

Efficacy and safety of the fixed-ratio combination of insulin degludec and liraglutide by baseline glycated hemoglobin, body mass index and age in Japanese individuals with type 2 diabetes: A subgroup analysis of two phase III trials

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Keywords

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ABSTRACT

Aims/Introduction: To assess efficacy and safety of insulin degludec/liraglutide (IDegLira) in Japanese participants with type 2 diabetes across different baseline characteristics.

Materials and Methods: Data from two randomized controlled trials were used: DUAL I Japan ($n = 819$ insulin-naïve participants) and DUAL II Japan ($n = 210$ insulin-experienced participants). Outcomes were assessed according to baseline glycated hemoglobin (HbA_{1c} : $<8.0\%$, ≥ 8.0 – $<9.0\%$, $\geq 9.0\%$), body mass index (<25 , ≥ 25 – <30 , ≥ 30 kg/m²) and age (<65 , ≥ 65 years).

Results: In DUAL I Japan, reductions in HbA_{1c} with IDegLira versus degludec and liraglutide were observed across all subgroups (treatment differences: -0.48% to -0.72% vs degludec, -0.29% to -0.73% vs liraglutide). Results were similar with IDegLira versus degludec in DUAL II Japan (treatment differences: -0.82% to -1.61%). Treatment-by-subgroup interactions were significant for IDegLira versus liraglutide for baseline HbA_{1c} and age in DUAL I Japan, and for IDegLira versus degludec for baseline HbA_{1c} in DUAL II Japan. In DUAL I Japan, IDegLira was associated with less weight gain than degludec in most subgroups. In DUAL II Japan, IDegLira was associated with a small mean weight loss (except for baseline $HbA_{1c} \geq 9.0\%$) versus a small gain for degludec (except for age ≥ 65 years subgroup); treatment-by-subgroup interactions were not significant. Total daily insulin dose was lower with IDegLira versus degludec across all categories, except for age >65 years in DUAL II Japan.

Conclusions: IDegLira reduced HbA_{1c} in Japanese participants with type 2 diabetes across baseline HbA_{1c} , body mass index and age categories, without unexpected safety issues.

INTRODUCTION

Insulin degludec/liraglutide (IDegLira) is a soluble fixed-ratio combination of insulin degludec (degludec) and the glucagon-

like peptide-1 receptor agonist, liraglutide¹. The global DUAL clinical trial program investigated the efficacy and safety of IDegLira across a range of patient populations with type 2 diabetes^{2–9}. Following this trial program, two randomized trials, DUAL I Japan and DUAL II Japan, investigated the use of IDegLira in Japanese participants with type 2 diabetes

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uncontrolled on previous diabetes treatment with an oral antidiabetic drug or basal or pre-mix insulin, respectively^{10,11}.

In DUAL I Japan, IDegLira was associated with significantly greater glycated hemoglobin (HbA_{1c}) reductions versus liraglutide 1.8 mg and degludec after 52 weeks (both $P < 0.0001$)¹⁰. Bodyweight increased to a lesser extent with IDegLira versus degludec, but, as expected, there was a significant difference in favor of liraglutide versus IDegLira. The rate of severe or blood glucose (BG)-confirmed hypoglycemia (<3.1 mmol/L [<56 mg/dL]) for IDegLira was lower compared with degludec, but higher compared with liraglutide¹⁰. Gastrointestinal adverse events (AEs) were reported by 34.9%, 22.9% and 41.8% of participants in the IDegLira, degludec and liraglutide groups, respectively¹⁰. In DUAL II Japan, IDegLira provided superior reduction from baseline in HbA_{1c} after 26 weeks versus degludec ($P < 0.0001$)¹¹. IDegLira was associated with bodyweight loss compared with weight gain for degludec, and the rates of severe or BG-confirmed hypoglycemia were comparable between treatment groups¹¹.

Disease progression and clinical characteristics, such as HbA_{1c}, body mass index (BMI) and age, are often considered when individualizing diabetes treatment options. Elderly patients represent a unique group due to increased risk of hypoglycemia and frailty, and therefore careful consideration is required when setting glycemic targets and choosing treatments¹². The Japan Diabetes Society/Japan Geriatrics Society recommend specific glycemic targets in elderly patients depending on various characteristics¹³. Hence, it is important to investigate the results of DUAL I Japan and DUAL II Japan regarding these characteristics to inform physicians which patients might benefit most from IDegLira treatment.

We report subgroup analyses of DUAL I Japan and DUAL II Japan investigating the efficacy and safety of IDegLira in patients grouped according to trial baseline characteristics (HbA_{1c}, BMI and age).

MATERIALS AND METHODS

For the present subgroup analyses of DUAL I Japan and DUAL II Japan (further details in Supporting Information)^{10,11}, patients were grouped according to baseline HbA_{1c} ($<8.0\%$, ≥ 8.0 – $<9.0\%$, $\geq 9.0\%$), BMI (<25 , ≥ 25 – <30 , ≥ 30 kg/m²) and age (non-elderly [<65 years] and elderly [≥ 65 years]). Baseline HbA_{1c} cut-offs were chosen to ensure a similar number of patients in each HbA_{1c} subgroup. The obesity and age cut-offs aligned with the BMI/age categories, as defined by the Japan Society for the Study of Obesity and the Japan Diabetes Society/Japan Geriatrics Society, respectively^{13,14}.

Statistical analysis

In the subgroup analyses, changes in HbA_{1c} and bodyweight, end-of-trial (EOT) total daily insulin dose, and confirmed hypoglycemia rates were assessed for each study across baseline HbA_{1c}, BMI and age categories using the cut-offs described above. Analyses of all end-points assessed across baseline HbA_{1c}

categories were post-hoc, as were the analyses of change in bodyweight and total insulin dose by baseline BMI, and total insulin dose by age.

Changes from baseline in HbA_{1c} and bodyweight, and EOT total daily insulin dose were analyzed using an analysis of covariance (ANCOVA) model, which included treatment, pre-trial diabetes treatment, subgroup (baseline HbA_{1c}, BMI or age), and interaction between treatment and subgroup as fixed factors. For analysis of change in HbA_{1c} and bodyweight, corresponding baseline value was included as a covariate. For analysis of total daily insulin dose, baseline HbA_{1c} (both trials) and baseline insulin dose (DUAL II Japan only) were included as covariate(s). In each case, missing data were imputed using last observation carried forward.

From the model, treatment differences with 95% confidence intervals were estimated for each subgroup, and the treatment-by-subgroup interaction was tested to assess if the treatment effect was affected by the subgroups. The number of severe or BG-confirmed hypoglycemia and AEs (including gastrointestinal AEs) are presented descriptively by treatment and subgroup.

RESULTS

All 819 participants from DUAL I Japan were included in the analysis. From DUAL II Japan, all 210 participants were included in the analysis.

Participant distribution across baseline HbA_{1c}, baseline BMI and age categories is shown in Table 1 and discussed in the Supporting Information.

The overall results for the subgroup analyses on change in HbA_{1c}, change in bodyweight and EOT insulin dose are summarized in Table S1 and presented in more detail below.

Change in HbA_{1c}

Estimated treatment differences

Based on the 95% confidence intervals of the estimated treatment differences (ETDs), IDegLira was associated with greater improvements in HbA_{1c} versus both degludec and liraglutide across all participant subgroups (baseline HbA_{1c}, baseline BMI and age) in both DUAL I Japan and DUAL II Japan (Figure 1). In DUAL I Japan, the ETD ranged from -0.48% to -0.72% for IDegLira versus degludec, and from -0.29% to -0.73% for IDegLira versus liraglutide. In DUAL II Japan, the ETDs were similar with IDegLira versus degludec, ranging from -0.82% to -1.61% .

Treatment interaction

In DUAL I Japan, although the magnitude of the ETD in HbA_{1c} between IDegLira and degludec increased with increasing baseline HbA_{1c}, the treatment-by-subgroup interaction was not significant ($P = 0.4432$). In contrast, the interaction for IDegLira versus liraglutide was significant ($P = 0.0194$), showing that IDegLira was more effective than liraglutide for change in HbA_{1c} with increasing baseline HbA_{1c}.

Table 1 | Number of participants in each baseline characteristic category

	IDegLira	Degludec	Liraglutide 1.8 mg
DUAL I Japan (total)	275	271	273
Baseline HbA _{1c} , <i>n</i> (%)			
<8.0%	107 (39)	105 (39)	128 (47)
≥8.0 to <9.0%	80 (29)	70 (26)	71 (26)
≥9.0%	88 (32)	96 (35)	74 (27)
Baseline BMI, <i>n</i> (%)			
<25 kg/m ²	122 (44)	117 (43)	118 (43)
≥25 to <30 kg/m ²	112 (41)	107 (39)	109 (40)
≥30 kg/m ²	41 (15)	47 (17)	46 (17)
Age, <i>n</i> (%)			
<65 years	197 (72)	183 (68)	202 (74)
≥65 years	78 (28)	88 (32)	71 (26)
DUAL II Japan (total)	105	105	
Baseline HbA _{1c} , <i>n</i> (%)			
<8.0%	29 (28)	27 (26)	
≥8.0 to <9.0%	40 (38)	46 (44)	
≥9.0%	36 (34)	32 (30)	
Baseline BMI, <i>n</i> (%)			
<25 kg/m ²	26 (25)	28 (27)	
≥25 to <30 kg/m ²	64 (61)	53 (50)	
≥30 kg/m ²	15 (14)	24 (23)	
Age, <i>n</i> (%)			
<65 years	75 (71)	85 (81)	
≥65 years	30 (29)	20 (19)	

BMI, body mass index; HbA_{1c}, glycated hemoglobin; IDegLira, insulin degludec/liraglutide; *n*, number of participants.

In DUAL II Japan, the treatment-by-subgroup interaction according to baseline HbA_{1c} was statistically significant for IDegLira versus degludec ($P = 0.0312$), again indicating that IDegLira was more effective than degludec for change in HbA_{1c} with increasing baseline HbA_{1c}.

The treatment-by-subgroup interaction for change in HbA_{1c} according to baseline BMI was not significant ($P > 0.05$; Table S1 a and b) for IDegLira versus liraglutide (DUAL I Japan) or IDegLira versus degludec (DUAL I Japan and DUAL II Japan).

The treatment-by-subgroup interaction for change in HbA_{1c} according to age was significant ($P = 0.0481$) for IDegLira versus liraglutide (DUAL I Japan), indicating that IDegLira was more effective than liraglutide in participants aged <65 years. It was not significant for IDegLira versus degludec in either trial.

CHANGE IN BODYWEIGHT

Estimated treatment differences

In DUAL I Japan, IDegLira was associated with less weight gain than degludec regardless of baseline HbA_{1c}, baseline BMI or age (Figure 2). The ETD ranged from −0.24 kg to −1.47 kg for IDegLira versus degludec, and from +3.34 kg to +4.83 kg for IDegLira versus liraglutide. In liraglutide-treated patients, there was an overall decrease in bodyweight in all subgroups,

compared with an increase in those treated with IDegLira; ETDs favored liraglutide across all subgroups (Figure 2).

In DUAL II Japan, IDegLira treatment was associated with bodyweight loss in participants with baseline HbA_{1c} <8.0%, baseline HbA_{1c} ≥8.0 to <9.0%, baseline BMI ≥25 to <30 kg/m² and age <65 years, versus weight gain for degludec-treated participants; in all of these subgroups, there was an overall decrease in bodyweight in IDegLira-treated patients, compared with an overall increase in those treated with degludec (Figure 2). There was a greater weight loss associated with IDegLira treatment in the participants aged ≥65 years versus those aged <65 years (Figure 2). The magnitude of the ETDs ranged from −0.06 to −2.29 kg for IDegLira versus degludec.

Treatment interaction

The treatment-by-subgroup interaction for change in bodyweight was not statistically significant ($P > 0.05$; Table S1) for any of the analyses in DUAL I Japan or DUAL II Japan.

EOT INSULIN DOSE

Estimated treatment differences

In DUAL I Japan, the EOT daily total insulin dose was numerically lower for IDegLira versus degludec across all participant subgroups (baseline HbA_{1c}, baseline BMI and age; Figure 3). The magnitude of the ETDs ranged from −4.39 U to −17.62 U.

In DUAL II Japan, the EOT daily total insulin dose was lower for IDegLira versus degludec regardless of baseline HbA_{1c} or baseline BMI; however, it was lower in participants aged <65 years and greater in those aged ≥65 years (Figure 3). The magnitude of the ETDs across participant subgroups (baseline HbA_{1c}, baseline BMI and age) ranged from −4.24 U to +3.17 U.

Treatment interaction

In DUAL I Japan, the treatment-by-subgroup interaction for insulin dose was not statistically significant for baseline HbA_{1c} or age, but was statistically significant for baseline BMI (IDegLira vs degludec; $P = 0.0190$; Figure 3c; Table S1e). In DUAL II Japan, the interaction was not statistically significant for baseline HbA_{1c} or baseline BMI, but was statistically significant for age ($P = 0.037$; Figure 3f; Table S1f).

Hypoglycemia

In DUAL I Japan, the rates of severe or BG-confirmed hypoglycemia were lower with IDegLira versus degludec across all subgroups (Table S2a). In DUAL II Japan, the rate was lower with IDegLira versus degludec for the baseline HbA_{1c} <8.0% and ≥8.0 to <9.0% subgroups, but higher than IDegLira versus degludec for the baseline HbA_{1c} ≥9.0% subgroup (Table S2b). In DUAL II Japan, the rate was lower with IDegLira versus degludec for the baseline BMI ≥25 to <30 kg/m² subgroup, but higher with IDegLira versus degludec in the baseline BMI <25 kg/m² subgroup (Table S2b). Compared with degludec, hypoglycemia rates for IDegLira were higher in non-elderly participants and lower in elderly participants.

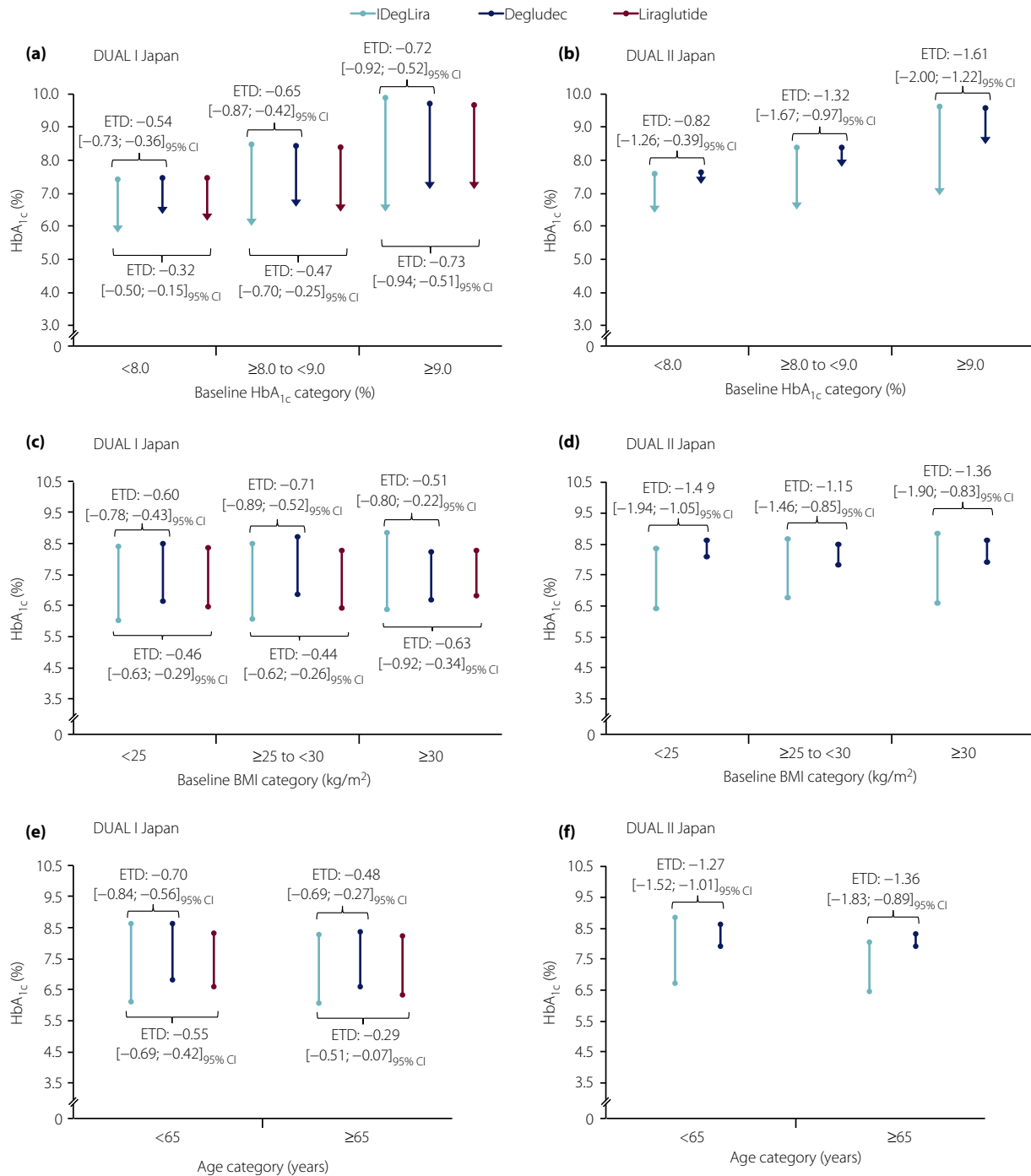


Figure 1 | Change in glycated hemoglobin (HbA_{1c}) with insulin degludec/liraglutide (IDegLira), degludec and liraglutide according to (a,b) baseline glycated hemoglobin (HbA_{1c}), (c,d) baseline body mass index (BMI) and (e,f) age in DUAL I Japan and DUAL II Japan. Points represent the observed mean HbA_{1c} at baseline and the arrows represent the observed mean HbA_{1c} at end-of-trial. Changes from baseline in HbA_{1c} were analyzed using an analysis of covariance (ANCOVA) model, which included treatment, pre-trial diabetes treatment, subgroup (baseline HbA_{1c}, BMI or age), and interaction between treatment and subgroup as fixed factors. For analysis of change in HbA_{1c}, baseline HbA_{1c} was included as a covariate. Missing data were imputed using last observation carried forward. From the model, treatment differences with 95% confidence intervals (95% CI) were estimated for each subgroup, and the treatment-by-subgroup interaction was tested to assess if the treatment effect was affected by the subgroups. ETD, estimated treatment difference.

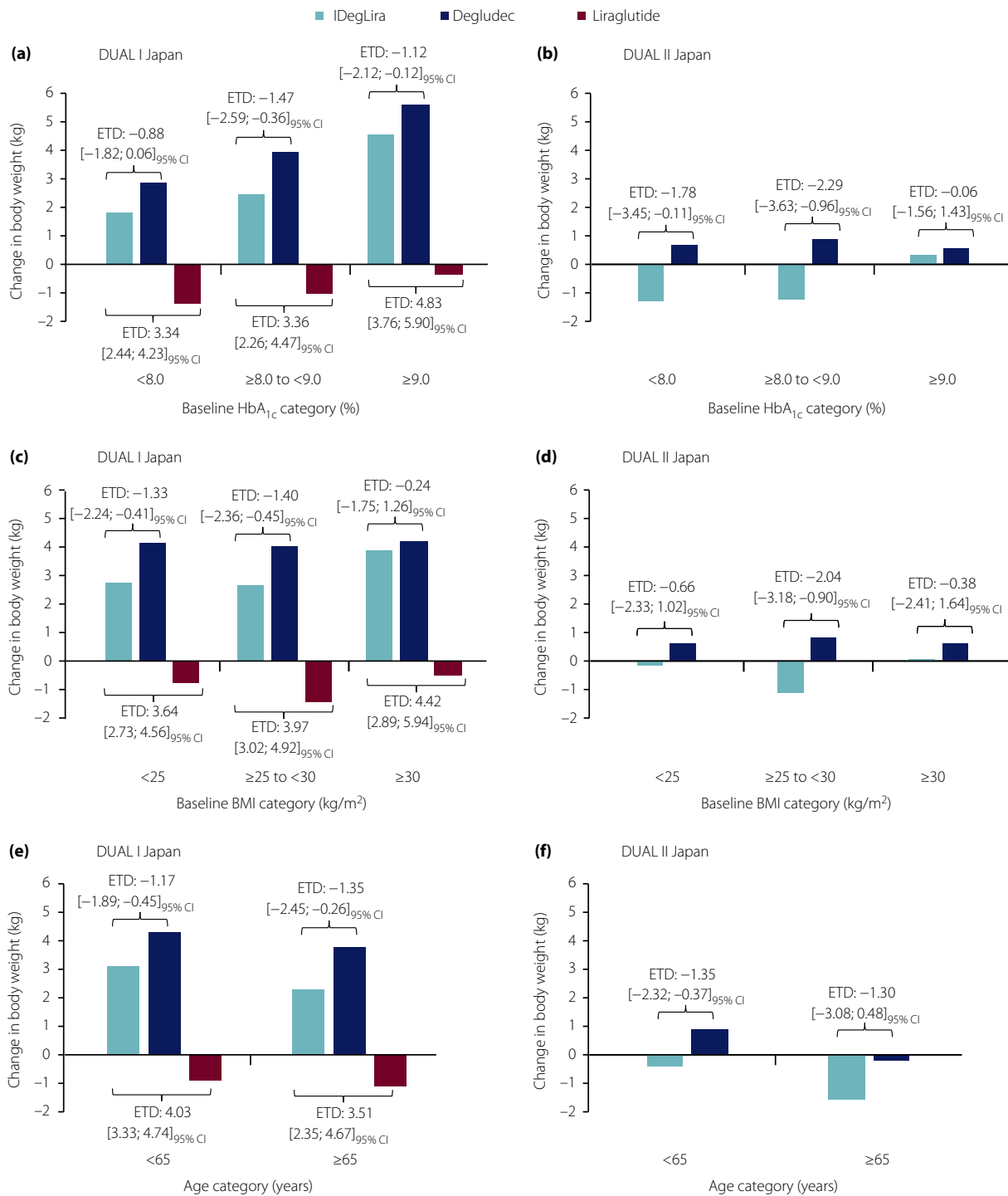


Figure 2 | Change in bodyweight with insulin degludec/liraglutide (IDegLira), degludec and liraglutide according to (a,b) baseline glycated hemoglobin (HbA_{1c}), (c,d) baseline body mass index (BMI) and (e,f) age in DUAL I Japan and DUAL II Japan. Bars represent the observed mean change from baseline to end-of-trial (EOT) in bodyweight. Changes from baseline in bodyweight were analyzed using an analysis of covariance (ANCOVA) model, which included treatment, pre-trial diabetes treatment, subgroup (baseline HbA_{1c}, BMI or age), and interaction between treatment and subgroup as fixed factors. For analysis of change in bodyweight, baseline bodyweight was included as a covariate. Missing data were imputed using last observation carried forward. From the model, treatment differences with 95% confidence intervals (95% CI) were estimated for each subgroup, and the treatment-by-subgroup interaction was tested to assess if the treatment effect was affected by the subgroups. ETD, estimated treatment difference.

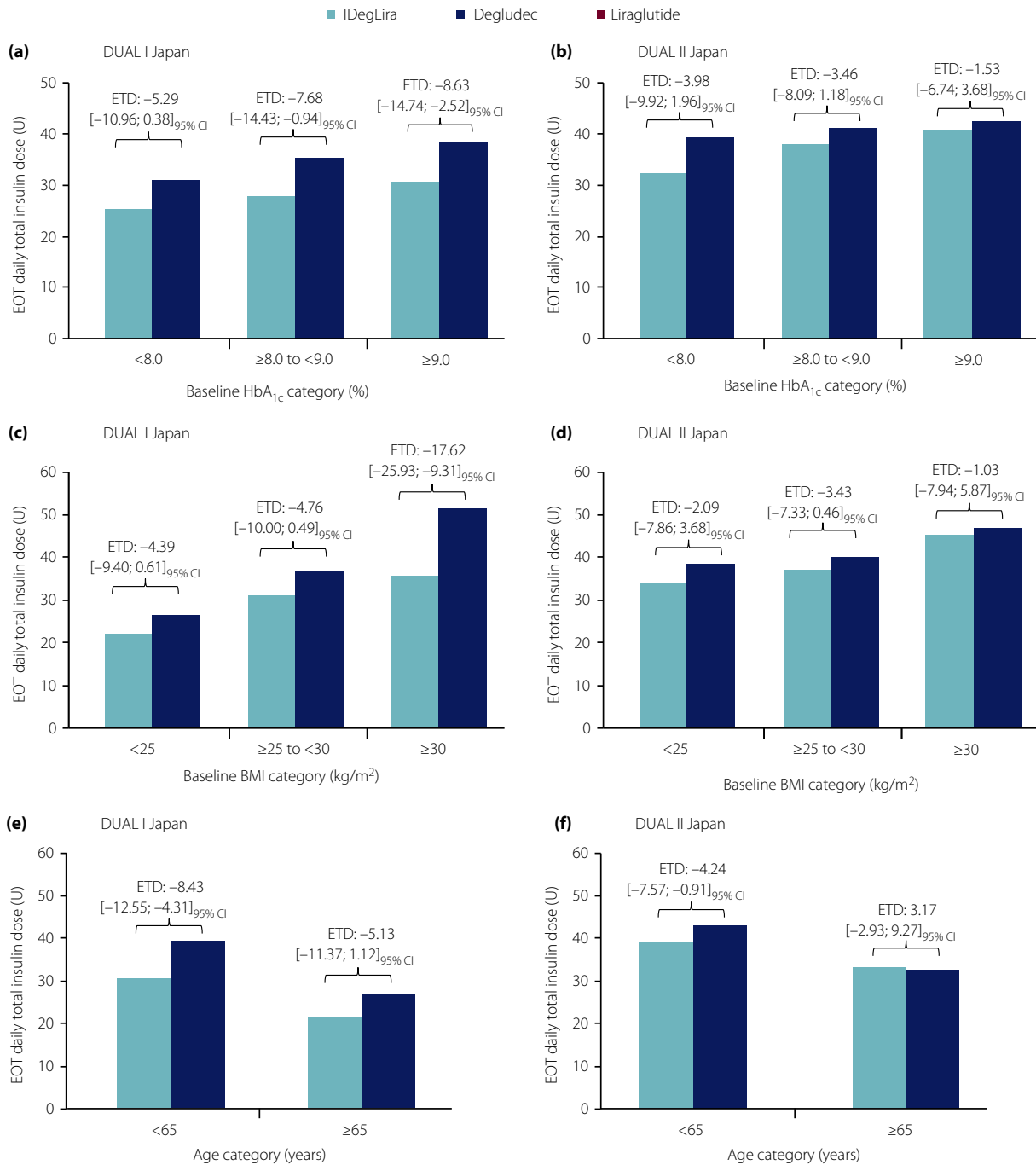


Figure 3 | End-of-trial (EOT) daily total insulin dose in insulin degludec/liraglutide (IDegLira)- and degludec-treated participants according to (a,b) baseline glycated hemoglobin (HbA_{1c}), (c,d) baseline body mass index (BMI) and (e,f) age in DUAL I Japan and DUAL II Japan. Bars represent the observed mean EOT daily total insulin dose. EOT total daily insulin dose was analyzed using an analysis of covariance (ANCOVA) model, which included treatment, pre-trial diabetes treatment, subgroup (baseline HbA_{1c}, BMI or age), and interaction between treatment and subgroup as fixed factors. Baseline HbA_{1c} (both trials) and baseline insulin dose (DUAL II Japan only) were included as covariate(s). Missing data were imputed using last observation carried forward. From the model, treatment differences with 95% confidence intervals (95% CI) were estimated for each subgroup, and the treatment-by-subgroup interaction was tested to assess if the treatment effect was affected by the subgroups. ETD, estimated treatment difference.

As expected, rates of severe or BG-confirmed hypoglycemia were higher with IDegLira and degludec versus liraglutide across all subgroups (DUAL I Japan; Table S2a).

AEs

There was no consistent pattern in overall AE rates for IDegLira versus degludec across the subgroups in DUAL I Japan or DUAL II Japan (Table S3). In contrast, the rate of gastrointestinal AEs was consistently higher with IDegLira than degludec across all subgroups in DUAL I Japan and DUAL II Japan (Table S4). Rates of gastrointestinal AEs in DUAL I Japan were lower with IDegLira versus liraglutide for those with baseline HbA_{1c} $\geq 8.0\%$ (Table S4a).

CONCLUSIONS

The aim of the current subgroup analyses of DUAL I Japan and DUAL II Japan was to understand the treatment response with IDegLira for patients in clinical practice by evaluating the efficacy and safety across patient subgroups split by baseline HbA_{1c}, baseline BMI and age.

Based on the ETDs, IDegLira was associated with improvements in HbA_{1c} versus degludec monotherapy and liraglutide monotherapy in all participant subgroups; that is, irrespective of their baseline HbA_{1c}, baseline BMI or age. The magnitude of the ETD in HbA_{1c} between IDegLira and comparators increased with increasing baseline HbA_{1c} in both DUAL I Japan and DUAL II Japan, suggesting, as one might expect, that combination treatment is more effective in those with higher baseline HbA_{1c}. A significant treatment-by-baseline HbA_{1c} interaction was observed for IDegLira versus liraglutide in insulin-naïve participants (DUAL I Japan). For IDegLira versus degludec, this trend was more pronounced in DUAL II Japan (significant interaction) than DUAL I Japan (no significant interaction). This might be because the degludec dose was capped in the DUAL II Japan trial (maximum dose 50 U), but not in DUAL I Japan. There was also a significant treatment interaction with age for IDegLira versus liraglutide in DUAL I Japan, indicating that although IDegLira provides effective glycemic control in both younger (aged <65 years) and older participants (aged ≥ 65 years), it is more effective than liraglutide in the former.

As previously reported, the effects of a glucagon-like peptide-1 receptor agonist are expected to be affected by remaining β -cell function¹⁵. For example, Usui *et al.* reported the relationship between β -cell function and the glucose-lowering effect of liraglutide in combination with basal insulin¹⁵. Their results suggested that, for individuals with depleted β -cell function (C-peptide index <1.103 ng/mL), liraglutide + basal insulin requires additional oral antidiabetic drug therapy or bolus insulin to achieve glycemic control (HbA_{1c} <7.0% 1 year after treatment initiation). IDegLira might be similarly affected. However, as C-peptide or other β -cell function-related parameters were not measured in DUAL II Japan, we did not carry out subgroup analyses by β -cell function this time. Further consideration is required on this point.

The EOT insulin dose was numerically lower with IDegLira than degludec across all subgroups, except older age, in DUAL II Japan. However, the ETD favored IDegLira in only some groups (baseline HbA_{1c} ≥ 8.0 to 9.0% and $\geq 9.0\%$ in DUAL I Japan, baseline BMI ≥ 30 kg/m² in DUAL I Japan and age <65 years in both studies). The treatment interaction was significant for baseline BMI in DUAL I Japan and age in DUAL II Japan, suggesting that IDegLira has a greater insulin-sparing effect in those with insulin-naïve type 2 diabetes with a baseline BMI ≥ 30 kg/m² and in younger insulin-experienced patients. Therefore, IDegLira could be particularly effective in insulin-naïve patients with obesity and insulin-experienced patients aged <65 years.

In insulin-naïve participants (DUAL I Japan), both IDegLira and degludec were associated with mean weight gain; however, the magnitude of the increase was lower with IDegLira in all subgroups, except those with a baseline BMI ≥ 30 kg/m². Liraglutide was associated with mean weight loss, and the ETD versus IDegLira favored liraglutide in all subgroups. In insulin-experienced participants (DUAL II Japan), IDegLira was associated with a small mean weight loss in most subgroups, whereas degludec was associated with a small mean weight gain; ETDs favored IDegLira for some, but not all, subgroups. However, there was no significant treatment interaction for weight change for any of the subgroups. Although uncertain, the weight gain observed with IDegLira in the HbA_{1c} $\geq 9.0\%$ subgroup may have resulted from the greater insulin dose required for these participants compared with participants in the other HbA_{1c} subgroups. Furthermore, participants with baseline HbA_{1c} $\geq 9.0\%$ might have had glycosuria, which likely improved as they received the diabetes treatment, resulting in weight gain versus baseline.

The present results are broadly consistent with those of the post-hoc analyses of the global DUAL I and DUAL II studies¹⁶, in which Rodbard *et al.* showed that HbA_{1c} reductions were significantly greater with IDegLira versus degludec or liraglutide alone across four categories of baseline HbA_{1c} (<7.5–9.0%) in DUAL I. In DUAL II, HbA_{1c} reductions were significantly greater with IDegLira than with degludec in all but the lowest HbA_{1c} category. Although categories of baseline BMI were not explored in that report, they have been investigated by Lingvay *et al.* in the post-hoc analyses of DUAL V, which included participants with type 2 diabetes uncontrolled on basal insulin¹⁷. Lingvay *et al.*¹⁷ reported reductions in mean HbA_{1c} across all baseline HbA_{1c}, fasting plasma glucose and BMI categories, with significantly greater reductions versus insulin glargine 100 units/mL. Contrary to our findings in participants with type 2 diabetes uncontrolled on basal insulin (DUAL II Japan), IDegLira was associated with weight loss across all baseline BMI categories; in DUAL II Japan, negligible weight change was associated with IDegLira treatment in participants with baseline BMI <25 kg/m² and baseline BMI ≥ 30 kg/m². The differing bodyweight results might be due to the difference in EOT total insulin dose associated with IDegLira treatment across baseline BMI categories <25, ≥ 25 to <30 and ≥ 30 kg/m², respectively: 37 U, 42 U and 45 U in DUAL V¹⁷, and 34.1 U, 37.2 U and 45.4 U in DUAL II Japan.

Hypoglycemia rates were lower in participants with baseline BMI ≥ 30 kg/m² versus those with baseline BMI ≥ 25 to < 30 kg/m² or BMI < 25 kg/m², observed in both DUAL I Japan and DUAL II Japan, and consistent with the results of the post-hoc analyses of DUAL V¹⁷. For participants of DUAL I Japan, who were insulin-naïve, IDegLira treatment was associated with a numerically higher rate of hypoglycemia in elderly participants than non-elderly participants, potentially due to varying food intake between participants in the two age subgroups. Notably, the rate of gastrointestinal AEs was numerically higher in elderly participants versus non-elderly participants. Although IDegLira does not pose any particular concerns regarding severe hypoglycemia, attention should be paid to the occurrence of hypoglycemia in elderly patients, who are generally prone to hypoglycemia.

Interpretation of some of these analyses is limited by the post-hoc nature and the relatively low number of participants in each subgroup. In Japan, elderly patients aged ≥ 75 years account for one-third of the total population with type 2 diabetes¹⁸. Therefore, a possible limitation of the current analyses is that the number of elderly patients included, especially those aged ≥ 75 years, might not have been sufficient to support the conclusion of the treatment-by-subgroup interaction for the efficacy and safety profiles according to age. In addition, the limitations of DUAL II Japan apply to the subgroup analyses of these data reported here. That is, that the dose of degludec was capped at 50 U and that, consequently, it is unclear whether the same outcomes would have been observed in participants switching from basal or pre-mix insulin of > 50 U.

The strengths of these subgroup analyses include that the data used were from two randomized controlled trials. In addition, these analyses add to the body of evidence that consistently shows the clinical benefits of IDegLira^{3-5,7,8,19-21}.

In summary, the results of these subgroup analyses show that IDegLira is an effective treatment option for Japanese patients with type 2 diabetes across a broad range of baseline HbA_{1c}, BMI and age categories.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Overall results for subgroup analysis of change in (a,b) glycated hemoglobin, (c,d) bodyweight and (e,f) end-of-trial total daily insulin dose with insulin degludec/liraglutide, degludec and liraglutide in DUAL I Japan and DUAL II Japan.

Table S2 | Rates of severe or blood glucose-confirmed hypoglycemia across participant subgroups in (a) DUAL I Japan and (b) DUAL II Japan.

Table S3 | Rates of adverse events across participant subgroups in (a) DUAL I Japan and (b) DUAL II Japan.

Table S4 | Rates of gastrointestinal adverse events across participant subgroups in (a) DUAL I Japan and (b) DUAL II Japan.