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Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial.

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ClinicalTrials.gov: NCT00311818APOLLO=**A** **p**arallel design comparing an **O**HA (oral hypoglycaemic agent) combination therapy with either **L**antus once daily or **L**ispro at mealtimes in patients with type 2 diabetes inadequately controlled with **O**HA's.

SUMMARY

Background: As type 2 diabetes mellitus progresses, oral hypoglycaemic agents often fail to maintain blood glucose control and insulin is needed. We investigated whether the addition of once-daily insulin glargine is non-inferior to three-times daily prandial insulin lispro in overall glycaemic control in adults with inadequately controlled type 2 diabetes mellitus taking oral hypoglycaemic agents.

Methods: In the 44-week, parallel, open study that was undertaken in 69 study sites across Europe and Australia, 418 patients with type 2 diabetes mellitus that was inadequately controlled by oral hypoglycaemic agents were randomly assigned to either insulin glargine taken once daily at the same time every day or to insulin lispro administered three times per day. The primary objective was to compare the change in haemoglobin A_{1c} from baseline to endpoint (week 44) between the two regimens. Randomisation was done with a central randomisation service. Analysis was per protocol. This study is registered with ClinicalTrials.gov, number NCT00311818.

Findings: 205 patients were randomly assigned to insulin glargine and 210 to insulin lispro. Mean haemoglobin A_{1c} decrease in the insulin glargine group was -1.7% (from 8.7% [SD 1.0] to 7.0% [0.7]) and -1.9% in the insulin lispro group (from 8.7% [1.0] to 6.8% [0.9]), which was within the pre-defined limit of 0.4% for non-inferiority (difference=0.157; 95% CI -0.008 to 0.322). 106 (57%) patients reached haemoglobin A_{1c} of 7% or less in the glargine group and 131 (69%) in the lispro group. In the glargine group, the fall in mean fasting blood glucose (-4.3 [SD 2.3] mmol/L vs -1.8 [2.3] mmol/L; p<0.0001) and nocturnal blood glucose (-3.3 [2.8] mmol/L vs -2.6 [2.9] mmol/L; p=0.0041 was better than it was in the insulin lispro group, whereas insulin lispro better controlled postprandial blood glucose throughout the day (p<0.0001). The incidence of hypoglycaemic events was less with insulin glargine than with lispro (5.2 [95% CI 1.9-8.9] vs 24.0 [21-28] events per patient per year; p<0.0001). Respective mean weight gains were 3.01 (SD 4.33) kg and 3.54 (4.48) kg. The improvement of treatment satisfaction was greater for insulin glargine than for insulin lispro (mean difference 3.13; 95% CI 2.04-4.22).

Interpretation: A therapeutic regimen involving the addition of either basal or prandial insulin analogue is equally effective in lowering haemoglobin A_{1c}. We conclude that insulin glargine provides a simple and effective option that is more satisfactory to patients than is lispro for early initiation of insulin therapy, since it was associated with a lower risk of hypoglycaemia, fewer injections, less blood glucose self monitoring, and greater patient satisfaction than was insulin lispro.

INTRODUCTION

The association between poor glycaemic control and the occurrence of microvascular and, to a lesser extent, macrovascular complications in patients with type 2 diabetes mellitus is well known (1, 2). Glycaemic control, preferably with haemoglobin A_{1c} concentrations less than 7% (optimally 6.5%), can substantially reduce the risk of such complications (3) and is now recommended internationally for clinical practice (4-6). However, achieving and maintaining such a glycaemic target represents a major challenge when treating patients with type 2 diabetes. Despite decreasing haemoglobin A_{1c} concentration initially with oral hypoglycaemic agents, secondary failure (haemoglobin A_{1c} >7%) occurs in 40–60% of patients after a few years of treatment (2, 7, 8), and supplementary insulin therapy becomes necessary to achieve and sustain good glycaemic control (4-6).

Several barriers exist for the initiation and subsequent optimisation of insulin therapy, including the risk of hypoglycaemia (9) and concern about daily injections (10) or restrictions to lifestyle (11). For example, the efficacy profiles of intermediate-acting human insulins are often associated with interprandial and nocturnal hypoglycaemia, and can thus hinder the achievement of good metabolic control (9, 12). New insulin analogues, both short acting and long acting, offer the possibility of reducing some of the drawbacks associated with conventional insulin preparations, including hypoglycaemia (13).

The basal insulin analogue glargine has a long duration of action (about 24 h), with little or no discernible peak in insulin concentration in the blood and a lower variability between patients than there is with neutral protamine Hagedorn (NPH) insulin or ultralente insulin (14-17). Furthermore, an injection of insulin glargine once a day can confer glycaemic control equivalent to NPH insulin in patients with type 2 diabetes mellitus (18, 19), but with a lower rate of hypoglycaemia (18-22). The short-acting insulin analogue lispro, which is given three times a day at mealtimes, also compares favourably with NPH insulin in terms of improvements in haemoglobin A_{1c}, and has similar rates of hypoglycaemia (23). Until

recently, opinion on how or when to start insulin treatment in type 2 diabetes mellitus was divided (6). However, combination therapy of oral hypoglycaemic agents with a basal insulin analogue like insulin glargine can be regarded as an effective first choice for introducing insulin as part of a stepwise approach, adapting to the progressive β-cell failure. The Introduction of insulin glargine once a day (at bedtime or before breakfast) has several advantages, including a substantial improvement in glycaemic control, fewer episodes of hypoglycaemia than with conventional NPH insulin, a reduction of daily insulin requirements when combined with oral hypoglycaemic agents (18-22), and less weight gain (24). The United Kingdom Insulin Initiation Study (UKIIS) Group (25) and the International Diabetes Federation (IDF) (5) concur with this regimen, which is well accepted in clinical practice.

However, there is ongoing debate as to whether and when it is most beneficial to treat patients: to target postprandial blood glucose concentrations with meal-related insulin, or continue to target fasting blood glucose concentrations with basal insulin that is restricted only by hypoglycaemia. Several studies have shown that fasting blood glucose concentrations correlate equivalently or better with overall glycaemic control on the basis of haemoglobin A_{1c} concentrations (26-29), whereas others have shown that postprandial blood glucose concentrations are a better predictor of haemoglobin A_{1c} values and glycaemic control (23, 30). Monnier and colleagues (31) provided an explanation for such opposing views by showing that postprandial blood glucose contributes more to glycaemic control in patients with mild or moderate hyperglycaemia than in those with poorly controlled diabetes mellitus, in whom fasting hyperglycaemia is the main contributor to overall hyperglycaemia.

The APOLLO study (A Parallel design comparing an Oral antidiabetic drug combination therapy with either Lantus once daily or Lispro at mealtime in type 2 diabetes patients failing Oral treatment) aimed to establish whether the addition of once-daily insulin glargine targeting fasting blood glucose is non-inferior to three-times daily prandial insulin lispro

targeting postprandial blood glucose in overall glycaemic control in adults with inadequately controlled type 2 diabetes mellitus taking oral hypoglycaemic agents. In addition to glycaemic control, patient satisfaction with treatment is an important consideration in deciding between available treatments for this disease. Therefore we investigated whether people given insulin glargine plus oral hypoglycaemic agents were more satisfied with their treatment regimen than were those given insulin lispro plus oral hypoglycaemic agents.

Methods

Patients

The study was conducted at 69 study sites across Europe and Australia between June 25, 2003, and May 31, 2005. Male and female patients were eligible for enrolment if they were aged between 18 and 75 years, had type 2 diabetes mellitus for 1 year or more with haemoglobin A_{1c} concentrations between 7.5% and 10.5%, on oral hypoglycaemic agents (excluding alpha-glucosidase inhibitors) for at least 6 months with stable doses for 3 months or more before study entry, had fasting blood glucose concentrations of 6.7 mmol/L or more, and had body-mass index of 35 kg/m^2 or less. All particpants were willing to monitor blood glucose themselves.

Patients meeting any of the following criteria were not included in the study: treatment with any insulin in the past 4 weeks before study entry; positive for glutamic-acid-decarboxylase (GAD) antibodies; diabetic retinopathy with surgical treatment in the 3 months before study entry; clinically relevant cardiovascular, gastrointestinal, hepatic, neurological, endocrine, or haematological disease; history of drug or alcohol misuse; impaired hepatic function, as shown by alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal; or impaired renal function, as shown by serum creatinine greater than 177 µmol/L. Patients who were pregnant were also excluded from the study.

The study was approved by ethics committees of the participating centres and was

undertaken in accordance with the Declaration of Helsinki. All patients provided written informed consent for their participation before study entry.

Procedures

In this open-label study, randomisation to the two treatment groups was done with a central randomisation service that was generated by the eCRF programme (InForm). The randomisation schedule was stratified by centre and co-treatment with metformin on a 1:1 basis.

At the baseline visit, patients were randomly assigned to either insulin glargine (Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) taken once daily at the same time every day or to insulin lispro (Lilly Deutschland GmbH, Bad Homburg, Germany) given three times per day immediately before breakfast, lunch, and dinner (preferably at 0600–0900h, 1200–1400h, and 1800–2100h). Insulin glargine was given with the OptiSet injection (Sanofi-Aventis) device and insulin lispro with the Humalog Pen (Lily Deutschland GmbH). The starting dose for insulin glargine was 10 U and for insulin lispro the dose was 4 U before every meal. In both groups, the dose of oral hypoglycaemic agents was kept stable during the 4-week screening period and the 44-week treatment phase. During the screening period, patients who were pretreated with sulphonylurea hypoglycaemia agents either changed to the equivalent dose of glimepiride (2, 3 or 4 mg, decided by the investigator) or remained on their present glimepiride dose. Glimepiride was given in the morning, before breakfast (preferably 0600–0900 h). Thereafter, the dose of glimepiride or other oral hypoglycaemic agents remained unchanged throughout the study.

Participants were trained to self-monitor their blood glucose with the same type of blood-glucose meter (Accu Check, Roche Diagnostics, Mannheim, Germany) provided by the sponsor, and to self-inject insulin with the OptiSet pen (glargine) or the Humalog Pen (lispro). At start of screening, at week 20, and at week 44 (study endpoint), a previously

validated diabetes treatment satisfaction questionnaire (DTSQ) was given to the patients (32,33). The questionnaire was linguistically validated in eight languages that were appropriate for the participating centres. It consisted of eight which were all measured by a 7-point numeric rating scale from 0 to 6. The treatment satisfaction score was calculated as the sum of six items (items one and four-eight) with higher scores on the 0-36 scale indicating greater patient satisfaction with their treatment. By contrast, for items two (perceived frequency of hyperglycaemia: “How often have you felt that your blood sugars have been unacceptably high recently?”) and three (perceived frequency of hypoglycaemia: “How often have you felt that your blood sugars have been unacceptably low recently?”), higher scores on the 0-6 scale indicate perception of more frequent hyperglycaemia or hypoglycaemia (33).

During the treatment phase, insulin doses were adjusted by a forced titration regimen (panel) to a target fasting blood glucose less than 5.5 mmol/L in the insulin glargine group, and a preprandial blood glucose of less than 5.5 mmol/L and a postprandial blood glucose of less than 7.5 mmol/ L in the insulin lispro group, in accordance with the insulin titration algorithms proposed by the European Diabetes Policy Group (34). Insulin doses were titrated every week according to self-monitored capillary blood glucose measurements. The insulin dose and injection time was recorded in each patient’s diary. Fasting, pre-prandial, and postprandial blood glucose concentrations, as well as hypoglycaemic episodes, were also recorded.

Participants visited the research site at baseline and were contacted by telephone at week 3, 5, 7, and 10 to discuss dose changes. Patients were to test glucose whenever they had symptoms that might be related to hypoglycaemia and to record the results. Additionally, participants tested their blood glucose at eight points throughout the day (before and 2 h after breakfast, lunch, and dinner; at bedtime; and at 0300 h) starting 2 days before visits at week 2, 8, 20, 28, 36, and 44. When glucose concentrations in the target range were

obtained, investigators were allowed to stop titration or temporarily reduce the dose when they believed further titration would be hazardous. After the forced titration phase, diary checks were part of the subsequent study visits at the research site (at week 12, 16, 20, 24, 28, 32, 36, 40, and 44).

<Panel>

We recorded haemoglobin A_{1c}, fasting plasma glucose, GAD antibodies, clinical chemistry varibles (creatinine, aspartate aminotransferase, alanine aminotransferase, sodium, and potassium), and lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and non-esterified fatty acid) with standard methods at the central laboratory (INTERLAB, Munich, Germany). We did a routine physical examination at the baseline and end visit. Assessment of vital signs was done at every visit at the site.

The primary objective was to compare the change in haemoglobin A_{1c} from baseline to endpoint (week 44) between the oral hypoglycaemic agent combination therapy with either insulin glargine once daily or insulin lispro at mealtimes. The secondary objectives included the proportion of participants achieving a haemoglobin A_{1c} of 6.5% or less or 7.0% or less, the change in fasting blood glucose during the treatment period, and proportion reaching a fasting blood glucose of 5.5 mmol/L or less. We also compared baseline to endpoint changes in nocturnal blood glucose and blood-glucose profiles at eight points throughout the day (including mean daytime and mean daily blood glucose concentration), and the percentage of patients with nocturnal, severe and symptomatic hypoglycaemia. Hypoglycaemia was defined as an event with or without symptoms consistent with hypoglycaemia, not needing the assistance of another person, and associated with blood glucose concentrations less than 3.3 mmol/L. Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia, requiring the assistance of another person, associated with a blood glucose concentration less than 2.0 mmol/L, or recovery

after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycaemia was defined as hypoglycaemia, occurring whilst the individual was asleep and before getting up in the morning. Whenever participants awoke during the night and had symptoms of hypoglycaemia, self-monitoring blood glucose was done and documented in the patients' diary.

An investigator examined patients and recorded adverse events at every visit or during telephone contact, instructing patients to report any events occurring during the study period. For the purposes of the study, the period of observation for each individual extended from the time the patient gave informed consent until 7 days after the last dose of study drug. The term adverse event referred to any unfavourable and unintended sign, symptom, syndrome, or illness that developed or worsened during the study. A serious adverse event was defined as one that at any dose (including overdose) resulted in death, was life threatening, required inpatient admission to hospital or extension of existing admission, resulted in persistent or substantial disability or incapacity, was a congenital anomaly or birth defect, or was an important medical event.

Statistical analysis

The primary analysis was per protocol,,and included all patients without any major protocol violations. Figure 1 shows the criteria for inclusion in the per-protocol population. With the assumption of an equivalence region of 0.4% and standard deviation of 1.3% for the differences of haemoglobin A_{1c} reduction between the two groups, one-sided therapeutic non-inferiority can be demonstrated with an error of α=0.025 (one-sided) and β=0.2 with 167 participants per group (total of 334 participants). With an expected non-evaluable rate of 20% (i.e., not suitable for per-protocol analysis), a total of 420 individuals (210 in each treatment group) were randomly assigned. We planned to recruit this sample in roughly 70 centres. The recommended minimum number of individuals per centre was four, with a maximum of 20.

The intention-to-treat population was defined as patients who, after randomisation, had received at least one dose of insulin study drug and had both baseline haemoglobin A_{1c} and at least one haemoglobin A_{1c} value during the treatment period. Statistical testing was done at a significance level of α=0.05. The primary efficacy analysis was done as a two-step procedure. The first hypothesis tested was the non-inferiority of insulin glargine versus insulin lispro. The subsequent superiority testing of the difference in haemoglobin A_{1c} was done for the intention-to-treat population.

We tested the hypotheses with analyses of covariance (ANCOVA) with treatment group, country, and intake of metformin at baseline as fixed variables, and baseline haemoglobin A_{1c} as a covariate to compare changes in haemoglobin A_{1c}. We calculated adjusted mean changes in haemoglobin A_{1c} and corresponding two-sided 95% CIs. For secondary efficacy variables, ANCOVA analyses were done. We compared categorical variables between treatment groups by Cochran-Mantel-Haenszel tests, controlling for country and intake of metformin at baseline. We analysed time-dependent variables with the Kaplan-Meier method. Statistical testing was done by logrank test.

The rate of patients with hypoglycaemic episodes and number of episodes were analysed with a Cochran-Mantel-Haenszel test on the basis of the insulin safety population (figure 1). The number of hypoglycaemic events per patient and per patient year was summarised as a quantitative variable. Comparisons between treatment groups were done by an analysis of variance (ANOVA) model. Analyses were also undertaken for the following subtypes of hypoglycaemic events: nocturnal, severe, symptomatic, and asymptomatic. Additionally, hypoglycaemic events (overall, nocturnal and symptomatic) that were confirmed by blood glucose concentration of 3.3 mmol/L or less were analysed by patient and event..

We used ANCOVA to compare changes in every item of the DTSQ and the treatment satisfaction composite score that was made up of six items. We entered treatment group,

language, and present intake of oral hypoglycaemic agents as fixed factors; corresponding scores at screening were entered as covariates.

This study is registered with ClinicalTrials.gov, number NCT00311818.

Role of the funding source

The sponsor coordinated the study, monitored investigator sites, collected and managed the data, and undertook the statistical analyses. UN wrote the study protocol. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

RESULTS

Figure 1 shows the trial profile. 412 patients were in the intention-to-treat population (204 in insulin glargine group and 208 in insulin lispro group). A total of 35 patients were excluded owing to major protocol deviations during the study (figure 1); thus the per-protocol population consisted of 377 patients (186 in insulin glargine group and 191 in insulin lispro group), who were included in our analysis.

<Figure 1 Trial Profile>

Table 1 shows the demographics and baseline characteristics of the per-protocol and intention-to-treat populations. After randomisation, most patients received metformin therapy throughout the study (156 [76%] and 153 [74%] in the insulin glargine and insulin lispro treatment groups, respectively). Most patients in both treatment groups were given glimepiride, with only 11 (6%) patients assigned to insulin glargine and 14 (7%) to insulin lispro not receiving glimepiride. Patient demographics and glycaemic control (haemoglobin A_{1c} and fasting blood glucose) were much the same between the two groups at baseline (table 1).

<Table 1- Demographics and baseline characteristics of the study population>

The mean decreases in haemoglobin A_{1c} were similar between the insulin glargine and the insulin lispro groups (–1.72%, from 8.7% [SD 1.0] to 7.0% [0.7]%; p<0.0001 vs –1.83%, from 8.7 [1.0] to 6.8 [0.9]; p<0.0001) with similar differences between the adjusted means (–1.71% vs –1.87%), which was within the predefined 0.4% limit for non-inferiority between the groups (figure 2). This finding was confirmed in the intention-to-treat population: the mean adjusted decreases in haemoglobin A_{1c} were similar between the glargine and the lispro groups (–1.69% vs –1.82%); differences between the adjusted means were not significantly different, showing non-inferiority (Δ=0.137% [95% CI –0.022 to 0.297]; p=0.0908).

Compared with baseline, 106 (57%) patients in the insulin glargine group reached haemoglobin A_{1c} concentration of 7% or less and 131 (69%) in the lispro groups of the per-protocol population (116 [58%] vs 138 [68%] in the intention-to-treat population). A haemoglobin A_{1c} concentration between 6.5% and 7% was achieved by 51` (27%) in the glargine group and 58 (30%) in the lispro group of those treated per protocol (54 [27%] vs 61 [30%] in the intention-to-treat population). Optimum haemoglobin A_{1c} concentrations less than 6.5% were reached by 55 (30%) in the glargine group and 73 (38%) in the lispro group in the per-protocol population (62 [31%] vs 77 [38%] in the intention-to-treat population.

<Figure 2 >

At baseline, no patient had a fasting blood glucose concentration of 5.5 mmol/L or less, but more patients reached this target with insulin glargine than with insulin lispro at study endpoint (71 [38%] vs 11 [6%] in the per-protocol population). The intention-to-treat analysis confirmed the significance of the result (72 [35%] vs 11 [5%]; p< 0.0001).

<Table 2 Concentrations of blood glucose at baseline and endpoint>

At baseline, the diurnal glucose profiles at eight points throughout the day were similar for

both treatment groups (figure 3). The entire blood-glucose profile decreased significantly ($p<0.0001$) in both treatment groups from baseline to endpoint (figure 3). As expected, the fall in the mean nocturnal blood glucose and morning fasting blood glucose were significantly greater with insulin glargine than insulin lispro (table 2). This result was confirmed with the intention-to-treat analysis for nocturnal blood glucose (-3.3 [SD 2.7] vs. -2.7 [2.9] mmol/L; $p=0.0017$) and morning fasting blood glucose (-4.1 [2.4] vs. -1.9 [2.3] mmol/L; $p<0.0001$). Conversely, in the intention-to-treat population, a significantly greater reduction was achieved with insulin lispro than insulin glargine postprandially after breakfast (-4.6 [4.0] vs 4.2 [3.4] mmol/L), lunch (-4.3 [3.7] vs. -3.1 [3.1] mmol/L), dinner (-5.0 [3.2] vs. -3.2 [3.7] mmo/L, and bedtime (-4.3 [4.8] vs. -3.2 [3.6] mmol/L). Figure 3 shows the corresponding data from the per-protocol population.

However, both insulin preparations were also effective beyond the targets of their titration algorithms (table 2). Significant results were also obtained when the intention-to-treat population was examined by the same method (data not shown).

<Figure 3>

During the insulin-treatment phase the number of participants who had hypoglycaemic events was lower in the insulin glargine treatment group (136 [66%]) than in the insulin lispro group (189 [89%]). Additionally, the total number of hypoglycaemic events was substantially lower in the insulin glargine group (n=876) than in the insulin lispro group (n=4125), resulting in significantly lower overall number of hypoglycaemic events per patient in the insulin glargine treatment group (table 3).

The rates of all, confirmed (blood glucose 3.3 mmol/L or less), and symptomatic hypoglycaemic episodes were significantly lower with insulin glargine than with insulin lispro (all $p<0.0001$; figure 4, table 3). However, the rates of nocturnal and severe hypoglycaemia

were similar in both groups (figure 4, table 3).

<Table 4 near here>

<Figure 4 near here>

During the course of the study, the mean daily insulin dose increased similarly in both treatment groups, from 9.86 [SD 0.88] U to 42.38 [25.54] U with insulin glargine and from 12.03 [1.44] U to 45.03 [25.68] U with insulin lispro (webfigure). At endpoint, the insulin lispro dose was split equally between breakfast (17.06 U), lunch (12.66U), and dinner (15.72 U). Additionally, concomitant treatment with oral hypoglycaemic agents by type and daily dose were also similar at baseline in both treatment groups (table 1).

At baseline, scores for treatment satisfaction were much the same in both groups (table 4), suggesting fairly high levels of satisfaction. The mean score for treatment satisfaction improved in both treatment groups (table 4). The magnitude of change was significantly greater with insulin glargine than with insulin lispro for the treatment satisfaction score for five of the six items ($p<0.01$) contributing to that score. The exception was the item about satisfaction with understanding of diabetes, which had similar scores in both treatment groups (data not shown). The mean overall difference of the satisfaction score between insulin glargine and insulin lispro at the end of the study adjusted for baseline was 3.13 (95% CI 2.04-4.22; $p<0.0001$). Improvements in mean scores were seen on all items in both groups (data not shown) apart from the scores for the convenience item, which deteriorated in the lispro group (0.66 glargine group vs -0.17 in lispro group).

Screening scores for the perceived frequency of hyperglycaemia were around 4 in both groups on this 0-6 scale. This finding suggests that patients recognised that their blood glucose concentrations were too high on many occasions, as would be expected for this sample of patients for whom one inclusion criterion was haemoglobin A_{1c} between 7.5% and

10.5%. Although both groups reported an improved score at endpoint, the score was significantly better with insulin glargine than insulin lispro (table 4). At screening, scores for the perceived frequency of hypoglycaemia were low in this sample. By endpoint, however, both groups reported increased hypoglycaemia, although the increase in hypoglycaemia was significantly less with insulin glargine than with insulin lispro (table 4).

We recorded weight gain between baseline and endpoint in both the insulin glargine (3.01 [SD 4.33] kg) and insulin lispro (3.54 [SD 4.48] kg) groups, although the difference between the two groups was not significance (p=0.23).Clinical chemistry parameters showed only minor changes from baseline to endpoint (webtable). We noted a non-significant reduction of triglycerides and non-esterified fatty acids by insulin glargine and insulin lispro, respectively (webtable).

With insulin glargine, 135 (66%) patients had at least one adverse event from treatment compared with 124 patients (59%) patinents with insulin lispro, with the overall number of treatment emergent adverse events being slightly higher with insulin lispro (N=453) than with insulin glargine (n= 421). The most frequent events were upper-airway or other common infections (68 [33%] in insulin glargine group vs 60 [28%] in insulin lispro group), musculoskeletal and connective tissue disorders (38 [19%] vs 33 [16%]), nervous system disorders (32 [16%] vs 32 [15%]), and gastrointestinal disorders (29 [14%] vs 33 [16%]). Two patients receiving insulin glargine and four receiving insulin lispro withdrew because of adverse events related to treatment. During the course of the study, a similar number of serious adverse events were reported in both treatment groups (21 [10%] with insulin glargine group vs 28 [12%] with insulin lispro). Only one event of hypoglycaemia in the insulin lispro group was considered related to the study drug.

Discussion

Our results suggest that treatment with once-daily insulin glargine is non-inferior to three-times daily insulin lispro in achieving overall glycaemic control as represented by haemoglobin A_{1c} in patients with type 2 diabetes mellitus that is poorly controlled on oral hypoglycaemic agents. We noted similar significant reductions in haemoglobin A_{1c} over the 44-week treatment period in both groups.

In practice, monotherapy fails to achieve or maintain the glycaemic target of haemoglobin A_{1c} of 7% or less in most patients with type 2 diabetes mellitus, emphasising the need to introduce additional therapeutic options without undue delay (8, 35, 36). Our findings show that patients were able to reach this target with the addition of insulin to existing treatment with oral hypoglycaemic agents. When target haemoglobin A_{1c} could not be obtained with insulins glargine or lispro, addition of the other insulin could be helpful in reaching the target.

However, the treatment regimens showed different effects on circadian regulation of blood glucose. Decreases in fasting and nocturnal blood glucose were significantly greater with insulin glargine than with the insulin lispro regimen. A much greater proportion of patients achieved a fasting blood glucose concentrations of 5.5 mmol/L or less with insulin glargine than with insulin lispro. Conversely, insulin lispro was associated with lower postprandial concentrations, especially after lunch and dinner. These findings are consistent with those recorded in a previous study of people with type 2 diabetes mellitus which is inadequately controlled by treatment with oral hypoglycaemic agents. Insulin lispro substantially reduced postprandial blood glucose, whereas NPH insulin reduced the fasting blood glucose with a greater reduction of haemoglobin A_{1c} in the lispro group (23). In that study, the fasting blood glucose at the end of treatment was 8.5 (SD 2.4) mmol/L in patients given NPH insulin compared with 6.1 (1.4) mmol/L in those given glargine in our study. In view of the discussion about whether fasting or postprandial blood glucose concentrations have a

greater effect on haemoglobin A_{1c} in patients with poor control, we would expect that one therapeutic regimen would be better to the other. However, targeting fasting blood glucose or postprandial blood glucose were both equally effective in improving haemoglobin A_{1c}. Moreover, we recorded no differences in the adherence to titration targets when we compared maximum (baseline) or minimum (endpoint) haemoglobin A_{1c} concentrations for insulin glargine and insulin lispro treatment. Thus, our data suggest that the reduction of haemoglobin A_{1c} is more dependent on targeted insulin therapy per se rather than a specific glucose profile.

Tight glycaemic control is known to increase the risk of hypoglycaemia, representing a major barrier to sustained good glycaemic control with insulin therapy (9, 12). Therefore, an insulin regimen that is associated with a reduced risk of hypoglycaemia can ease the introduction and titration of insulin therapy. Our results show that, despite similar improvements in glycaemic control between the two insulin regimens, the additi on of insulin glargine to existing treatment with oral hypoglycaemic agents was associated with a much lower incidence of overall hypoglycaemia that was noted when insulin lispro was added. Although it could be suggested that asymptomatic hypoglycaemia might have been detected more often in the lispro group than in the glargine group simply because they were monitoring their blood glucose concentrations more often preprandially, symptomatic hypoglycaemia was also significantly less with insulin glargine than with insulin lispro The incidence was lower for all categories of hypoglycaemia in the insulin glargine than in the lispro group, apart from nocturnal hypoglycaemia which did not differ significantly between groups, showing the low overall incidence of hypoglycaemia in the night compared to daytime.

The low rate of hypoglycaemia with the basal insulin regimen that we recorded supports the feasibility of continued titration to achieve target glycaemic concentrations in even more patients than we noted in our study. Improvement in glycaemic control and low incidence of

hypoglycaemia were obtained with similar insulin doses in both treatment regimens. In the group given basal insulin, doses at the end of the study were similar to those obtained from previous insulin glargine studies (18-22).

Other barriers to achieving recommended targets for glycaemic control include diffculty of managing several injections and the associated requirement for self-monitoring blood glucose many times throughout the day (10, 11, 37). Therefore, simple but effective regimens are especially important when starting insulin therapy in patients with type 2 diabetes mellitus. The regimen of insulin glargine plus oral hypoglycaemic agents in this study needed only a one daily injection and a single blood-glucose test before breakfast to guide therapy compared with the three injections required with insulin lispro administration, necessitating several tests for blood glucose throughout the day. Study participants taking insulin glargine reported greater overall treatment satisfaction, with specific improvements in convenience of treatment, than did those taking insulin lispro. Patients taking insulin glargine also reported a greater reduction in perceived frequency of hyperglycaemia and a smaller increase in perceived frequency of hypoglycaemia than did those taking insulin lispro. These ratings together with a lower prevalence of hypoglycaemia with insulin glargine than with insulin lispro despite similar reductions in HbA_{1c} show that the glargine regimen is more acceptable to patients than is the lispro regimen.

The APOLLO study represents a long-term, direct comparison between two different insulin analogue treatment strategies. Previous studies have compared insulin glargine and NPH insulin for safety within treatment strategies involving basal insulin (18-22, 38). Holman and colleagues (42) recently published 1-year interim data from their 4-T study comparing the addition of biphasic, prandial and basal insulin to oral therapy when glycaemic control was less than optimum. The study design and overall baseline characteristics of the patients were similar those in the APOLLO study. Both studies noted a lower risk of hypoglycaemia

with basal than with prandial-insulin supplementation. The reduction of haemoglobin A_{1c} in both these treatment groups was less in the 4-T study than in the APOLLO study. Furthermore, twice as many patients in the basal insulin cohort reached haemoglobin A_{1c} of less than 7% in this study compared with the 4-T study despite apparently equivalent insulin doses between the two studies and despite insulin detemir needing to be given twice daily in a third of patients in the 4-T study. Compliance with the structured titration algorithm use in our study in combination with only once daily insulin glargine partly accounts for the difference in glycaemic outcome.

The use of the incretin mimetic exenatide is one of the emerging therapies for patients with type 2 diabetes who have poor glycaemic control despite taking oral hypoglycaemic agents. Exenatide is injected once or twice per day, lowers blood glucose concentrations by mobilising insulin from the pancreas during meals, and has the advantage compared with insulin therapy that it is associated with a decrease of bodyweight. In a trial directly comparing insulin glargine and exenatide (43), the effect of lowering blood glucose in both treatment groups was identical, but was less than was recorded in the APOLLO study. Patients receiving exenatide had a higher incidence of gastrointestinal symptoms than did those receiving glargine, and 9.5% of the exenatide group were reported to have withdrawn from the study because of adverse events compared with 0.7% of those receiving insulin glargine. Treatment satisfaction in patients remaining in the exenatide group for at least 12 weeks was reported to be comparable with that of the glargine group (44). Thses findings accord with the consideration of exenatide as an alternative treatment to the addition of insulin. However, more studies will be needed to to establish the effect of adverse events and to identify patients who are most likely to benefit from exenatide or insulin.

Whether patients with type 2 diabetes and cardiovascular disease benefit from a strategy of intensive glycaemic control including insulin administration continues to be debated. The blood glucose lowering part of the ACCORD trial was stopped prematurely because of a

20% increased rate of mortality in the intensive group, targeting a haemoglobin A_{1c} concentration of less than 6% compared with the standard group with a tagrget of 7.0-7.9% (45). In the APOLLO trial, about a third of the participants reached haemoglobin A_{1c} concentrations in the range of the intensively-treated group. We noted that the rate of acute cardiovascular events was 11.3 per 1000 patient years and no deaths occurred; overall 350 patient years were assessed. The protocols of both trials differ substantially from each other in terms of the design and implementation of the study-eg, the inclusion criteria, variety of study drug, the number od visits during the titration phase, and time of observation period per patient, all of which potentially explain the different outcome of mortality (46). More studies will be needed to address the open issue of an optimum balance between risks and benefits of intensive glycaemic control in patients with diabetes who are at high risk for cardiovascular disease. It might be particularly important to control potassium concentrations and autonomic cardiac activity when haemoglobin A_{1c} is aggressively lowered.

The addition of insulin glargine to oral hypoglycaemic agents is a simple and well-tolerated intervention that can be helpful in overcoming major barriers to timely insulin initiation in settings of primary and secondary care (47). The use of a simple self-administered titration algorithm is equally as effective at improving glycaemic control as is titration managed by physician (48). Evidence from the APOLLO study suggests that the addition of insulin glargine to therapies with oral hypoglycaemic agents can be regarded as a first-line insulin initiation approach in type 2 diabetes mellitus, as has been recommended in a joint consensus guildeline by the American Diabetes Association and European Association for the Study of Diabetes (6).

Contributors

All authors participated in various aspects of the study analysis and interpretation of the data, and to the development of the report. The final version was seen and approved by all authors. RGB was principal investigator and chairman of the steering committee and

together with UN contributed to the study concept and interpretation of the data. WL was involved in the drafting and development of the report. DRO contributed to both the developmental of the report and the critical discussion of the concept of analyses. CB advised on the use and interpretation of the diabetes treatment satisfaction questionnaire and the discussion. TL contributed to data collection, development of the report, and was the leading author during the reviewing process.

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Conflict of interest statement

RGB served as a consultant to or gave lectures organized by Bayer, Develogen, GSK, Lilly, MSD, Novo Nordisk and Sanofi-Aventis. UN was an employee of Sanofi-Aventis, left the company after completion of the study, and is a consultant for clinical studies. WL is an employee of Sanofi-Aventis. DRO served as a consultant for Sanofi -Aventis, MSD, Pfizer, Novo Nordisk, Roche, and Novartis, and gave lectures at various symposia sponsored by these companies. CB is a copyright holder of the diabetes treatment satisfaction questionnaire and director of Health Psychology Research (HPR) that licenses questionnaires to pharmaceutical companies. CB has served as consultant for Sanofi-Aventis and other companies, has given lectures at symposia sponsored by Sanofi-Aventis, served on an advisory board for Lilly, and received research grants from Sanofi-Aventis and Lilly. TL has received an unrestricted research grant from Sanofi -Aventis.

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Panel: Dose titration algorithm and monitoring

Insulin glargine

Titration monitoring	Starting dose: 10 U per day Direct investigator contact. Additional calls to adjust insulin
Insulin dose titration algorithm	Starting dose: 10 U per day If self-monitored fasting flood glucose for 2 consecutive days with no severe hypoglycaemia: >8.9 mmol/L: add 8 U/day >7.8 − ≤8.9 mmol/L: add 6 U/day >6.7 − ≤7.8 mmol/L: add 4 U/day >5.5 − ≤6.7 mmol/L: add 2 U/day ≤5.5 mmol/L: no further titration

Insulin lispro

Titration monitoring	Starting dose: 4 U per day Direct investigator contact. Additional calls to adjust insulin dose if haemoglobin A_{1c} >7%
Insulin dose titration algorithm	Preprandial blood glucose: >11.1 mmol/L: add 3 U before main meal >8.3 − ≤11.1 mmol/L: add 2 U before main meal >5.5 − ≤8.3 mmol/L): add 1 U before main meal <5.5 mmol/L: no further titration Postprandial blood glucose: >10.3 mmol/L: add 2 U before main meal >7.5 − ≤10.3 mmol/L): add 1 U before main meal ≤7.5 mmol/L: no further titration

Table 1: Demographics and baseline characteristics of the study population

	Insulin glargine plus OHAs		Insulin lispro plus OHAs	
	Intention-to-treat population (n=204)	Per-protocol population (n-186)	Intention-to-treat population (n=208)	Per-protocol population (n=191)
Men	107 (52%)	102 (55%)	122 (59%)	113 (59%)
Women	97 (48%)	84 (45%)	86 (41%)	78 (41%)
Age (years)	60.0 (9.0)	59.7 (9.0)	59.7 (9.0)	59.7 (9.0)
Weight (kg)	83.9 (14.9)	84.1 (15.0)	84.4 (14.9)	84.2 (14.9)
BMI (kg/m^2)	29.2 (3.7)	29.2 (3.6)	29.4 (3.5)	29.3 (3.5)
Duration of diabetes (years)	9.0 (6.8)	9.1 (6.8)	8.5 (6.1)	8.6 (6.3)
Duration of OHA treatment (years)	7.0 (5.8)	7.2 (5.9)	7.0 (5.5)	7.1 (5.6)
Metformin treatment	155 (76%)	141 (76%)	155 (74%)	143 (75%)
HbA_{1c} (%)	8.70 (0.96)	8.73 (0.97)	8.67 (0.97)	8.67 (0.97)
FBG (mmol/L)	10.3 (2.0)	10.4 (2.0)	9.9 (2.3)	9.8 (2.2)
C-Peptide (mmol/L)	3.56 (2.2)	3.52 (2.0)	3.60 (2.1)	3.58 (2.2)
Previous treatment with				
Sulfonylureas	186 (91%)	172 (92%)	189 (91%)	174 (91%)
Metformin	159 (78%)	145 (78%)	157 (76%)	147 (77%)
Alpha glucosidase inhibitors	4 (2%)	3 (2%)	6 (3%)	5 (3%)
Thiazolidinediones	4 (2%)	4 (2%)	5 (2%)	5 (3%)
Coexisting disorders related to diabetes*				
Retinopathy	21 (10%)	21 (11%)	21 (10%)	20 (11%)
Neuropathy	45 (22%)	40 (22%)	58 (28%)	53 (28%)
Nephropathy	13 (6%)	12 (7%)	16 (8%)	15 (8%)
Macroangiopathy	25 (12%)	25 (13%)	23 (11%)	23 (12%)

Data are median (IQR), mean (SD), or number (%).

OHAs=oral hypoglycaemic agents. BMI=body-mass index. FBG=fasting blood glucose. HbA_{1c}=haemoglobin A_{1c}.

*The presence of retinopathy, neuropathy, macroangiopathy, or nephropathy was determined by the investigator.

Table 2. Concentrations of blood glucose at baseline and endpoint

	Insulin glargine plus OHAs (n = 186)	Insulin lispro plus OHAs (n = 191)	p value between groups
FBG baseline (mmol/L)	10.4 (2.0)	9.8 (2.2)	
FBG endpoint (mmol/L)	6.1 (1.4)	8.0 (1.8)	
Baseline–endpoint change in FBG (mmol/L)	–4.3 (2.3) (p<0.0001)	–1.8 (2.3) (p<0.0001)	<0.0001
Nocturnal BG baseline (mmol/L)	9.9 (2.5)	9.7 (2.9)	
Nocturnal BG endpoint (mmol/L)	6.6 (2.2)	7.1 (1.8)	
Baseline–endpoint change in nocturnal BG (mmol/L)	–3.3 (2.8) (p<0.0001)	–2.6 (2.9) (p<0.0001)	0.0041
Daytime BG baseline (mmol/L)	9.9 (2.0)	9.6 (2.4)	
Daytime BG endpoint (mmol/L)	6.9 (1.5)	6.4 (1.3)	
Baseline–endpoint change in BG (mmol/L)	–3.0 (2.1) (p<0.0001)	–3.2 (2.4) (p<0.0001)	0.0019
Baseline mean daily BG (mmol/L)	11.1 (2.2)	10.8 (2.6)	
Endpoint mean daily BG (mmol/L)	7.7 (1.6)	7.2 (1.4)	
Baseline–endpoint change in mean BG (mmol/L)	–3.4 (2.3) (p<0.0001)	–3.6 (2.6) (p<0.0001)	0.0147

Data are mean(SD). p values given in parentheses are for change within group. Fasting blood glucose was measured daily and as part of eight-point profiles after breakfast (0600–0900 h), and nocturnal blood glucose was measured at 0300 h. Mean daytime blood glucose was calculated as the mean of seven of the eight measurements (excluding the measurement taken at 0300 h). Mean daily blood glucose was calculated as the mean of all eight points of the profile.

BG=blood glucose. FBG=fasting blood glucose. OHA=oral hypoglycaemic agents.

Table 3. Rates of hypoglycaemia in participants receiving at least one dose of insulin (safety analysis population)

Type of hypoglycaemia	Insulin glargine plus OHAs n = 205	Insulin lispro plus OHAs n = 210	P value
All hypoglycaemia			
Per patient	4.27 (3.27 to 5.26)	19.46 (16.2 to 22.7)	<0.0001
Per patient per year	5.21 (4.02 to 6.40)	24.00 (20.10 to 27.90)	<0.0001
Confirmed all hypoglycaemia (BG ≤3.3 mmol/L)			
Per patient	2.53 (1.92 to 3.14)	15.83 (12.70 to 19.00)	<0.0001
Symptomatic hypoglycaemia			
Per patient	3.46 (2.53 to 4.39)	11.02 (9.24 to 12.80)	<0.0001
Per patient per year	4.23 (3.12 to 5.34)	13.55 (11.44 to 15.66)	<0.0001
Confirmed symptomatic hypoglycaemia (BG ≤3.3 mmol/L)			

Per patient	1.73 (1.25 to 2.21)	7.40 (6.17 to 8.64)	<0.0001
Nocturnal hypoglycaemia			
Per patient	0.42 (0.29 to 0.55)	0.27 (0.16 to 0.38)	0.0709
Per patient per year	0.52 (0.36 to 0.68)	0.34 (0.20 to 0.48)	0.0739
Confirmed nocturnal hypoglycaemia (BG ≤3.3 mmol/L) Per patient	0.25 (0.17 to 0.34)	0.21 (0.12 to 0.30)	0.5190
Severe hypoglycaemia (investigator or protocol defined)* Per patient	0.02 (-0.0007 to 0.0407)	0.06 (0.0219 to 0.0981)	0.0989
Per patient per year	0.03 (0.0052 to 0.0548)	0.08 (0.0300 to 0.1303)	0.0656

Data are rate (95% CI). OHAs=oral hypoglycaemic agents. BG= blood glucose.

*Severe hypoglycaemia was defined as an event with symptoms consistent with hypoglycaemia during which the person required the assistance of another person, *and* which was associated with a blood glucose less than 2.0 mmol/L, and/or with recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Table 4: Assessment of treatment satisfaction

	Insulin glargine (n=188)			Insulin lispro (n=191)			p-value
	N	Mean	SD	N	Mean	SD	
Treatment satisfaction *							
Baseline	187	25.98	7.99	188	26.38	7.87	
Endpoint	187	32.21	4.57	188	29.12	6.51	
Difference	187	6.23	8.35	188	2.74	8.41	< 0.0001
Perceived frequency of hyperglycaemia+							
Baseline	184	3.86	1.90	183	4.02	1.86	
Endpoint	184	1.60	1.68	183	2.15	1.79	
Difference	184	-2.26	2.57	183	-1.87	2.41	0.0036
Perceived frequency of hypoglycaemia ++							
Baseline	187	0.96	1.57	186	1.01	1.53	
Endpoint	187	1.20	1.33	186	1.96	1.64	
Difference	187	0.24	1.87	186	0.95	2.14	< 0.0001

Data are number of questionnaires administered and mean score (SD) The analyses were done for participants completing both the diabetes treatment satisfaction questionnaire (DTSQ) at visit 2 (baseline) and at least one at visit 15 or visit 21 (endpoint). The participants' last on-treatment observation carried forward was used in all the analyses.

* Sum of (DTSQ) items one and four- eight. Higher scores on the 0-36 scale indicate greater patient satisfaction with their treatment.

+ DTSQ Item two: scores ranging from 0 (not at all) to 6 (most of the time)

++ The analysis were done for participants competing both the DTSQ at screening visit 2 (baseline) and at least one at visit 15 or visit 21 (end point).

FIGURE LEGENDS

Figure 1. Trial profile

HbA_{1c}=haemoglobin A_{1c}; OHA=oral hypoglycaemic agents

Figure 2. Improvement in haemoglobin A_{1c} with insulin glargine plus oral hypoglycaemic agents (OHAs) versus insulin lispro plus OHA

Adjusted mean (SE) decrease from baseline (before insulin initiation] to endpoint in the per-protocol population. HbA_{1c}=haemoglobin A_{1c}

Figure 3. 24-h self-monitored blood glucose profiles at eight points throughout the day at baseline (before insulin initiation) and endpoint in insulin glargine plus oral hypoglycaemic agents (OHAs) and insulin lispro plus OHA treatment group in the per-protocol population *p=0.0041; †p=0.0041; ‡p=0.0137 for between treatment comparisons. Times indicated are approximate, with the assumptions that fasting/breakfast was at 0700 h, lunch at 1200 h, dinner at 1800 h and bedtime at 2200 h.

Figure 4. Incidence of overall, symptomatic and severe hypoglycaemic events with insulin glargine and insulin lispro plus oral hypoglycaemic agents during the 44-week treatment period in the safety analysis population.

Figure 1

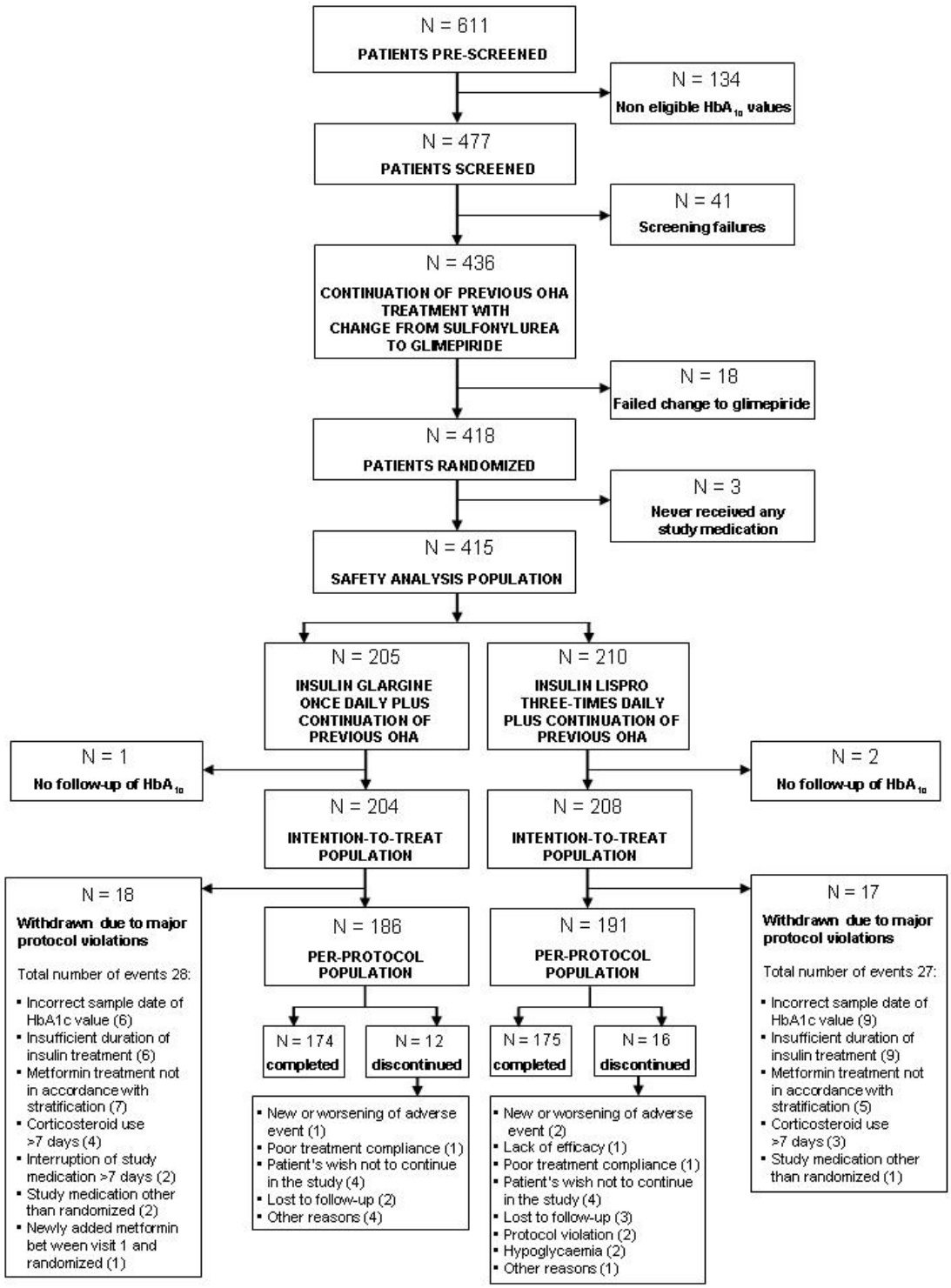

N = 611
PATIENTS PRE-SCREENED
N = 134
Non eligible HbA1c values
N = 477
PATIENTS SCREENED
N = 41
Screening failures
N = 436
CONTINUATION OF PREVIOUS OHA TREATMENT WITH CHANGE FROM SULFONYLUREA TO GLIMEPIRIDE
N = 18
Failed change to glimepiride
N = 418
PATIENTS RANDOMIZED
N = 3
Never received any study medication
N = 415
SAFETY ANALYSIS POPULATION
N = 205
INSULIN GLARGINE ONCE DAILY PLUS CONTINUATION OF PREVIOUS OHA
N = 210
INSULIN LISPRO THREE-TIMES DAILY PLUS CONTINUATION OF PREVIOUS OHA
N = 1
No follow-up of HbA1c
N = 2
No follow-up of HbA1c
N = 204
INTENTION-TO-TREAT POPULATION
N = 208
INTENTION-TO-TREAT POPULATION
N = 18
Withdrawn due to major protocol violations
Total number of events 28:
▪ Incorrect sample date of HbA1c value (6)
▪ Insufficient duration of insulin treatment (6)
▪ Metformin treatment not in accordance with stratification (7)
▪ Corticosteroid use >7 days (4)
▪ Interruption of study medication >7 days (2)
▪ Study medication other than randomized (2)
▪ Newly added metformin bet ween visit 1 and randomized (1)
N = 186
PER-PROTOCOL POPULATION
N = 191
PER-PROTOCOL POPULATION
N = 17
Withdrawn due to major protocol violations
Total number of events 27:
▪ Incorrect sample date of HbA1c value (9)
▪ Insufficient duration of insulin treatment (9)
▪ Metformin treatment not in accordance with stratification (5)
▪ Corticosteroid use >7 days (3)
▪ Study medication other than randomized (1)
N = 174
completed
N = 12
discontinued
N = 175
completed
N = 16
discontinued
▪ New or worsening of adverse event (1)
▪ Poor treatment compliance (1)
▪ Patient's wish not to continue in the study (4)
▪ Lost to follow-up (2)
▪ Other reasons (4)
▪ New or worsening of adverse event (2)
▪ Lack of efficacy (1)
▪ Poor treatment compliance (1)
▪ Patient's wish not to continue in the study (4)
▪ Lost to follow-up (3)
▪ Protocol violation (2)
▪ Hypoglycaemia (2)
▪ Other reasons (1)

Figure 2

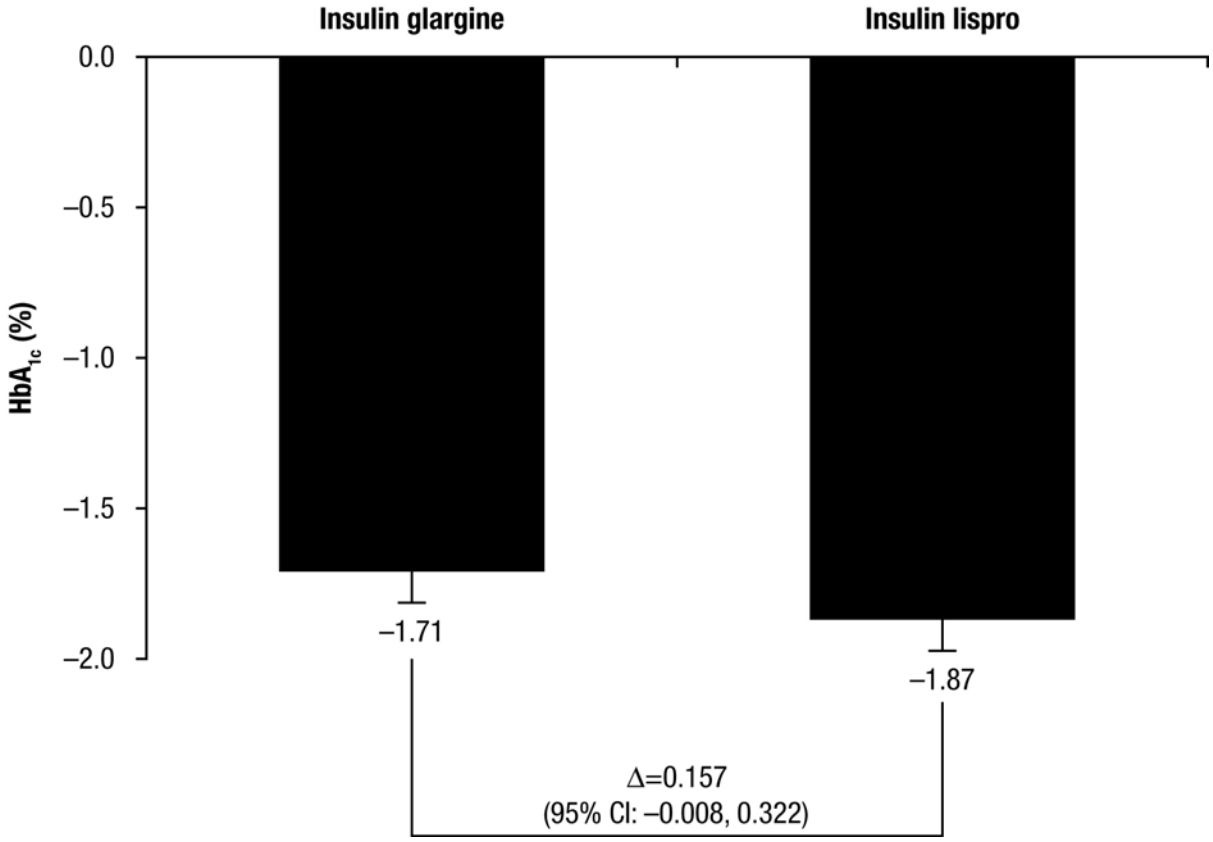

Insulin glargine
Insulin lispro
0.0
−0.5
−1.0
−1.5
−2.0
HbA1c (%)
−1.71
−1.87
Δ=0.157
(95% CI: −0.008, 0.322)

Figure 3

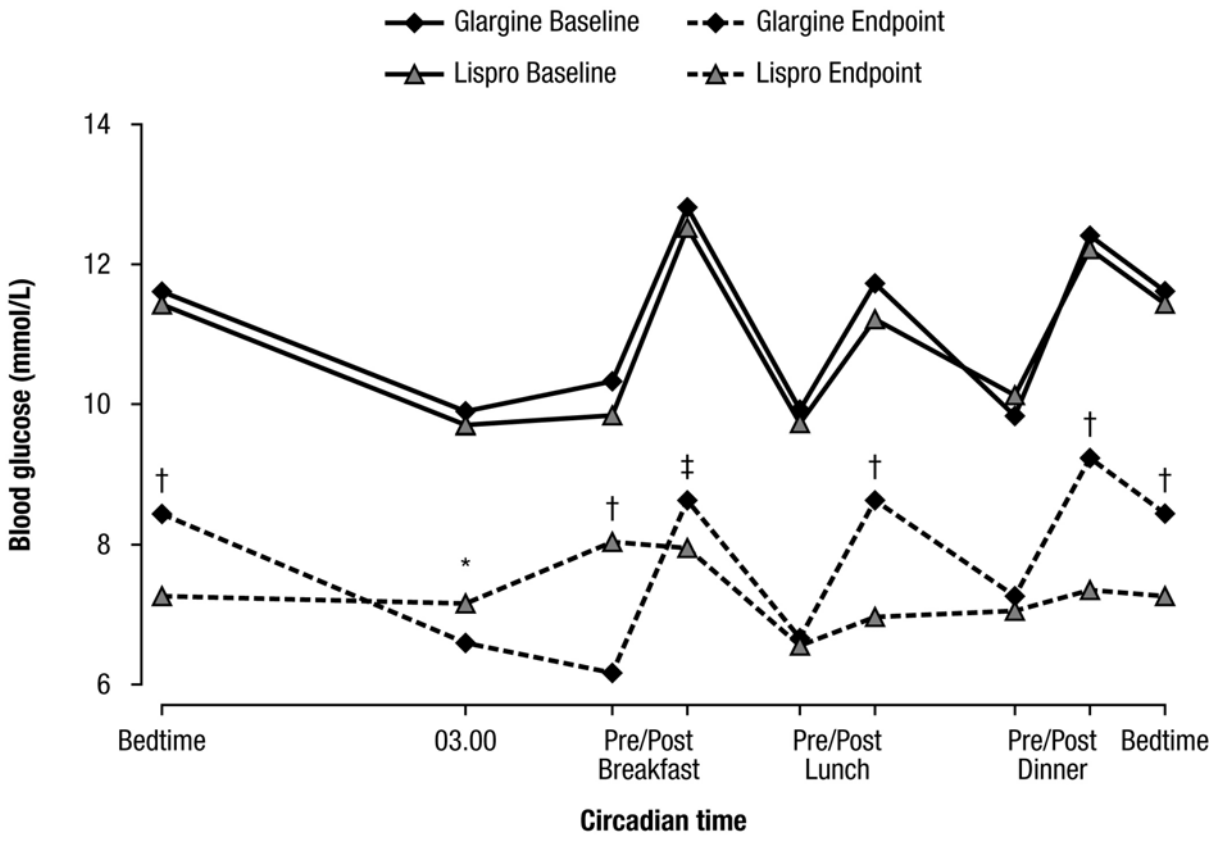
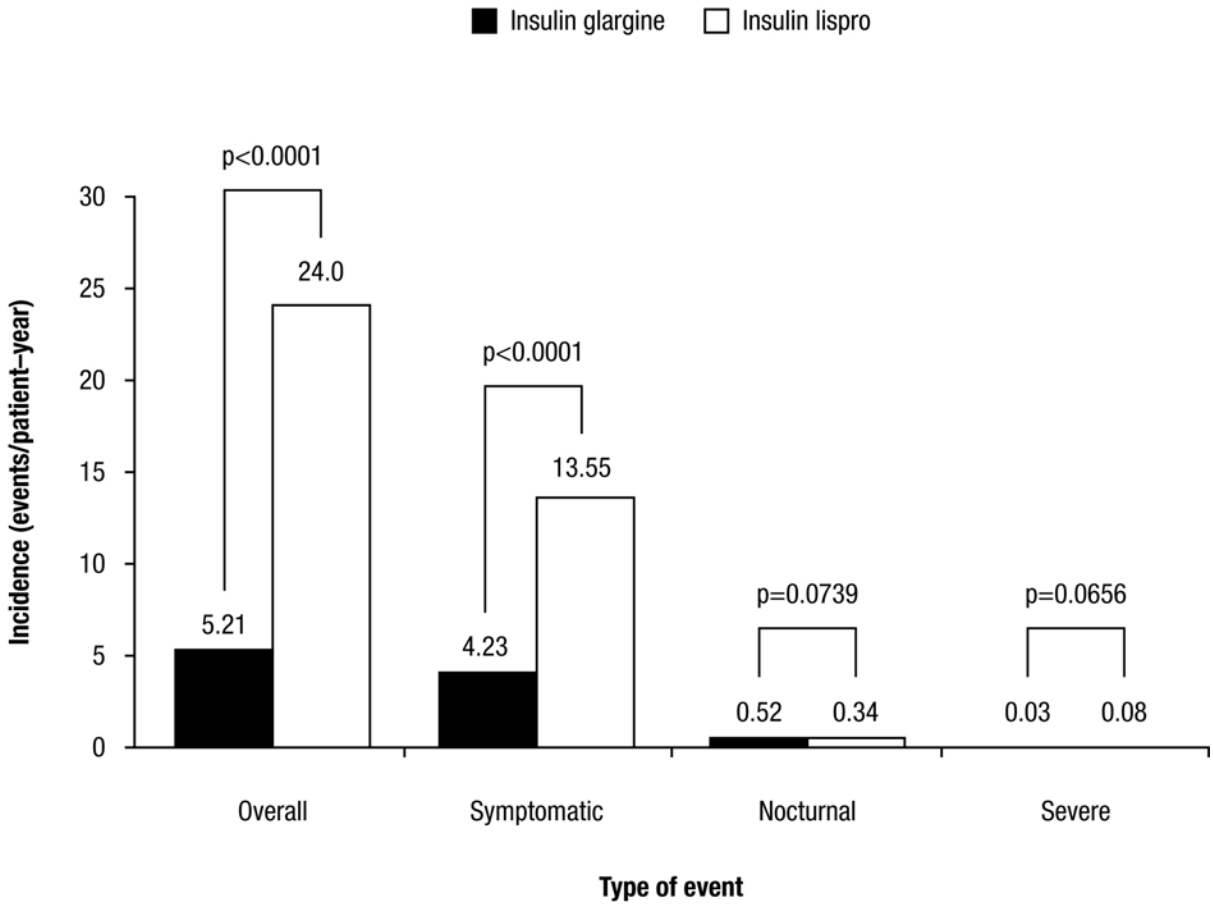

Glargine Baseline
Glargine Endpoint
Lispro Baseline
Lispro Endpoint
Blood glucose (mmol/L)
14
12
10
8
6
†
*
†
‡
†
†
†
Bedtime
03.00
Pre/Post Breakfast
Pre/Post Lunch
Pre/Post Dinner
Bedtime
Circadian time

Figure 4


Insulin glargine
Insulin lispro
p<0.0001
24.0
p<0.0001
13.55
p=0.0739
p=0.0656
5.21
4.23
0.52
0.34
0.03
0.08
30
25
20
15
10
5
0
Incidence (events/patient–year)
Overall
Symptomatic
Nocturnal
Severe
Type of event