A novel, long-acting glucagon-like peptide receptor-agonist: dulaglutide

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Background: Dulaglutide is a new, long-acting glucagon-like peptide analogue in the treatment of type 2 diabetes. It is available in two doses, 0.75 and 1.5 mg, given by injection once weekly. This systematic review reports the effectiveness and safety of dulaglutide in type 2 diabetes in dual and triple therapy.

Methods: MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, and conference abstracts were searched from 2005 to August 2014, and updated in January 2015. Company websites and references of included studies were checked for potentially relevant studies. European Medicines Agency and US Food and Drug Administration websites were searched.

Results: Four trials were included. All were manufacturer-funded randomized controlled trials from the Assessment of Weekly Administration of Dulaglutide in Diabetes (AWARD) program. AWARD-1 compared dulaglutide 1.5 mg against exenatide 10 µg twice daily and placebo, AWARD-2 compared dulaglutide 0.75 and 1.5 mg against insulin glargine, AWARD-5 compared dulaglutide 0.75 and 1.5 mg against sitagliptin 100 mg and placebo, and AWARD-6 compared dulaglutide 1.5 mg against liraglutide 1.8 mg. The duration of follow-up in the trials ranged from 26 to 104 weeks. The primary outcome of all the included trials was change in HbA_{1c}. At 26 weeks, greater HbA_{1c} reductions were seen with dulaglutide than with twice daily exenatide (dulaglutide 1.5/0.75 mg: -1.5%/-1.3%; exe: 0.99%) and sitagliptin (1.5/0.75 mg -1.22%/-1.01%; sitagliptin: -0.6%). HbA_{1c} change was greater with dulaglutide 1.5 mg (-1.08%) than with glargine (-0.63%), but not with dulaglutide 0.75 mg (-0.76%). Dulaglutide 1.5 mg was found to be noninferior to liraglutide 1.8 mg. More patients treated with dulaglutide achieved HbA_{1c} targets of <7% and ≤6.5%. Reduction in weight was greater with dulaglutide than with sitagliptin and exenatide. Hypoglycemia was infrequent. The main adverse events were nausea, diarrhea, and vomiting.

Conclusion: Dulaglutide is effective in the treatment of patients with type 2 diabetes but we need long follow-up data for safety concerns.

Keywords: dulaglutide, glucagon-like peptide analogue, type 2 diabetes, effectiveness, glycemic control

Introduction

Type 2 diabetes mellitus

Type 2 diabetes mellitus (formerly known as noninsulin dependent diabetes mellitus) is a chronic metabolic disease characterized by increased blood glucose levels (hyperglycemia), which over time can cause microvascular complications such as retinopathy, nephropathy, and neuropathy, and macrovascular complications such as ischemic heart disease and stroke. Patients with type 2 diabetes are usually overweight or obese, leading to insulin resistance. Initially, there is increased insulin production to counter

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this, but over time insulin production falls. The main aim of treatment of patients with type 2 diabetes is to achieve and maintain blood glucose levels and thereby reduce the occurrence of complications.¹

Around 380 million people worldwide were known to have diabetes in 2013, and this figure is estimated to rise to 590 million by 2053.² The number of people suffering from type 2 diabetes will increase mainly due to rising prevalence of obesity, increasing life expectancy, and decreased physical activity. The cost of treating diabetes is also increasing worldwide. In 2013, around 550 billion USD was spent worldwide for diabetes.²

People with type 2 diabetes are initially managed by education on lifestyle changes, with advice to lose weight by changing dietary habits and increasing physical activity. If patients fail to improve their blood glucose level to the HbA_{1c} level of <7%, suggested as adequate glucose control by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD),^{3,4} and maintain it, then they are usually started on metformin. A sulfonylurea (SU) is considered when patients cannot tolerate metformin or if it is contraindicated. However, other antidiabetic drugs such as dipeptidyl peptidase-4 (DPP-4) inhibitors, a thiazolidinediones, or sodium glucose transport 2 (SGLT2) inhibitors may be considered according to individual patients' need.⁴ If patients fail to achieve satisfactory control on metformin, another oral glucose-lowering drug is added, usually SU added to metformin (a combination of two oral agents is referred to as "dual therapy"). When dual therapy fails, a third drug is added (the combination is referred to as "triple therapy"). The third drug could be an oral glucose-lowering drug of another class such as pioglitazone, DPP-4 inhibitors (such as sitagliptin or saxagliptin), or a SGLT2 inhibitor (such as dapagliflozin or canagliflozin), or an injectable glucagon-like peptide-1 (GLP-1) analogue (liraglutide or exenatide, albiglutide, and now dulaglutide). Some GLP-1 receptor agonists are now available in long-acting form given only once a week. In type 2 diabetes, postprandial hyperglycemia is common. The rise in blood glucose level may be partly because of high glucagon levels. The incretin-based drugs reduce the increased postprandial glucagon level. There are two types of incretin-based drugs, DPP-4 inhibitors and GLP-1 receptor agonists.

The glucagon-like peptide-1 receptor agonists

GLP-1 receptor agonists are glucose-lowering drugs that have to be injected. The GLP-1 receptor agonists act like the naturally occurring incretin hormone GLP-1, a gastrointestinal

hormone that is secreted by the body following consumption of food, that regulates plasma glucose levels by delaying gastric emptying of food and reducing hunger, by inhibiting secretion of glucagon, and by stimulating secretion and biosynthesis of insulin.^{5,6} GLP-1 receptor agonists thus leads to glucose control and reduces weight.

There are more details about mechanism of action of GLP-1 receptor agonists, and the differences between long-acting and short-acting forms, in several good quality systematic reviews.^{7–11}

There are now five GLP-1 receptor agonists available in the market: exenatide in twice daily form (Byetta, AstraZeneca plc, London, UK) and as the long-acting, once-weekly version (Bydureon, AstraZeneca), once-daily liraglutide (Victoza, Novo Nordisk A/S, Bagsværd, Denmark), once-daily lixisenatide (Lyxumia, Sanofi-Aventis, Bridgewater, NJ, USA), weekly albiglutide (Tanzeum, GlaxoSmithKline plc, London, UK), and recently, weekly dulaglutide (Eli Lilly and Company, Indianapolis, IN, USA). Taspoglutide (GlaxoSmithKline) has been dropped from the market following serious risk of hypersensitivity reactions and gastrointestinal side effects. In the UK, GLP-1 receptor agonists are recommended as triple therapy,¹² while in USA, they are often used in dual therapy.³

Dulaglutide

Dulaglutide (trade name Trulicity) is manufactured by Eli Lilly. It is a once-weekly injectable GLP-1 analogue,¹³ and is "indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes ... is not recommended as first-line therapy for patients inadequately controlled on diet and exercise".^{13,14} Dulaglutide has already been approved by the US Food and Drug Administration (FDA)¹⁵ and European Medicines Agency (EMA)¹⁴ as indicated above. Similar to all GLP-1 receptor agonists, there are also alerts about risk of thyroid C-cell tumors, pancreatitis, and hypersensitivity reactions.^{13,14}

This systematic review assesses the effectiveness of dulaglutide in type 2 diabetes mellitus in dual and triple therapy (AWARD [Assessment of Weekly Administration of Dulaglutide in Diabetes] 1, 2, 5 and 6).

Methods

Search strategies

An iterative procedure was followed to develop a search strategy with input from previous systematic reviews.¹⁶ Comprehensive electronic searches identified references relating to type 2 diabetes and dulaglutide. Searches were undertaken in August 2014 in MEDLINE, MEDLINE

In-Process and Other Non-Indexed Citations, EMBASE (via OVID), Science Citation Index, and Conference Proceedings (via Web of Knowledge). The databases were searched from 2005 to August 2014; the actual date range for each of the databases searched depended on the coverage of the individual database. In addition, company websites and references of included studies were also checked for potentially relevant studies. The searches were updated in January 2015, but we did not find any new studies to include in the review.

The websites of the FDA and the European Medicines Evaluation Agency (EMA) were searched for information on the efficacy and safety. Current controlled trials <http://www.controlled-trials.com> and clinicaltrials.gov were also checked for ongoing trials.

All the retrieved records were collected in a specialized database Endnote X7. Duplicate records were identified and removed from the database.

Details of the electronic search strategies used for the review of the clinical effectiveness are given in Table S1.

Study selection

Two independent reviewers (TG and DS) screened all the identified titles and abstracts. Potentially relevant full

texts reports were then retrieved and examined separately. Disagreements between the two reviewers were resolved by a third reviewer (NW).

The study flow and reasons for exclusion of full text papers were documented in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) study flow diagram (Figure 1).

Our inclusion criteria were randomized controlled trials (RCTs) that included adults (over 18 years of age) with type 2 diabetes inadequately controlled with oral glucose-lowering drugs. We mainly included articles published in full, but meeting abstracts were considered if they, or published protocols, contained sufficient data on outcomes, study design, and quality. Trials with minimum duration of 12 weeks with dulaglutide in combination with metformin or SU or both were considered.

Since GLP-1 agonists are not licensed for use as first-line therapy in treatment of naïve patients, the inclusion criteria are based on the comparisons which are considered to be relevant to clinical practice as suggested by the National Institute for Health and Care Excellence (NICE) guideline (NICE CG66), SIGN guideline, and by the ADA/EASD joint statement.^{3,17,18} The draft NICE

Figure 1 PRISMA flow diagram.

Abbreviations: PRISMA, preferred reporting items for systematic reviews and meta-analyses; GLP-1, glucagon-like peptide-1.

2015 guideline for type 2 diabetes adopts a similar position.¹⁹

Our exclusion criteria were:

- Use of dulaglutide in patients naïve to treatment, ie, patients need to have been diagnosed with type 2 diabetes for at least a year and on at least one oral hypoglycemic drug for 6 months. If trials did not give sufficient detail, we accepted them if the mean duration of diabetes exceeded 2 years.
- Dulaglutide used as a monotherapy, whether compared with placebo or another drug.
- Trials of dulaglutide on patients who have failed only on an SU or a glitazone without having been tried on metformin. In practice, some trials include people who have failed on either a metformin or an SU, and may not give results separately. We accepted such trials if 70% or more had been on metformin.
- Trials or arms using nonstandard doses were excluded.

The dosages of dulaglutide in the trials were 0.75 and 1.5 mg (both doses are marketed).

Validity assessment

The RCTs were quality-assessed by two authors (TG and DS) using the Cochrane collaboration risk of bias (ROB) tool. The criteria include method of randomization; allocation concealment; blinding of participants; incomplete outcome data or missing data by investigating dropout, losses to follow-up, and withdrawals; reporting bias and whether groups were comparable at baseline; and sample size calculation. Any disagreements were resolved by consensus.

The risk of bias assessment falls into three categories of high, low, and unclear risk of bias. The assessments were provided in ROB tables and summary graphs.

Data abstraction

Relevant data were extracted independently by two reviewers using predefined prepiloted extraction forms. The extracted data included details of study (eg, author, country, design, study duration, study intervention, and outcome measures). The extracted data were checked by the second reviewer and any disagreements were resolved via discussion. If necessary, further discrepancies were resolved by a third reviewer.

Primary outcomes measures were:

- glycemic control as measured by glycated hemoglobin (HbA_{1c})
- hypoglycemia, graded as mild (symptoms easily controlled by individual), moderate (normal activities interrupted but assistance not required), severe (individual requiring assistance, and associated with blood glucose

level less than 50 mg/dL [3.4 mmol/L] or with prompt recovery after oral carbohydrate or glucagon or intravenous glucose) (DCCT 1993), serious (life threatening or required subject to be admitted to hospital). However, definition of hypoglycemia may slightly vary in AWARD trials and any variation in this has been taken into consideration. Note that in the trials, a cutoff of 3.9 was used, which is above the lower limit of normal, and hence exaggerates the frequency of hypoglycemia.

- weight gain or loss/change in body mass index
- Other outcomes were:

- FPG (fasting blood glucose)
- PPG (postprandial glucose)
- plasma lipids
- β -cell function (HOMA [homeostatic model assessment] cell function)
- heart rate
- blood pressure
- health-related quality of life.

Data synthesis

Dichotomous data were expressed as relative risk. Continuous data were expressed as weighted mean differences with 95% confidence intervals (CIs). Analysis was done comparing dulaglutide against placebo and active comparators.

Results

One hundred and fifty-six articles were retrieved through electronic searches, of which, 46 records were screened after removing duplicates. Of these, 24 records were excluded at title/abstract. The remaining 22 records were examined in full. Of these 22 records, only four papers were included, all RCTs based on the AWARD program (AWARD 1, 2, 5, and 6).^{20–23} AWARD-2 was available in abstract form; however, this was included since adequate information were reported. The main reason for exclusion were use of dulaglutide as monotherapy (AWARD-3),¹⁸ type 2 diabetes patients uncontrolled on conventional insulin therapy (AWARD-4),²⁴ and studies published only as abstracts (with insufficient details).

Study characteristics

The characteristics of the four included RCTs are summarized in Table 1. Two trials (AWARD 1 and 6)^{20,23} were conducted in multiple sites in many countries. Dungan et al²⁰ conducted AWARD-6 at 62 sites in 9 countries: Czech Republic, Germany, Hungary, Mexico, Poland, Romania, Spain, Slovakia, and USA. Wysham et al²³ conducted AWARD-1 in three countries namely Mexico, Argentina, and USA.

Table 1 Characteristics of the included studies

Study and country	Interventions	Characteristics of participants	Study duration	Outcomes measured
Wysham et al ²³ (AWARD-1) Mexico, Argentina, and USA (multicenter)	Dulaglutide 1.5/0.75 mg; exenatide 10 µg; placebo	Number: 976 Mean age: 55–56 years Sex: 40%–44% female HbA _{1c} (%): dula 1.5, 0.75 mg, exenatide 10 µg, placebo: 8.1. BMI (kg/m ²): dula 1.5, 0.75 mg, and placebo: 33; exenatide 10 µg: 34. Ethnicity: Hispanic or Latino (32%–36%); not Hispanic or Latino (64%–68%); American Indian (13%–14%); Asian (1%–4%); black (7%–9%); multiple, 1%; Native Hawaiian (0%–<1%); white (73%–76%) Diabetes duration: 9 years Previous medication (at screening) (metformin and pioglitazone): 1 OAM, (20%–31%); 2 OAMs (44%–56%)	52 weeks	Primary: HbA _{1c} change at 26 weeks Secondary: HbA _{1c} change at 52 weeks, change in central laboratory FSG, 8-point SMPG profiles, change in body weight, and β-cell function and insulin sensitivity indices (updated HOMA2)
Giorgino et al ²¹ (abstract) (AWARD-2) Country: N/A	Dulaglutide 1.5 mg; Dulaglutide 0.75 mg; Insulin glargine	Number: 807 Mean age: 57 years Sex: N/A HbA _{1c} (%): 8.1 BMI (kg/m ²): N/A Weight (kg): 86.3 Ethnicity: N/A Diabetes duration: N/A Previous medication: maximal dose of metformin and glimepiride	78 weeks	Primary: HbA _{1c}
Nauck et al ²² (AWARD-5) Country: NR	Dulaglutide 1.5 mg; Dulaglutide 0.75 mg; Sitagliptin 100 mg 100 mg; placebo	Number: 1,098 Mean age: 54–55 years Sex: 49%–56% female HbA _{1c} (%): dula 1.5 mg, 8.1; dula 0.75 mg, 8.2; sita, 8.1; placebo, 8.1 BMI (kg/m ²): dula 1.5 mg, 31; dula 0.75 mg, 31; sita, 31; placebo, 31 Ethnicity: Aboriginal (0%–<1%); black (2%–5%); white (50%–54%); East Asian (16%–17%); Hispanic (17%–22%); Native American (0%–<1%); West Asian (6%–10%) Diabetes duration: 7 years Previous medication: oral glucose-lowering monotherapy or combination therapy (metformin plus other drugs); OAM (93%–94%); one medication class (64%–69%); two or more medication class (24%–30%)	104 weeks	Primary: HbA _{1c} Secondary: body weight, FPG (central laboratory measure), and fasting insulin; B-cell function and insulin sensitivity indices (updated HOMA2) and lipids Others: safety
Dungan et al ²⁰ (AWARD-6) 62 sites in 9 countries (Czech Republic, Germany, Hungary, Mexico, Poland, Romania, Spain, Slovakia, and USA)	Once-weekly dulaglutide 1.5 mg; Once-daily liraglutide 1.8 mg	Number: 599 Mean age: 56.5–56.8 years Sex: 50%–54% female HbA _{1c} (%): dula 1.5 mg and lira 1.8 mg: 8.1 BMI (kg/m ²): dula 1.5 mg, 33.5; lira 1.8 mg, 33.6 Ethnicity: Hispanic or Latino (25%–24%); not Hispanic or Latino (75%–76%) Diabetes duration: 7.1–7.3 years Previous medication: metformin	26 weeks	Primary: HbA _{1c} Secondary: change in fasting plasma serum glucose (evaluated at a central laboratory), seven-point self-monitored plasma glucose profiles, bodyweight, BMI, and β-cell function assessed with the homeostasis model assessment (HOMA2-%B). Others: safety, health-related quality of life with exploratory patients-reported outcome measures

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; Sita, sitagliptin; Lira, liraglutide; NR, not reported; N/A, not available; HbA_{1c}, glycated hemoglobin; HOMA, homeostatic model assessment; BMI, body mass index; FPG, fasting plasma glucose; OAM, oral antihyperglycemic medications; FSG, fasting serum glucose; SMPG, self-monitored plasma glucose.

The remaining studies (AWARD 2 and 5) did not report details of study sites. A total of 3,480 participants were randomized across the four RCTs with the individual trial sample sizes ranging from 599²⁰ to 1,098²² participants.

The mean age of participants in the trials ranged from 53²² to 57²¹ years. Mean baseline HbA_{1c} was 8.1%, and mean body mass index (BMI) ranged between 31²² and 34²³ kg/m². The proportion of females in the studies was 40%²³–56%²². The duration of the trials ranged from 26²⁰ to 104 weeks.²² The two doses, 1.5 and 0.75 mg, of dulaglutide were compared against exenatide 10 µg twice daily,²³ sitagliptin 100 mg,²² and glargine.²¹ One trial compared dulaglutide 1.5 mg with liraglutide 1.8 mg.²⁰ All the four trials were sponsored by Eli Lilly and Company.

There were no trials against lixisenatide or against weekly exenatide.

AWARD-1 (dulaglutide vs exenatide 10 µg)

A randomized controlled, multicenter, parallel-arm study was conducted in 976 people with type 2 diabetes, aged between 55 and 56 years.²³ The participants were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide 10 µg, and placebo. The duration of the study was 52 weeks. The primary outcome measure was mean change in HbA_{1c} from baseline to 26 weeks. The secondary efficacy measures were mean change in HbA_{1c} from baseline to 52 weeks.

AWARD-2 (dulaglutide vs glargine)

A randomized controlled, parallel-arm, open-label 78 weeks study was conducted in 807 people with type 2 diabetes.²¹ The mean age of participants was 57 years. The study compared once-weekly dulaglutide 1.5 mg or dulaglutide 0.75 mg against insulin glargine in combination with metformin and glimepiride. The dose of glargine could be titrated to try to achieve target level. At baseline, mean HbA_{1c} and mean weight were 8.1% and 86.5 kg, respectively. The outcome measures were change in HbA_{1c} (percentages of patients with HbA_{1c} <7.0%) and weight change from baseline to 52 and 78 weeks.

AWARD-5 (dulaglutide vs sitagliptin 100 mg)

A randomized controlled, multicenter, double blind study comparing the two doses of dulaglutide (1.5 and 0.75 mg) vs sitagliptin 100 mg or placebo add on to metformin in 1,098 patients with type 2 diabetes.²² The mean baseline age of participants ranged between 54 and 55 years. At baseline, mean HbA_{1c} was 8.1% and weight 86.4 kg. The study lasted for 104 weeks. The primary outcome measure was change in HbA_{1c} from baseline to 52 weeks.

AWARD-6 (dulaglutide 1.5 mg vs liraglutide 1.8 mg)

This was a randomized, multicenter, open-label, parallel-group study conducted in 62 sites, in nine countries, in patients with type 2 diabetes inadequately controlled with metformin.²⁰ The study compared once-weekly dulaglutide 1.5 mg against liraglutide 1.8 mg once daily. The duration of the study was 26 weeks. Mean baseline age of participants was 57 years, HbA_{1c} was 8.1%, and weight ranged between 94 and 95 kg. The primary outcome measure was change in HbA_{1c} from baseline to 26 weeks.

Study quality

Three studies (AWARD 1, 5, and 6)^{20,22,23} were rated as having low risk of bias and one (AWARD-2)²¹ was rated as having unclear risk (Figure 2). Random sequence generation and allocation concealment were adequate (low risk) in two trials (AWARD 1 and 6),^{20,23} but were unclear in the other two trials (AWARD 2 and 5).^{21,22} Two trials (AWARD 2 and 6)^{20,21} were open label, but in one trial²⁰ “the participants, treating physicians, investigators, and sites staff were not blinded to the treatment allocation, however the study statistician and medical personnel from the sponsors were blinded”. The AWARD-5 trial²² was a double blinded study, whereas the design of AWARD-2 was unclear.²¹ Other domains such as attrition bias and reporting bias were satisfactory in three trials (AWARD 1, 5, and 6),^{20,22,23} but unclear in AWARD-2.²¹ The baseline characteristics were comparable in AWARD 1, 5, and 6.^{20,22,23} The sample size calculation was unclear in AWARD 1 and 2.^{21,23}

Change in HbA_{1c} from baseline

AWARD-1

Figure 3 (created using the data reported) shows that at 26 weeks, dulaglutide led to greater reduction in HbA_{1c} than exenatide 10 µg twice daily or placebo.²³ The least square (LS) mean changes from baseline to 26 weeks were –1.5%; standard deviation (SD), 1.002 and –1.30%; SD, 1.003, respectively, with dulaglutide 1.5 and 0.75 mg and –0.99%; SD, 0.99 with exenatide 10 µg and –0.46% with placebo.

Similarly, the LS mean HbA_{1c} changes from baseline to 52 weeks were –1.36%; SD, 1.33 with dulaglutide 1.5 mg, –1.07%; SD, 1.33 with 0.75 mg, and –0.80% with exenatide 10 µg.

AWARD-2

Figure 3 shows the HbA_{1c} changes from baseline at 52 and 78 weeks.²¹ At both time-points, the reductions with dulaglutide 1.5 mg (–1.08%; SD, 0.9 and –0.9%; SD, 1.1 at

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Groups comparable at baseline	Sample size calculation
Dungan et al ²⁰ (AWARD-6)	+	+	−	+	+	+	+
Giorgino et al ²¹ (AWARD-2)	?	?	−	?	?	?	?
Nauck et al ²² (AWARD-5)	?	?	+	+	+	+	+
Wysham et al ²³ (AWARD-1)	+	+	?	+	+	+	?

−	High risk of bias	?	Unclear risk of bias	+	Low risk of bias
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Figure 2 Risk of bias.

Abbreviation: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes.

52 and 78 weeks, respectively) were greater ($P<0.001$) than with insulin glargine (−0.63%; SD, 0.9 and −0.59%; SD, 1.1, respectively). The reductions with dulaglutide 0.75 mg (−0.76%; SD, 0.9 and −0.62%; SD, 1.1, respectively) were noninferior to insulin glargine. The mean dose of glargine at study end was not reported.

AWARD-5

At 26 weeks, the mean changes in HbA_{1c} from baseline to 26 weeks were statistically significantly greater with both doses of dulaglutide ($P<0.001$) than with placebo and sitagliptin 100 mg (Figure 4).²² At 52 weeks, the mean HbA_{1c} changes from baseline were significantly greater ($P<0.001$) with both doses of dulaglutide (−1.1%; SD, 1.04 with dulaglutide 1.5 mg, −0.87%; SD, 1.04 with dulaglutide 0.75 mg) compared to sitagliptin 100 mg (−0.39%; SD, 1.06). At 104 weeks, both doses of dulaglutide were reported to be statistically superior to sitagliptin 100 mg (Figure 4).

AWARD-6

AWARD-6 reported that dulaglutide 1.5 mg was noninferior to liraglutide 1.8 mg.²⁰ Both drugs significantly reduced HbA_{1c} from baseline (Figure 4). The mean treatment difference was −0.06% (95% CI, −0.19 to 0.07; noninferiority <0.0001).

Proportion of patients achieving HbA_{1c} target of $<7\%$ and $\leq 6.5\%$

AWARD-1

At 26 weeks, the percentages of patients who achieved the target of $<7\%$ were significantly higher in both dulaglutide arms (1.5 mg [78%] and 0.75 mg [66%]) than in the exenatide (52%) ($P<0.001$, both comparisons) and placebo arm (43%) ($P<0.001$, both comparisons) (Figure 5).²³ Similarly, HbA_{1c} target of $\leq 6.5\%$ was achieved by significantly greater proportions of patients in the two dulaglutide treatment arms (63%, −1.5 mg; 53%, −0.75 mg) compared to the exenatide

Figure 3 Mean change in HbA_{1c} from baseline to follow-up (AWARD 1 and 2).

Notes: (A) AWARD-1: * $P < 0.001$, superiority vs exenatide; ** $P < 0.001$, superiority vs placebo; *** $P < 0.001$ vs placebo. (B) AWARD-2: *,** indicate multiplicity adjusted one-sided $P < 0.001$ for noninferiority or superiority vs glargine, respectively.

Abbreviations: LS, least square; HbA_{1c}, glycated hemoglobin; AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; Exe, exenatide; P, placebo.

(38%) and placebo (24%) arms ($P < 0.0001$, all comparisons). At 52 weeks, 57% of patients in the dulaglutide 1.5 mg arm and 48% of patients in the 0.75 mg dulaglutide arm achieved HbA_{1c} target of $\leq 6.5\%$ compared to only 35% in the exenatide arm.

An additional post hoc analysis from the same trial²² was conducted to determine the influence of baseline HbA_{1c} ($< 8.5\%$ and $\geq 8.5\%$) at 26 weeks. For those with baseline HbA_{1c} of $< 8.5\%$, the LS mean changes from baseline in HbA_{1c} were greater with dulaglutide 1.5 mg ($P < 0.001$) than with placebo and exenatide. The proportions of patients reaching targets of $< 7\%$ and $\leq 6.5\%$ were also significantly

more ($P < 0.05$) on dulaglutide 1.5 mg compared to placebo and exenatide (Table 2). Dulaglutide 0.75 mg led to significant changes for both baseline groups compared to placebo ($P < 0.05$). However, in those with baseline HbA_{1c} of $\geq 8.5\%$, the change in HbA_{1c} with dulaglutide 0.75 mg was not statistically significantly different compared to exenatide 10 μg .

AWARD-2

The trial only reported the results of those achieving an HbA_{1c} target of $< 7\%$ at 52 and 78 weeks.²¹ At 52 weeks, around 53% and 37% of patients met the target of $< 7\%$ with dulaglutide 1.5 and 0.75 mg, respectively, compared to 31%

Figure 4 Mean change in HbA_{1c} from baseline to follow-up (AWARD 5 and 6).

Notes: (A) AWARD-5: * $P < 0.001$ vs sitagliptin; ** $P < 0.001$, superiority vs placebo; *** $P < 0.001$ vs placebo; # $P < 0.001$, superiority vs sitagliptin. (B) AWARD-6: $P < 0.0001$ noninferiority of dulaglutide vs liraglutide.

Abbreviations: LS, least square; HbA_{1c}, glycated hemoglobin; AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; P, placebo; Sita, sitagliptin; Lira, liraglutide.

with insulin glargine ($P < 0.05$) (Figure 5). At 78 weeks, 49% of patients with dulaglutide 1.5 mg and 34% patients with dulaglutide 0.75 mg achieved the HbA_{1c} target compared to 30% of patients with glargine ($P < 0.05$).

AWARD-5

Overall, the proportions of patients achieving an HbA_{1c} target of $< 7\%$ and $\leq 6.5\%$ at weeks 26, 52, and 104 were significantly greater with dulaglutide 1.5 and 0.75 mg compared to sitagliptin 100 mg and placebo (Figure 6).²² At 26 weeks, the percentages of patients attaining $< 7\%$ target were 61% and 55% in the dulaglutide 1.5 and 0.75 mg treatment groups, respectively, compared to 38% in the sitagliptin 100 mg group

($P < 0.001$, all comparisons) and 21% in the placebo group ($P < 0.001$, both comparisons). At 26 weeks, 47% in the dulaglutide 1.5 mg and 31% in the dulaglutide 0.75 mg groups compared with 22% in the sitagliptin 100 mg ($P < 0.001$, both comparisons) and 13% in the placebo arm ($P < 0.001$, both comparisons; $P = 0.005$, sitagliptin 100 mg comparison with placebo) achieved the target of $\leq 6.5\%$

At 52 and 104 weeks, the proportions of patients achieving the target level of $< 7\%$ were greater in the two dulaglutide groups (58% with 1.5 mg dulaglutide; 49% with 0.75 mg dulaglutide) than in the sitagliptin 100 mg group (33%). More patients in the two dulaglutide groups (42% with 1.5 mg dulaglutide; 29% with 0.75 mg dulaglutide)

Figure 5 Proportion of patients achieving a target HbA_{1c} level of <7% and ≤6.5% (AWARD 1 and 2).

Notes: (A) AWARD-1: * $P < 0.001$ vs exenatide; ** $P < 0.001$ vs placebo; # $P < 0.001$ vs exenatide. (B) AWARD-2: * indicated two-sided $P < 0.05$ vs glargine.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; HbA_{1c}, glycated hemoglobin; Dula, dulaglutide; P, placebo; Exe, exenatide; Glar, glargine.

achieved the target HbA_{1c} level of ≤6.5% than sitagliptin 100 mg group (19%).

AWARD-6

At 26 weeks, the proportions of patients achieving the target HbA_{1c} level of <7% were similar in dulaglutide 1.5 mg and liraglutide 1.8 mg groups (68%) (Figure 6).²⁰ However, at the same time-point, slightly more patients (55%) in the dulaglutide 1.5 mg group met the target HbA_{1c} level of ≤6.5% than those in the liraglutide 1.8 mg group (51%).

Body weight changes from baseline AWARD-1

The mean change in body weight from baseline to 26 weeks was greater with dulaglutide 1.5 mg (−1.30 kg; SD, 4.84) than with exenatide 10 µg (−1.07 kg; SD, 4.39) (P -value comparing the two not reported) (Figure 7).²³ In contrast, those receiving dulaglutide 0.75 mg and placebo gained weight, 4.85 kg; SD, 0.20 and 1.24 kg; SD, 4.39, respectively. At 52 weeks, the mean change in body weight change was greater in the 1.5 mg dulaglutide group (−1.01 kg) than in

the exenatide 10 µg (−0.71 kg) and the dulaglutide 0.75 mg groups (−0.54 kg).

AWARD-2

At 52 weeks, the mean changes in weight with dulaglutide 1.5 and 0.75 mg were −1.87 SD; 3.9 kg and −1.33 SD; 3.9 kg, respectively, while those in the insulin glargine group gained weight of 1.44 SD; 3.8 kg ($P<0.05$ vs glargine) (Figure 7).²¹ The findings were similar at 78 weeks.

AWARD-5

At 26 weeks, mean weight reductions from baseline were significantly ($P<0.001$) greater with both dulaglutide doses (−3.04 kg; SD, 3.48 with dulaglutide 1.5 mg; −2.65 kg; SD, 3.47 with dulaglutide 0.75 mg) than on sitagliptin 100 mg (−1.39 kg; SD, 3.54) and placebo (−1.42 kg; SD, 3.5).²² At 52 weeks, the mean changes in body weight from baseline with dulaglutide 1.5 mg (−3.03 kg; SD, 3.48) and 0.75 mg (−2.60 kg; SD, 3.47) were significantly ($P<0.001$) greater than on sitagliptin 100 mg (−1.53 kg; SD, 3.54) and placebo (−1.42 kg; SD, 3.5). At 104 weeks, both dulaglutide doses (1.5 mg: −2.88 kg; 0.75 mg: −2.39 kg) showed significantly greater weight reduction ($P<0.001$) compared to sitagliptin 100 mg (−1.75 kg) (Figure 8).

AWARD-6

The mean changes in body weight from baseline at 26 weeks were greater with liraglutide 1.8 mg (−3.61 kg; SD, 3.8) than with dulaglutide 1.5 mg (−2.9 kg; SD, 3.8) (Figure 8).²⁰

Fasting plasma glucose and postprandial plasma glucose (FPG and PPG)

At 26 weeks, the AWARD-1²³ trial showed significantly greater ($P<0.001$) reductions in FPG concentration from baseline with dulaglutide −1.5 mg (−43 mg/dL; SD, 33.4 or −2.4 mmol/L) and with 0.75 mg (−34 mg/dL; SD, 33.4 or 1.89 mmol/L) than with exenatide 10 µg (−24 mg/dL; SD, 33.4 or 1.33 mmol/L) and placebo (−5 mg/dL; SD, 35 or 0.28 mmol/L) (Table 3). At 52 weeks, both dulaglutide doses significantly reduced mean FPG (1.5 mg: $P<0.001$; 0.75 mg: $P=0.005$) when compared with exenatide 10 µg.

The mean eight-point self-monitored plasma glucose profiles showed greater reductions with both dulaglutide 1.5 and 0.75 mg ($P<0.001$) than with placebo and exenatide. PPG also showed greater reductions with all active treatment groups ($P<0.001$ compared with placebo; for dulaglutide 1.5 mg vs exenatide 10 µg, $P=0.047$). Similar reductions were reported for 2-hour PPG by patients on dulaglutide 1.5 mg

($P=0.003$) and exenatide 10 µg ($P<0.001$) compared with placebo. The excursions of postprandial glucose after midday and evening meal were greater with dulaglutide compared to exenatide. The changes were greater with dulaglutide groups than ($P<0.001$) with exenatide 10 µg (only P -value reported, data not reported).

AWARD-2 trials did not report FPG and PPG

In the AWARD-5 trial,²² FPG reductions were higher with both dulaglutide doses (no data provided, but values read from Figure 2D and are approximate; 1.5 mg dulaglutide: −45 mg/dL or −2.5 mmol/L; 0.75 mg dulaglutide: −37 mg/dL or −2.06 mmol/L) than with sitagliptin 100 mg (−20 mg/dL or −1.11 mmol/L) and placebo (−10 mg/dL or −0.56 mmol/L) at 26 weeks.²¹ At 52 weeks, the reduction was greater with both dulaglutide ($P<0.001$) than with sitagliptin 100 mg (1.5 mg dulaglutide: −45 mg/dL or −2.5 mmol/L; 0.75 mg dulaglutide: −30 mg/dL or −1.67 mmol/L; sitagliptin: −20 mg/dL or −1.11 mmol/L).

The AWARD-6 trial²⁰ reported that at 26 weeks both dulaglutide 1.5 mg (−1.93 mmol/L) and liraglutide 1.8 mg (−1.90 mmol/L) reduced the FPG concentration with no significant difference between the two (difference of −0.03, $P=0.83$). Similarly, there was no difference between the two in terms of PPG (Table 3).

Blood pressure

AWARD 1, 5, and 6 reported on systolic blood pressure (SBP) (Table 3). The reduction in SBP was slightly greater with dulaglutide 1.5 mg (−3.36 mmHg) than with liraglutide 1.8 mg (−2.82 mmHg). In AWARD-1, SBP increased in patients on the higher dose of dulaglutide (+0.11 mmHg) and on exenatide 10 µg (0.06 mmHg), whereas, SBP reduced in those taking lower dose of dulaglutide (−0.36 mmHg). At 26 weeks, the reductions in SBP were similar in those taking sitagliptin 100 mg (−1.9 mmHg) and dulaglutide (−1.7 mmHg with dulaglutide 1.5 mg; −1.4 mmHg with dulaglutide 0.75 mg). Data for AWARD-2 trial¹⁷ were not available.

Hypoglycemia

All four trials defined “total hypoglycemia” or “hypoglycemia” as a PG level of ≤ 70 mg/dL (≤ 3.9 mmol/L) with or without symptoms or signs attributable to hypoglycemia, and defined “severe hypoglycemia” as an episode requiring help of another person.

Total hypoglycemia (as defined above) was slightly more common (9% vs 6%) on dulaglutide than on liraglutide 1.8 mg

Table 2 Changes in HbA_{1c}, weight and BMI

Study	HbA _{1c} (change from baseline)	P-value	HbA _{1c} <7% (change from baseline %)	P-value
Dula 1.5/0.75/exe/placebo				
Wysham et al ²³	26 weeks:	26 weeks:	26 weeks:	26 weeks:
AWARD-1	Dula 1.5: -1.51%, SD 1.002	Dula 1.5 and 0.75: adjusted one-sided	Dula 1.5: 218 (78.2)	Dula 1.5 and 0.75:
	Dula 0.75: -1.3%, SD 1.003	<i>P</i> <0.001 for superiority, vs Exe or P,	Dula 0.75: 184 (65.8)	two-sided <i>P</i> <0.05 vs P
	Exe: -0.99%, SD 0.99	respectively, for HbA _{1c} change only	Exe: 144 (52.3)	two-sided <i>P</i> <0.05 vs Exe
	P: -0.46%, SD 0.94	Exe: two-sided <i>P</i> <0.05 vs P	P: 60 (42.9)	Exe: 2 sided <i>P</i> <0.05 vs P
	52 weeks:	52 weeks:	52 weeks:	52 weeks:
	Dula 1.5: -1.36%, SD 1.33	Dula 1.5 and 0.75: adjusted	Dula 1.5: 197 (70.8)	Dula 1.5 and 0.75:
	Dula 0.75: -1.07%, SD 1.33	one-sided <i>P</i> <0.001 for superiority, vs	Dula 0.75: 165 (59.1)	two-sided <i>P</i> <0.05 vs Exe
	Exe: -0.80%, SD 1.32	Exe for HbA _{1c} change only	Exe: 136 (49.2)	
Dula 1.5/0.75 mg/glargine				
Giorgino	52 weeks:	Dula 1.5: adjusted <i>P</i> <0.001	52 weeks:	(Two-sided <i>P</i> <0.05 vs
et al ²¹ AWARD-2	Dula 1.5: -1.08%, SD 0.9	for superiority vs glargine	Dula 1.5: 145 (53.2)	glargine)
(abstract)	Dula 0.75: 0%-0.76%, SD 0.9	for A _{1c} change	Dula 0.75: 101 (37.1)	Two-sided <i>P</i> <0.05 vs
	Glar: 0.63%, SD 0.9	Dula 0.75: adjusted <i>P</i> <0.001	Glar: 81 (30.9)	glargine
	78 weeks:	for nonsuperiority vs glargine	78 weeks:	
	Dula 1.5: -0.9%, SD 1.1	for A _{1c} change	Dula 1.5: 134 (49)	
	Dula 0.75: -0.62%, SD 1.1		Dula 0.75: 93 (34.1)	
	Glar: -0.59%, SD 1.1		Glar: 80 (30.5)	
Dula 1.5/0.75 mg/sita/placebo				
Nauck et al ²²	26 weeks:	26 weeks:	26 weeks:	26 weeks:
AWARD-5	Dula 1.5: -1.22%, SD 0.87	Dula 1.5 and 0.75: adjusted	Dula 1.5: 185 (61)	Dula 1.5 and 0.75:
	Dula 0.75: -1.01%, SD 1.04	one-sided <i>P</i> <0.001 for	Dula 0.75: 167 (55.2)	two-sided <i>P</i> <0.001 vs P
	Sita: -0.61%, SD 0.88	superiority vs P for A _{1c} change	Sita: 119 (37.8)	Two-sided <i>P</i> <0.001 vs
	(two-sided <i>P</i> <0.001 vs P)	Two-sided <i>P</i> <0.001 vs sita	P: 37 (21)	sita
	P: 0.03%, SD 0.93	52 weeks:	52 weeks:	52 weeks:
	52 weeks:	Dula 1.5 and 0.75: adjusted	Dula 1.5: 175 (57.6)	Dula 1.5 and 0.75:
	Dula 1.5: -1.1%, SD 1.04	one-sided <i>P</i> <0.001 for superiority vs	Dula 0.75: 147 (48.8)	two-sided <i>P</i> <0.001 vs sita
	Dula 0.75: -0.87%, SD 1.04	Sita for A _{1c} change	Sita: 104 (33)	104 weeks:
	Sita: -0.39%, SD 1.06	104 weeks:	104 weeks:	Dula 1.5 and 0.75:
	104 weeks:	Dula 1.5 and 0.75: adjusted	Dula 1.5: 165 (54.3)	two-sided <i>P</i> <0.001 vs sita
	Dula 1.5: -1%, SD 1.04	one-sided <i>P</i> <0.001 for superiority vs	Dula 0.75: 135 (44.8)	
	Dula 0.75: -0.71%, SD 1.2	Sita for A _{1c} change only	Sita: 98 (31.1)	
	Sita: 0.32%, SD 1.06			
Dula/lira				
Dungan et al ²⁰	26 weeks:	From baseline: <0.0001	26 weeks:	Not given
(AWARD-6)	Dula: -1.4%, SD 0.86	From baseline: <0.0001	Dula: 200/293 (68)	
	Lira: -1.36%, SD 0.86	Difference between groups (95% CI): -0.06% (-0.19 to 0.07) <i>P</i> ≤0.0001 (noninferiority of dula vs lira)	Lira: 199/293 (68)	
Bain 2014⁴⁴ (abstract) post hoc analysis at 26 weeks to determine the influence of baseline HbA_{1c} in the AWARD-1 trial				
		Baseline <8.5%	Baseline ≥8.5%	P-value
Dula 1.5 mg		-1.16 (0.07)%	-2.37 (0.10)%	<0.001, all comparisons
Placebo		0.17 (0.10)%	-0.76 (0.16)%	
Exenatide 10 µg		-0.64 (0.07)%	-1.86 (0.11)%	
Proportion of patients achieving HbA _{1c} targets				
		Baseline <8.5%	Baseline ≥8.5%	
Dula 1.5 mg				<0.05, all comparisons
<7%		92%	47%	
≤6.5		80%	26%	
Placebo				
<7%		55%	10%	
≤6.5		32%	3%	
Exe				
<7%		65%	21%	
≤6.5		50%	9%	
Dula 0.75 mg reported significant changes for both baseline groups vs placebo				<0.05, both outcomes,
Dula 0.75 mg with exenatide 10 µg in the baseline HbA _{1c} ≥8.5% groups				all comparisons
				Statistically not significant

HbA _{1c} <6.5% (change from baseline)	P-value	Weight change from baseline (kg)	P-value	BMI
26 weeks: Dula 1.5: 176 (63) Dula 0.75: 148 (53) Exe: 105 (38) P: 34 (24) 52 weeks: Dula 1.5: 57% Dula 0.75: 48% Exe: 35%	$P < 0.001$ all comparisons Not given	26 weeks: Dula 1.5: -1.30, SD 4.84 Dula 0.75: 0.20, SD 4.85 Exe: -1.07, SD 4.39 P: 1.24, SD 4.39 52 weeks: Dula 1.5: -1.01, SD 6.3 Dula 0.75: 0.54, SD 6.3 Exe: -0.71, SD 6.31	26 weeks: Dula 1.5: two-sided $P < 0.05$ vs P Dula 0.75: two-sided $P < 0.05$ vs Exe and P 52 weeks: Dula 0.75: two-sided $P < 0.05$ vs Exe	Not given
Not given		52 weeks: Dula 1.5: -1.87, SD 3.9 Dula 0.75: -1.33, SD 3.9 Glar: 1.44, SD 3.8 78 weeks: Dula 1.5: -1.96, SD 4.2 Dula 0.75: -1.54, SD 4.2 Glar: +1.28, SD 4.2	Two-sided $P < 0.05$ vs glargine	N/A
26 weeks: Dula 1.5: 143 (47) Dula 0.75: 94 (31) Sita: 69 (22) P: 23 (13) 52 weeks: Dula 1.5: 128 (42) Dula 0.75: 88 (29) Sita: 60 (19) 104 weeks: Not given	$P < 0.001$, both comparisons ($P < 0.001$ both dula comparisons; $P = 0.005$ sita comparison) $P \leq 0.001$ vs sita, both comparisons	26 weeks: Dula 1.5: -3.04, SD 3.48 Dula 0.75: -2.65, SD 3.47 Sita: -1.39, SD 3.54 P: -1.42, SD 3.5 52 weeks: Dula 1.5: -3.03, SD 3.83 Dula 0.75: -2.6, SD 3.9 Sita: -1.53, SD 3.9 104 weeks: Dula 1.5: -2.88, SD 4.3 Dula 0.75: -2.39, SD 4.5 Sita: -1.75, SD 4.4	26 weeks: Dula 1.5 and 0.75: two-sided $P < 0.001$ vs P Two-sided $P < 0.001$ vs sita 52 weeks: Dula 1.5 and 0.75: two-sided $P < 0.001$ vs sita 104 weeks: Dula 1.5: two-sided $P < 0.001$ vs sita Dula 0.75: two-sided $P = 0.054$ vs sita	Not given
26 weeks: Dula: 169 (55%) Lira: 149 (51%)		26 weeks: Dula: -2.9, SD 3.88 Lira: -3.61, SD 3.8	From baseline $P < 0.0001$ From baseline $P < 0.0001$ Difference between groups (95% CI): 0.71 (0.17–1.26) $P = 0.011$	Consistent with weight finding

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; HbA_{1c}, glycated hemoglobin; Dula, dulaglutide; P, placebo; Exe, exenatide; Glar, glargine; Sita, sitagliptin; Lira, liraglutide; BMI, body mass index; N/A, not available; SD, standard deviation; CI, confidence interval.

Figure 6 (A) and (B) Proportion of patients achieving a target HbA_{1c} level of <7% and ≤6.5% (AWARD 5 and 6).

Notes: AWARD-5: * $P < 0.001$ vs sitagliptin and placebo; ** $P < 0.001$ vs placebo; *** $P < 0.001$ vs sitagliptin; # $P < 0.05$ vs sitagliptin; ## $P < 0.001$ vs sitagliptin.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; HbA_{1c}, glycated hemoglobin; Dula, dulaglutide; P, placebo; Sita, sitagliptin; Lira, liraglutide.

(AWARD-6) (P -value not reported).²⁰ In AWARD-5,²² the incidence of hypoglycemia at 52 weeks was significantly higher in dulaglutide 1.5 mg than in sitagliptin 100 mg (0.4 events/patient/year vs 0.1 events/patient/year, P -value not reported), whereas the incidence was similar at 26 weeks. In AWARD-1,²³ more patients in the exenatide 10 µg arm (16%) experienced hypoglycemia ($P < 0.007$) than in the two dulaglutide arms (1.5 and 0.75 mg) at 26 weeks (10% and 11%, respectively). The incidence of hypoglycemia was reported to be lower in the dulaglutide arms (1.5 mg) compared to exenatide 10 µg arm at 52 weeks, but no data were reported. At 78 weeks, patients in both dulaglutide arms (1.7 mg, 1.7 mg) had lower rates of hypoglycemia compared to glargine 3.0 events/patient/year ($P \leq 0.002$) (AWARD-2).²¹

Severe hypoglycemia was seen only in a few patients in both dulaglutide and glargine arms in AWARD-2, it was not reported whether they were also on an SU.

Adverse events

Details of the adverse events are shown in Table 4. The most commonly reported adverse events in all trials were nausea, vomiting, and diarrhea, which were significantly more common in the GLP-1-treated groups than in placebo-treated groups. Discontinuation in the trials due to adverse events was also higher in all the actively treated groups, and the main reasons for discontinuation were nausea in AWARD 1, 6, and 5^{19,20,23} and hyperglycemia in AWARD-5.¹⁹ The numbers of patients with severe adverse events were similar across all actively treated groups.

Deaths were reported by AWARD 5 and 1.^{22,23} In AWARD-5²², four patients died – one patient in dulaglutide 1.5 mg arm (due to nonhemorrhagic stroke 6 months postrandomization), one in sitagliptin 100 mg arm (cause of death not reported), and two patients in placebo arm (cause of death not reported). In AWARD-1,²³ four patients

Figure 7 Mean change in weight (kg) from baseline to follow-up (AWARD 1 and 2).

Notes: (A) AWARD-1: * two-sided $P < 0.05$ vs placebo; ** two-sided $P < 0.05$ vs exenatide. (B) AWARD-2: *two-sided $P < 0.05$ vs glargine.

Abbreviations: LS, least square; AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; Exe, exenatide; P, placebo.

died – two patients in each dulaglutide arm 1.5 mg (one due to myocardial infarction at around 13 weeks after randomization and one patient died due to pancreatic cancer 9 months after discontinuing dulaglutide, which the patient took for about 6 months) and 0.75 mg (one died at around 14 weeks after randomization due to natural causes, but had a history of cardiovascular risk factors and cause of death in one patient not reported), respectively.

Three cases of acute pancreatitis were reported in AWARD-5,²² two patients on sitagliptin 100 mg and one patient on placebo/sitagliptin 100 mg (while on sitagliptin), while none of the patients receiving the two dulaglutide doses developed pancreatitis. No cases of pancreatic cancer or pancreatitis were reported in AWARD-6.²⁰ One patient receiving liraglutide in AWARD-6 was diagnosed with papillary thyroid carcinoma, but none in the dulaglutide group. None of the patients developed C-cell hyperplasia or medullary thyroid carcinoma (MTC). In AWARD-1,²³ one

patient in the dulaglutide 1.5 mg arm was diagnosed with chronic pancreatitis 7 months after study drug initiation, and one patient on dulaglutide 1.5 mg for 6 months was diagnosed with pancreatic cancer and died at 9 months after study discontinuation.

The trials in total involved 3,048 patients followed for at most 78 weeks, and longer follow-up with larger numbers will be necessary to provide safety data.

Discussion

This review included four Phase III studies. The AWARD-2²¹ study was available only as an abstract, while all the remaining three trials were published in full. The comparisons were dulaglutide 1.5 mg vs liraglutide 1.8 mg (AWARD-6) add on to metformin, dulaglutide (1.5/0.75 mg) vs glargine (AWARD-2) add on to metformin and SU, dulaglutide (1.5/0.75 mg) vs sitagliptin 100 mg and placebo (AWARD-5) add on to metformin, and AWARD-1 had dulaglutide

Figure 8 Mean change in weight (kg) from baseline to follow-up (AWARD 5 and 6).

Notes: AWARD-5: *two-sided $P < 0.001$ vs sitagliptin; **two-sided $P < 0.001$ vs placebo.

Abbreviations: LS, least square; AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; P, placebo; Sita, sitagliptin; Lira, liraglutide.

(1.5/0.75 mg) vs exenatide 10 µg twice daily and placebo add on to metformin and thiazolidinediones. All trials were funded by Eli Lilly.

Summary of principal findings

The results suggested that dulaglutide is effective in improving glycemic control and promoting weight loss, with a low risk of hypoglycemia.

HbA_{1c}

Both doses of dulaglutide were reported to show noninferiority against liraglutide 1.8 mg, while dulaglutide was found to be superior to sitagliptin 100 mg by 0.71% (1.5 mg dulaglutide) to 0.48% (0.75 mg dulaglutide), respectively. HbA_{1c} change was greater with 1.5 mg dulaglutide than with glargine; however, the reduction with 0.75 mg dulaglutide was nonsuperior against glargine.

HbA_{1c} target of <7% and ≤6.5%

The proportions of patients who achieved HbA_{1c} targets of <7% and ≤6.5% were reported to be significantly higher among dulaglutide-treated patients compared to exenatide 10 µg twice daily, sitagliptin 100 mg, liraglutide 1.8 mg, and glargine. Separate post hoc analysis conducted for subgroups according to baseline HbA_{1c} levels of <8.5% and ≥8.5% found that greater proportions of patients reached targets of <7% and ≤6.5%, irrespective of their baseline HbA_{1c} level, on dulaglutide than on placebo and exenatide 10 µg.

Weight loss

The results varied among studies. Dulaglutide led to greater reduction in weight compared to sitagliptin 100 mg and exenatide 10 µg. In contrast, patients receiving liraglutide 1.8 mg lost more weight than those receiving dulaglutide 1.5 mg in AWARD-6. The weight reductions

with dulaglutide in AWARD-6 and AWARD-1 trials differed. In the former, at 26 weeks, the reduction with dulaglutide 1.5 mg was 2.9 kg, while in the latter, at the same time-point, the reduction was only 1.3 kg. At baseline, mean BMIs (33.5–33.6 kg/m² in AWARD-6; 33–34 kg/m² in AWARD-1) and mean weight were similar (93.8–94.4 kg in AWARD-6; 94–96 kg in AWARD-1) in the two trials; therefore, it was not clear why there was a difference between the two studies. Mean duration of diabetes in AWARD-1 was slightly greater than in AWARD-6 (9 vs 7 years).

Hypoglycemia and adverse events

The incidence of hypoglycemia was low with dulaglutide, and there were few cases of severe hypoglycemia with dulaglutide and glargine. The main adverse effects of dulaglutide were nausea, diarrhea, and vomiting. There was one report of death due to pancreatic cancer 9 months after discontinuing treatment with dulaglutide (6 months therapy) in AWARD-1. No other cases of pancreatic cancer or adjudicated pancreatitis were reported in other AWARD trials.

Strengths and limitations

The review followed a systematic approach to identify and appraise all the relevant papers on the effectiveness of dulaglutide in patients with type 2 diabetes mellitus, who are not achieving satisfactory glycemic control with “combinations of oral glucose-lowering drugs, or such combinations with basal insulin”. All the included studies are RCTs comparing dulaglutide against placebo or against active treatments (such as other GLP-1 agonists). All but one of the articles included in the review were published in full. One was published as an abstract, but was included since there was adequate information on design and quality²⁵ with results on secondary outcomes. We excluded studies where dulaglutide was used in treatment of naïve patients, to reflect clinical practice as patients would be treated with a cheaper oral hypoglycemic agent such as metformin before expensive injectable drugs like the GLP-1 receptor agonists are prescribed.

Limitations of the review

AWARD 2 and 6 included in the review were of open-label design. The treatment allocation was not blinded to participants, physicians, investigators, and site staff; therefore, there could be some risk of observer bias. The review did not undertake an indirect comparison or network meta-analyses to compare efficacy and safety of dulaglutide against other GLP-1 receptor agonists and other glucose-lowering drugs.

Three trials where dulaglutide was used as monotherapy were not included in the review because of our inclusion/exclusion criteria. AWARD-3 compared dulaglutide 1.5 mg against metformin in patients naïve to treatment.²⁶ The study by Grunberger et al²⁷ compared dulaglutide (0.1, 0.5, 1.0, 1.5 mg) vs placebo in patients naïve to treatment. Another monotherapy study by Terauchi et al²⁸ compared dulaglutide (0.25, 0.5, or 0.75 mg) against placebo in patients with type 2 diabetes, who were treated with diet/exercise or oral antidiabetic drug.

The AWARD-4 trial was also excluded from the review because the study compared dulaglutide against glargine, both combined with mealtime insulin lispro with or without metformin in type 2 diabetes uncontrolled on conventional insulin therapy.²⁴

One notable thing in the AWARD study comparing dulaglutide against sitagliptin was the small reduction in HbA_{1c} with sitagliptin (–1.1% with dulaglutide 1.5 mg, –0.86% with dulaglutide 0.75 mg, and –0.39% with sitagliptin 100 mg). This is lower than seen in other trials of sitagliptin.^{29,30}

The question still remains as to how effective dulaglutide is against other GLP-1 preparations which are used once-weekly like long-acting exenatide. Unfortunately, there is no trial comparing these drugs. The relative efficacy of dulaglutide against other GLP-1 receptor agonists could have been assessed using an indirect comparison, but this was outside the remit of this review. Also using indirect comparison methods, the efficacy and safety of this drug could have been compared against the new class of oral hypoglycemic drugs, SGLT2 inhibitors (such as dapagliflozin, canagliflozin, and empagliflozin), but since these are oral and less expensive, one would expect them to be used before GLP-1 receptor agonists. The SGLT2 inhibitors reduce blood glucose level by reducing the absorption of glucose in the kidneys.

Although dulaglutide appears to be clinically effective, the price of the drug is not yet known, and it remains to be seen whether it will be cost-effective. However, it is available in a ready to use pen compared to other GLP-1 receptor agonists, therefore there is no need to handle the needle and premix the drug, which may increase patient compliance, but it remains to be seen. In the UK, the NICE uses a cost-effectiveness threshold of £20,000–£30,000 per quality-adjusted life year (QALY), and a drug with costs per QALY which falls below this threshold is considered to be cost-effective and is usually accepted. The risk of developing thyroid and pancreatic cancers requires monitoring, but is unproven since the trials are not long enough.

Table 3 Fasting plasma glucose, postprandial plasma glucose, and blood pressure

Study	FPG (change from baseline) mmol/L	P-value	PPG (change from baseline) mmol/L
Dula 1.5/0.75/exe/placebo			
Wysham et al ²³	26 weeks:	Mean difference	Mean eight-point self-monitored plasma glucose (SMPG) profile (mmol/L) at baseline and
AWARD-1	Dula 1.5: -43, SD 33.4	between dula 1.5 mg	26 weeks: dula 1.5 g and dula 0.75 mg were
	Dula 0.75: -34, SD 33.4	and 0.75 mg vs exe	associated with a greater reduction in the mean
	Exe: -24, SD 33.4	-18 mg/dL and	of all premeal PG compared with placebo and
	P: -5, SD 35	-10 mg/dL ($P<0.001$,	exe ($P<0.001$, both comparisons)
	52 weeks:	both comparisons)	Postprandial PG: all active treatment arms
	Both dula arms continued with		had significantly greater LS mean reductions
	significantly greater changes from		compared with placebo ($P<0.001$)
	baseline in FSG compared with		Patients receiving dula 1.5 mg had a significantly
	exenatide 10 µg ($P<0.001$, dula		greater reduction in the mean of all postprandial
	1.5 mg; $P=0.005$, dula 0.75 mg)		PG values compared with exenatide 10 µg
			($P=0.047$)
			2-hour postprandial PG: patients receiving dula
			1.5 mg and exenatide had significantly greater
			reductions in the mean 2-hour postprandial PG
			excursions compared with placebo ($P=0.003$, dula
			1.5 mg; $P<0.001$, exenatide 10 µg), with changes
			in the exenatide group significantly greater than in
			the dula groups ($P<0.001$, both comparisons)
			52 weeks:
			Similar results for active treatment arms (data
			not shown)
Dula 1.5/0.75 mg/glargine			
Giorgino et al ²¹	N/A	N/A	N/A
Dula 1.5/0.75 mg/sita/placebo			
Nauck et al ²²	There was significant reduction in	52 weeks:	NR
AWARD-5	FPG in the first 2 weeks with both	<0.001 , both	
	dulaglutide doses and with sitagliptin	comparisons	
	100 mg and the FPG levels remained	with placebo.	
	stable thereafter, whereas those in the		
	placebo arm showed small and slower		
	reduction in FPG overtime.		
	52 weeks:		
	Dula 1.5: -26 mg/dL (mean difference)		
	Dula 0.75: -13 mg/dL (mean difference)		
Dula 1.5 mg/lira			
Dungan et al ²⁰	26 weeks:	Reduction from baseline	26 weeks:
(AWARD-6)	Dula: -1.93, SD 2.07	<0.0001 (both groups)	Dula: -2.56, SD 1.55
	Lira: -1.9, SD 2.07	Between groups: 0.83	Lira: -2.43, SD 1.5

Note: * $P<0.05$.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; P, placebo; Exe, exenatide; Sita, sitagliptin; Lira, liraglutide; N/A, not available; SD, standard deviation; NR, not reported; FPG, fasting plasma glucose; FSG, fasting serum glucose; SMPG, self-monitored plasma glucose; DBP, diastolic blood pressure; SBP, systolic blood pressure; PPG, postprandial glucose; PG, plasma glucose; LS, least square.

Insulin degludec

There is a new generation, long-acting insulin analogue called “insulin degludec”, trade name “Tresiba”, marketed in the UK as basal insulin for people with type 2 diabetes. However, it has not been approved by FDA. Some trials have already been published. One trial compared insulin degludec against insulin glargine in patients previously treated with basal insulin.³¹ Another trial compared degludec against insulin

glargine in people naïve to insulin therapy.³² Insulin degludec has also been compared against sitagliptin in patients naïve to insulin therapy.³³ So far, no trials have been published comparing degludec with dulaglutide.

On-going trials

Searches for ongoing trials on <https://clinicaltrials.gov> showed a number of on-going studies. Some of the trials

P-value	SBP (change from baseline) mmHg	P-value	DBP (change from baseline) mmHg	P-value
26 weeks: Dula 1.5: 0.11, SD 13.8* Dula 0.75: -0.36, SD 13.7* Exe: 0.06, SD 13.7* P: 3.4, SD 13.4 52 weeks: Dula 1.5: 0.83, SD 14.5 Dula 0.75: 1.62, SD 14.2 Exe: 0.02, SD 14.6	*P<0.05 vs placebo	26 weeks: Dula 1.5: 0.76, SD 9.1 Dula 0.75: 0.56, SD 0.0 Exe: -0.11, SD 9.1 P: 1.25, SD 8.9 52 weeks: Dula 1.5: 0.89, SD 9.5 Dula 0.75: 0.76, SD 0.02 Exe: 0.02, SD 9.6		
N/A	N/A	N/A	N/A	N/A
NR	26 weeks: Dula 1.5: -1.7, SD 12.2* Dula 0.75: -1.4, SD 12.1* Sita: -1.9, SD 12.4* P: 1.1, SD 11.9 52 weeks: Dula 1.5: -0.8, SD 12.2 Dula 0.75: -0.5, SD 12.1 Sita: -0.5, SD 12.4	*P<0.05 vs placebo	26 weeks: Dula 1.5: -0.4, SD 6.9 Dula 0.75: -0.2, SD 6.9 Sita: -1.1, SD 7.09 P: 0.7, SD 7.9* 52 weeks: Dula 1.5: 0.3, SD 8.7 Dula 0.75: 0.3, SD 8.6 Sita: -0.2, SD 8.8	*P<0.05 vs placebo
From baseline <0.0001 (both groups) Between groups: 0.26	Dula: -3.36, SD 12.1 Lira: -2.82, SD 12.1	0.60	Dula: -0.22, SD 6.9 Lira: -0.31, SD 6.9	0.88

have been completed without results yet, while some trials are still recruiting. They include

- comparison of once-weekly dulaglutide with once-daily insulin glargine in patients with type 2 diabetes mellitus on metformin and/or an SU.
- comparison of dulaglutide to sitagliptin in patients with type 2 diabetes mellitus on metformin.

Results of one trial have been posted on the website clinicaltrials.gov (NCT01584232), but not yet published. It

was again sponsored by Eli Lilly and company. It is a Phase III, randomized controlled trial conducted in Japan, comparing the efficacy of dulaglutide against insulin glargine in 361 patients with type 2 diabetes. The primary outcome was change in HbA_{1c} at 26 weeks.

Mean HbA_{1c} changes from baseline to primary end-point are reported to show superiority of dulaglutide over insulin glargine (mean dose not reported) ($P<0.001$). Greater percentages of patients in the dulaglutide arm

Table 4 Adverse events, withdrawals, and hypoglycemia

Study	Discontinuation due to adverse events, n (%)	At least one treatment-emergent adverse event, n (%)	Gastrointestinal events, n (%)		
			Nausea	Vomiting	Diarrhea
Dula 1.5/0.75/Exe/P					
Wysham et al ²³	26 weeks: 8 (3)/	26 weeks:	26 weeks: 78 (28)*/	26 weeks: 47 (17)***/	26 weeks: 31 (11)/
AWARD-1	4 (1)/9 (3)/3 (2)	215 (77)/199 (71)/	45 (16)***/71 (26)*/	17 (6)***/30 (11)*/	22 (8)/16 (6)/8 (6)
	52 weeks: 9 (3)/	198 (72)/104 (74)	8 (6) 52 weeks:	2 (1) 52 weeks:	52 weeks: 36 (13)/
	4 (1)/10 (4)	52 weeks: 226 (81)/	81 (29)/47 (17)**/77 (28)	47 (17)/17 (6)**/	26 (9)/21 (8)
		220 (79)/221 (80)		33 (12)	
Dula 1.5/0.75 mg/ glargine					
Giorgino et al ²¹	NR	NR	42 (15.4)/	NR	29 (10.6)/25 (9.2)/
AWARD-2			21 (7.7)/4 (1.5)		15 (5.7)
Dula 1.5/0.75/sita/P					
Nauck et al ²²	26 weeks: 21 (7)/	26 weeks: 208 (68)***/	26 weeks: 51 (17)*#/	26 weeks: 36 (12)*#/	26 weeks:
AWARD-5	12 (4)/14 (4)/	204 (68)***/185 (59)/	38 (13)*#/14 (4)/7 (4)	22 (7)***/6 (2)/1 (1)	39 (13)*#/
	24 (14)	111 (63)	52 weeks: 53 (17)*/	52 weeks:	27 (9)*/8 (3)***/
	52 weeks:	52 weeks: 233 (77)/	42 (14)*/16 (5)	39 (13)*/23 (8)***/7 (2)	11 (6)
	33 (11)/23 (8)/	231 (77)/219 (70)			52 weeks:
	30 (10)				44 (15)*/30 (10)*/
				9 (3)	
Dula 1.5 mg/lira					
Dungan et al ²⁰	18 (6)/18 (6)	185 (62)/189/63	61 (20)/54 (18)	21 (7)/25 (8)	36 (12)/36 (12)
AWARD-6	P=0.99	P=0.78	P=0.46	P=0.55	P=0.995

Notes: * $P < 0.001$ versus sitagliptin; * $P < 0.001$ versus placebo; ** $P < 0.05$ versus exenatide 10; *** $P < 0.05$ versus placebo; **** $P < 0.05$ versus sitagliptin.

Abbreviations: AWARD, Assessment of Weekly Administration of Dulaglutide in Diabetes; Dula, dulaglutide; P, placebo; Exe, exenatide; Sita, sitagliptin; Lira, liraglutide; SD, standard deviation; NR, not reported; TE, treatment-emergent; SE, standard error of the mean.

reached HbA_{1c} targets ($\leq 6.5\%$: 51%; $< 7\%$: 71%) than in the glargine arm ($\leq 6.5\%$: 24%; $< 7\%$: 46%). Weight decreased with dulaglutide but increased with glargine ($P < 0.005$). The incidence of hypoglycemia was lower in

patients with dulaglutide (26%) than those on glargine (48%). The most common gastrointestinal adverse events reported by patients treated with dulaglutide were nausea, vomiting, and diarrhea.

Other gastrointestinal events	Serious adverse events, n (%)	Pancreatitis, n (%)	Positive immunogenicity	Deaths, n (%)	Mild/moderate/overall hypos, n (%)	Severe hypos, n (%)
26 weeks: Dyspepsia: 22 (8)***/ 5 (2)**/19 (7)4 (3) Constipation: 12 (4)/ 5 (2)/5 (2)/2 (1) Flatulence: 14 (5)/3 (1)/ 6 (2)/3 (2) 52 weeks: Dyspepsia: 23 (8)/ 6 (2)**/20 (7) Constipation: 16 (6)/ 5 (2)/5 (2) Flatulence: 16 (6)/ 3 (1)/7 (3)	26 weeks: 12 (4)/ 15 (5)/15 (5)12 (9) 52 weeks: 18 (7)/ 22 (8)/27 (10)	NR	Anti-drug antibodies 26 weeks (1.5/0.75/ exe/P): antibodies: 4(1.4)/2(0.7)/ 12 (4.3) 2 (1.4) 52 weeks: (1.5/ 0.75/exe): 5 (1.8)/ 3 (1.1)/14 (5.1)	26 weeks: 1 (0.4)/1 (0.4)/ 0 (0)/0 (0) 52 weeks: 1 (0.4)/1 (0.4)/ 0 (0)	26 weeks: dula 1.5/0.75/ exe/P: 29 (10.4)/30 (10.7)/44 (15.9)/ 50 (3.5) Mean 1 year adjusted rates of total hypoglycemia 0.45/1.10/1.47/0.37 events/patient/year 52 weeks: rates and incidence of total hypoglycemia remained lower for dulaglutide 1.5 mg compared to exenatide 10 µg	Exe: 2 None in dulaglutide groups
NR	NR	NR	NR	NR	78 weeks symptomatic hypoglycemia (≤70 mg/dL) event/ patient/year) 1.7/1/7/3 (P≤0.002 both)	Severe hypoglycemia was minimal with dula and glargine
26 weeks: Abdominal pain: 13 (4)/ 11 (4)6 (2)/3 (2) Dyspepsia: 13 (4)/ 14 (5)/8 (3)/2 (1) Abdominal distension: 12 (4)/12 (4)/3 (1)/1 (1) 52 weeks: Abdominal pain: 18 (6)/ 12 (4)/10 (3) Dyspepsia: 14 (5)/ 18 (6)/9 (3) Abdominal distension: 12 (4)/14 (5)/3 (1)	26 weeks: 17 (6)/ 10 (3)/11 (4)/ 6 (3) 52 weeks: 26 (9)/16 (5)/ 17 (5)	Acute pancreatitis: Dula/Sita/P: 0/2/1	26 weeks: dula anti-drug antibodies (1.5/0.75/sita/P): 2 (<1)/ 6 (2)/ 1 (<1)/0(0) 52 weeks: (1.5/0.75/ sita): 2(<1)/7(2)/ 2(<1)	26 weeks: 1 (<1)/0 (0)/ 0 (0)/0 (0) 52 weeks: 1 (<1)/ 0 (0)/2 (<1)	26 weeks: NR 52 weeks: Mean (SD) 1 year adjusted rates (events/patient/year) Dula 1.5: 0.4, SD 1.6 Dula 0.75: 0.3, SD 2.6 Sita: 0.1, SD 1.1	There were no severe hypoglycemic events reported
Dyspepsia: 24 (8)/ 18 (6), P=0.33 Constipation: 11 (4)/ 17 (6), P=0.25	5 (2)/11 (4) P=0.13	No cases of pancreatic cancer or adjudicated pancreatitis	3 (1%) patient developed TE antibodies to dulaglutide. Liraglutide group was not assessed. None of these patient developed hypersensitivity reactions	0	Dula/lira: 26 (9)/ 17 (6) Overall rate (events/patient/year): Mean event rate of 0.34 (SE 1.44) events/patient /year for dula compared with 0.52 (3.01) for lira	None in all groups

Pancreatitis /pancreatic cancer and thyroid cancer risks

Concern has been raised about the risk of acute pancreatitis and pancreatic tumors with GLP-1 receptor agonists,³⁴ and

the FDA noted the pancreatitis risk in connection with long-acting exenatide. However, since then several studies have found no increased risk of pancreatitis. Li et al³⁵ carried out a good quality systematic review of 55 randomized trials and 5

observational studies and concluded that the GLP-1 receptor agonists drugs did not increase the risk of pancreatitis.

Faillie et al³⁶ used data from the UK Clinical Practice Research Database on 20,748 users on incretin drugs (liraglutide, exenatide, and four DPP-4 inhibitors) and found no increase in pancreatitis compared to people with type 2 diabetes on SU, but did not report results separately for the GLP-1 receptor agonists. Montori³⁷ concluded that the evidence to date suggests that the incretin drugs do not increase the incidence of pancreatitis.

Both the FDA³⁸ and the EMA¹⁴ state that the safety profile of dulaglutide is similar to the safety profile of other GLP-1 receptor agonists. They add that there may be a risk of pancreatic and thyroid cancer, but there are no long-term data available. Therefore, EMA has requested the manufacturer to submit periodic safety update reports.¹⁴ FDA has also made recommendations for postmarketing risk evaluation and mitigation strategies to assess the risk of thyroid C-cell tumor and pancreatitis.³⁸ The FDA has also asked the manufacturer to undertake the following: a study in a pediatric population, a toxicity study in immature rats, setting up of a MTC case registry of at least 15 years duration to record cases of MTC related to dulaglutide, a study comparing dulaglutide and insulin glargine in patients with moderate to severe renal impairment, and a study on cardiovascular outcomes.³⁸

Research needs

As with all new drug entities, long-term surveillance will be required to detect rare adverse events. The FDA issued a warning for long-acting exenatide about the need for monitoring for thyroid cancer, while noting that the evidence for an increase in risk comes from rats and that there is no evidence that a similar effect could occur in humans.³⁸

Robinson et al³⁹ noted a slight increase in heart rate by about 2 beats per minute with GLP-1 receptor agonists, more evident for liraglutide and long-acting exenatide than twice-daily exenatide, but of uncertain clinical significance. A review of trial data on five long-acting GLP-1 receptor agonists (exenatide, taspoglutide, albiglutide, LY2189265, and CJC-1134-PC) concluded that they were more likely to raise heart rate than short-acting GLP-1 receptor agonists.⁴⁰

A study of the long-acting GLP-1 agonist PF-04603629 reported a rise of 23 beats per minute in heart rate at 24 hours after injection of the higher dose together with a rise in diastolic pressure.⁴¹

Ferdinand et al⁴² investigated the effect of dulaglutide on blood pressure and heart rate in patients with type 2 diabetes and found that it led to reduction in 24-hour SBP (1.5 mg vs placebo: -2.8 mmHg, 95% CI: -4.6 to -1.0) and an increment

in 24-hour heart rate (dulaglutide 0.75 mg vs placebo: 1.6 bpm, 95% CI: 0.3–2.9; 1.75 mg vs placebo: 2.8 bpm, 95% CI: 1.5–4.2). The evidence to date on dulaglutide is only in people with type 2 diabetes, but there is a little evidence that this group of drugs may be of benefit in type 1 diabetes too, and further research is needed there. Once-weekly exenatide has been tried in type 1 diabetes mellitus in combination with continuous subcutaneous insulin infusion therapy.⁴³

Conclusion

The review finds that dulaglutide is effective in the treatment of patients with type 2 diabetes mellitus, and may have advantages, such as in weight change, over some active comparators. Dulaglutide was found to be noninferior to liraglutide 1.8 mg. The incidence of hypoglycemia was found to be lower with dulaglutide. Longer term follow-up data are needed for reassurance on safety.

Disclosure

DSS is currently employed by Eli Lilly. However, while undertaking this review he was only employed by the University of Warwick. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 Search strategy: MEDLINE

1. Exp glucagon-like peptides/
2. (Glucagon like peptide* or GLP-1).tw.
3. (Dulaglutide or LY2189265 or GLP-1 Fc).tw.
4. 1 or 2 or 3
5. (Random* or blind* or placebo or trial).tw.
6. Randomized controlled trial.pt.
7. Random\$.tw.
8. 5 or 6 or 7
9. Diabetes mellitus, type 2/
10. Type 2 diabetes mellitus.tw.
11. 9 or 10
12. 4 and 8 and 11
13. Limit 12 to (English language and humans and year = "2005–current")

Note: The above search strategy was adopted for other databases.

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