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BRIEF REPORT

Insulin degludec/liraglutide (IDegLira) was effective across a range of dysglycaemia and body mass index categories in the DUAL V randomized trial

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This study assessed the efficacy of insulin degludec/liraglutide (IDegLira) vs insulin glargine U100 (IGlar) across categories of baseline glycated haemoglobin (HbA1c; ≤7.5%, >7.5% to ≤8.5% and >8.5%), body mass index (BMI; <30, ≥30 to <35 and ≥35 kg/m^2) and fasting plasma glucose (FPG; <7.2 and ≥7.2 mmol/L) in patients with type 2 diabetes (T2D) uncontrolled on basal insulin, using *post hoc* analyses of the DUAL V 26-week trial. With IDegLira, mean HbA1c was reduced across all baseline HbA1c (1.0%-2.5%), FPG (1.5%-1.9%) and BMI categories (1.8%-1.9%), with significantly greater reductions compared with IGlar U100. For all HbA1c, FPG and BMI categories, IDegLira resulted in weight loss and IGlar U100 in weight gain; hypoglycaemia rates were lower for IDegLira vs IGlar U100. More patients achieved HbA1c <7% with IDegLira than IGlar U100 across all HbA1c (59%-87% vs 31%-66%), FPG (71%-74% vs 40%-51%) and BMI categories (71%-73% vs 40%-54%). IDegLira improved glycaemic control and induced weight loss in patients with T2D previously uncontrolled on basal insulin, across the categories of baseline HbA1c, FPG or BMI that were tested.

KEYWORDS

body mass index, clinical trial, IDegLira, insulin therapy, type 2 diabetes

1 | INTRODUCTION

Because of the progressive nature of type 2 diabetes (T2D), achieving and maintaining glycaemic control and selecting the optimum therapy for an individual patient can be challenging.[1–3] Characteristics such as glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), and body mass index (BMI) are often taken into consideration when individualizing treatment; therefore, information on how specific therapies perform with regard to such characteristics is essential in order to individualize diabetes treatment options.

The DUAL clinical trial programme investigated the efficacy and safety of the fixed-ratio combination insulin degludec/liraglutide (IDegLira) in various T2D populations, including insulin-naïve participants uncontrolled on oral antidiabetic drugs (OADs; DUAL I, IV and VI),[4–7] on glucagon-like peptide-1 receptor agonists (GLP-1RAs) and OADs (DUAL III),[8] or on basal insulin and OADs (DUAL II and V).[9,10]

Post hoc analyses of DUAL I and II indicated that IDegLira was efficacious regardless of HbA1c or BMI at baseline.[5,11]

To help identify which patient populations would benefit most from IDegLira treatment, we report *post hoc* analyses of DUAL V, evaluating whether glycaemic control, weight and hypoglycaemia benefits associated with IDegLira were consistent across patient subgroups.

2 | MATERIALS AND METHODS

The detailed trial design and methods have been reported previously.[10] The trial was approved by institutional review boards, and was registered at clinicaltrials.gov (NCT01952145). DUAL V was a phase III, multinational, multicentre, randomized, 26-week clinical trial conducted in patients with T2D who were uncontrolled on IGlar U100 (20-50 units) in combination with metformin. A total of 557 patients were randomized 1:1 to either convert from IGlar U100 to IDegLira or continue uptitration of IGlar U100.[10] The IDegLira starting dose was 16 dose steps (16 units IDeg/0.6 mg liraglutide) and maximum dose was 50 dose steps (50 units IDeg/1.8 mg liraglutide). IGlar U100 treatment was started at pre-trial dose, with no maximum dose. Both treatments were dosed once daily and titrated to a FPG target of 4 to 5 mmol/L (to convert to mg/dL multiply by 18.02).[10]

For the present *post hoc* analyses, patients were grouped according to baseline HbA1c (≤7.5%, >7.5% to ≤8.5% and >8.5%), FPG (<7.2 and ≥7.2 mmol/L)[12] and BMI (<30, ≥30 to <35 and ≥35 kg/m^2).

The following endpoints were analysed for each category at end-of-trial (EOT): change in HbA1c; change in body weight; number of confirmed hypoglycaemic episodes during the trial; patients reaching the European Association for the Study of Diabetes/American Diabetes Association target of HbA1c <7%[12] and composite endpoints (HbA1c <7% without hypoglycaemia [in the last 12 weeks], and HbA1c <7% without hypoglycaemia [in the last 12 weeks] and without weight gain); and daily insulin dose. Confirmed hypoglycaemia was defined as plasma glucose <3.1 mmol/L or severe hypoglycaemia (unable to self-treat). Details of statisistical analyses are provided in Appendix S1.

3 | RESULTS

The distribution of patients across baseline HbA1c, BMI and FPG categories is shown in Table S1, Appendix S1.

3.1 | Efficacy of IDegLira by baseline HbA1c

With IDegLira, the mean EOT HbA1c for all baseline HbA1c categories was <7% (Figure 1A), with greater HbA1c reductions achieved with increasing baseline HbA1c. IDegLira resulted in significantly greater HbA1c reductions than IGlar U100 across all baseline HbA1c categories (Figure 1A; $P < .0001$ for all categories). The estimated treatment difference (ETD) between baseline categories was not significantly different (interaction analysis, $P = .6406$), indicating a similar benefit of IDegLira vs IGlar U100 across categories.

For all baseline HbA1c categories, IDegLira was associated with a mean weight loss and IGlar U100 with a mean weight gain (Figure 1B), with an increasing weight difference with higher baseline HbA1c (interaction analyses $P < .0001$).

Confirmed hypoglycaemia rates were lower for IDegLira (1.5-3.1 episodes/per patient-year exposure [PYE]) compared with IGlar U100 (2.7-6.2 episodes/PYE) for all baseline HbA1c categories (Figure S1A, Appendix S1).

In addition, a greater proportion of patients treated with IDegLira vs IGlar U100 achieved HbA1c <7%, HbA1c <7% without hypoglycaemia, and HbA1c <7% without hypoglycaemia and no weight gain (Figure 2A). The odds ratios (OR) for all composite endpoints were similar across baseline HbA1c categories, indicating a similar beneficial effect of IDegLira vs IGlar U100 (results of interaction analyses, $P = .8841$, $P = .6587$ and $P = .2784$ for HbA1c <7%, HbA1c <7% without hypoglycaemia, and HbA1c <7% without hypoglycaemia and no weight gain, respectively).

The mean daily EOT insulin dose was similar for IDegLira (40-42 units) for all baseline HbA1c categories and significantly lower than IGlar U100 (60-73 units; Figure S1B, Appendix S1). Across baseline HbA1c categories, a similar proportion of patients reached the maximum IDegLira dose of 50 units after 26 weeks: HbA1c >7.5%, 42.9%; HbA1c >7.5% to ≤8.5%, 44.3%.

3.2 | Efficacy of IDegLira by baseline FPG

IDegLira treatment resulted in similar, significantly greater, HbA1c reductions for both baseline FPG categories than for IGlar U100 (Figure 1C, both $P < .0001$; results of interaction analysis, $P = .1764$).

IDegLira was associated with weight loss and IGlar U100 with weight gain for both baseline FPG categories (Figure 1D), with a similar ETD for both categories (results of interaction analysis, $P = .5257$).

Hypoglycaemia rates were numerically lower for IDegLira vs IGlar U100 for both baseline FPG categories, but this difference was only significant ($P < .0001$) for baseline FPG ≥7.2 mmol/L (Figure S2A, Appendix S1).

In both FPG categories, more IDegLira-treated patients than IGlar U100-treated patients achieved HbA1c <7%, HbA1c <7% without hypoglycaemia, and HbA1c <7% without hypoglycaemia and no weight gain (Figure 2B).

At EOT, the mean daily insulin dose was significantly greater ($P < .0001$) for IGlar U100 (55-72 units) vs IDegLira (38-42 units) for both baseline FPG categories (Figure S2B, Appendix S1).

3.3 | Efficacy of IDegLira by baseline BMI

Similar HbA1c reductions were observed with IDegLira across baseline BMI categories (all to <7%), and all were significantly greater vs IGlar U100 (Figure 1E). The interaction analysis indicated a similar beneficial effect of IDegLira vs IGlar U100 across BMI categories ($P = .7873$).

For all baseline BMI categories, IDegLira was associated with weight loss and IGlar U100 with weight gain (Figure 1F), with similar ETDs across categories (results of interaction analyses $P = .5350$).

The rates of hypoglycaemia with IDegLira were low for baseline BMI categories (1.5-3.2 episodes/PYE) and were consistently lower vs IGlar U100 (Figure S3A, Appendix S1). The highest hypoglycaemia rate was seen in patients with a BMI <30 kg/m^2.

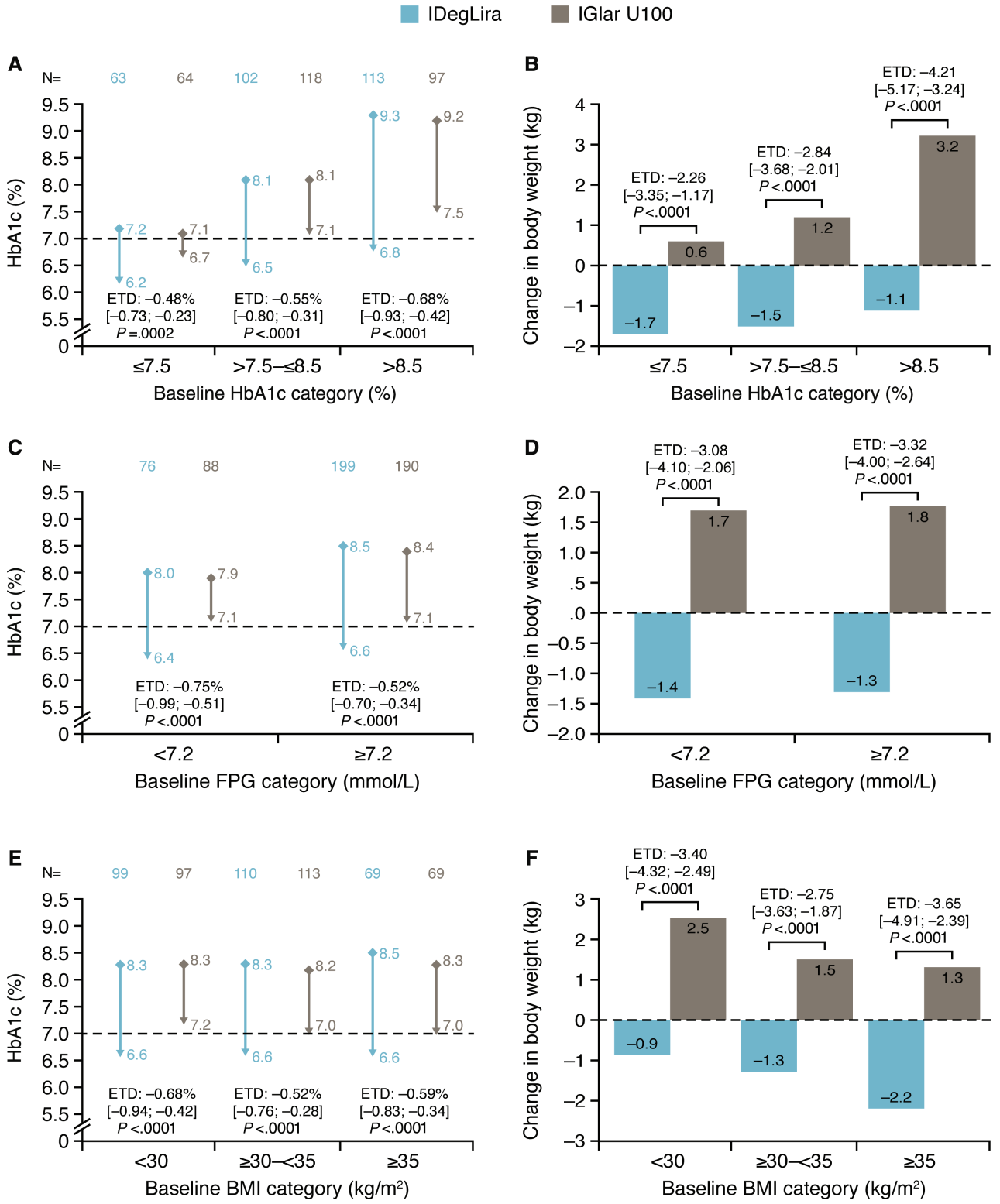

FIGURE 1 Change in HbA1c and body weight with IDegLira across categories of baseline HbA1c (A and B), FPG (C and D) and BMI (E and F). Data based on the full analysis set, with missing data imputed by last observation carried forward. Data are mean values with ETD (95% confidence interval) based on analysis of covariance. For (A), (C) and (E) dotted line represents American Diabetes Association HbA1c target <7.0%

For each baseline BMI category, the proportion of patients achieving responder and composite endpoints was greater with IDegLira vs IGlar U100 (Figure 2C); the difference in ORs was significant ($P < .01$) for all comparisons except the composite of HbA1c <7% without hypoglycaemia in the baseline BMI ≥35 kg/m^2 category ($P = .0509$). For HbA1c <7%, HbA1c <7% without hypoglycaemia, and HbA1c <7% without hypoglycaemia and no weight gain, the OR was similar (results of interaction analyses, $P = .6776$, $P = .2195$ and $P = .7346$, respectively), indicating a similar effect of IDegLira vs IGlar U100 across all baseline BMI categories.

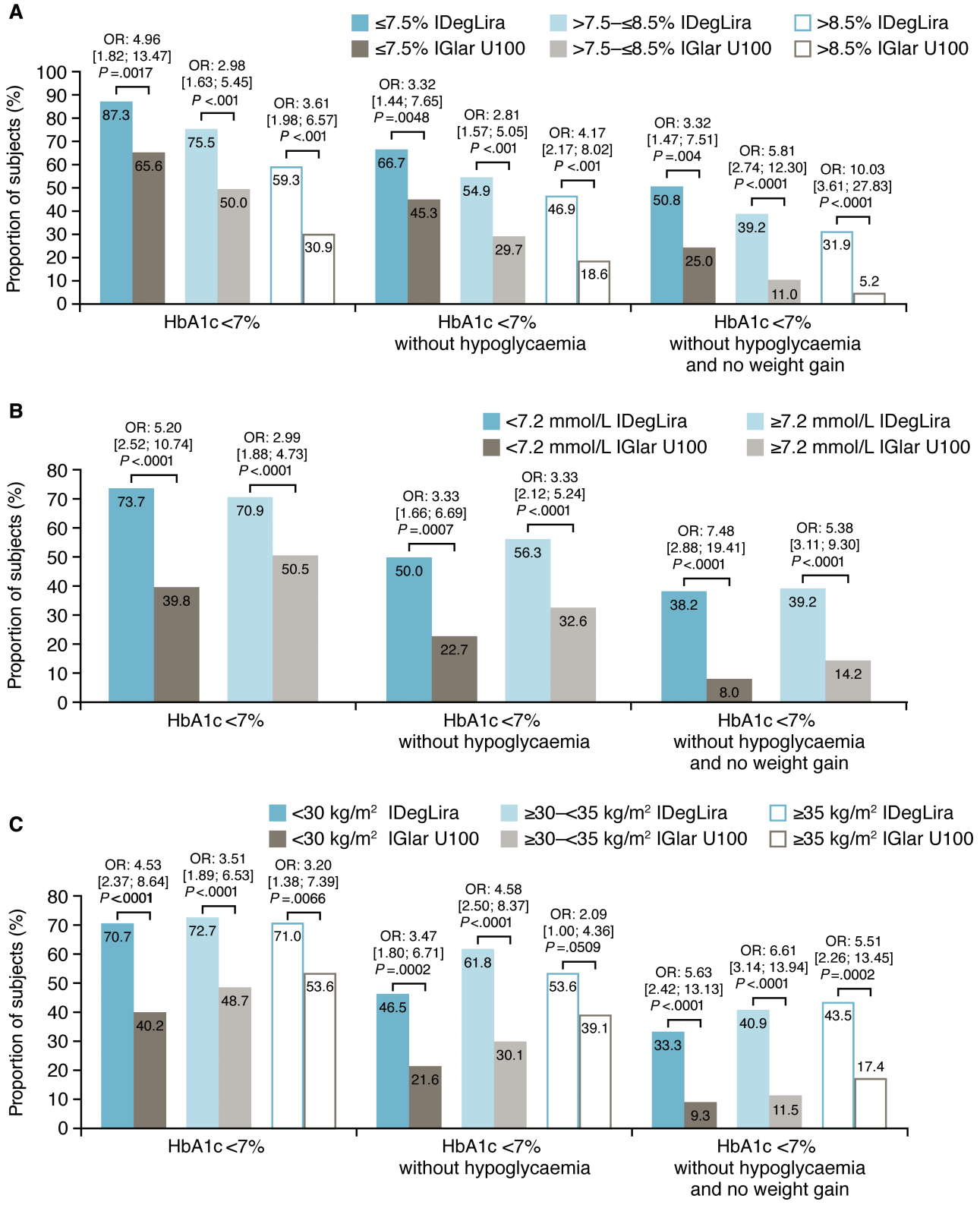

FIGURE 2 HbA1c responders with IDegLira vs IGlar U100 in patients stratified according to baseline A, HbA1c; B, FPG and C, BMI. Data are percentage of patients reaching HbA1c target <7% and composite endpoints at EOT, based on the full analysis set with missing data imputed by last observation carried forward. Hypoglycaemic events defined as patient unable to self-treat and/or plasma glucose <3.1 mmol/L occurring during the last 12 weeks of treatment

The EOT IDegLira dose ranged from 37 to 45 dose steps, with a higher proportion of patients in the higher baseline BMI categories reaching the maximum dose of 50 dose steps after 26 weeks: <30 kg/m^2, 25.3%; ≥30 to <35 kg/m^2, 41.8%; ≥35 kg/m^2, 62.3%. Daily insulin dose was significantly higher (P < .0001) for IGlar U100 (56-73 units) vs IDegLira for all baseline BMI categories (Figure S3B, Appendix S1).

4 | DISCUSSION

The DUAL V study showed that IDegLira is an efficacious alternative to uptitration of IGlar U100, providing glycaemic control with a low rate of hypoglycaemia and without weight gain.[10] These *post hoc* analyses further demonstrate the applicability of IDegLira in different patient populations according to baseline HbA1c, FPG and BMI, helping predict the treatment response for patients in clinical practice and highlighting the efficacy and safety of IDegLira in patients at higher risk.

IDegLira effectively reduced HbA1c to similar levels for all baseline HbA1c categories, with greater overall reductions in HbA1c for patients with higher HbA1c levels at baseline. Interestingly, the daily insulin dose at EOT was similar for IDegLira across all baseline HbA1c categories (40-42 units), but increased according to baseline HbA1c for IGlar U100 (60-73 units). A similar trend was also observed in analyses by baseline FPG, suggesting that in patients with T2D uncontrolled on basal insulin, it may be more appropriate to use a therapy that addresses postprandial glucose, and/or suppresses glucagon, than continuing to increase basal insulin dose.[13] These results also underline the complementary effects of using the combination product IDegLira, even in patients with high HbA1c and FPG.

Across baseline BMI categories, IDegLira resulted in similar HbA1c reductions, all resulting in an EOT HbA1c of 6.6%. This consistent benefit of IDegLira contrasts with, and could potentially challenge, some clinical guidelines that suggest the benefits of GLP-1RAs are only realized in patients with a BMI ≥35 kg/m^2 or significant obesity-related comorbidities.[14]

The proportion of patients achieving HbA1c levels <7% and the composite endpoints was consistently higher for IDegLira vs IGlar U100 across all baseline HbA1c, FPG and BMI categories. As expected, the proportion of responders decreased with both treatments, with increasing baseline HbA1c; this pattern was not evident for the analyses of FPG and BMI. The proportion of patients achieving HbA1c <7% without hypoglycaemia and with no weight gain increased with baseline BMI for both IDegLira and IGlar U100, although the proportions achieving the target was significantly higher with IDegLira vs IGlar U100, possibly resulting from increased insulin resistance with increasing BMI. Additionally, mean daily insulin dose for the ≥30 to <35 and ≥35 kg/m^2 baseline categories increased from baseline >2-fold by EOT, suggesting that, while some patients with a high BMI can achieve major improvements in HbA1c with large increases in daily dose of basal insulin, this may come at the cost of further weight gain and hypoglycaemia, which could be mitigated by switching patients to IDegLira.

Hypoglycaemia rates were higher for both IDegLira and IGlar U100 for the lowest baseline BMI category; however, hypoglycaemia rates were inversely proportional to BMI category with IGlar U100, a trend not seen with IDegLira. An explanation for this could be that patients with lower BMI tend to be more insulin sensitive and, therefore, may be more vulnerable to insulin-induced hypoglycaemia.[15]

The interpretation of our analysis is limited by its *post hoc* nature and by the fact that patients with a very high HbA1c level (>10%) or BMI (>40 kg/m^2) were excluded from the trial. Nevertheless, the data are from a well-conducted randomized controlled trial, with a large cohort of participants and large numbers of participants in most categories, allowing a meaningful analysis.

In conclusion, in the present study, IDegLira was efficacious across the categories of baseline HbA1c, FPG or BMI tested, confirming the findings of previous studies in patients with T2D uncontrolled on OADs or basal insulin with or without OADs.[11] These results show that IDegLira treatment provides better glycaemic control, together with weight loss and lower proportions of patients experiencing hypoglycaemia, compared with basal insulin uptitration.

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Conflict of interest

I. L. has received research funding form Novo Nordisk, Pfizer, Merck, Novartis, GI Dynamics and has received publication support and/or other in-kind services from Novo Nordisk, Boheringer Ingelheimer, Astra Zeneca and Sanofi. S. H. has received research support from Novo Nordisk, Sanofi, Merck, Abbott, Janssen and AstraZeneca, has served on an advisory panel for Novo Nordisk, Sanofi, Merck, AstraZeneca, Lilly/BI, Amgen, Abbott and Janssen, has served as a consultant for Novo Nordisk, Sanofi, Merck, Abbott, Janssen and AstraZeneca, and/or other in-kind services for CIHR, CDA, and The Lawson Foundation. E. J. has served on advisory panels and/or speaker bureaus for Novo Nordisk, Lilly, AstraZeneca, Boehringer, MSD, Janssen, Roche and Novartis, is a board member for Novo Nordisk and Lilly, and has received research support from Novo Nordisk, Novartis, Gilead, Roche, Miltenyi Biotech, Biotest, Wacker Chemie, Fresenius, DFG, BMBF, EU, JDRF and VW-Stiftung. K. C. is a Novo Nordisk employee. M. F. R. is a Novo Nordisk employee and shareholder. E. J. has received consultant fees from Amgen, AstraZeneca, Lilly, MSD and Novo Nordisk, has been a clinical investigator for AstraZeneca, Boehringer, GSK, Janssen, Lilly, MSD, Novo Nordisk and Pfizer, and has served on speaker bureaus for AstraZeneca, GSK, Lilly, MSD and Novo Nordisk.

Author contributions

I. L., S. H., E. J. and E. J. were investigators on the DUAL V trial. All authors confirm that they meet the International Committee of Medical Journal Editors requirements for authorship and that they have contributed to the critical analysis and interpretation of the data, drafting/critically revising the manuscript and share in the final responsibility for the content of the manuscript and the decision to submit it for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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