Efficacy and Tolerability of Self-Titrated Biphasic Insulin Aspart 70/30 in Patients Aged >65 Years With Type 2 Diabetes: An Exploratory Post Hoc Subanalysis of the INITIATEplus Trial

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ABSTRACT

Background: The Initiation of Insulin to reach A1C Target (INITIATEplus) trial studied the effect of self-titrating biphasic insulin aspart 70/30 (BiAsp 30) twice daily during 24 weeks in insulin-naïve patients with type 2 diabetes who were poorly controlled by oral medication, and originally randomized according to frequency of dietary counseling interventions.

Objective: The purpose of this study was to compare the efficacy and tolerability of biphasic insulin aspart 70/30 (BIAsp 30, NovoLog Mix 70/30) in INITIATEplus patients ≤65 versus >65 years old, irrespective of dietary counseling frequency, and to test the hypothesis that self-titrating BIAsp 30 in patients >65 years old could be well-tolerated and effective in this age group.

Methods: An exploratory post hoc subanalysis, using standard statistical methods, was performed on patients stratified according to age. Data collected from 3492 patients in the intent-to-treat population who were ≤65 years old and 716 patients who were >65 years old compared glycosylated hemoglobin (HbA_{1c}) and plasma glucose changes from baseline. Hypoglycemia rates and adverse event (AE) incidence were compared for the tolerability population of 4007 patients ≤65 years old and 805 patients >65 years old.

Results: Baseline-adjusted HbA_{1c} changes for patients ≤65 versus >65 years old were –2.38% versus –2.73% ($P < 0.0001$), with final HbA_{1c} achieving 7.55% and 7.06%, respectively. Thirty-nine percent of patients ≤65 years old achieved HbA_{1c} ≤7% compared with 51% of patients >65 years old. Baseline-adjusted fasting plasma glucose decreases were greater for the >65 year old population (85.2 vs 91.2 mg/dL; $P = 0.004$; ≤65 vs >65 years old, respectively). Minor hypoglycemia was reported in 9.7% and 7.7% of patients ≤65 versus >65 years old, respectively (0.52 vs 0.41 episodes per patient per year [ppy]; $P = 0.01$). Major hypoglycemia occurred in 1.5% and 3.1% of patients (0.05 vs 0.14 episodes ppy, ≤65 vs >65 years old, respectively; $P < 0.0001$). Nocturnal major hypoglycemia was reported for 0.4% and 0.6% of patients ($P = 0.0028$), whereas nocturnal minor hypoglycemia was reported for 3.8% and 2.6% ($P = 0.007$) of patients ≤65 and >65 years old, respectively. AEs were reported for 24% and 28% of patients ≤65 and >65 years old, respectively, serious AEs were reported for 4% and 9% of patients, respectively, and AE-related withdrawals were reported for 1.3% and 2% of patients, respectively.

Conclusions: Self-titrated biphasic insulin aspart 70/30 was found to be well-tolerated and effective in type 2 diabetes patients >65 years old, as well as in patients ≤65 years old. HbA_{1c} and fasting plasma glucose decreases were significantly ($P < 0.05$) higher for patients >65 years old versus patients ≤65 years old. Tolerability was indicated by major and minor hypoglycemia rates at or below <0.5 episodes ppy in both age groups. Overall rates of AE

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and serious AEs were higher among patients > 65 years; withdrawals related to AEs were 2% compared with 1.3% in the younger age group. ClinicalTrials.gov identifier: NCT 00101751. (*Clin Ther.* 2011;33:874–883)

Key words: BIAsp 30, biphasic insulin aspart 70/30, elderly patients, hypoglycemia, insulin self-titration, NovoLog® Mix 70/30.

INTRODUCTION

Many patients with diabetes are still not receiving appropriate pharmacologic treatment to control and manage their glucose levels, as evidenced in reports showing high numbers of patients with glycosylated hemoglobin (HbA_{1c}) levels above the American Diabetes Association (ADA) target of 7%. Poor glucose control can contribute to the development of microvascular complications. This may have greater importance for patients >65 years old with diabetes, because this age group may exhibit more medical conditions than a younger population. Diabetic complications in the presence of such conditions may contribute to a larger burden of disability.[1]

According to an analysis of National Health and Nutrition Examination Survey data collected for 2005 to 2006 for diabetes incidence in the United States, the prevalence of previously diagnosed and undiagnosed diabetes was 31.49% in the population ≥65 years old. An additional 40% were estimated to be prediabetic.[2] Reflecting these numbers in the general population, approximately 32% of nursing home residents have diabetes.[3] These numbers are expected to grow in the forthcoming years because of the aging of the baby boomer generation, many of whom previously have diabetes, and because the incidence of obesity, a risk factor for diabetes, is already high and increasing in the general population.[4,5]

The risk of hypoglycemia among diabetic patients >65 years old is possibly more serious in this group than in a younger population because of the greater susceptibility to central nervous system changes and to falls. Microvascular complications such as retinopathy,[6] sensory and muscular neuropathies,[7,8] cognitive disabilities,[9,10] and cardiovascular problems[11–14] may develop, making diabetes care more difficult to manage. Glycemic control in this older population must be more carefully balanced with safety, especially hypoglycemia risk. Because of this, some health care providers and residential facilities may err on the side of avoiding hypoglycemia at the expense of effective glucose control. Despite these issues, there is no single set of guidelines for glycemic control for an elderly population.

The published glucose target recommendations by the ADA and the American Association of Clinical Endocrinologists are not age-adjusted. The American Medical Directors Association and the American Geriatric Society[15–17] do have age-adjusted targets, but they are not predicated on evidence-based studies. It is difficult to support establishment of guidelines that strictly delineate blood glucose targets, because each diabetic patient must be considered individually. The glucose target for an individual has to be placed in context with their other needs and limitations.This is why the current recommendations are to individualize treatment regimens.[15–17] Zarowitz et al[18] published an insulin treatment algorithm that addressed these concerns and that summarized treatment options. With the aging of the US population, and with the increasing incidence of type 2 diabetes, it becomes more important to have treatment options that can serve an older population. The data derived from this subanalysis of the INITIATEplus trial may therefore be pertinent.

METHODS

Overall Study Design

This 24-week multicenter, open-label study in insulin-naive subjects with type 2 diabetes assessed insulin self-titration upon initiation of twice daily biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection [rDNA origin]; NovoLog® Mix 70/30*).

The study enrolled 4875 adult patients ≥18 years of age at 934 predominantly primary care centers in the United States. Approvals were obtained from an institutional review board/internal ethics committee, and all patients provided written informed consent before study initiation. Novo Nordisk supplied the trial products and covered the costs of all procedures related to treatments.

Patients were originally randomized to either 3, 1, or no dietary counseling interventions[19] over the length of the study. Of the patients in the intent-to-

*Trademark: NovoLog® Mix 70/30, BIAsp 30 (Novo Nordisk, Bagsvaerd, Denmark).

Table I. Insulin dose titration algorithm.

Pre-breakfast and Pre-dinner SMPG	Adjustment
<80 mg/dL	− 3 U
80–110 mg/dL	No adjustment
111–140 mg/dL	+ 3 U
141–180 mg/dL	+ 6 U
>180 mg/dL	+ 9 U

Glycemic target: pre-breakfast and pre-supper self-monitored plasma glucose (SMPG) value of 80 to 110 mg/dL.

treat (ITT) population, 716 were >65 years old (mean [SD] age 72 [5.2] years). Their efficacy outcomes were compared against those of 3492 patients ≤65 years (mean [SD] age, 50.3 [9.4] years). All patients provided written informed consent before trial-related activities. The study was conducted in accordance with the Declaration of Helsinki clinical practice guidelines.[20] This exploratory post hoc subanalysis compared the tolerability and efficacy of BIAsp 30 in patients ≤65 versus >65 years old, without stratification by dietary counseling intervention frequency.

Treatments

One day before initiation of BIAsp 30 treatment, patients discontinued use of prestudy secretagogue oral hypoglycemic agents, but continued other oral agents. All patients had a 1-hour session with a diabetes educator before beginning insulin therapy. The topics covered were the importance of good glucose controls, use of the home glucose meter, injection technique for insulin, basic dietary principles, and the risk of hypoglycemia. The insulin titration algorithm was explained. Afterwards, patients then initiated insulin therapy with 6 U of BIAsp 30 (NovoLog Mix 70/30) injected subcutaneously 15 minutes before breakfast and before supper. The initial dose was self-adjusted every 3 to 5 days using a titration algorithm (**Table I**) based on the average self-monitored plasma glucose (SMPG) value of the 3 days preceding the titration.[19,21] The breakfast dose was titrated to the pre-supper SMPG value, and the evening dose was titrated to pre-breakfast SMPG value. Patients were encouraged to titrate 1 of the doses every 3 to 5 days unless an episode of hypoglycemia occurred. If hypoglycemia occurred within 24 hours before a scheduled titration, the patient deferred any dose increase and re-evaluated their insulin dose levels on the following day. Blood glucose was measured with a OneTouch UltraSmart monitor (LifeScan, Inc., Milpitas, California) calibrated to provide results as PG.

Efficacy Assessments

Efficacy end points included the percentages of patients achieving HbA_{1c} values ≤7.0%, the mean HbA_{1c} at the end of the study, and the mean reduction in HbA_{1c} from baseline. HbA_{1c} values were calculated in the physician's office using the A1CNow (Metrika, Inc., Sunnyvale, California). Efficacy end points also included the PG values from 8-point SMPG profiles. The first SMPG measurements were taken starting with visit 1, before BIAsp initiation. PG measurements for the 8-point profiles were recorded 30 minutes before and 2 hours after breakfast, lunch, and dinner, and at bedtime and 3 AM. Fasting PG (FPG) measurements were considered the pre-breakfast reading.

Tolerability Assessments

Tolerability was assessed by physical examination findings, hypoglycemic episodes, and adverse events (AEs) reports. Minor hypoglycemic episodes were defined as PG values <56 mg/dL with or without symptoms that were self-treated. Major hypoglycemia was defined as an episode with severe central nervous system symptoms consistent with hypoglycemia that required assistance of another individual and PG values <56 mg/dL, or reversal of symptoms after either food intake or glucagon/IV glucose administration.

Statistical Analysis

Efficacy data were analyzed for the ITT population, who were defined as patients for whom any post-baseline efficacy data were available and received at least 1 dose of study drug. A linear statistical model with the change of HbA_{1c} or FPG from baseline to the end of the study as the dependent variable and the age group as a fixed factor was used to perform between group comparisons. Baseline values of HbA_{1c} or FPG were included in the model as a covariate. This linear statistical model was used to estimate the mean change in HbA_{1c} or FPG and the mean differences between the age groups at the end of the trial. The 95% CIs for the mean change differences and *P* values for group com-

Table II. Demographic and baseline characteristics.

Characteristic	All patients	≤65 y	>65 y
Total	4208	3492	716
Age, y	54.0 (2.01)	50.3 (9.4)	72 (5.2)
% M:F	50.5:49.5	50.2:49.8	52:48
White	2885 (68.6%)	2341 (67%)	544 (76%)
African American	1024 (24.3%)	890 (25.5%)	134 (18.7%)
Asian	105 (2.5%)	91 (2.6%)	14 (2.0%)
Other	194 (4.6%)	170 (4.9%)	24 (3.3%)
Non-Hispanic	3718 (88.4%)	3059 (87.6%)	659 (92%)
Hispanic	489 (11.6%)	432 (12.4%)	57 (8.0%)
HbA_{1c}, %	9.91 (1.65)	10.02 (1.7)	9.41 (1.5)
FPG, mg/dL	228.6 (78.2)	232.5 (77.7)	209.4 (73.8)
Body weight, kg (range)	98.7 (23.9) (40.5–181.8)	100.6 (24) (40.5–181.8)	89.4 (20.6) (41.8–175)
BMI, kg/m^2 (range)	34.06 (7.30) (17.4–55)	34.6 (7.3) (17.4–54.9)	31.5 (6.6) (17.9–55)

Intent-to-treat population.
Glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) shown as means [SD].
FPG baseline was taken from the first SMPG measurement.
Body weight and body mass index (BMI) data shown as mean [SD].

parisons are also provided. Missing data were imputed by carrying the last observation forward. The SMPG profiles were analyzed by time point using a similar model as for HbA_{1c}. The percentage of patients achieving HbA_{1c} <7% in the 2 age groups were compared using a logistic regression with baseline HbA_{1c} as a covariate. Many of these methods were used for analyzing data presented in the primary publication for this trial.[19]

Differences in hypoglycemia rates between the 2 age groups were analyzed using a Poisson regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset. Mean hypoglycemia rates were calculated as number of hypoglycemic events per patient-year (ppy) per group. All relative risk ratios were adjusted for the reported total number of years exposed to drug to correct for exposure. The SEs of the rate ratios were adjusted for dispersion by rescaling the covariance matrix and then used to calculate 95% CIs.

Baseline, end of study values for body weight, and weight-adjusted daily insulin dose were analyzed by a general linear model, with age as a fixed factor and presented as observed means. Statistical significance was considered $P < 0.05$.

RESULTS

Demographics Characteristics/Patient Disposition

Patients in the INITIATEplus trial were originally randomized to 3 groups that had a different number of dietary counseling sessions, but who had no other differences in their treatment regimens with BiAsp 30. Each group contained equal numbers of patients stratified by age, race and ethnic demographic characteristics, weight, and body mass index (BMI). The results as reported by Oyer et al[19] showed similar HbA_{1c} decreases for all counseling groups, with major hypoglycemia significantly ($P < 0.05$) lower for patients in the most frequent dietary counseling arm as the only significant difference between groups. For the purposes of this exploratory post hoc analysis, data from patients were consequently grouped only by age, ≤65 and >65 years, irrespective of original counseling cohort.

Table II lists baseline characteristics for the patients in this exploratory subanalysis. Seventeen percent (n = 544) of patients were >65 years old. Mean (SD) age for the patients ≤65 years old was 50.3 (9.4) years and 72

(5.2) years for the >65 years old treatment group. Of the ≤65 years old group, 50.2% were male, and 52% of the >65 years old group were male. The ≤65 years old group had higher body weights (100.6 vs 89.4 kg), BMI (34.6 vs 31.5 kg/m^2), baseline HbA_{1c} (10.02 % vs 9.41%), and baseline FPG values (232.5 vs 209.4 mg/dL). There was a higher percentage of African American patients (25.5% vs 18.7%), and a lower percentage of white patients (67% vs 76%) in the ≤65 years old group.

Efficacy

HbA_{1c} and FPG Changes

Both patient subpopulations achieved mean HbA_{1c} changes from baseline that were –2.38% and –2.73%, ≤65 vs >65 years old, respectively (**Table III**). Mean estimated HbA_{1c} differences between groups (0.35%; $P < 0.0001$) favored the >65 years old population. There was no gender dependency on HbA_{1c} changes from baseline for either age group. Among patients ≤65 years old, 39.1% achieved the ADA goal of HbA_{1c} values <7%, whereas 51.3% of the >65 years old population achieved the same goal ($P < 0.0001$).

Similarly, mean FPG decreases from baseline were greater for patients >65 years old, with a mean estimated difference between groups of 6.03 mg/dL ($P = 0.004$). The post-breakfast PG readings were significantly different between groups ($P = 0.03$) and favored patients ≤65 years old, whereas at other time points, there were no significant ($P > 0.05$) differences between groups. The SMPG profiles for 8 time points are shown in **Figure 1**, and indicate nearly complete overlap in postprandial glucose values between the 2 groups at study end.

Tolerability

Hypoglycemia

Data shown in **Figure 2** and **Table IV** summarize hypoglycemia incidence and rates among patients in both age groups. In the ≤65 years old group, 9.7% of patients experienced minor hypoglycemic episodes compared with 7.7% in the >65 years old group. Rates for minor hypoglycemia were significantly lower for the >65 years old group (0.52 and 0.41 events/ppy; $P = 0.011$). Major hypoglycemia was reported by 1.5% and 3.1% of patients (rates, 0.05 and 0.14 ppy; $P < 0.001$) in the ≤65 vs >65 years old groups. Minor nocturnal hypoglycemia was reported by 3.8% of patients in the ≤65 years old group versus 2.6% in the >65 years old group (0.15 and 0.11 events ppy; $P =$

Table III. Efficacy outcomes.

Characteristic	≤65 y	>65 y	*P*	Estimated Differences (95% CI)
Overall final HbA_{1c}	7.55 (1.52)	7.06 (1.14)		
ΔHbA_{1c} (overall, baseline adjusted)	-2.38 (95% CI, -2.4 to -2.3)	-2.73 (95% CI, -2.8 to -2.6)	<0.0001	0.35 (0.23 to 0.47)
ΔHbA_{1c} (males, baseline adjusted)	-2.43 (95% CI, -2.5 to -2.4)	−2.75 (95% CI, -2.9 to -2.6)	<0.0001	0.32 (0.16 to 0.48)
ΔHbA_{1c} (females, baseline adjusted)	-2.34 (95% CI, -2.4 to -2.3)	-2.72 (95% CI, -2.9 to -2.6)	<0.0001	0.39 (0.22 to 0.55)
Final FPG	143.8 (51.4)	134.8 (38.1)		
ΔFPG (baseline adjusted)	-85.2 (95% CI, -86.8 to -83.5)	-91.2 (95% CI, -94.9 to -87.5)	0.004	6.03 (1.95 to 10.11)

Δ = change.
Efficacy data were collected from the intent-to-treat population with last observations carried forward.
Final glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) values shown are observed means (SD).
The baseline adjusted least square mean changes from baseline are from a linear statistical model with age as fixed effect and HbA_{1c} or FPG at baseline as covariates.

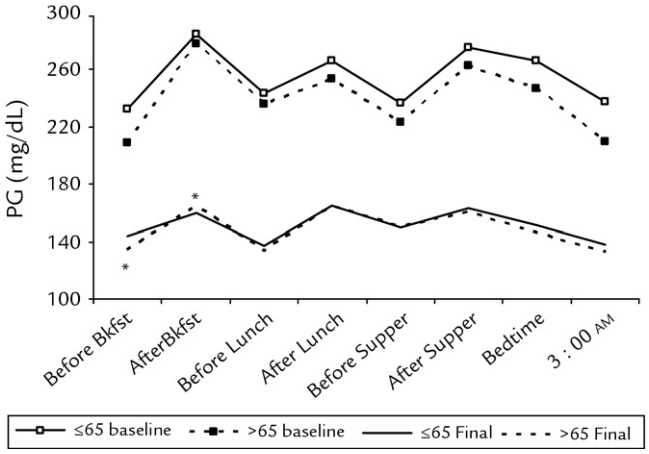

Figure 1. Eight-point self-monitored blood glucose before and after twice-daily 24-week BIAsp 30 treatment. *$P <$ 0.05 for between group comparisons. Eight-point self-measured blood glucose readings were taken 30 minutes before breakfast (Bkfst), lunch, and dinner, 2 hours after breakfast, lunch, and dinner, and at bedtime and 3:00 AM. PG = plasma glucose.

0.007), and major nocturnal hypoglycemia was reported by 0.4% of patients in the ≤65 years old group versus 0.6% in the >65 years old group (0.01 and 0.02 events ppy; $P = 0.0028$).

Body Weight and Final Insulin Dose

There were significantly ($P <0.0001$) lower baseline weights for the >65 years old group (Table V). Body weight increased less for the >65 years old group (3.17 vs 2.02 kg; $P < 0.0001$). This was also true on a percent of baseline weight basis (3.1% vs. 2.3%; $P <$ 0.0001, for patients ≤65 vs >65 years old, respectively). Final weight-adjusted daily insulin doses were significantly higher for the ≤65 years old group (0.75 vs 0.66 U/kg; $P < 0.0001$, respectively).

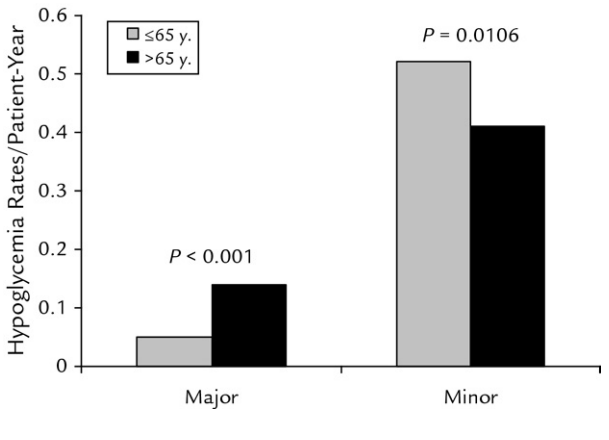

Figure 2. Overall major and minor hypoglycemia rates between patients ≤65 and >65 years old.

Adverse Events

Table VI shows patient AE disposition. AEs were reported for 24% and 28% of patients ≤65 and >65 years old, serious AEs (SAEs) were reported for 4% and 9% of patients, and withdrawals due to AEs comprised 1.3% and 2% of the 2 age groups, respectively. Sixteen patients (0.4%) ≤65 years old and 9 patients (1.25%) >65 years old experienced SAEs that were considered possibly or probably related to study drug. Ten patients (0.25%) ≤65 years old experienced hypoglycemic events, 1 (0.025%) had a hyperglycemic event, 1 (0.025%) exhibited chest pain, 2 (0.05%) had cardiac disorders, and 2 (0.05%) exhibited diabetic ketoacidosis. Seven patients (0.87%) >65 years old experienced hypoglycemia, 1 (0.12%) experienced a hyperglycemic episode, and 1 (0.12%) had a cardiac arrest from which the patient recovered. No deaths in either age group were considered related to treatment. The male:female ratio for SAEs was similar for patients in both age groups; 9:7 for patients ≤65 years old and 4:5 for patients >65 years old.

Table IV. Hypoglycemia results.

Characteristic	≤65 y (N = 4007)	>65 y (N = 805)	*P*
Overall minor hypoglycemia			
No.	388 (9.7%)	62 (7.7%)	
Events	859	136	
Rates	0.52	0.41	
	Ratio = 1.28 (95% CI,1.06–1.55)		0.0106
Overall major hypoglycemia			
No.	62 (1.5%)	25 (3.1%)	
Events	81	46	
Rates	0.05	0.14	
	Ratio = 0.36 (95% CI, 0.3–0.42)		<0.0001
Nocturnal minor hypoglycemia			
No.	154 (3.8%)	21 (2.6%)	
Events	247	37	
Rates	0.15	0.11	
	Ratio = 1.36 (95% CI, 1.09–1.69)		0.0071
Nocturnal major hypoglycemia			
No.	18 (0.4%)	5 (0.6%)	
Events	21	6	
Rates	0.01	0.02	
	Ratio = 0.71 (95% CI, 0.57–0.89)		0.0028

Hypoglycemia analysis was performed for the safety population.
Poisson regression analysis was used to derive *P* values for rate ratios.
Rate: Events/patient-year.
Ratio: ≤65 rate divided by >65 rate.

DISCUSSION

Poor glycemic control in patients with diabetes may allow microvascular complications to develop. In elderly patients, comorbidities might exist that could increase the impact of these microvascular complications.

Because the elderly population comprises individuals whose health is more fragile, glycemic control must be more acutely balanced with tolerability, particularly the risk for inducing hypoglycemia. Hypoglycemia may increase the risk of falling, cause adverse cognitive effects that may be confused with dementia, and carries the risk of actual cerebrovascular events.[7,22] These events may combine to increase mortality rates among patients >65 years old with diabetes, which are higher than in a similarly aged population without diabetes.[23] However, when risk avoidance is allowed to be the predominant factor in establishing therapeutic options, glycemic control can often suffer and the consequences of chronic hyperglycemia can progress. It is therefore important to develop treatment strategies that can be tolerated by an elderly population. An insulin regimen that is well-tolerated and that can be self-titrated can be a valuable treatment option for patients with type 2 diabetes.

The INITIATEplus trial was originally comprised of >4800 insulin-naïve patients in whom oral antidiabetic drug therapy failed, and who initiated insulin therapy with twice daily BIAsp 30 using an algorithm that allowed self-titration to be performed.[19] The data discussed in this study were an exploratory post hoc analysis that tested the hypothesis that BIAsp 30 treatment of patients >65 years old would be tolerated and effective in this age group, and compared treatment efficacy and hypoglycemia rates between these patients with those who were ≤65 years old. Seventeen percent (n = 544) of the trial population analyzed were <65 years old. The results reported herein showed that the INITIATEplus biphasic insulin aspart (BIAsp 30;

Table V. Body weights and insulin doses.

Characteristic	≤65 y	>65 y	*P*
Body weight, kg			
Baseline	100.3 (24.2)	88.8 (20.2)	<0.0001
Final	103.4 (23.8)	91.4 (20.7)	<0.0001
Change	3.17 (7.45)	2.02 (5.52)	<0.0001
Final weight-adjusted insulin dose, U/kg)	0.75 (0.51)	0.66 (0.40)	<0.0001

Baseline, final body weights, body weight changes from baseline, and weight-adjusted insulin doses are shown as observed means (SD).
Data are taken from the safety population.

NovoLog Mix 70/30) self-titration regimen provided better glycemic control for patients >65 and ≤65 years old with regard to reductions in HbA_{1c} and PG, moderated intraday glucose variation, and reduced hyperglycemic excursions. The regimen was well tolerated in patients >65 years old, as well as in patients ≤65 years old, as the overall major and minor hypoglycemia rates for patients in both age groups were ≤0.52 episodes ppy. Overall AE incidence occurrence was comparable between groups (24% and 28%, ≤65 vs >65 years old), yet SAEs were higher for patients >65 years old (4% vs 9%). AEs related to withdrawals were similar for both groups and comprised 1.3% and 2% of the ≤65 versus >65 years old population, respectively.

Efficacy outcomes of this study, HbA_{1c} and FPG, were similar for both age groups, and the decreases from baseline for the >65 years old group were statistically significantly greater ($P < 0.05$). Differences in insulin utilization or other metabolic differences between age groups might account for some of these observed differences. Of the ≤65 year old patients, 39% achieved the HbA_{1c} goal of <7% compared with 51% in the >65 years old group.

The >65 years old population exhibited statistically significant ($P < 0.05$) lower overall and nocturnal hypoglycemia rates, but had major hypoglycemia rates that were higher and statistically significant from those reported for patients ≤65 years old. These major and minor hypoglycemia rates were ≤0.52 events ppy in

Table VI. Proportion of patients exhibiting adverse events (AEs).

	≤65 y (n = 4007)*			>65 y (n = 805)*			Total (N = 4812)*	
AE	n	%	% of Total	N	%	% of Total	n	%
All AEs	944	23.6	19.6	227	28.2	4.7	1171	24.3
All SAEs	165	4.1	3.4	76	9.4	1.5	241	5.0
AEs possibly or probably related to drug	206	5.1	4.4	39	4.8	0.8	249	5.2
SAEs possibly or probably related to drug	16	0.4	0.3	9	1.1	0.2	25	0.5
AE-related withdrawals	53	1.3	1.1	16	2	0.3	69	1.4
Deaths	13	0.3	0.3	12	1.5	0.2	25	0.5

SAEs = serious adverse events.
*Data from the safety population.

both age groups. This implied that the probability of the occurrence of a hypoglycemic episode was ≤1 episode in 2 years. Due to the low hypoglycemia rates in both groups, the relative importance of statistically significant differences between the groups was not clear.

It was interesting to note that the patients >65 years old had 12% lower body weights, final weight-adjusted insulin doses that were 12% lower, and smaller weight gains than the ≤65 year old patients. The latter 2 observations might have been due to lower food consumption by the patients >65 years old, whose lower BMIs would make them more insulin sensitive and allow for lower insulin requirements. Insulin-mediated glucose uptake reported in patients with diabetes >65 years old (mean age 74 years) was reduced by only 20% compared with healthy individuals,[24] whereas in middle-aged patients (defined as 50 years old) glucose uptake was reduced by 50%. This might account for the higher insulin usage and slightly lower efficacy in the ≤65 year old patients reported here (mean age, 50 years) compared with the >65 years old group (mean age, 72 years).

The limitations of this post hoc analysis included the study not being randomized with each age group to having equal numbers of patients, nor were they randomized for comorbidites, race or ethnicity, and baseline glucose parameters. Nonetheless, the data presented herein suggest that insulin initiation and self-titration with BIAsp 30 could successfully be carried out in an insulin-naïve population >65 years old, providing glucose control with hypoglycemia rates at <1 event ppy. Withdrawals due to AEs occurred in 1.3% and 2% of the ≤65 and >65 years old populations, respectively, suggesting that the treatment was well-tolerated and to a similar extent by patients in either age group.

Many patients >65 years old face difficulties not shared by younger patients. These may include risk of more severe complications associated with hypoglycemia, as well as dexterity and visual problems that may rule out manually mixing isophane insulin suspension with regular human insulin, and cognition issues that may undermine the ability to follow a complicated dosing algorithm. Irregular eating habits by the elderly is of less concern with an insulin analog premix because it can be dosed in closer proximity to the meal without losing efficacy.[25–27] In addition, premixes eliminate the possibility of errors that may occur by mixing regular human insulin and isophane insulin suspension. The data from this trial suggested that glycemic control and tolerability could be obtained with a simple regimen of twice daily BIAsp 30 (NovoLog Mix 70/30), which could benefit patients >65 years old.

CONCLUSION

Self-titrated biphasic insulin aspart 70/30 was found to be well-tolerated and effective in type 2 diabetes patients >65 years old, as well as in patients ≤65 years old. HbA_{1c} and FPG decreases were significantly ($P < 0.05$) greater for patients aged >65 years versus patients aged ≤65 years. Tolerability was indicated by major and minor hypoglycemia rates at or below <0.5 episodes ppy in both age groups. Overall rates of AEs and SAEs were higher among patients aged >65 years; withdrawals related to AEs were 2% compared with 1.3% in the younger age group.

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