Comparison of Safety and Efficacy of Insulin Glargine and Neutral Protamine Hagedorn Insulin in Older Adults with Type 2 Diabetes Mellitus: Results from a Pooled Analysis

Pearl Lee, MD, MS,[†] Annette Chang, MD,[*‡] Caroline Blaum, MD, MS,[*†] Aleksandra Vlajnic, MD,[§] Ling Gao, MS,[§] and Jeffrey Halter, MD[*]*

OBJECTIVES: To compare the safety and efficacy of adding insulin glargine or neutral protamine Hagedorn (NPH) insulin to existing oral antidiabetic drug (OAD) regimens in adults with type 2 diabetes mellitus.

DESIGN: Pooled analysis of data from five randomized controlled trials with similar designs.

SETTING: Three hundred forty-two centers in more than 30 countries worldwide.

PARTICIPANTS: Randomly selected individuals aged ≤80 with a body mass index ≤40 kg/m^2 and a glycosylated hemoglobin (HbA1c) level of 7.5% to 12.0%.

MEASUREMENTS: Fixed- and random-effects models were used to compare outcomes after 24 or 28 weeks of treatment (insulin glargine, n = 1,441; NPH insulin, n = 1,254) according to age (≥65, n = 604 vs < 65, n = 2,091) and age based on treatment (e.g., ≥65 receiving insulin glargine vs NPH insulin). Outcomes included change in HbA1c, fasting blood glucose (FBG), insulin dose, and hypoglycemia incidence and event rates.

RESULTS: At end point, participants aged 65 and older receiving insulin glargine had greater reductions in HbA1c and FBG than those receiving similar doses of NPH insulin. In contrast, for participants younger than 65, there were no statistically significant differences in reductions in HbA1c or FBG between insulin glargine and NPH insulin. Daytime hypoglycemia rates were similar in all groups, although the rates of nocturnal symptomatic and severe hypoglycemia were lower with insulin glargine than NPH insulin.

CONCLUSION: Addition of insulin glargine to oral antidiabetic drugs in older adults with poor glycemic control may have modestly better glycemic benefits than adding NPH insulin, with low risk of hypoglycemia. **J Am Geriatr Soc 60:51–59, 2012.**

Key words: diabetes mellitus; geriatric; insulin

Nearly one-quarter of all Americans aged 60 and older (12.2 million) have diabetes mellitus.[1] The prevalence of diabetes mellitus in older adults is expected to rise to epidemic proportions in future decades because of the aging of the population; by 2050, the prevalence of diagnosed diabetes mellitus is expected to increase 252% in women aged 65 to 74 and 537% in men aged 75 and older from rates reported in 2000.[2]

The complex health conditions and susceptibility to medication adverse effects of older adults complicates their diabetes mellitus treatment, particularly with respect to glycemic control. The American Geriatrics Society (AGS)[3] and the American Diabetes Association (ADA)[4] have recommended individualization of glycemic targets for older adults based on their health status and risk of adverse effects. For healthy older adults with few comorbid conditions, the standard glycemic target of the AGS and the ADA is a glycosylated hemoglobin (HbA1c) level of 7.0%.

Although most individuals with type 2 diabetes mellitus are initially treated with oral antihyperglycemic agents, progressive loss of pancreatic beta-cell function and decreased insulin sensitivity are often associated with increasing levels of fasting blood glucose (FBG) and HbA1c.[5,6] Thus, many people eventually require exogenous insulin therapy to achieve and maintain recommended glycemic control targets.[5–7] The rate of insulin initiation in people with type 2 diabetes mellitus has been estimated to be low, varying from 1%[8] to 5.8%[9] per year. Risk of hypoglycemia is often a deterrent for healthcare providers to initiate insulin treatment, and people with diabetes mellitus are often reluctant to use insulin.[10–12]

From the [*]Department of Internal Medicine, University of Michigan, and [†]Veterans Affairs Ann Arbor Healthcare System Geriatric Research, Education and Clinical Center (GRECC), Ann Arbor, Michigan; [‡]Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan; and [§]Sanofi-aventis U.S., Bridgewater, New Jersey.

Address correspondence to Pearl Lee, Department of Geriatrics, University of Michigan, 300 North Ingalls, Room 920, Ann Arbor, MI 48109. E-mail: pearllee@med.umich.edu

DOI: 10.1111/j.1532-5415.2011.03773.x

0002-8614/12/$15.00

Despite the availability of various forms of insulin with different pharmacological properties, there has been limited analysis of the comparative safety and effectiveness of insulin regimens in older adults. For older adults with type 2 diabetes mellitus and suboptimal glycemic control while taking oral antidiabetic drug (OAD) therapy, findings from previous studies support the addition of insulin glargine as an alternative to simply increasing OAD dosage.[13]

Insulin glargine, a long-acting recombinant human insulin analog with a 24-hour action profile and no significant peak,[14] is thought to be a potential insulin of choice for older adults. Previous randomized controlled trials not targeting older adults have consistently shown that people treated with insulin glargine can attain similar glycemic control with a lower risk of hypoglycemia than those treated with other forms of insulin.[15–20] The goal of the current study was to compare the safety and efficacy of adding insulin glargine with that of adding neutral protamine Hagedorn (NPH) insulin in older and younger adults with poorly controlled diabetes mellitus while taking OADs. Given that there are no randomized controlled trials specifically designed to assess these differences in older adults, a pooled analysis of five sanofi-aventis-sponsored multisite randomized clinical trials with similar research methodologies was performed.

METHODS

A pooled analysis was performed of participants in five international randomized controlled trials (RCTs) with similar study designs[15,21–24] to examine the effects of age and insulin treatment in a large population of patients with type 2 diabetes mellitus. All participant-level data from the five selected trials were combined for analyses.

Study Selection

Twenty-two sanofi-aventis-sponsored RCTs in adults with type 2 diabetes mellitus were screened for inclusion in this analysis. Studies were included if they compared the safety and efficacy of adding insulin glargine with that of adding NPH insulin in participants with known type 2 diabetes mellitus who had suboptimal glycemic control while taking OADs and met the following criteria:

- Studies were prospective, randomized, controlled, and of 24 weeks' duration and longer.
- Participants had poor glycemic control based on high FBG or HbA1c levels.
- After randomization, basal insulin (insulin glargine or NPH insulin) was given once daily, with no prandial or bolus insulin administration.
- Basal insulin was titrated based on fasting glucose targets.
- Participants continued to take their original OADs or another OAD predetermined by the trial.

Studies were conducted according to the Good Clinical Practice Guidelines and in accordance with the Declaration of Helsinki. All participants were relatively healthy and active, with few comorbidities. All participants must have had the ability to understand and willingness to perform self-administered insulin injections and self-monitoring of blood glucose multiple times per day.

Five trials met the above criteria and had been conducted as multicenter, open-label RCTs in the United States, Canada, Latin America, Europe, and Asia between 1999 and 2002.[15,21–24]

Study Participants

Participant enrollment criteria for each of the trials are summarized in Table 1. Participants were aged ≤80 and had a body mass index (BMI) ≤40 kg/m^2 and a HbA1c level between 7.5% and 12.0% at randomization. Participants in two trials continued their baseline OADs, whereas those in the other three trials were maintained on stable doses of glimepiride. Major exclusion criteria for the five trials were similar and included pregnancy, recent insulin use, history of ketoacidosis, and inability to recognize hypoglycemia.

Intervention

After randomization, all participants received once-daily administration of insulin glargine or NPH insulin at bedtime or before breakfast. Four studies[15,17,22,23] examined insulin treatment over 24 weeks, and one[24] had a 28-week treatment phase. During the treatment phase, the insulin dose was titrated on a predefined regimen based on self-measured FBG using standard meters and self-reported hypoglycemia episodes. Participants submitted blood samples to have their fasting plasma glucose (FPG) periodically measured in each study's central laboratory (studies 4001, 4013, 3102, and 4002) or a local accredited laboratory (study 4012). HbA1c levels were measured in laboratories using the standardized Diabetes Control and Complications Trial method (studies 3102, 4002, 4012, and 4013) or the comparable BioRad DIAMAT method (study 4001), where the normal range was 4% to 6%.

Outcomes Assessed

The efficacy of insulin glargine and NPH insulin was measured according to reduction in HbA1c and FBG and change in insulin dose from baseline to end of treatment.

Safety was measured based on symptomatic and severe hypoglycemia events during the treatment period. Symptomatic hypoglycemia was defined for the pooled data as self-monitored blood glucose less than 70 mg/dL (<3.89 mmol/L). Nocturnal hypoglycemia was defined as hypoglycemia that occurred while participants were asleep, after bedtime following the evening injection and before waking up in the morning. Cases of severe hypoglycemia were identified from events meeting criteria as defined in each of the individual studies (Table 1). Severe hypoglycemia was defined as hypoglycemic symptoms requiring the assistance of another person; prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration; or a blood glucose level less than 50 mg/dL (<2.78 mmol/L) in four studies or less than 56 mg/dL (<3.11 mmol/L) in one study (data were converted from plasma glucose).[15]

Table 1. Participant Enrollment Criteria and Severe Hypoglycemia Definition for Each Trial Selected for Pooled Analysis

Study Number	Age	Aged ≥ 65, n	Body Mass Index, kg/m^2	Glycosylated Hemoglobin,%	Fasting Blood Glucose*		OAD	Major Exclusion Criteria	Severe Hypoglycemia Definition
					mg/dL	mmol/L			
4001[21]	<75	247	<35	7.5–10.5	≥120	6.66	Glimepiride	Pregnancy, previous insulin use within 3 months, clinically relevant somatic or mental disease	Symptoms of hypoglycemia that required the assistance of another person and blood glucose <50 mg/dL (<2.78 mmol/L) or recovery after glucose or glucagon treatment
4002[15]	30–70	132	26–40	7.5–10.0	>140	7.77	Each participant's previous OAD	Previous insulin use, history of ketoacidosis or inability to recognize hypoglycemia	Symptoms of hypoglycemia that required the assistance of another person and plasma glucose <56 mg/dL (<3.11 mmol/L) or recovery after glucose or glucagon treatment
4012[22]	40–80	73	20–35	7.5–10.5	>120	6.66	Glimepiride	Pregnancy, history of ketoacidosis, previous insulin use within 3 months	Symptoms of hypoglycemia that required the assistance of another person and blood glucose <50 mg/dL (<2.78 mmol/L) or recovery after glucose or glucagon treatment
4013[23]	≤75	101	≤35	7.5–10.5	≥100	5.55	Glimepiride	Pregnancy, previous insulin use within 3 months	Symptoms of hypoglycemia that required the assistance of another person and blood glucose <50 mg/dL (<2.78 mmol/L) or recovery after glucose or glucagon treatment
3102[24]	20–70	51	< 30	8.0–12.0	NA		Each participant's previous OAD	Pregnancy, history of ketoacidosis, history of previous insulin use	Symptoms of hypoglycemia that required the assistance of another person or recovery with supplemental glucose and blood glucose <50 mg/dL (<2.78 mmol/L)

* Glucose was converted from mg/dL to mmol/L using 0.0555 as a multiplier.

OAD = oral antidiabetic drug; NA = not available.

Statistical Analysis

The intention-to-treat (ITT) population included all participants who received a dose of study medication (N = 2,695); these participants were included in the safety comparisons. After six participants who did not have HbA1c, FBG, or insulin dose measurements during the posttreatment phase were excluded, the remaining 2,689 participants constituted the modified ITT (mITT) population. Results for HbA1c, FBG, and insulin dose were based on participants in the mITT population who had measurements available at baseline and end point (week 24 or 28) for each of these variables individually (n = 2,644 for HbA1c, n = 2,669 for FBG, and n = 2,684 for insulin dose). Blood glucose values were converted from FPG to FBG for two studies (3102 and 4002[15]) for pooling using 0.875 as the multiplier.

For the glycemic efficacy outcomes of interest, fixed- and random-effects models were used to compare all participants according to treatment (insulin glargine vs NPH insulin) and age category (≥ 65 vs <65) separately and then according to treatment and age groups together. Age-by-treatment interactions were also examined. The fixed-effects models included baseline values (HbA1c, FBG, insulin dose for each respective analysis), insulin dose at randomization, and duration of diabetes mellitus as covariates and treatment, age category, age by treatment and study as factors. The interactions of study by age category, study by treatment, study by baseline, treatment by age category, treatment by baseline, and age category by baseline values were included in the models if they were statistically significant ($P < .01$). The random-effects models included baseline values, insulin dose at randomization, duration of diabetes mellitus, treatment, age category, and age by treatment as fixed effects, with study, study by age category, and study by treatment as random effects. The interactions between treatment or age category and baseline values were included as fixed effects, and the interactions between study and treatment or baseline values were included as random effects if they were statistically significant ($P < .01$). Heterogeneity tests (e.g., one-way *t*-test for the difference between two treatment groups according to age category and study, and analysis of covariance models for efficacy variables at treatment end point and change from baseline to end point between treatment groups and age categories according to trials) were conducted to assess model fit.

For safety outcomes, descriptive analysis was performed for incidence (percentage of participants with ≥ 1 symptomatic or severe hypoglycemia events) and event rates (number of symptomatic or severe hypoglycemic events per person-year). The Cochran–Mantel–Haenszel test was performed for difference in incidence between treatment arms or age categories. A rank analysis of variance including trials as factors was used to assess the difference in event rate between treatment groups or age categories. Hypoglycemia incidence was analyzed using fixed- and random-effects models using a binomial distribution logit link (SAS version 9.1.3, PROC GENMOD, SAS Institute, Inc., Cary, NC). Hypoglycemia event rates were analyzed using fixed- and random-effects models using a Poisson distribution log link (SAS version 9.1.3, PROC GENMOD), which accounted for overdispersion. Both fixed-effects models included factors of treatment, baseline HbA1c, BMI, duration of diabetes mellitus, and insulin dose at randomization; age category; study; and treatment by age category. The random-effects models included treatment, baseline HbA1c, BMI, duration of diabetes mellitus, and insulin dose at randomization; age category; and treatment by age category as fixed effects, with study and study by age category as random effects.

For glycemic efficacy and safety outcomes, results from the fixed-effects models were applied if they agreed with that from the random-effects model; otherwise, the results from the random-effects models were applied as the conservative analysis. In cases of very few hypoglycemia events in a treatment arm and age category, such as severe hypoglycemia, only results from the fixed-effects model were applied. For transparency, nominal (unadjusted, raw) values were reported along with modeled (adjusted) values and statistical comparisons.

RESULTS

Baseline Characteristics

Two thousand six hundred ninety-five participants from the five selected sanofi-aventis-sponsored trials were included in the ITT population; their demographic and diabetes mellitus characteristics at baseline are shown in Table 2. Participants younger than 65 (n = 2,091) and aged 65 and older (n = 604) were compared. For each of these two participant groups, those who received insulin glargine and NPH insulin had a similar mean age, percentage of men, mean weight, and mean BMI and no statistical difference in prior use of OADs. For participants aged 65 and older, the insulin glargine group had higher baseline HbA1c, FBG, and initial insulin dose at randomization than did the NPH insulin group. In participants younger than 65, the insulin glargine group had a shorter duration of diabetes mellitus than did the NPH insulin group and received a higher initiating insulin dose at randomization.

Efficacy: Glycemic Control and Insulin Dose

Treatment Effect

Overall, participants treated with insulin glargine and NPH insulin had similar nominal mean reductions in HbA1c (−1.3% vs −1.2%), FBG (−4.7 mmol/L vs −4.3 mmol/L), and insulin dose (Δ = 23 U/d vs 21 U/d) at the end of treatment. After 24 or 28 weeks of treatment, mean HbA1c was 7.7% and 7.7% (adjusted difference −0.12%, 95% CI = −0.28–0.04, $P = .11$), mean FBG was 6.5 and 6.6 mmol/L (adjusted difference −0.2 mmol/L, 95% CI = −0.53–0.09, $P = .12$), and mean daily insulin doses were 36 and 33 U (adjusted difference 1.4 U, 95% CI = −1.57–4.38, $P = .26$) for the insulin glargine and the NPH insulin groups, respectively. Differences between the treatment groups reached statistical significance for HbA1c ($P = .004$) and FBG ($P = .001$) in

Table 2. Participant Characteristics at Baseline (Intention-to-Treat Group)

Participant Characteristic	Aged < 65 (n = 2,091)		Aged ≥ 65 (n = 604)	
	Insulin Glargine (n = 1,112)	NPH Insulin (n = 979)	Insulin Glargine (n = 329)	NPH Insulin (n = 275)
Age, mean ± SD	53 ± 7.7	54 ± 7.1	69 ± 3.4	69 ± 3.4
Male, n (%)	580 (52)	486 (50)	163 (50)	148 (54)
Weight, kg, mean ± SD	79.0 ± 19.3	78.4 ± 19.3	75.4 ± 16.3	74.7 ± 17.5
Body mass index, kg/m^2, mean ± SD	28.3 ± 5.2	28.4 ± 5.2	27.7 ± 4.4	27.4 ± 4.6
Diabetes mellitus duration, years, mean ± SD	9.2 ± 5.9*	9.8 ± 5.9	12.3 ± 7.7	11.5 ± 6.3
Glycosylated hemoglobin, %, mean ± SD	8.9 ± 1.0	9.0 ± 1.0	9.0 ± 1.0*	8.8 ± 0.9
FBG, mmol/L, mean ± SD†	11.2 ± 3.0	11.0 ± 2.9	11.2 ± 3.1*	10.7 ± 3.0
Insulin dose at randomization, U/d, mean ± SD	13 ± 8.7*	12 ± 7.1	15 ± 9.2*	12 ± 7.8
Prior use of OADs, n (%)‡				
Metformin only	397 (40.6)	407 (48.0)	91 (29.7)	98 (39.7)
Sulfonylureas only	507 (51.9)	388 (45.8)	187 (61.1)	125 (50.6)
Thiazolidinediones only	5 (0.5)	2 (0.2)	1 (0.3)	0 (0.0)
Metformin and sulfonylurea	6 (0.6)	3 (0.4)	4 (1.3)	4 (1.6)
Other OADs only	61 (6.2)	47 (5.5)	23 (7.5)	20 (8.1)

* $P < .05$ versus neutral protamine Hagedorn (NPH) insulin within age category.
† Two of the studies (3102 and 4002[15]) measured fasting plasma glucose values, which were then converted to fasting blood glucose (FBG) for pooling using 0.875 as the multiplier.
‡ Excluding participants from study 3102, in which the information is not available in English.
OADs = oral antidiabetic drugs; SD = standard deviation.

the fixed-effects but not the more-conservative random-effects model.

Age Effect

There was no statistical difference between the age groups in HbA1c, FBG, or insulin dose overall. At end point, mean HbA1c was 7.7% in the group younger than 65 and 7.8% in the group aged 65 and older. Nominal mean HbA1c reductions were −1.3% and −1.1%, respectively (adjusted difference −0.05%, 95% CI = −0.15–0.05, $P = .33$). FBG decreased 4.48 and 4.51 mmol/L to mean values of 6.6 mmol/L in those younger than 65 and 6.4 mmol/L in those aged 65 and older (adjusted difference 0.17 mmol/L, 95% CI = 0.01–0.35, $P = .06$). Mean insulin dose at end point was 36 U in the younger group and 29 U in the older group. The amount of daily insulin used with titration over the course of 24 to 28 weeks increased by 24 U and 16 U, respectively. Differences between age groups were significant in the fixed-effects model ($P < .001$) but not in the random-effects model (adjusted mean difference 5.8 U, 95% CI = −0.98–12.64, $P = .08$).

Treatment by Age Effect

There were statistically significant age by treatment interactions for HbA1c ($P = .009$) and FBG ($P = .01$) but not insulin dose ($P = .27$) at end point.

Participants aged 65 and older treated with insulin glargine had significantly greater decreases in HbA1c (−1.5% vs −1.1%), and FBG (−4.7 vs −4.1 mmol/L) from baseline ($P < .001$ for both), with similar changes in insulin dose at the end of the treatment (17 U/d for both), compared to those treated with NPH insulin (Figure 1). However, in participants younger than 65, the two treatment groups had similar changes on all three measures (HbA1c, −1.4% vs −1.3%; FBG, −4.3 vs −4.2 mmol/L; and insulin dose, 24 vs 22 U at end point for insulin glargine vs NPH insulin, respectively, Figure 1). Mean values at end point (unadjusted and after adjustment) and statistical comparisons are presented in Table 3.

Participants receiving insulin glargine aged 65 and older had similar change in HbA1c (−1.34% vs −1.45%) as those younger than 65 but greater change in FBG (−4.3 vs −4.7 mmol/L, $P = .002$) and less change in insulin dose (24 vs 17 U/d, $P = .01$) at end point. Conversely, participants receiving NPH insulin aged 65 and older had significantly less mean change in HbA1c at end point than those younger than 65 (−1.1% vs −1.3%, $P = .02$) and no statistically significant difference in FBG (−4.1 vs −4.2 mmol/L, $P = .59$) or insulin dose changes (17 vs 22 U, $P = .07$) from baseline to end point (Figure 1 and Table 3).

Safety: Incidence and Event Rates of Symptomatic and Severe Hypoglycemia

Treatment Effect

The incidence and event rates of symptomatic and severe hypoglycemia for each age group based on insulin treatment are presented in Table 4. Overall, participants receiving insulin glargine (n = 1,441) and those receiving NPH insulin (n = 1,254) had similar incidence of daytime symptomatic (38% vs 41%, odds ratio (OR) = 0.92, 95% CI = 0.77–1.09, $P = .31$) and severe (1.3% vs 1.2%, OR = 1.31, 95% CI = 0.58–2.94, $P = .50$) hypoglycemia. The insulin glargine group had lower incidence of nocturnal symptomatic (20% vs 34%, OR = 0.61, 95% CI = 0.42–0.89, $P = .008$) and severe (0.8% vs 2.2%,

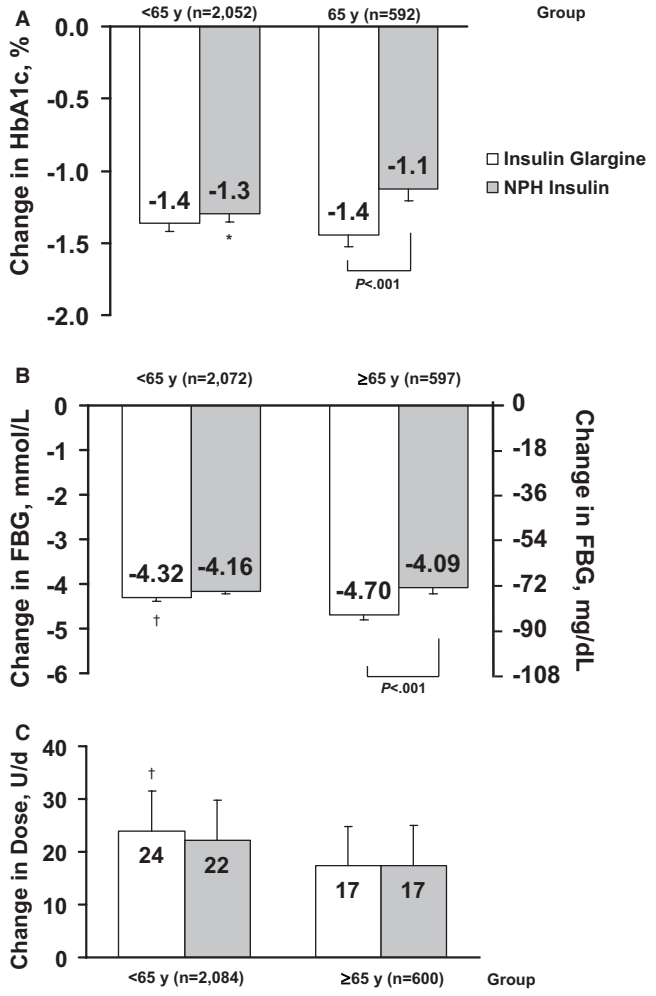

Figure 1. Adjusted mean (standard error) reduction from baseline to end point in glycosylated hemoglobin (HbA1c) (**A**), fasting blood glucose (FBG) (**B**), and insulin dose (**C**) for all participants (modified intention-to-treat group). *P*-values shown in the figure are significant differences for insulin glargine versus neutral protamine Hagedorn (NPH) insulin in participants aged 65 and older. $^{*}P < .005$ between age categories in NPH insulin–treated participants. $^{\dagger}P < .01$ between age categories in insulin glargine-treated participants.

OR = 0.38, 95% CI = 0.19–0.77, $P = .007$) hypoglycemia. The same pattern was true for hypoglycemia event rates.

Age Effect

Combining the two insulin treatment groups, participants younger than 65 and those aged 65 and older had similar incidences of daytime and nocturnal symptomatic hypoglycemia (daytime, 39% vs 41%, OR = 0.87, 95% CI = 0.71–1.07, $P = .18$; nocturnal, 26% vs 27%, OR = 0.87, 95% CI = 0.69–1.10, $P = .24$), and severe (daytime, 1.2% vs 1.2%, OR = 1.04, 95% CI = 0.43–2.49, $P = .94$; nocturnal, 1.4% vs 1.8%, OR = 0.68, 95% CI = 0.32–1.43, $P = .30$; Table 4). Only nocturnal symptomatic hypoglycemia event rate was significantly higher in participants aged 65 and older than in those younger than 65 (1.98 vs 2.24 events/participant per year, rate ratio (RR) = 0.73, 95% CI = 0.46–1.15, $P = .047$).

Treatment by Age Effect

There were no treatment by age interactions for any of the hypoglycemia measures. There were no statistical differences between groups on daytime hypoglycemia measures and no differences between treatments in the group of patients aged 65 and older, although participants younger than 65 treated with insulin glargine had lower incidence and event rates of nocturnal symptomatic and severe hypoglycemia than those receiving NPH insulin (nocturnal symptomatic: incidence: 20% vs 34%, OR = 0.57, 95% CI = 0.39–0.85, $P = .005$, event rate: 1.27 vs 2.78 events/participant per year, RR = 0.66, 95% CI = 0.45–0.97, $P = .03$; nocturnal severe: incidence: 0.7% vs 2.2%, OR = 0.35, 95% CI = 0.15–0.82, $P = .01$, event rate: 0.02 vs 0.07 events/participant per year, RR = 0.27, 95% CI = 0.11–0.071, $P = .007$; Table 4).

DISCUSSION

Consistent with studies in adults of any age with type 2 diabetes mellitus, as summarized in two meta-analyses,[25,26] this pooled analysis indicates that adding insulin glargine in older adults on an existing OAD regimen is more effective in reducing HbA1c and FBG during 24 or 28 weeks of treatment than adding a single daily dose of NPH insulin, and elicits less nocturnal symptomatic and severe hypoglycemia. These findings are also consistent with the pharmacological properties of these two insulins; NPH insulin is an intermediate-acting insulin that can last up to 20 hours, whereas insulin glargine is a long-acting insulin that usually lasts up to 24 hours.[14,27]

The present study also found that, with lower doses of insulin glargine, older adults (≥ 65) can achieve glycemic improvements greater than or similar to those of younger adults (<65) (Table 3). Although younger and older study participants were similar in terms of FBG and HbA1c at baseline, potential contributing factors not assessed in this study included poorer renal function and less physical activity in older than in younger adults.[28]

Daytime hypoglycemia occurred with equal prevalence in all groups, with an incidence of symptomatic hypoglycemia of approximately 40%. There was no greater risk of symptomatic or severe daytime hypoglycemia in adults aged 65 and older than in younger adults when insulin glargine- and NPH insulin-treated subgroups were analyzed together or separately. Nocturnal symptomatic hypoglycemia event rates were higher in the older participants when the two treatment groups were combined and higher in the NPH group when the two age groups were combined. Nocturnal symptomatic and severe hypoglycemia were higher in the NPH group than in the insulin glargine group whether measured as incidence or event rates. This difference seems to be driven by the younger group, in which all measures were significantly greater in the NPH insulin group. The older group receiving NPH insulin also experienced more nocturnal hypoglycemia, but this did not reach statistical significance.

Rates of severe hypoglycemia in the current analysis were low and consistent with those of previous clinical trials of insulin therapy in adults with type 2 diabetes mellitus aiming to achieve a mean HbA1c of

Table 3. Efficacy of Treatments at Endpoint According to Insulin and Age Categories

	Aged < 65				Aged ≥ 65				Age Group (<65 vs ≥ 65)			
									Insulin Glargine		NPH Insulin	
Measurement	Insulin Glargine	NPH Insulin	Difference (95% CI)	*P*-Value	Insulin Glargine	NPH Insulin	Difference (95% CI)	*P*-Value	Adjusted Difference (95% CI)	*P*-Value	Adjusted Difference (95% CI)	*P*-Value
Glycosylated hemoglobin, %												
Unadjusted, mean±SD	7.7 ± 1.2	7.7 ± 1.2			7.7 ± 1.2	7.9 ± 1.3						
Adjusted, mean (SE)	7.6 (0.06)	7.7 (0.06)	–0.06 (–0.15–0.03)	.16	7.5 (0.08)	7.8 (0.08)	–0.32 (–0.48 to –0.15)	<.001	0.08 (–0.05–0.21)	.22	–0.17 (–0.31 to –0.03)	.02
Fasting blood glucose, mmol/L												
Unadjusted, mean±SD	6.6 ± 2.1	6.6 ± 2.0			6.2 ± 1.8	6.7 ± 2.4						
Adjusted, mean (SE)	6.7 (0.62)	6.9 (0.65)	–0.16 (–0.32–0.01)	.07	6.4 (0.11)	7.0 (0.12)	–0.61 (–0.93 to –0.30)	<.001	0.39 (0.15–0.63)	.002	–0.07 (–0.33–0.19)	.59
Insulin dose, U/d												
Unadjusted, mean±SD	37.8 ± 24.2	34.9 ± 22.6			30.4 ± 18.8	27.7 ± 18.4						
Adjusted, mean (SE)	36.8 (7.5)	35.0 (7.5)	1.77 (–0.33–3.88)	.10	30.1 (7.6)	30.2 (7.6)	–0.12 (–3.38–3.15)	.94	6.7 (1.62–11.81)	.01	4.8 (–0.30–9.95)	.07

Data shown are from the modified intention-to-treat group. Blood glucose was converted from mg/dL to mmol/L using 0.0555 as a multiplier. Statistical comparisons were performed using analyses adjusted for treatment, age category, study, and baseline values of each corresponding variable, as well as duration of diabetes mellitus and insulin dose at randomization and treatment according to age category.
NPH = neutral protamine Hagedorn; CI = confidence interval; SD = standard deviation; SE = standard error.

Table 4. Incidence and Event Rates of Symptomatic (Self-Monitored Blood Glucose <70 mg/dL) and Severe Hypoglycemia in Each Age Group and Overall According to Age and Insulin Treatment

	Aged < 65			Aged ≥ 65			Overall	
Hypoglycemia	Insulin Glargine (n = 1,112)	NPH Insulin (n = 979)	Overall (n = 2,091)	Insulin Glargine (n = 329)	NPH Insulin (n = 275)	Overall (n = 604)	Insulin Glargine (n = 1,441)	NPH Insulin (n = 1,254)
Daytime hypoglycemia incidence, n (%)								
Symptomatic	422 (38)	403 (41)	825 (39)	132 (40)	117 (43)	249 (41)	554 (38)	520 (41)
Severe	15 (1.4)	11 (1.1)	26 (1.2)	3 (0.9)	4 (1.5)	7 (1.2)	18 (1.3)	15 (1.2)
Daytime rate, events/person per year								
Symptomatic	3.38	3.80	3.58	3.12	3.67	3.37	3.32	3.77
Severe	0.03	0.04	0.03	0.03	0.04	0.03	0.03	0.04
Nocturnal hypoglycemia incidence, n (%)								
Symptomatic	222 (20)*†	331 (34)	553 (26)	69 (21)	92 (33)	161 (27)	291 (20)‡	423 (34)
Severe	8 (0.7)*	21 (2.2)	29 (1.4)	4 (1.2)	7 (2.6)	11 (1.8)	12 (0.8)‡	28 (2.2)
Nocturnal rate, events/person per year								
Symptomatic	1.27*	2.78	1.98	1.46	3.16	2.24§	1.32‡	2.86
Severe	0.02*	0.07	0.04	0.06	0.12	0.08	0.03‡	0.08

Incidence is the percentage of participants with at least 1 symptomatic or severe hypoglycemic event.

Rate is the number of symptomatic or severe hypoglycemic events/person per year. Data shown are raw data. Statistical comparisons were performed using analyses with fixed- and random-effects models, adjusted for treatment, baseline glycosylated hemoglobin, duration of diabetes mellitus, insulin dose at randomization, body mass index, age, and treatment by age as fixed effects in both models, and study and study by age as fixed effects in the fixed-effects models and as random effects in the random-effects models.

* $P < .05$ insulin glargine versus neutral protamine Hagedorn (NPH) insulin in the <65 group; † $P < .05$ insulin glargine in the <65 group versus insulin glargine in the ≥65 group;‡ $P < .05$ insulin glargine versus NPH insulin overall;§ $P < .05$ aged ≥65 versus <65.

approximately 7.0%.[18,29–32] Severe hypoglycemic events, although rare, can lead to neurological impairment, seizures, coma, and death,[33] and are a potential deterrent to the use of insulin in older adults. Studies of hypoglycemic risk during insulin use in this potentially vulnerable population are limited. The current ADA treatment guidelines consider hypoglycemia avoidance important in the treatment of type 2 diabetes mellitus, particularly in older adults.[4] These guidelines suggest that treatment decisions, such as basal insulin selection, should be individualized to minimize the risk of hypoglycemia for each person.

One of the strengths of the current study is that, to the knowledge of the authors, this is the first analysis specifically evaluating the efficacy and safety of adding insulin glargine or NPH insulin to an OAD regimen in older adults. Such analyses have not been done in the past because of the limited number of older adults being included in individual randomized controlled trials. Another strength is that the analysis is based upon individual participants' data from the original RCTs instead of using published data aggregates. Pooled analysis from individual trials' published data is usually insufficient to calculate a pooled estimate because published estimates are based on heterogeneous populations, different study designs, and different statistical models.[34] The current pooled analysis of individual participants' data minimized the heterogeneity of the trials and may have produced more-reliable results.

One limitation of this study is that participants were given only once-daily doses of NPH insulin, whereas in clinical settings, many people receive NPH insulin twice per day or with mixed insulin injections.[35] A previous study compared the administration of insulin glargine with OADs with switching participants to twice-daily premixed 70% NPH and 30% regular insulin (70/30) without OADs.[31] Of the 130 insulin-naive participants aged 65 and older with baseline HbA1c of 7.5% to 10.5% with OADs, the addition of insulin glargine was found to be more effective at glycemic control, with less confirmed hypoglycemia, than was twice-daily 70/30 alone (3.7 vs 9.1 events/person per year). Thus, the estimation in the current study of hypoglycemia risk in the NPH insulin-treated participants may be lower than what may be seen in clinical dosing.

Another limitation of the current analyses is that, because of study inclusion and exclusion criteria, participants were likely to be more functional and have fewer comorbidities than the general older adult population. Of community-dwelling individuals aged 65 and older, 62% have two or more chronic medical conditions,[36] and many also have co-occurring geriatric syndromes, such as urinary incontinence and falls.[37] Older adults may have less-intense hypoglycemic symptoms and may be less aware of their hypoglycemia and consequently be less likely to perform effective self-treatment of hypoglycemia.[33,38] Case reports have found that older adults with hypoglycemia and cognitive impairment may present with atypical hypoglycemia symptoms and may have hypoglycemia unawareness.[39,40] Based on a review of these issues, the AGS has recommended HbA1c goals of 7.0% or less for older adults with good functional status and a less-stringent HbA1c goal of 8.0% for frail adults with a life expectancy of less than 5 years.[3] The ADA treatment guidelines echo this.[4] Future studies should evaluate the safety and efficacy of different insulin regimens in older adults with various functional statuses and multiple comorbidities.

In conclusion, the present analyses suggest that, in appropriately selected older adults with type 2 diabetes

mellitus, adding insulin glargine to an existing OAD regimen may be more effective than adding NPH insulin, with a low risk for inducing hypoglycemia.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Louise Traylor, PhD, sanofi-aventis U.S., for statistical support and assistance. Editorial support was provided by Traci Anna Stuve, MA, of Embryon, and funded by sanofi-aventis U.S.

Conflict of Interest: Dr. Halter has received honoraria from Takeda Global R&D and Abbott Nutrition Health Institute and has been a consultant for Takeda Global R&D.

Author Contributions: PL, JH: Concept and design. PL, AC, CB, AV, JH: Acquisition of data. PL, AC, CB, AV, LG, JH: Analysis and interpretation of data, critical revision of the manuscript for important intellectual content and approval of final manuscript to be published. LG: Statistical analysis.

Sponsor's Role: Study and editorial support was funded by sanofi-aventis U.S.

REFERENCES

1. National Diabetes Fact Sheet, 2007. Centers for Disease Control and Prevention [on-line]. Available at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf Accessed December 10, 2010.
2. Boyle JP, Honeycutt AA, Narayan KM et al. Projection of diabetes burden through 2050: Impact of changing demography and disease prevalence in the U.S. Diabetes Care 2001;24:1936–1940.
3. Brown AF, Mangione CM, Saliba D et al. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51 (Suppl 5):S265–S280.
4. American Diabetes Association. Standards of Medical Care in Diabetes—2010. Diabetes Care 2010;33(Suppl 1):S11–S61.
5. UK Prospective Diabetes Study Group, UKPDS. U.K. Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease. Diabetes 1995;44:1249–1258.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853.
7. Wright A, Burden ACF, Paisey RB et al.; for the U.K. Prospective Diabetes Study Group. Sulfonylurea inadequacy: Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). Diabetes Care 2002;25:330–336.
8. Perez N, Moisan J, Sirois C et al. Initiation of insulin therapy in elderly patients taking oral antidiabetes drugs. Can Med Assoc J 2009;180:1310–1316.
9. Donnan PT, Steinke DT, Newton RW et al. Changes in treatment after the start of oral hypoglycaemic therapy in type 2 diabetes: A population-based study. Diabet Med 2002;19:606–610.
10. Korytkowski M. When oral agents fail: Practical barriers to starting insulin. Int J Obes Relat Metab Disord 2002;26(Suppl 3):S18–S24.
11. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy: The basis of patient reluctance. Diabetes Care 1997;20:292–298.
12. Brunton S, Carmichael B, Funnell M et al. Type 2 diabetes: The role of insulin. J Fam Pract 2005;54:445–452.
13. Papa G, Fedele V, Chiavetta A et al. 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. Acta Diabetol 2008;45:53–59.
14. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care 2000;23(5):644–649.
15. Riddle MC, Rosenstock J, Gerich J. Insulin Glargine 4002 Study Investigators. The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086.
16. Massi Benedetti M, Humburg E, Dressler A et al. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. Horm Metab Res 2003;35:189–196.
17. Fritsche A, Schweitzer MA, Häring H-U. Glimepiride combined with morning insulin glargine, bedtime neutral protamine Hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes: A randomized, controlled trial. Ann Intern Med 2003;138:952–959.
18. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: The LANMET study. Diabetologia 2006;49:442–451.
19. Bretzel RG, Nuber U, Landgraf W et al. 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. Lancet 2008;371:1073–1084.
20. Janka HU, Plewe G, Riddle MC et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005;28:254–259.
21. Fariello RG. Pharmacodynamic and pharmacokinetic features of cabergoline. Rationale for use in Parkinson's disease. Drugs 1998;55(Suppl 1):10–16.
22. Pan CY, Sinnassamy P, Chung KD et al. Insulin glargine versus NPH insulin therapy in Asian type 2 diabetes patients. Diabetes Res Clin Pract 2007;76:111–118.
23. Eliaschewitz FG, Calvo C, Valbuena H et al. Therapy in type 2 diabetes: Insulin glargine versus NPH insulin both in combination with glimepiride. Arch Med Res 2006;37:495–501.
24. Kawamori R. Efficacy and safety of insulin glargine in concurrent use with oral hypoglycaemic agents for the treatment of type 2 diabetes patients. Rinsho Iyaku 2003;19:445–464.
25. Bazzano LA, Lee LJ, Shi L et al. Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: A meta-analysis of randomized controlled trials. Diabet Med 2008;25:924–932.
26. Rosenstock J, Dailey G, Massi-Benedetti M et al. Reduced hypoglycemia risk with insulin glargine: A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28:950–955.
27. Rosenstock J, Riddle MC. Insulin therapy in type 2 diabetes. In: Cefalu WT, Gerich JE, LeRoith D, ed. The CADRE Handbook of Diabetes Management. New York: Medical Information Press. 2004, pp 145–168.
28. Chelliah A, Burge MR. Hypoglycaemia in elderly patients with diabetes mellitus: Causes and strategies for prevention. Drugs Aging 2004;21:511–530.
29. Siderowf A. Parkinson's disease: Clinical features, epidemiology and genetics. Neurol Clin 2001;19:565–578, vi.
30. Abraira C, Colwell JA, Nuttall FQ et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM): Results of the feasibility trial. Diabetes Care 1995;18:1113–1123.
31. Janka HU, Plewe G, Busch K. 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 2007;55:182–188.
32. Grossman SP. The role of glucose, insulin and glucagon in the regulation of food intake and body weight. Neurosci Biobehav Rev 1986;10:295–315.
33. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: Pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28:2948–2961.
34. Blettner M, Sauerbrei W, Schlehofer B et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. Int J Epidemiol 1999;28:1–9.
35. Mooradian AD, Bernbaum M, Albert SG. Narrative review: A rational approach to starting insulin therapy. Ann Intern Med 2006;145:125–134.
36. Anderson G, Horvath J. The growing burden of chronic disease in America. Public Health Rep 2004;119:263–270.
37. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: The Health and Retirement Study. J Am Geriatr Soc 2009;57:511–516.
38. Matyka K, Evans M, Lomas J et al. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. Diabetes Care 1997;20:135–141.
39. Dharmarajan TS, Russell RO, Dabhi K. Recurrent, refractory hypoglycemia presenting as a behavioral disorder in an older woman. J Am Geriatr Soc 1999;47:380–381.
40. Kumari J, Dharmarajan TS. Insulin glargine induced persistent intractable hypoglycemia, with variable presentations in older diabetic patients: An experience of 4 cases. J Am Med Dir Assoc 2009;10:672–673.