CLINICAL RESEARCH STUDY

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A_{1c} Control in a Primary Care Setting: Self-titrating an Insulin Analog Pre-mix (INITIATE*plus* Trial)

David S. Oyer, MD,[a] Mark D. Shepherd, MD,[b] Franklin C. Coulter, MD,[c] Anuj Bhargava, MD,[d] Jason Brett, MD,[e] Pei-Ling Chu, PhD,[e] and Bruce S. Trippe, MD,[f] on behalf of The INITIATE*plus* Study Group*

[a]Feinberg School of Medicine, Northwestern University, Chicago, Ill; [b]Endocrinology Consultants, Tupelo, Miss; [c]Coulter Clinic, Orangeburg, SC, [d]Iowa Diabetes and Endocrinology Center, Des Moines; [e]Novo Nordisk Inc., Princeton, NJ; [f]Endocrinology Associates, Montgomery, Ala.

ABSTRACT

PURPOSE: To study glycemic control and hypoglycemia development upon initiation of insulin through a self-titration schedule in a 24-week trial, conducted with 4875 insulin-naïve patients with poorly controlled type 2 diabetes, predominantly in a primary care setting.

METHODS: Subjects initiated twice-daily biphasic insulin aspart 70/30 with 6 units prebreakfast and 6 units presupper, self-titrating according to self-measured blood glucose values. Subjects were randomized (1:1:1) to telephone counseling provided by a registered dietician: no counseling (NC), 1 counseling session (1C), or 3 sessions (3C).

RESULTS: Mean baseline HbA_{1c} (9.9% across groups) decreased ~2.5% to 7.49% ± 1.48, 7.48% ± 1.50, and 7.44% ± 1.46 in the NC, 1C, and 3C groups, respectively. Within these groups, a hemoglobin A_{1c} (HbA_{1c}) value <7% was achieved by 40.2%, 41.6%, and 41.8% of subjects, respectively. Eight-point blood glucose profiles were substantially improved from baseline for all groups. Hypoglycemia was experienced by 10.2%-11.4% of the subjects in each group. Rates of minor and major hypoglycemia were low but decreased as dietary counseling increased (minor hypoglycemia: 56 vs 50 vs 45 episodes per 100 patient-years; major hypoglycemia, 9 vs 6 vs 4 episodes per 100 patient-years, for the NC vs 1C vs 3C groups, respectively; $P < .001$, 3C vs NC). Weight increased by 3.13, 3.40, and 2.88 kg for the NC, 1C, and 3C groups, respectively.

CONCLUSION: In the primary care setting, self-titration of biphasic insulin aspart 70/30 was effective in achieving recommended HbA_{1c} goals even with minimal dietary counseling.

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KEYWORDS: Biphasic insulin aspart 70/30; Hypoglycemia; Insulin self-titration; NovoLog® Mix 70/30

The numbers of adults and children diagnosed with type 2 diabetes increase annually in the US and worldwide.[1,2] However, insufficient numbers of diabetes specialists are available to treat these rising numbers. Thus, in the US, the majority of diabetes patients are treated by primary care physicians.

*The members of the INITIATE*plus* Study Group are listed online.

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Requests for reprints should be addressed to David S. Oyer, MD, 211 East Chicago Avenue, Chicago, IL 60611.

E-mail address: d-oyer@northwestern.edu

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Recent reports based on data from the National Health and Nutrition Examination Survey (NHANES) have demonstrated improvements in overall glycemic control through significant decreases in mean hemoglobin A_{1c} (HbA_{1c}) values from 1999-2000 through 2003-2004.[3,4] The NHANES survey data show that the percent of adults with diabetes achieving the American Diabetes Association (ADA) target HbA_{1c} <7% improved from 37% to 57%. Unfortunately, there remains 43% of patients with diabetes, most of whom have type 2 diabetes, still in poor control and not achieving the glycemic target proposed by the ADA.[4,5] Even more patients are not achieving the glycemic target proposed by the American Association of Clinical Endocrinologists (AACE target HbA_{1c} ≤6.5%).[6] The benefits of improved long-term glycemic control on the incidence and progression of diabetic complications for type 2 diabetes are well established and documented in the United Kingdom Prospective Diabetes Study.[7] Often, lack of control results from reluctance of both the patient and the physician to intensify therapy when needed. Intensified treatment often translates into insulin therapy that is proven to be the most efficacious drug for lowering blood glucose values and achieving control.[8-12] The ADA and the European Association for the Study of Diabetes have proposed that insulin therapy should be initiated in type 2 diabetes when HbA_{1c} is ≥7.0% after 2-3 months,[13] and that insulin therapy should be considered earlier in the treatment algorithm rather than attempting to control diabetes with potentially dangerous oral agents.

CLINICAL SIGNIFICANCE

- Patients can be educated and empowered to self-titrate insulin dosage and successfully achieve good glycemic control.
- A simple dosing algorithm allowed patients with high HbA_{1c} values (study mean = 9.9%) to regain glycemic control (endpoint mean HbA_{1c} = 7.4%).
- Daily blood glucose self-monitoring is an important component for effective self-adjusted insulin dose titration.
- Biphasic insulin aspart 70/30, twice a day, is an effective treatment option for patients with type 2 diabetes in a primary care setting.

Numerous barriers prevent more widespread use of insulin. A major problem is the work involved by the physician and staff teaching insulin therapy to a patient. The majority of patients with diabetes are cared for in primary care offices. Initiation of insulin and insulin adjustment can absorb significant, under-reimbursed physician and staff time. A therapy protocol that is easily taught and self-titrated will allow more patients to initiate insulin therapy, with follow-up visits and telephone calls reduced.

In this phase IV study, physicians of patients with type 2 diabetes initiated insulin therapy using biphasic insulin aspart 70/30 for those patients who were failing on oral hypoglycemic agents, where failure was defined as HbA_{1c} >8%, one of the inclusion criteria for the trial. Mean overall HbA_{1c} was 9.9 ± 1.7%. The study was performed to assess efficacy and safety when initiating insulin therapy with biphasic insulin aspart 70/30 in a self-titration schedule combined with a modest degree of dietary intervention in the primary care setting.

METHODS

Overall Study Design

This 24-week, randomized, multi-center, open-label, parallel-group study in 4875 insulin-naive type 2 diabetes subjects assessed insulin self-titration upon initiation of twice-daily biphasic insulin aspart 70/30 (NovoLog Mix 70/30, Novo Nordisk, Bagsvaerd, Denmark). The study enrolled adult subjects (≥18 years of age) at 934 predominantly primary care centers in the US. Baseline HbA_{1c} measurements were taken at the first visit (Day 0), which served as both the screening visit and the randomization visit. Inclusion in the study required the HbA_{1c} to be 8% or higher, with no upper limit on the HbA_{1c}. Subjects received dietary counseling and diabetes education about living with diabetes and taking insulin from Certified Diabetes Educators or similarly trained dieticians who telephoned the patients at home.[14] All subjects provided written informed consent before trial-related activities. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.[15]

Treatments

Subjects initiated insulin therapy 15 minutes before breakfast and dinner with subcutaneous injection of 6 units biphasic insulin aspart 70/30. Before initiation of biphasic insulin aspart 70/30 treatment, subjects discontinued use of prestudy secretagogue oral hypoglycemic agents, but continued other oral agents. The initial dose was self-adjusted every 3-5 days using a titration algorithm based on the average self-measured blood glucose value of the 3 days preceding the titration (Table 1). Blood glucose was measured with a OneTouch® UltraSmart® monitor (LifeScan, Inc., Milpitas, CA) calibrated to read plasma glucose. The

Table 1 Insulin Titration Algorithm

Prebreakfast and Predinner SMBG	Adjustment
<80 mg/dL	−3 units
80-110 mg/dL	No adjustment
111-140 mg/dL	+3 units
141-180 mg/dL	+6 units
>180 mg/dL	+9 units

SMBG = self-measured blood glucose. Glycemic target: prebreakfast and presupper SMBG value of 80 to 110 mg/dL.

breakfast dose was titrated to the predinner, self-measured blood glucose value, and the evening dose was titrated to the prebreakfast, self-measured blood glucose value. Subjects were encouraged to titrate one of the doses every 3 to 5 days unless an episode of hypoglycemia had occurred. If hypoglycemia occurred within 24 hours before a scheduled titration, the subject deferred any dose increase and re-evaluated their insulin dose levels on the following day.

Coupled with insulin initiation, all subjects received subject-centered instruction by a Certified Diabetes Educator about living with diabetes and taking insulin. The educator focused on self-care skills including basic information related to the diabetic disease process, the benefits of good glycemic control, the avoidance and management of hypoglycemia, blood glucose monitoring, and medication use. Subjects were then randomly assigned (1:1:1) to one of the following 3 dietary counseling groups: no dietary counseling (NC or Standard Treatment group), 1 counseling session (1C), or 3 counseling sessions (3C). Subjects in the 1C group received one individualized telephone-based dietary counseling session during the first weeks of the trial. Subjects in the 3C group received 3 sessions that occurred at Week 1, Week 2, and Week 12. The dietician counseled subjects on their current dietary habits and areas needing education and improvement. There were a total of 5 primary care visits: the first on day 0 and then at weeks 1, 2, 12, and 24. During these visits, the patient met with physicians, nurses, or Certified Diabetes Educators. In addition to dietary counseling, subjects in the 1C and 3C groups received a meal planning guide and booklet describing carbohydrate and calorie counting.

Efficacy Assessments

The efficacy endpoints included the percentages of subjects achieving HbA_{1c} values $<7.0\%$ and $\leq 6.5\%$, the mean HbA_{1c} at the end of the study, and the mean reduction in HbA_{1c} from baseline. HbA_{1c} values were measured in the office using the A1CNow® (Metrika, Inc., Sunnyvale, Calif). Efficacy endpoints also included the blood glucose values from 8-point self-measured blood glucose profiles. Blood glucose measurements for the 8-point profiles were recorded 30 minutes before and 2 hours after breakfast, lunch, and dinner, at bedtime, and at 3:00 AM.

Safety Assessments

Safety was assessed by physical examination findings, and by reporting hypoglycemic episodes and adverse events reporting. Minor hypoglycemic episodes were defined as plasma glucose values <56 mg/dL or whole blood glucose (BG) <50 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 a plasma glucose values <56 mg/dL or whole BG values <50 mg/dL, or reversal of symptoms after either food intake or glucagon/intravenous glucose administration.

Statistical Considerations

The data were analyzed for the intent-to-treat population defined as subjects for whom any postbaseline efficacy data were available. The intent-to-treat population was comprised of 4212 subjects (1415, 1420, and 1377 subjects in the NC, 1C, and 3C groups, respectively). Power calculations performed before study initiation helped ascertain numbers of patients required. Of the original 4875 patients who were randomized, 84 were lost due to inadequate process control by one trial site. The bulk of the others withdrew due to adverse events, noncompliance, or various personal reasons before week 12 when data were collected. Those who withdrew after week 12 were part of the intent-to-treat population and their data were captured as part of the last observation carried forward.

The percentage of subjects achieving an HbA_{1c} $<7\%$ or $\leq 6.5\%$ between treatment groups was compared using a chi-squared test. The mean end-of-study HbA_{1c} value and mean change in HbA_{1c} from baseline were analyzed by an analysis of covariance model, with treatment as fixed effect, and HbA_{1c} at baseline as a covariate. The blood glucose values from the self-measured blood glucose profiles were analyzed by timepoint using a similar analysis of covariance model as for HbA_{1c}. Missing data were imputed by carrying the last observation forward. Values presented are means $\pm$ standard deviations (SD) unless otherwise noted.

RESULTS

Disposition and Demographics

A total of 4875 subjects were randomized into the study. Eighty percent of subjects completed the study, 20% withdrew, with similar distributions across the 3 dietary intervention groups (Table 2). Baseline demographic characteristics appeared to be similar across dietary counseling groups (Table 2). Mean baseline HbA_{1c}values were equal for all groups and averaged about 9.9%. A substantial percentage of subjects ($\sim$42%) had HbA_{1c} values $\geq$10% (Figure 1). A comparison of HbA_{1c} by racial characteristics (Table 2) showed that African-American subjects appeared to have higher mean HbA_{1c} values at baseline ($\sim$10.4%) than did white subjects ($\sim$9.7%) ($P < .001$).

Efficacy

At the end of the study, HbA_{1c} decreased from baseline (overall average of 9.9%) by 2.4% to 2.5% for each treatment group. Final HbA_{1c} values were similar across treatment groups (7.4% to 7.5%) at the end of the study. As a reflection of the similar end-of-study HbA_{1c} values, a similar percentage of subjects in each treatment group achieved the HbA_{1c} targets of $<7.0\%$ (40.2%, 41.6%, and 41.8% for the NC, 1C, and 3C groups, respectively) or $\leq 6.5\%$ (28.6%, 27.8%, and 28.3%, respectively). Data in Figure 1 demonstrate this shift in HbA_{1c} to lower values. At endpoint, 1759 subjects displayed HbA1c values below 7%, and 1231 subjects achieved values between 7% and 8%, compared with

Table 2 Characteristics of Enrolled Subjects and Subject Disposition

	Standard Treatment	1 Counseling Session	3 Counseling Sessions
Subjects randomized	1625	1624	1626
Age (years)	53.6 ± 12.20	53.4 ± 12.26	53.8 ± 12.24
Sex, male/female (%)	50/50	49/51	52/48
Height (cm)	169.2 ± 10.6	168.9 ± 10.4	169.3 ± 10.5
Weight (kg)	98.8 ± 24.6	98.3 ± 23.5	98.0 ± 23.8
BMI (kg/m^2)	34.1 ± 7.4	34.0 ± 7.1	33.8 ± 7.3
Race, W/B/A/O (%)	67/25/3/5	68/25/2/5	67/26/3/4
Ethnicity (%)			
Not Hispanic/Latino	88	86	89
Hispanic/Latino	12	14	11
HbA_{1c} (%) overall	9.9 ± 1.7	9.9 ± 1.7	9.9 ± 1.6
HbA_{1c} (%) by race			
White	9.72 ± 1.56	9.75 ± 1.57	9.69 ± 1.54
Black	10.41 ± 1.83	10.49 ± 1.79	10.43 ± 1.75
Asian	9.86 ± 1.51	10.07 ± 1.25	9.94 ± 1.70
Other	10.04 ± 1.92	9.89 ± 1.62	10.02 ± 1.49
Smoking history (%)			
Never/former/current	49/30/21	48/31/21	48/30/22
Subjects completing study, n (%)	1291 (79.4)	1304 (80.3)	1273 (78.3)
Subjects discontinuing study, n (%)	305 (18.8)	297 (18.3)	321 (19.7)
Subjects of unknown status, n (%)	29 (1.8)	23 (1.4)	32 (2.0)
Reason for discontinuation, n (%)			
Adverse event	34 (2.1)	21 (1.3)	14 (0.9)
Lost to follow-up	62 (3.8)	65 (4.0)	68 (4.2)
Subject died	10 (0.6)	4 (0.2)	4 (0.2)
Voluntarily withdrew	103 (6.3)	117 (7.2)	118 (7.3)
Noncompliance	68 (4.2)	57 (3.5)	84 (5.2)
Other	28 (1.7)	33 (2.0)	33 (2.0)

BMI = body mass index; W/B/A/O = White/Black/Asian/Other.
Data are means ± SD unless otherwise noted.

10 and 232 subjects, respectively, at baseline. This amounted to 41.6% of the endpoint population reaching an endpoint HbA_{1c} <7%, and 70.7% of the endpoint population achieving HbA_{1c} <8%, compared with 0.2% and 4.8%, respectively, at baseline. The most substantial decreases in mean HbA_{1c} values occurred in the first 12 weeks of the study and continued to decrease during the remainder of the trial (Figure 2). Mean HbA_{1c} values decreased similarly from baseline by 2.4% to 2.5% across the racial demographic groups. HbA_{1c} values were slightly higher at baseline for African-American subjects than for all other groups. Accordingly, the mean HbA_{1c} values at the end of the study were higher in African-American subjects than in white and other subjects (white 7.31 ± 1.40%; African-American 7.90 ± 1.65%; Asian 7.54 ± 1.36%; other 7.61 ± 1.41%). HbA_{1c} decreases were 2.41 ± 1.85%, 2.54 ± 2.04%, 2.37 ± 1.78%, and 2.35 ± 1.94%, respectively.

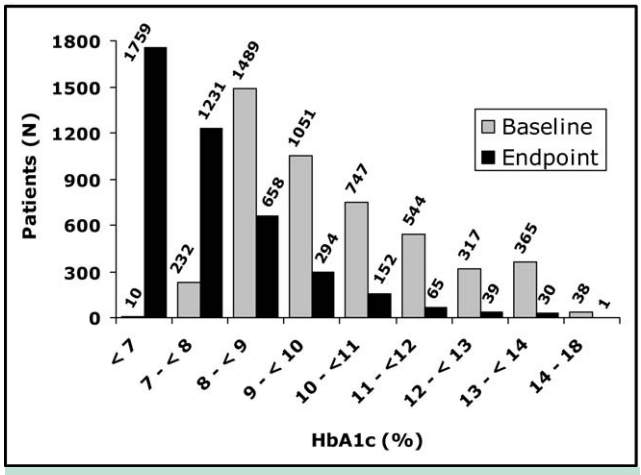

Figure 1 Number of subjects within incremental HbA_{1c} ranges at baseline and endpoint. Numbers above bars indicate numbers of patients within each HbA_{1c} range.

The 8-point self-measured blood glucose profiles were substantially improved from baseline for all treatment groups at the end of the study (Figure 3). The decreases from baseline in mean blood glucose values at the end of the study ranged from a minimum of 82.7 mg/dL to a maximum decrease of 125 mg/dL, depending upon timepoint, for all treatment groups. Most of the end-of-study blood glucose values were similar across treatment groups at the respective timepoints in the 8-point profile. However, the 3C

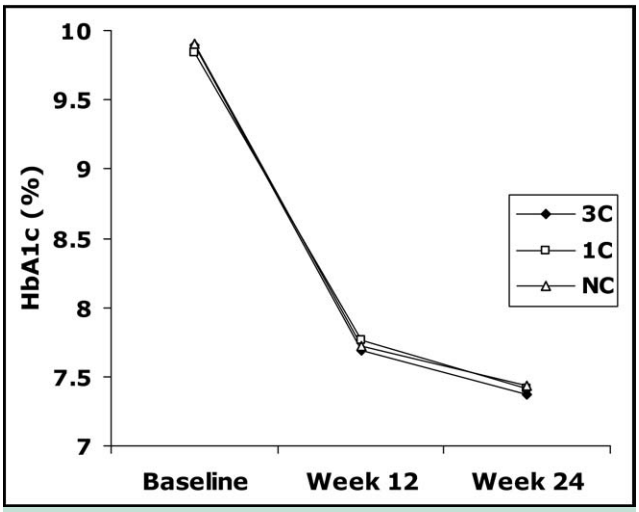

Figure 2 Similar decreases in HbA_{1c} over time were observed for all treatment groups. Number of subjects at each timepoint: Baseline: 1409, 1415, 1370; Week 12: 1405, 1413, 1365; Week 24: 1285, 1297, 1252; for NC, 1C, and 3C, respectively.

group had a blood glucose value at bedtime that was significantly less than the bedtime value in the standard treatment group (148.9 ± 56.54 vs 154.0 ± 60.85, respectively; $P = .020$). The 3:00 a.m. mean blood glucose value of the 3C group was significantly less than the corresponding value of the standard treatment group (NC) (134.8 ± 48.04 vs 139.5 ± 53.70, respectively, $P = .024$).

Final daily insulin doses for the intent-to-treat population at the end of the study were similar across treatment groups (76.4, 75.1, and 74.0 units/day for the NC, 1C, and 3C groups, respectively). The overall weight-adjusted insulin dose for the study population was 0.73 ± 0.49 units/kg; the dose was slightly greater for white (0.78 ± 0.52 units/kg) and Asian subjects (0.79 ± 0.47 units/kg) and was slightly lower for African-American subjects (0.60 ± 0.40 units/kg).

Safety

Mean body weights increased similarly in all treatment groups by the end of the study and were not statistically significant between groups (3.13 ± 5.76, 3.40 ± 6.07, and 2.88 ± 5.88 kg for the NC, 1C, and 3C groups, respectively). Median and minimum/maximum body weight changes were 2.73 and −17.7/+25.9 kg, 2.73 and −19.1/+27.7 kg, 2.73 and −19.5/+27.3 kg for the NC, 1C and 3C groups, respectively.

The percentages of subjects reporting a hypoglycemic episode (blood glucose <56 mg/dL) were low and similar across treatment groups (10.2% to 11.4%). The rates of daily minor and major hypoglycemia were relatively low but decreased as dietary intervention increased (minor hypoglycemia: 56 vs 50 vs 45 episodes per 100 patient-years; major hypoglycemia, 9 vs 6 vs 4 episodes per 100 patient-years, for the NC vs 1C vs 3C groups, respectively). The rates of daily major and minor hypoglycemia in the 3C group were significantly less than the respective rates in the NC group (49 vs 65 events per 100 patient-years, respectively, $P < .001$). The rates of daily minor and major hypoglycemia in the 1C group were not significantly different from those in the NC group.

Nocturnal hypoglycemia was experienced by a small and similar percentage of subjects in each treatment group (3.3% to 4.7%) at a low rate of occurrence (14 to 18 episodes per 100 patient-years). Hypoglycemia was the reason for study withdrawal of 4 subjects in the NC group, 4 subjects in the 1C group, and 1 subject in the 3C group.

Adverse events were reported by a similar percentage of subjects (23.5% to 25.5%) in each treatment group, with 5% of the subjects in each group reporting a serious adverse event. Serious adverse events related to cardiac disorders comprised ~25% of the serious events in each treatment group, followed by events related to infection (10% to 20%) and metabolism (8% to 14%). Twenty-five subjects died during the course of the study (14 subjects in the NC group, 5 subjects in the 1C group, and 6 subjects in the 3C group). Most deaths were from cardiovascular events (10 subjects) or cancer (6 subjects). None of the deaths were deemed by the investigator to be related to study treatment. However, hypoglycemia was suspected in a fatal motor vehicle accident. Six patients in the NC group (NC), 5 in the 1C group (1C), and 6 in the 3C group (3C) reported hypoglycemia that was determined to be a serious adverse event. Fifteen of these patients were seen by emergency practitioners or were admitted because of this condition.

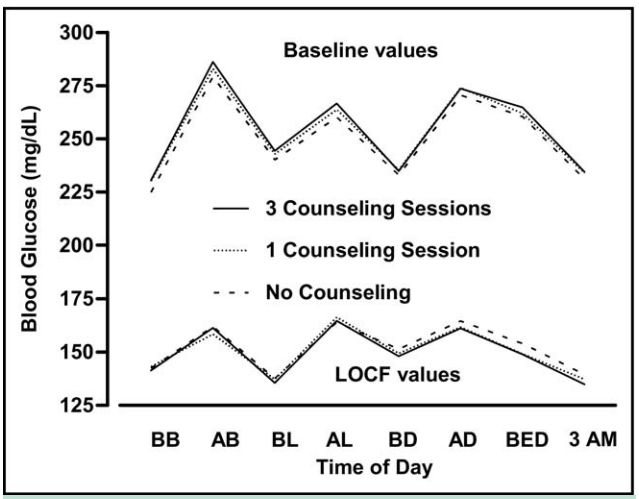

Figure 3 Eight-point self-measured blood glucose readings. Measurements were taken 30 minutes before breakfast, lunch, and dinner (BB, BL, and BD); 2 hours after breakfast, lunch, and dinner (AB, AL, and AD); at bedtime (Bed); and at 3:00 a.m. Number of data points at each timepoint at baseline: 1141 to 1364; at the end of the study, last observation carried forward: 1155 to 1352 (upper limit is for before breakfast, lower limit for 3:00 AM, for both baseline and last observation carried forward).

A low discontinuation rate due to adverse events (1% to 2%) was observed among all 3 counseling groups. The overall discontinuation rate was between 18.3% and 19.7% among the 3 dietary counseling groups (Table 2). A further demographic breakdown of all patients who discontinued therapy, independent of counseling group, showed 17% of all white patients discontinued, as did 23% of African-American, 21% of Asian, and 26.6% of other patients. Of those who withdrew voluntarily or due to noncompliance, 9.7% of white patients, 14.3% of the African-American, 11.5% of Asian, and 17.7% of others were in these categories.

DISCUSSION

All treatment groups had marked decreases in HbA_{1c} of 2.4% to 2.5% when administering and self-adjusting biphasic insulin aspart 70/30 twice daily using a relatively simple dose titration schedule. The decreases in HbA_{1c} in this study enabled approximately 41% of the subjects to achieve the ADA goal of $<7\%$ and 28% to achieve the AACE HbA_{1c} goal of $\leq 6.5\%$. The percentage achieving the AACE goal in this study appears to be greater than the percentage of subjects recently reported to have achieved this goal in the 4T (Treat-To-Target in Type 2 diabetes) Study (17%), where subjects also were initiating biphasic insulin therapy upon failing on oral hypoglycemic agents.[16] Notably, more subjects in the current study were able to reach the AACE goal despite the mean baseline HbA_{1c} value being greater (9.9%) than in the 4T Study (8.5%). The greater efficacy in the current study could have resulted from the self-titration algorithm that provided subjects with opportunities to adjust their insulin dose every 3-4 days compared with more structured physician-directed adjustments in the 4T study. In most trials using insulin, the most substantial decrease in HbA_{1c} usually occurs during the first 12 weeks of the study, with little improvement thereafter. In this study, however, the HbA_{1c} kept improving throughout the study period (Figure 2), indicating that self-titration was performed successfully throughout the study.

The HbA_{1c} decreases observed in the current study also were similar to those observed in the INITIATE Study (baseline HbA_{1c} of 9.7% and mean decrease of 2.8%) and in the 1-2-3 Study (baseline HbA_{1c} of 8.7% and mean decrease of 1.9%), where type 2 subjects also administered twice-daily biphasic insulin aspart 70/30.[17,18] The substantial mean decrease in HbA_{1c} and the resultant percentage of subjects that achieved glycemic control in the current study attest to the relative ease by which patients can initiate insulin therapy with a biphasic insulin analog using a simple titration algorithm with relatively minor dietary guidance from health care professionals. It is valuable to know that the dietary sessions were not mandatory to the success of the protocol, making the initiation of insulin therapy easier to accomplish.

In the current study, the overall rates of major and minor hypoglycemia were quite low across treatment groups. Nonetheless, the 3C dietary intervention group had combined rates of minor and major hypoglycemia significantly lower than those in the NC group. Notably, few subjects withdrew from the study because of major hypoglycemia in the 1C group (3 subjects) and NC group (2 subjects), while none withdrew from the 3C group. The guidance provided by telephone counseling sessions may have assisted subjects in the 3C group on dietary practices and insulin adjustments to prevent withdrawals because of hypoglycemia.

Adverse events accounted for a low discontinuation rate (1%-2%) across all 3 counseling groups. As the discontinuation rate for voluntary withdrawals and noncompliance were very similar in all counseling groups, we can conclude that it was not due to dietary counseling issues. An additional demographic breakdown of all patients who discontinued therapy showed a slightly greater discontinuation rate among African-American and other patients, and similarly higher voluntary and noncompliant discontinuations for the African-American and other patients. The significance of these findings is being further evaluated, and further demographic analyses of these and other results are required. However, these data may imply that perhaps greater attention to some patients' racial backgrounds may be important for health care providers to consider in order to ensure their long-term treatment compliance.

In this large study, conducted primarily in the primary care setting, the mean baseline HbA_{1c} value of the enrolled subjects (9.9%) was substantially higher than the proposed ADA target ($<7\%$), supporting the suggestion that many physicians are not initiating insulin therapy in their patients with type 2 diabetes until HbA_{1c} values are $>9\%$.[9,19] The high HbA_{1c} entry values indicate that although the latest NHANES data show important improvements in glycemic control, there remain many patients who would benefit with earlier insulin usage and better adherence to the ADA/European Association for the Study of Diabetes consensus algorithm.

Although basal insulins are commonly used to initiate insulin therapy, biphasic analog premixes also are suitable for some patients and may be particularly beneficial for patients with higher HbA_{1c} values.[10,13] Notably, biphasic insulin aspart 70/30 was significantly more effective than a basal insulin analog in reducing HbA_{1c} for subjects who entered the INITIATE study with HbA_{1c} values $>8.5\%$.[17] The rapid-acting component of biphasic insulin aspart 70/30 provides postprandial glycemic control, thereby giving the biphasic insulin analog mix a distinct advantage over a basal insulin preparation.

The results above are generalizable in the context of a patient population that consisted of poorly controlled patients failing oral antidiabetic drug therapy. The data show that these patients self-titrated an insulin analog premix to successfully bring their glucose levels close to ADA targets. There were no significant differences in outcomes as a function of dietary counseling for the degree of counseling used in this study.

The decision to start insulin is a major event in the life of a patient with diabetes, who must weigh clinical benefits versus inconvenience, potential hypoglycemia, and weight gain. Insulin therapy is more attractive if the protocol is simple and effective. The INITIATE*plus* study accomplishes these goals and is unique because of the large number of patients in the trial, the self-titration, and the location of most of the patients in primary care physician offices. Thus, the INITIATE*plus* study is highly relevant for primary care physicians who treat the majority of patients with type 2 diabetes, demonstrating that biphasic insulin aspart is a viable option for initiating insulin therapy in those patients who have difficulty meeting glycemic goals with oral agents alone.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjmed.2008.12.026.