Impact of Active Versus Usual Algorithmic Titration of Basal Insulin and Point-of-Care Versus Laboratory Measurement of HbA_{1c} on Glycemic Control in Patients With Type 2 Diabetes

The Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial

LAURENCE KENNEDY, MD, FRCP[1]
WILLIAM H. HERMAN, MD, MPH[2]
POUL STRANGE, MD, PHD[3]
ANTHONY HARRIS, PHD[3]
FOR THE GOAL A1C TEAM

OBJECTIVE — The objective of this study was to assess the impact of active versus usual monitoring of algorithmic insulin titration and point-of-care (POC) versus laboratory HbA_{1c} (A1C) measurement on glycemic control in primary care.

RESEARCH DESIGN AND METHODS — The Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study was a 24-week, randomized, parallel-group, four-arm, open-label study of 7,893 adults with type 2 diabetes uncontrolled by oral antidiabetic agents and requiring insulin. Patients were randomly assigned by investigators from 2,164 sites in the U.S. to insulin glargine with either *1*) usual (no unsolicited contact between visits) insulin titration using a simple algorithm with laboratory A1C testing, *2*) usual titration with POC A1C testing, *3*) active (weekly monitored) titration with laboratory A1C testing, or *4*) active titration with POC A1C testing. Outcome measures included a change in A1C and fasting self-monitoring of blood glucose (SMBG) levels, percentage of patients achieving A1C <7.0%, and hypoglycemia frequency.

RESULTS — Significant A1C and SMBG reductions were observed in all arms ($P < 0.0001$). Compared with usual insulin titration, active titration achieved greater A1C reduction (1.5 vs. 1.3%; $P < 0.0001$), SMBG reduction (88 vs. 79 mg/dl; $P < 0.0001$), and proportion of patients achieving A1C <7.0% (38 vs. 30%; $P < 0.0001$). Among patients receiving active titration, POC A1C testing was associated with an increase in the proportion achieving an A1C <7.0% (41% for POC vs. 36% for laboratory; $P < 0.0001$). Hypoglycemia rates were low (usual vs. active groups: 3.7 vs. 6.0 all confirmed episodes/patient-year [$P < 0.001$]; 0.09 vs. 0.14 severe episodes/patient-year [NS]).

CONCLUSIONS — In a predominantly primary care setting, addition of insulin glargine using a simple algorithm achieved significant improvements in glycemic control in patients with type 2 diabetes in all four study arms. Active titration resulted in significant incremental improvements in glycemic control, and, among patients receiving active titration, POC A1C testing resulted in a greater portion achieving A1C <7.0%.

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Combination therapy with basal insulin and oral antidiabetic agents can safely improve glycemic control (1–3); however, insulin is often delayed or inadequately titrated in patients with type 2 diabetes, resulting in failure to achieve glycemic targets (4,5). Recently, a forced-titration algorithm for basal insulin was shown to be effective in reducing HbA_{1c} (A1C) in two large multicenter clinical trials (2,6). Both trials used the same titration algorithm, but only in the trial in which algorithm adherence was actively monitored was an average A1C level of <7.0% achieved in the majority of patients. We seek here to formally test the impact of active versus usual monitoring of algorithm adherence.

Another monitoring approach that may improve glycemic control is point-of-care (POC) A1C testing. The immediate availability of an A1C result during an office visit may enhance the ability to make timely and appropriate adjustments to therapy and facilitate patient education (7,8). The anticipated benefits of POC A1C testing compared with routine A1C testing have yet to be demonstrated convincingly (9).

The Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) study was designed to examine the influence of active (weekly monitored) insulin titration versus usual titration of insulin glargine using a simple titration algorithm and office-based POC A1C testing versus laboratory A1C testing on glycemic control in patients with type 2

From the [1]Division of Endocrinology, Department of Medicine, University of Florida, Gainesville, Florida; the [2]Department of Internal Medicine and Epidemiology, University of Michigan Health System, Ann Arbor, Michigan; and [3]sanofi-aventis, Bridgewater, New Jersey.

Address correspondence and reprint requests to Laurence Kennedy, MD, Professor and Chief, Division of Endocrinology, Department of Medicine, Shands Hospital at the University of Florida, Gainesville, FL 32610. E-mail: kenneal@medicine.ufl.edu.

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Abbreviations: GOAL A1C, Glycemic Optimization with Algorithms and Labs at Point of Care; ITT, intent to treat; LOCF, last observation carried forward; POC, point of care; SMBG, self-monitoring of blood glucose; TEAE, treatment-emergent adverse event; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

diabetes uncontrolled by oral antidiabetic therapy. Secondary objectives were to evaluate whether such treatment strategies to facilitate achievement of glycemic goals could be readily implemented in a predominantly primary care setting and to assess demographic and epidemiologic characteristics in a large nationwide sample of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Eligible patients included men and women 18 years of age or older who had a diagnosis of type 2 diabetes for at least 1 year, had inadequate glycemic control (A1C >7.0%) despite diet, exercise, and oral antidiabetic agents, and were identified by their physicians as candidates for starting insulin. Patients had to be taking stable doses of their current oral antidiabetic medications for at least 2 months before randomization.

Exclusion criteria included severe heart failure (cardiac status New York Heart Association Classification III–IV), known clinically significant renal or hepatic disease (serum creatinine ≥3.0 mg/dl [≥265.2 μmol/l] or serum glutamate pyruvate transaminase ≥2.5 times upper limit of normal range), pregnancy or lactation, malignancy within the last 5 years (except adequately treated basal cell carcinoma), dementia, hypersensitivity to insulin glargine, or any other condition that could interfere with study completion. Patients treated with metformin who had impaired renal function (shown by, but not limited to, serum creatinine ≥1.5 mg/dl for men or ≥1.4 mg/dl for women) were excluded. Because of an unexpectedly large number of exclusions resulting from elevated creatinine concentrations concurrent with metformin therapy (10), the protocol was amended after 498 randomized patients to allow such patients to continue the protocol provided that metformin was discontinued.

This was a 24-week, randomized, parallel-group, four-arm, open-label study conducted between 26 March 2002 and 30 September 2003 at 2,164 sites in the U.S. The protocol was reviewed and approved by local ethical review committees/institutional review boards. Each study site was to randomly assign four patients (i.e., one patient to each study arm).

Eligible patients gave informed consent and were consecutively and immediately randomly assigned (no screening period) through a telephone interactive voice response system to begin algorithmic titration of insulin glargine in one of the following arms: *1*) usual titration of insulin glargine and laboratory A1C testing, *2*) usual titration and POC A1C testing, *3*) active titration and laboratory A1C testing, or *4*) active titration and POC A1C testing.

"Usual titration" was defined as patient instruction at study visits (every 6 weeks) but no unsolicited patient contact between visits. Active titration was defined as weekly patient contact (via telephone, E-mail, or fax) to evaluate general well-being, review glucose values, and reinforce the insulin titration and follow-up visit schedule, in addition to instruction at study visits occurring every 6 weeks. Self-monitoring of blood glucose (SMBG) levels, insulin dose changes, and hypoglycemic events were documented on titration sheets and faxed weekly by study coordinators at each site to the centralized study monitor. At each visit, patients in the POC A1C arms had A1C values tested via fingerstick using the A1cNow monitor (Metrika, Sunnyvale, CA). Patients in the central laboratory A1C testing arms (Quest Diagnostics Clinical Trials Laboratory, Van Nuys, CA) did not have current A1C values available at study visits. The laboratory A1C value was measured at each visit and then made available to the physician within 2 or 3 days; among patients assigned to usual titration with laboratory A1C testing, this value may not have been acted upon until the subsequent study visit (because there was no unsolicited patient contact).

Protocol and study medications

Clinic visits occurred at study initiation (visit 1) and every 6 weeks up to 24 weeks (visits 2–5). Visit 1 included a complete medication history, urine pregnancy test, serum chemistry (i.e., serum glutamate pyruvate transaminase and serum creatinine by venipuncture), monofilament testing, and fasting SMBG and A1C measurements (via fingerstick and capillary collection tube) by both POC testing (to determine eligibility before randomization) and laboratory testing. Efficacy assessments were based on the laboratory A1C values (visits 1 and 5 only for patients assigned to POC testing; visits 1–5 for patients assigned to laboratory A1C testing) and fasting SMBG values (measured once daily before breakfast). SMBG was assessed using the Accu-Chek Advantage glucose meter (Roche Diagnostics, Laval, Quebec, Canada), which converted the fingerstick capillary blood glucose values to plasma glucose values. Vital signs were recorded at each visit, and weight, BMI, and diabetes complications/risk factors were recorded at visits 1 and 5. Safety assessments included any adverse events or hypoglycemic episodes throughout the study.

Patients were to continue their oral antidiabetic agents at a fixed dose (dose at randomization). Thiazolidinediones (TZDs) were discontinued at or before randomization because of concerns about their use with insulin (11,12). Thus, with the exception of TZDs and, in some cases, metformin, patients continued their oral antidiabetic agents and received long-acting (24-h) basal insulin glargine (Lantus; Aventis Pharmaceuticals) once daily, subcutaneously, at bedtime. Patients were instructed on insulin administration and provided with a one-page instructional pamphlet on the dose titration (APPENDIX 1). The starting dose of insulin glargine was 10 IU/day, titrated weekly until the average of the last 2–4 days of morning fasting SMBG values was ≤100 but ≥70 mg/dl. Insulin was increased by 0–2, 2, 4, 6, or 8 units for corresponding mean fasting SMBG ≥100–<120 mg/dl, ≥120–<140 mg/dl, ≥140–<160 mg/dl, ≥160–<180 mg/dl, and ≥180 mg/dl, respectively. If the fasting SMBG value was <70 mg/dl, the insulin dose was decreased to the previous lower dose. If severe hypoglycemia (e.g., SMBG <36 mg/dl) occurred, upward titration was stopped for 1 week. If the A1C was >8.0% after visit 1, the insulin glargine dose could be increased, at the investigator's discretion, by up to 5 additional units to meet glycemic targets at each subsequent study visit.

Outcome assessments

The primary outcome was the mean change in A1C from baseline to end point. Secondary outcomes included the change in fasting SMBG from baseline to end point and the proportion of patients achieving A1C levels of <7.0%. The influence of baseline factors (i.e., age, sex, race, BMI, and diabetes duration) on the change in A1C was evaluated. Safety assessments included incidence of hypoglycemia and other adverse events. Serious events included those that were life threatening or resulted in death, hospitalization, prolongation of hospitalization, or persistent or significant disability or incapacity. Hypoglycemia was defined as a SMBG level <70 mg/dl. Hypoglycemic events were characterized as severe if the

Table 1—*Patient disposition randomization

	Usual titration and laboratory A1C	Usual titration and POC A1C	Active titration and laboratory A1C	Active titration and POC A1C
n	1,978	1,975	1,967	1,973
Did not start insulin†	46	39	47	37
No data beyond visit 1‡	40	26	24	29
Safety population§	1,892	1,910	1,896	1,909
Modified ITT population‖	1,774	1,764	1,765	1,763
Reason for discontinuation				
Death	4 (1.0)	9 (2.5)	7 (1.9)	6 (1.6)
Adverse events	24 (6.2)	29 (7.9)	25 (6.9)	20 (5.3)
Failed entry criteria	28 (7.2)	37 (10.1)	30 (8.3)	34 (9.1)
Withdrew consent	74 (19.1)	69 (18.9)	73 (20.1)	66 (17.6)
Treatment failure	21 (5.4)	21 (5.8)	17 (4.7)	18 (4.8)
Protocol violation	19 (4.9)	9 (2.5)	20 (5.5)	23 (6.1)
Lost to follow-up	60 (15.5)	57 (15.6)	35 (9.6)	46 (12.3)
Other reason	59 (15.2)	48 (13.2)	60 (16.5)	63 (16.8)
No reason	98 (25.3)	86 (23.6)	96 (26.4)	98 (26.2)
Population completing¶	1,591	1,610	1,604	1,599
Primary analysis population#	1,491	1,363	1,501	1,366

Data are *n* or *n* (%). $N = 7,893$. *All patients were randomized by the interactive voice response system. †All randomized patients who did not take study medication because they did not meet the inclusion/exclusion criteria. ‡Patients who took the study medication but only had data for visit 1. §All patients who were randomized, who took the study medication, and for whom there was an opportunity to collect safety data. ‖All patients who were randomized, who were included in the safety analysis population, and who either *1*) had a blood glucose measurement at visit 1 before randomization and another after the start of study medication but not more than 2 days after the end of study medication or *2*) had an A1C measurement performed at an outside laboratory at visit 1 and another after the start of study medication but not more than 7 days after the end of study medication. ¶Patients in the modified ITT population who completed the study. #Patients in the modified ITT population who completed the study and had both baseline and end-of-study laboratory A1C values.

patient required assistance and *1*) there was prompt response to treatment (e.g., glucose or glucagon) or *2*) SMBG level <36 mg/dl. Per protocol, severe hypoglycemic episodes were reported as serious events. If the SMBG level was <70 mg/dl but did not meet the criteria for severe hypoglycemia, it was considered moderate (<50 mg/dl) or mild (≥50 but <70 mg/dl). Nocturnal hypoglycemia included episodes occurring between midnight and 6 A.M.

Standardization procedures

More than 2,000 investigators were to be involved in the study; therefore, several measures were taken to ensure consistency of study procedures and accuracy of the data. These are noted in APPENDIX 2.

Statistical methods

Randomization of 8,000 patients was estimated to provide 90% power to detect an absolute treatment difference of 0.2% in the primary outcome measure (change in A1C). A nominal $\alpha = 0.0167$ was chosen to offset multiple comparisons. Patients who completed the study and had a 24-week laboratory A1C measurement constituted the primary analysis population. This population represents the most complete set of data and will be the primary analysis population for subsequent epidemiologic analyses. An intent-to-treat (ITT) analysis with the last observation carried forward (LOCF) was not conducted for the change in A1C, because this parameter was only measured at baseline and at the end point for patients in the POC testing arms (thus, if patients did not have an end point A1C, the baseline value would have been carried forward, creating bias). An ITT analysis was, however, carried out for SMBG to assure that the results did not vary from those obtained from the primary analysis population. Homogeneity of baseline characteristics across study arms was assessed using a one-way ANOVA for continuous variables, Pearson's χ^2 test for discrete variables, and the Kruskal-Wallis nonparametric test for nonnormally distributed variables.

The primary outcome (change from baseline in A1C) was analyzed using ANCOVA with baseline A1C as the primary covariate. The secondary outcome (change in SMBG from baseline) was analyzed in the same manner with baseline SMBG as the primary covariate. APPENDIX 3 provides additional details on the statistical analyses.

The number and percentage of patients achieving the goal A1C <7.0% were summarized descriptively. A logistic regression model (treatment, patient number, treatment by patient number, and baseline A1C were included, with responder rate as the dependent variable) was fit to the data. The SAS LOGIT procedure was used to conduct the analysis, and significance of the effects was assessed via Wald χ^2 statistics from a logistic regression analysis (13).

The effects of demographic and epidemiologic factors on the primary end point were analyzed using ANCOVA with subgroup, treatment, and patient number as factors and baseline A1C as a covariate. The subgroups were stratified based on age (<65 and ≥65 years), BMI (<28 kg/m^2 [normal to slightly overweight], 28–40 kg/m^2 [overweight to obese], and >40 kg/m^2 [extremely obese], respectively), diabetes duration (<5 and ≥5 years), and race. *P* values for pairwise comparisons in these subgroup analyses were interpreted descriptively.

Safety assessments were based on the population of patients who were randomized, received study medication, and had follow-up data. The proportions of patients in each treatment group reporting at least one hypoglycemic event, severe hypoglycemic events, and nocturnal hypoglycemic events were compared across the four study arms via Wald χ^2 statistics from a logistic regression analysis. The rates of all and severe hypoglycemic

Table 2—*Patient characteristics by treatment group*

	Usual titration and laboratory A1C	Usual titration and POC A1C	Active titration and laboratory A1C	Active titration and POC A1C	Total
n	1,491	1,363	1,501	1,366	5,721*
Age (years)	57 ± 11	57 ± 12	57 ± 12	57 ± 11	57 ± 12
Sex, male/female (%)	52/48	53/47	49/51	50/50	51/49
Race					
White	1,057 (71)	968 (71)	1,026 (68)	983 (72)	4,034 (71)
Black	237 (16)	201 (15)	269 (18)	207 (15)	914 (16)
Hispanic	149 (10)	146 (11)	154 (10)	138 (10)	587 (10)
Other	45 (3)	41 (3)	51 (4)	35 (3)	172 (3)
Duration of diabetes (years)	8.4 ± 6.4	8.4 ± 6.4	8.6 ± 6.4	8.7 ± 6.4	8.5 ± 6.4
BMI (kg/m^2)	34.5 ± 7.4	34.3 ± 7.4	34.2 ± 7.6	34.4 ± 7.5	34.3 ± 7.5
A1C (%)	8.9 ± 1.5	8.9 ± 1.6	8.9 ± 1.6	8.8 ± 1.5	8.9 ± 1.5
Fasting SMBG (mg/dl)	209 ± 69	212 ± 71	212 ± 73	209 ± 68	211 ± 70
Prior therapy (%)					
Sulfonylurea alone	13	12	14	12	13
Metformin alone	9	8	8	8	8
TZD alone	1	1	1	1	1
Sulfonylurea + metformin	39	40	40	41	40
Sulfonylurea + TZD	4	5	5	3	4
Metformin + TZD	4	4	3	3	3
Sulfonylurea + metformin + TZD	18	19	17	18	18

Data are means ± SD, *n* (%), or *n* unless otherwise noted. *N varies based on availability of data.

events were analyzed using Poisson regression.

RESULTS

Study investigators and sites

A total of 2,164 investigators participated in the study. Primary care or internal medicine physicians represented 76% of investigators. Less than 10% of the investigators were endocrinologists, and the remaining 14% were categorized as "other specialty" or "unknown." More than half of the 2,164 participating sites (n = 1,255) enrolled the planned four patients each. To compensate for lower recruitment rates at other sites, some sites (n = 190) were permitted to enroll up to eight patients; 235 sites enrolled one patient, and 123 sites enrolled eight patients.

Patient disposition

A total of 7,893 eligible patients were randomized (Table 1). Of the total patients randomized, 169 patients (2.1%) did not take the study medication and 119 patients (1.5%) had no follow-up data; the remaining 7,605 patients (96.4%) composed the safety population. The overall completion rate for the study was 81.0% (n = 6,404), with no significant differences in patient disposition among the four study arms. Of 6,404 patients, 5,721 who had a laboratory A1C measurement at week 24 comprised the primary analysis population, as defined in RESEARCH DESIGN AND METHODS.

Patient characteristics

Baseline characteristics were comparable across all study arms (Table 2). The racial distribution of the primary analysis population was 71% (4,034) white, 16% (914) black, 10% (587) Hispanic, and 3% (172) other groups. Mean baseline BMI was 34 kg/m^2; 60% of patients had a BMI between 28 and 40 kg/m^2, and 20% had BMI ≥40 kg/m^2. The mean age was 57 years, with 26% (n = 1,470) of patients aged ≥65 years. Across the four arms, the mean duration of diabetes was 8.5 years, and ~28% of patients had diabetes for >10 years. The mean fasting plasma glucose level was 211 mg/dl and mean laboratory A1C level was 8.9%. Baseline A1C was ≥9.8% in 25% of patients and was higher among patients who had a lower BMI (9.1% for BMI <28 kg/m^2 vs. 8.8% for BMI ≥28 kg/m^2) or were younger (9.0% for those <65 years vs. 8.5% in those ≥65 years). Patients who were black or Hispanic had higher baseline A1C levels (9.5 and 9.2%, respectively) than white patients (8.7%) (Table 2). The majority of patients (77%) were receiving combination therapy, most commonly a sulfonylurea plus metformin (40%), followed by triple therapy with a sulfonylurea, metformin, and a TZD (18%). The distribution of oral therapy was similar across the four arms (Table 2).

Insulin dose

Because all groups followed the same titration algorithm, the insulin dose was titrated weekly and increased in a similar pattern across the study arms; however, the active titration groups consistently had higher doses from week 6 onward. At end point, the average insulin dose in the usual titration groups was 50 IU (interquartile range 24–66) compared with 55–56 IU (28–76) in the active titration groups. The insulin dose at the end of the study was significantly higher in the active titration groups versus the usual titration groups ($P < 0.001$).

Primary outcome: change in A1C

A1C improved significantly from baseline to end point in all four arms ($P < 0.0001$). Patients in the usual titration groups had mean A1C reductions of 1.3% from baseline to end point, whereas patients in the active titration groups achieved a mean reduction of 1.5% (a significant incremental reduction of 0.2%; $P < 0.0001$). By the final study visit, mean A1C values for the usual and active groups were 7.6 and 7.3%, respectively. Figure 1*A* depicts the decline in A1C over the 24-week study duration. The change in A1C for groups receiving POC A1C testing versus laboratory testing was not significantly

Table 3—*Effect of baseline patient characteristics on change in A1C*

		Usual laboratory		Usual POC		Active laboratory		Active POC	
	*N**	Baseline A1C	Change in A1C	Baseline A1C	Change in A1C	Baseline A1C	Change in A1C	Baseline A1C	Change in A1C
n		1,491		1,363		1,501		1,366	
Overall	5,721	8.8	–1.3	8.9	–1.3	8.9	–1.5	8.8	–1.5
Age									
<65 years	4,241	9.0	–1.4	9.0	–1.4	9.1	–1.7	9.0	–1.7
≥65 years	1,470	8.5	–1.0	8.6	–1.0	8.6	–1.3	8.4	–1.1
Race									
White	4,034	8.7	–1.2	8.7	–1.2	8.7	–1.4	8.6	–1.5
Black	914	9.4	–1.5	9.6	–1.9	9.5	–1.9	9.3	–1.7
Hispanic	587	9.2	–1.5	9.1	–1.4	9.3	–1.7	9.2	–1.8
Other	172	9.1	–1.1	8.9	–1.1	9.7	–1.9	9.1	–1.2
Duration of diabetes									
<5 years	1,653	8.8	–1.4	9.0	–1.6	8.8	–1.6	8.9	–1.8
≥5 years	4,037	8.9	–1.3	8.9	–1.2	9.0	–1.5	8.8	–1.4
BMI									
<28 kg/m^2	1,096	9.0	–1.5	9.0	–1.4	9.2	–1.8	9.0	–1.7
28 kg/m^2 ≤ BMI <40 kg/m^2	3,322	8.8	–1.3	8.9	–1.3	8.9	–1.5	8.8	–1.5
≥40 kg/m^2	1,176	8.8	–1.1	9.0	–1.3	8.8	–1.3	8.8	–1.5
Baseline A1C									
25th percentile		7.7	–0.4	7.8	–0.3	7.8	–0.6	7.7	–0.5
50th percentile		8.5	–1.0	8.7	–1.1	8.6	–1.2	8.6	–1.3
75th percentile		9.6	–1.7	9.8	–1.7	9.8	–2.0	9.7	–2.1
90th percentile		10.8	–3.1	11	–3.4	11.1	–3.6	10.8	–3.4

*N varies based on availability of data. $P < 0.01$ for all age, diabetes duration, and BMI subgroups in all study arms.

different ($P = 0.2771$ and $P = 0.0888$ for POC vs. laboratory testing with either usual or active titration, respectively). Interaction between the type of insulin titration monitoring and the method of A1C testing was not statistically significant. Based on statistical analysis, there is no evidence that the number of study subjects previously treated or the treatment arm assigned had an impact on a patient's outcome.

Secondary outcomes

Proportion of patients achieving A1C <7.0%. The proportion of patients achieving the goal A1C <7.0% was 30% for usual titration monitoring groups versus 38% for active titration monitoring groups ($P < 0.0001$). Within the active titration group, a significantly greater proportion of patients in the POC group achieved the A1C goal than did patients in the laboratory A1C group (41 vs. 36%; $P < 0.0001$). When stratified by baseline A1C, pairwise comparisons indicated that a baseline A1C <8.5% was associated with the greatest proportion (45–50%, across study arms) of patients achieving their A1C goal. In contrast, a baseline A1C >10.0% was associated with only 14–27% of patients attaining an A1C <7.0% (Fig. 2). Within the active groups, POC A1C testing significantly increased the proportion of patients who achieved A1C <7.0% for the subgroup of patients whose baseline A1C was >10.0% ($P < 0.0021$ vs. laboratory A1C testing). Based on model-adjusted estimates at the same baseline A1C, POC testing resulted in a greater proportion of patients achieving the target A1C compared with laboratory testing (for baseline A1C at the 75th percentile [9.7%], $P = 0.0387$ and for baseline A1C at the 90th percentile [10.7%], $P = 0.0423$).

Subgroup analysis for A1C. Subgroup analysis revealed that significant reductions in A1C from baseline to end point were observed in all study arms regardless of baseline age, race, BMI, and duration of diabetes. Although greater reductions in A1C were associated with age <65 years, BMI <28 kg/m^2, and duration of illness of <5 years, these differences did not reach statistical significance. Medication discontinuation was similar across the four arms, and the change in A1C from baseline to end point was significant regardless of baseline oral antidiabetic medications; however, the subgroup of patients who discontinued TZD and/or metformin therapy at study entry had a higher mean A1C at end point than patients who did not discontinue oral agents.

Change in fasting SMBG. Fasting SMBG improved significantly from baseline to end point in all four arms ($P < 0.0001$). In the usual titration groups, mean fasting SMBG at end point was 133 mg/dl compared with 123 mg/dl in the active titration groups. Figure 1*B* depicts the decline in fasting SMBG over the 24-week study. Patients in the usual titration groups had mean reductions in SMBG from baseline to end point of 77–81 mg/dl, whereas patients in the active titration groups achieved mean reductions of 87–89 mg/dl (a significant incremental reduction of 9 mg/dl; $P < 0.0001$). The change in SMBG for groups receiving POC A1C testing versus laboratory testing was not significantly different ($P = 0.1309$ and $P = 0.2891$ for POC vs. laboratory testing with either usual or active titration, respectively). The ITT analysis with LOCF (as described in RESEARCH DESIGN AND METHODS) for fasting SMBG showed significant mean reductions of 79 mg/dl for the usual titration groups and 89–90 mg/dl for the active titration groups ($P < 0.0001$ from baseline to end

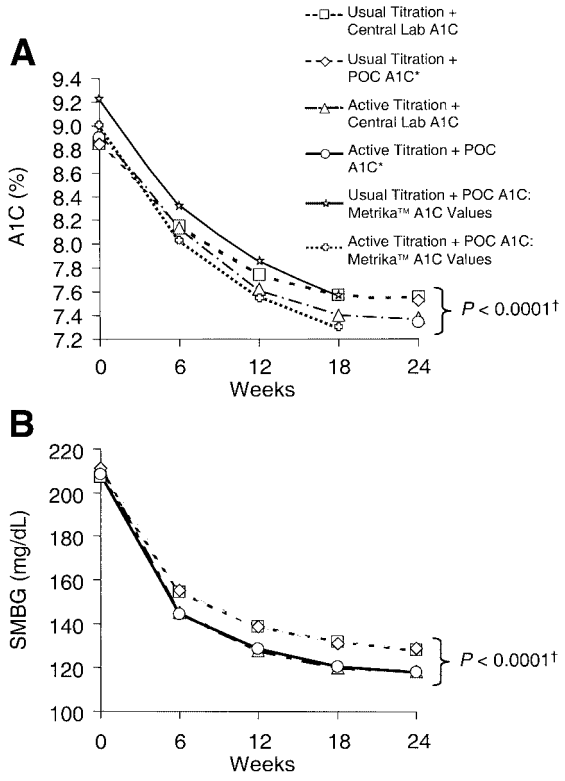

Figure 1—*Impact of active versus usual titration of basal insulin glargine on glycemic control. A: Mean A1C over time. B: Mean fasting SMBG over time. *For the POC A1C arms, central laboratory A1C values were available at baseline and end point only. †P < 0.0001 between the active and usual treatment arms.*

point and between active and usual groups).

Hypoglycemia. Mild, moderate, and severe hypoglycemia was reported in 33, 10, and 3% of patients, respectively. Nocturnal hypoglycemic events were reported by ~10 and 17% of patients in the usual titration and active titration groups, respectively. Expressed as events per patient-year, the rate of hypoglycemia (blood glucose <70 mg/dl) was 3.7 in the usual titration groups and ~6.0 in the active groups ($P < 0.0001$); the rate of moderate and severe events was ~0.53 and 0.09, respectively, in the usual titration groups and 0.69 and 0.14, respectively, in the active titration groups (NS). Overall, only nine patients (0.1%) discontinued participation because of treatment-emergent hypoglycemic events.

Changes in weight and BMI. Mean increases in weight and BMI ranged from 1.6 to 2.0 kg and from 0.4 to 0.8 kg/m^2, respectively, across the four study arms (baseline to end point, $P < 0.0001$). No significant differences were seen among the arms.

Safety and tolerability

There were no unexpected findings in the frequency or spectrum of adverse events. A total of 2,737 (35%) patients reported at least one treatment-emergent adverse event (TEAE); of these, 751 (10%) reported one TEAE that was assessed as possibly related to study medication. A total of 642 (8%) of patients reported at least one serious TEAE. Serious TEAEs reported by >0.1% of patients included, in order of decreasing frequency: hypoglycemia (160 patients; 2.1%), cardiac failure (46 patients; 0.6%), chest pain (39 patients; 0.5%), coronary artery disease (35 patients; 0.5%), cellulitis (27 patients; 0.4%), pneumonia (27 patients; 0.4%), myocardial infarction (25 patients; 0.3%), transient ischemic attack (14 patients; 0.2%), and cerebrovascular accident (13 patients; 0.2%). Possibly related serious TEAEs were reported in 129 (1.7%) patients; among these, only hypoglycemia was reported in >0.1% of patients across study arms. Overall, 95 (1.2%) patients discontinued the study medication because of adverse events. A total of 35 (0.4%) patients died; the majority of deaths were due to cardiovascular causes, and none were assessed by investigators as possibly related to the study medication.

CONCLUSIONS— This study was designed to determine the impact of active versus usual monitoring of the use of a simple insulin dose titration algorithm and POC versus laboratory A1C testing on glycemic control and whether these strategies could be readily implemented in a predominantly primary care setting for patients with type 2 diabetes who had not achieved glycemic targets with oral antidiabetic therapy.

With minimal instruction, patients were able to follow the insulin dose titration algorithm and achieve significant A1C reductions, regardless of the intensity of titration monitoring. All groups showed significant reductions in A1C over 6 months, with significantly greater reductions in the active titration arms compared with the usual titration arms (1.5 vs. 1.3%; $P < 0.0001$). These A1C reductions are of clinical importance as each 1.0% reduction corresponds to a 35% reduction in the risk of microvascular complications (14) and an 18–21% reduction in the risk of cardiovascular events (15,16). Although available time

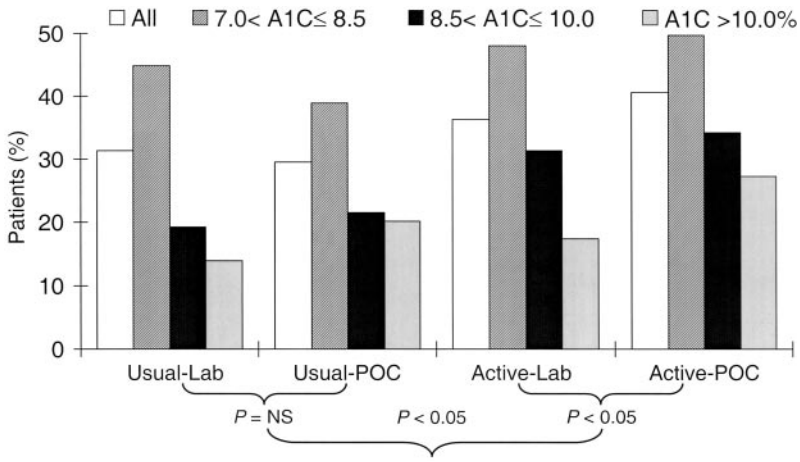

Figure 2—*Percentage of patients with A1C <7.0% at week 24 in each treatment arm, stratified by baseline A1C.*

and resources in clinical practice may limit the application of active titration monitoring, this approach provides a significant but marginal benefit and may be considered for patients whose diabetes is most uncontrolled. Significant reductions in A1C were achieved in all study arms regardless of baseline age, race, BMI, or duration of diabetes. Because laboratory A1C testing was done only at the baseline and end-of-study visits for the two POC A1C testing arms, an ITT analysis was not conducted to avoid bias. However, because SMBG was measured at every visit in all four arms, an ITT analysis using LOCF was conducted and demonstrated results consistent with those of the primary analysis population.

Active titration with POC A1C testing compared with laboratory testing resulted in a greater proportion of patients achieving the goal A1C of <7.0% (41 vs. 36%; $P < 0.0001$). Stratification by baseline A1C levels suggested that immediate availability of an A1C result may be more likely to have an impact on glycemic control in patients with higher baseline A1C values (>10.0%).

There are several notable differences between the current study and previous reports. More than 2,000 investigators were involved in GOAL A1C, and the majority (75%) were research-naive primary care physicians with busy clinical practices. Because the study assessed methods of monitoring patient management rather than therapeutic interventions, investigator technique had the potential to affect outcomes. However, standardized investigator training sessions and rigorous trial monitoring were implemented to minimize variability. The insulin dosing algorithm was less aggressive than that in previous studies (2) to minimize the potential of hypoglycemia; nevertheless, the algorithm resulted in average daily insulin doses of at least 50 IU in all four treatment arms within 6 months. Although obtaining complete glucose profiles would have been ideal for assessing pre- and postprandial glucose control and hypoglycemia (especially asymptomatic episodes), we felt that, for the addition of basal insulin treatment in this patient population, limiting monitoring to one test daily before breakfast would encourage greater compliance with the protocol. Overall, the approach and outcomes in the large nationwide patient sample represented in the GOAL A1C study may more closely reflect what can be anticipated with the adoption of a similar insulin algorithm in primary care clinical practices attended by most patients with type 2 diabetes in the U.S.

In general, the immediate availability of an A1C value at the clinic visit (POC testing) did not have any additional impact on glycemic control beyond active titration. This could be because insulin dose titration was primarily driven by a fasting SMBG target <100 mg/dl, which may correlate with A1C <7% (17). In addition, the POC testing device was not certified by the National Glycohemoglobin Standardization Program at the time of this study, and a post hoc analysis revealed poor precision of the POC A1C methodology when baseline POC A1C results were compared with the baseline laboratory A1C results; this lack of precision may have resulted in diminished investigator reliance on POC A1C results (18).

The overall safety profile of insulin glargine was similar to or better than that observed in prior studies of insulin therapy in type 2 diabetes (2,19). Riddle et al. (2) reported a rate of hypoglycemia (<70 mg/dl) of 9 and 13 events/patient-year for the glargine and neutral protamine Hagedorn insulin groups, respectively. Rates of severe events were ~0.05 for both groups. In the U.K. Prospective Diabetes Study, the rate of hypoglycemic events per year for ultralente insulin was 52–70 for any hypoglycemic events (4–12 for severe hypoglycemic events) (19). In the current study, the overall rate of confirmed episodes of SMBG <70 mg/dl was relatively low (4–6 events/patient-year). The rate of severe hypoglycemia in GOAL A1C was extremely low (≤0.15 event/patient-year) with no difference across study arms. Mild to moderate hypoglycemia was reported in a significantly greater proportion of patients who were monitored weekly, probably as a result of increased ascertainment by these patients.

In summary, the GOAL A1C study demonstrates that basal insulin glargine treatment can be initiated with ease in a predominantly primary care setting using a simple titration algorithm and safely results in significant A1C reduction. Addition of basal insulin therapy should be considered in all patients with type 2 diabetes previously uncontrolled with oral antidiabetic agents alone. Weekly monitored (active) insulin titration resulted in significant improvement in glycemic control compared with every 6 weeks monitored (usual) titration. POC A1C may have an additional impact compared with laboratory monitoring among patients with baseline A1C >10.0%. Regardless of study arm, the majority of patients achieved significant and clinically important improvements in glycemic control.

APPENDIX 1

Implementation of titration algorithm

Dose titration table. The starting dose was 10 IU administered subcutaneously at bedtime. Titration occurred weekly according to the fasting SMBG value based on the mean of the last 2–4 days' morning fasting SMBG values. Adjustments to the daily basal insulin dose were made every 7 days based on fasting SMBG as shown in Table 1*A*.

Patient instruction at baseline. Patients were instructed on insulin administration and were required to demonstrate the self-injection technique. To simplify and assure consistent education, all patients received a one-page educational pamphlet providing instructions on the insulin dose titration. Patients were also required to demonstrate proper use of the glucose meter and were given written instructions. Finally, patients were instructed to record all SMBG readings in diary cards and were informed that the meter's memory was to be reviewed periodically to check the accuracy of their glucose diaries.

APPENDIX 2

Standardization procedures

The protocol, case report forms, and study procedures were reviewed and discussed at identically structured meetings across the U.S. In addition, 350 investigators who were unable to attend a meeting were provided with a Web-based training session. After these investigator training sessions and before the shipment of study supplies, phone calls were made to each site to clarify any issues relating to the protocol, procedure, or supplies. Most study monitoring was coordinated and conducted through a call center. All titration sheets were forwarded to a central study coordinator (ParExel) for review. On-site monitoring visits were made only to sites that had reported a serious adverse event or were found to be noncompliant to monitoring calls. Laboratory tests were performed by a National Glycohemoglobin Standardization Program–certified centralized laboratory (Quest Diagnostics Clinical Trials).

Table 1A—*Weekly dose titration for basal insulin glargine*

Mean of fasting SMBG from preceding 2–4 days	Increase of insulin dosage (IU/day)*
≥180 mg/dl	8
≥160–<180 mg/dl	6
≥140–<160 mg/dl	4
≥120–<140 mg/dl	2
≥100–<120 mg/dl	0–2
Glycemic target: fasting SMBG ≤100 mg/dl and no hypoglycemia (SMBG <70 mg/dl)	No change
If mean fasting SMBG <70 mg/dl†	Dose decreased to the previous lower dose

*If the subject's A1C was >8.0% after visit 1, the investigator may have, at his or her discretion, increased the insulin glargine dose by up to 5 additional units to meet glycemic targets at each subsequent study visit. †Upward titration was to be stopped for 1 week after an occurrence of severe hypoglycemia.

APPENDIX 3

Statistical methods

Assessment of potential carryover effect, period effect, and study arm interaction. The potential for a carryover effect (as an investigator's experience with one study arm might influence the outcome in subsequent study arms) was examined using ANCOVA with treatment, previous number of patients enrolled at a given site, and effect of prior treatments as factors and baseline A1C as covariate. Only the first four patients enrolled at a site were included in the analysis.

The possibility of a period effect (i.e., cumulative experience might improve investigator proficiency and possibly improve outcomes) was also addressed by using ANCOVA, applying the SAS generalized linear models procedure to compare changes in A1C among the study arms. The model included treatment and patient number as factors, treatment by patient number and treatment by baseline interactions, and baseline A1C as covariate. If the treatment by baseline interaction was not statistically significant, it was dropped from the model. In contrast, the treatment by patient number interaction remained in the model regardless of its significance/lack of significance. The significance of model effects was assessed using type III sums of squares. Pairwise comparisons of treatment effects, based on least squares means, were conducted.

A secondary analysis was conducted to determine whether there was an interaction between the method of capture for A1C and the type of titration monitoring. This analysis was conducted using ANCOVA with method of capture of A1C, type of titration monitoring, and patient number as factors; A1C method of capture by type of titration monitoring interaction; and baseline A1C as covariate.

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The primary authors participated in design and monitoring, controlled data evaluation/interpretation, and prepared the manuscript.

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