Initiating Insulin Therapy in Type 2 Diabetic Patients Failing on Oral Hypoglycemic Agents

Basal or prandial insulin? The APOLLO trial and beyond

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Type 2 diabetes is a chronic disease characterized by coexisting insulin deficiency and insulin resistance, with the resultant hyperglycemia leading to micro- and macrovascular complications. A large number of intervention trials demonstrated that improving glycemic control achieves considerable reductions of such complications (1–7).

It has been estimated using the homeostasis multiple assessment (HOMA) that, at the time of diagnosis, ~50% of pancreatic β-cell function has been lost, with almost 4% further loss of function expected per year thereafter (8,9). Therefore, type 2 diabetes is a chronic progressive disease characterized by worsening hyperglycemia and escalating deterioration in the function of pancreatic β-cells and loss of β-cell mass (10). Because of the progressive nature of the disease, an evolving treatment strategy is therefore necessary to maintain both fasting and postprandial glycemic control. Recently, an American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) Consensus recommended a target of A1C <7% for good glucose control in clinical practice (11). Insulin therapy is required when dietary restrictions and lifestyle modifications combined with oral hypoglycemic agents (OHAs) failed to provide acceptable metabolic control (12). One major lesson learned from the milestone U.K. Prospective Diabetes Study (UKPDS) is the increasing requirement for multiple therapies in patients with type 2 diabetes to achieve blood glucose (BG) target control (13).

The augmentation of insulin to OHAs contributed to several beneficial metabolic effects, as recently reviewed (14). However, there is ongoing debate as to whether it is more rewarding to target postprandial BG concentrations with meal-related insulin, or to target fasting BG concentrations with basal insulin. Monnier et al. (15,16) provided data to explain the relative contribution of fasting and postprandial BG to A1C in patients with mild-to-moderate hyperglycemia (A1C <7.3%) than in those with more poorly controlled blood glucose.

The APOLLO trial (*A P*arallel design comparing an *O*ral antidiabetic drug combination therapy with either *L*antus once daily or *L*ispro at mealtime in type 2 diabetic patients failing *O*ral treatment), a multicenter randomized prospective study, addressed the issue of targeting either prandial or fasting BG concentrations (17).

HOW TO INITIATE BASAL OR PRANDIAL INSULIN THERAPY: THE APOLLO TRIAL

— In the 44-week parallel open study that was performed in 69 study sites across Europe and Australia, 418 individuals with type 2 diabetes inadequately controlled by OHAs (excluding α-glucosidase inhibitors) were randomly assigned to either basal insulin glargine (Lantus; sanofi-aventis, Frankfurt, Germany) once daily, at the same time every day, or to mealtime insulin lispro (Humalog; Eli Lilly, Bad Homburg, Germany) administered thrice daily in addition to the OHAs. The primary objective was to compare the change in A1C from baseline to end point (week 44) between the two regimens. In addition, secondary objectives included the percentage of participants who achieved A1C of 6.5 or 7.0% or less, respectively, the number of hypoglycemic events, the change in body weight in both treatment arms, and treatment satisfaction.

Male and female patients were eligible for enrollment if they were aged between 18 and 75 years. Additional inclusion criteria: type 2 diabetes for ≥1 year with an A1C concentration between 7.5 and 10.5%, OHA treatment for at least 6 months with stable doses for ≥3 months before study entry, fasting BG concentrations of ≥6.5 mmol/l, and BMI of ≤35 kg/m^2. All participants were willing to perform self-monitoring of BG, and all provided written informed consent for their participation before study entry.

Of 412 patients in the intention-to-treat population, a total of 35 patients were excluded because of major protocol deviations during the study. Thus, the per-protocol population comprised 377 patients (186 in the insulin glargine and 191 in the insulin lispro groups) who were included in our analyses. After randomization, 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 groups were prescribed glimepiride, with only 11 (6%) patients assigned to insulin glargine, and 14 (7%) to insulin lispro, without glimepiride. Patient demographics (mean age, 59.7 years in both arms; BMI: 29.2/29.3 kg/m^2; duration of OHA treatment: 6.8/6.3 years, glycemic control: A1C: 8.73/8.67%, and fasting

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Table 1—*Insulin glargine dose titration algorithm and monitoring*

Starting dose: 10 IU/day		
Titration monitoring	Direct investigator contact. Fasting BG and insulin dose submitted to coordinating center by electronic data capture. Additional weekly calls to adjust insulin dose if A1C >7%	
Insulin dose titration algorithm	If self-monitored fasting BG for 2 consecutive days with no severe hypoglycemia:	
	>8.9 mmol/l (>160 mg/dl)	Add 8 IU/day
	>7.8 to ≤8.9 mmol/l (>140 to ≤160 mg/dl)	Add 6 IU/day
	>6.7 to ≤7.8 mmol/l (>120 to ≤140 mg/dl)	Add 4 IU/day
	>5.5 to ≤6.7 mmol/l (>100 to ≤120 mg/dl)	Add 2 IU/day
	5.5 mmol/l (≤100 mg/dl)	No further titration

BG: 10.4/9.8 mmol/l, in both groups, respectively) were similar at baseline.

During the treatment phase, insulin doses were adjusted by a forced titration regimen to a target fasting BG <5.5 mmol/l in the insulin glargine group, and a preprandial BG <5.5 mmol/l and a postprandial BG <7.5 mmol/l in the insulin lispro group, in accordance with the insulin titration algorithms proposed by the European Diabetes Policy Group in 1999 (18). Insulin dose titration algorithms and monitoring are presented in Tables 1 and 2. At the start of screening, at week 20, and at week 44 (study end point), a validated diabetes treatment satisfaction questionnaire was distributed among the patients (19).

Hypoglycemia was defined as an event with or without symptoms consistent with hypoglycemia, not requiring the assistance of another person, and associated with BG concentration of <3.3 mmol/l. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia, necessitating assistance, associated with a BG concentration of <2.0 mmol/l, or recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as hypoglycemia, occurring while the individual was asleep and before arising in the morning. Whenever participants awoke during the night and experienced symptoms of hypoglycemia, self-monitoring of BG was performed and documented in the patients' diary.

Table 2—*Insulin lispro dose titration algorithm and monitoring*

Starting dose: 4 IU/meal		
Titration monitoring	Direct investigator contact. Fasting BG and insulin dose submitted to coordinating center by electronic data capture. Additional weekly calls to adjust insulin dose if A1C >7%	
Preprandial BG Insulin dose titration algorithm	>10.3 mmol/l (>185 mg/dl)	Add 3 IU before main meal
	>8.3 to ≤11.1 mmol/l (>150 to ≤200 mg/dl)	Add 2 IU before main meal
	>5.5 to ≤8.3 mmol/l (>100 to ≤150 mg/dl)	No further titration
Postprandial BG Insulin dose titration algorithm	>10.3 mmol/l (>185 mg/dl)	Add 2 IU before main meal
	>7.5 to ≤10.3 mmol/l (>135 to ≤185 mg/dl)	Add 1 IU before main meal
	≤7.5 mmol/l (≤135 mg/dl)	No further titration

Both treatment regimens were equally effective in lowering A1C concentrations to target (≤7%) at study end, with similar differences between the adjusted means (−1.71 vs. −1.87%), which was within the predefined 0.4% limit for parity for the differences of A1C between the groups (Fig. 1).

Figure 2 illustrates reductions of fasting BG concentrations over the 44-week trial period as well as the difference in the degree of change from baseline to end point between the groups ($P < 0.0001$). Insulin glargine achieved a reduction in the fasting glucose level from 10.4 to 6.2 mmol/l (Fig. 2). In comparison, a much smaller reduction in fasting glucose level from 9.8 to 8.08 mmol/l was seen in the insulin lispro group (Fig. 2).

Compared with baseline, 106 (57%) patients in the insulin glargine group and 131 (69%) patients in the insulin lispro group achieved the A1C target of ≤7% (Table 3). Significantly more patients in the insulin glargine group reached the fasting BG target of ≤5.5 mmol/l than with insulin lispro at study end point (71 [38%]) versus 11 [6%]) (Table 3). Conversely, a significantly greater reduction of the 2-h postprandial BG was achieved with insulin lispro than insulin glargine after breakfast: −4.6 vs. 4.2 mmol/l ($P = 0.0421$); lunch: −4.3 vs. −3.1 mmol/l ($P < 0.0001$); and dinner: −5.0 vs. −3.2 mmol/l ($P < 0.0001$), respectively. Both insulin preparations were also effective beyond the targets of their titration algorithms. Insulin glargine resulted in a highly significant ($P < 0.0001$) absolute reduction of mean daytime glucose level from baseline to end point: 9.9 ± 2.0 to 6.9 ± 1.5 mmol/l, which corresponds to −3.0 ± 2.1 mmol/l. The insulin lispro group showed an absolute reduction from baseline to end point of 9.7 ± 2.9 to 7.1 ± 1.8 mmol/l corresponding to −1.8 ± 2.3 mmol/l, which was also highly significant ($P < 0.0001$).

The mean score for treatment satisfaction improved in both groups from baseline to end point, but the magnitude of change was significantly greater with insulin glargine than with insulin lispro

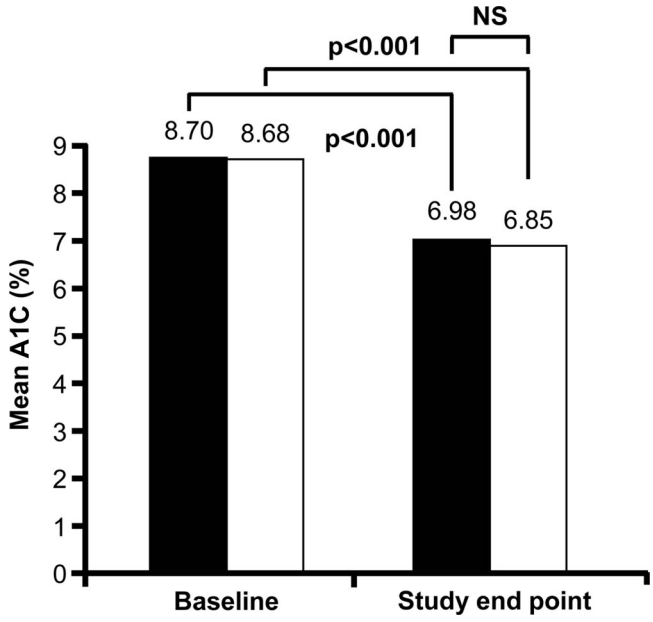

Figure 1—*Improvement in A1C with insulin glargine plus OHAs (■) versus insulin lispro plus OHAs (□) from baseline to end point (44 weeks) in the per-protocol population. Change from baseline not significantly different between both groups.*

(difference of the magnitude of change 3.49; $P < 0.0001$) (Fig. 3).

As can be seen in Fig. 4, the rates of all, including confirmed all (BG ≤3.3 mmol/l), symptomatic, and confirmed symptomatic hypoglycemic episodes (BG ≤3.3 mmol/l), were significantly lower with insulin glargine than with insulin lispro (all $P < 0.0001$). However, the rates of nocturnal, confirmed nocturnal, and severe hypoglycemic episodes were comparable in both groups (Fig. 4).

Weight gain was recorded between baseline and end point in both the insulin glargine (3.01 ± 4.33 kg) and insulin lispro (3.54 ± 4.48 kg) groups, although the difference did not reach significance ($P = 0.23$). There was no significant variation in the rates of adverse and severe adverse events between the two treatment groups.

A similar study, the Treating to Target in Type 2 Diabetes Trial (4-T study), recently published the 1-year interim analysis (20). In their basal insulin treatment group, insulin detemir (Novo Nordisk, Bagsvaerd, Denmark) was used once or twice daily and insulin aspart (Novo Nordisk) administered premeal thrice daily, representing the prandial insulin treatment group. Data on an additional group of patients who received premixed insulin twice daily is not discussed here. Excluding the latter, the study design and overall baseline characteristics were analogous to those in the APOLLO trial.

The reduction of A1C in both (basal and prandial) treatment groups was lower in the 4-T study than in the APOLLO trial (Table 3). Furthermore, twice as many patients in the basal insulin cohort achieved target A1C <7% in the APOLLO trial compared with the 4-T study, despite apparently equivalent insulin doses administered in both studies, and despite the twice-daily dose of basal insulin detemir that was required in 34% of the patients in the 4-T study (Table 3). In the APOLLO trial, the quality-of-life assessment improved in both groups with significant ($P < 0.0001$) advantage of basal insulin treatment over the prandial regimen, using a different quality-of-life assessment score (21). In the 4-T study, there was no significant difference between the groups (Table 3).

Both studies also noted a significantly lower risk of hypoglycemia with basal compared with prandial insulin treatment (Table 3). The patients of the 4-T study on insulin detemir reported on 50% less incidences of hypoglycemia per patient year compared with those on insulin glargine in the APOLLO trial. This effect may be explained by the lower magnitude of A1C reduction in the 4-T study group compared with baseline (Δ baseline versus end point −1.75 in the APOLLO trial and −0.80 in the 4-T study).Weight gain after 1 year was significantly lower in the basal insulin detemir group compared with the prandial insulin aspart group in the 4-T study, whereas weight gain after 44 weeks was only slightly less in the basal insulin glargine group, but the difference with prandial insulin lispro did not reach statistical significance in the APOLLO trial.

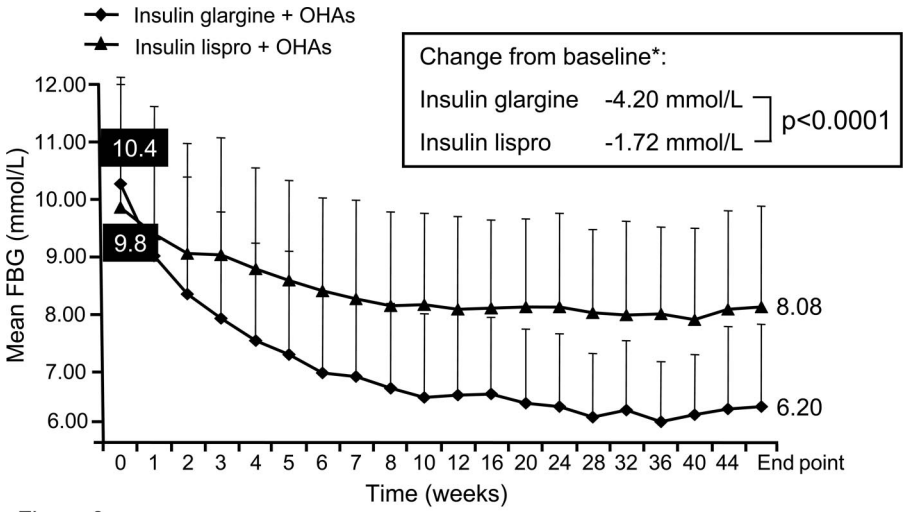

Figure 2—*Reduction in fasting blood glucose (FBG) with insulin glargine plus OHAs versus insulin lispro plus OHAs from baseline to end point (44 weeks) in the per-protocol population. Change from baseline significantly greater in the glargine group.*

SHOULD NPH INSULIN OR INSULIN GLARGINE BE USED FOR BASAL INSULIN THERAPY?

— It has been shown that the supplementation of basal insulin reduces the entire 24-h fasting BG profile (22). This improvement results predominantly from suppression of overnight hepatic glucose production, both via direct effects on the liver and indirect effects

Table 3—*Main outcomes in the APOLLO trial and the 4-T study*

	APOLLO		4-T	
	Target A1C ≤7% at 44 weeks		Target A1C ≤7% at 52 weeks	
	Basal*	Prandial†	Basal*	Prandial†
A1C (%)				
At baseline	8.73	8.67	8.40	8.60
At endpoint	6.98	6.80	7.60	7.20
Δ (baseline vs. endpoint)	−1.75	−1.87		−1.40
Responder rate (% patients achieving A1C target)				
≤7.0%	57	69	28	49
≤6.5%	30	38	8	24
Responder rate (% patients achieving FBG target)	38	6		
Insulin dose (IU/day) at end point	42	45	42	56
Treatment satisfaction score‡ (Δ change from baseline)	+6.23	+2.74	±0	−0.02
Number of overall hypoglycemic events per patient-year	5.2	24.0 (×4.6)	2.3	12.0 (×5.2)
Change in body weight (Δ kg from baseline)	+3.0	+3.5	+1.9	+5.7

*Basal insulin: insulin glargine for APOLLO trial, insulin detemir for 4-T study. †Prandial insulin: insulin lispro for APOLLO trial, insulin aspart for 4-T study. ‡Assessed by Diabetes Treatment Satisfaction Questionnaire scores (19) in the APOLLO trial and assessed by EuroQol 5-Dimension Self-Report Questionnaire scores (21) in the 4-T study.

through suppression of free fatty acid release from adipose tissue. Furthermore, targeting fasting BG levels reduce the overall glucose load and may improve pancreatic β-cell insulin secretion to a certain extent (23). Therefore, basal insulin as a first-line insulin initiation therapy is now recommended in a joint consensus guideline by the ADA and EASD (11).

Clinical trials have demonstrated that type 2 diabetic patients treated with insulin glargine exhibited significant improvements in glycemic control, which are at least equivalent (24–27), or superior (28,29), to improvements associated with NPH insulin. Furthermore, a recent meta-analysis concluded that patients treated with insulin glargine are at lower risk of hypoglycemia, and in particular, nocturnal hypoglycemia, compared with NPH insulin-treated patients (30). To further clarify this issue of the overnight action profile of insulin glargine and NPH insulin, a randomized placebo-controlled double-blind three-way crossover clamp study in type 2 diabetic patients, comparing bedtime injections of either insulin glargine or NPH insulin, was conducted to investigate the rates of endogenous glucose production and glucose disposal during the night and in the morning (31). The study confirmed delayed onset of insulin glargine compared with NPH insulin in these patients (31). Insulin glargine was associated with a greater reduction of endogenous glucose production in the morning between 6:00 and 8:00 A.M. compared with NPH insulin, when the insulins were administered at bedtime. The joint actions of insulin glargine would therefore be expected to contribute to the reduced risk of nocturnal hypoglycemia and lower fasting BG compared with NPH insulin (31).

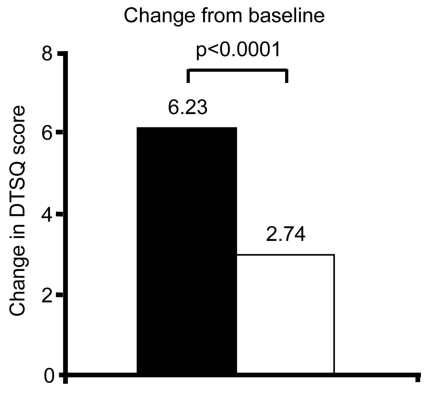

Figure 3—*Change in treatment satisfaction in both groups as analyzed by the Diabetes Treatment Satisfaction Questionnaire (DTSQ [19]). Change from baseline significantly greater in the glargine group. ■, Insulin glargine + OHAs; □, insulin lispro + OHAs.*

Insulin glargine has an additional advantage over NPH insulin. It can be administered once daily at the same time of day, owing to its relatively peakless and extended hypoglycemic profile in type 2 diabetic patients, whereas NPH insulin requires to be given twice daily in most cases (24,28,32).

SUMMARY AND CONCLUSIONS

— The APOLLO trial, designed as a noninferiority study, clearly demonstrated that a single dose of basal insulin glargine is as effective as thrice-daily prandial insulin lispro in controlling glucose metabolism when used in combination with OHAs in individuals with type 2 diabetes. Moreover, the basal insulin regimen was associated with a significantly lower risk of hypoglycemia and a greater improvement in quality of life and treatment satisfaction compared with the prandial insulin regimen. Fewer insulin injections and less self-monitoring of BG required with basal insulin glargine therapy may have contributed to the greater treatment satisfaction experienced compared with a thrice-daily prandial insulin regimen.

A comparable study, the 4-T study, using different basal and prandial insulin analogs and different titration algorithms, documented a similar beneficial effect of the basal insulin approach with respect to hypoglycemic risk and body weight increase.

Overall, insulin glargine has proved superior to NPH insulin in basal insulin regimens for the management of type 2 diabetes. Recent results of a 5-year long-term study with insulin glargine versus NPH insulin have also demonstrated no harmful effects on diabetic retinopathy progression with insulin glargine over that expected by BG lowering, a lower incidence of hypoglycemic episodes, and less weight gain. These data were recently published (33).

The addition of insulin glargine to OHAs is a simple and well-tolerated intervention that may prove helpful in overcoming major barriers to timely insulin initiation in settings of both primary and secondary care (34). Furthermore, it has been demonstrated that the use of a simple self-administered titration algorithm is equally as effective at improving glycemic control as is titration management by staff at hospital-based diabetes centers

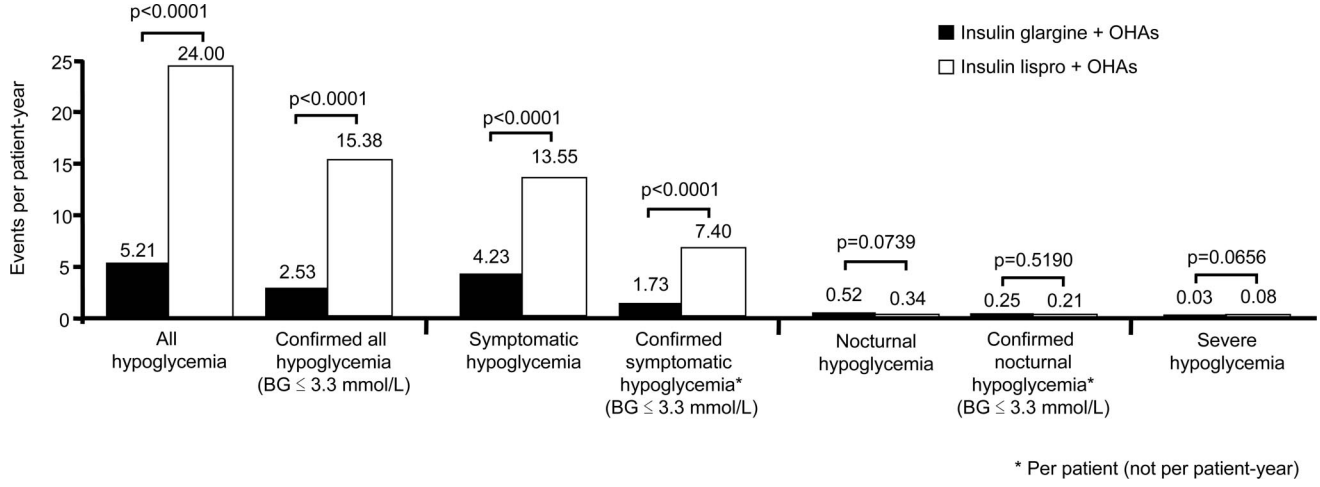

Figure 4—*Rates of hypoglycemia in participants receiving at least one dose of insulin (safety analysis population).*

(27,35). Results of a large observational study of daily practice in >10,000 individuals with type 2 diabetes inadequately controlled on OHAs confirmed the benefits from supplementation of basal insulin treatment with glargine, since the patients demonstrated improved glycemic control with little or no weight gain (36).

Finally, when basal insulin therapy in type 2 diabetes is insufficient to control daily BG profiles, a single injection of prandial insulin before the mealtime that induces the largest postprandial BG excursion (measured 2 h after the start of the meal) may be given (37). Over time and with progression of the disease, additional prandial boluses of insulin may be required to sustain daytime glycemic control. This strategy of basal insulin to control fasting BG first and, if needed, followed by an additional single prandial insulin injection ("basal plus" concept) offers a simple, stepwise approach in progressing from a basal insulin to a basal-bolus regimen (37,38).

In conclusion, evidence from the APOLLO trial suggests that the addition of basal insulin analog glargine to therapies with OHAs can be regarded as a first-line insulin initiation approach in inadequately controlled type 2 diabetes (39).

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