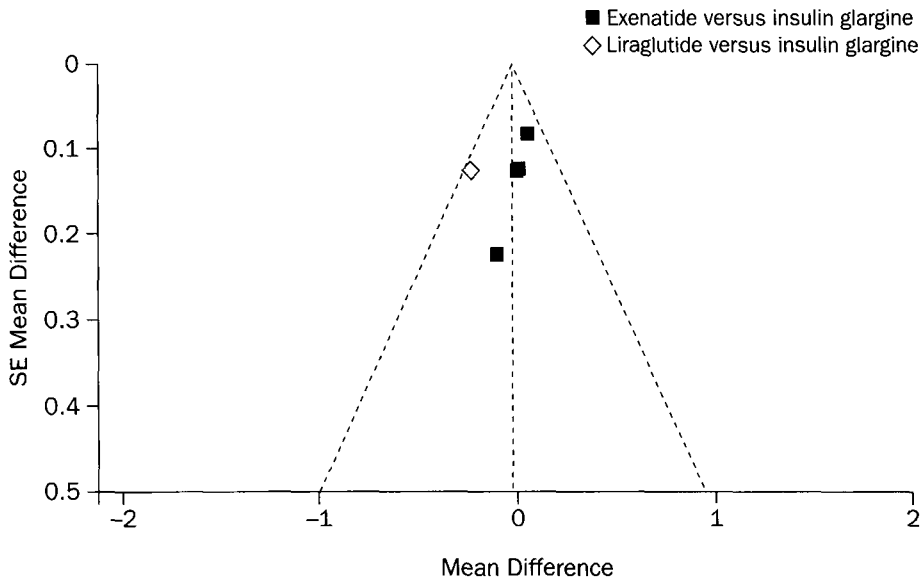

Figure 2. Funnel plot of the change in glycosylated hemoglobin levels in the 5 studies assessed in the meta-analysis.[26–30]

both exenatide and insulin glargine had statistically significant baseline-to-end point improvement in the DSC-R total score ($P < 0.001$ for both treatment groups), the DTSQ Satisfaction Score ($P < 0.001$ for both treatment groups), and the SF-36 Vitality Subscale Score ($P = 0.005$ for exenatide and $P < 0.04$ for insulin glargine). Group differences were examined with general linear models controlling for country and baseline scores. There were no significant differences between the 2 groups in the DSC-R overall score, EQ-5D index score, TFS score, DTSQ Score, and SF-36 Vitality Subscale Score. This secondary analysis found that, although the exenatide-treated patients had a greater number of injections and gastrointestinal AEs, the weight-reduction benefits associated with the drug offset its disadvantages. Meta-analysis of the secondary indicators follows.

GLYCEMIC CONTROL

Change in Glycosylated Hemoglobin Levels

There was no significant difference between GLP-1 receptor agonists and insulin glargine (n = 1521; MD [95% CI], –0.03 [–0.13 to 0.08]) in regard to the reduction of HbA_{1c} levels from baseline to end point (**Figure 3**). Heterogeneity test results indicated $P = 0.42$ and $I^2 = 0\%$ using the fixed-effects model for data consolidation. The study by Barnett et al[27] (crossover design) was subjected to a sensitivity analysis and the results were stable (n =1266; MD [95% CI], –0.03 [–0.15 to 0.08]).

Proportion of Subjects Achieving Glycosylated Hemoglobin ≤7%

No significant difference was found between GLP-1 receptor agonists and insulin glargine for proportion of subjects achieving HbA_{1c} ≤7% (n = 1563; RR [95% CI],

Study or Subgroup	GLP-1 Receptor Agonists Mean (SD), %	Total	Insulin Glargine Mean (SD), %	Total	Weight, %	Mean Difference IV, Fixed, 95% CI, %
Exenatide vs Insulin Glargine						
Barnett et al[27]	−1.36 (1.03)	130	−1.36 (1.01)	125	17.8	0 (−0.25 to 0.25)
Bunck et al[28]	−0.8 (0.6)	36	−0.7 (1.15)	33	5.8	−0.10 (−0.54 to 0.34)
Davies et al[30]	−1.25 (0.89)	98	−1.26 (0.9)	102	18.2	0.01 (−0.24 to 0.26)
Heine et al[26]	−1.00 (1.00)	275	−1.05 (0.97)	260	40.1	0.05 (−0.12 to 0.22)
Subtotal (95% CI)		539		520	81.9	0.02 (−0.10 to 0.14)
Heterogeneity: $\chi^2 = 0.44$, $df = 3$ ($P = 0.93$); $I^2 = 0\%$						
Test for overall effect: $z = 0.33$ ($P = 0.74$)						
Liraglutide vs Insulin Glargine						
Russell-Jones et al[29]	−1.33 (1.36)	230	−1.09 (1.37)	232	18.1	−0.24 (−0.49 to 0.01)
Subtotal (95% CI)		230		232	18.1	−0.24 (−0.49 to 0.01)
Heterogeneity: Not applicable						
Test for overall effect: $z = 1.89$ ($P = 0.06$)						
Total (95% CI)		769		752	100	−0.03 (−0.13 to 0.08)
Heterogeneity: $\chi^2 = 3.87$, $df = 4$ ($P = 0.42$); $I^2 = 0\%$						
Test for overall effect: $z = 0.50$ ($P = 0.61$)						
Cut off: $\chi^2 = 3.42$, $df = 1$ ($P = 0.06$); $I^2 = 70.8\%$						

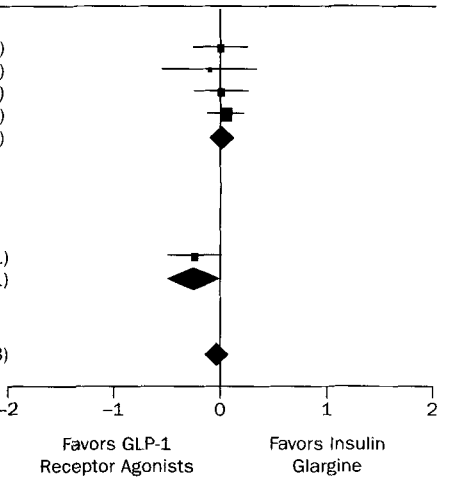

Figure 3. Forest plot illustrating the change in glycosylated hemoglobin levels following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. IV = inverse variance.

1.11 [0.91–1.35]) (**Figure** 4). The heterogeneity test indicated $P < 0.001$ and $I^2 = 82\%$; therefore, the random-effects model was used for data consolidation. The results remained unchanged after the removal of the crossover trial[27] (n = 1300; RR [95% CI], 1.17 [0.90–1.51]).

Change in Fasting Blood Glucose Levels

There was a significant reduction (n = 1085; MD [95% CI], 1.31 [1.04–1.58]; $P < 0.001$) in fasting blood glucose (FBG) levels in insulin glargine–treated patients compared with exenatide-treated patients (**Figure** 5). The included 4 trials[26–28,30] had no heterogeneity ($P = 0.94$, $I^2 = 0\%$). This remained significant after sensitivity analysis without the crossover trial (n = 822; MD [95% CI], 1.34 [1.04–1.65]; $P < 0.001$). The SD of FBG was not obtained; therefore, the results of liraglutide versus insulin glargine were only described.[29] Final reductions in FBG from baseline in the liraglutide and insulin glargine groups were 1.55 and 1.79 mmol/L, respectively.

Percentage of Patients Achieving Fasting Blood Glucose <5.6 mmol/L

There were significant increases in the insulin glargine arm compared with the exenatide arm (n = 1032; RR [95% CI], 0.35 [0.25–0.49]; $P < 0.001$) for the percentage of patients achieving FBG <5.6 mmol/L in 3 trials (**Figure** 6).[26,27,30] The heterogeneity test indicated that $P = 0.66$ and $I^2 = 0\%$. This significance remained after removal of the crossover trial (n = 769; RR [95% CI], 0.37 [0.26–0.52]; $P < 0.001$). The other 2 trials had no data on GLP-1 receptor agonists; therefore, we could not make a pooled estimate. The trial by Bunck et al[28] reported that 100% of subjects achieved FBG <5.6 mmol/L in the insulin glargine arm. Another study[29] reported that 20% of patients achieved FBG <5.6 mmol/L in the insulin glargine arm.

Postprandial Blood Glucose Levels

Four trials[26–29] reported this indicator in a way that could not contribute to the meta-analysis. We can only describe the results of these trials, because the conclusions were consistent. The study by Heine et al[26] found that exenatide-treated patients had a statistically significant reduction, compared with insulin glargine–treated patients, in after-breakfast (n = 549; MD [95% CI], –0.91 [–1.39 to –0.43]; $P < 0.002$) and after-dinner (n = 549; MD [95% CI], –1.41 [–1.89 to –0.93]; $P < 0.001$) blood glucose. A crossover study[27] also reported that the exenatide group was associated with significantly lower postprandial plasma glucose (PPG) concentrations compared with the insulin glargine group in the evening (MD [95% CI], –1.5 [–2.1 to –0.9]; $P < 0.001$). The same study found significantly lower 2-hour PPG excursions compared with insulin glargine in the morning (MD [95% CI], –2.2 [–2.8 to –1.7]; $P < 0.001$), at midday (MD [95% CI], –0.5 [0.9 to –0.1]; $P = 0.016$), and in the evening (MD [95% CI], –2.1 [–2.7 to –1.5]; $P < 0.001$). The trial by Bunck et al[28] suggested a significant reduction of blood glucose after breakfast and after dinner in the exenatide group, but no specific data were shown. A similar reduction in PPG from baseline was reported by Russell-Jones et al[29] in the liraglutide group (1.81 mmol/L) and insulin glargine group (1.61 mmol/L).

Study or Subgroup	GLP-1 Receptor Agonists Events	Total	Insulin Glargine Events	Total	Weight, %	Risk Ratio M-H, Random, 95% CI, %
Exenatide vs Insulin Glargine						
Barnett et al[27]	51	136	51	127	16.7	0.93 (0.69 to 1.27)
Bunck et al[28]	36	36	33	33	27.1	1.00 (0.95 to 1.06)
Davies et al[30]	46	118	21	116	11.4	2.15 (1.38 to 3.37)
Heine et al[26]	127	275	125	260	22.5	0.96 (0.80 to 1.15)
Subtotal (95% CI)		565		536	77.8	1.10 (0.87 to 1.39)
Total events	260		230			
Heterogeneity: $\tau^2 = 0.04$, $\chi^2 = 16.67$, $df = 3$ ($P < 0.001$); $I^2 = 82\%$						
Test for overall effect: $z = 0.76$ ($P = 0.45$)						
Liraglutide vs Insulin Glargine						
Russell-Jones et al[29]	122	230	106	232	22.2	1.16 (0.96 to 1.40)
Subtotal (95% CI)		230		232	22.2	1.16 (0.96 to 1.40)
Total events	122		106			
Heterogeneity: Not applicable						
Test for overall effect: $z = 1.58$ ($P = 0.12$)						
Total (95% CI)		795		768	100	1.11 (0.91 to 1.35)
Heterogeneity: $\tau^2 = 0.04$, $\chi^2 = 22.59$, $df = 4$ ($P = 0.002$); $I^2 = 82\%$						
Test for overall effect: $z = 1.00$ ($P = 0.32$)						

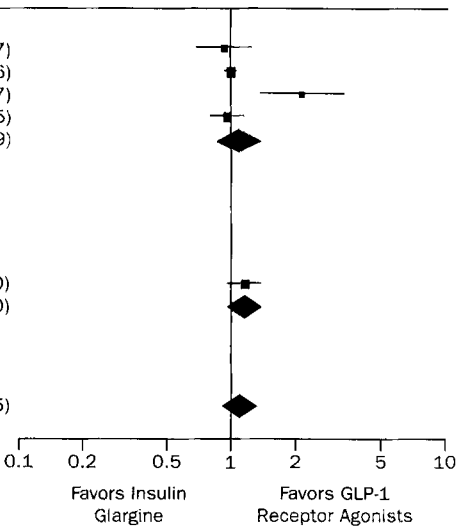

Figure 4. Forest plot illustrating the proportion of subjects who achieved glycosylated hemoglobin ≤7% following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. M-H = Mantel-Haenszel.

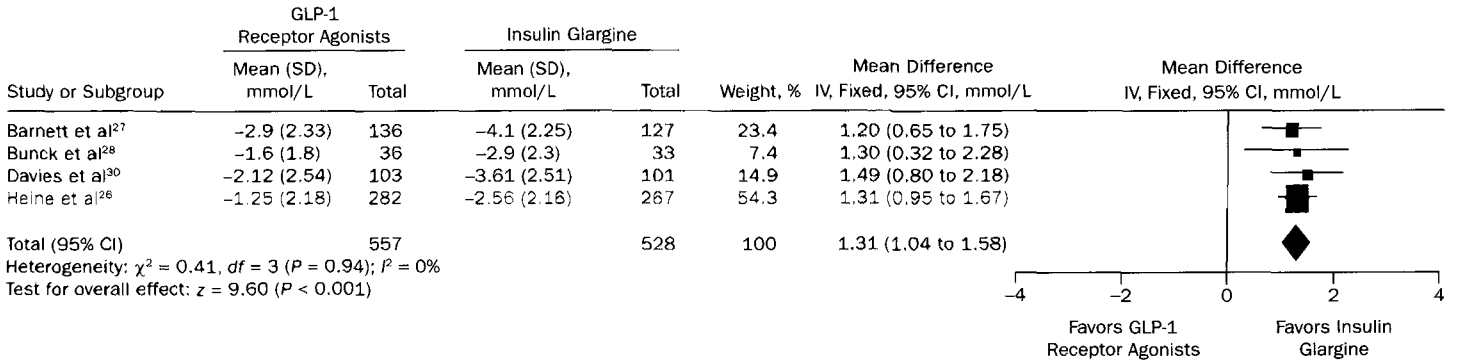

Figure 5. Forest plot illustrating the change in fasting blood glucose levels following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. IV = inverse variance.

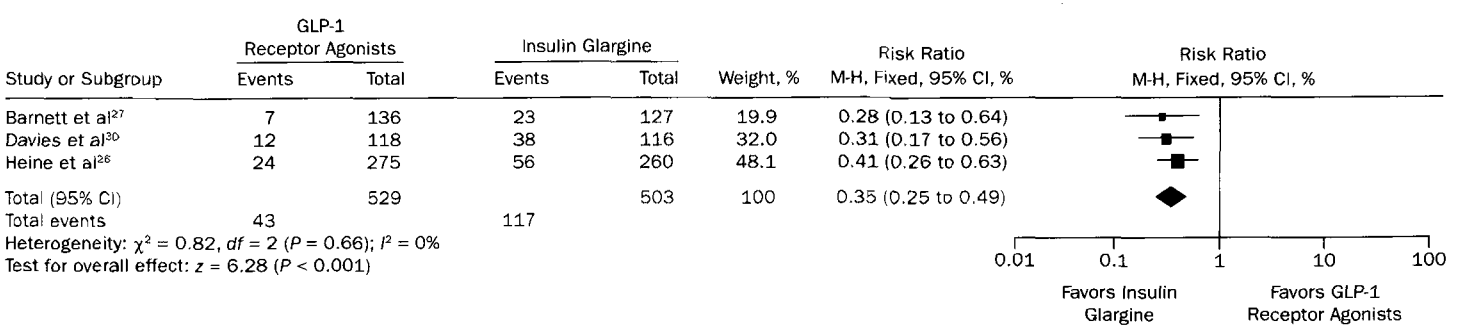

Figure 6. Forest plot illustrating the percentage of patients achieving the target fasting blood glucose level of <5.6 mmol/L following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. M-H = Mantel-Haenszel.

PLASMA LIPID LEVELS

Exenatide-treated patients had a statistically significant reduction in LDL-C levels from baseline to end point (n = 745; MD [95% CI], −0.18 [−0.28 to −0.08]; $P < 0.001$) compared with insulin glargine–treated patients, but there was no significant difference in regard to TC, HDL-C, or TG (**Figure 7**).

FASTING AND POSTPRANDIAL INSULIN AND C-PEPTIDE LEVELS

No suitable data could be merged for fasting and postprandial insulin and C-peptide levels, so we only describe the results of 3 trials.[26,28,29] Heine et al[26] suggested that, after 26 weeks of exenatide treatment, the fasting ($P = 0.003$) and 2-hour ($P = 0.004$) postprandial insulin level and the 1-, 2-, and 3-hour postprandial serum glucose excursions in patients with T2DM were significantly lower than that in insulin glargine–treated patients. Bunck et al[28] found that, after 52 weeks of exenatide treatment, there was a statistically significant improvement in first- and second-phase C-peptide response to glucose with C-peptide response to arginine at 15 mmol/L glucose concentration (n = 60; $P < 0.001$). The proinsulin-to-C-peptide ratio was observed to determine the function of islet β-cells in the study by Russell-Jones et al.[29] They found a significant improvement in the liraglutide group compared with the insulin glargine group (MD [95% CI], −0.00366 [−0.00597 to −0.00136]; $P < 0.002$).

WEIGHT (OR BODY MASS INDEX)

The GLP-1 receptor agonists group had significantly greater reduction in weight from baseline to end point than the insulin glargine group (n = 1473; MD [95% CI], −3.96 [−5.14 to −2.77]; $P < 0.001$) (**Figure 8**). We used the random-effects model to merge data. The results were consistent through sensitivity analysis for a crossover design trial (n = 1210; MD [95% CI], −4.42 [−5.46 to −3.38]; $P < 0.001$).

BLOOD PRESSURE (SBP/DBP)

Exenatide-treated patients had a significant reduction in SBP (n = 780; MD [95% CI], −3.59 [−5.74 to −1.43]; $P = 0.001$) compared with insulin glargine–treated patients based on the data of 2 trials (**Figure 9**).[26,30] Because the SD of the BP change data was unavailable, we only describe the results of the study by Russell-Jones et al.[29] They found that liraglutide-treated patients had a 4.0–mm Hg decrease, but insulin glargine–treated patients had a 0.54–mm Hg increase in SBP ($P < 0.001$). No significant difference in DBP was observed between GLP-1 receptor agonists and insulin glargine in these trials.[26,29,30]

WAIST AND HIP CIRCUMFERENCE, WAIST/HIP RATIO

Two trials[29,30] reported the change of waist circumference, but no data were available for a pooled estimate. In the study by Russell-Jones et al,[29] the liraglutide group had a 1.50-cm reduction but the insulin glargine group had a 0.89-cm increase (n = 462; MD [95% CI], −2.39 [−3.14 to −1.65]; $P < 0.001$). In the study by Davies et al,[30] the exenatide group had a 1.90-cm reduction and the insulin glargine group had

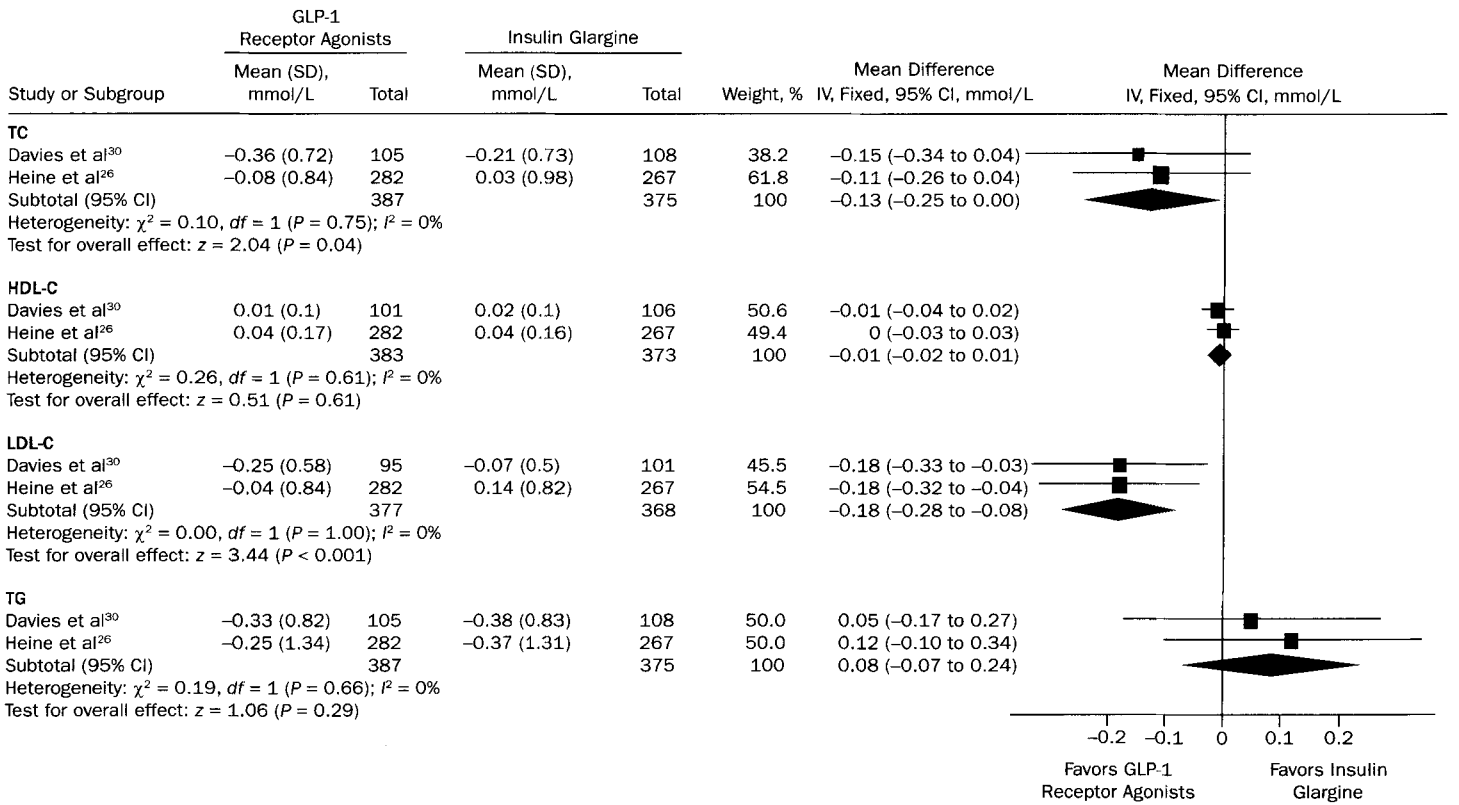

Figure 7. Forest plot illustrating the change in fasting plasma lipid levels following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. IV = inverse variance; TC = total cholesterol; TG = triglycerides.

Study or Subgroup	GLP-1 Receptor Agonists Mean (SD), kg	Total	Insulin Glargine Mean (SD), kg	Total	Weight, %	Mean Difference IV, Random, 95% CI, kg
Exenatide vs Insulin Glargine						
Barnett et al[27]	−1.6 (3.5)	136	0.6 (3.38)	127	21.3	−2.20 (−3.03 to −1.37)
Bunck et al[28]	−3.6 (3.6)	36	1.0 (4.6)	33	14.4	−4.60 (−6.56 to −2.64)
Davies et al[30]	−2.73 (3.1)	100	2.98 (3.16)	104	21.1	−5.71 (−6.57 to −4.85)
Heine et al[26]	−2.32 (3.19)	231	1.75 (3.28)	244	22.5	−4.07 (−4.65 to −3.49)
Subtotal (95% CI)		503		508	79.2	−4.11 (−5.62 to −2.60)
Heterogeneity: $\tau^2 = 2.04$, $\chi^2 = 33.63$, $df = 3$ ($P < 0.001$); $I^2 = 91\%$						
Test for overall effect: $z = 5.35$ ($P < 0.001$)						
Liraglutide vs Insulin Glargine						
Russell-Jones et al[29]	−1.8 (5.0)	230	1.6 (5.03)	232	20.8	−3.40 (−4.31 to −2.49)
Subtotal (95% CI)		230		232	20.8	−3.40 (−4.31 to −2.49)
Heterogeneity: Not applicable						
Test for overall effect: $z = 7.29$ ($P < 0.001$)						
Total (95% CI)		733		740	100	−3.96 (−5.14 to −2.77)
Heterogeneity: $\tau^2 = 1.54$, $\chi^2 = 35.07$, $df = 4$ ($P < 0.001$); $I^2 = 89\%$						
Test for overall effect: $z = 6.54$ ($P < 0.001$)						

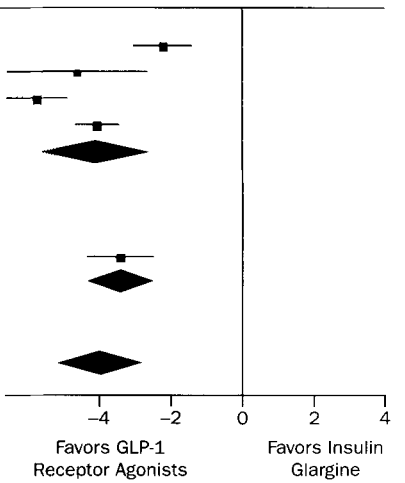

Figure 8. Forest plot illustrating the change in body weight from baseline to end point following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. IV = inverse variance.

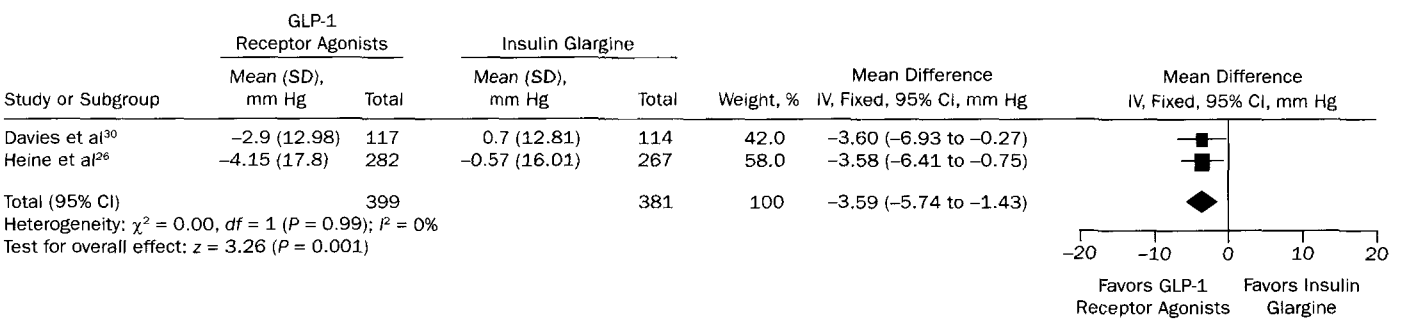

Figure 9. Forest plot illustrating the change in systolic blood pressure following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. IV = inverse variance.

a 1.86-cm increase (n = 231; MD [95% CI], −3.76 [−5.21 to −2.31]; $P < 0.001$). No trials reported on indicators of hip circumference or waist/hip ratio.

HYPOGLYCEMIA

The Overall Incidence of Hypoglycemia

No significant difference in the overall incidence of hypoglycemia (%) between GLP-1 receptor agonists and insulin glargine was observed (n = 796; RR [95% CI], 0.69 [0.42 to 1.14]) (**Figure 10**). The results of a sensitivity analysis was stable (n = 531; RR [95% CI], 0.69 [0.27 to 1.74]). The study by Heine et al[26] found no significant difference in the overall (end point) incidence of hypoglycemic episodes (events/patient-year) between exenatide and insulin glargine (n = 549; MD [95% CI], 1.1 [−1.3 to 3.4]).

Incidence of Nocturnal Hypoglycemic Episodes

Two trials[26,27] found that significantly more nocturnal hypoglycemic episodes (events/patient-year) occurred among insulin glargine–treated patients than exenatide-treated patients. Heine et al[26] reported 2.4 vs 0.9 episodes, respectively; $P < 0.001$. Barnett et al[27] reported 1.3 vs 0.4; $P < 0.001$. Davies et al[30] reported a greater incidence of nocturnal hypoglycemia (%) (n = 234; RR [95% CI], 0.40 [0.23–0.71]; $P = 0.002$) in insulin glargine–treated patients; however, these trials did not include suitable data for a pooled estimate.

ADVERSE EFFECTS

The GLP-1 receptor agonists group had significantly more overall incidence of treatment-emergent AEs (TEAEs) than the insulin glargine group (n = 1510; RR [95% CI], 1.23 [1.09–1.39]; $P < 0.001$) (**Figure 11**). The result is unchanged after sensitivity analysis (n = 1245; RR [95% CI], 1.23 [1.05–1.44]; $P = 0.008$).

The details of the specific AEs are shown in **Table III**. There are significant increases in the incidence of gastrointestinal AEs (eg, nausea, vomiting had $P < 0.001$; diarrhea, dyspepsia, constipation, and upper abdominal pain had $P \leq 0.01$) in the GLP-1 receptor agonists group compared with the insulin glargine group. No difference between the 2 groups existed for other AEs such as headache, dizziness, nasopharyngitis, cough, back pain, or arthralgia. Only the incidence of influenza had a significant increase in the insulin glargine–treated patients ($P < 0.05$).

COST-EFFECTIVENESS

Four articles[32–35] reported the cost-effectiveness of exenatide versus insulin glargine treatment. These patient characteristics and treatment effect data were all derived from a single RCT.[26] Three of the articles were based on data from the United Kingdom, Germany, and Switzerland. The articles' conclusions are consistent in that exenatide had higher direct medical costs compared with insulin glargine (the increased cost was £9912 over a 35-year time horizon, €3854 over a 10-year time horizon, and CHF [Swiss Franc] 8378 over a 35-year time horizon, respectively, in the 3 settings). But exenatide treatment suggested comparable or better life expectancy and an improvement

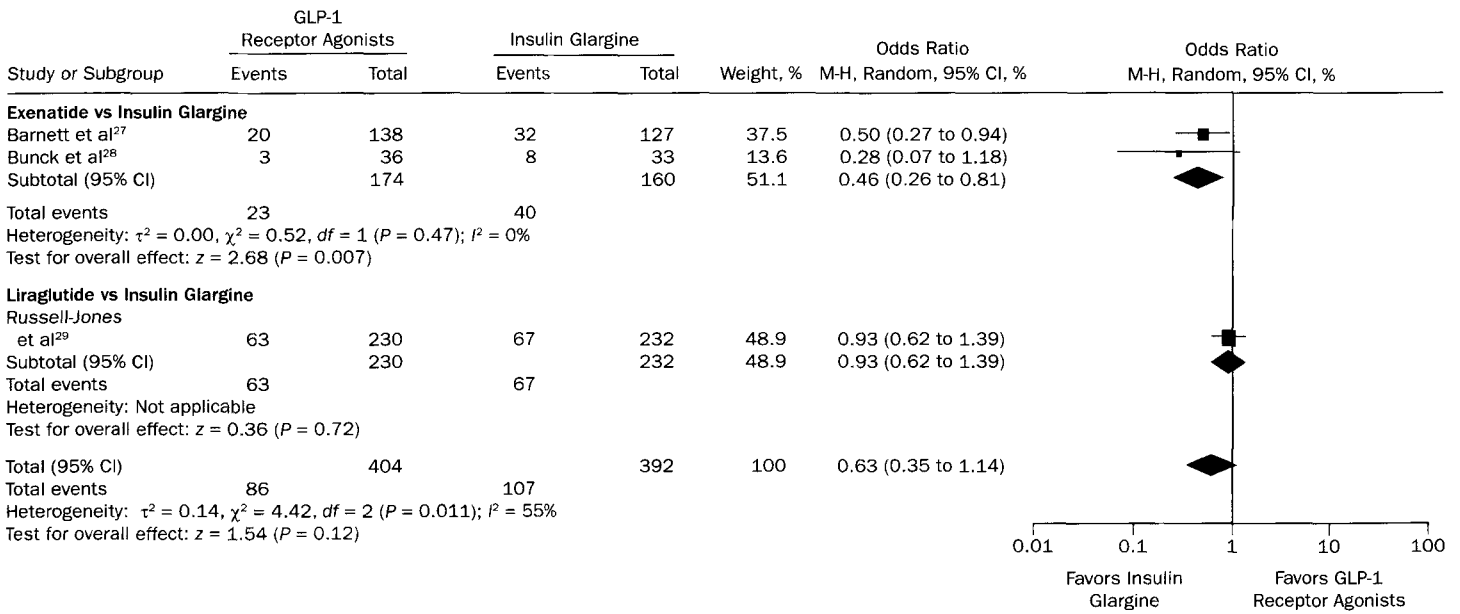

Figure 10. Forest plot illustrating the overall incidence of hypoglycemia following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. M-H = Mantel-Haenszel.

Study or Subgroup	GLP-1 Receptor Agonists Events	Total	Insulin Glargine Events	Total	Weight, %	Risk Ratio M-H, Random, 95% CI, %
Exenatide vs Insulin Glargine						
Barnett et al[27]	89	138	67	127	18.3	1.22 (0.99 to 1.50)
Davies et al[30]	106	118	94	116	29.5	1.11 (1.00 to 1.23)
Heine et al[26]	226	282	152	267	28.0	1.41 (1.25 to 1.59)
Subtotal (95% CI)		538		510	75.8	1.24 (1.04 to 1.47)
Total events	421		313			
Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 9.54$, $df = 2$ ($P = 0.009$); $I^2 = 79\%$						
Test for overall effect: $z = 2.43$ ($P = 0.01$)						
Liraglutide vs Insulin Glargine						
Russell-Jones et al[29]	151	230	127	232	24.2	1.20 (1.03 to 1.39)
Subtotal (95% CI)		230		232	24.2	1.20 (1.03 to 1.39)
Total events	151		127			
Heterogeneity: Not applicable						
Test for overall effect: $z = 2.38$ ($P = 0.02$)						
Total (95% CI)		768		742	100	1.23 (1.09 to 1.39)
Total events	572		440			
Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 9.19$, $df = 3$ ($P = 0.03$); $I^2 = 67\%$						
Test for overall effect: $z = 3.32$ ($P < 0.001$)						

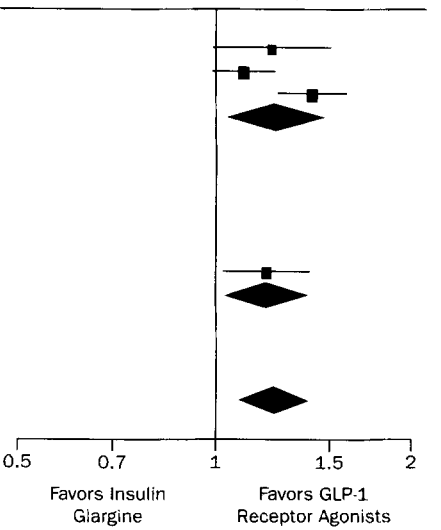

Figure 11. Forest plot illustrating the overall incidence of treatment-emergent adverse events following treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or insulin glargine. M-H = Mantel-Haenszel.

Table III. Adverse events associated with glucagon-like peptide-1 (GLP-1) receptor agonists versus insulin glargine.

Adverse Event	Study	GLP-1, n/N	Glargine, n/N	RR (95% CI)	*P*
Nausea	Russell-Jones et al[29]	32/230	3/232	10.76 (3.34–34.64)	
	Heine et al[26]	161/282	23/267	6.63 (4.43–9.92)	
	Barnett et al[27]	58/138	4/127	13.34 (4.99–35.70)	
	Davies et al[30]	57/118	3/116	18.68 (6.02–57.96)	
	Total (fixed model)			8.90 (6.33–12.51)	<0.001
Vomiting	Russell-Jones et al[29]	15/230	1/232	15.13 (2.02–113.60)	
	Heine et al[26]	49/282	10/267	4.64 (2.40–8.97)	
	Barnett et al[27]	13/138	4/127	2.99 (1.00–8.94)	
	Total (fixed model)			4.87 (2.84–8.34)	<0.001
Diarrhea	Russell-Jones et al[29]	23/230	3/232	7.73 (2.35–25.40)	
	Heine et al[26]	24/282	8/267	2.84(1.30–6.21)	
	Barnett et al[27]	4/138	3/127	1.23 (0.28–5.38)	
	Davies et al[30]	22/118	14/116	1.54 (0.83–2.87)	
	Total (random model)			2.48 (1.21–5.05)	0.01
Dyspepsia	Russell-Jones et al[29]	15/230	4/232	3.78 (1.27–11.23)	
	Heine et al[26]	10/282	1/267	9.47 (1.22–73.46)	
	Barnett et al[27]	3/138	0/127	6.45(0.34–123.58)	
	Total (fixed model)			5.09 (2.05–12.61)	<0.001
Constipation	Heine et al[26]	10/282	1/267	9.47 (1.22–73.46)	
	Barnett et al[27]	4/138	1/127	3.68 (0.42–32.50)	
	Total (fixed model)			6.55 (1.50–28.60)	0.01
Upper abdominal pain	Heine et al[26]	12/282	2/267	5.68 (1.28–25.15)	
	Barnett et al[27]	3/138	1/127	2.76 (0.29–26.20)	
	Total (fixed model)			4.70 (1.37–16.09)	0.01

(continued)

Table III (continued).

Adverse Event	Study	GLP-1, n/N	Glargine, n/N	RR (95% CI)	*P*
Headache	Russell-Jones et al[29]	22/230	13/232	1.71 (0.88–3.31)	
	Heine et al[26]	25/282	23/267	1.03 (0.60–1.77)	
	Barnett et al[27]	17/138	12/127	1.30 (0.65–2.62)	
	Davies et al[30]	17/118	18/116	0.93 (0.50–1.71)	
	Total (fixed model)			1.18 (0.87–1.61)	0.28
Dizziness	Heine et al[26]	15/282	6/267	2.37 (0.93–6.01)	
	Barnett et al[27]	9/138	7/127	1.18 (0.45–3.08)	
	Total (fixed model)			1.73 (0.89–3.34)	0.10
Nasopharyngitis	Russell-Jones et al[29]	21/230	26/232	0.81 (0.47–1.41)	
	Heine et al[26]	22/282	24/267	0.87 (0.50–1.51)	
	Barnett et al[27]	5/138	6/127	0.77 (0.24–2.45)	
	Davies et al[30]	24/118	23/116	1.03 (0.62–1.71)	
	Total (fixed model)			0.89 (0.66–1.20)	0.44
Influenza	Heine et al[26]	7/282	15/267	0.44 (0.18–1.07)	
	Barnett et al[27]	11/138	15/127	0.67 (0.32–1.41)	
	Total (fixed model)			0.56 (0.32–0.98)	0.04
Cough	Heine et al[26]	11/282	8/267	1.30 (0.53–3.19)	
	Barnett et al[27]	6/138	11/127	0.50 (0.19–1.32)	
	Total (fixed model)			0.84 (0.44–1.58)	0.58
Back pain	Heine et al[26]	17/282	8/267	2.01 (0.88–4.58)	
	Barnett et al[27]	3/138	5/127	0.55 (0.13–2.26)	
	Total (fixed model)			1.45 (0.73–2.87)	0.29
Arthralgia	Heine et al[26]	9/282	10/267	0.85 (0.35–2.06)	
	Barnett et al[27]	3/138	4/127	0.69 (0.16–3.02)	
	Total (fixed model)			0.81 (0.38–1.72)	0.58

Glargine = insulin glargine; RR = risk ratio.

in quality-adjusted life expectancy (0.442, 0.28, and 0.43 quality-adjusted life-years [QALYs], respectively) compared with insulin glargine; the incremental cost-effectiveness ratio was £22,420, €13,746, and CHF19,450 per QALY gained. The study by Woehl et al[34] used a different simulation model analysis and found that, for the higher lifetime medical costs for exenatide and insulin glargine (£14,568 and £9280 per patient, respectively), exenatide was not cost-effective compared with insulin glargine.

DISCUSSION

There are several (systematic) reviews[7,15,36] about GLP-1 receptor agonists for T2DM, but few meta-analyses exist that focus on the assessment of GLP-1 receptor agonists compared with long-acting insulin analogues. Some recent trials[28–30] were not included in the previously relevant meta-analysis.[36]

The ultimate goal of treating diabetes is to improve mortality, microvascular and macrovascular complications, and quality of life. But in this systematic review, we did not find data regarding mortality and diabetes-related complications. No included RCTs were specifically designed to evaluate these clinical end point outcomes. Only 1 trial reported health-related quality of life[26]; a secondary analysis of that study suggested that both exenatide and insulin glargine were associated with significant improvements in patient-reported outcomes when added to oral medications for patients with T2DM.[31] In general, patient satisfaction is necessary to maximize treatment effectiveness. Only patients who are satisfied with their treatment will adhere to prescribed regimens. The secondary analysis also found that treatment satisfaction between the 2 groups was the same.[31]

Because evidence on primary end point outcomes was lacking, the efficacy of GLP-1 receptor agonists compared with insulin glargine was assessed on secondary outcomes (eg, HbA_{1c}, lipids, BP). Many studies have suggested that the incidence of clinical end point outcomes is significantly associated with glycemic control, lipids, and BP.[37–42] Meta-analysis of secondary indicators found that GLP-1 receptor agonists compared with insulin glargine were not significantly different in regard to the reduction of HbA_{1c} levels and more effective at reducing postprandial blood glucose, LDL-C, SBP, weight, and at improving islet β-cell function. Patients treated with insulin glargine had significantly lower FBG levels and a greater percentage of patients who met targets such as FBG <5.6 mmol/L than patients treated with GLP-1 receptor agonists.

In many countries, long-acting insulin analogues are used when diet and oral medication fail.[8] A large number of clinical practices have found that insulin glargine can reduce basal blood glucose safely and effectively,[8] which is consistent with the present analysis. Obesity is an important risk factor for cardiovascular disease.[43] Many patients with T2DM are overweight and obese[44]; weight reduction for these patients to further reduce the blood glucose and cardiovascular complications is of great significance. Moreover, postprandial blood glucose, LDL-C, and SBP are all cardiovascular disease risk factors.[45,46] If these multiple cardiovascular disease risk factors can be improved, this may be a good feature for any hypoglycemic agents.

In addition to evaluating clinical efficacy, TEAEs were also considered in this meta-analysis. GLP-1 receptor agonists were not significantly different compared with insulin glargine in the overall incidence of hypoglycemia, with a greater overall incidence of TEAEs, especially gastrointestinal AEs (eg, nausea, vomiting). Insulin glargine–treated patients had more incidences of nocturnal hypoglycemic episodes and influenza than GLP-1 receptor agonist-treated patients.

GLP-1 is associated with satiety and reduced rates of gastric emptying and food intake.[12] These might be a mechanism for the weight loss and gastrointestinal discomfort associated with GLP-1 receptor agonists. Some studies[26–30] found that gastrointestinal AEs and weight loss do not always occur in the same patient; moreover, as GLP-1 receptor agonist-treatment continues, such AEs may gradually slow down. How to create GLP-1 receptor agonists that play a role in weight loss, but with fewer gastrointestinal AEs, is worthy of further study.

The results of this meta-analysis suggest that GLP-1 receptor agonists are an option as the next step of treatment for diabetic patients who have not achieved treatment goals with oral hypoglycemic agents, especially in overweight or obese patients. However, this should be further validated by future clinical practice. More trials should focus on the following aspects: durability of glycemic control, weight loss, improvement of β-cell secretory function, prevention of vascular complications, reduction of overall mortality, decreased medical costs, greater safety, high quality of life, and life expectancy.

LIMITATIONS

There are several potential limitations in this review. First, this meta-analysis was based on 5 published RCTs. There are many unfinished studies; a relatively small number of available trials is a potential limitation for any meta-analysis. If we obtain the results of the 11 ongoing trials, this meta-analysis will be updated in the future. The small number of studies also prevented us from fully assessing the potential for publication bias. The lack of gray literature (eg, presentations, unpublished data, government reports, other traditional or nontraditional sources of evidence) is also a limitation of this systematic review. All included RCTs were sponsored by relevant pharmaceutical companies (Eli Lilly and Company, Novo Nordisk), and only published literature in the English language was retrieved in this meta-analysis, which may lead to a potential publication bias.

Shorter observation periods and the lack of some important indicators (eg, mortality and diabetes-related complications) in these included trials are another limitation. Due to lack of the data regarding long-term follow-up, our meta-analysis still cannot define the long-term efficacy or safety profiles of GLP-1 agonists.

Finally, if the blinding method of the 5 included studies had not been well-implemented, a higher performance bias might result. These trials reported that the reason for using the open-label design in patients receiving long-acting insulin analogue (insulin glargine) treatment was because the patient must use titration methods to adjust the dose of insulin glargine according to self-monitored blood glucose levels. It is difficult to carry out blinding for participants (patients) in a clinical trial, but objective outcomes (eg, blood glucose) would be less influenced by lack of blinding.

The included trials did not indicate whether statisticians or outcome assessors were blinded to treatment. Outcome assessors and data analysts might be influenced by lack of blinding, especially for subjective outcomes (eg, health-related quality of life). A number of indicators were incomplete or no SD existed in our included trials, which might affect the results of the meta-analysis.

CONCLUSIONS

In this meta-analysis of 5 RCTs, insulin glargine significantly reduced FBG, but with a higher rate of nocturnal hypoglycemic episodes and influenza, compared with GLP-1 receptor agonists. GLP-1 receptor agonists significantly reduced postprandial blood glucose, LDL-C, SBP, and weight, and improved islet β-cell function, but had more associated gastrointestinal AEs compared with insulin glargine. GLP-1 receptor agonists are not significantly different from insulin glargine in regard to the reduction of HbA_{1c} levels and the overall incidence of hypoglycemia. It remains unclear whether GLP-1 receptor agonists influence mortality or complications in patients with T2DM.

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The authors have indicated that they have no conflicts of interest regarding the content of this article.

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