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**Paper:**

## Original research

# Use of a basal-plus insulin regimen in persons with type 2 diabetes stratified by age and body mass index: A pooled analysis of four clinical trials

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## ABSTRACT

*Aims:* To evaluate the efficacy and safety of adding a single bolus dose of insulin glulisine to basal insulin ('basal-plus') in persons with type 2 diabetes.

*Methods:* Data from patients with poor glycemic control on oral antihyperglycemic drugs who were initiated on a 'basal-plus' regimen for up to 6 months were pooled from four randomized, multicenter studies. Glycated hemoglobin (HbA1c), fasting blood glucose, postprandial glucose (PPG), insulin dose and demographics were measured at baseline and end of study.

*Results:* 711 patients with a mean age of 59.9 years and a mean duration of diabetes of 11.0 years were included in the analysis population. A 'basal-plus' regimen was associated with significant decreases in HbA1c and PPG at 6 months, an increase in glargine and glulisine doses and small, but statistically significant, changes in body weight and BMI in all patient subsets. The proportion of patients with HbA1c < 7% also increased in all populations studied, while the prevalence of severe hypoglycemia was low and did not significantly differ across patient groups.

*Conclusions:* These results suggest that the use of 'basal-plus' can achieve a good therapeutic response with a low risk of hypoglycemia and weight gain, regardless of a patient's age or BMI.

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# 1.    Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by a progressive decline of β-cell function and/or mass in the presence of insulin resistance that requires timely treatment intensification to achieve and maintain optimum metabolic control [1]. Currently, basal insulin represents the simplest and most effective method for controlling fasting hyperglycemia [2,3]. Nonetheless, only approximately half of all patients achieve target glycated hemoglobin (HbA1c) goals despite adequate dose titration and the achievement of near normoglycemia, thus indicating a need for additional treatment to control postprandial glucose (PPG) excursions [4,5]. This can be achieved using different therapeutic modalities, including (1) a fixed combination of a rapid-acting insulin analog (RAA) and an intermediate-acting insulin, i.e., premixed insulins; (2) a combination of a basal insulin and a glucagon-like peptide-1 (GLP-1) receptor agonist; and (3) a 'basal-bolus' regimen, i.e., administration of a RAA to ongoing basal insulin before each meal. More recently, a 'basal-plus' stepwise treatment regimen, i.e., a single injection of prandial insulin prior to the meal associated with the largest PPG excursion, has been proposed. Several clinical trials have demonstrated the efficacy and safety of adding single bolus doses of insulin glulisine to basal insulin glargine [6–11]; however, the effect of individual factors such as a patient's age or BMI on the efficacy of this treatment strategy has yet to be clarified.

Therefore, a retrospective analysis of previous studies was performed to evaluate both the efficacy and safety of adding a single bolus of the 'basal-plus' regimen in patients with T2D when stratified by age and BMI.

# 2.    Methods

## 2.1.    Study design and patient population

Patient-level data were pooled retrospectively from four randomized, controlled, multicenter parallel-group studies designed to evaluate the efficacy and safety of a 'basal-plus' regimen in patients with T2D (OPAL [NCT00272012], ELEONOR [NCT00272064], 1-2-3 [NCT00135083], and a proof-of-concept study [NCT00360698]) [9,12–14]. Participants aged ≥ 18 years who had a diagnosis of T2D and who were poorly controlled (HbA1c ≥ 6.5% or 48 mmol/mol) using basal insulin glargine in addition to oral antidiabetic agents (OADs), with both baseline and end of study HbA1c and BMI measurements available, were deemed eligible for inclusion in this pooled study population. All included patients were initiated on a basal insulin glargine in addition to OADs, to which insulin glulisine was subsequently added once daily ('basal-plus' approach) for up to 6 months. Insulin glargine was titrated to protocol-defined fasting blood glucose (FBG) targets (with the exception of one study [13] in which no titration was undertaken), while insulin glulisine was introduced and dose titrated to protocol-defined preprandial or PPG targets [9,12–14].

## 2.2.    Outcomes and clinical end of studies

Demographic and clinical characteristics (gender, age, weight, height, BMI, duration of diabetes and age at first diagnosis of diabetes) as well as antidiabetic drug usage (duration of prior OAD and/or insulin use, age at initiation of OAD and/or insulin use and insulin glulisine administration time) were collected and analyzed. Efficacy of the 'basal-plus' insulin regimen was determined from the insulin dose and the (1) change of HbA1c levels from baseline and proportion of patients achieving HbA1c < 7% (< 53.0 mmol/mol); (2) change of FBG level from baseline and proportion of patients at < 110 mg/dL (< 6.1 mmol/L); (3) change of PPG levels from baseline and proportion of patients at < 180 mg/dL (< 10.0 mmol/L); and (4) change of weight and BMI over the study periods.

Safety measurements comprised the frequency of episodes of severe hypoglycemia, nocturnal hypoglycemia and symptomatic hypoglycemia (as defined in each trial and determined from data collected during the respective trials [Appendix]) [9,12–14].

Efficacy and safety measurements were then analyzed following stratification by age (< 55, 55–64 and ≥ 65 years) and BMI (< 30, 30–35 and ≥ 35 kg/m$^2$).

## 2.3.    Statistical analyses

Due to the requirement for HbA1c and BMI data at baseline and at end of study, the total available number of patients was reduced (hereafter referred to as the 'analysis population') (Table A1) [9,12–14]. A patient-level meta-analysis was conducted to allow for study-to-study differences. Descriptive statistics were used to measure and describe clinical characteristics and patient demographics as well as efficacy and safety outcome measurements. $p$ values, unadjusted for study origin, were provided by $\chi^2$ test or analysis of variance (ANOVA) when appropriate. Baseline and end of study efficacy measurements were compared with $p$ values calculated using paired $t$-tests; a $p$ value < 0.05 was used to determine the level of statistical significance, again unadjusted for study origin.

A generalized linear model was used to assess the difference between end of study and baseline measurements for HbA1c, weight and BMI while adjusting for patient age, gender, duration of diabetes and different studies. A multivariate logistic regression model was used to assess the impact of patient characteristics on the risk of hypoglycemia.

The outcomes were combined across studies using the random effects meta-analysis approach of DerSimonian and Laird [15]. All statistical analyses were carried out using SAS® version 9.3 (SAS Institute Inc., Cary, NC).

# 3.    Results

## 3.1.    Baseline characteristics

A total of 711 patients comprised the analysis patient population; 53.3% were male, mean age 59.9 ± 9.5 years, and the mean known duration of T2D was 11.0 ± 7.0 years (Table 1). Prior to the study periods the mean duration of OAD use was 6.5 ± 5.7 years and the mean duration of basal insulin use

**Table 1 – Baseline demographics and clinical characteristics.**

| | Analysis population | Age (y) | | | | BMI (kg/m²) | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | <55 | 55–64 | ≥65 | p value[*] | <30 | 30–35 | ≥35 | p value[*] |
| Patients (n) | 711 | 199 | 253 | 259 | – | 315 | 218 | 178 | – |
| Age (y) | 59.9 (9.5) | 48.0 (5.3) | 59.2 (2.9) | 69.6 (3.8) | <0.001 | 62.1 (8.9) | 59.1 (9.4) | 56.8 (9.7) | <0.001 |
| Male (n (%)) | 379 (53.3) | 109 (54.8) | 134 (53.3) | 136 (52.5) | 0.9 | 179 (57.0) | 120 (55.1) | 80 (44.9) | 0.03 |
| Body weight (kg) | 89.7 (19.8) | 98.5 (23.0) | 88.4 (19.1) | 84.3 (15.2) | <0.001 | 75.6 (10.0) | 91.3 (10.9) | 112.8 (18.9) | <0.001 |
| BMI (kg/m²) | 31.9 (6.0) | 34.2 (7.5) | 31.7 (5.5) | 30.2 (4.6) | <0.001 | 27.0 (1.8) | 32.3 (1.5) | 40.0 (5.4) | <0.001 |
| HbA1c (%) (mmol/mol) | 7.6 (0.9) | 7.6 (1.0) | 7.7 (0.8) | 7.6 (0.8) | 0.4 | 7.5 (0.8) | 7.6 (0.9) | 7.7 (0.9) | 0.02 |
| HbA1c (mmol/mol) | 59.6 | 59.6 | 60.7 | 59.6 | 0.4 | 58.5 | 59.6 | 60.7 | 0.02 |
| FBG (mg/dL) | 118.6 (37.1) | 123.1 (46.6) | 121.4 (36.4) | 112.3 (27.7) | <0.01 | 114.0 (32.9) | 121.1 (34.5) | 123.5 (45.5) | 0.02 |
| PPG (mg/dL) | 194.9 (44.5) | 190.3 (43.0) | 199.4 (42.4) | 193.3 (46.8) | 0.15 | 195.6 (44.2) | 197.2 (46.1) | 189.7 (42.7) | 0.34 |
| Duration of diabetes (y) | 11.0 (7.0) | 8.7 (5.4) | 10.7 (6.5) | 12.9 (7.9) | <0.001 | 11.6 (7.4) | 11.2 (6.8) | 9.4 (6.1) | <0.01 |
| Duration of OAD use (y) | 6.5 (5.7) | 5.0 (4.3) | 5.9 (5.0) | 8.1 (6.8) | <0.001 | 6.9 (6.5) | 6.0 (4.9) | 6.2 (5.1) | 0.2 |
| Duration of insulin use (y) | 2.2 (2.2) | 1.7 (1.6) | 2.3 (2.3) | 2.3 (2.2) | 0.2 | 2.4 (2.5) | 2.1 (1.8) | 2.0 (1.9) | 0.4 |
| Age at first diagnosis (y) | 48.9 (10.2) | 39.2 (6.9) | 48.5 (6.7) | 56.7 (8.5) | <0.001 | 50.4 (10.0) | 48.0 (10.2) | 47.2 (10.3) | <0.01 |

All data presented as mean (±SD) unless otherwise stated.
* Comparison between subgroups.

was $2.2 \pm 2.2$ years (Table 1). The mean age at first OAD and insulin usage was $53.5 \pm 9.7$ years and $60.6 \pm 9.2$ years, respectively. The majority of patients received an injection of insulin glulisine at dinner time (41.3%); of the remaining patients, 35.8% and 22.9% received their dose prior to breakfast and lunch, respectively. The majority of patients were receiving either metformin (77.7%) or sulfonylureas (69.0%) at baseline, with smaller numbers receiving thiazolidinediones, glinides, or other OADs.

At baseline and study endpoint the mean dose of insulin glulisine was 4.91 U and 13.21 U, respectively; the mean insulin glargine dose was 36.78 U and 41.91 U, respectively.

The mean dose/weight of insulin glulisine was 0.06 U/kg and 0.14 U/kg, respectively; the mean insulin glargine dose was 0.40 U/kg and 0.45 U/kg, respectively.

For the subanalyses of patients by age (<55, 55–64 and ≥65 years) and BMI (<30, 30–34 and ≥35 kg/m²), a total of 711 patients were included. In general, baseline demographics and clinical characteristics were essentially similar across the two cohorts. However, there were significant differences within the two subgroups according to weight, BMI, duration of diabetes and age at first diagnosis (Table 1).

### 3.2. Analysis population

The addition of a single injection of insulin glulisine at the main meal in patients already receiving an existing therapy of OADs and once-daily basal insulin resulted in significant decreases (mean $\pm$ SD) in HbA1c of $-0.4 \pm 0.1\%$ ($p < 0.0001$), FBG $2.8 \pm 3.7$ mg/dL ($p = 0.05$) and PPG $-58.9 \pm 9.1$ mg/dL ($p < 0.0001$) over a 6-month follow-up. These findings were confirmed in a meta-analysis of changes in HbA1c, FBG and PPG (Table 2).

Furthermore, after 6 months of 'basal-plus' insulin therapy, more than twice as many patients achieved target HbA1c levels (<7% [<53.0 mmol/mol]) at end of study compared with baseline (45.3% vs. 20.3%, $p < 0.001$) (Fig. 1). Also, a much higher proportion of patients (80.4% vs. 40.5%, $p < 0.001$) achieved target PPG levels (<180 mg/dL [<10.0 mmol/L]), while there were no differences in the proportion of patients achieving target FBG at end of study compared with baseline (<110 mg/dL [<6.1 mmol/L]; 40.0% vs. 44.4%).

Both overall daily doses (U) of basal insulin glargine and insulin glulisine increased from baseline to end of study (+6.9 U to $\pm$15.4 [$p < 0.0001$] and +8.4 U to $\pm$10.4 [$p < 0.0001$], respectively). Similar results were observed when insulin doses were expressed per kg body weight (U/kg; +0.07 to $\pm$0.14 [$p < 0.0001$] and +0.05 to $\pm$0.22 [$p < 0.0001$]), respectively). A small, though statistically significant ($p < 0.0001$), increase in body weight (+0.9 to $\pm$4.0 kg) and BMI (+0.3 $\pm$1.4 kg/m²) was observed.

In the analysis population, 1.7%, 12.4% and 37.9% of patients experienced a severe, nocturnal or symptomatic hypoglycemia event (as defined in each study protocol), respectively. The mean number of events per year for severe, nocturnal or symptomatic hypoglycemia was 0.03 ($\pm$0.2), 0.6 ($\pm$2.3) and 4.7 ($\pm$11.4), respectively (Fig. 2A). Nearly half the population (44.3%) achieved target HbA1c goals without experiencing severe or symptomatic hypoglycemia (43.0%).

| Table 2 – Change in key efficacy and safety outcomes from baseline to end of study. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Analysis population* | Age (years)** | | | p value*** | BMI (kg/m²)** | | | p value*** |
| | | <55 | 55–64 | ≥65 | | <30 | 30–35 | ≥35 | |
| Patients (n) | 711 | 199 | 253 | 259 | – | 315 | 218 | 178 | – |
| ΔHbA1c between baseline and end of study (%) | −0.4 (0.1) | −0.3 (0.07) | −0.6 (0.05) | −0.5 (0.05) | 0.02 | −0.42 (0.05) | −0.50 (0.07) | −0.51 (0.06) | 0.46 |
| ΔFBG between baseline and end of study (mg/dL) | 2.8 (3.7) | 9.8 (3.84) | 2.5 (2.71) | 0.6 (2.15) | 0.07 | 5.9 (2.19) | 2.1 (3.09) | 2.2 (3.75) | 0.52 |
| ΔPPG between baseline and end of study (mg/dL) | −58.9 (9.1) | −52.2 (4.43) | −59.2 (3.77) | −51.2 (3.69) | 0.27 | −57.1 (3.29) | −53.1 (4.27) | −49.8 (4.70) | 0.45 |
| ΔWeight between baseline and end of study (kg) | 1.0 (0.5) | 1.4 (0.36) | 0.7 (0.22) | 0.6 (0.22) | 0.08 | 0.9 (0.21) | 0.5 (0.24) | 1.2 (0.37) | 0.27 |
| ΔBMI between baseline and end of study (kg/m²) | 0.4 (0.2) | 0.5 (0.12) | 0.3 (0.08) | 0.2 (0.08) | 0.11 | 0.3 (0.08) | 0.2 (0.09) | 0.4 (0.13) | 0.38 |

All data presented as mean (SE) unless otherwise stated.
* Overall averages calculated using the random effects meta-analysis.
** Subgroup means based on pooled data.
*** Comparison between subgroups.

No predictors for an increased risk of severe hypoglycemia could be identified. When nocturnal hypoglycemia was considered, both female gender (odds ratio [OR] 1.81; $p < 0.05$) and diabetes duration (OR 1.06; $p < 0.01$) emerged as risk predictors. Moreover, insulin glargine dose (OR 1.02; $p < 0.0001$), female gender (OR 1.92; $p < 0.001$) and diabetes duration (OR 1.04; $p < 0.01$) were risk factors for symptomatic hypoglycemia.

The forest plots (Fig. 3) from the meta-analyses show changes from baseline to end of study, demonstrating that HbA1c decreased, while weight and BMI increased slightly.

### 3.3. Age cohort

Table 1 illustrates the characteristics of the study population stratified according to age. Both BMI and FPG declined across the three age categories, whereas age at diagnosis and diabetes duration increased. There were no differences for HbA1c.

The 'basal-plus' regimen resulted in significant ($p < 0.001$) reductions in mean HbA1c and PPG within each of the three age groups, with the smallest reduction in HbA1c occurring in the younger age group (Table 2). Conversely, there was an increase in mean FBG from baseline to end of study in all three age groups (Table 2), with a significant change in the < 55 years age group compared with the other age groups ($p < 0.05$).

Fig. 1 shows the proportion of patients at HbA1c target (< 7% [< 53.0 mmol/mol]) at baseline and 6 months after initiation of the 'basal-plus' regimen. A greater proportion of patients achieved HbA1c target at end of study compared with baseline in all age groups; however, in patients aged ≥ 65 years, the difference from baseline to end of study was less pronounced. Doses of insulin glargine and insulin glulisine increased in all age groups ($p < 0.0001$), with the highest dose increases observed in the younger (< 55 years) patients (10.5 U and 10.7 U, respectively).

There were small but significant ($p < 0.05$) increases in both weight and BMI in all three age groups from baseline to end of study, with the magnitude of the weight and BMI gain markedly lower in the older (55–64 and ≥ 65 years) age groups (Table 2).

In the three age groups (< 55, 55–64 and ≥ 65 years), 2.0%, 0.8% and 2.3% of patients experienced a severe hypoglycemic event (as defined in each study protocol), respectively. There was no significant difference between the three subgroups in the incidence of severe or symptomatic hypoglycemic events; however, there were more nocturnal hypoglycemic events in the two older age groups ($p < 0.05$) (Fig. 2B).

### 3.4. BMI cohort

There were no significant differences between the BMI subgroups with respect to change in HbA1c, FBG and PPG (Table 2). For both HbA1c and PPG, the observed decreases were significant in all three BMI groups ($p < 0.001$). An increase in FBG levels was apparent in all three subgroups, which reached significance only in the BMI < 30 kg/m² group ($p < 0.001$).

As compared with baseline, the 'basal-plus' regimen was associated with an increased proportion of patients achieving target HbA1c levels (< 7% [< 53.0 mmol/mol]), which was more apparent in patients with a higher BMI (Fig. 1). Similar findings were observed with respect to FBG and PPG levels.
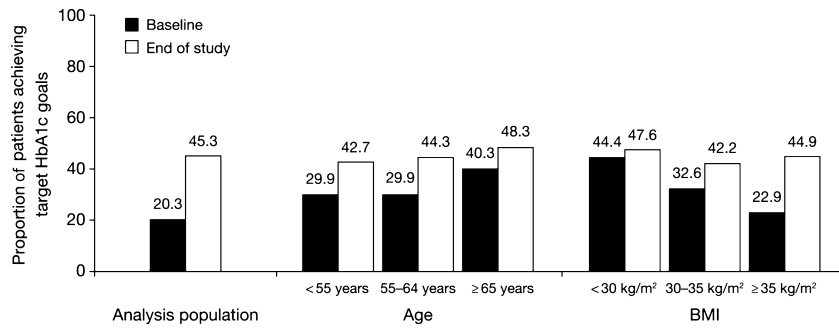
**Fig. 1 – Proportion of patients achieving target HbA1c goals at baseline and end of study.**

Both basal insulin glargine and insulin glulisine doses increased ($p < 0.0001$) from baseline to end of study in all three BMI subgroups, with the highest dose increases observed for the $\geq 35\,kg/m^2$ group (both 12.3 U).

Over the duration of the study, there were small but significant ($p < 0.05$) increases in both weight and BMI within each BMI group, with no significant differences between the three subgroups (Table 2).

The percentage of patients experiencing hypoglycemia was generally low in the three BMI groups ($< 30$, 30–34 and $\geq 35\,kg/m^2$) at 2.5%, 1.8% and 0.0%, respectively, and virtually absent in those with the highest BMI. In particular, there were no significant differences between the three subgroups in the incidence (events per year) of severe or nocturnal hypoglycemia. However, there were significant differences in the number of symptomatic hypoglycemic events, with
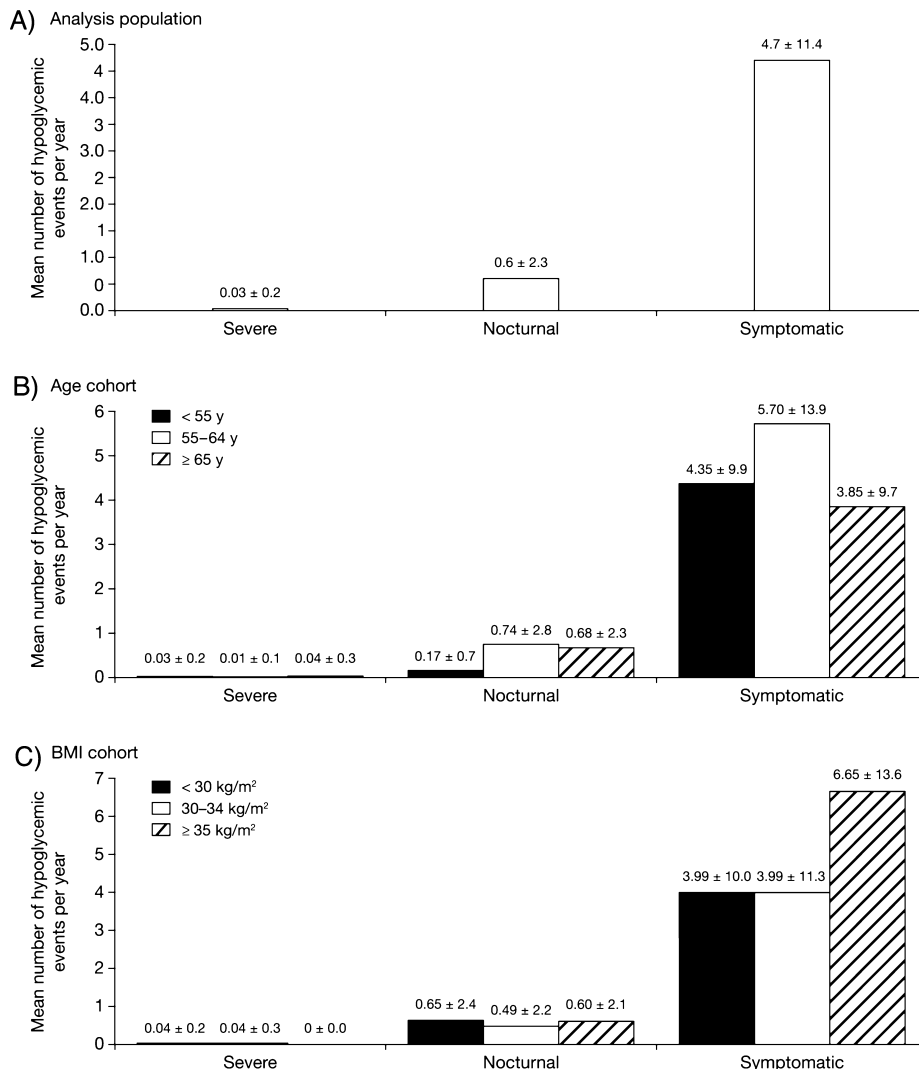


**Fig. 2 – Incidence of hypoglycemic events per year in the (A) analysis population, (B) age cohort and (C) BMI study cohort.**
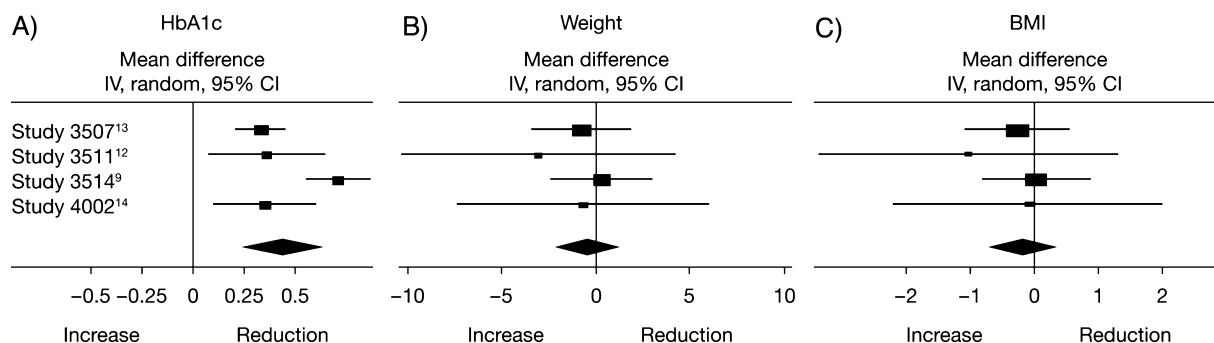
**Fig. 3 – Meta-analysis of (A) HbA1c (%), (B) weight change (kg) and (C) BMI change (kg/m$^2$) of study populations treated with 'basal-plus' insulin regimen. Meta-analysis with random effect model was used for the analysis; meta-analysis has been performed on unadjusted mean changes, without interaction terms (DerSimonian & Laird method) [15]. $p$ value for heterogeneity: $p < 0.0001$.**

the highest events rate observed in the $\geq 35\,\text{kg/m}^2$ group (Fig. 2C).

## 4. Discussion

The findings of this analysis demonstrate that a 'basal-plus' regimen with insulin glulisine added to basal insulin glargine is effective and well tolerated in patients with T2D who are poorly controlled on basal insulin with/without OADs. Interestingly, individual factors such as a patient's age or BMI appear to have only a minimal impact on these outcomes.

As expected in this analysis of patients treated with a 'basal-plus' regimen, significant reductions in HbA1c, FBG and PPG were observed at end of study for the analysis population. However, while there were reductions in both HbA1c and PPG for patients stratified by both age and BMI, FBG was seen to increase in both patient populations. Interestingly, when we consider the individual data from each study, it is apparent that there is considerable heterogeneity across all four studies. Notably, we observed that there was a large increase in FBG in the OPAL study [13] compared with relatively small increases (or reductions) in the other three studies analyzed (Table A1). As the OPAL study comprised more than 40% of the analysis population, and no glargine titration was undertaken in this study, this unexpected finding appears to be driven by the data from this study alone.

A higher proportion of patients achieved target HbA1c levels (<7% [<53.0 mmol/mol]) at end of study compared with baseline. Whilst HbA1c may be affected by other factors than insulin, i.e., diet, physical activity, and other hypoglycemic agents, it was interesting to note that, with increasing age and BMI, fewer patients achieved target HbA1c goals at end of study (compared with baseline) when using this regimen. In addition to HbA1c, FBG and PPG changes, the overall daily doses of basal insulin and glulisine increased significantly from baseline to end of study in all patient populations, with the greatest increases seen in the younger age groups and those with the highest initial BMI. While there were also small increases in body weight (and BMI) for all patient populations observed, the least weight gain was seen in the oldest age group ($\geq 65$ years). Interestingly, weight gain has been

correlated directly with insulin dose [16] which, as previously described, was lowest in the oldest patient subgroup. Overall, there was a low prevalence of hypoglycemia, including severe hypoglycemia, for all patient populations, with no significant differences between patients stratified by age or BMI. A low incidence of hypoglycemia has been associated with a reduced propensity for snacking [17,18], which may have positively contributed to the low levels of weight gain observed in this study.

The meta-analysis (Fig. 3) gives us a further means by which to assess the between-study variation in the results, as well as providing an overall estimate of effect. These findings confirm that while HbA1c decreased, weight and BMI increased slightly.

We acknowledge that there are a number of limitations associated with our meta-analysis, including publication bias (i.e., selection of specific results for publication), use of different study designs and data collection methods and lack of a comparator or placebo group. As described above, the considerable heterogeneity observed across all four studies included in this pooled analysis (Table A1) may have influenced the overall findings. Nevertheless, despite these limitations, the results of this study have shown that a 'basal-plus' approach using a RAA such as insulin glulisine in addition to basal insulin glargine is still a relevant option for many patients, even considering the availability of new GLP-1 mimetics.

## 5. Conclusions

The use of 'basal-plus' as an initial stepwise insulin treatment regimen, involving a single preprandial injection of insulin glulisine (on a background of basal insulin glargine) given before the meal associated with the largest PPG excursion, can achieve a good therapeutic response with a low risk of hypoglycemia and weight gain, regardless of the patient's age or BMI. The findings of our analysis demonstrate the efficacy and safety of a 'basal-plus' regimen in the different patient subsets studied, and provide clinicians with a relevant, alternative therapeutic option in this difficult-to-treat population with T2D. Future studies, comparing a 'basal-plus' treatment

| Table A1 – Individual studies comprising the meta-analyses. | | | | | |
|---|---|---|---|---|---|
| Study | Study period (treatment duration) | Study population | Treatment (ITT population) | Primary analysis | Analysis population findings (N = 711) |
| OPAL study (3507), Lankisch, et al. [13] | June 2004 to September 2006 (24 weeks) | Aged ≥ 18 years, prior treatment with insulin glargine and OADs (excluding α-glucosidase inhibitors) ≥ 3 months, A1c 6.5–9%, FBG ≤ 120 mg/dL | 393 patients (insulin glulisine at breakfast [n = 196], insulin glulisine at main meal [n = 197]) | To investigate whether the addition of a single bolus of insulin glulisine, administered at either breakfast or main mealtime, in combination with basal insulin glargine and OADs, provides equivalent glycemic control in patients with T2D, irrespective of the time of glulisine injection | HbA1c n = 315 Mean change (SE) = –0.3 (0.0)  FBG n = 261 Mean change (SE) = 10.3 (1.5)  PPG n = 298 Mean change (SE) = –44.3 (2.9) |
| ELEONOR study (3514), Del Prato, et al. [9] | October 2005 to May 2008 (24 weeks) | Aged 35–70 years, prior treatment with combined OADs or maximal dose metformin ≥ 3 months, A1c 7.5–11%, BMI > 25 kg/m$^2$ | 241 patients (telecare [n = 115], common SMBG [n = 126]) | To compare the change in HbA1c from baseline (visit 3) with end of treatment phase (visit 5) for patients in the telecare and SMBG programs | HbA1c n = 241 Mean change (SE) = –0.7 (0.1)  FBG n = 237 Mean change (SE) = 0.4 (2.9)  PPG n = 186 Mean change (SE) = –67.4 (3.9) |
| 1-2-3 study (3511), Davidson, et al. [12] | August 2004 to November 2007 (24 weeks) | Aged 18–79 years, T2D ≥ 6 months, current treatment with two or three OADs from three therapeutic classes, HbA1c ≥ 8%, fasting C-peptide concentration > 0.27 nmol/L | Insulin glargine plus insulin glulisine administered once a day (n = 115), twice a day (n = 113), three times a day (n = 115) | To demonstrate noninferiority in the change in glycemic control as measured by HbA1c | HbA1c n = 107 Mean change (SE) = –0.4 (0.1)  FBG n = 94 Mean change (SE) = –4.3 (6.7)  PPG (not evaluated) |
| Proof-of-concept study (4002), Owens, et al. [14] | June 2006 to August 2008 (24 weeks) | Aged 18–75 years, prior treatment with basal insulin and at least 1 g metformin daily for ≥ 3 months, HbA1c 7.5–9.5%, BMI 25–45 kg/m$^2$ | 106 patients (insulin glulisine at main meal [n = 49], control [no insulin glulisine, n = 57]) | To evaluate the proportion of patients achieving HbA1c < 7.0% at end of study | HbA1c n = 48 Mean change (SE) = –0.4 (0.1)  FBG n = 46 Mean change (SE) = 1.0 (4.9)  PPG n = 45 Mean change (SE) = –66.3 (8.1) |

FBG, fasting blood glucose; HbA1c, glycated hemoglobin; ITT, intent-to-treat; OAD, oral antidiabetic drug; T2D, type 2 diabetes; SMBG, self-monitoring of blood glucose.

regimen with newer treatment options, such as the GLP-1 mimetics, may be of interest.

## Conflict of interest statement

## Author contributions

## Acknowledgments

## Appendix A

Table A1.

### A.1. *Definitions of hypoglycemia*

- Symptomatic hypoglycemia was defined as follows:
  - ○ OPAL Study (3507), Lankisch, et al. [13]: An event with characteristic symptoms consistent with hypoglycemia, or asymptomatic if no symptoms occurred but was confirmed by blood glucose levels ≤ 60 mg/dL.
  - ○ 1-2-3 Study (3511), Davidson, et al. [12]: An event with symptoms consistent with hypoglycemia and a self-measured blood glucose (SMBG) level ≥ 36 mg/dL (≥ 2.0 mmol/L) but < 70 mg/dL.
  - ○ Proof-of-Concept Study (4002), Owens, et al. [14]: An event with clinical symptoms that were considered to result from hypoglycemia (confirmed or not by a blood glucose measurement) and associated with prompt recovery after oral carbohydrate administration.
- Severe hypoglycemia was defined as follows:
  - ○ OPAL Study (3507), Lankisch, et al. [13]: An event associated with a blood glucose level < 36 mg/dL (2.0 mmol/L)

and/or an administration of oral carbohydrate or intravenous glucose or glucagons, with symptoms consistent with hypoglycemia, during which the person required the assistance of another person.
  - ○ 1-2-3 Study (3511), Davidson, et al. [12]: An event with symptoms consistent with hypoglycemia in which the assistance of another party was required (not merely requested) and either (A) a recorded SMBG of < 36 mg/dL (< 2.0 mmol/L), or (B) there was treatment with oral carbohydrates, intravenous glucose or glucagon, and there was prompt response to that therapy.
  - ○ Trial 3514: An event associated with a blood glucose level < 36 mg/dL (2.0 mmol/L) and/or with prompt recovery after oral carbohydrate or intravenous glucose or glucagons, with clinical symptoms that were considered to result from hypoglycemia, in which the person required the assistance of another person.
- Nocturnal hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia that occurred while the patient was asleep, between bedtime and getting up in the morning.

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