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Once-weekly dulaglutide versus insulin glargine in the early control of fasting serum glucose and HbA1c☆

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ABSTRACT

Aims: To determine the early benefit:risk balance of dulaglutide versus insulin glargine in patients with type 2 diabetes mellitus (T2DM).
Methods: This post hoc analysis used data from a randomized, open-label study (AWARD-2; modified intention-to-treat group) in which suboptimally controlled metformin + glimepiride-treated patients received dulaglutide 1.5 mg (n = 273) or insulin glargine (n = 262). Two composite endpoints were used: for weeks 2–20, fasting serum glucose (FSG) <130 mg/dL (<7.2 mmol/L) without hypoglycemia (blood glucose ≤70 mg/dL [≤3.9 mmol/L] or severe hypoglycemia); at week 26, patients with glycated hemoglobin (HbA1c) <7.0% (<53.0 mmol/mol) or reduction from baseline ≥1.0% (≥10.9 mmol/mol), no hypoglycemia (as defined above) and no weight gain. Odds ratios (ORs) were generated using logistic regression analysis.
Results: The probability of reaching the FSG target without hypoglycemia was higher with dulaglutide than with insulin glargine at weeks 4 (OR 1.78; 95% confidence interval [CI] 1.22–2.60) and 8 (OR 1.69; 95% CI 1.15–2.48). The proportion of patients achieving the 26-week endpoint was higher with dulaglutide (37.4% vs. 10.3%; OR 5.28; 95% CI 3.28–8.48).
Conclusions: Dulaglutide's balanced efficacy-to-safety profile compares favorably with that of insulin glargine and is apparent soon after treatment initiation and after 6 months of therapy.

1. Introduction

AWARD-2 (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes-2) was a 78-week open-label, randomized study designed to compare the efficacy and safety of a glucagon-like peptide-1 receptor agonist (GLP-1 RA) – once-weekly dulaglutide 0.75 or 1.5 mg – with that of daily insulin glargine in patients with type 2 diabetes mellitus (T2DM) who were receiving stable and maximally tolerated doses of metformin and glimepiride.[1] The study showed that, compared with daily insulin glargine (without forced titration) at 52 weeks, dulaglutide 1.5 mg was associated with greater reductions in glycated hemoglobin (HbA1c) and bodyweight, lower risk of hypoglycemia, and higher risk of gastrointestinal adverse events.[1] We present data from this study using composite efficacy and safety endpoints that incorporate glycemic control and risk of hypoglycemia, with or without an effect on bodyweight.

The most recent American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines recommend GLP-1

☆ Declaration of competing interest: Irene Romera is an employee of Eli Lilly and Company. Ignacio Conget has received honoraria for lectures and consulting fees from Medtronic, Bayer GlaxoSmithKline, Eli Lilly and Company, Novo Nordisk, Sanofi-Aventis, Novartis, and MSD. Luis Alberto Vazquez was a full-time employee of Eli Lilly and Company until October 2016, is currently a minor shareholder, and has received honoraria and consulting fees from Astra Zeneca, Eli Lilly, and Novo Nordisk. Raffaella Gentilella is an employee of Jazz Pharmaceuticals - Jazz Healthcare Italy s.r.l. and a minor shareholder of Eli Lilly. Jeremie Lebrec works as a consultant for Eli Lilly and Company. Esteban Jódar has received research support and personal fees from AstraZeneca, Janssen, Lilly and Company, MSD, Novo Nordisk, Pfizer, and Sanofi. Jesús Reviriego is an employee of and stock shareholder in Eli Lilly and Company.

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RAs as second- or third-line therapy in many patient subgroups, including those with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease, and those with a compelling need to minimize hypoglycemia and/or prevent weight gain/promote weight loss.[2] GPL-1 RAs are also recommended as the first injectable medication in the majority of patients who require additional glucose lowering despite therapy with two or three oral antidiabetic drugs (OADs), although combination GLP-1 RA + insulin treatment may be considered if HbA1c is >10% (>86 mmol/mol) or >2% (>23 mmol/mol) above target.[2] Insulin should be considered as first injectable medication if HbA1c is >11% (>97 mmol/mol), if the patient shows symptoms of catabolism, or if type 1 diabetes mellitus (T1DM) is a possibility.[2] It is recognized by current guidelines that sodium-glucose co-transporter-2 inhibitors and GLP-1 RAs have both demonstrated antihyperglycemic efficacy – in association with weight loss and a lower risk of hypoglycemia than insulin – in patients with HbA1c >9% (>75 mmol/mol).[2] The increased emphasis on the use of GLP-1 RA therapies in the 2018 ADA/EASD guidelines[2] compared with the recommendations of the same organizations in 2012[3] – and, in particular, the recommendation that GLP-1 RAs should be the first injectable therapy in the majority of patients – support the design of AWARD-2 and the analysis reported herein.

It is important that any antihyperglycemic therapy shows good efficacy and safety in the first few months of treatment. In view of this, our analysis reports AWARD-2 data from the first 26 weeks of the clinical trial. HbA1c is a good indicator of glycemic status stability or change over a period of 2–3 months[4] but is not appropriate for shorter-term assessment of changes in glycemia. In contrast, fasting glucose levels reflect immediate changes in glycemic status and are typically used to monitor response to treatment in the early stages of follow-up.[5] This analysis incorporates assessment of both these glycemic endpoints. However, there is growing recognition that glycemia is not the only relevant endpoint in the assessment of an antidiabetic agent and that the agent's benefit:risk profile – which can be explored using a balanced efficacy and safety composite endpoint – is also important.[6–9] For patients with T2DM, the effects of therapy on glycemia, hypoglycemic risk, and bodyweight are all clinically relevant.[2] Hypoglycemia, in particular, remains a significant burden for many patients receiving antidiabetic therapy, particularly insulin therapy.[10,11] The burden of hypoglycemia stems not only from its associations with mortality[10,12] and physical morbidity[13] but also from its impacts on psychological morbidity, patient wellbeing,[10,11,14,15] and patients' ability to achieve glycemic control.[13,14] The importance of hypoglycemia in patients with T2DM requires emphasis: as a result of increases in life expectancy[16] and the global prevalence of T2DM,[17] combined with ongoing recommendations for intensification of insulin regimens where indicated,[2] we now have a situation where more hypoglycemic episodes occur in patients with T2DM than in those with T1DM.[11]

Our objective in this analysis was to use data from AWARD-2 to determine – during the first 6 months of treatment – the benefit: risk balance of once-weekly dulaglutide 1.5 mg versus daily insulin glargine when administered as first injectable treatments to patients with poorly controlled T2DM who were receiving concomitant metformin and glimepiride. The post-hoc analyses performed involved assessment of composite efficacy and safety endpoints in both the short and medium term: fasting serum glucose (FSG) <130 mg/dL (<7.2 mmol/L) plus no hypoglycemic events at 2, 4, 8, 14, and 20 weeks; HbA1c <7.0% (<53.0 mmol/mol) or reduction from baseline ≥1.0% (≥10.9 mmol/mol) plus no hypoglycemic events plus no weight gain at 26 weeks.

The 1.5-mg dose of dulaglutide was chosen for the current analysis because dulaglutide was used as add-on therapy in AWARD-2.[1] Approval as add-on therapy has been granted for both the 0.75 mg and 1.5 mg doses in the United States,[18] and for the 1.5 mg dose in the European Union.[19] The higher dose was therefore deemed most suitable for this analysis, given that it is approved for this indication in both jurisdictions.

2. Materials and methods

AWARD-2 was an open-label study in which patients with T2DM who were receiving metformin and glimepiride were randomized to receive dulaglutide 1.5 mg (no dose titration; n = 273), dulaglutide 0.75 mg (n = 272), or insulin glargine (n = 265; only 262 patients received any treatment).[1] For each patient, metformin and glimepiride were adjusted to doses that were maximally tolerated, no higher than the maximum locally approved dose, and no lower than the minimal required dose (at least 1500 mg/day and at least 4 mg/day, respectively). Dose adjustment (decrease or discontinuation) of glimepiride, followed by metformin, was allowed if the patient experienced recurrent hypoglycemia.

The insulin glargine titration algorithm aimed to achieve a self-monitored fasting plasma glucose (FPG) level of <100 mg/dL (<5.6 mmol/L). It was recommended that the dose should be assessed every 3–4 days in the first 4 weeks of treatment and once weekly through week 8, with adjustments of 0–2 units in response to FPG levels of 100–119 mg/dL (5.6–6.6 mmol/L).[1]

Change in HbA1c from baseline to 26 weeks, percentage of patients achieving HbA1c <7.0% (<53.0 mmol/mol) at 26 weeks, FSG values at 26 weeks, and change in bodyweight from baseline at 26 weeks were all secondary endpoints in AWARD-2. Episodes of hypoglycemia (as defined in Section 2.1) were documented throughout the study. We present data from the dulaglutide 1.5 mg (approved dosage for these patients in the European Union) and insulin glargine treatment arms only.

2.1. Composite endpoint from 2 to 20 weeks

At each of weeks 2, 4, 8, 14, and 20 of the study, we determined the percentage of patients in the modified intention-to-treat (ITT) group (all patients randomized and treated, without post-rescue visits) who had FSG <130 mg/dL (<7.2 mmol/L) at that visit. Odds ratios (ORs; dulaglutide vs. insulin glargine) for the probability of reaching FSG <130 mg/dL (<7.2 mmol/L) without hypoglycemia (blood glucose ≤70 mg/dL [≤3.9 mmol/L] and/or severe hypoglycemia) in the previous inter-visit interval were determined by logistic regression analysis, with the following factors included in the analysis: treatment, week, treatment-by-week interaction, and baseline FSG. The inter-visit interval ran from treatment initiation to week 2 for the week 2 assessment and between assessments for other weeks (e.g., from week 2 to week 4 for the week 4 assessment). Severe hypoglycemia was defined as a hypoglycemic episode that required assistance from another person to actively administer therapy.

At each of weeks 2, 4, 8, 14, and 20, for the subgroup of patients with FSG <130 mg/dL (<7.2 mmol/L), we determined (i) mean weekly hypoglycemia rate (episodes with blood glucose ≤70 mg/dL [≤3.9 mmol/L]/patient/week or severe hypoglycemia) for the previous inter-visit interval; (ii) mean daily glimepiride dose; and (iii) mean daily insulin glargine dose. The mean daily glimepiride and insulin doses were calculated at each visit from the last available dose.

2.2. Composite endpoint at 26 weeks

Using data from the modified ITT population (population defined above), we identified patients who fulfilled all three of the following criteria at week 26: (i) HbA1c <7.0% (<53.0 mmol/mol) or reduction from baseline ≥1.0% (≥10.9 mmol/mol); (ii) no hypoglycemic events (blood glucose ≤70 mg/dL [≤3.9 mmol/L] and/or a severe hypoglycemic event, as defined in Section 2.1) since baseline; (iii) no net weight gain (where "weight gain" = weight change >0.0 kg [precision to one decimal point]) between baseline and week 26. In this analysis, the last-observation-carried-forward method was used for missing data imputation.

Table 1
Baseline characteristics of the modified intention-to-treat (ITT) population (all patients randomized and treated, without post-rescue visits).

Variable	Dulaglutide 1.5 mg N = 273	Insulin glargine N = 262
Female, n (%)	129 (47)	128 (49)
Age (years)	56 ± 10	57 ± 9
Weight (kg)	85 ± 18	88 ± 20
BMI (kg/m^2)	31 ± 5	32 ± 6
Diabetes duration (years)	9 ± 6	9 ± 6
HbA1c (%)	8.2 ± 1.0	8.1 ± 1.0
HbA1c (mmol/mol)	65.9 ± 11.3	65.0 ± 10.4
Fasting serum glucose (mg/dL)	165 ± 49	163 ± 48
Fasting serum glucose (mmol/L)	9.2 ± 2.7	9.1 ± 2.7
Glimepiride dose (mg/day)	6.3 ± 1.7	6.2 ± 1.6

Data are mean ± standard deviation unless otherwise indicated.
BMI, body mass index; HbA1c, glycated hemoglobin.

Logistic regression, with adjustments for baseline HbA1c and country effects, was used to compare the dulaglutide- and insulin glargine-treated patients who fulfilled these criteria. Logistic regression was also used to compare the two treatment groups in two subsets of these patients: (i) HbA1c <7.0% (<53.0 mmol/mol), no hypoglycemia, and no weight gain; (ii) HbA1c reduction from baseline ≥1.0% (≥10.9 mmol/mol), no hypoglycemia, and no weight gain.

Throughout the analyses (2- to 20-week and 26-week data), there was no adjustment for multiplicity. All results were deemed statistically significant if $P < 0.05$.

3. Results

The baseline characteristics of the modified ITT group are shown in Table 1 (dulaglutide 1.5 mg, n = 273; insulin glargine, n = 262). All characteristics, including mean FSG and HbA1c values, were similar in the two groups.

3.1. Composite endpoint from 2 to 20 weeks

As shown in Fig. 1, the percentage of patients achieving FSG <130 mg/dL (<7.2 mmol/L) was numerically higher in the dulaglutide 1.5 mg group than in the insulin glargine group from the first assessment at week 2 and throughout the first 14 weeks of treatment. The difference between groups was particularly marked in the first few weeks after treatment initiation (week 2: 58.9% vs. 44.4%; week 4: 58.7% vs. 48.2%).

The probability of a patient reaching FSG <130 mg/dL (<7.2 mmol/L) without hypoglycemia was significantly higher in the dulaglutide-treated group than in the group receiving insulin glargine at weeks 4 (OR 1.78; 95% confidence interval [CI] 1.22–2.60) and 8 (OR 1.69; 95% CI 1.15–2.48) (Fig. 2). Among patients achieving FSG <130 mg/dL (<7.2 mmol/L) at each visit, the mean weekly hypoglycemia rate was significantly higher for the dulaglutide-treated patients at week 2 (dulaglutide, 0.47 episodes/patient/week; insulin glargine, 0.27 episodes/patient/week; $P = 0.01$) and significantly lower in this group at week 20 (dulaglutide, 0.11 episodes/patient/week; insulin glargine, 0.23 episodes/patient/week; $P = 0.02$) (Fig. 3). At all other timepoints, there was no significant difference between groups in this outcome. One patient in each treatment arm experienced an episode of severe hypoglycemia during the first 20 weeks of treatment.

In patients with FSG <130 mg/dL (<7.2 mmol/L) at any timepoint, the mean daily dose of glimepiride showed a slight but consistent downward trend between weeks 2 and 20, from values of 4.8 and 5.1 mg for the dulaglutide 1.5 mg- and insulin glargine-treated groups, respectively, at week 2, to values of 4.1 and 4.5 mg at week 20 (Fig. 1). In contrast, the mean daily dose of insulin glargine (absolute dose and dose rate) increased steadily from week 2 to 20 (0.14 IU/kg at week 2; 0.25 IU/kg at week 20). Although the cohort of patients with FSG <130 mg/dL differed at each timepoint, these data are useful as a means of understanding how glimepiride and insulin glargine doses may evolve over time.

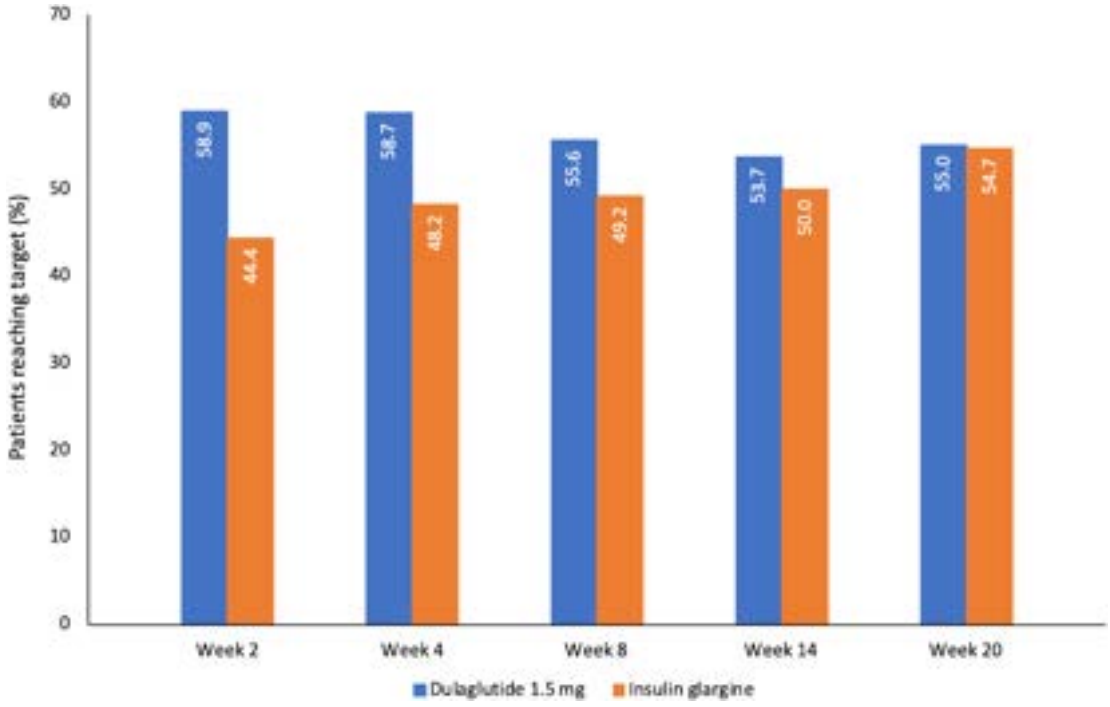

Fig. 1. Percentage of patients achieving FSG <130 mg/dL (<7.2 mmol/L) and mean daily glimepiride dose at each visit (2 to 20 weeks).

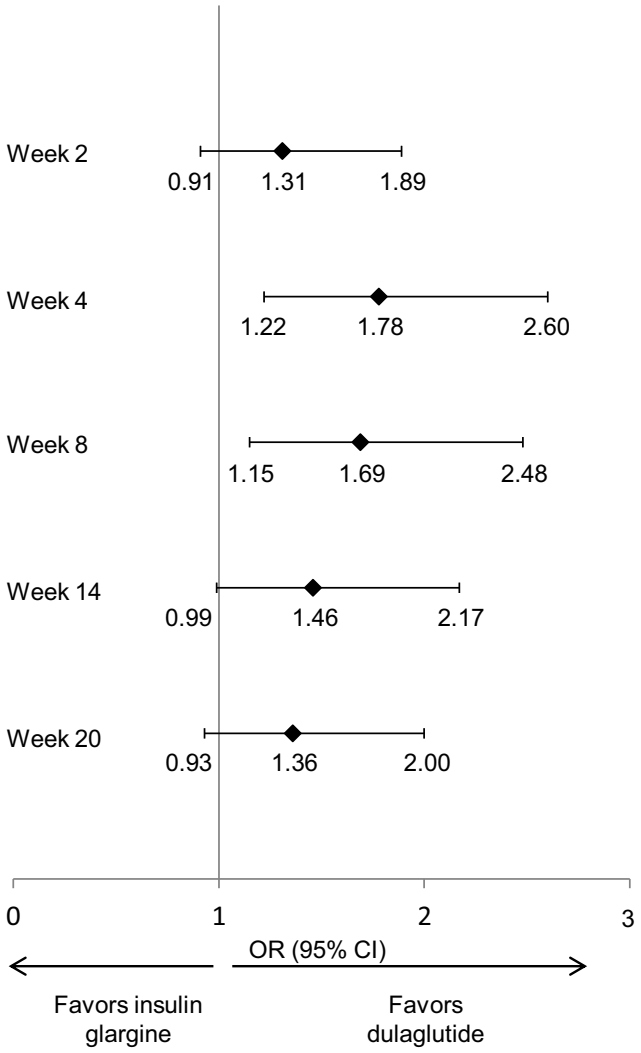

Fig. 2. Odds ratios of reaching fasting serum glucose <130 mg/dL (<7.2 mmol/L) without hypoglycemia* (dulaglutide vs. insulin glargine) (2–20 weeks). *Blood glucose ≤70 mg/dL (≤3.9 mmol/L) or severe hypoglycemia (hypoglycemic episode that required assistance from another person to actively administer therapy). CI, confidence interval; OR, odds ratio.

3.2. Composite endpoint at 26 weeks

The probability of a patient reaching HbA1c <7.0% (<53.0 mmol/mol) or reduction from baseline ≥1.0% (≥10.9 mmol/mol) and experiencing no hypoglycemia events and no weight gain was significantly higher in the dulaglutide group at 26 weeks (OR 5.28; 95% CI 3.28–8.48) (Fig. 4). Treatment with dulaglutide was also associated with significantly higher probabilities of patients experiencing no hypoglycemia events and no weight gain and either (i) HbA1c <7.0% (<53.0 mmol/mol) (OR 6.76; 95% CI 3.61–12.65) or (ii) HbA1c reduction from baseline ≥1.0% (≥10.9 mmol/mol) (OR 6.17; 95% CI 3.48–10.65) (Fig. 4). Removal of the weight gain criterion from the composite endpoint (to generate an endpoint that was similar to the week 2–20 composite endpoint) still resulted in a higher percentage of the dulaglutide group achieving the composite endpoint (Fig. 4). The only severe hypoglycemic events reported during the first 26 weeks of treatment were those reported in Section 3.1.

4. Discussion

The superior antihyperglycemic efficacy of dulaglutide versus insulin glargine has already been established: in AWARD-2, once-weekly dulaglutide 1.5 mg demonstrated greater reduction in overall glycemia than insulin glargine as measured by HbA1c changes at 52 weeks.[1] The post-hoc analyses of the AWARD-2 study reported here have shown that, compared with daily insulin glargine, once-weekly dulaglutide 1.5 mg resulted in a significantly higher probability of patients reaching FSG <130 mg/dL (<7.2 mmol/L) without hypoglycemia in the initial weeks of treatment (OR at 4 weeks 1.78; 95% CI 1.22–2.60). In addition, a significantly greater number of patients had a clinically significant glycemic response with no hypoglycemia and no weight gain at 26 weeks (OR 5.28; 95% CI 3.28–8.48).

With some pharmacological regimens, improved glucose lowering has been associated with an increased risk of hypoglycemia and greater weight gain.[20,21] The results presented here demonstrate that good control of glycemia can be achieved without hypoglycemia or weight gain in approximately one-quarter to one-third of patients within 26 weeks of treatment initiation (Fig. 4). These data support the favorable benefit:risk profile of once-weekly dulaglutide.

The composite efficacy and safety endpoint chosen for the 26-week analysis is similar to those used in the evaluation of other antidiabetic agents.[22] Endpoints such as this balance the benefits of glycemic control against the risks of hypoglycemia,[3] support the multifactorial approach to management of T2DM that is recommended,[2] and demonstrate a patient-centered approach to diabetes management. Inclusion of a glycemic control improvement criterion (reduction of HbA1c of at least 1.0% [10.9 mmol/mol]) is important. Using data from both clinical trials and real-world evidence, Conget et al.[23] showed that including both a glycemic improvement criterion and an absolute HbA1c cut point (e.g., <7.0% [<53.0 mmol/mol]) in a composite endpoint allowed identification of more patients who had experienced clinically meaningful responses to treatment.

The glycemic cut points used in our composite endpoints are supported by management guidelines and epidemiological studies: FSG <130 mg/dL (<7.2 mmol/L) is the upper limit of the target recommended by the ADA for pre-prandial plasma glucose in non-pregnant adults[24] and HbA1c <7.0% (<53.0 mmol/mol) is the target recommended by the 2018 ADA/EASD guidelines for non-pregnant adults.[2] Support for the clinical relevance of a 1.0% (10.9 mmol/mol) reduction in HbA1c comes from United Kingdom Prospective Diabetes Study (UKPDS) follow-up data, which showed that each 1.0% (10.9 mmol/mol) reduction in mean HbA1c was associated with reductions in the risk of diabetes-related death and a range of microvascular and macrovascular complications.[25] Moreover, the United Kingdom's National Institute for Health and Care Excellence guidelines recommend that GLP-1 mimetic therapy should only be continued if the patient demonstrates an HbA1c reduction of at least 1.0% (10.9 mmol/mol).[9]

The importance of including hypoglycemia and weight gain criteria in a composite endpoint is emphasized by the 2018 ADA/EASD guidelines,[2] which promote early consideration of these factors, both of which are associated with reduced compliance.[26,27] In addition, hypoglycemia is unpleasant[28] and potentially life threatening,[29,30] and avoidance of weight gain – which is a frequent consequence of insulin therapy[3] – is important because of the positive relationship between bodyweight and magnitude of cardiovascular risk factors.[31] It could be argued that the weight change criterion (no net weight gain) is not of comparable import to the other endpoint components used in the 26-week analysis (achievement of HbA1c <7.0% [<53.0 mmol/mol], HbA1c reduction from baseline ≥1.0% [≥10.9 mmol/mol], no hypoglycemic events). However, even when the weight criterion was removed from the composite endpoint, leaving only the glycemic and hypoglycemic outcomes (Fig. 4), dulaglutide was associated with ORs vs. insulin glargine that were significantly >1 (OR [95% CI]: 2.28 [1.59–3.29] to 2.51 [1.64–3.84]). Moreover, in addition to the negative impact of bodyweight increase on compliance,[26,27] there is strong evidence that the relationship between bodyweight and risk of mortality is positive and continuous above a body mass index (BMI) of approximately 20–25 kg/m^2 in mixed populations[32–35] and 28–30 kg/m^2 in people with

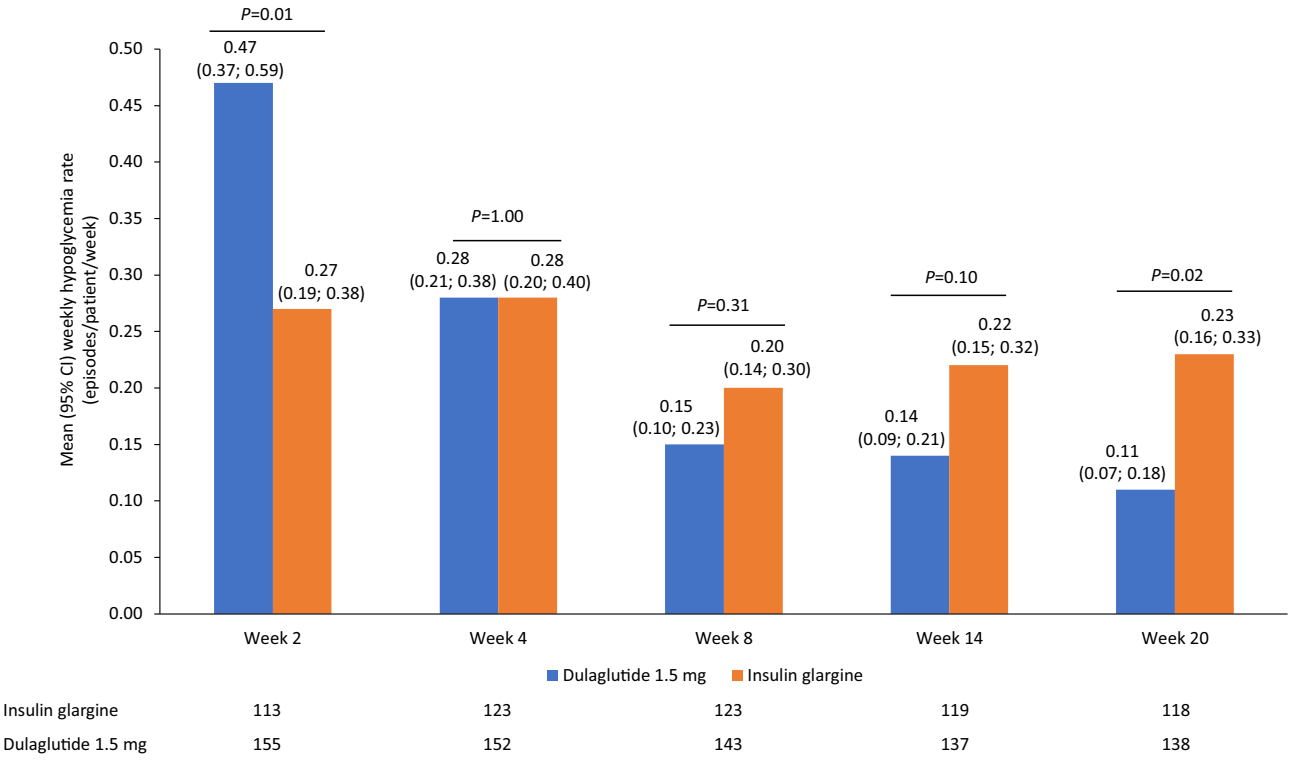

Fig. 3. Mean weekly hypoglycemia rate* in patients achieving fasting serum glucose <130 mg/dL (<7.2 mmol/L) at each visit (2 to 20 weeks). Numbers of patients achieving FSG <130 mg/dL (<7.2 mmol/L) at each week are shown below the graph. *Mean weekly hypoglycemia rate for week 2 calculated since treatment initiation; for other timepoints, calculated since the previous assessment; hypoglycemia defined as blood glucose ≤70 mg/dL (≤3.9 mmol/L) or severe hypoglycemia (hypoglycemic episode that required assistance from another person to actively administer therapy). One patient in each treatment arm experienced an episode of severe hypoglycemia during the first 20 weeks of treatment. CI, confidence interval.

T2DM.[35] Given that the mean BMI at baseline in AWARD-2 was approximately 31 kg/m^2,[1] it is likely that weight gain would be detrimental for the majority of AWARD-2 patients, particularly as they were receiving concomitant glimepiride.

The advantages of dulaglutide over insulin glargine that we have demonstrated in the current analyses suggest that dulaglutide fulfils many of the recommendations given by the most recent ADA/EASD consensus statement, including those relating to the early treatment period.

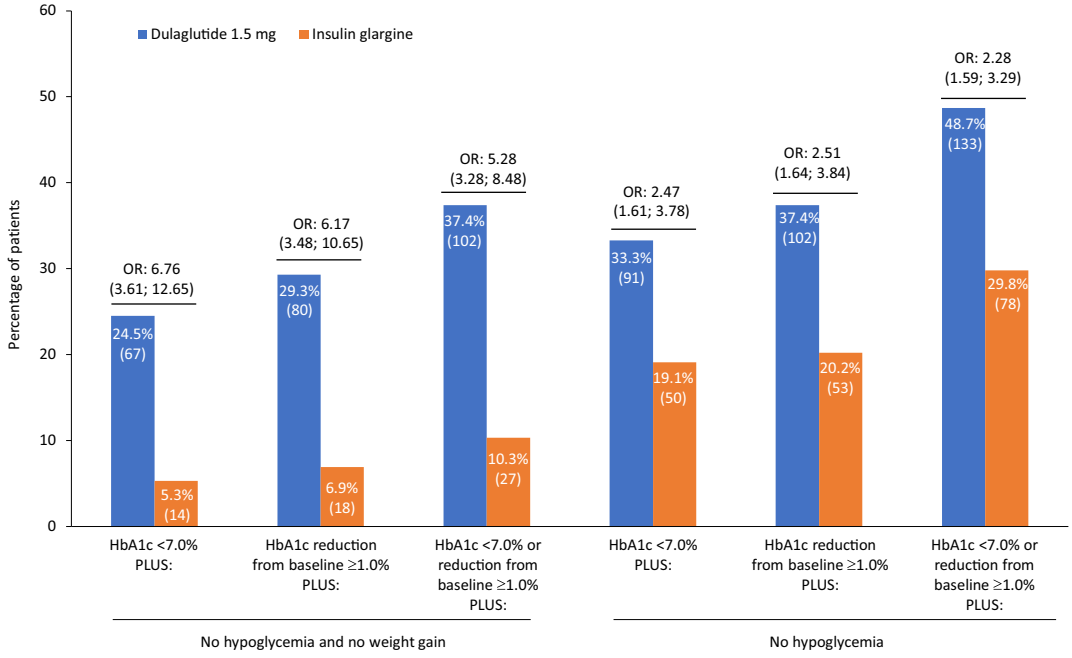

Fig. 4. Achievement of composite endpoints Endpoint components include: HbA1c <7.0% (<53.0 mmol/mol); HbA1c reduction from baseline ≥1.0% (≥10.9 mmol/mol); no hypoglycemic events*; no weight gain. Graph shows percentage (number) of patients and OR (95% CI) of probability of reaching various composite endpoints (dulaglutide vs. insulin glargine at 26 weeks) *Blood glucose ≤70 mg/dL (≤3.9 mmol/L) or severe hypoglycemia (hypoglycemic episode that required assistance from another person to actively administer therapy). Dulaglutide 1.5 mg, n = 273; insulin glargine, n = 262. CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

In this context, dulaglutide's rapid onset of antidiabetic action (Fig. 1) is advantageous, as this has been associated with greater antidiabetic effect in patients receiving this agent.[36] Moreover, an early response to GLP-1 RA therapy has been associated with significantly better adherence and a lower risk of discontinuation.[37] However, as recommended in the current dulaglutide SmPC and other recent publications,[19,38] a reduction in the dose of any concomitantly administered sulfonylurea should be considered at the time of dulaglutide initiation. This was not mandated in the AWARD-2 trial protocol, and in fact – in all treatment groups – the dose of glimepiride (followed by metformin) could be decreased or discontinued only in patients who experienced recurrent hypoglycemia.[1] Concomitant administration of dulaglutide 1.5 mg/week and maximally tolerated doses of a sulfonylurea may help to explain the disparity in the incidence of hypoglycemia between the two treatment groups at week 2 (Fig. 3), the only timepoint at which the mean weekly rate of hypoglycemic episodes was higher in dulaglutide-treated patients who achieved glycemic control than in insulin glargine-treated patients who achieved control (0.47 vs. 0.27 episodes/patient/week, respectively; $P = 0.01$). The study protocol mandated that patients should initiate dulaglutide therapy at 1.5 mg/week, without titration. In contrast, insulin glargine therapy was initiated at a low dose and then titrated per protocol. It should be noted that, by week 20, the rate of hypoglycemia was twofold higher in the insulin glargine group than in the dulaglutide group (0.23 vs. 0.11 episodes/patient/week; $P = 0.02$) and that this difference occurred in the context of a non-forced insulin glargine titration regimen.

At the 2-week timepoint, a considerably lower proportion of insulin glargine-treated patients had achieved the target FSG level. The low rate of glycemic control in this group is almost certainly related to the insulin glargine starting dose and non-forced titration algorithm employed. These were based on the insulin glargine prescribing information and the GOAL A1c trial weekly dose titration algorithm, respectively,[1,39] with no central oversight of insulin titration during the trial. It was not until week 20, when the mean insulin dose was 0.25 IU/kg, that the proportions of patients achieving the target FSG level were similar between treatments.

One limitation of this analysis is that the cohort of patients with FSG <130 mg/dL (<7.2 mmol/L) differed at each of weeks 2, 4, 8, 14, and 20. As a result, we cannot comment on the evolution of glycemic control in individual patients or determine how likely it is that a patient who achieves an early response to therapy will maintain glycemic control in the future. The post-hoc nature of the analysis represents a further limitation. However, the results of this investigation show that, in the study population as a whole, dulaglutide compares favorably with insulin glargine during the early treatment period in patients with T2DM. The first few weeks and months of a new antidiabetic treatment regimen represent a period of uncertainty for physician and patient, both of whom are trying to balance glycemic control and hypoglycemic risk. The likelihood of weight gain is also a concern for many patients. The composite endpoints used in this analysis – which encompassed glucose- and hypoglycemia-related endpoints, with or without a weight gain component – are therefore clinically relevant and directly applicable to clinical practice. The data presented demonstrate that, in addition to being safe and convenient, with no requirement for titration, once-weekly dulaglutide 1.5 mg is an efficacious treatment option, even in the short term, when compared with basal insulin in metformin + glimepiride-treated patients with T2DM who require improved glycemic control. The balanced clinical profile demonstrated by these results is apparent in the very early weeks of dulaglutide treatment and after 6 months of therapy.

CRediT authorship contribution statement

Irene Romera: Conceptualization, Methodology, Data curation, Writing - review & editing.**Ignacio Conget:**Conceptualization, Data curation, Writing - review & editing.**Luis Alberto Vazquez:** Conceptualization, Formal analysis, Data curation, Writing - original draft, Writing - review & editing.**Raffaella Gentilella:**Data curation, Writing - review & editing.**Jeremie Lebrec:**Data curation, Writing - original draft, Writing - review & editing.**Esteban Jódar:**Investigation, Data curation, Writing - review & editing,**Jesús Reviriego:**Conceptualization, Methodology, Data curation, Writing - review & editing.

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