Incidence of Hypoglycaemia in Patients with Type 2 Diabetes – A Subgroup Analysis from the GINGER study

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Abstract

Introduction: The Glulisine in Combination with Insulin Glargine in an Intensified Insulin Regimen (GINGER) study compared insulin glargine plus insulin glulisine with premixed insulin in the treatment of patients with Type 2 diabetes mellitus (T2DM). This was a post-hoc analysis of hypoglycaemia rates in subgroups from the GINGER study. **Methods:** This analysis compared the once-daily glargine plus mealtime glulisine group (n=153, four injections/day) with the overall twice-daily premixed insulin group (n=157, two injections/day), which consisted of two subgroups receiving either neutral protamine Hagedorn (NPH) plus regular insulin (n=93) or biphasic insulin aspart 70/30 (n=63). Observed and predicted hypoglycaemia rates relative to endpoint HbA_{1c} for both the total population and those patients who experienced ≥1 episodes of any hypoglycaemia were estimated. **Results:** The overall hypoglycaemic event rate (episodes per patient-year) for patients receiving glargine plus glulisine was numerically but not significantly lower (–24.5 %) compared with the overall premixed insulin group (14.0±24.2 versus 18.5±36.9; p=0.12) and significantly lower (–43.3 %) compared with the biphasic insulin aspart 70/30 subgroup (24.7±48.5; p=0.02). In patients with ≥1 episode of hypoglycaemia during treatment, the overall hypoglycaemic event rate was significantly lower (–26.5 %) in patients receiving glargine plus glulisine versus overall premixed insulin (18.5±26.3 versus 25.1±41.1; p=0.044) and significantly lower (–40.7 %) than in patients receiving biphasic insulin aspart 70/30 (31.1±52.7; p=0.009). Glargine/glulisine treatment maintained a more consistent and numerically lower hypoglycaemia rate at all achieved HbA_{1c} endpoints compared with premixed insulin treatment. **Conclusion:** This post-hoc analysis of the GINGER study showed that the frequency of hypoglycaemia in T2DM patients was lowered to a greater extent by insulin glargine plus insulin glulisine in a comparison with premixed biphasic insulin aspart 70/30 than was previously shown in a comparison with overall premixed insulin. **Trial Identifier:** NCT00174668

Keywords

Basal-bolus, hypoglycaemia, insulin glargine, insulin glulisine, premixed insulin

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Hypoglycaemia is a clinically important and potentially dangerous side effect of insulin therapy in patients with Type 2 diabetes mellitus (T2DM).[1,2] The basal-bolus insulin strategy has been studied in the Glulisine in Combination with Insulin Glargine in an Intensified Insulin Regimen (GINGER) study in a population with long-standing insulin-treated T2DM, with or without metformin, who were not controlled adequately with their previous premixed insulins.[3] The study demonstrated that an intensified basal-bolus regimen using insulin glargine plus insulin glulisine provided significantly better glycaemic control and numerically lower overall hypoglycaemia than premixed insulin therapy.

The premixed insulin group in the GINGER study comprised two subgroups: those taking neutral protamine Hagedorn (NPH) insulin plus regular insulin and those taking biphasic insulin aspart 70/30. The aim of this post-hoc analysis was to determine the overall hypoglycaemic event rates in the insulin glargine plus insulin glulisine group with that of the premixed insulin subgroups, and to compare hypoglycaemia risk relative to the glycaemic control achieved at the end of the GINGER study.

Methods

Details of the study design and patient population have been published previously.[3] In brief, this was a 52-week, open-label, active-controlled, randomised, multi-national clinical trial that compared basal insulin glargine plus mealtime insulin glulisine with an optimised conventional therapy of twice-daily premixed insulin therapy. Male and female patients aged 18 to 75 years were eligible for inclusion in the study if they had had T2DM for ≥5 years and had been treated with a stable regimen of twice-daily injections of premixed insulin (NPH plus regular insulin, or NPH plus either lispro or aspart in a ratio of 70/30), with or without metformin for ≥3 months before screening, and had HbA_{1C} between 7.5 % and 11.0 % at screening and randomisation. Oral antidiabetic drugs, except metformin, were not allowed. Exclusion criteria included body mass index >38 kg/m² and ≥2 severe hypoglycaemic episodes within the past 3 months.

Patients were randomised to an insulin regimen with glargine plus glulisine (n=153) consisting of once-daily glargine injections and three times daily glulisine injections at mealtimes or to premixed insulin combinations consisting of twice daily injections (n=157).

In the premixed insulin group, 93 patients received NPH insulin plus regular insulin, and 63 patients received biphasic insulin aspart 70/30. During the first 8 weeks of treatment, insulin doses in both groups were adjusted using a forced titration regimen. The titration targets were the same for both regimens: fasting blood glucose ≤5.5 mmol/L (≤100 mg/dL) and postprandial blood glucose ≤7.5 mmol/L (≤135 mg/dL).

The primary endpoint of the GINGER study was the change in HbA_{1c} from baseline to endpoint. Secondary endpoints included the rate of hypoglycaemia. A hypoglycaemic event was defined as an event with symptoms consistent with hypoglycaemia and/or a confirmed plasma glucose (PG) level ≤60 mg/dL (≤3.3 mmol/L).

For the post-hoc analysis, hypoglycaemic event rates (events per patient-year) were estimated for the total study population and for those patients who experienced ≥1 episodes of any hypoglycaemia, using a negative binomial regression model.[4] In addition, hypoglycaemia event rates were plotted against the endpoint HbA_{1c} for each patient in each group or subgroup. All tests were adjusted for baseline HbA_{1c} and duration of diabetes. To account for the relatively large number of patients with no event, a logistic regression analysis was performed and the p values of both methods combined to form the adjusted p values reported for each treatment group.

Results

Overall, the total study population (n=310) was 49 % female, had a mean±SD age of 61±8 years and had a body mass index of 30.1±3.7 kg/m². Mean duration of T2DM was 13±6 years, with mean insulin use of 5±4 years. Baseline HbA_{1c} was 8.56±0.85%. The demographics and baseline characteristics of the two groups were well matched.[3]

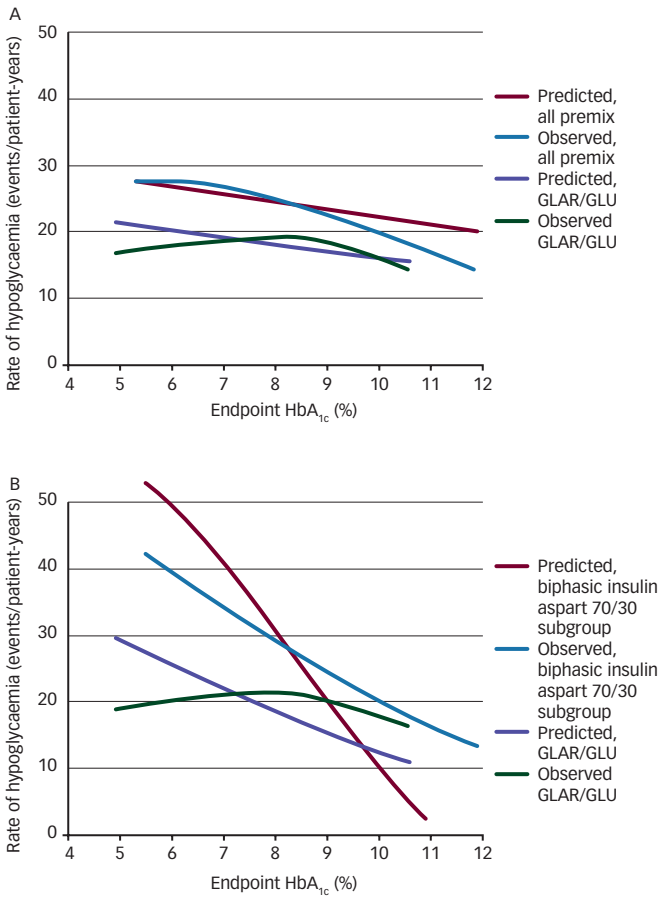
The glargine plus glulisine group had a greater change from baseline HbA_{1c} at study endpoint (–1.31±1.19%) than the overall premixed insulin group (–0.80±1.01%; p=0.0001) or the biphasic insulin aspart 70/30 subgroup (–0.70±1.08%; p=0.0009).[3]

For overall hypoglycaemia, the adjusted event rate (episodes/patient-year), was 24.5% lower for glargine plus glulisine (14.0±24.2) than for the overall premixed insulin group (18.5±36.9), but this difference was not significant (p=0.12). However, there was a significantly lower hypoglycaemic event rate for the glargine plus glulisine group (43.3%) compared with the biphasic insulin aspart 70/30 subgroup (24.7±48.5; p=0.02).

In the analysis of patients with ≥1 episodes of hypoglycaemia during the study (n=232, 74.8% of participants), patients receiving glargine plus glulisine had a significantly lower (26.5%) event rate (18.5±26.3) than the overall premixed insulin group (25.1±41.1; p=0.044) and a 40.7% lower rate than the biphasic insulin aspart 70/30 subgroup (31.1±52.7; p=0.009).

Similar results were obtained when calculating event rates of confirmed hypoglycaemia with PG ≤3.3 mmol/L (data not shown). In addition, comparing the glargine plus glulisine group with the NPH/regular insulin premixed subgroup showed similar hypoglycaemia event rates in both groups (data not shown).

Figure 1: Plots from Negative Binomial Regression Analysis Showing the Relationship between Hypoglycaemia and Endpoint HbA_{1c}



GLAR = glargine; GLU = glusiline.

Expected and observed hypoglycaemic event rates relative to endpoint HbA_{1c} for the glargine plus glulisine group compared with the overall and biphasic aspart 70/30 premixed insulin subgroup are shown in *Figures 1A and 1B*, respectively. These graphs indicate that the glargine plus glulisine treatment maintains a numerically lower level of hypoglycaemic events over the entire range of HbA_{1c} levels compared with the premixed insulin treatments, which showed higher hypoglycaemic event rates at lower HbA_{1c} levels, but this declined at higher HbA_{1c} levels. The graphs also show a more pronounced difference in the hypoglycaemic event rate between the glargine plus glulisine group and the biphasic insulin aspart 70/30 subgroup (graph B) at lower HbA_{1c} levels than was observed between the glargine plus glulisine group and the overall premixed insulin group (graph A).

Discussion

In the GINGER study, rates of hypoglycaemic events were numerically, but not significantly, lower for patients taking once-daily insulin glargine plus mealtime insulin glulisine than for those taking twice-daily premixed insulin.[3] In this post-hoc analysis of the GINGER study, actual rates of overall hypoglycaemia were determined as a function of endpoint HbA_{1c} for patients in each of the two groups. Using a negative binomial regression model,[4] the predicted rates for the basal-bolus group were compared with those of the overall premixed insulin group. Adjusting for endpoint HbA_{1c} did not alter the original outcome between the glargine plus glulisine and the overall premixed

insulin groups: overall hypoglycaemic events were numerically, but not significantly, lower for patients taking once-daily insulin glargine plus mealtime insulin glulisine.

A substantial number of patients in the two groups did not experience any hypoglycaemic events. When only those patients who experienced one or more events were analysed, the rate of hypoglycaemic events was significantly lower with glargine plus glulisine than with the overall premixed insulin group.

For the premixed insulin aspart subgroup, rates of overall hypoglycaemia were significantly greater than those of glargine plus glulisine whether all patients or only those who experienced a hypoglycaemic event were analysed.

Differences in dosing frequency between the glargine plus glulisine regimen (given as four injections daily) versus the premixed insulin regimen (given as two injections daily) were unlikely to have affected study endpoints.

Previous studies in inadequately controlled diabetes patients have shown that dose intensification of premixed insulins does not appear to alter endpoint HbA_{1C} levels or the incidence of hypoglycaemic events.[5–7]

The study results suggest that when both endpoint HbA_{1C} and overall hypoglycaemic events are considered, a basal–bolus regimen with insulin glargine plus insulin glulisine has a better benefit-to-risk profile than premixed insulin therapy, especially than insulin aspart 70/30, in patients with T2DM.

Summary

1. A post-hoc analysis of the GINGER study was conducted to evaluate hypoglycaemia rates relative to endpoint HbA_{1C} in patients with T2DM who were receiving insulin glargine plus insulin glulisine versus premixed insulin
2. The overall adjusted hypoglycaemic event rate (events per patient-year) was numerically lower for those patients receiving insulin glargine plus insulin glulisine compared with the overall premixed insulin group (p=0.12) but significantly lower compared with the biphasic insulin aspart 70/30 subgroup (p=0.02)
3. Similarly, in patients with ≥1 episode of symptomatic and/or confirmed hypoglycaemia during treatment the overall adjusted hypoglycaemic event rate was lower for those patients receiving insulin glargine plus insulin glulisine compared with both the overall premixed insulin group (p=0.044) and the biphasic insulin aspart 70/30 subgroup (p=0.009)
4. Insulin glargine/glulisine treatment was associated with a numerically lower hypoglycaemia event rate that was maintained at all achieved HbA_{1C} endpoints compared with premixed insulin treatment

Author Contributions

Andreas Fritsche, Wolfgang Landgraf and Almut Hahn researched the data, contributed to the discussion and reviewed and edited the manuscript. Hans-Ulrich Häring reviewed and edited the manuscript. ■

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