Published in final edited form as:

Pediatrics. 2009 April ; 123(4): e673–e678. doi:10.1542/peds.2008-3027.

Institution of Basal-Bolus Therapy at Diagnosis for Children With Type 1 Diabetes Mellitus

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Abstract

OBJECTIVE—We studied whether the institution of basal-bolus therapy immediately after diagnosis improved glycemic control in the first year after diagnosis for children with newly diagnosed type 1 diabetes mellitus.

METHODS—We reviewed the charts of 459 children ≥ 6 years of age who were diagnosed as having type 1 diabetes between July 1, 2002, and June 30, 2006 (212 treated with basal-bolus therapy and 247 treated with a more-conventional neutral protamine Hagedorn regimen). We abstracted data obtained at diagnosis and at quarterly clinic visits and compared groups by using repeated-measures, mixed-linear model analysis. We also reviewed the records of 198 children with preexisting type 1 diabetes mellitus of >1 -year duration who changed from the neutral protamine Hagedorn regimen to a basal-bolus regimen during the review period.

RESULTS—Glargine-treated subjects with newly diagnosed diabetes had lower hemoglobin A1c levels at 3, 6, 9, and 12 months after diagnosis than did neutral protamine Hagedorn-treated subjects (average hemoglobin A1c levels of 7.05% with glargine and 7.63% with neutral protamine Hagedorn, estimated across months 3, 6, 9, and 12, according to repeated-measures models adjusted for age at diagnosis and baseline hemoglobin A1c levels; treatment difference: 0.58%). Children with long-standing diabetes had no clinically important changes in their hemoglobin A1c levels in the first year after changing regimens.

CONCLUSION—The institution of basal-bolus therapy with insulin glargine at the time of diagnosis of type 1 diabetes was associated with improved glycemic control, in comparison with more-conventional neutral protamine Hagedorn regimens, during the first year after diagnosis.

Keywords

glargine; hemoglobin A1c; honeymoon; glycemic control; pediatric

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The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Basal-bolus therapy provides an alternative treatment strategy for children with T1DM and has been shown to be as effective as conventional, split-mixed, insulin regimens in maintaining glycemic control.

What This Study Adds

Basal-bolus therapy with insulin glargine initiated at the time of diagnosis of T1DM was associated with improved glycemic control for the first year after diagnosis, compared with more-conventional regimens using NPH.

The Diabetes Control and Complications Trial demonstrated that “intensive” insulin therapy for patients with type 1 diabetes mellitus (T1DM) was associated with significantly improved glycemic control and decreased rates of comorbidities such as retinopathy, nephropathy, and peripheral neuropathy.¹ Even incremental improvements in glycemic control are now known to be associated with reductions in microvascular complications.

Over the past several years, the definition of intensive therapy has changed as new insulin analogs have become available. The normal pancreas secretes a relatively constant basal amount of insulin into the circulation between meals and then responds to the ingestion of a meal by secreting a larger bolus of insulin to maintain euglycemia. Long-acting insulin analogs such as insulin glargine, paired with rapid-acting insulin analogs (RAIAs) (lispro, aspart, or glulisine), allow subcutaneous insulin regimens to approximate normal endogenous secretory patterns more closely. The efficacy of such “basal-bolus” combinations, compared with more-traditional insulin regimens, has been studied extensively. Insulin glargine, paired with a RAIA, is at least as effective² in maintaining glycemic control in children with T1DM as are more-conventional regimens using a combination of an intermediate-acting insulin (such as neutral protamine Hagedorn [NPH], levels of which peak ~6 hours after injection) with the RAIAs mentioned above. Most studies have suggested equal efficacy with respect to glycemic control,³⁻¹¹ with significantly reduced rates of hypoglycemia for patients treated with basal-bolus regimens, whereas a few studies have suggested improved glycemic control in selected subpopulations.¹²⁻¹⁶

To date, however, there have been few reports on the use of basal-bolus regimens for children and adolescents with newly diagnosed T1DM. The recent report by Paivarinta et al⁷ on the effect of switching from NPH to glargine for children with T1DM specifically excluded all children with recent diagnoses or still-detectable C-peptide levels. One small, randomized, controlled trial suggested that, among children who were assigned randomly to receive either glargine or NPH after 3 months of treatment with a conventional NPH regimen, glycemic control was significantly improved in the glargine-treated group 3 months after randomization.¹³ To our knowledge, there have been no reports relating the experience of starting basal-bolus therapy on the day of T1DM diagnosis.

Children with newly diagnosed T1DM represent a unique subpopulation, because preservation of their remaining β -cell mass is the subject of intense investigation in many studies throughout the world.¹⁷⁻²¹ The purpose of this study was to determine whether the institution of a basal-bolus regimen using insulin glargine at the time of diagnosis for children with newly diagnosed T1DM would be associated with improved glycemic control in the first year after diagnosis, compared with more-traditional regimens using NPH.

METHODS

Diabetes Care Protocol

All children suspected of having diabetes at Children's Medical Center Dallas are evaluated with a standard protocol, including a detailed history and physical examination and biochemical tests, including venous blood gas, basic metabolic profile, serum glucose, and hemoglobin A1c assessments. The diagnosis is confirmed on the basis of American Diabetes Association criteria (fasting blood glucose levels of ≥ 126 mg/dL or random blood glucose levels reproducibly of ≥ 200 mg/dL, with symptoms of diabetes). T1DM is diagnosed on the basis of the presence of ≥ 1 of 3 types of diabetes-associated autoantibodies (anti-glutamic acid decarboxylase 65, anti-islet antigen 2, or antiinsulin antibodies) and lack of evidence of insulin resistance. Children with acidosis (pH of < 7.30) are initially treated with intravenously administered fluids and insulin, with conversion to a subcutaneous insulin regimen after resolution of the acidosis. Children without acidosis begin subcutaneous insulin treatment immediately.

All patients considered to have T1DM are hospitalized for initiation of insulin therapy and education (typically for ~48 hours). Before March 2003, almost all children at our institution began with an insulin regimen consisting of mixed intermediate-acting insulin (NPH) and a RAIA (lispro or, later, aspart) at breakfast, a second dose of RAIA at dinner, and a second dose of NPH at bedtime. Since the middle of 2003, increasing numbers of patients (including those with new diagnoses) have been treated with a basal-bolus regimen, consisting of a bedtime dose of glargine and doses of a RAIA before meals. Decisions regarding insulin regimens are based on family and physician preferences after consideration of factors such as willingness to take insulin regularly at lunch, weighed against the more-flexible daily routine permitted with basal-bolus regimens. All children, regardless of their regimens, are advised to perform self-monitoring of their blood glucose levels 4 times per day (at meals and at bedtime), with administration of correction doses of RAIA for hyperglycemia. Parents are advised to send (through fax or e-mail) blood glucose logs to our diabetes educators for dose adjustments once or twice per week initially, with decreases in frequency as appropriate. All children begin with a constant-carbohydrate diet.

Subjects

Charts were reviewed under a protocol approved by the institutional review board at the University of Texas Southwestern Medical Center. For the primary analysis, we identified all children >6 years of age who were diagnosed as having T1DM between July 1, 2002, and June 30, 2006.

In a separate analysis, we identified all children with preexisting T1DM of >1 -year duration who had been diagnosed after their sixth birthday and who, during the study period, changed from a traditional NPH regimen to a basal-bolus regimen using glargine. At our center, children who wish to change their insulin regimen usually are asked to attend an intensive insulin management class that teaches the principles of using an insulin/ carbohydrate ratio, which allows greater flexibility in meal choices. This serves as a basis for families to move toward basal-bolus therapy (for patients on an NPH regimen) or toward continuous subcutaneous insulin infusion therapy. Children who changed from NPH to glargine were identified from among all children who attended the class during the 4-year study period.

Design and Analyses

We recorded demographic data, initial biochemical parameters, and total daily doses of insulin at discharge for all patients with newly diagnosed T1DM. Subjects with newly diagnosed T1DM were grouped according to the long-acting insulin analog (either NPH or glargine)

chosen at the time of diagnosis. Data were collected from each quarterly clinic visit from the time of diagnosis. Hemoglobin A1c levels were determined by using a DCA2000 instrument (Siemens, Deerfield, IL). Data are presented as means $\pm$ SDs unless otherwise noted. Statistical analyses were performed with SAS 9.1.3 (SAS Institute, Cary, NC).

For subjects with newly diagnosed T1DM, baseline characteristics were compared between NPH and glargine with 2-sample *t* tests. Because of skewness, β -hydroxybutyrate levels were logarithmically transformed before analysis. Hemoglobin A1c responses to glargine and NPH were compared over the first 12 months of treatment through repeated-measures analyses using a mixed-linear model approach,²² with an autoregressive covariance structure. All models contained a between-group treatment factor, treatment duration as the repeated factor, and a treatment-duration interaction factor. Treatment effects were adjusted for baseline hemoglobin A1c levels, age at diagnosis (as a continuous variable), and year of diagnosis. Because significant interactions between age at diagnosis and treatment response were found, the effect of age at diagnosis was further evaluated by separating patients into 2 groups (< 10.5 and ≥ 10.5 years of age) on the basis of the median age at diagnosis.

For all children with long-standing T1DM who switched to glargine from NPH during the same time period, we collected the last hemoglobin A1c measurement before their change in regimen and then collected quarterly measurements over the course of the year after the change. Mean hemoglobin A1c levels for each period were analyzed by using mixed-model, repeated-measures analysis, to determine whether there was any significant change in glycemic control.

RESULTS

Demographic Characteristics

During the 4-year review period, a total of 459 children >6 years of age were diagnosed as having T1DM at Children's Medical Center Dallas. A total of 247 of those children were treated with a conventional insulin regimen using 3 injections per day, including a combination of NPH and a RAIA; for 212 children, a basal-bolus regimen using insulin glargine in combination with a RAIA was instituted immediately.

Table 1 illustrates the chronologic increase in the use of glargine for subjects with newly diagnosed T1DM at our institution and how such treatment eventually became the de facto standard of care. Before March 20, 2003, all children with newly diagnosed T1DM at our institution were treated with NPH. After November 8, 2005, almost all children were treated with glargine. Between those dates, either regimen was selected, on the basis of previously identified factors. For clarity, children diagnosed before March 20, 2003, are referred to as subgroup 1, children diagnosed between March 20, 2003, and November 8, 2005, as subgroup 2, and children diagnosed after November 8, 2005, as subgroup 3.

During the study period, children treated with NPH were slightly younger, on average, than their glargine-treated counterparts, with corresponding lower auxologic characteristics (Table 2). They also were more acidotic at presentation, as measured with bicarbonate and serum β -hydroxybutyrate levels, and were discharged with a slightly greater dose of insulin.

Hemoglobin A1c Observations

Children With Newly Diagnosed T1DM—Hemoglobin A1c responses averaged 0.58% (95% confidence interval [CI]: 0.36%–0.81%; $P < .0001$) lower for the first year with glargine treatment, compared with NPH treatment (7.05% with glargine and 7.63% with NPH, estimated across months 3, 6, 9, and 12, according to repeated-measures models adjusted for age at diagnosis and baseline hemoglobin A1c levels) (Fig 1). A significant interaction ($P = .04$) was observed between age, duration of therapy, and treatment response; therefore, responses

stratified according to age group are shown in Table 3. Treatment responses according to age (dichotomized at 10.5 years), with adjustment for baseline hemoglobin A1c levels, are shown in Fig 2. A greater treatment effect was observed for patients ≥ 10.5 years of age at diagnosis, with a hemoglobin A1c difference of 0.86% (95% CI: 0.52%–1.19%; 6.81% with glargine and 7.67% with NPH; $P < .0001$), than for younger patients (0.37% [95% CI: 0.08%–0.67%]; 7.27% with glargine and 7.64% with NPH, estimated across months 3, 6, 9, and 12; $P = .01$).

Children With Long-standing T1DM—During the same time period, 198 children with longstanding T1DM (diagnosed at >6 years of age and ≥ 1 year before the change in insulin regimens) changed from a traditional NPH regimen to a basal-bolus regimen. These children averaged 13.2 years of age and had been diagnosed as having T1DM 3.4 years before their change in regimens. For these children, there was a small improvement in hemoglobin A1c levels at 3 months (0.2%; $P < .01$), which was not sustained for the remainder of the first year after the change in regimens (Table 4).

DISCUSSION

Our study suggested that institution of basal-bolus therapy at the time of diagnosis of T1DM (usually within 1 day) was associated with improved glycemic control during the first year after diagnosis, compared with a traditional insulin regimen using NPH. In contrast, and in keeping with the literature,³⁻¹¹ a change to basal-bolus therapy for children with long-standing T1DM resulted in no clinically significant change in hemoglobin A1c levels for up to 1 year after the change. To our knowledge, this is the first report of an institution's experience with basal-bolus therapy instituted at the time of diagnosis of T1DM.

As a retrospective analysis, this study has inherent limitations. The numbers of patients available for analysis at each of the 4 quarterly time points (in both the newly diagnosed T1DM and long-standing T1DM groups) were less than the numbers available at baseline, because of missed appointments and less-than-perfect adherence to recommendations to maintain quarterly clinic visits.

Children with newly diagnosed T1DM at our institution are treated with 1 of 2 insulin regimens (see above). Our older regimen uses 3 injections and has the advantage of not always requiring an injection at school, because NPH (levels of which peak ~6 hours after administration) provides the “bolus” coverage needed for the lunchtime meal. In contrast, true basal-bolus therapy, although requiring a lunchtime injection, provides patients and their families with a small increase in flexibility in their daily schedules, because mealtimes can be changed from day to day more easily than for children receiving a combination of an intermediate-acting insulin and a RAI. A.

An analysis such as this, which aims to determine retrospectively the effect of a gradual change in the de facto standard of care for a condition, has 2 major potential confounders, that is, selection bias and additional unsuspected, gradual, or incompletely defined changes in treatment occurring over time. Although there is the possibility of selection bias attributable to nonrandomization of the treatment regimen instituted at the time of diagnosis of T1DM, basal-bolus therapy became the de facto standard of care at our institution by November 2005, whereas NPH treatment was the standard until March 2003. When the analysis was repeated with the exclusion of patients (subgroup 2) in the transitional period from April 2003 through October 2005 (an exclusion that would effectively eliminate potential selection bias, because all children in the 2 time periods remaining in the analysis received the same longer-acting insulin), the results were essentially unchanged, with an overall treatment difference of 0.56% (95% CI: 0.27%–0.86%; average hemoglobin A1c levels of 6.99% with glargine and 7.55% with NPH, estimated across months 3, 6, 9, and 12, according to repeated-measures models

adjusted for age at diagnosis and baseline hemoglobin A1c levels; data not shown). This suggests that selection bias did not play a significant role in our observations.

Moreover, it might reasonably be expected that any putative selection bias for the children with newly diagnosed T1DM would be present also for the children with long-standing T1DM. In the latter group, however, changing to glargine after an average of 3.4 years of NPH therapy resulted in no sustained change in glycemic control, as determined with hemoglobin A1c levels, over the same period of observation. These latter data are largely consistent with literature findings. Because patients in the Diabetes Control and Complications Trial had better glycemic control with regimens incorporating ≥ 3 daily injections, compared with 2 injections,¹ many clinicians assume that a relationship between the number of daily injections and glycemic control applies for ≥ 4 injections as well. However, our data and literature findings largely argue against this position, at least for children with long-standing T1DM. The largest randomized trial to date comparing NPH and glargine for children with long-standing T1DM suggested no significant improvement in hemoglobin A1c levels for children assigned randomly to receive basal-bolus therapy.¹¹

To address the possibility of a significant time confounder, we performed a separate analysis restricted to subgroup 2 (patients diagnosed between April 2003 and October 2005); patients diagnosed during the periods of nearly exclusive therapy with either NPH (subgroup 1) or glargine (subgroup 3) were excluded. The subgroup 2 analysis showed results very comparable to the overall results, with a treatment difference of 0.69% (95% CI: 0.33%–1.04%; hemoglobin A1c levels of 7.12% with glargine and 7.81% with NPH, estimated across months 3, 6, 9, and 12, according to repeated-measures models adjusted for age at diagnosis and baseline hemoglobin A1c levels; data not shown), which suggests that time was not a significant confounder in the analysis.

There is evidence that the use of glargine is associated with significantly fewer hypoglycemic events, compared with NPH.^{3,9} However, our retrospective analysis was unable to determine rates of hypoglycemia accurately.

This study relates our experience with the initiation of treatment with insulin glargine at the time of diagnosis for children with T1DM. Although we report our experience with children 6 to 18 years of age, physicians at our institution gradually instituted glargine treatment as their routine practice starting with older adolescents and progressing toward younger children over time. This is reflected in the average ages of the 2 treatment groups with newly diagnosed T1DM. During the period of observation in this study, children treated with NPH were slightly younger, on average, than their glargine-treated counterparts. Older children are known to have longer “honeymoons” than their younger counterparts, which represent longer periods of sustained endogenous insulin secretory capacity after the initial diagnosis of T1DM.^{23,24} In our analyses, patients treated with glargine had better glycemic control even after adjustment for age at diagnosis. When the results were dichotomized according to the median age at diagnosis, older subjects received greater apparent benefit from glargine than did their younger counterparts.

The mechanism underlying these results remains to be elucidated. The fact that children with long-standing T1DM failed to exhibit improvement after changing from NPH to glargine, whereas children with newly diagnosed T1DM seemed to fare significantly better with glargine, might reflect better compliance for subjects with newly diagnosed T1DM (who were not yet set in their habits of compliance or lack thereof). Among patients with long-standing T1DM (and their families), however, only those who expressed interest and willingness in changing regimens were switched from NPH to glargine. This implies a treatment bias in the direction of more-compliant patients with longstanding T1DM receiving glargine. Because

changes in regimens for patients with long-standing T1DM had no sustained effect on glycemic control, this suggests that differences in compliance are very unlikely to underlie our observations for patients with newly diagnosed T1DM. There may be a physiologic explanation for the apparent beneficial effect of glargine use being confined to patients with new-onset T1DM.

The largest difference between children with newly diagnosed T1DM and those with long-standing disease is the β -cell function that is still present in children with newly diagnosed disease. Preservation of this residual insulin secretory capacity is the subject of intense collaborative efforts, such as the Type 1 Diabetes TrialNet. Previous research showed that improved glycemic control was associated with greater duration of endogenous insulin secretory capacity.^{25,26} Our data suggest that it may be prudent to ensure that all subjects with T1DM who participate in research trials aiming to preserve endogenous β -cell function be treated with basal-bolus therapy to optimize their blood glucose control for the year after their diagnosis, and possibly longer. Whether the institution of basal-bolus therapy at the time of diagnosis of T1DM is associated independently with the preservation of endogenous insulin reserve can be determined only with a prospective, randomized, controlled trial with measurement of C-peptide levels at appropriate time points.

CONCLUSIONS

Our study suggests that the institution of basal-bolus therapy with insulin glargine at the time of diagnosis of T1DM is associated with improved glycemic control during the first year after diagnosis, in comparison with a traditional insulin regimen using NPH with a RAI. To our knowledge, this is the first report detailing an institution's experience with basal-bolus therapy instituted at the time of diagnosis of T1DM.

Acknowledgements

Partial grant support was provided by National Institutes of Health Clinical and Translational Science Award UL1-RR-024982.

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Abbreviations

T1DM	type 1 diabetes mellitus
RAIA	rapid-acting insulin analog
CI	confidence interval
NPH	neutral protamine Hagedorn

FIGURE 1.

Comparison of hemoglobin A1c (HgbA1c) levels in the first year after diagnosis. Symbols and error bars represent unadjusted means and SEs, respectively, connected by dashed lines. Solid lines represent linear model estimates adjusted for age at diagnosis and baseline hemoglobin A1c levels.

FIGURE 2.

Hemoglobin A1c (HgbA1c) levels dichotomized according to age. A, Age of < 10.5 years; B, age of ≥ 10.5 years. Symbols and error bars represent unadjusted means and SEs, respectively, connected by dashed lines. Solid lines represent linear model estimates adjusted for age at diagnosis and baseline hemoglobin A1c levels.

TABLE 1

Chronologic Increase in Use of Insulin Glargine

Subgroup	Date	<i>n</i>	
		Treated With Glargine	Treated With NPH
1	July 1, 2002, to December 31, 2002	0	55
1	January 1, 2003, to March 19, 2003	0	25
2	March 20, 2003, to June 30, 2003	3	17
2	July 1, 2003, to December 31, 2003	4	44
2	January 1, 2004, to June 30, 2004	11	55
2	July 1, 2004, to December 31, 2004	21	34
2	January 1, 2005, to June 30, 2005	53	12
2	July 1, 2005, to November 8, 2005	39	5
3	November 9, 2005, to December 31, 2005	16	0
3	January 1, 2006, to June 30, 2006	65	0

TABLE 2
Demographic Features and Initial Serum Biochemical Values

	NPH	Glargine	Long-standing T1DM
Gender, <i>n</i>			
Male	125	111	95
Female	122	101	103
Race, <i>n</i>			
White	166	148	146
Black	38	28	26
Hispanic	33	29	18
Other	10	7	
Age, mean $\pm$ SD, y ^a	10.1 $\pm$ 2.5	11.3 $\pm$ 3.0	13.2 $\pm$ 2.8
Height, mean $\pm$ SD, cm ^a	141 $\pm$ 15	146 $\pm$ 18	
Weight, mean $\pm$ SD, kg ^a	38 $\pm$ 15	42 $\pm$ 15	
Bicarbonate concentration, mean $\pm$ SD, meq/L ^a	18 $\pm$ 7	20 $\pm$ 7	
β -Hydroxybutyrate level, mg/dL			
Mean $\pm$ SD ^a	4.1 $\pm$ 3.1	3.7 $\pm$ 3.6	
Median (interquartile range)	3.7 (1.2–6.4)	2.6 (0.8–5.8)	
Total daily discharge dose, U/kg per d ^a	0.74 $\pm$ 0.14	0.71 $\pm$ 0.14	

^a $P < .05$, NPH versus glargine.

TABLE 3
Hemoglobin A1c Levels in Children With Newly Diagnosed T1DM in First Year After Diagnosis

	Hemoglobin A1c Level, Mean ± SD, %										<i>P</i> ^d
	Glargine (<i>N</i> = 212)					NPH (<i>N</i> = 247)					
	Baseline (<i>N</i> = 212)	3 mo (<i>N</i> = 134)	6 mo (<i>N</i> = 154)	9 mo (<i>N</i> = 147)	12 mo (<i>N</i> = 160)	Baseline (<i>N</i> = 247)	3 mo (<i>N</i> = 198)	6 mo (<i>N</i> = 182)	9 mo (<i>N</i> = 157)	12 mo (<i>N</i> = 138)	
All (<i>N</i> = 459)	11.4 ± 1.9	6.6 ± 1.1	6.6 ± 1.4	7.2 ± 1.7	7.5 ± 1.6	11.6 ± 1.8	7.2 ± 31.2 ^b	7.3 ± 1.4 ^b	7.9 ± 1.4 ^b	8.2 ± 1.8 ^b	< .0001
Age at diagnosis ^c											
< 10.5 y (<i>N</i> = 237)	11.3 ± 1.8	6.8 ± 1.0	6.8 ± 1.2	7.5 ± 1.7	7.8 ± 1.6	11.5 ± 1.9	7.1 ± 1.1 ^d	7.4 ± 1.3 ^d	8.0 ± 1.4	8.0 ± 1.6	.01
≥ 10.5 y (<i>N</i> = 222)	11.5 ± 1.9	6.5 ± 1.1	6.4 ± 1.6	6.9 ± 1.7	7.3 ± 1.6	11.9 ± 1.7	7.4 ± 1.2 ^e	7.2 ± 1.5 ^e	7.8 ± 1.4 ^e	8.4 ± 1.9 ^e	< .0001

All subjects had a baseline measurement and $\geq$ 1 other measurement between 3 and 12 months (inclusively).

^a *P* values from mixed-model, repeated-measures analysis of treatment effect.

^b *P* < .003, glargine versus NPH for the same visit month.

^c Analyses were performed according to age group after a significant interaction (*P* = .04) between age, treatment, and duration was observed.

^d *P* < .03, glargine versus NPH for the same visit month.

^e *P* < .004, glargine versus NPH for the same visit month; a nadir between p = 0.5 and Uactual start one the 3rd result was observed due to multiple testing.

TABLE 4

Hemoglobin A1c Levels in Subjects With Long-standing T1DM (Changing Therapies)

Time After Switch	<i>N</i>	Hemoglobin A1c Level, Mean $\pm$ SD, %	<i>P</i>
Baseline	198	8.4 $\pm$ 1.5	
3 mo	159	8.2 $\pm$ 1.4	.01
6 mo	142	8.3 $\pm$ 1.4	.27
9 mo	129	8.5 $\pm$ 1.6	.31
12 mo	118	8.5 $\pm$ 1.6	.11