

Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) act by increasing insulin secretion, decreasing glucagon secretion, slowing gastric emptying, and increasing satiety.

Objective: Published evidence directly comparing GLP-1RAs with other approved treatments for type 2 diabetes (T2D) was systematically reviewed.

Methods: A literature search was performed using MEDLINE and Embase databases to identify papers comparing GLP-1RAs with other classes of glucose-lowering therapy in patients with T2D.

Results: Of the 1303 papers identified, 57 met the prespecified criteria for a high-quality clinical trial or retrospective study. The efficacy and tolerability of approved GLP-1RAs (exenatide twice daily or once weekly, dulaglutide, liraglutide, lixisenatide, and albiglutide) were compared with insulin products (23 prospective studies + seven retrospective studies), dipeptidyl peptidase-4 inhibitors (11 prospective studies + three retrospective studies), sulfonylureas (nine prospective studies + one retrospective study), thiazolidinediones (five prospective studies), and metformin (two prospective studies). GLP-1RAs are effective as a second-line therapy in improving glycemic parameters in patients with T2D. Reductions in glycosylated hemoglobin from baseline with GLP-1RAs tended to be greater or similar compared with insulin therapy. GLP-1RAs were consistently more effective in reducing body weight than most oral glucose-lowering drugs and insulin and were associated with lower hypoglycemia risk versus insulin or sulfonylureas. GLP-1RAs improved cardiovascular risk factors, and preliminary data suggest they improve cardiovascular outcomes in patients with T2D compared with oral glucose-lowering drugs. However, results from ongoing studies are awaited to confirm these early findings.

Conclusion: This systematic review found that GLP-1RAs are an effective class of glucose-lowering drugs for T2D.

Keywords: antidiabetic drugs, randomized controlled trials, retrospective, type 2 diabetes

Introduction

Diabetes mellitus is a chronic disease affecting a substantial proportion of the population.¹ In adults (age 20–79 years), the 2015 prevalence of diabetes worldwide was estimated at 8.8%, with type 2 diabetes (T2D) comprising 91% of cases.² By 2030, diabetes is expected to be the seventh leading cause of death.³

Several classes of glucose-lowering agents are currently available for the treatment of T2D, each with different mechanisms of action and therapeutic effects. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of glucose-lowering drugs that act on the glucagon-like peptide-1 (GLP-1) receptor on pancreatic beta cells and increase insulin secretion, decrease glucagon secretion, slow gastric emptying, and increase satiety; clinical trials have shown that GLP-1RAs decrease body weight,

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postprandial glucose excursions, and some cardiovascular risk factors, without increasing the risk of hypoglycemia.⁴ Clinical trials have also studied the effects of GLP-1RA therapy on cardiovascular outcomes in patients with T2D.^{5,6}

The purpose of this systematic review was to compare the efficacy of GLP-1RAs with other glucose-lowering therapies, using comparative data from clinical trials or observational cohort studies.

Literature search strategy and filtering

Embase and MEDLINE databases were searched on April 8, 2016, using the following search string: (glucagon like peptide 1 receptor agonist or “Glucagon-Like Peptide 1”) OR ([“Glucagon-like peptide-1” or “Glucagon-like peptide 1” or GLP1R or GLP-1 or GLP-1-R] AND [agonist or suppress* or block* or inhibit* or anti* or mimetic]) OR (lixisenatide or exenatide or liraglutide or albiglutide or dulaglutide) AND ([diabetes or diabetic or DM] and [“Type 2” or “Type-2” or “Type2” or “Type II” or “Type-II” or “Noninsulin-dependent” or “Noninsulin dependent” or “Non insulin-dependent” or “Non insulin dependent”]).

The search string was limited to keywords in the abstract or title. Articles indexed as animal studies, case reports, books, and conference/symposium presentations were excluded. The limits applied were English language and articles published between January 2005 and April 2016. Duplicates were removed, leaving 1303 articles. The articles identified were filtered manually and only those describing a head-to-head comparison between a GLP-1RA and another class of glucose-lowering therapy in ≥ 100 patients, regardless of study design, follow-up duration, or medication doses, were included in the final total.

A total of 57 articles were included in the analysis (Figure 1); of these, 37 were randomized controlled trials (RCTs), seven were open-label extensions of RCTs, 11 were retrospective analyses, and two were prospective observational studies.

Efficacy of GLP-1RAs versus other glucose-lowering therapies

GLP-1RAs versus dipeptidyl peptidase-4 inhibitors (DPP-4is)

Eleven prospective studies⁷⁻¹⁷ and three retrospective studies compared GLP-1RAs with DPP-4is.¹⁸⁻²⁰

Prospective studies

Exenatide once weekly (QW) was associated with significantly greater ($P < 0.001$) reductions in glycated hemoglobin

(HbA1c) and fasting glucose (FG) compared with sitagliptin after 26 weeks in the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION)-2 and DURATION-4 studies (Table 1).^{8,9} Although both exenatide QW and sitagliptin recipients lost weight, patients receiving exenatide QW had significantly greater weight loss from baseline.^{8,9} One study comparing exenatide twice daily (BID) with sitagliptin found that exenatide BID recipients had a reduction in FG similar to sitagliptin recipients, but a significantly greater reduction in weight.⁷

In the Assessment of Weekly Administration of LY2189265 in Diabetes (AWARD)-5 study, after 52 weeks of treatment, reductions from baseline in HbA1c, FG, and weight were significantly greater with dulaglutide than with sitagliptin (Table 1).¹⁰ These benefits were sustained over 104 weeks of treatment.¹¹

Generally, liraglutide-treated patients had greater or similar reductions from baseline in HbA1c, FG, and weight compared with sitagliptin- or vildagliptin-treated patients (Table 1).^{12-14,16} In an open-label extension study, patients switching from sitagliptin to liraglutide had further reductions in these parameters.¹⁵

When administered for 24 weeks, lixisenatide produced reductions from baseline in HbA1c and FG that were similar to sitagliptin (Table 1);¹⁷ however, weight loss was significantly greater among lixisenatide versus sitagliptin recipients.

Hypoglycemia rates in patients receiving GLP-1RAs or DPP-4is were low, with only one instance of major/severe hypoglycemia reported across all studies (in a patient receiving liraglutide 1.2 mg).^{13,14} In studies of exenatide QW, minor hypoglycemia rates ranged from 1% to 3.6% with exenatide QW, with the highest hypoglycemia rates for concomitant sulfonylurea use, and from 0% to 3.0% with DPP-4is.⁷⁻⁹ Patients receiving dulaglutide 1.5 mg generally had numerically higher hypoglycemia rates than patients receiving dulaglutide 0.75 mg or sitagliptin (10.2% vs 5.3% and 4.8%; 12.8% vs 8.6% and 8.6%, respectively).^{10,11} Rates of hypoglycemia were similar for all liraglutide doses investigated versus DPP-4i comparators.^{12-14,16} Furthermore, the incidence of gastrointestinal adverse events (AEs; nausea, diarrhea, and vomiting) was higher^{7-11,13-15,17} or similar¹⁶ in patients receiving GLP-1RAs versus DPP-4is; gastrointestinal AEs led to treatment withdrawal in a higher percentage of patients receiving GLP-1RA therapy in these studies.^{8,10,11} Some studies reported that gastrointestinal AEs peaked on treatment initiation in the GLP-1RA group and then stabilized over the study period.^{10,11,13}

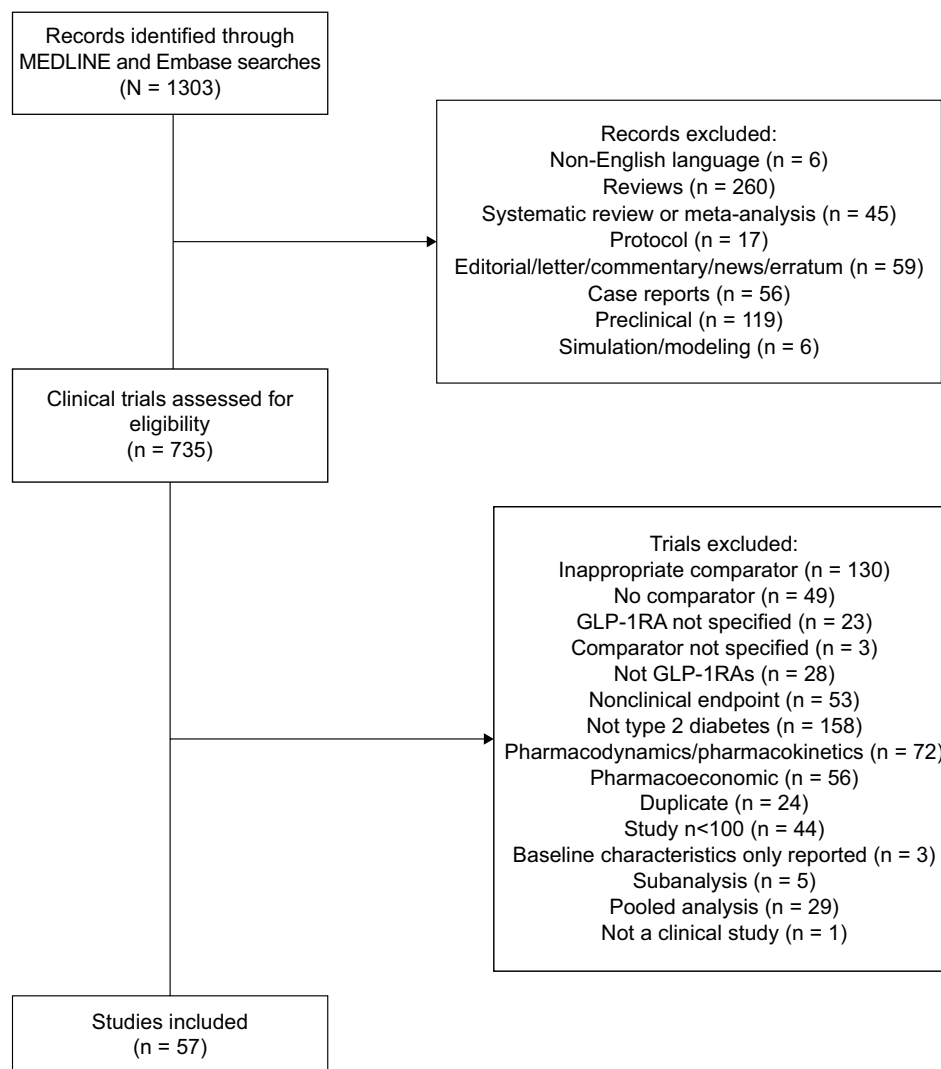


Figure 1 PRISMA flow diagram.

Abbreviation: GLP-1RA, glucagon-like peptide-1 receptor agonist.

Retrospective studies

Retrospective studies had similar results to the prospective studies (Table 2), with GLP-1RAs demonstrating greater or similar reductions in HbA1c, FG, and weight versus DPP-4is.^{18–20} Generally, hypoglycemia rates were not reported, although in one study the rate was similar between GLP-1RAs and DPP-4is.¹⁹ Nausea/vomiting was more frequent with exenatide compared with sitagliptin (incidence rate, 0.39 vs 0.032) in one study.¹⁹

GLP-1RAs versus metformin

Two prospective studies comparing GLP-1RAs and metformin were identified.^{9,21}

Prospective studies

Both studies (RCTs) reported reductions from baseline in HbA1c, FG, and weight (Table 1).^{9,21} In DURATION-4,

exenatide QW and metformin reduced HbA1c from baseline by ~1.5%, with no significant difference between groups at 26 weeks. In AWARD-3, dulaglutide 0.75 mg and 1.5 mg QW reduced HbA1c significantly more than metformin ($P < 0.05$) after 26 weeks. After 52 weeks, significant differences were observed in the reduction from baseline in HbA1c between dulaglutide 1.5 mg and metformin, but not between dulaglutide 0.75 mg and metformin.

Two RCTs investigated the effects of exenatide QW and dulaglutide on FG and weight, with no significant differences between these drugs in the reductions of these endpoints at 26 weeks.^{9,21} Treatment with dulaglutide at both dosages resulted in similar reductions in FG versus metformin at 26 weeks; at 52 weeks, recipients of dulaglutide 1.5 mg had a significantly greater reduction in FG than metformin recipients ($P < 0.05$; Table 1). The magnitude of weight loss achieved in

Table 1 Study details and efficacy results of comparative trials of GLP-IRAs and oral glucose-lowering therapies

Publications (acronym/ ClinicalTrials.gov record)	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-IRAs versus comparator		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Dipeptidyl peptidase-4 inhibitors						
Berg et al ⁷	CO, DB, DD, R in pts with T2D (2 × 4 weeks)	ExBID 10 µg/SITA 100 mg QD (41) SITA 100 mg QD/ExBID 10 µg (42)	MET (n = 82) TZD (n = 1)	NR	ExBID: -1.6 SITA: -1.6	ExBID: -1.4* SITA: -0.9
Bergental et al ⁸ (DURATION-2; NCT00637273)	DB, DD, MC, PG, R in pts with T2D (26 weeks)	ExQW 2 mg (160) SITA 100 mg QD (166) PIO 45 mg QD (165)	MET	ExQW: -1.5*** SITA: -0.9	ExQW: -1.8** SITA: -0.9	ExQW: -2.3*** SITA: -0.8
Russell-Jones et al ⁹ (DURATION-4; NCT00676338)	DB, MC, PG, R in treatment-naive pts with T2D (26 weeks)	ExQW 2 mg (248) MET 2000 mg/day (246) PIO 45 mg QD (163) SITA 100 mg QD (163)	None	ExQW: -1.5*** SITA: -1.2	ExQW: -2.3*** SITA: -1.1	ExQW: -2.0*** SITA: -0.8
Nauck et al ¹⁰ (AWARD-5; NCT00734474)	DB, MC, PG, R in pts with T2D (52 weeks)	DULA 0.75 mg QW (302) DULA 1.5 mg QW (304) SITA 100 mg QD (315) PBO (177)	MET	DULA 0.75: -0.9*** DULA 1.5: -1.1*** SITA: -0.4	DULA 0.75: -1.6*** DULA 1.5: -2.4*** SITA: -0.9	DULA 0.75: -2.6*** DULA 1.5: -3.0*** SITA: -1.5
Weinstock et al ¹¹ (AWARD-5; NCT00734474)	DB, MC, PG, R in pts with T2D (104 weeks)	DULA 0.75 mg QW (302) DULA 1.5 mg QW (304) SITA 100 mg QD (315) PBO (177)	MET	DULA 0.75: -0.7*** DULA 1.5: -1.0*** SITA: -0.3	DULA 0.75: -1.4*** DULA 1.5: -2.0*** SITA: -0.5	DULA 0.75: -2.4 DULA 1.5: -2.9*** SITA: -1.8
Charbonnel et al ¹² (NCT01296412)	OL, MC, PG, R in pts with T2D (26 weeks)	LIRA 1.2 mg/day ^a (253) SITA 100 mg OD ^b (269)	MET	LIRA: -1.4 SITA: -1.3	LIRA: -2.2 SITA: -1.9	LIRA: -2.8 SITA: -0.4
Pratley et al ¹³ (NCT00700817)	OL, MC, PG, R in pts with T2D (52 weeks)	LIRA 1.2 mg/day (225) LIRA 1.8 mg/day (221) SITA 100 mg QD (219)	MET	LIRA 1.2: -1.3*** LIRA 1.8: -1.5*** SITA: -0.9	LIRA 1.2: -1.7*** LIRA 1.8: -2.0*** SITA: -0.6	LIRA 1.2: -2.8*** LIRA 1.8: -3.7*** SITA: -1.2
Pratley et al ¹⁵ (NCT00700817)	OL extension of pts with T2D completing the 1860-LIRA- DPP-4 core study (26 weeks)	SITA 100 mg to LIRA 1.2 mg (67) SITA 100 mg to LIRA 1.8 mg (68)	MET	LIRA 1.2: -0.2† LIRA 1.8: -0.5††	LIRA 1.2: -0.8† LIRA 1.8: -1.4††	LIRA 1.2: -1.6†† LIRA 1.8: -2.5††
Takeshita et al ¹⁶	OL, PG, R in Japanese pts with T2D not adequately controlled by SITA-based therapy (12 weeks)	LIRA 0.9 mg QD (54) VILD 50 mg BID (58)	None	LIRA: -0.7* VILD: -0.4	LIRA: -1.0 VILD: -0.8	LIRA: -1.6*** VILD: +0.1
Van Gaal et al ¹⁷ (NCT00976937)	DB, DD, MC, PG, R in young, obese pts with T2D (24 weeks)	LIXI 20 µg QD (158) SITA 100 mg QD (161)	MET	LIXI: -0.7 SITA: -0.7	LIXI: -0.5 SITA: -0.7	LIXI: -2.5*** SITA: -1.2
Metformin						
Russell-Jones et al ⁹ (DURATION-4; NCT00676338)	DB, MC, PG, R in treatment-naive pts with T2D (26 weeks)	ExQW 2 mg (248) MET 2000 mg/day (246) PIO 45 mg QD (163) SITA 100 mg QD (163)	None	ExQW: -1.5 MET: -1.5	ExQW: -2.3 MET: -2.0	ExQW: -2.0 MET: -2.0
Umpierrez et al ²¹ (AWARD-3; NCT01126580)	DB, DD, MC, PG, R in pts with T2D (52 weeks ^c)	DULA 0.75 mg QW (270) DULA 1.5 mg QW (269) MET ≥ 1500 mg/day (268)	None	At 26 weeks DULA 0.75: -0.7* DULA 1.5: -0.8** MET: -0.6 At 52 weeks DULA 0.75: -0.6 DULA 1.5: -0.7* MET: -0.5	At 26 weeks DULA 0.75: -1.4 DULA 1.5: -1.6 MET: -1.3 At 52 weeks DULA 0.75: -1.0 DULA 1.5: -1.6* MET: -1.2	At 26 weeks DULA 0.75: -1.4** DULA 1.5: -2.3 MET: -2.2 At 52 weeks DULA 0.75: -1.1*** DULA 1.5: -1.9 MET: -2.2

(Continued)

Table 1 (Continued)

Publications (acronym/ ClinicalTrials.gov record)	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-IRAs versus comparator		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Sulfonylureas						
Derosa et al ²²	MC, R, SB in overweight pts with T2D poorly controlled on MET (12 months)	ExBID 10 µg ^d (63) GLYB 5 mg TID ^d (65)	MET	ExBID: -1.5 GLYB: -1.8	ExBID: -1.5 GLYB: -1.8	ExBID: -8.0*** GLYB: +4.3
Derosa et al ²³	MC, R, SB in overweight pts with T2D poorly controlled on MET (12 months)	ExBID 10 µg ^d (57) GLIM 2 mg TID ^d (54)	MET	ExBID: -1.2 GLIM: -1.4	ExBID: -1.5 GLIM: -1.6	ExBID: -5.1 GLIM: -0.9
Gallwitz et al ²⁴ (EUREXA; NCT00359762)	OL, R, MC in overweight pts with T2D poorly controlled on MET (~3 years)	ExBID 10 µg ^d (490) GLIM 1 mg TID ^s (487)	MET	ExBID: -0.4** GLIM: -0.2	ExBID: -0.9* GLIM: -0.4	ExBID: -3.3*** GLIM: +1.2
Nauck et al ³² (LEAD-2; NCT00318461)	DB, DD, MC, PG, R in pts with T2D (26 weeks)	LIRA 0.6 mg QD (242) LIRA 1.2 mg QD (240) LIRA 1.8 mg QD (242) GLIM 4 mg QD (242) PBO (121)	MET	LIRA 0.6: -0.7 LIRA 1.2: -1.0 LIRA 1.8: -1.0 GLIM 4: -1.0	LIRA 0.6: -1.1 LIRA 1.2: -1.6 LIRA 1.8: -1.7 GLIM 4: -1.3	LIRA 0.6: -1.8*** LIRA 1.2: -2.6*** LIRA 1.8: -2.8*** GLIM 4: +1.0
Nauck et al ²⁸ (LEAD-2; NCT00318461)	OL extension of pts with T2D completing the LEAD-2 core study (18 months)	LIRA 0.6 mg QD (184) LIRA 1.2 mg QD (178) LIRA 1.8 mg QD (174) GLIM 4 mg QD (183) PBO (61)	MET	LIRA 0.6: -0.4 LIRA 1.2: -0.6 LIRA 1.8: -0.6 GLIM 4: -0.5	LIRA 0.6: -0.8 LIRA 1.2: -1.2* LIRA 1.8: -1.2 GLIM 4: -0.6	LIRA 0.6: -2.1*** LIRA 1.2: -3.0*** LIRA 1.8: -2.9*** GLIM 4: +0.7
Garber et al ²⁵ (LEAD-3 Mono; NCT00294723)	DB, DD, MC, PG, R in pts with early T2D (52 weeks)	LIRA 1.2 mg QD (251) LIRA 1.8 mg QD (247) GLIM 8 mg QD (248)	None	LIRA 1.2: -0.8** LIRA 1.8: -1.1***† GLIM: -0.5	LIRA 1.2: -0.8* LIRA 1.8: -1.4***† GLIM: -0.3	LIRA 1.2: -2.0*** LIRA 1.8: -2.5*** GLIM: +1.1
Garber et al ²⁶ (LEAD-3 Mono; NCT00294723)	OL extension of pts with T2D completing the LEAD-3 core study (52 weeks)	LIRA 1.2 mg QD (110) LIRA 1.8 mg QD (114) GLIM 8 mg QD (97)	None	LIRA 1.2: -0.9* LIRA 1.8: -1.1** GLIM: -0.6	LIRA 1.2: -1.3** LIRA 1.8: -1.5*** GLIM: -0.3	LIRA 1.2: -2.1*** LIRA 1.8: -2.7*** GLIM: +1.1
Seino et al ³⁰ (NCT00393718)	DB, DD, MC, PG, R in Japanese pts with T2D (24 weeks)	LIRA 0.9 mg QD (272) GLYB 2.5 mg/day ^d (139)	None	LIRA: -1.9*** GLYB: -1.4	LIRA: -3.6*** GLYB: -2.9	LIRA: -0.9*** GLYB: +1.0
Kaku et al ²⁷ (NCT00393718)	OL extension of Seino study in Japanese pts with T2D (52 weeks)	LIRA 0.9 mg QD (268) GLYB 2.5 mg/day ^d (132)	None	LIRA: -1.5 GLYB: -1.0	LIRA: -3.2 GLYB: -2.5	LIRA: -0.8 GLYB: +1.0
Thiazolidinediones						
DeFronzo et al ³⁴ (NCT00135330)	OL, MC, PG, R in MET-treated pts with T2D (20 weeks)	ExBID 10 µg ^d (45) ROSI 4 mg BID ^d (45) ExBID 10 µg + ROSI 4 mg BID ^d (47)	MET	ExBID: -0.9 ROSI: -1.0	ExBID: -1.5 ROSI: -1.8	ExBID: -2.8*** ROSI: +1.5
Xu et al ³⁵ (CONFIDENCE; NCT01147627)	OL, MC, PG, R in treatment- naive pts with newly diagnosed T2D (48 weeks)	ExBID 10 µg ^d (142) PIO 30-45 mg QD (136) ILis 0.2 IU/kg BID ^f (138)	None	ExBID: -1.8** PIO: -1.5	ExBID: -1.9 PIO: -2.0	ExBID: -3.5*** PIO: 0
Bergental et al ⁸ (DURATION-2; NCT00637273)	DB, DD, MC, PG, R in pts with T2D (26 weeks)	ExQW 2 mg (160) SITA 100 mg QD (166) PIO 45 mg QD (165)	MET	ExQW: -1.5* PIO: -1.2	ExQW: -1.8 PIO: -1.5	ExQW: -2.3*** PIO: +2.8

(Continued)

Table 1 (Continued)

Publications (acronym/ ClinicalTrials.gov record)	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-IRAs versus comparator		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Russell-Jones et al ⁹ (DURATION-4; NCT00676338)	DB, MC, PG, R in treatment-naive pts with T2D (26 weeks)	ExQW 2 mg (248) MET 2000 mg/day (246) PIO 45 mg QD (163) SITA 100 mg QD (163)	None	ExQW: -1.5 PIO: -1.6	ExQW: -2.3 PIO: -2.6	ExQW: -2.0*** PIO: +1.5
Marre et al ³³ (LEAD-1 SU; NCT00318422)	DB, DD, MC, PG, R in pts with T2D treated with oral GLT for ≥ 3 months (26 weeks)	LIRA 0.6 mg/day (233) LIRA 1.2 mg/day (228) LIRA 1.8 mg/day (234) ROSI 4 mg/day (232) PBO (114)	GLIM	LIRA 0.6: -0.6 LIRA 1.2: -1.1*** LIRA 1.8: -1.1*** ROSI 4: -0.4	LIRA 0.6: -0.7 LIRA 1.2: -1.6** LIRA 1.8: -1.6** ROSI 4: -0.9	LIRA 0.6: +0.7*** LIRA 1.2: +0.3*** LIRA 1.8: -0.2*** ROSI 4: +2.1

Notes: ^aAfter 12 weeks, LIRA up-titrated to 1.8 mg/day in patients with HbA1c ≥ 7.0% (53 mmol/mol); ^bafter 12 weeks, GLIM 1 or 2 mg/day added to regimen of patients with HbA1c ≥ 7.0% (53 mmol/mol) and FG > 6.1 mmol/L; ^cprimary end point was the change from baseline in HbA1c at 26 weeks. Secondary end points included the change from baseline in HbA1c at 52 weeks, and the change from baseline in FG and BW at 26 and 52 weeks; ^dadministered at half the named dosage for the first month of the study; ^edosage adjusted every 4 weeks up to the maximum tolerated dosage according to country-specific labeling information; ^fdosage was titrated according to self-monitored blood glucose levels. **P* < 0.05; ***P* < 0.01; ****P* ≤ 0.001, GLP-IRA versus comparator; †*P* < 0.01, ††*P* ≤ 0.0001 versus baseline (start of extension); ‡*P* < 0.05 versus LIRA 1.2 mg.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; BID, twice daily; BW, body weight; CO, crossover; CONFIDENCE, Comparison of Glycaemic Control and β-Cell Function Amongst Newly Diagnosed Patients With Type 2 Diabetes Treated With Exenatide, Insulin or Pioglitazone: A Multicentre Randomized Parallel-Group Study; DB, double blind; DD, double dummy; DPP-4, dipeptidyl peptidase 4; DULA, dulaglutide; DURATION, Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly; EUREXA, European Exenatide Study; ExBID, exenatide twice daily; ExQW, exenatide once weekly; FG, fasting glucose; GLIM, glimepiride; GLP-IRA, glucagon-like peptide-1 receptor agonist; GLT, glucose-lowering therapy; GLYB, glyburide; HbA1c, glycated hemoglobin; ILis, insulin lispro; LEAD, Liraglutide Effect and Action in Diabetes; LIRA, liraglutide; LIXI, lixisenatide; MC, multicenter; MET, metformin; NR, not reported; OL, open label; PBO, placebo; PG, parallel group; PIO, pioglitazone; pts, patients; QD, once daily; QW, once weekly; R, randomized; ROSI, rosiglitazone; SB, single blind; SITA, sitagliptin; T2D, type 2 diabetes; TID, three times a day; TZD, thiazolidinedione; VILD, vildagliptin.

AWARD-3 was similar between the dulaglutide 1.5 mg and metformin groups at 26 and 52 weeks; dulaglutide 0.75 mg recipients lost significantly less weight than patients receiving metformin at both time points.

Minor hypoglycemia was reported in 2.0% of exenatide QW recipients versus 0.0% of metformin recipients, while dulaglutide and metformin recipients had similar total hypoglycemia rates (12.3%, 11.1%, and 12.7% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively).^{9,21} The incidence of gastrointestinal AEs was similar between treatment groups in AWARD-3,²¹ whereas in DURATION-4, nausea was reported in 11.3% and vomiting in 4.8% of exenatide-treated patients compared with 3.3% who experienced vomiting on metformin.⁹

GLP-IRAs versus sulfonylureas

Nine prospective studies investigated the comparative efficacy of GLP-IRAs and sulfonylureas.^{22–30} One retrospective study was identified: a comparison of liraglutide and glimepiride in outpatients in Italy.³¹

Prospective studies

Generally, exenatide BID recipients had greater or similar reductions from baseline in HbA1c, FG, and weight compared with glyburide or glimepiride recipients (Table 1).^{22–24} Furthermore, glycemic control was maintained for a longer

duration with exenatide BID compared with glimepiride in the European Exenatide Study (EUREXA).²⁴ Compared with glimepiride, liraglutide resulted in greater or similar reductions in HbA1c and FG, and consistently greater reductions in weight.^{25,26,28,32} Similar results were seen when liraglutide was compared with glyburide, with greater or similar reductions from baseline in HbA1c and FG; however, weight loss with liraglutide was not consistently greater versus glyburide.^{27,30}

Patients receiving GLP-IRAs generally had significantly (*P* < 0.05) lower rates of hypoglycemia than sulfonylurea-treated patients;^{22–30} in cases where the *P* value was not stated, the rates were numerically different in favor of the GLP-IRA. The incidence of gastrointestinal AEs was generally higher with GLP-IRAs compared with sulfonylureas,^{25–28,30} however, one study reported similar incidence of gastrointestinal AEs with exenatide and glibenclamide.²² The incidence of treatment withdrawal due to gastrointestinal AEs was also higher with GLP-IRAs compared with sulfonylureas,^{22–24,32} differences in rates of gastrointestinal AEs were seen within 4 weeks in three studies^{29,30} and within 6 months in another study.²⁴

Retrospective studies

In the retrospective analysis, liraglutide produced significantly greater reductions in HbA1c and FG from baseline compared with glimepiride (Table 2; *P* < 0.001).³¹

Table 2 Study details and efficacy results of retrospective studies of GLP-IRAs and oral glucose-lowering therapies or insulin

Publications	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-IRAs versus comparator		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Dipeptidyl peptidase-4 inhibitors						
Horton et al ¹⁸	Retrospective analysis of adult pts with T2D using data from the GEC database (3–12 months)	EXE (6280) INS (32,398) SITA (5861)	OADs	EXE: –0.5 SITA: –0.6	EXE: –0.6 SITA: –0.8	EXE: –3.0 SITA: –1.1
Montilla et al ¹⁹	Retrospective database analysis of adult pts with T2D in primary care in Italy (3–12 months)	EXE (21,064) SITA (38,811) VILD (17,989)	OADs	EXE: –1.0 SITA: –0.9 VILD: –0.9	NR	EXE: ↓3.5% SITA: ↓ ~1.0%–1.5% VILD: ↓ ~1.0%–1.5%
Nyeland et al ²⁰	Retrospective database analysis of adult pts with T2D in primary care in UK (6 months)	LIRA (287) SITA (2781)	OADs	LIRA: –0.9** SITA: –0.6	NR	LIRA: –3.8*** SITA: –1.1
Insulins						
Baser et al ⁵⁸	Retrospective analysis of adult pts with T2D using data from IMPACT national managed care database (1 year)	EXE (1958) IG (381)	OADs	EXE: –0.9 IG: –1.2*	NR	NR
Bounthavong et al ⁵⁹	Retrospective analysis of adult pts with T2D using data from the VHA (2 years)	ExBID (446) IG or IDet (51,531)	NR	ExBID: –0.6 LAI: –0.7	NR	NR
Dalal et al ⁶⁰	Retrospective analysis of adult pts with T2D using data from IMPACT national managed care database (1 year)	EXE or LIRA (1705) RAI (5013)	Basal INS	GLP-IRA: –0.6 RAI: –0.6	NR	NR
Horton et al ¹⁸	Retrospective analysis of adult pts with T2D using data from the GEC database (3–12 months)	EXE (6280) INS (32,398) SITA (5861)	OADs	EXE: –0.5 INS: –1.0	EXE: –0.6 INS: –1.4	EXE: –3.0 INS: +0.6
Pawaskar et al ⁶¹	Retrospective analysis of adult pts with T2D using data from the GEC database (1 year)	EXE (4494) IG (5424)	OADs	EXE: –0.6* IG: –0.4	NR	EXE: –2.6* IG: –0.2
Pawaskar et al ⁶²	Retrospective analysis of elderly pts (≥ 65 years) with T2D using data from the GEC database (1 year)	EXE (1023) IG (2238)	OADs	EXE: –0.5* IG: –0.2	NR	EXE: –2.8* IG: –0.2
Sudhakaran et al ⁶³	Retrospective analysis of adult pts with T2D in India (24 weeks)	ExBID 5–10 µg (47) IG QD (54) NPH QD or BID (23)	OADs	ExBID: –1.0 IG: –0.8 NPH: –0.7	ExBID: –0.5 IG: –0.8 NPH: –0.8	ExBID: –1.6 IG: +1.8 NPH: +2.3
Sulfonylureas						
Chiefari et al ³¹	Retrospective analysis in adult out-pts with T2D in Italy (18 months)	LIRA 1.8 mg/day (76) GLIM 4 mg/day (103)	MET	LIRA: –1.4*** GLIM: –0.4	LIRA: –2.1*** GLIM: –0.8	LIRA: –4.0*** GLIM: 0.0

Notes: * $P < 0.05$; ** $P < 0.01$; *** $P \leq 0.001$, GLP-IRA versus comparator.

Abbreviations: BID, twice daily; BVV, body weight; ExBID, exenatide twice daily; EXE, exenatide; FG, fasting glucose; GEC, general electric centricty; GLP-IRA, glucagon-like peptide-1 receptor agonist; GLIM, glimepiride; HbA1c, glycated hemoglobin; IDet, insulin detemir; IG, insulin glargine; INS, insulin; LAI, long-acting insulin; LIRA, liraglutide; MET, metformin; OAD, oral antidiabetes drug; NPH, neutral protamine Hagedorn insulin; NR, not reported; pts, patients; QD, once daily; RAI, rapid-acting insulin; SITA, sitagliptin; T2D, type 2 diabetes; VHA, Veterans Health Administration; VILD, vildagliptin.

Liraglutide recipients also lost significantly more weight than glimepiride-treated patients ($P < 0.001$). As in the prospective studies, rates of hypoglycemia were lower with liraglutide than glimepiride.³¹ The incidence of gastrointestinal AEs was higher in the liraglutide group compared with the glimepiride group ($P < 0.001$).³¹

GLP-IRAs versus thiazolidinediones

Five prospective studies compared GLP-IRAs with thiazolidinediones.^{8,9,33–35}

Prospective studies

Exenatide BID produced similar reductions in HbA1c to rosiglitazone and significantly greater reductions than pioglitazone ($P < 0.01$; Table 1).^{34,35} Similar reductions in FG were seen between exenatide BID and rosiglitazone and pioglitazone. Patients receiving exenatide BID had significantly greater weight loss than those receiving thiazolidinediones ($P < 0.0001$); in both studies, exenatide BID recipients had weight loss of ~3 kg, while patients receiving rosiglitazone gained weight and patients receiving pioglitazone had no change in weight.

Studies of exenatide QW showed that reductions from baseline in HbA1c, FG, and weight were either greater or similar than with thiazolidinedione comparators (Table 1).^{8,9} In the DURATION-2 study, exenatide QW recipients had significantly greater reductions in HbA1c versus pioglitazone, while in DURATION-4, reductions in HbA1c with exenatide QW and pioglitazone were similar; reductions in FG with exenatide QW and pioglitazone were similar. Significant reductions in weight were seen with exenatide QW in DURATION-2 and -4, whereas patients receiving pioglitazone gained weight (as expected in the presence of a sulfonyleurea) in both studies ($P < 0.0001$ between groups).

The Liraglutide Effect and Action in Diabetes (LEAD)-1 SU study showed that liraglutide (0.6, 1.2, and 1.8 mg/day) was generally more effective as a second-line therapy in improving glycemic parameters and weight than rosiglitazone (Table 1).³³ Liraglutide 1.2 mg and 1.8 mg was associated with significantly greater reductions in HbA1c ($P < 0.0001$) and FG ($P < 0.001$) than rosiglitazone. Recipients of liraglutide 0.6 mg or 1.2 mg and rosiglitazone gained weight, whereas recipients of liraglutide 1.8 mg lost weight (Table 1); however, the weight gain with the lower dosages of liraglutide was significantly less than that with rosiglitazone, so the differences from baseline in weight were significant between rosiglitazone and all doses investigated ($P < 0.0001$).

Overall, the rate of hypoglycemia seen with GLP-1RAs was slightly greater than or similar to that seen with thiazolidinediones.^{8,9,33-35} The incidence of gastrointestinal AEs was higher with GLP-1RAs compared with thiazolidinediones.^{8,9,33-35} Gastrointestinal AEs led to treatment withdrawal in a higher number of patients in the exenatide group compared with thiazolidinediones in one study.³⁵

GLP-1RAs versus insulin products

Twenty-three prospective studies³⁵⁻⁵⁷ and seven retrospective studies^{18,58-63} compared GLP-1RAs with insulin products.

Prospective studies

Four trials compared GLP-1RAs and insulin aspart (Table 3).^{38,47,54,55} Exenatide studies showed that exenatide BID produced a similar or lesser reduction in HbA1c and FG than insulin aspart.^{38,47,55} In contrast, exenatide BID recipients lost weight, while those using insulin aspart gained weight. In two of the three exenatide studies, the between-group difference in weight was significant ($P < 0.001$).

In the BEGINTM: VICTOZA[®] ADD-ON study, liraglutide significantly reduced HbA1c and weight versus insulin aspart, while reductions in FG were similar between treatments

(Table 3).⁵⁴ When liraglutide 1.8 mg was compared with insulin degludec, the reductions in HbA1c and FG were similar between groups; patients receiving liraglutide lost weight while patients receiving insulin gained weight.⁵⁰

After 26 weeks of treatment, exenatide QW recipients had a significantly greater reduction from baseline in HbA1c than insulin detemir recipients and similar reductions in FG. Similar to liraglutide, those receiving exenatide lost weight, while insulin detemir recipients gained weight (between-group difference, $P < 0.0001$; Table 3).⁴¹

Twelve studies compared GLP-1RAs with insulin glargine (Table 3).^{36,37,39,40,42,44-46,48,51,52,57} In the exenatide (BID and QW) studies, reductions from baseline in HbA1c were greater or similar to those with insulin glargine, whereas reductions in FG were similar or smaller (Table 3). Furthermore, a significant difference was generally observed between the weight loss with exenatide and the weight gain with insulin glargine (Table 3).

In the AWARD-4 study, compared with insulin glargine, treatment with dulaglutide for 26 weeks resulted in significantly greater reductions in HbA1c in patients also receiving insulin lispro and significantly smaller reductions in FG.³⁹ Patients receiving dulaglutide 1.5 mg lost weight versus baseline, while recipients of dulaglutide 0.75 mg and insulin glargine gained weight; however, the differences between the dulaglutide and insulin glargine groups were significant, irrespective of dulaglutide dose (Table 3).

The comparisons between liraglutide and insulin glargine in the Efficacy Assessment of Insulin Glargine Versus Liraglutide After Oral Agents Failure (EAGLE) and LEAD-5 studies were inconsistent with regard to HbA1c and FG; in the EAGLE study, liraglutide resulted in a lesser reduction in HbA1c and FG than insulin glargine, whereas in the LEAD-5 study, the reduction in HbA1c was greater with liraglutide versus insulin glargine and the reduction in FG was similar between groups.^{40,57} The change in weight was consistent between the two studies, with liraglutide recipients losing weight and insulin glargine recipients gaining weight (Table 3).

Two studies compared exenatide BID with insulin lispro (Table 3).^{35,43} In both studies, exenatide BID and insulin lispro reduced HbA1c from baseline to a similar degree. Reductions from baseline in FG were greater or similar with exenatide BID versus insulin lispro; exenatide BID treatment consistently resulted in weight loss, while insulin lispro recipients consistently gained weight.

Generally, the rate of hypoglycemia was lower with GLP-1RAs versus insulin products,^{35,38-40,43,46,47} or similar

Table 3 Study details and efficacy results of prospective (randomized controlled and noninterventional) trials of GLP-IRAs versus insulin products

Publications (acronym/ ClinicalTrials.gov record)	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-IRAs versus insulin		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Insulin						
Ostenson et al ⁵⁶ (CHOICE; NCT00635492)	MC, O study in pts with T2D (12 months)	ExBID (1096) INS (1239)	OADs	ExBID: -1.0 INS: -1.8	NR	ExBID: -3.3 INS: +1.9
Mathieu et al ⁵³ (CHOICE; NCT00635492)	MC, O study in pts with T2D (24 months)	ExBID (1114) INS (1274)	OADs	ExBID: -1.0 INS: -1.7	NR	ExBID: -3.2 INS: +2.2
Insulin aspart						
Bergenstal et al ³⁸ (NCT00097877)	MC, OL, PG, R in pts with T2D (24 weeks)	ExBID 5-10 µg (124) Biphasic IAsp 30 QD (124) Biphasic IAsp 30 BID (124)	MET SU	ExBID: -1.8 IAsp QD: -2.3†† IAsp BID: -2.8††	ExBID: -1.2 IAsp QD: -2.9†† IAsp BID: -3.5††	ExBID: -1.9 IAsp QD: +2.8 IAsp BID: +4.1
Gallwitz et al ⁴⁷ (NCT00434954)	MC, OL, PG, R in pts with T2D (26 weeks)	ExBID 5-10 µg (182) Biphasic IAsp 30 TID (181)	MET	ExBID: -1.0 IAsp: -1.1	NR	ExBID: -4.1*** IAsp: +1.0
Nauck et al ⁵⁵ (NCT00082407)	MC, OL, PG, R in pts with T2D (52 weeks)	ExBID 5-10 µg (253) Biphasic IAsp BID (248)	SU	ExBID: -1.0 IAsp: -0.9	ExBID: -1.8 IAsp: -1.7	ExBID: -2.5*** IAsp: +2.9
Mathieu et al ⁵⁴ (BEGIN: VICTOZA ADD-ON; NCT01388361)	MC, OL, PG, R in insulin-naive pts with T2D (26 weeks)	LIRA 0.6-1.8 mg/day (88) IAsp QD (89) ^a	IDeg MET	LIRA: -0.7** IAsp: -0.4	LIRA: -0.1 IAsp: -0.04	LIRA: -2.8*** IAsp: +0.9
Insulin degludec						
Gough et al ⁵⁰ (DUAL-I; NCT01336023)	MC, OL, PG, R in pts with T2D (26 weeks)	IDeg/LIRA QD (834) LIRA 0.6-1.8 mg QD (415) IDeg QD (414)	MET ± PIO	LIRA: -1.3 IDeg: -1.4	LIRA: -1.8 IDeg: -3.6	LIRA: -3.0 IDeg: +1.6
Gough et al ⁴⁹ (DUAL-I; NCT01336023)	Extension of DUAL-I in pts with T2D (52 weeks)	IDeg/LIRA QD (665) LIRA 0.6-1.8 mg QD (313) IDeg QD (333)	MET ± PIO	LIRA: -1.2 IDeg: -1.4	LIRA: -1.7 IDeg: -3.4	LIRA: -3.0 IDeg: +2.3
Insulin detemir						
Davies et al ⁴¹ (NCT01003184)	MC, OL, PG, R in pts with T2D (26 weeks)	ExQW 2 mg (111) IDet QD or BID (105)	MET ± SU	ExQW: -1.3*** IDet: -0.9	ExQW: -2.3 IDet: -2.4	ExQW: -2.7*** IDet: +0.8
Insulin glargine						
Barnett et al ³⁷ (NCT00099619)	CO, MC, OL, R in pts with T2D (2 × 16 weeks)	ExBID 5-10 µg/IG QD (68) IG QD/ExBID 5-10 µg (70)	MET (55.1%) SU (44.9%)	ExBID: -1.4 IG: -1.4	ExBID: -2.9 IG: -4.1††	ExBID: -1.6*** IG: +0.6
Davies et al ⁴² (HEELA)	MC, OL, PG, R in pts with T2D (26 weeks)	ExBID 5-10 µg (118) IG QD (117)	MET SU TZD	ExBID: -1.3 IG: -1.3	ExBID: -2.1 IG: -3.6††	ExBID: -2.7*** IG: +3.0
Diamant et al ⁴⁶ (DURATION-3; NCT00641056)	MC, OL, PG, R in pts with T2D (26 weeks)	ExQW 2 mg (233) IG QD (223)	MET ± SU	ExQW: -1.5* IG: -1.3	ExQW: -2.1 IG: -2.8††	ExQW: -2.6*** IG: +1.4
Diamant et al ⁴⁵ (DURATION-3 extension; NCT00641056)	OL extension of DURATION-3 in pts with T2D (84 weeks)	ExQW 2 mg (233) IG QD (223)	MET ± SU	ExQW: -1.2* IG: -1.0	ExQW: -2.4 IG: -3.0†	ExQW: -2.1*** IG: +2.4
Diamant et al ⁴⁴ (DURATION-3 extension; NCT00641056)	OL extension of DURATION-3 in pts with T2D (156 weeks)	ExQW 2 mg (194) IG QD (196)	MET ± SU	ExQW: -1.0* IG: -0.8	ExQW: -1.7 IG: -2.7††	ExQW: -2.5*** IG: +2.0

(Continued)

Table 3 (Continued)

Publications (acronym/ ClinicalTrials.gov record)	Study design (study duration)	Treatment (patient number)	Background therapy	Change from baseline at study end, GLP-1RAs versus insulin		
				HbA1c (%)	FG (mmol/L)	BW (kg)
Heine et al ⁵¹ (NCT00082381)	MC, OL, PG, R in pts with T2D (26 weeks)	ExBID 5–10 µg (282) IG QD (267)	MET SU	ExBID: –1.1 IG: –1.1	ExBID: –1.4 IG: –2.9††	ExBID: –2.3 IG: +1.8
Inagaki et al ⁵² (NCT00935532)	MC, OL, PG, R in Japanese pts with T2D (26 weeks)	ExQW 2 mg (215) IG QD (212)	BG ± TZD	ExQW: –1.1*** IG: –0.7	ExQW: –2.6 IG: –2.3	ExQW: –1.7*** IG: +0.3
Araki et al ³⁶ (NCT01584232)	MC, OL, PG, R in Japanese pts with T2D (26 weeks)	DULA 0.75 mg QW (181) IG QD (180)	BG ± SU	DULA 0.75: –1.4*** IG: –0.9	DULA 0.75: –1.9 IG: –2.1	DULA 0.75: –0.5*** IG: +0.9
Blonde et al ³⁹ (AWARD-4; NCT01191268)	MC, OL, PG, R in pts with T2D (52 weeks ^b)	DULA 0.75 mg QW (293) DULA 1.5 mg QW (295) IG QD (296)	ILis MET	At 26 weeks DULA 0.75: –1.6* DULA 1.5: –1.6** IG: –1.4	At 26 weeks DULA 0.75: –0.2 DULA 1.5: –0.3 IG: –1.6††	At 26 weeks DULA 0.75: +0.2*** DULA 1.5: –0.9*** IG: +2.3
D'Alessio et al ⁴⁰ (EAGLE)	MC, OL, PG, R in pts with T2D (24 weeks)	LIRA 0.6–1.8 mg QD (489) IG QD (489)	MET ± SU	LIRA: –1.8 IG: –1.9*	LIRA: –2.4 IG: –2.8††	LIRA: –3.0*** IG: +2.0
Giorgino et al ⁴⁸ (AWARD-2; NCT01075282)	MC, OL, PG, R in pts with T2D (78 weeks ^c)	DULA 0.75 mg QW (272) DULA 1.5 mg QW (273) IG QD (262)	MET GLIM	At 52 weeks DULA 0.75: –0.8*** DULA 1.5: –1.1*** IG: –0.6	At 52 weeks DULA 0.75: –0.9 DULA 1.5: –1.5 IG: –1.8†† ^d	At 52 weeks DULA 0.75: –1.3*** DULA 1.5: –1.9*** IG: +1.4
Russell-Jones et al ⁵⁷ (LEAD-5; NCT00331851)	MC, OL, PG, R in pts with T2D (26 weeks)	LIRA 1.8 mg QD (230) IG QD (232) PBO (114)	MET GLIM	LIRA: –1.3** IG: –1.1	LIRA: –1.6 IG: –1.8	LIRA: –1.8*** IG: +1.6
Insulin lispro						
Diamant et al ⁴³ (NCT00960661)	MC, OL, PG, R in pts with T2D (30 weeks)	ExBID 5–10 µg (315) ILis TID (312)	MET IG	ExBID: –1.1 ILis: –1.1	ExBID: –0.5** ILis: +0.2	ExBID: –2.5*** ILis: +2.1
Xu et al ³⁵ (CONFIDENCE; NCT01147627)	MC, OL, PG, R in treatment-naïve pts with newly diagnosed T2D (48 weeks)	ExBID 5–10 µg (142) PIO 30–45 mg QD (136) ILis BID (138)	None	ExBID: –1.8 ILis: –1.7	ExBID: –1.9 ILis: –1.6	ExBID: –3.5*** ILis: +1.0

Notes: ^aTreatment arms were also compared with a nonrandomized group of patients who received IDeg alone (n = 236); ^bprimary end point was change from baseline in HbA1c at 26 weeks; ^cprimary end point was change from baseline in HbA1c at 52 weeks; ^dsignificant difference applies to IG QD versus DULA 0.75 mg QW comparison only. *P < 0.05; **P < 0.01; ***P < 0.001, GLP-1RA versus INS comparator; †P < 0.01; ††P < 0.001, INS comparator versus GLP-1RA.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; BG, biguanide; BID, twice daily; BW, body weight; CHOICE, Changes to Treatment and Outcomes in Patients With Type 2 Diabetes Initiating Injectable Therapy; CO, crossover; CONFIDENCE, Comparison of Glycaemic Control and β-Cell Function Amongst Newly Diagnosed Patients With Type 2 Diabetes Treated With Exenatide, Insulin or Pioglitazone: A Multicentre Randomized Parallel-Group Study; DUAL, Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes; DULA, dulaglutide; DURATION, Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly; EAGLE, Efficacy Assessment of Insulin Glargine versus Liraglutide After Oral Agent Failure; ExBID, exenatide twice daily; ExQW, exenatide once weekly; FG, fasting glucose; GLIM, glimepiride; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HEELA, Helping Evaluate Exenatide in Patients With Diabetes Compared With Long-Acting Insulin; IAsp, insulin aspart; IDeg, insulin degludec; IDet, insulin detemir; IG, insulin glargine; ILis, insulin lispro; INS, insulin; LEAD, Liraglutide Effect and Action in Diabetes; LIRA, liraglutide; MC, multicenter; MET, metformin; NR, not reported; O, observational; OAD, oral antidiabetes drug; OL, open label; PBO, placebo; PG, parallel group; PIO, pioglitazone; pts, patients; QD, once daily; QW, once weekly; R, randomized; SU, sulfonylurea; T2D, type 2 diabetes; TID, three times daily; TZD, thiazolidinedione.

between groups.^{41,55,57} Overall, the incidence of gastrointestinal AEs among GLP-1RA-treated patients was higher than in insulin-treated patients,^{37–42,44–47,50–52,54,55,57} gastrointestinal AEs were generally observed on initiation of treatment with GLP-1RAs^{39,44,45,47,50,57} and sometimes led to treatment withdrawal.^{37,39,42,47,52}

Retrospective studies

Seven retrospective studies compared GLP-1RAs and insulin products (Table 2),^{18,58–63} with similar results to the prospective studies; the reduction in HbA1c was greater with GLP-1RAs than insulin in most studies. Where reported, reductions from baseline in FG were not statistically different between

groups. In studies in which the change in weight was reported, GLP-1RA treatment resulted in weight loss, while insulin treatment resulted in weight gain.

Where reported, the incidence of hypoglycemia was either similar between GLP-1RA and insulin treatment groups or lower in those receiving GLP-1RAs.^{58,60–63} Treatment-related nausea was reported in 10 patients in the exenatide group in one study and did not lead to treatment discontinuation.⁶³

Effect of GLP-IRAs versus other glucose-lowering therapies on cardiovascular risk factors

The comparative studies identified by the literature search reported only limited information on cardiovascular risk factors and did not assess cardiovascular outcomes.

GLP-IRAs versus DPP-4is

Of the 10 prospective trials of GLP-1RAs and DPP-4is, all reported effects on blood pressure (BP) and/or lipid cardiovascular risk factors (Table S1).^{7–16} Two retrospective studies comparing GLP-1RAs with DPP-4is also reported changes in cardiovascular risk factors (Table S2).^{18,20} Changes in both diastolic BP and systolic BP (SBP) were variable for GLP-1RAs and DPP-4is, and changes in lipids were generally not significantly different between treatment groups. However, in AWARD-5, dulaglutide 1.5 mg resulted in a significantly greater reduction in low-density lipoprotein cholesterol compared with sitagliptin¹⁰ (Table S1).

GLP-IRAs versus metformin

Two studies reported data on cardiovascular risk factors after treatment with GLP-1RAs compared with metformin, neither of which showed any clinically significant between-group differences in cardiovascular risk factors (Table S1).^{9,21}

GLP-IRAs versus sulfonylureas

Seven of the nine studies comparing GLP-1RAs with sulfonylureas reported data on cardiovascular risk factors (Table S1),^{24–28,30,32} along with one retrospective study (Table S2).³¹ In general, results indicated that the GLP-1RAs were associated with greater reductions in SBP than the sulfonylureas, with numerical reductions in various lipids observed in several studies comparing GLP-1RAs with sulfonylureas.

GLP-IRAs versus thiazolidinediones

All five prospective studies comparing GLP-1RAs with thiazolidinediones reported reductions from baseline in BP

or fasting lipids (Table S1).^{8,9,33–35} Exenatide significantly reduced measures of cholesterol versus thiazolidinediones in three of these studies.^{8,34,35}

GLP-IRAs versus insulin

Two of four trials comparing GLP-1RAs and insulin aspart reported changes in cardiovascular risk factors (Table S3).^{54,55} One trial reported a significantly smaller increase in high-density lipoprotein cholesterol with exenatide BID versus insulin aspart.⁵⁵

Eight of ten prospective studies and two extension studies comparing GLP-1RAs with insulin glargine reported changes in cardiovascular risk factors (Table S3).^{36,39,40,42,44–46,48,52,57} Overall, numerical reductions in SBP were observed in most of these studies, with greater reductions generally seen with GLP-1RAs than for insulin glargine; significant differences between treatments for fasting lipids also generally favored GLP-1RAs.

Exenatide BID was compared with insulin lispro in two studies (Table S3).^{35,43} No significant differences between treatment groups were reported for changes in BP or lipids.

Of the seven retrospective studies comparing GLP-1RAs and insulin products, four reported data on cardiovascular risk factors (Table S2).^{18,61–63} Numerical reductions in BP and lipid measures were observed across exenatide and insulin therapies.

Discussion

GLP-1RAs represent an effective therapeutic option for patients with T2D. Currently, multiple studies provide data on the efficacy of approved GLP-1RAs in T2D (Figure 2). Although their glycemic efficacy is well established versus multiple classes of agents, including insulin, albeit with a notable lack of comparative studies versus sodium-glucose cotransporter 2 inhibitors, GLP-1RAs have additional benefits of modest weight loss and a favorable tolerability profile (Figure 3).⁶⁴ These beneficial effects of GLP-1RAs should be considered in context with the increased frequency of nausea with GLP-1RAs, which may limit adherence, and the need for self-injection on a once- or twice-daily or weekly basis.

The efficacy of GLP-1RAs is generally greater than DPP-4is, owing to the supraphysiological concentrations of GLP-1 after administration of the former.⁶⁵ This effect on incretin also accounts for the greater weight loss experienced by patients who receive GLP-1RAs versus the neutral weight effects produced by DPP-4is.^{65,66} Glycemic control was also mostly

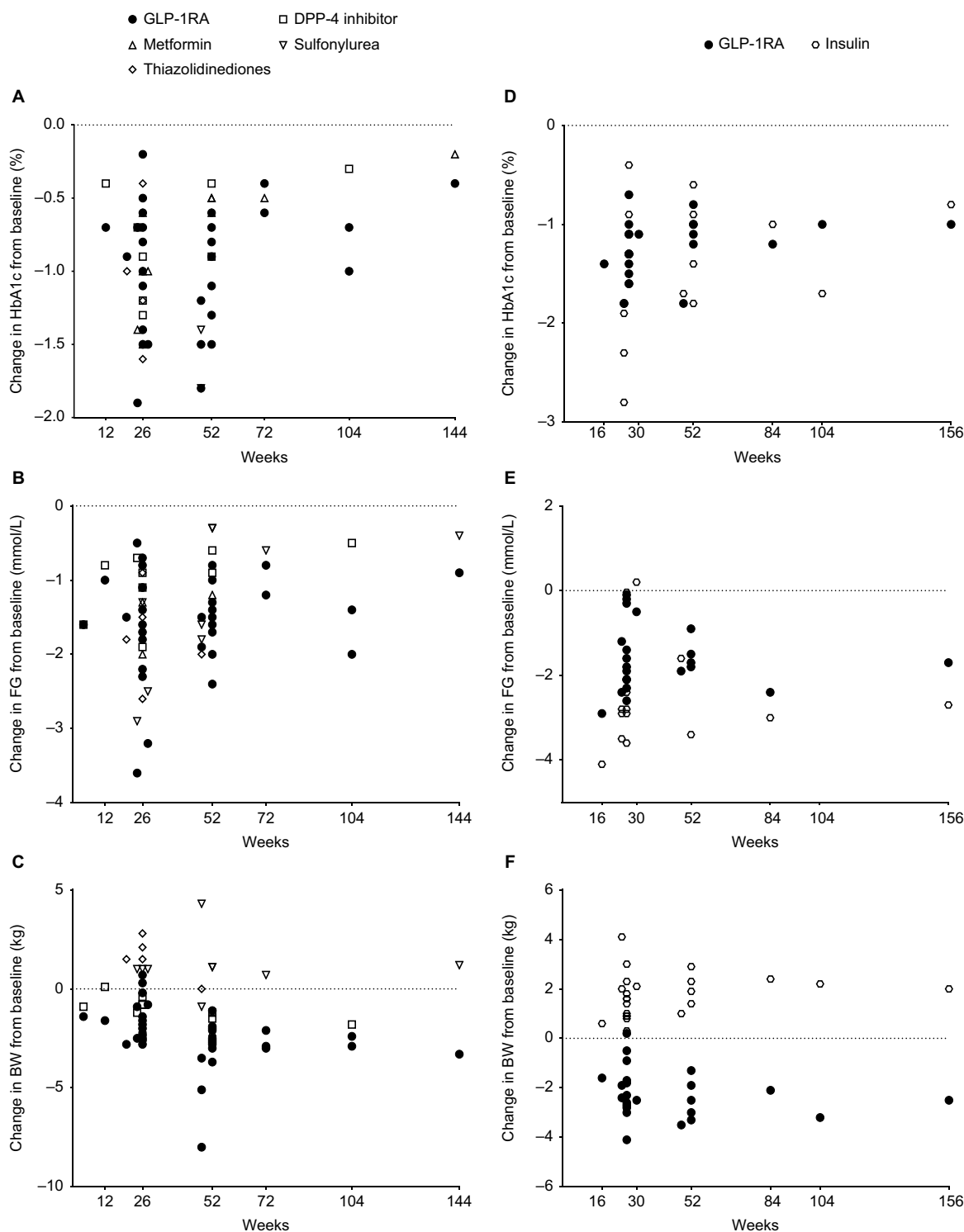


Figure 2 Efficacy of glucose-lowering treatments in type 2 diabetes. Changes from baseline in (A) glycated hemoglobin (HbA1c), (B) fasting glucose (FG), and (C) body weight (BW) in prospective studies comparing glucagon-like peptide-1 receptor agonists (GLP-IRAs) with other oral glucose-lowering therapies and changes from baseline in (D) HbA1c, (E) FG, and (F) BW in prospective studies comparing GLP-IRAs with insulin products. **Abbreviation:** DPP-4, dipeptidyl peptidase-4.

similar to that with insulin, largely driven by improvements in postprandial glucose with the short-acting GLP-1RAs, with similar effects on FG as insulin. However, real-world evidence suggests similar glycaemic reductions between GLP-1RAs and

insulin and within the GLP-1RA class. A real-world study in patients with T2D reported that addition of exenatide BID to basal insulin was as effective as addition of mealtime insulin in reducing HbA1c levels in these patients, with significant

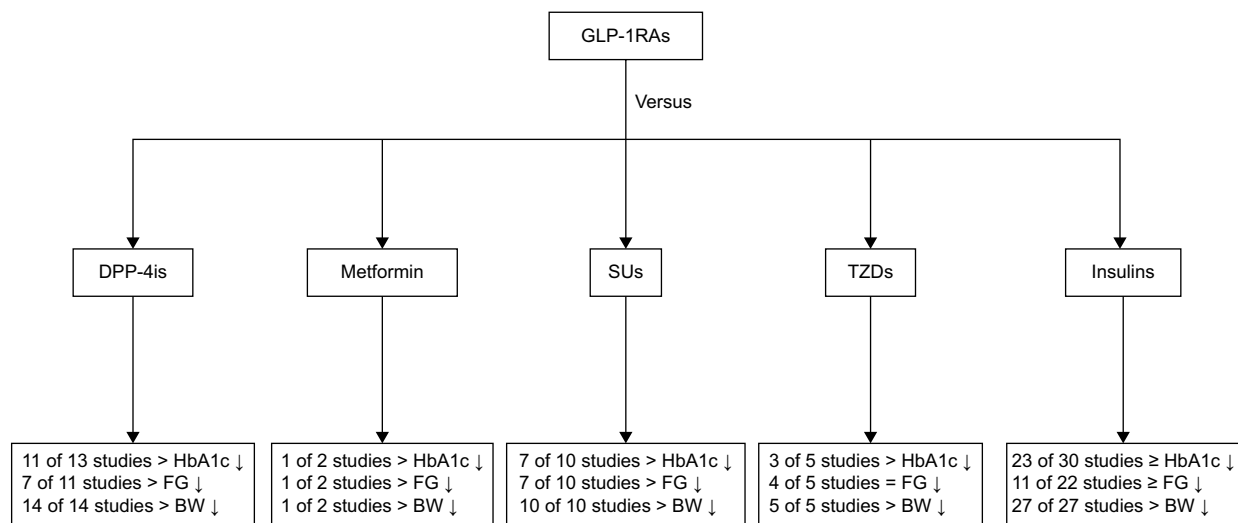


Figure 3 Comparison of efficacy of GLP-IRAs with other glucose-lowering treatments in type 2 diabetes. General trends in glycemic parameters and body weight (BW) in comparative trials of glucagon-like peptide-1 receptor agonists (GLP-IRAs) and other glucose-lowering therapies. The total number of studies includes studies that reported these parameters.

Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; FG, fasting glucose; HbA1c, glycated hemoglobin; SU, sulfonylurea; TZD, thiazolidinedione.

reductions in weight ($P < 0.01$) and hypoglycemia ($P < 0.03$) compared with mealtime insulin.⁶⁷

Data comparing the effects of GLP-IRAs and other classes of glucose-lowering therapy on cardiovascular risk factors were limited but showed favorable effects on BP and lipid levels. Increases in heart rate have been observed with GLP-IRAs in clinical trials, although the underlying mechanisms and clinical relevance of these increases have yet to be established.⁶⁸ The size and duration of increases in mean 24-hour heart rate vary between GLP-IRAs, ranging from transient (1–12 hours) increases of 1–3 beats per minute (bpm) with the short-acting GLP-IRAs exenatide BID and lixisenatide to more prolonged increases during treatment with longer-acting GLP-IRAs (3–4 bpm with exenatide QW or dulaglutide and 6–10 bpm with liraglutide or albiglutide).⁶⁸ Data from cardiovascular outcome trials indicate that the observed increases in heart rate were not associated with an adverse effect on cardiovascular outcomes in patients with T2D.^{5,6,68,69}

Limited clinical data are available regarding the effects of the various GLP-IRAs on cardiovascular outcomes, and none of these studies compared a GLP-1RA with another class of glucose-lowering therapy. The first published study with prospective outcomes data was the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial,⁷⁰ which found no significant difference in rates of cardiovascular events with lixisenatide versus placebo.⁶ A similar study investigating the effects of liraglutide on cardiovascular outcomes, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, showed

improved effects of liraglutide on cardiovascular outcomes versus placebo.⁵ Finally, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), which evaluated the effect of semaglutide (added on to standard care) on cardiovascular outcomes, demonstrated the noninferiority of semaglutide to placebo, with a significant reduction in cardiovascular death, nonfatal stroke, or nonfatal myocardial infarction in the semaglutide group.⁶⁹

Results of the EXenatide Study of Cardiovascular Event Lowering (EXSCEL) trial, evaluating the effect of exenatide QW on major adverse cardiovascular events (MACE) when given in addition to usual care;⁷¹ the Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) study, evaluating the effects of dulaglutide on MACE;⁷² and the HARMONY Outcomes study, evaluating the effects of albiglutide on MACE,⁷³ are all awaited and are expected to help contribute to the existing evidence regarding the impact of the GLP-1RAs on cardiovascular outcomes.

With the limited availability of prospective data, we can glean some information from meta-analyses and pooled analyses that have been conducted in an attempt to elucidate the effects of GLP-1RAs on cardiovascular outcomes. For example, a prespecified meta-analysis, which evaluated cardiovascular risk in the dulaglutide clinical development program,⁷⁴ indicated that there were no significant differences between dulaglutide and placebo groups with regard to the risk of MACE. Similarly, a meta-analysis of cardiovascular events occurring during treatment with albiglutide, placebo,

or active comparators in the HARMONY clinical trial program⁷⁵ determined there was no significant difference between albiglutide and comparator for the risk of MACE or hospital admission for unstable angina.

The effect of exenatide BID on cardiovascular outcomes has also been assessed in a pooled meta-analysis of cardiovascular safety data from 12 long-term, randomized, placebo- or insulin comparator-controlled trials.⁷⁶ The pooled relative risk for primary MACE for users of exenatide BID versus the comparator favored exenatide, suggesting no increased cardiovascular risk associated with exenatide use versus insulin or placebo. Two additional meta-analyses did not find any increase in the incidence of MACE in users of GLP-1RAs compared with comparators.^{77,78} Both studies showed that the GLP-1RAs were associated with a significantly lower risk of MACE compared with placebo, but not with active comparators (with the exception of pioglitazone).^{77,78} Consistent with these two studies, a sequential analysis of long-term trials comparing the effect of GLP-1RAs with other glucose-lowering drugs or placebo⁷⁹ as well as a large comparative safety study of GLP-1RAs versus other glucose-lowering agents⁸⁰ both demonstrated no significant difference in the risk of cardiovascular events between drug classes.

Real-world data can also provide some insight into the impact of the GLP-1RAs on cardiovascular risk in patients with T2D. Retrospective studies have suggested that exenatide BID, with or without concomitant insulin, significantly reduced the risk of cardiovascular events compared with insulin⁸¹ and that exenatide BID is associated with a lower risk of cardiovascular events and hospitalizations versus other glucose-lowering therapies.⁸²

The present review included prospective and retrospective studies that compared the efficacy and safety of approved GLP-1RAs with other currently available glucose-lowering therapies in the treatment of patients with T2D, with data showing clinical benefit of GLP-1RAs over other glucose-lowering therapies. However, it is critical to consider the patient selection criteria, background medications, properties of the individual GLP-1RAs, drug exposure across dose intervals, and outcome definitions of each study. Furthermore, the patient characteristics in these studies need to be taken into account to assess the generalizability of the results to the T2D population at large; overly strict criteria limit the applicability of the data to everyday clinical practice.

Conclusion

This systematic analysis shows that GLP-1RAs were generally as effective as, or more effective than, oral

glucose-lowering therapies in improving glycemic parameters such as HbA1c and FG in patients with T2D. The reduction in HbA1c with GLP-1RAs tended to be similar or smaller compared with the reductions achieved with insulin therapy, with less hypoglycemia. GLP-1RAs were consistently more effective at reducing weight than oral glucose-lowering therapies and insulin. Additionally, the GLP-1RAs appeared to have favorable effects on cardiovascular risk factors such as BP and lipid levels. In summary, GLP-1RAs are an effective, safe, and well-tolerated treatment option for T2D, with minimal risk of hypoglycemia and providing modest weight loss.

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Author contributions

All authors have contributed sufficiently to the project to be included as authors. The authors contributed equally to the conception and design of the systematic review and literature search, interpretation of the results, and drafting of the manuscript.

Disclosure

PA Levin has received grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, and Sanofi. He is a consultant for AstraZeneca, Novo Nordisk, and Sanofi, and a speaker for AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Novo Nordisk, and Sanofi. H Nguyen was an employee of AstraZeneca at the time this review was conceived and drafted. ET Wittbrodt is an employee of AstraZeneca. SC Kim has received research grants to the Brigham and Women's Hospital from AstraZeneca, Bristol-Myers Squibb, Genentech, Lilly, and Pfizer. The authors report no other conflicts of interest in this work.

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