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ORIGINAL ARTICLE

Comparison of glycaemic control in patients with Type 2 diabetes on basal insulin and fixed combination oral antidiabetic treatment: results of a pilot study

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Abstract This randomised, open-label, two-way cross-over study compared the coefficient of variance (CV) of fasting and postprandial blood glucose (FBG and PPBG) with insulin glargine (glargine) versus neutral protamine Hagedorn (NPH) insulin treatment in patients with Type 2 diabetes (T2DM). Patients ($N = 20$) on oral antidiabetic drugs (OADs) were treated with NPH (at bedtime) or glargine (at dinnertime) for 12 weeks of each cross-over treatment period; OADs were continued. The FBG CV was calculated from self-monitored BG values and PPBG using venous blood samples, or continuous glucose monitoring system (CGMS). Both insulins provided similar improvements in glycaemic control; however, PPBG was significantly lower after a standard meal test (performed at 13:00 h the day after insulin injection) with glargine versus NPH ($p = 0.02$). Thirteen versus 15 patients experienced $\geq$1 episode of hypoglycaemia with glargine versus NPH. The results suggest that glargine plus OADs is more effective in reducing PPBG fluctuations during the day than NPH plus OADs.

Keywords T2DM · Glycaemic control · Insulin glargine · Neutral protamine Hagedorn · Fasting blood glucose · Postprandial blood glucose

Results from this study have been presented as a poster at the American Diabetes Association annual congress 2007 (Diabetes 2007; 56[Suppl 1]: A148 [Abstract 555-P]).

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Introduction

Type 2 diabetes mellitus is a progressive disease in which good glycaemic control is essential to prevent or delay the onset of microvascular or macrovascular complications [1]. Continuous glucose monitoring system (CGMS) determinations show that standard measurements of glycaemic control underestimate the occurrence of hyperglycaemia in real-life in Type 2 diabetes mellitus. Given the microvascular and macrovascular damage caused by fasting and postprandial hyperglycaemia, CGMS provides an excellent tool to evaluate alternative therapeutic strategies to reduce hyperglycaemia blood glucose (BG) excursions [2].

A recent study, under real-life conditions found that the 24-h pharmacodynamic profile of insulin glargine was associated with better CGMS BG profiles with smaller BG excursions during the day compared with neutral protamine Hagedorn (NPH) insulin [3], and a similar study found that switching from NPH insulin to insulin glargine also resulted in improved CGMS profiles [4]. Diet and exercise are initially recommended to improve glycaemic control; however, over time this strategy is usually insufficient to maintain glycaemic control, necessitating the introduction of oral antidiabetic drugs (OADs) [5]. As the disease progresses, management with OADs alone becomes increasingly difficult and the addition of insulin therapy is required [6].

Insulin glargine (LANTUS®, sanofi-aventis, Paris, France) is a long-acting human insulin analogue with a smooth action profile and no pronounced peak in action [7] that more closely mimics endogenous basal insulin to provide 24-h cover. Insulin glargine is also associated with a reduced risk of hypoglycaemia compared with the traditionally used, intermediate-acting, NPH insulin [8]. Although the effect of insulin glargine on fasting blood

glucose (FBG) is well characterised in Type 2 diabetes mellitus, less is known about its effects on postprandial glucose handling. Therefore, the aim of the present study was to determine either by CGMS or by venous plasma glucose excursion measurement the relative impact of insulin glargine and NPH insulin on FBG and postprandial glucose handling after a mixed meal in patients with Type 2 diabetes mellitus.

Here, we report results of a pilot study of insulin glargine versus NPH insulin, both in combination with OADs, in a two-way cross-over study to determine their effects on glucose variability after 12 weeks of treatment.

Methods

Objectives

The primary objective of this study was to evaluate the coefficient of variability (CV) of FBG calculated from self-monitored blood glucose (SMBG) values.

The secondary objectives of the study included: glycaemic control (including measurements of glycated haemoglobin [HbA_{1c}] and FBG levels); hypoglycaemia; changes in body weight, final insulin dose and lipid profile; and profiles of patients that best fitted each of the algorithms with the dependent variable of change in HbA_{1c} and independent variables, such as age, gender, race, tobacco use, diabetes complications, initial HbA_{1c}, initial weight, duration of diabetes mellitus, general education and diabetes education. Safety was assessed by the monitoring of adverse events and other routine laboratory parameters.

Study design

This was an open-label, national, single-centre, randomised, controlled, two-way cross-over exploratory study. The study comprised a 1-week run-in phase, followed by two 12-week treatment phases and a 2-week safety follow-up phase (Fig. 1).

Study endpoints

The primary endpoint was FBG CV calculated from SMBG values obtained during the last 4 weeks before Visit (V)3 (end of Treatment Phase 1) and V4 (end of Treatment Phase 2). The secondary endpoints were glycaemic control, as measured by HbA_{1c}, FBG, insulin and C-peptide. In addition, glycaemic control was measured by the glucose levels after a standard meal test determined from venous blood samples or using a CGMS (Glucoday®, A.Menarini Diagnostics, Florence, Italy). Other parameters investigated were changes in urinary albumin-to-creatinine ratio; changes in lipid profiles (serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides); frequency of hypoglycaemia; general safety and any adverse events reported by patients at each visit; and changes in weight and final insulin dose as documented throughout treatment cycles. The analysis of HbA_{1c}, plasma insulin, C-peptide, glucagon and free fatty acids was performed at Exacta Lab (Verona, Italy).

Patients

The primary inclusion criteria included male or female patients ≥45 years old with a diagnosis of Type 2 diabetes mellitus (duration ≥5 years); treatment with OADs in fixed combination (glibenclamide [2.5 mg] + metformin [400 mg]; two or three tablets per day) at a stable dose in the last 3 months; HbA_{1c} ≥8 and ≤11%; body mass index >27 and <35 kg/m^2; and willingness and ability to inject insulin and perform SMBG. The primary exclusion criteria included patients diagnosed with Type 1 insulin-dependent diabetes mellitus; patients with fasting C-peptide levels <1 ng/ml (to potentially exclude patients with latent autoimmune diabetes of adults); cardiac status New York Heart Association III–IV; impaired renal function as shown by (but not limited to) serum creatinine ≥1.5 mg/dl for males or ≥1.4 mg/dl for females; and planned pregnancy, pregnant or lactating females. The study was conducted in accordance with the

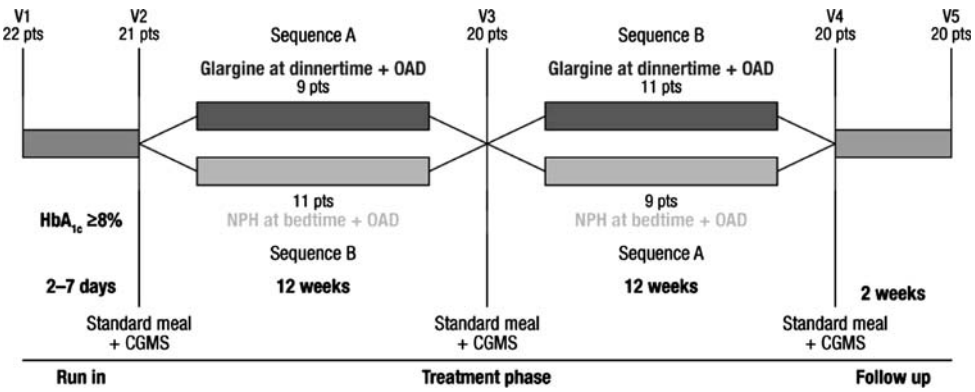

Fig. 1 Study design and visit schedule. *V* visit, *pts* patients, *OAD* oral antidiabetic drugs, *HbA_{1c}* haemoglobin A1c, *NPH* neutral protamine Hagedorn insulin, *CGMS* continuous glucose monitoring system

Declaration of Helsinki. Approval by an institutional ethics committee was obtained. All patients provided written informed consent prior to study entry.

Study protocol

After a standard clinical evaluation (V1), eligibility was confirmed and patients were given standardised diet instructions at study entry. At V2 (baseline), patients were randomised to either Sequence A (insulin glargine followed by NPH insulin) or Sequence B (NPH insulin followed by insulin glargine) (Fig. 1). Study drugs were crossed over after 12 weeks of treatment (V3), followed by a fourth visit (V4) performed at the end of the second 12-week treatment cycle. A final follow up (V5) was undertaken 2 weeks after the end of the second 12-week treatment phase (Fig. 1). The starting insulin glargine/NPH insulin dose was 10 IU/day and was titrated every 3 days according to SMBG levels (target FBG: <100 mg/dl), using a modified algorithm (Table 1) based on the Treat-to-Target study [9].

At V2, V3 and V4, participants were fitted with the CGMS device and underwent a mixed meal test, comprising 350 kCal (55% carbohydrates, 26% lipids, 19% proteins) at 13:00 h. Venous blood samples were taken before the meal and 30, 60 and 120 min after the end of the meal, in addition to CGMS monitoring. Throughout the study, SMBG was performed by patients using a glucometer stick test. Measurements of glycaemia in the 48 h after V2, V3 and V4 were performed by CGMS.

Table 1 Insulin titration algorithm

Mean FBG (mg/dl)	Change in insulin dose (U/IU)
>180	+6
160–180	+5
140–159	+4
120–139	+2
100–119	+1
70–99	No change
<70	−2

The starting insulin glargine/NPH insulin dose was 10 U/IU per day. The dose of insulin glargine/NPH insulin was to be titrated every 3 days according to the SMBG level, based on the mean FBG value over the last 2 days. Titration was performed using the algorithm presented in Table 1. Up-titration was to be stopped temporarily for 1 week in the event of severe hypoglycaemia, unless there was an explanation for the event (e.g. omission of a meal). Insulin glargine was to be administered at dinnertime; NPH insulin was to be administered at bedtime

NPH neutral protamine Hagedorn, *SMBG* self-monitored blood glucose, *FBG* fasting blood glucose

Statistical analysis

The efficacy and safety analyses were performed in the intent-to-treat population. Descriptive summary statistics (number of patients, mean, standard deviation, minimum, maximum) were provided for quantitative variables, while frequency (absolute and relative) distributions were provided for categorical variables. The continuous variables recorded at V2, V3 and V4 were analysed using an analysis of variance (ANOVA) according to a cross-over design, with period and treatment effect. Multiple comparisons were calculated for the general mean of the baseline insulin glargine and NPH insulin values. The comparisons were performed compared with the baseline mean and between treatments and are reported with the corresponding 95% confidence interval (CI). For each parameter recorded during the meal test, the area under the curve (AUC) adjusted for the basal value (time 0) was calculated according to the trapezoidal rule and analysed with the same cross-over model used in the ANOVA applied to the main parameters. Multiple comparisons were also carried out with the related 95% CI.

Results

Study population

Twenty-one patients were randomised to receive the assigned treatment, of whom ten were assigned to Sequence A (insulin glargine followed by NPH insulin) and 11 were assigned to Sequence B (NPH insulin followed by insulin glargine). One patient assigned to Sequence A discontinued the study at V2 owing to consent withdrawal. Therefore, 20 patients completed the total study period (9 in Sequence A and 11 in Sequence B). The baseline characteristics were similar between the treatment groups (Table 2).

Table 2 Baseline characteristics of 20 patients completed

Characteristic	
Males/females (*n* [%])	14 (70)/6 (30)
Age (years)	59.4 ± 8.2
Weight (kg)	82.7 ± 8.7
Body mass index (kg/m^2)	29.5 ± 2.0
HbA_{1c} (%)	9.3 ± 1.4
Fasting blood glucose (mg/dl)	203.6 ± 58.3

All data are mean ± standard deviation unless otherwise stated

HbA_{1c} haemoglobin A_{1c}

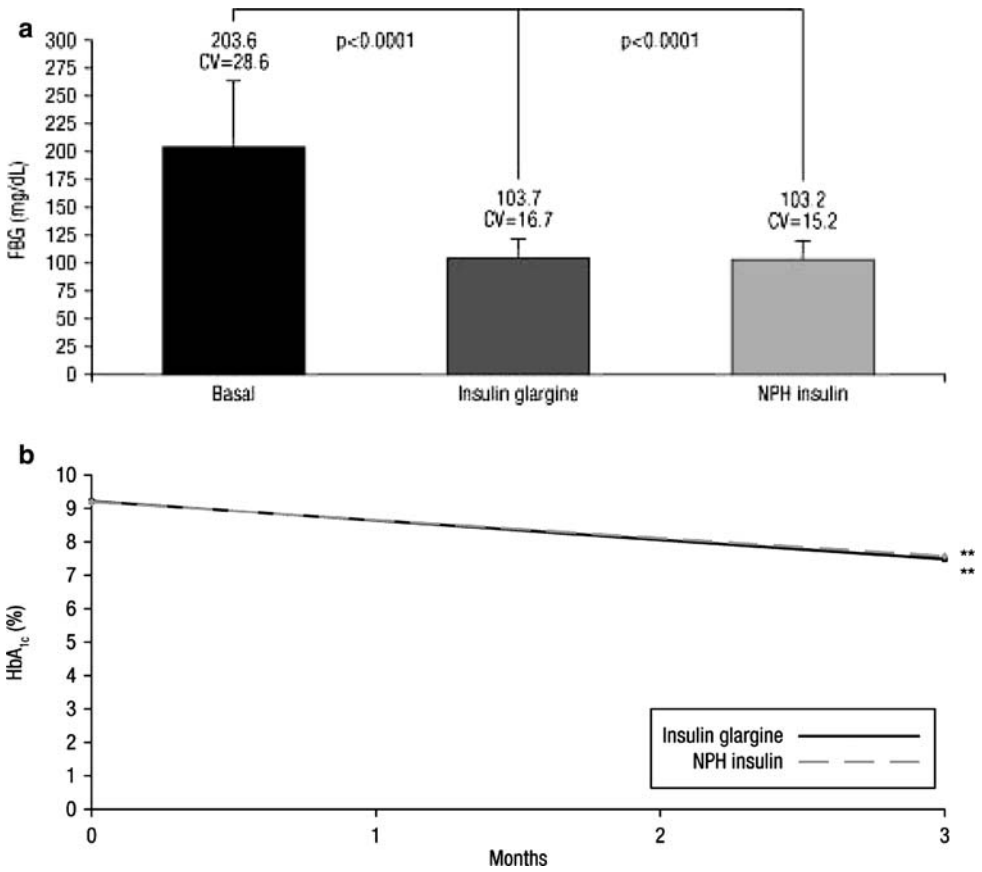

Fig. 2 **a** Fasting blood glucose as measured by self-monitoring at baseline and at endpoint. Results are means ± coefficient of variation. *CV* coefficient of variation, *FBG* fasting blood glucose, *NPH* neutral protamine Hagedorn. **b** HbA_{1c} levels across both study drugs. HbA_{1c} haemoglobin A1c, *NPH* neutral protamine Hagedorn; $^{**}p < 0.01$ versus baseline

Glycaemic control

Over the duration of the study, the decrease in FBG values was significant for both study therapies ($p < 0.0001$ for both) with no significant differences between the two insulins ($p = 0.95$) (Fig. 2a). HbA_{1c} decreased significantly with both insulin glargine (mean ± standard deviation [SD]: −1.7 ± 1.6%) and NPH insulin (−1.6 ± 1.6%) compared with baseline ($p < 0.0001$ for both) (Fig. 2b). The mean amplitude of glucose excursions (MAGE) index measured in the SMBG tended to improve between baseline and endpoint with both insulin glargine (−17.0 mg/dl; 95% CI: −34.5, 0.6 mg/dl; $p = 0.058$) and with NPH insulin (−13.1 mg/dl; 95% CI: −31.4, 5.3 mg/dl; $p = 0.152$), but there was no difference between the two insulins ($p = 0.603$). Mean daily BG (MDBG) measured in the SMBG improved significantly between baseline and endpoint with both insulin glargine (−40.9 mg/dl; 95% CI: −57.0, −24.8 mg/dl; $p < 0.0001$) and with NPH insulin (−43.9 mg/dl; 95% CI: −59.9, −27.8 mg/dl; $p < 0.0001$): there were no differences between the two insulins ($p = 0.701$).

Meal test

The CGMS-determined post-meal test BG profile revealed a lower BG excursion with insulin glargine than with NPH insulin ($p < 0.05$ at 5-h post-meal test and $p < 0.01$ at 6-h post-meal test; Fig. 3a). In response to the standard meal test, postprandial BG control was better overall with insulin glargine, with a significantly lower AUC at endpoint ($p = 0.02$) compared with NPH insulin (Fig. 3b). The plasma insulin AUC decreased between baseline and endpoint with both insulin glargine (−61.5 mU/l min; 95% CI: −97.2, −25.7 mU/l min; $p = 0.002$) and NPH insulin (−31.8 mU/l min; 95% CI: −66.5, 2.9 mU/l min; $p = 0.070$), the magnitude of which tended to be greater with insulin glargine, although this was not significant ($p = 0.109$). The plasma glucagon AUC (μg/l min) was similar with insulin glargine and NPH insulin (mean ± SD: 148.7 ± 12.6 vs. 153.5 ± 12.4 μg/l min; $p = 0.3682$), and was unchanged from baseline (146.4 ± 12.3 μg/l min; $p > 0.05$ for both). The plasma C-peptide AUC increased between baseline and endpoint with both insulin glargine (+17.6 μg/l min; 95% CI: −3.4, 38.7 μg/l min; $p = 0.096$) and with NPH insulin (+39.1 μg/l min; 95% CI: 16.0, 62.2 μg/l min; $p = 0.002$). Although the change tended to be greater with NPH insulin, this was not significant ($p = 0.090$).

Insulin therapy

The total daily dose at endpoint was 28.8 U versus 34.7 IU for insulin glargine versus NPH insulin, respectively.

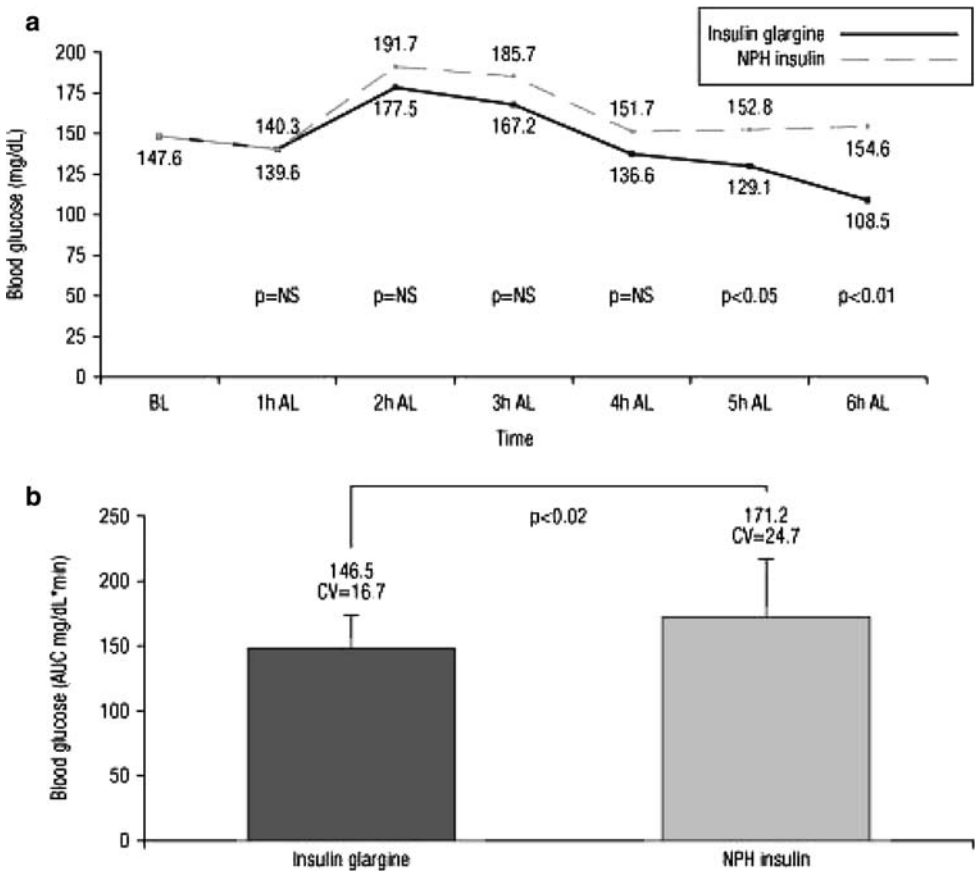

Fig. 3 **a** Continuous glucose monitoring system profiles in response to the meal test. *BL* before lunch, *NS* non-significant, *AL* after lunch, *NPH* neutral protamine Hagedorn. **b** Meal test blood glucose levels after each treatment. Results are means ± coefficient of variation. *AUC* area under the curve, *CV* coefficient of variation, *NPH* neutral protamine Hagedorn

Hypoglycaemia and safety

Thirteen insulin glargine-treated patients and 15 NPH insulin-treated patients experienced at least one episode of hypoglycaemia during treatment. Of those patients receiving insulin glargine, four patients had one episode, three patients had two episodes, two patients had three episodes and four patients had more than five episodes of hypoglycaemia. Among patients receiving NPH insulin, one patient had one episode, two patients had two episodes, three patients had three episodes, two patients had five episodes and seven patients had more than five episodes. None of the episodes in either treatment group was considered to be severe. Overall, the incidence of hypoglycaemia was lower with insulin glargine versus NPH insulin (1.04 vs. 2.12 episodes/patient per month).

Three patients experienced at least one adverse event during treatment with insulin glargine. None of the events was considered to be related to study drug.

Other secondary parameters

No significant changes were observed in either treatment group at any time point for other secondary parameters, including body weight, haematology or blood chemistry.

Discussion

This study demonstrates that the initiation of insulin therapy with OADs effectively improves glycaemic control in patients with Type 2 diabetes mellitus. Both insulins achieved similar improvements in FBG, MAGE, MDBG and HbA_{1c} over 12 weeks of treatment, with comparable improvements in within-patient variability, and supporting the perception that there was no clinically different impact on glycaemic control. Aside from the overall measures of glycaemic control, participants in our study also underwent standard meal tests (at 13:00 h), at baseline and after each 12-week treatment period.

Although both treatments provided comparable improvements in glycaemic control, blood glucose AUCs were significantly higher with NPH insulin (administered once daily at bedtime) compared with insulin glargine (administered once daily at dinnertime). Taking into account the cross-over study design, these results indicate that insulin glargine may provide better control of the postprandial glucose levels, as measured by the meal test. This finding may be related to a waning of the effect of NPH insulin, which was administered at bedtime (approximately 22:00 h), owing to its duration of action of 12–18 h [7] and rate of subcutaneous absorption [10]. It may be that, if

NPH insulin had been administered twice daily, the post-meal glucose levels may have more closely matched those achieved with insulin glargine.

Owing to the relatively small sample size of our study (20 patients completed both arms of the study), and the fact that there is some evidence for a carry-over effect after cross-over, results presented here should be interpreted with caution. However, the results of this pilot study warrant prospective evaluation in a larger population of patients, which could be powered based on the magnitude of differences between the two treatment groups. Further studies are warranted using a larger patient population to better compare the differences in post-meal glucose handling between insulin glargine and NPH insulin to better define the qualitative aspect of each HbA_{1c} level detected at the end of each treatment. It is clear from our results that insulin glargine provides significant improvements in glycaemic control at lunchtime compared with NPH insulin. Nevertheless, management of the fasting and postprandial components of glycaemic control is important owing to their contributions to overall glycaemic control [11]. The introduction of short-acting insulin at mealtimes may help these patients achieve their glycaemic goals. It may be that, with better understanding of the impact of insulin glargine on postprandial glycaemia, the administration of prandial insulin at the meal associated with the highest glucose excursion may provide the required improvements in glycaemic control [12]. Indeed, this was partly evaluated in the Orals Plus insulin glulisine and insulin glargine (OPAL) study, in which patients treated with insulin glargine plus OADs were randomised to receive once-daily insulin glulisine at either breakfast or the main meal (defined as the meal associated with the largest prandial glucose excursion). In that study, the improvements in glycaemic control were comparable in both treatment groups (equivalence of breakfast versus main meal administration was shown), but there was a tendency for more patients in the main meal versus breakfast group to reach HbA_{1c} $\leq$6.5% (33.8 vs. 27.8%) [13]. Accordingly, future studies could evaluate the postprandial glucose excursions using CGMS in a 'real-life' situation of patients treated with insulin glargine at dinnertime or bedtime. The lower blood glucose fluctuations during the day with glargine versus NPH can be detected by additional qualitative measurements of glycaemic control or new CGMS measurements on top of traditional quantitative HbA_{1c} values [14]. In fact, a recent study conducted in patients with diabetes by Nathan and colleagues found that a linear relationship exists between HbA_{1c} levels and average glucose (AG), as measured by CGMS in a clinically relevant range of glycaemia [15].

The control of glycaemic levels by limiting the magnitude of hyperglycaemia spikes (Fig. 3a) or hypoglycaemia troughs in the management of insulin therapy of Type 2 diabetes mellitus patients can prevent the development of long-term diabetes complications, such as cardiovascular disease, nephropathy, retinopathy and neuropathy [16–18]. The quantitative measurement of HbA_{1c} levels is a widely used, reliable, simple and easy method for assessing glycaemic control [17, 19, 20]. Indeed, current diabetes guidelines have delineated target HbA_{1c} levels to prevent long-term diabetic complications [16–18, 21]. However, measuring glycaemic control by utilising standard measurements of HbA_{1c} levels can limit, by masking the true nature of glycaemic variability, the clear interpretation of biological efficiency of insulin treatment from a long-term perspective [22, 23] for people with diabetes and especially for those with Type 2 diabetes mellitus [24].

In conclusion, the results indicate that adding insulin glargine to existing OADs is more effective in reducing postprandial BG fluctuations during the day compared with NPH insulin plus OADs, with a lower incidence of hypoglycaemia.

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Conflict of interest statement The authors have received funding from sanofi-aventis for consulting and speaking, as well as reimbursement for attending a symposium.

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