Glucagon like peptide-1 receptor agonist (GLP-1RA) therapy in management of type 2 diabetes: choosing the right agent for individualised care

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Abstract

Glucagon like peptide-1 receptor agonists (GLP-1RAs) are a new class of injectable agent used in the management of type 2 diabetes (T2DM). In the UK, NICE approved the use of GLP-1RAs in combination with metformin and sulphonylurea in people with T2DM whose glycaemic control is above target (≥7.5%, 58 mmol/mol) and body mass index (BMI) ≥35 kg/m² with other medical problems associated with obesity or for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities in people with BMI <35 kg/m². Unlike many other classes of glucose lowering agents, GLP-1RAs not only improve glycaemic control but also promote weight loss with a low risk of hypoglycaemia. In randomised controlled trials, treatment with GLP-1RAs either as monotherapy or in combination with oral hypoglycaemic agents or insulin, has demonstrated significant improvement in glycaemic control by 1–2% with weight loss of approximately 1–5 kg. In addition, they exert a positive effect on cardio-metabolic risk factors by reducing body weight, lowering blood pressure and improving the lipid profile. Gastrointestinal side effects are the most common adverse events with GLP-1RA therapy. Since the first GLP-1RA was approved in 2005, a number of other GLP-1RAs are now available. However, their glycaemic efficacy, safety profiles and mode of delivery differ, and this review article aims to give an overview of differences among GLP-1RAs and to provide decision makers with an overview of the evidence when choosing a particular GLP-1RA for individualised therapy.

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Introduction

Type 2 diabetes (T2DM) is a metabolic disorder characterised by chronic hyperglycaemia due to complex pathophysiological mechanisms recently described as the "ominous octet".[1] This includes reduced insulin secretion from β-cells, increased glucagon production from α-cells, increased hepatic glucose output, increased lipolysis, increased renal glucose reabsorption, insulin resistance (in the periphery, where it reduces glucose uptake, and in the brain, where it promotes greater food intake), neurotransmitter dysfunction, and a reduced incretin effect.[1,2] Incretins are gut hormones produced from intestinal cells in response to oral glucose ingestion, which in turn stimulates insulin secretion. In people without diabetes, an oral glucose load elicits a greater insulin response than intravenous glucose administration, known as the "incretin effect".[3] However, this effect is blunted in people with T2DM.[4] With a better understanding of the incretin effect in people with T2DM and specifically targeting the incretin system, a novel class of therapeutic agents, called glucagon like peptide-1 receptor agonists (GLP-1RAs) has been developed. In addition to glucose-dependent insulin secretion, GLP-1RAs suppress glucagon production, reduce hepatic glucose output, inhibit satiety centre and delay gastric emptying, resulting in improved glucose control and promoting weight loss.[5]

The first GLP-1RA, exenatide, was approved by the US Food and Drug Administration (FDA) in 2005. Although structured education and life-style modifications are the basic pillars in managing T2DM, achieving and maintaining glycaemic control becomes a challenge as the condition progresses despite the availability and use of multiple glucose lowering therapies.[2] Moreover, the conventional therapies used in the management of T2DM can be associated with undesirable side effects such as hypoglycaemia and weight gain. However, treatment with GLP-1RAs has the added benefit of weight loss and a low risk of hypoglycaemia in addition to improving glycaemic control. They have been shown to improve cardiovascular risk factors in many studies.

All GLP-1RAs available to date are administered subcutaneously either daily or once weekly. Exenatide (Byetta®), liraglu-

tide (Victoza®) and lixisenatide (Lyxumia®) are daily preparations whereas once-weekly exenatide (Bydureon®), albiglutide (Eperzan® or Tanzeum®), dulaglutide (Trulicity®), semaglutide (in development) and taspoglutide (discontinued) are once-weekly preparations. In order to retain the mode of action for an extended period, they have been formulated either as microspheres (once-weekly exenatide), combined with recombinant human albumin (albiglutide), bound to modified human IgG4 (dulaglutide), increased albumin affinity and secured full stability against metabolic degradation (semaglutide) or modified amino acid sequence (taspoglutide). To date, once-weekly, exenatide (2 mg), albiglutide (30 or 50 mg) and dulaglutide (0.75 or 1.5 mg) are licensed by the FDA and European Medicine Agency (EMA) to be used in the management of T2DM. Development of taspo-glutide (10 or 20 mg) was discontinued in 2010 due to undue side-effects and therefore it is not clinically available while semaglutide is being studied in phase 3 trials.[6]

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines recommend the use of GLP-1RAs as an adjunctive therapy to life style modification and metformin.[7] In the UK, the use of GLP-1RAs is advocated by the National Institute for Health and Care Excellence (NICE) in patients with T2DM who have a body mass index (BMI) ≥35 kg/m^2 and HbA_{1c} ≥7.5% (58 mmol/mol) unless comorbidities such as obstructive apnoea or occupational issues precluding insulin use are present. This article aims to review the clinically relevant cardio-metabolic efficacy and safety of currently licensed GLP-1RAs including twice-daily (10 µg) exenatide (EBID),[8-19] liraglutide (1.2 or 1.8 mg, LEAD studies),[20-26] once-weekly exenatide (2 mg, DURATION studies),[27-32] lixisenatide (20 µg, GetGoal studies),[33-42] albiglutide (30 mg, HARMONY studies)[43-49] and dulaglutide (1.5 mg, AWARD studies) (Tables 1–2).[50-55]

Efficacy of GLP-1RAs on cardio-metabolic parameters

Effect on glycaemic control and body weight

The glycaemic efficacy and changes in body weight are summarised in Supplementary Tables S1–6 (see Appendix 1, available online at bjd-abcd.com). Therapy with GLP-1RAs, either as monotherapy or in combination with oral hypoglycaemic agents including metformin, sulphonylurea (SU) or thiazolidinediones (TZD), has demonstrated improvement in glycaemic control. Compared to placebo, significant HbA_{1c} reductions were observed with both daily and once-weekly GLP-1RAs; 0.5–1.0% with EBID, 0.6–1.1% with liraglutide, 0.3–1.1% with lixisenatide, 0.8–1.0% with albiglutide, 1.0–1.2% with dulaglutide (Tables S1–6). Marginally greater difference was noted when compared to metformin.[30,52] However, GLP-1RAs have shown significantly better glycaemic control compared with SU and TZD. HbA_{1c} reductions were 0.4–0.6% with liraglutide (vs SU),[21,22] 0.6–0.7% with liraglutide (vs TZD),[20] and 0.3% with once-weekly exenatide (vs TZD),[28] respectively. Likewise, a significantly greater reduction in HbA_{1c} of 0.4–0.6% was observed with liraglutide, once-weekly exenatide and albiglutide compared with sitagliptin.[26,28,49] Short acting GLP-1RAs (EBID) are equivalent in glycaemic efficacy to basal insulin whereas long acting GLP-1RAs (once-weekly exenatide, liraglutide, albiglutide and dulaglutide) are superior to basal insulin by 0.2–0.6%.[14,15,17,19,24,29,46,48,51,53] Addition of GLP-1RAs exenatide and lixisenatide to insulin resulted in further HbA_{1c} reduction of 0.5–0.7% in both randomised controlled trials (RCTs) and observational studies.[18,34,41,42,56,57]

In head to head comparisons (Table 1), once-weekly exenatide, dulaglutide and liraglutide 1.8 mg were associated with better glycaemic control compared to EBID; HbA_{1c} reductions were 0.5–0.7% (p<0.0001),[27,31] 0.7% (p<0.001)[50] and 0.3% (p<0.0001) respectively.[25] Compared with liraglutide 1.8 mg, dulaglutide and once-weekly exenatide showed marginally better HbA_{1c} reductions of 0.1% (p<0.0001)[55] and 0.2% (p=0.02),[32] suggesting that these GLP-1RAs may have similar glycaemic efficacy clinically. Among daily GLP-1RAs, liraglutide was more efficacious in achieving glycaemic control than lixisenatide and EBID by 0.6% and 0.3% respectively (p<0.0001).[25,58] However, no significant difference was found between lixisenatide and EBID.[36]

GLP-1RAs also improved fasting plasma glucose (FPG) compared with placebo in a similar pattern to HbA_{1c} reductions, ranging from 0.7–2.8 mmol/L, contributing to overall improvements in glycaemic control (Tables S1–6). However, basal insulin glargine was superior to GLP-1RAs, EBID, once-weekly exenatide, albiglutide and dulaglutide.[14,16,17,46,53] GLP-1RAs also attenuate postprandial glucose (PPG) excursion and reductions were greater with daily GLP-1RAs, EBID,[59] liraglutide (LEAD 1-5)[60] and lixisenatide (GetGoal studies).[33-42] Compared with a longer acting liraglutide, EBID and lixisenatide (short acting GLP-1RAs) yielded greater PPG reduction with a treatment difference of 1.4–2.5 mmol/L (p<0.001).[25,58,61]

In RCTs, treatment with GLP-1RAs has consistently shown a beneficial effect on weight loss. Compared with placebo, weight reductions were -1.6 to -2.8 kg with EBID, -1.4 to -2.6 kg with liraglutide, -0.5 to -1.3 kg with lixisenatide, and -2.5 to -3.5 kg with exenatide once-weekly and dulaglutide. This is in line with the findings in a mixed treatment analysis.[62] However, no significant change in weight was observed with albiglutide compared to placebo in HARMONY studies.[47,63] Unlike weight gain with other conventional therapies such as SU, TZD or insulin, treatment with both daily and once-weekly GLP-1RAs resulted in significant weight loss; -2.8 kg (p<0.0001), -5.1 kg (p<0.0001), -5.7 kg (p<0.001) compared to SU[22], TZD[28] and insulin glargine[17] respectively. Weight loss was also significantly greater with GLP-1RAs (1.9–2.3 kg, p<0.001) when compared to the weight neutral agent sitagliptin.[26,28,30] In a head to head comparison of GLP-1RAs, the greatest difference in weight was observed with liraglutide 1.8 mg vs albiglutide (-1.5 kg, p<0.0001).[49]

In addition, a dose related weight loss effect was observed with liraglutide 1.2 mg and 1.8 mg in the LEAD studies.[60] In the recently published SCALE Diabetes study, a higher dose of liraglutide (3 mg) promoted greater weight loss with 6% reduction of initial body weight when compared to lower doses, 4.7% (1.8 mg) and 2% (placebo) in people with diabetes.[64] Similarly, weight loss was maintained at 56 weeks with liraglutide 3 mg in people without diabetes when compared to placebo (-8.0% vs -2.6%, <0.001).[65]

Table 1 Summary of randomised controlled trials comparing one GLP-1RA against another

Study	Duration of the study (weeks)	Background therapy	Comparators	Baseline HbA_{1c} (%)	Mean difference versus comparator (p)					Injection site reaction (%)
					HbA_{1c} (%)	FPG (mmol/L)	Body weight (kg)	SBP (mmHg)	Total Cholesterol (mmol/L)	
DURATION 1 (Drucker) (2008)	30	MF± SU±TZD	EQW vs EBID	8.3	-0.5 (0.002)	-0.9 (<0.0001)	NS	NS	NS	22.3 vs 11.7
DURATION 5 (Belvins) (2011)	24	MF± SU±TZD	EQW vs EBID	8.4	-0.7 (<0.0001)	-1.2 (0.0008)	NS	NS	-0.52 (<0.01)	10 vs 13
DURATION 6 (Buse) (2013)	26	MF± SU	EQW vs Lira (1.8 mg)	8.5	-0.2 (0.02)	NS	-0.9 (0.02)	NS	NS	15.8 vs 2
LEAD 6 (Buse) (2009)	26	MF ± SU	Lira (1.8 mg) Vs EBID	8.2	-0.3 (<0.0001) Lira (1.8 mg)	-1.0 (<0.0001) Lira (1.8 mg)	-0.4 (0.22) Lira (1.8 mg)	-0.5 (0.064) Lira (1.8 mg)	-0.1 (0.09) Lira (1.8 mg)	Not stated
GetGoal-X (Rosenstock) (2013)	24	MF	Lixi vs EBID	8.0	NS (Not inferior to EBID)	NS (Not inferior to EBID)	1.0 (0.05) (Greater weight loss with EBID)	Not stated	Not stated	8.5 vs 1.6
AWARD 1 (Wysham) (2014)	52	MF+TZD	Dula vs EBID	8.1	-0.5 (<0.001)	-1.0 (<0.001)	NS	NS	Not stated	0.4 vs 0.4
AWARD 6 (Dungan) (2014)	26	MF	Dula vs Lira (1.8 mg)	8.1	-0.1 (<0.0001)	NS	0.7 (0.01)	NS	Not stated	0.3 vs 0.7
HARMONY 7 (Pratley) (2014)	32	MF± SU±TZD	Albi vs Lira (1.8 mg)	8.1	NS	0.5 (0.0048)	-1.5 (<0.0001)	Not stated	Not stated	6.9 vs 1.2
Nauck	26	MF	Lira (1.8 mg) vs Lixi	8.4	-0.6 (<0.0001)	-1.2 (<0.0001)	NS	NS	NS	Not stated

MF=Metformin, SU=Sulphonylurea, TZD=Thiazolidinediones, EBID= Twice-daily exenatide (10 mcg BD), EQW=Once-weekly exenatide , Lira=Liraglutide, Lixi=Lixisenatide, Albi=Albiglutide (30 mg), Dula=Dulaglutide (1.5 mg), NS=Not significant

Effect on cardiovascular risk factors

Treatment with GLP-1RAs is associated with a modest reduction in systolic blood pressure (SBP), -2.2 to -7.5 mmHg with EBID (Table S1), -0.9 to -5.6 mmHg with liraglutide (Table S2) and -2.0 to -4.0 mmHg with once-weekly exenatide (Table S4). In a meta-analysis, once-daily GLP-1RAs (exenatide and liraglutide) decreased SBP by -1.8 mmHg and -2.4 mm Hg (p<0.001) compared to placebo and active control, respectively. However, reduction in diastolic blood pressure failed to reach statistical significance; -0.5 mmHg vs placebo and -0.5 mm Hg vs active control.[66] In addition, a meta-analysis of 35 RCTs showed that GLP-1RAs were associated with modest reductions in total cholesterol, LDL-C, and triglycerides but no significant improvement in HDL-C.[67] Exenatide and liraglutide 1.8 mg decreased total cholesterol by -0.16 to -0.27 mmol/L (p<0.001) versus placebo and TZD. The decrease was more evident with once-weekly exenatide and liraglutide 1.8 mg once daily. A significant reduction in LDL-C was detected for all GLP-1RAs versus placebo, insulin and TZD. A significant reduction in triglyceride levels was observed with liraglutide 1.8 mg (-0.30 mmol/L, p<0.0001) versus placebo.[67]

Although GLP-1RAs showed improvements in SBP and lipid profile, there was an increase in heart rate of 0.9, 2.1, 2.7 and 2.2 bpm with EBID, once-weekly exenatide, liraglutide and dulaglutide, respectively, when compared with placebo.[66] In head to head comparisons, longer acting GLP-1RAs raised the pulse rate significantly more than short acting ones; 3.6 bpm (p=0.0001)[58] with liraglutide vs lixisenatide and 1.6 bpm (p<0.05) with dulaglutide vs EBID (AWARD 1). No significant difference in heart rate was noted between liraglutide and dulaglutide (AWARD 6) or between lixisenatide and EBID (GetGoal-X). The impact of increased heart rate remains unclear. Further evidence is needed to determine if

Table 2 Factors to consider in clinical use comparing one GLP-1RA against another

GLP-1RA (Approved by FDA/EMA)	Class Long acting (L) or Short acting(S)	Dose titration and frequency used in clinical practice	HbA_{1c} reduction (%)	Pronounced effect on FPG or PPG	Weight loss (kg)	Licensed to be used with insulin UK	eGFR (ml/min/1.73 m^2)	CV Outcomes study
Twice-daily Exenatide (Byetta®) (FDA/EMA)	S	5 µg BD (4 weeks) 10 µg BD (maintenance dose) Within 60 min of meal	0.5–1.0	PPG	1.5–2.0	Basal insulin	No dose adjustment if 50–80 Cautious escalation of dose if 30–50 Avoid if <30	
Lixisenatide (Lyxumia®) (FDA/EMA)	S	10 µg OD (14 days) 20 µg OD (maintenance dose) Within the hour prior to the first meal of the day or the evening meal	0.5–1.0	PPG	1.0–1.5	Basal insulin	No dose adjustment if 50–80 Cautious escalation of dose if 30–50 Avoid if <30	ELIXA
Liraglutide (Victoza®) (FDA/EMA)	L	0.6 mg OD (1 week) 1.2 mg OD (maintenance dose) 1.8 mg OD (exceptional circumstance) Anytime of the day with or without meal	1–1.5	FPG	1.0–3.5	Basal insulin	No dose adjustment if 30–90 Avoid if <30	LEADER
Once-weekly Exenatide (Bydureon®) (FDA/EMA)	L	2 mg once weekly Anytime of the day with or without meal	1.5–2.0	FPG	1.5–3.0	Not licensed	No dose adjustment if 50–90 Avoid if <50	EXSCEL
Dulaglutide (Trulicity®) (FDA/EMA)	L	1.5 mg once weekly Anytime of the day with or without meal	1.0–2.0	FPG	1.5–3.0	Insulin	No dose adjustment if 50–90 Avoid if <30	REWIND
Albiglutide (Tanzeum®/ Eperzan®) (FDA/EMA)	L	30–50 mg once weekly Anytime of the day with or without meal	0.4–0.8	FPG	0.2–1.2	Basal insulin	No dose adjustment if 30–90 Avoid if <30	

CV=Cardiovascular, eGFR=estimated glomerular filtration rate, FDA=US Food and Drug Administration, EMA=European Medicine Agency, FPG=Fasting plasma glucose, PPG=Post-prandial glucose

improvements in SBP and lipid profiles might translate into reductions in cardiovascular outcomes.

Safety and tolerability of GLP-1RAs

Gastrointestinal effects

Treatment associated gastrointestinal (GI) symptoms (nausea, vomiting, diarrhoea) are well recognised adverse effects of GLP-1RAs and are demonstrated to be higher than with other glucose lowering therapies.[68] Longer-acting GLP-1RAs were associated with a lower risk of GI side effects (with an exception of albiglutide and once-weekly exenatide) compared to short acting GLP-1RAs (EBID, lixisenatide).[25,27,50] Of the two short acting GLP-1RAs, lixisenatide demonstrated a lower rate of GI side effects than EBID.[36] The risk is also dose related and was found to be greater with the higher dose of liraglutide (3 mg vs 1.8 mg vs 1.2 mg) in the LEAD studies and the SCALE Diabetes study.[60,64]

Hypoglycaemia

In all RCTs, the risk of total and severe hypoglycaemia was significantly lower with GLP-1RAs compared to placebo or other glucose lowering therapies. Concomitant use of SU or insulin increased the risk of hypoglycaemia. In a head to head comparison, albiglutide and lixisenatide were shown to have a slightly lower risk than other GLP-1RAs.[36,49]

Pancreatitis and pancreatic cancer

Based on a small number of case reports and animal studies, there was growing concern about the association between incretin-based therapies and pancreatitis in late 2000.[69] Most safety data have been acquired through the FDA adverse event reporting system. A meta-analysis conducted from pooled data of 27 RCTs of GLP-1RAs did not suggest an increased risk of pancreatitis among patients using incretin therapies compared to placebo.[70] Recently, a large population-based study involving over 12,000 patients hospitalised for acute pancreatitis in Denmark reported that the risk of pancreatitis in people treated with GLP-1RAs remained low and comparable to that of other glucose lowering therapies.[71] Nauck also argued that there is no firm evidence to suggest that GLP-1RA therapy is associated with an increased risk of malignancy including pancreatic cancer from available pre-clinical and clinical studies.[72,73] The evaluation of lixisenatide in acute coronary syndrome (ELIXA) study and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) study both reported no increased risk of pancreatitis or pancreatic cancer with lixisenatide and liraglutide.[74,75] The conclusion was that cardio-metabolic benefits of GLP-1RAs therapy outweigh the risk of pancreatitis or pancreatic cancer. To date, no definite causal relationship has been established between pancreatitis or pancreatic cancer and GLP-1RA therapy but caution needs to be exercised.

Injection site reactions

Injection site reactions are commonly reported with both daily and once-weekly injections. However, more injection site reactions such as nodules and pruritus are observed with once-weekly exenatide due to the formulation and delivery technology (microspheres) than with dulaglutide or liraglutide.[76]

Cardiovascular safety

All new drugs for T2DM are required by the FDA to demonstrate cardiovascular safety and currently several GLP-1RAs are undergoing large-scale, long-term trials specifically designed for cardiovascular outcomes. In a meta-analysis, treatment with GLP-1RAs was not associated with an increased risk of cardiovascular events compared to active comparators.[77] In fact, a significant reduction in the incidence of cardiovascular events was observed in comparison with placebo and pioglitazone.[77] The first cardiovascular safety study (ELIXA) completed among all GLP-1RAs reported non-inferiority versus placebo for the composite cardiovascular endpoint, thus satisfying the FDA requirements of cardiovascular safety.[74] However, more recently, the LEADER trial demonstrated the cardiovascular benefit of liraglutide in high-risk cardiovascular patients with T2DM.[75] In fact, liraglutide has demonstrated superiority to placebo with a 13% relative risk reduction in the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke and a 22% reduction in mortality due to cardiovascular causes. This is the first cardiovascular safety trial among incretin-based therapies that has demonstrated a positive outcome on cardiovascular effect. Other ongoing international RCTs examining cardiovascular safety of GLP-1RAs are once-weekly exenatide (EXSCEL), dulaglutide (REWIND), and semaglutide (SUSTAIN 6).

Combination therapy of insulin and GLP-1RA

Recently, a fixed-ratio combination of basal insulin degludec and liraglutide (IDegLira) was developed based on complementary therapeutic effects of these agents on FPG and PPG. IDegLira was superior in glycaemic efficacy to liraglutide with lower GI adverse events and non-inferior to degludec with no increased hypoglycaemic events (DUAL I).[78] Moreover, treatment with IDegLira demonstrated significantly greater HbA_{1c} reduction with fewer hypoglycaemic episodes, lower insulin requirement and weight loss compared to insulin glargine (DUAL V).[79] Another fixed-ratio combination of basal insulin glargine and lixisenatide (LixiLan) is in development. The proof of concept trial of 24 weeks' duration revealed that adding LixiLan to metformin in insulin naïve patients improved glycaemic control by 1.8%, more than 80% of the participants achieving HbA_{1c} <7%.[80] This combination is being evaluated in phase 3 trials, which are due to report soon. GLP-1RAs and insulin combinations are therefore particularly advantageous for obese patients with long standing T2DM for mitigating the weight gain associated with insulin therapy, improving glycaemic control and possibly reducing insulin requirement. This advantage may lead to greater adherence and patient satisfaction.

Real life clinical experience of GLP-1 use in the UK

The Association of British Clinical Diabetologists undertook nationwide audits on the use of EBID and liraglutide in real clinical practice to determine their effects on HbA_{1c}, weight, blood pressure and lipids. Data were collected from centres around the UK involving over 6,700 patients for EBID in 2009 and 2,300 for liraglutide in 2011 over 6 months. The baseline HbA_{1c} and BMI were 9.5% and 39.8 kg/m^2 for EBID and 9.3% and 39.1 kg/m^2 for liraglutide. Both baseline HbA_{1c} and BMI were significantly higher in the audits compared to that in RCTs. By 6 months there were significant reductions in HbA_{1c} and weight of 0.75% and 6.6 kg with EBID and 0.93% and 3.7 kg with liraglutide. It may appear that treatment with liraglutide resulted in greater HbA_{1c} reduction but less weight loss compared to EBID. However, the authors commented that a major contributing factor was less insulin and TZD discontinuation observed in the liraglutide audit.[81]

At the time of the audit it was recommended by NICE that GLP-1RAs were not to be used with insulin. In both audits, 35–40% of patients were on combination therapy with insulin and stopping insulin was associated with greater weight reduc-

tion but lesser improvement in HbA_{1c}. There was a reduction in insulin dose of 42±2 units from baseline of 120±99 units with EBID and 16.6% discontinued insulin.[57] It was found that GLP-1RA treatments were more effective in non-insulin treated patients than in insulin treated patients.[82] Although approximately 60% of the patients in both audits achieved reductions in both HbA_{1c} and weight, only 25% in the liraglutide audit and 29% in the EBID audit met the NICE criteria of HbA_{1c} reduction ≥1% and weight reduction ≥3% to continue GLP-1 treatment.[82] GI side effects were reported to be higher with EBID (24%) than with liraglutide (16%).[81] Both EBID and liraglutide treatment were associated with a reduction in SBP, total cholesterol and triglycerides.[82]

Costs

The cost of GLP-1 RAs is significantly higher than other agents such as SU, pioglitazone, DPP-4 inhibitors or insulin glargine. Literature on the cost-effectiveness of the use of GLP-1RAs is limited. In a retrospective cohort study of real world data (US), diabetes-related pharmacy costs were greater with liraglutide than with EBID. However, a higher proportion of patients on liraglutide achieved HbA_{1c} <7%, resulting in a lower per-patient cost of HbA_{1c} goal achievement with liraglutide compared to EBID.[83] In the UK, Evan and colleagues conducted a retrospective audit in Wales. Over 1000 patients taking liraglutide, EBID or DPP-4 inhibitors were followed up for a median of 48 weeks. Costs per quality-adjusted life-year were £16,505, £16,648 and £20,661 for liraglutide, exenatide and DPP-4 inhibitors, respectively.[84] The authors concluded that, when prescribed according to NICE recommendations, incretin-based therapies were cost-effective options, with liraglutide providing greatest HbA_{1c} reductions.[84]

Generally, studies that have examined the cost implications of improving glucose management have reported that the glycaemic control costs were modest compared to total diabetes-related health expenditures.[85,86] Although some studies reported the acquisition cost, they did not evaluate or relate these findings to outcomes in HbA_{1c} or other compilations due to poor glycaemic control. Consequently, it is very hard to put the cost-effectiveness of these new drugs into perspective in the short term and therefore real world evidence has become increasingly important as a decision-making tool for policymakers and health care providers.

Discussion

GLP-1RAs are a novel class of therapeutic agent used in the management of T2DM. In comparison with other available glucose lowering therapies, GLP-1RAs demonstrate either superiority or non-inferiority in glycaemic efficacy with a favourable effect on body weight and a low risk of hypoglycaemia compared with SU, TZD or insulin. In addition, they appear to have beneficial effects on cardiovascular risk factors with a modest reduction in body weight, blood pressure and lipid profile, although there is an associated small risk of increased heart rate. Although ADA/EASD and NICE guidelines advocate the use of GLP-1RAs as an adjunct therapy to metformin and life style modification, there is no specific guidance as to which GLP-1RAs should be chosen.

It must be acknowledged that there are differences in cardio-metabolic and safety parameters among GLP-1RAs. In addition, other practical aspects such as the frequency of administration (twice daily vs once daily vs once weekly) and the ease with which the device can be used need to be considered from the patient's perspective in choosing a particular agent. Generally, long acting GLP-1RAs are more efficacious in reducing HbA_{1c}, have greater effect on FPG, and potentially offer better compliance than short acting GLP-1RAs. Hypoglycaemia risk is low and comparable within the class of agents. All GLP-1RAs have moderate effects in lowering SBP and lipid profile. Of all licensed clinically available GLP-1RAs, dulaglutide, once-weekly exenatide and liraglutide were associated with a greater reduction in HbA_{1c} and FPG compared with EBID; liraglutide having greater weight loss and once-weekly exenatide being better tolerated among the three.[87]

In clinical practice, after initiation of lifestyle modification and metformin therapy, a stepwise approach is adopted in advancing glucose lowering therapies before insulin initiation and intensification. Availability of GLP-1RAs offers an alternative to insulin in appropriate patients. When the glycaemic target is not achieved/maintained with a combination of oral therapies, either basal or prandial insulin is added. According to treat-to-target protocols, therapeutic agents are chosen to address both FPG and PPG. GLP-1RAs are either comparable or superior in efficacy to basal insulin in improving HbA_{1c} with an added benefit of weight loss and lower risk of hypoglycaemia, and therefore offer an alternative option to basal insulin in appropriate circumstances. In addition, short acting GLP-1RAs may have a role when glycaemic control is not adequately achieved with basal insulin.[34] Although the absolute reduction in HbA_{1c} with the short acting GLP-1RA lixisenatide (0.5–0.8%) is less than 1% as recommended by the NICE, it may be particularly applicable in cases where additional postprandial glucose lowering effect and weight loss is desirable after introduction of basal insulin.

Conclusion

GLP-1RAs are effective glucose lowering agents in managing T2DM with a favourable effect on weight reduction and a low risk of hypoglycaemia. Due to limited availability of studies directly comparing these agents, the choice among GLP-1RAs remains uncertain. A definite answer as to which GLP-1RA would suit a particular patient should be assessed on an individual basis. Of all the GLP-1RAs available to date in the UK, evidence suggests that treatment with once daily liraglutide provides a greater HbA_{1c} and weight reduction and, from the limited evidence available, it is more cost effective than EBID. Moreover, liraglutide is the very first GLP-1RA to demonstrate a positive cardiovascular benefit according to the LEADER study recently published. Currently, the choice is left to clinical judgment based on patient factors, preferences and experience of the clinician. Taking all the safety and efficacy factors into ac-

Key messages

- GLP-1RAs, a novel class of therapeutic agent, are efficacious in improving glycaemic control with the benefit of weight loss in management of overweight/obese patients with T2DM
- Risk of hypoglycaemia is relatively low unless used in combination with SU or insulin
- Gastrointestinal side effects are common.
- Although no definite casual relationship has been established between pancreatitis/pancreatic cancer with GLP-1RA, caution should be exercised especially in high risk patients
- Lixisenatide demonstrated non-inferiority (ELIXA study) and liraglutide, superiority (LEADER study) to placebo in CV safety studies

count, the choice should be individualised according to patient factors such as weight gain, hypoglycaemic risk, associated co-morbidities, frequency of injection, and tolerability of the medication. All in all, the question should not be whether one GLP-1RA is superior but instead whether individual GLP-1RA therapy is superior in a particular patient. Personalising GLP-1RA therapy to particular patients will allow effective glycaemic control while avoiding or minimising adverse effects with potentially better adherence to therapy.

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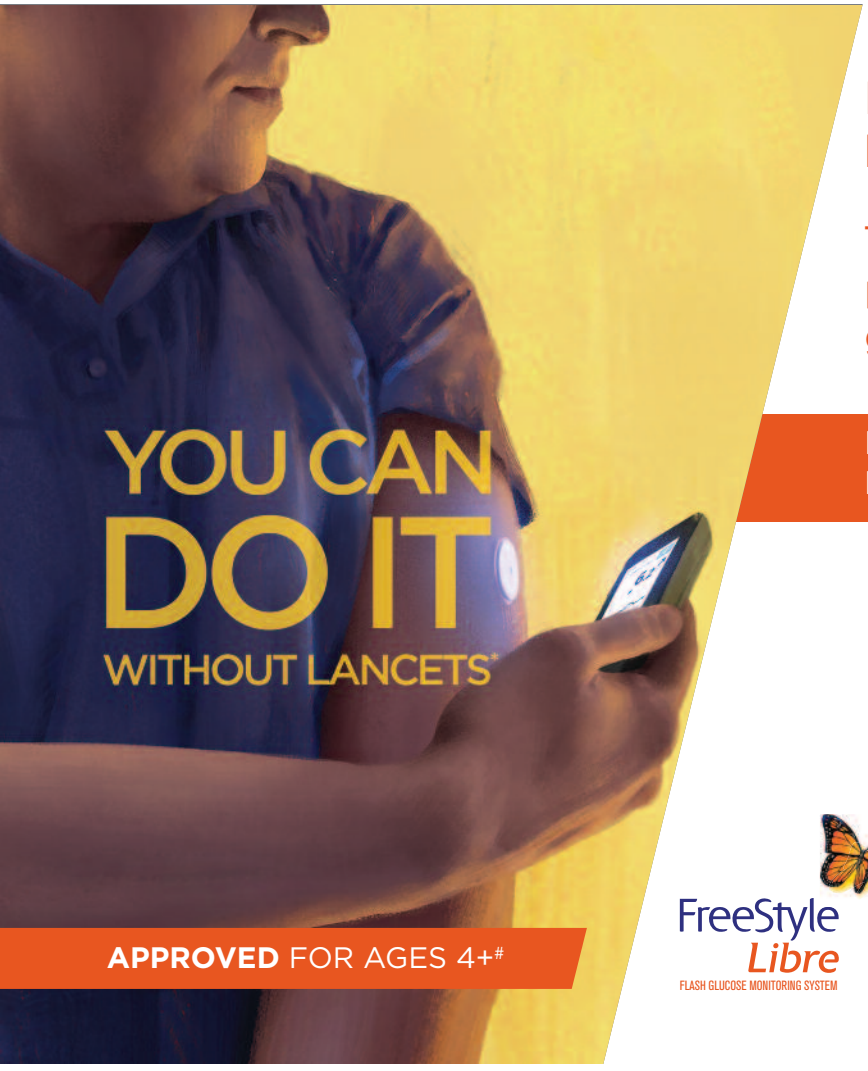

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† Data on file. Abbott Diabetes Care. The FreeStyle Libre system liberates you from the hassles of glucose monitoring. In a study conducted by Abbott Diabetes Care, 100% of patients surveyed (n=23) agreed that the FreeStyle Libre system reduces the hassle of glucose monitoring.

† To get a complete glycaemic picture the sensor must be replaced every 14 days and the sensor must be scanned at least once every 8 hours.

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Appendix 1 - Supplementary Table S1

Summary of randomised controlled trials (RCTs) of exenatide (ExBID)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1c(%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
De Fronzo (2005)	30	MF	Placebo	8.2 ± 1.1	-0.8 (<0.002)	-1.4 (0.0001)	-2.5 (<0.05)	Not stated	Not stated
Buse (2004)	30	SU	Placebo	8.6	-0.8 (<0.002)	-1.0 (≤0.05)	-1.0 (<0.05)	Not stated	Not stated
Kendall (2005)	30	MF+SU	Placebo	8.5	-1.0 (<0.0001)	-1.4 (<0.0001)	-0.7 (≤0.01)	Not stated	Not stated
Liutkus (2010)	26	TZD ± MF	Placebo	8.2	-0.8 (<0.001)	-1.0 (0.009)	No significant difference	No significant difference	No significant difference
Moretto (2008)	24	None	Placebo	7.8	-1.1 (<0.001)	-0.7 (0.02)	-1.7 (<0.001)	-2.3 (0.05)	Not stated
Apovian (2010)	24	Lifestyle	Placebo	7.6	-0.5 (<0.0001)	Not stated	-6.2 (0.03)	-7.5 (<0.001)	Not stated
Heine (2005)	26	MF + SU	Glargine	8.2	No significant difference	1.5 (<0.001)	-4.1 (<0.0001)	Not stated	Not stated
Nauck (2007)	26	MF + SU	Insulin aspart	8.6	No significant difference	Not stated	-5.1 (<0.001)	Not stated	Not stated
Barnett (2007)	32	MF or SU	Glargine	8.9	No significant difference	1.2 (<0.001)	-2.2 (<0.001)	Not stated	Not stated
Davies (2009)	26	MF ±SU/TZD	Glargine	8.7	No significant difference	1.1 (<0.001)	-5.7 (<0.001)	-2.2 (0.03)	-0.2 (0.12)
Buse (2011)	30	Glargine± MF/TZD	Placebo	8.4	-0.7 (<0.001)	NS	-2.74 (<0.001)	-4.4 (0.01)	No significant difference
Bunck (2009)	52	MF	Glargine	7.5	No significant difference	Not stated	-4.6 (0.0001)	Not stated	Not stated

Appendix 1 - Supplementary Table S2

Summary of randomised controlled trials (RCTs) of liraglutide (LEAD studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
LEAD 1 (Marre) (2009)	26	SU	Placebo	8.4	-1.3 (<0.0001) (Lira 1.2 mg) -1.4 (<0.0001) (Lira 1.8 mg)	-2.8 (<0.0001) (Lira 1.2 mg) -2.8 (<0.0001) (Lira 1.8 mg)	NS NS	NS NS	Not stated
LEAD 1 (Marre) (2009)	26	SU	TZD	8.4	-0.6 (<0.0001) (Lira 1.2 mg) -0.7 (<0.0001) (Lira 1.8 mg)	-0.7 (<0.01) (Lira 1.2 mg) -0.7 (<0.01) (Lira 1.8 mg)	-1.4 (<0.0001) (Lira 1.2 mg) -2.3 (<0.0001) (Lira 1.8 mg)	NS NS	Not stated
LEAD 2 (Nauck) (2009)	26	MF	Placebo	8.4	-1.1 (<0.0001) (Lira 1.2 mg) -1.1 (<0.0001) (Lira 1.8 mg)	-2.0 (<0.0001) (Lira 1.2 mg) -2.1 (<0.0001) (Lira 1.8 mg)	-1.5 (<0.01) (Lira 1.2 mg) -1.5 (<0.01) (Lira 1.8 mg)	Not stated	Not stated
LEAD 2 (Nauck) (2009)	26	MF	SU	8.4	NS (Lira 1.2 mg) NS (Lira 1.8 mg)	NS (Lira 1.2 mg) NS (Lira 1.8 mg)	-3.6 (<0.0001) (Lira 1.2 mg) -3.8 (<0.0001) (Lira 1.8 mg)	Not stated	Not stated
LEAD 3 (Garber) (2009)	52	None	SU	8.2	-0.4 (0.04) (Lira 1.2 mg) -1.1 (0.002) (Lira 1.8 mg)	-0.6 (0.02) (Lira 1.2 mg) -0.99 (0.0003) (Lira 1.8 mg)	-2.8 (<0.0001) (Lira 1.2 mg) -3.7 (<0.0001) (Lira 1.8 mg)	-0.86 (0.47) (Lira 1.2 mg) -1.9 (0.11) (Lira 1.8 mg)	Not stated

Appendix 1 - Supplementary Table S2 *continued*

Summary of randomised controlled trials (RCTs) of liraglutide (LEAD studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
LEAD 4 (Zinman) (2009)	26	MF + TZD	Placebo	8.5	-1.0 (<0.01) (Lira 1.2 mg) -1.3 (<0.01) (Lira 1.8 mg)	-1.8 (<0.001) (Lira 1.2 mg) -2.0 (<0.001) (Lira 1.8 mg)	-1.6 (<0.0001) (Lira 1.2 mg) -2.6 (<0.0001) (Lira 1.8 mg)	-5.6 (<0.0001) (Lira 1.2 mg) -4.5 (<0.0009) (Lira 1.8 mg)	NS NS
LEAD 5 (Russell-Jones) (2009)	26	MF + SU	Placebo	8.3	-1.1 (<0.0001) (Lira 1.8 mg)	-2.1 (<0.0001) (Lira 1.8 mg)	-1.4 (0.0001) (Lira 1.8 mg)	-2.2 (0.08) (Lira 1.8 mg)	Not stated
LEAD 5 (Russell-Jones) (2009)	26	MF + SU	Glargine	8.3	-0.2 (0.002) (Lira 1.8 mg)	NS	-3.4 (<0.0001) (Lira 1.8 mg)	-4.5 (0.0001) (Lira 1.8 mg)	Not stated
LEAD 6 (Buse) (2009)	26	MF ± SU	EBID	8.2	-0.3 (<0.0001) (Lira 1.8 mg)	-1.0 (<0.0001) (Lira 1.8 mg)	-0.4 (0.22) (Lira 1.8 mg)	-0.5 (0.064) (Lira 1.8 mg)	-0.11 (0.09) (Lira 1.8 mg)
Pratley (not LEAD study) (2010)	26	MF	Sitagliptin	8.5	-0.3 (<0.0001) (Lira 1.2 mg) -0.5 (<0.0001) (Lira 1.8 mg)	-1.9 (<0.0001) (Lira 1.2 mg) -2.1 (<0.0001) (Lira 1.8 mg)	0.4 (0.75) (Lira 1.2 mg) 0.2 (0.85) (Lira 1.8 mg)	-0.3 (<0.0001) (Lira 1.2 mg) -0.5 (<0.0001) (Lira 1.8 mg)	-0.01 (0.85) (Lira 1.2 mg) -0.16 (0.03) (Lira 1.8 mg)

Appendix 1 - Supplementary Table S3

Summary of randomised controlled trials (RCTs) of lixisenatide (GetGoal Studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
GetGoal-mono (Fonseca) (2012)	12	None	Placebo	8.0	-0.7 (<0.0001)	-1.1 (<0.0001)	NS	Not stated	Not stated
GetGoal-Duo 1 (Riddle) (2013)	24	Glargine+ MF ± TZD	Placebo	9.1	-0.3 (<0.0001)	NS	-0.9 (0.001)	Not stated	Not stated
GetGoal-Duo-F1 (Bolli) (2013)	24	MF	Placebo	8.0	-0.5 (<0.0001)	-0.7 (<0.001)	-1.0 (<0.01)	Not stated	Not stated
GetGoal-X (Rosenstock) (2013)	24	MF	EBID	8.0	NS **(Not inferior to EBID)**	NS **(Not inferior to EBID)**	1.0 (0.05) **(Greater weight loss with EBID)**	Not stated	Not stated
GetGoal-S (Rosenstock) (2014)	24	SU ± MF	Placebo	8.5	-1.1 (<0.0001)	-0.7 (0.05)	-0.1 (0.76)	Not stated	Not stated
GetGoal-P (Pinget) (2013)	24	TZD ± MF	Placebo	8.1	-0.6 (<0.0001)	-0.8 (<0.0001)	NS	Not stated	Not stated
GetGoal-M (Ahren) (2013)	24	MF	Placebo	8.1	-0.5 (0.0001)	-0.9 (0.005)	NS	Not stated	Not stated
GetGoal-M Asia (Yu Pan) (2014)	24	MF ± SU	Placebo	7.9	-0.4 (0.0004)	-0.5 (0.01)	NS	Not stated	Not stated
GetGoal-L (Riddle) (2013)	24	Basal insulin ± MF	Placebo	8.4	-0.4 (0.0002)	NS	-1.3 (0.0001)	Not stated	Not stated

Appendix 1 - Supplementary Table S3 *continued*

Summary of randomised controlled trials (RCTs) of lixisenatide (GetGoal Studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
GetGoal-L Asia (Seino) (2012)	24	Basal insulin ± SU	Placebo	8.5	-0.9 (<0.0001)	Not stated	NS	Not stated	Not stated
GetGoal-L Asia (Seino) (2012)	24	MF							

Appendix 1 - Supplementary Table S4

Summary of randomized controlled trials (RCTs) of once-weekly exenatide (EQW) (DURATION studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
DURATION 1 (Drucker) (2008)	30	MF± SU±TZD	Placebo EBID	8.3	Not stated -0.5 (0.002)	Not stated -0.9 (<0.0001)	Not stated NS	Not stated NS	Not stated NS
DURATION 2 (Bergenstal) (2010)	26	MF	Sitagliptin	8.5	-0.6 (<0.001)	-0.9 (0.004)	-2.3 (<0.0001)	-4.0 (0.006)	Not stated
DURATION 2 (Bergenstal) (2010)	26	MF	TZD	8.5	-0.3 (0.02)	NS	-5.1 (<0.0001)	NS	Not stated
DURATION 3 (Diamant) (2010)	26	MF± SU	Glargine	8.3	-0.2 (0.03)	0.6 (0.001)	-4.0 (<0.0001)	-2.0 (0.0001)	NS
DURATION 4 (Russell-Jones) (2012)	26	Placebo	MF	8.5	NS	Not stated	No significant difference	Not stated	Not stated
DURATION 4 (Russell-Jones) (2012)	26	Placebo	TZD	8.5	0.1 (0.32)	Not stated	-3.5 (<0.001)	Not stated	Not stated
DURATION 4 (Russell-Jones) (2012)	26	Placebo	Sitagliptin	8.5	-0.3 (<0.001)	Not stated	-1.2 (<0.001)	Not stated	Not stated
DURATION 5 (Belvins) (2011)	24	MF± SU±TZD	EBID	8.4	-0.7 (<0.0001)	-1.2 (0.0008)	NS	NS	-0.52 (<0.01)
DURATION 6 (Buse) (2013)	26	MF± SU	Lira (1.8 mg)	8.5	-0.2 (0.02)	NS	-0.9 (0.02)	NS	NS

Appendix 1 - Supplementary Table S5

Summary of randomised controlled trials (RCTs) of albiglutide (HARMONY studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
HARMONY 1 (Reusch) (2013)	52	TZD±MF	Placebo	8.1	-0.8 (<0.0001)	-1.6 (<0.0001)	NS	Not stated	Not stated
HARMONY 2 (Reinhardt) (2013)	52	None	Placebo	8.1	-1.0 (<0.001)		NS		
HARMONY 3 (Ahren) (2014)	104	MF	Placebo Sitagliptin SU	8.1	-0.9 (<0.0001) -0.4 (<0.0001) -0.3 (0.003)	-1.5 (<0.0001) -0.9 (0.0002) -0.6 (0.013)	NS NS -2.4 (<0.0001)	Not stated Not stated Not stated	Not stated Not stated Not stated
HARMONY 4 (Weissman) (2014)	52	MF± SU	Glargine	8.3	-0.1 (0.15)	1.2 (<0.0001)	-2.6 (<0.0001)	Not stated	Not stated
HARMONY 5 (Home) (2015)	52	MF+SU	Placebo TZD	8.2	-0.9 (<0.0001) 0.3 (0.08)	0.6 (<0.001) 1.1 (<0.001)	NS -4.9 (<0.0001)	Not stated	Not stated
HARMONY 6 (Rosenstock) (2014)	26	Basal insulin ±TZD±MF	Insulin lispro	8.5	NS	NS	-1.5 (<0.0001)	Not stated	Not stated
HARMONY 7 (Pratley) (2014)	32	MF± SU±TZD	Lira (1.8 mg)	8.1	NS	0.5 (0.0048)	-1.5 (<0.0001)	Not stated	Not stated

Appendix 1 - Supplementary Table S6

Summary of randomised controlled trials (RCTs) of dulaglutide (AWARD studies)

Study (RCT)	Duration of the study (weeks)	Background therapy	Comparator	Baseline HbA1C (%)	Difference in HbA1c (%) vs comparator	Difference in FPG (mmol/L) vs comparator	Difference in body weight (kg) vs comparator	Difference in SBP (mmHg) vs comparator	Difference in Total Cholesterol (mmol/L) vs comparator
AWARD 1 (Wysham) (2014)	52	MF+TZD	Placebo EBID	8.1	-1.0 (<0.001) -0.52 (<0.001)	Not stated -1.0 (<0.001)	-2.5 (<0.0001) NS	Not stated NS	Not stated Not stated
AWARD 2 (Giorgino) (2015)	52	MF+SU	Glargine	8.1	-0.6 (<0.001)	NS	-3.31 (<0.001)	Not stated	Not stated
AWARD 3 (Umpierrez) (2014)	52	None	MF	7.6	-0.20 (0.02)	-0.4 (0.025)	NS	NS	Not stated
AWARD 4 (Blonde) (2015)	52	Basal ± prandial insulin	Placebo Glargine	8.5	-1.2 (<0.001) -0.22 (0.005)	Not stated 1.31 (<0.0001)	Not stated -3.2 (<0.0001)	Not stated NS	Not stated NS
AWARD 5 (Nauck) (2014)	52	MF	Sitagliptin	8.1	-0.7 (<0.001)	Significant	-1.5 (<0.001)	NS	NS
AWARD 6 (Dungan) (2014)	26	MF	Lira (1.8 mg)	8.1	-0.1 (<0.0001)	NS	0.7 (0.01)	NS	Not stated