Acta Diabetol
DOI 10.1007/s00592-007-0023-6

ORIGINAL ARTICLE

Therapeutic options for elderly diabetic subjects: open label, randomized clinical trial of insulin glargine added to oral antidiabetic drugs versus increased dosage of oral antidiabetic drugs

G. Papa · V. Fedele · A. Chiavetta · I. Lorenti · C. Leotta · S. Luca · A. M. Rabuazzo · S. Piro · C. Alagona · L. Spadaro · F. Purrello · V. Pezzino

Received: 16 October 2007 / Accepted: 16 November 2007

Abstract Glycemic control in elderly persons with type 2 diabetes mellitus (T2DM) is challenging because they are more likely to have other age-associated medical conditions and to experience hypoglycemia during intensive therapy. A best therapeutic strategy for these patients has not yet been defined. We investigated the efficacy and safety of adding once-daily insulin glargine to patients' current oral antidiabetic drugs (OAD) regimen, compared to increasing the OAD doses. The study enrolled patients aged 65 years or more, with poor glycemic control. Patients were randomized to two groups and entered a 3-week titration period in which their actual therapy was adjusted to meet the study's glycemic goals, by either adding insulin glargine to current therapy (group A, 27 patients) or increasing current OAD dosages (group B, 28 patients). Thereafter, therapies were continued unchanged for a 24-week observation period. The mean therapeutic dosage of insulin glargine in group A was 14.9 IU/day (SD = 5.0 IU/day). During the observation period, mean levels of glycosylated hemoglobin (HbA_{1c}) reduced by 1.5% in group A and 0.6% in group B ($P = 0.381$). An HbA_{1c} level <7.0% was achieved by five patients in each group. Mean fasting blood glucose levels reduced by 29 and 15% in groups A and B, respectively ($P = 0.029$). Group A had fewer total hypoglycemic events (23 vs. 79, $P = 0.030$) and fewer patients experiencing any such event (9 vs. 17, $P = 0.045$). Neither a serious hypoglycemic event nor other adverse event occurred. These results suggest that, compared to increasing OAD dosage, the addition of insulin glargine to current OAD therapy is as effective but safer in terms of the risk for hypoglycemia in elderly patients with T2DM.

Keywords Type 2 diabetes · Elderly · Hypoglycemia · Glargine · Oral antidiabetics

G. Papa · A. M. Rabuazzo · S. Piro · C. Alagona · L. Spadaro · F. Purrello (✉) · V. Pezzino
Department of Internal Medicine, University of Catania, Ospedale Garibaldi Nesima, Via Palermo 636, 95122 Catania, Italy
e-mail: fpurrell@unict.it

A. M. Rabuazzo · S. Piro · C. Alagona · L. Spadaro · F. Purrello
Ospedale Garibaldi, Catania, Italy

V. Fedele · C. Leotta · S. Luca
U.O. of Geriatry, Catania, Italy

A. Chiavetta · I. Lorenti · V. Pezzino
U.O. of Diabetology, Ospedale Cannizzaro, Catania, Italy

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) increases with age, rising from 8% in the sixth decade to 18% in the eighth decade [1]. In elderly persons, T2DM increases the risk and severity of other age-associated medical conditions [2, 3]. As noted in guidelines of the American Geriatrics Society and the California Healthcare Foundation [4], T2DM in the elderly is associated with a higher prevalence of functional disability, hypertension, coronary heart disease (CHD) and stroke, and an increased risk of falling and premature death. Moreover, elderly persons with T2DM are more likely to suffer from major geriatric conditions including depression and cognitive impairment [5, 6]. Despite these healthcare issues, and the consequent economic and social burdens on society, the treatment of T2DM in elderly persons is often inadequate [7] and the therapeutic goals are as yet undefined.

Obvious treatment goals for elderly persons with T2DM are controlling glycemia and lowering the level of glycosylated hemoglobin (HbA_{1c}) [8]. These goals must be achieved, however, by an individualized treatment plan, especially when dealing with an elderly patient [4, 7]. In fact, although hyperglycemia is correlated with macrovascular complications even in elderly populations, these patients are at greater risk of experiencing hypoglycemia as a result of intensive glycemic control and are more prone to drug–drug and drug–disease interactions as a consequence of multidrug therapy. Hypoglycemia is not a trivial problem in older persons, who have lower plasma glucose thresholds for symptomatic and hormonal responses to hypoglycemia [9].

The choice of hypoglycemic drugs for elderly patients is still a matter of debate [7]. When faced with the need to correct poor glycemic control in older persons, clinicians often choose among increasing the dosage of oral antidiabetic drugs (OADs), adding once-daily insulin (human NPH or a basal insulin) to OADs, or starting multiple injection insulin therapy. All these options carry a significant adjunctive risk of severe hypoglycemic events [10]. Regarding insulin therapy for elderly patients, Janka et al. [11] reported that the addition of glargine to glimepiride was safer and more effective than two injections of NPH. Insulin glargine is a long-acting recombinant human insulin analog with a 24-h time–action profile and no significant peak [12, 13]. It has been increasingly used in the past years as a substitute for basal insulin secretion, in patients with both type 1 [14] and type 2 [15, 16] diabetes, but its efficacy and safety in elderly diabetic patients have not been widely evaluated. Nonetheless, given the perceived complexity and difficulty of insulin injections, elderly patients and doctors often prefer to increase the OAD dosage rather than initiate insulin treatment. Therefore, in the present study, we investigated the benefits of adding once-daily insulin glargine to ongoing OAD therapy, compared to increasing OAD dosages, in a group of elderly subjects with T2DM and poor metabolic control.

Patients and methods

Patients

The study enrolled consecutive elderly subjects with T2DM and poor metabolic control. Inclusion criteria were a diagnosis of T2DM, age $\geq$65 years, HbA_{1c} >7.5%, and treatment with any combination of OADs for at least 1 year. Patients were excluded if they were receiving insulin therapy, had a history of cardiac disease (congestive heart failure, angina pectoris, recent myocardial infarction), had impaired kidney or liver function, or had received therapy with other investigational drugs or corticosteroids within the last 6 months. Patients were recruited from the Clinic of Internal Medicine and the Diabetic Center of Cannizzaro Hospital during the period from March 2005 to March 2006. Eligible patients were explained the goals and risks of the study and gave informed consent to participate.

Study design

This was a parallel-group, open-label, randomized clinical trial consisting of a 3-week drug titration period and a 24-week observation period. The study design was approved by the ethics committee of Cannizzaro Hospital. Patients were randomized into two groups on the basis of computer-generated random numbers, by a person not involved in recruitment of patients.

At the beginning of the study (visit 1), patients were examined clinically and underwent blood testing to assess glycemic control. During the 3-week titration period, each patient's therapy was adjusted, during weekly contacts in the clinic or by phone, to reach the study's glycemic goals, i.e. a blood glucose (BG) of 115.2–129.6 mg/dL, before meals and at bedtime, and <144 mg/dL 2 h after meals (2h-BG). In patients assigned to group A, ongoing OAD therapy was supplemented with insulin glargine (Lantus, Aventis Pharma) given once daily in the evening. The starting dose of 10 IU, injected using Optiset (Aventis Pharma), was optimized during the 3-week titration period to reach glycemic goals. In patients assigned to group B, the dosages of currently assumed OADs were increased to reach the glycemic targets. At the end of the titration period, the optimized therapy was continued unaltered for 24 weeks. Patients were examined for efficacy and safety parameters at weeks 8, 16 and 24 (visits 2, 3 and 4, respectively).

Efficacy assessments

The primary efficacy endpoint was the difference between baseline and final (visit 4) HbA_{1c} levels. Blood samples for HbA_{1c} determination were analyzed by high-performance liquid chromatography (Hi-Auto A1c HA-8140; Arkray KDK, Kyoto, Japan); the normal range for non-diabetic subjects was considered to be 3.8–5.5%. Secondary efficacy measurements were the changes in fasting blood glucose (FBG) and 2h-BG at the end of the study.

Safety assessments

Hypoglycemic episodes (primary safety endpoint) and adverse events (AEs) were recorded by patients in their

diaries throughout the trial. Hypoglycemic episodes were defined as BG $\leq$ 72 mg/dL in the presence of clinical symptoms. For this reason, subjects were asked to test glycemia using a OneTouch Ultra BG meter (LifeScan, Milpitas, California, USA) whenever they experienced symptoms possibly related to hypoglycemia. Hypoglycemia was considered severe when the event required third-party assistance. For analysis, hypoglycemic episodes were further subdivided on the basis of glycemia ($\leq$59 and $\leq$49 mg/dL).

Adverse events were classified as serious if they resulted in death, life-threatening experiences, hospitalization, or persistent or significant disability or incapacity. All AEs not fulfilling these criteria were classified as non-serious.

Other safety assessments, made during the four scheduled clinic visits, included vital signs (pulse and blood pressure, taken after patients had been resting in a chair for 5 min), body weight, 12-lead electrocardiography, and hematological and biochemical laboratory tests.

Statistical analysis

The differences in clinical characteristics between groups at baseline were assessed for significance using the unpaired *t* test for discrete or continuous data and the chi-square test for frequency distributions. At study end, within-group changes from baseline in HbA_{1c}, FBG, 2h-BG and body weight were analyzed using the *t* test for paired data. The changes in FBG (from baseline to study end) were compared between groups using the unpaired *t* test, while the changes in HbA_{1c} and 2h-BG were compared between groups after adjusting for baseline values using analysis of covariance (ANCOVA) due to the significant difference in baseline values. Chi-square test was applied to compare the proportion of patients in each group who achieved the HbA_{1c} targets of 7.0 and 7.5%.

The changes in HbA_{1c}, FBG and 2h-BG over time (at baseline and at the 3 other visits) were studied using the repeated measurements ANOVA with treatment as grouping factor. In the case of HbA_{1c} and 2h-BG, the baseline value was included as covariate in the model of analysis.

The Wilcoxon's two-sample test was used to compare the number of hypoglycemic episodes in the two groups. The frequencies of patients who experienced at least one hypoglycemic episode during the treatment period were analyzed by logistic regression, and the odds ratio (OR) was calculated.

Statistical analyses were performed using SAS System version 9.1.2. A value of $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 55 patients (23 men and 32 women) of mean age 73.5 years entered and completed the trial (Table 1). Of these, 27 patients were randomly assigned to receive insulin glargine in addition to their current OAD therapy (group A) and 28 patients were assigned to undergo optimization of the dosage of current OAD therapy (group B). At the beginning of study, the two groups were similar regarding anthropometric data, type of OAD therapy and baseline FBG values, but they were significantly different as concerns baseline values of HbA_{1c} ($P = 0.002$) and 2h-BG ($P = 0.041$). Overall, the patients had a long duration of diabetes and borderline-to-poor glycemic control. They were in good general health and therefore likely to benefit from intensive glycemic control.

After titration to reach glycemic goals, the mean therapeutic dose of glargine in group A was 14.9 IU/day (SD = 5.0 IU/day). In group B, the daily doses of OADs increased as follows (values are mean $\pm$ SD): glibenclamide (glyburide), from 5.7 $\pm$ 2.8 to 9.5 $\pm$ 3.6 mg (19 patients); repaglinide, from 2.3 $\pm$ 0.5 to 4.0 $\pm$ 1.5 mg (6 patients); metformin, from 1,483 $\pm$ 256 to 1,933 $\pm$ 515 mg (23 patients); glimepiride, from 2.0 to 4.0 mg (1 patient). One patient had rosiglitazone dosage doubled (from 4 to 8 mg).

During the study, mean values of HbA_{1c}, FBG and 2h-BG tended to decrease in both groups (Fig. 1). Repeated measurements ANOVA on changes from baseline in HbA_{1c} (Fig. 1a) revealed that the difference in trends between groups was not statistically significant ($P = 0.068$) even if it approached the conventional 5% limit of significance. Regarding FBG, repeated measurements ANOVA indicated that the changes over time were significantly different between groups ($P = 0.040$) and larger in the OAD + glargine group (Fig. 1b). Finally, there was no significant difference between groups for the trends of 2h-BG values (Fig. 1c).

Regarding the primary efficacy endpoint, the reduction in HbA_{1c} from baseline to study end was 1.5% in group A (OAD + glargine) and 0.6% in group B (Table 2). After adjusting for baseline values, the mean between-group difference was -0.44% (95% CI, -1.00 to 0.12%); this difference was not significant ($P = 0.381$). An HbA_{1c} level $<$7.0% was achieved by five patients (19%) of group A and five patients (18%) of group B (chi-square test, $P = 0.948$); a level $<$7.5% was achieved by 12 patients (44%) of group A and 11 patients (39%) of group B (chi-square test, $P = 0.700$). Regarding the secondary efficacy endpoints, at week 24 we recorded a 29% reduction in FBG to 131.3 mg/dL in group A and a 15% reduction to 143.9 mg/dL in group B (mean between-group difference was -28.2 mg/dL in favor of the OAD + glargine group;

Table 1 Clinical characteristics at study entry for 55 elderly subjects with type 2 diabetes mellitus, by treatment group

	Group A (OADs + glargine) (n = 27)	Group B (optimized OADs) (n = 28)	P
Gender, n (%)			0.874 χ
Men	11 (41)	12 (43)	
Women	16 (59)	16 (57)	
Age, years	73.7 (5.1)	73.3 (5.6)	0.793†
Weight, kg	69.7 (13.2)	74.3 (13.9)	0.219†
BMI, kg/m^2	26.5 (4.0)	27.9 (4.0)	0.223†
Diabetes duration, years	17.9 (7.1)	16.0 (9.2)	0.410†
HbA_{1c}, %	9.3 (1.1)	8.5 (0.6)	0.002†
FBG, mg/dL	185.0 (41.1)	169.4 (48.6)	0.204†
2h-BG, mg/dL	212.1 (42.7)	188.1 (42.4)	0.041†
Ongoing OAD therapy, no. of patients (%)			
Gliclazide	1 (3.7)	0 (0)	ND
Glimepiride	0 (0)	1 (3.6)	ND
Repaglinide	0 (0)	3 (10.7)	ND
Repaglinide + rosiglitazone	0 (0)	1 (3.6)	ND
Repaglinide + metformin	3 (11.1)	2 (7.1)	ND
Glibenclamide + metformin	23 (85.2)	19 (67.9)	0.126 χ
Metformin + rosiglitazone	0 (0)	1 (3.6)	ND
Metformin + pioglitazone	0 (0)	1 (3.6)	ND

Values are mean (SD) unless otherwise indicated

OADs, Oral antidiabetic drugs; FBG, fasting blood glucose; 2h-BG, 2 h post-prandial glucose; †, unpaired t test; χ, chi square test; ND, not determined due to the low number of findings

P = 0.029). Finally, 2h-BG decreased by 22% to 164.6 mg/dL in group A and by 9% to 171.8 mg/dL in group B; the adjusted mean between-group difference (−14.5 mg/dL; 95% CI, −30.2 to 1.2) approached the 0.05 level of statistical significance in favor of the OAD + glargine group (P = 0.064). These results indicate that supplementary treatment with insulin glargine achieves slightly better improvements in glycemic control than does OAD dosage optimization, although the latter strategy is nonetheless effective.

Overall, during the 24-week observation period, hypoglycemic episodes (BG $\leq$ 72 mg/dL and clinical symptoms) were significantly less common in group A (OAD + glargine) than in group B (Table 3); when we considered more marked reductions in BG there were fewer events in group A but the differences were not significant. Moreover, significantly fewer patients in group A experienced at least one hypoglycemic episode. Thus, supplementary treatment with insulin glargine (group A) led to a 67.5% reduction in the risk of hypoglycemia (OR = 0.32; 95% CI, 0.11–0.97).

Despite the occurrence of hypoglycemic episodes in the two groups, no episode was classified as severe, requiring assistance. Moreover, no AE was recorded during the study. Body weight increased slightly, but significantly, during the course of the study in group A (from 69.7 ± 13.2 to 70.8 ± 13.6 kg, P = 0.020); there was no significant change in body weight in group B (from 74.3 ± 13.9 to 74.5 ± 14.1 kg). No other clinical or laboratory safety parameter exhibited significantly different variations between the groups during the study.

Discussion

Our study demonstrated that in diabetic patients aged ≥65 years and in poor metabolic control, the addition of insulin glargine to the pre-existing OAD therapy resulted in slightly better metabolic control and considerably fewer hypoglycemic events when compared to increasing the dosage of current OAD therapy. Both the total number of hypoglycemic events and the percentage of patients reporting at least one event during the study period were significantly lower in the group of patients treated with insulin glargine.

The California Healthcare Foundation–American Geriatrics Society guidelines on the care of older persons with T2DM [4] suggested to individualize the target HbA_{1c} level according to the general conditions of the patient: 7% or lower in relatively healthy patients with good functional status, but 8% in frail patients with life expectancy <5 years. Finding poor metabolic control in an elderly diabetic patient raises the question as to whether it is preferable to increase the dosage of OADs, add insulin to OADs or start multiple injection insulin therapy; this issue has not yet been clearly addressed in the literature. In adults with T2DM, a regimen that makes initiation of insulin simpler and more effective has been tested for

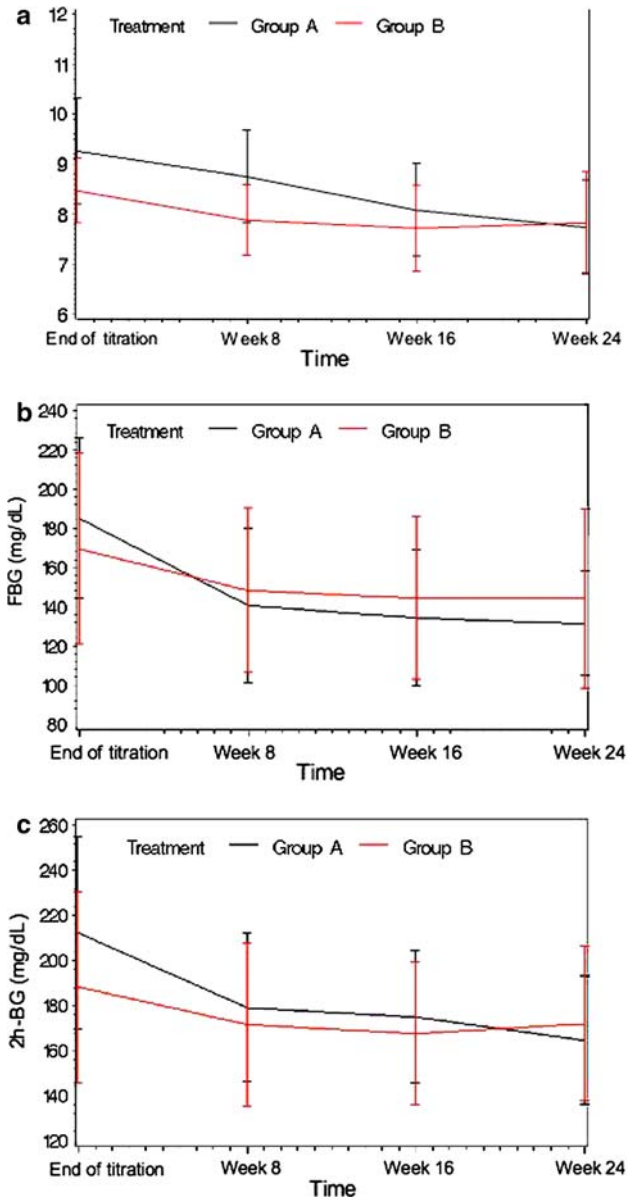

Fig. 1 Temporal profile of treatment efficacy parameters from baseline, through the 3-week titration period, and over the course of the 24-week observation period. **a** Glycosylated hemoglobin. **b** Fasting blood glucose. **c** 2 h post-prandial glucose. Values are mean and SD

several years [17–19]. More recently, long-acting insulin analogs have been shown to be safer and efficacious than NPH, by causing fewer nocturnal hypoglycemic events and by providing better post-prandial metabolic control [16, 20]. In particular, the treat-to-target trial [15] demonstrated that a bedtime injection of basal insulin can achieve the recommended target of HbA_{1c} (7%) in overweight T2DM adult patients, and suggested that insulin glargine is better suited than NPH insulin for providing this supplement. Finally, it has been recently shown that the addition of glargine to maximal doses of sulphonylureas and metformin was more effective than adding rosiglitazone, but led to more hypoglycemic events [21].

Our results confirm that a good glycemic control can be achieved by a single evening insulin injection, together with standard OAD therapy, and extend this finding to an elderly population aged ≥65 years. They also extend the findings of Janka et al. [11], who found better outcomes in elderly treated with insulin glargine added to one OAD (glimepiride) than with two NPH injections. Moreover, our study suggests that supplemental insulin treatment is superior to increasing the dosages of OAD therapy, because of the lower number of hypoglycemic events. Hypoglycemia is a serious complication of therapy in elderly patients with diabetes. The risk of severe or fatal hypoglycemia associated with the use of oral agents or insulin increases with age [22]. Epidemiological evidence suggests that frail elderly people are at higher risk of serious hypoglycemia than are healthy elderly people [22]. Moreover, hypoglycemic coma is a serious and not an uncommon problem among elderly patients with diabetes treated with insulin and/or OADs. A threshold for symptoms at lower blood glucose levels may also be the result of recurrent previous hypoglycemia, which constitutes a vicious cycle. Among the reasons for the increased susceptibility of elderly patients to hypoglycemia is that they may lack knowledge of the symptoms of hypoglycemia, have a reduced secretion of counter-regulatory hormones, have an impaired awareness of the autonomic warning symptoms and have an altered psychomotor performance during hypoglycemia, which prevents them from taking the necessary steps to return blood sugar to normal.

In our study, the average dose of insulin glargine at the end of the titration period was only 14.9 IU as compared to 47.2 IU in the treat-to-target trial [15], owing to less aggressive insulin titration, due to the advanced age of our patients. Because of the low insulin dose used in our study, an HbA_{1c} level <7.0% was achieved by <20% of patients in both treatment and a level of <7.5% in 44 and 37% of patients in groups A and B, respectively. Thus, it is possible that a slightly higher dose of glargine might yield a greater glycemic benefits in elderly patients. However, the same care was used in increasing the doses of hypoglycemic agents in group B patients. In our study the rate of hypoglycemic events in both groups was lower than the rates reported by others [15, 20].

The patients enrolled in this trial had a mean age of 73.5 years and borderline-to-poor glycemic control and were being treated with sulphonylureas, with or without metformin. We decided not to change the OAD therapy, even if this led to the inclusion of patients assuming different drugs according to different regimens. We believe that this choice increases the extendibility of our results to

Table 2 Assessment of treatments for efficacy in glycemic control, by study group

	Group A (OADs + glargine) (n = 27)	Group B (optimized OADs) (n = 28)	P
HbA_{1c}, %			
Week 24	7.7 (0.9)	7.8 (1.0)	
Change from baseline	−1.5 (1.2)[§]	−0.6 (0.9)**	
	[−2.0 to −1.0]	[−1.0 to −0.3]	
Adjusted change from baseline	−1.2	−0.8	0.318[#]
	[−1.6 to −0.8]	[−1.2 to −0.4]	
Difference in adjusted changes	−0.44		
	[−1.00 to 0.12]		
FBG, mg/dL			
Week 24	131.3 (26.7)	143.9 (45.6)	
Change from baseline	−53.7 (53.2)[§]	−25.4 (39.7)**	0.029[†]
	[−74.7 to −32.6]	[−40.8 to −10.1]	
Difference in changes	−28.2		
	[−53.6 to −2.9]		
2h-BG, mg/dL			
Week 24	164.6 (28.5)	171.8 (34.4)	
Change from baseline	−47.4 (47.7)[§]	−16.3 (3.3)*	
	[−66.3 to −28.6]	[−29.2 to −3.3]	
Adjusted change from baseline	−36.4	−21.9	0.064[#]
	[−47.6 to −25.2]	[−32.9 to −10.9]	
Difference in adjusted changes	−14.5		
	[−30.2 to 1.2]		

Values are mean (SD) [95% CI]. * $P < 0.05$; ** $P < 0.01$; [§]$P < 0.001$ versus baseline values of same group, t test for paired data. Between-groups comparisons: [#]ANCOVA, [†]unpaired t test

Table 3 Assessment of safety of antidiabetic treatments, by study group and blood glucose (BG) level

Hypoglycemic episodes with clinical symptoms	Group A (OADs + glargine) (n = 27)	Group B (optimized OADs) (n = 28)	P
BG ≤ 72 mg/dL			
Episodes, n (median, min–max)	23 (0, 0–6)	79 (1, 0–19)	0.030*
Number of patients experiencing one episode at least, n (%)	9 (33.3)	17 (60.7)	0.045 χ
BG ≤ 59 mg/dL			
Episodes, n (median, min-max)	5 (0, 0–2)	18 (0, 0–7)	0.442*
Number of patients experiencing one episode at least, n (%)	3 (11.1)	5 (17.9)	0.482 χ
BG ≤ 49 mg/dL			
Episodes, n (median, min–max)	0	3	ND
Number of patients experiencing one episode at least, n (%)	0 (0)	2 (7.1)	ND

* Wilcoxon's two-sample test

χ, Chi-square test by logistic regression; ND, not determined due to the low number of findings

patients assuming any hypoglycemic drug. The results of our study are limited, however, by the small number of patients enrolled. If we consider as clinically relevant the difference in effect of the two treatments on HbA_{1c} at the end of the study (mean −0.44% by ANCOVA), we should plan a roughly double-sized study (60 patients per group) to confirm this outcome with a power of 80% and a type I error of 5%.

Initiation of insulin therapy is often accompanied by an increase in weight [23]. We observed a slight but significant increase in body weight only in the OAD + insulin glargine group. No other safety issues were raised during the study. Moreover, there were no dropouts from the study, further supporting the tolerability of the treatments.

In conclusion, our study shows that the addition of glargine to the current OAD treatment was safe and

effective in improving metabolic control, both in terms of improved fasting glycemia and post-prandial glucose excursion and also regarding a lower risk for hypoglycemia, which can be considered an important additional benefit.

Acknowledgments Valerie Matarese provided scientific editing.

Conflict of interest The authors declare they have no competing interests.

References

1. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD (1998) Prevalence of diabetes, IFG and IGT in U.S. adults. The third national health and nutrition examination survey, 1988–94. Diabetes Care 21(4):518–524
2. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, Schreiner PJ, Margolis KL, Cauley JA, Nevitt MC, Black DM, Cummings SR (2002) Older woman with diabetes have a higher risk of falls: a prospective study. Diabetes Care 25(10):1749–1754
3. Songer TJ (1995) Disability in diabetes. In: Harris MI, Cowie CC, Stern MP et al (eds) Diabetes in America, 2nd edn. National Institutes of Health, Bethesda, pp 259–282
4. Brown AF, Mangione CM, Saliba D, Sarkisian CA (2003) California healthcare foundation/American geriatrics society panel on improving care for elders with diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 51(5 Suppl Guidelines):S265–S280
5. Peyrot M, Rubin RR (1997) Levels and risks of depression and anxiety symptomatology among diabetic adults. Diabetes Care 20(4):585–590
6. Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR (2000) Is diabetes associated with cognitive impairment and cognitive decline among older woman? Study of osteoporotic fractures research group. Arch Intern Med 160(2):174–180
7. Shorr RI, Franse LV, Resnick HE et al (2000) Glycemic control of older adults with type 2 diabetes: findings from the third national health and nutrition examination survey, 1988–1994. J Am Geriatr Soc 48(3):264–267
8. American Diabetes Association (2006) Standards of medical care for patients with diabetes mellitus. Diabetes Care 26(Suppl 1):S33–S50
9. Matyka K, Evans M, Lomas J, Cranston I, Macdonald I, Amiel SA (1997) Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care 20:135–141
10. Shorr RI, Ray WA, Daugherty JR, Griffin MR (1997) Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 157:1681–1686
11. Janka HU, Plewe G, Busch K (2007) Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. J Am Geriatr Soc 55(2):182–188
12. Bolli GB, Owens DR (2000) Insulin glargine (commentary). Lancet 356:443–444
13. Rosenstock J, Schawartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB (2001) Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE901) and NPH insulin. Diabetes Care 24:631–636
14. Hamann A, Matthaei S, Rosak C, Silestre L; HOE901/4007 Study Group (2003) A randomized clinical trial comparing breakfast, dinner or bedtime administration of insulin glargine in patients with type 1 diabetes. Diabetes Care 26(6):1738–1744
15. Riddle MC, Rosenstock J, Gerich J (2003) Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. The treat-to-target trial. Diabetes Care 26:3080–3086
16. Yki-Jarvinen H, Dressler A, Ziemen M; HOE 901/300s Study Group (2000) Less nocturnal hypoglycaemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. Diabetes Care 23:1130–1136
17. Taskinen MR, Sane T, Helve E, Karonen SL, Nikkita EA, Yki-Jarvinen H (1989) Bedtime insulin for suppression of overnight free fatty acid, blood glucose, and glucose production in NIDDM. Diabetes 38:580–588
18. Riddle MC (1990) Evening insulin strategy. Diabetes Care 13:676–686
19. Shank ML, Del Prato S, DeFronzo RA (1995) Bedtime insulin/daytime glipizide: effective therapy for sulfonylurea failures in NIDDM. Diabetes 44:165–172
20. Janka HU, Plewe G, Riddle MC et al (2005) Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 28:254–259
21. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G (2006) On behalf of the insulin glargine 4014 study investigators. Triple therapy in type 2 diabetes. Diabetes Care 29:554–559
22. Holstein A, Plaschke A, Egberts EH (2003) Clinical characterisation of severe hypoglycaemia: a prospective population-based study. Exp Clin Endocrinol Diabetes 111:364–369
23. Lager E (2005) Weight gain and insulin treatment. Diabetes Metab 31(4 Pt 2):4S54–4S56