The Treat-to-Target Trial

Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

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ON BEHALF OF THE INSULIN GLARGINE 4002 STUDY INVESTIGATORS*

OBJECTIVE — To compare the abilities and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy of type 2 diabetes to achieve 7% HbA_{1c}.

RESEARCH DESIGN AND METHODS — In a randomized, open-label, parallel, 24-week multicenter trial, 756 overweight men and women with inadequate glycemic control (HbA_{1c} >7.5%) on one or two oral agents continued prestudy oral agents and received bedtime glargine or NPH once daily, titrated using a simple algorithm seeking a target fasting plasma glucose (FPG) ≤100 mg/dl (5.5 mmol/l). Outcome measures were FPG, HbA_{1c}, hypoglycemia, and percentage of patients reaching HbA_{1c} ≤7% without documented nocturnal hypoglycemia.

RESULTS — Mean FPG at end point was similar with glargine and NPH (117 vs. 120 mg/dl [6.5 vs. 6.7 mmol/l]), as was HbA_{1c} (6.96 vs. 6.97%). A majority of patients (~60%) attained HbA_{1c} ≤7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤72 mg/dl [4.0 mmol/l]) with glargine (33.2 vs. 26.7%, $P < 0.05$). Moreover, rates of other categories of symptomatic hypoglycemia were 21–48% lower with glargine.

CONCLUSIONS — Systematically titrating bedtime basal insulin added to oral therapy can safely achieve 7% HbA_{1c} in a majority of overweight patients with type 2 diabetes with HbA_{1c} between 7.5 and 10.0% on oral agents alone. In doing this, glargine causes significantly less nocturnal hypoglycemia than NPH, thus reducing a leading barrier to initiating insulin. This simple regimen may facilitate earlier and effective insulin use in routine medical practice, improving achievement of recommended standards of diabetes care.

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Type 2 diabetes is a progressive disorder of β-cell dysfunction. Patients using oral therapy for it seldom achieve and maintain the recommended 7% HbA_{1c} goal (1,2) for glycemic control and are exposed to increasing risks of diabetic complications as control worsens over time (3–5). The U.K. Prospective Diabetes Study (UKPDS) (6) showed that intensive treatment can reduce these clinical risks, and a recently reported substudy of the UKPDS (7) confirmed that early addition of insulin to oral therapy can safely keep HbA_{1c} close to 7% in the first 6 years after diagnosis.

However, the majority of patients with a longer duration of diabetes remain poorly controlled with oral agents, and use of insulin, which could improve glycemic control, is often long delayed and not aggressive enough. The reluctance to initiate insulin therapy seems partly due to its perceived complexity, the belief that insulin is not effective for type 2 diabetes (8), and fear of hypoglycemia, which may be the greatest barrier (9).

A regimen that may make initiation of insulin simpler and more effective has been tested in several small studies (10–12). A single bedtime injection of long-acting (basal) insulin is added while prior oral agents are continued, and insulin is systematically titrated, seeking a defined fasting glucose target. However, this approach has yet to be tested in a large population with longer duration of diabetes and poor initial control. Glargine, a new long-acting insulin analog with a more favorable 24-h time-action profile (no pronounced peak) than long- or intermediate-acting human insulin preparations (13,14), may be especially suited to this regimen. We compared the abilities of glargine and NPH to reduce HbA_{1c} to 7% when added to ongoing oral therapy and the hypoglycemia accompanying this effort using a simple algorithm for insulin dosage titration seeking a fasting plasma glucose (FPG) target of 100 mg/dl (5.6 mmol/l).

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*A list of the Insulin Glargine 4002 Study Investigators can be found in the APPENDIX.

Abbreviations: FPG, fasting plasma glucose; ITT, intent to treat; UKPDS, U.K. Prospective Diabetes Study.

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

RESEARCH DESIGN AND METHODS

— Enrolled subjects were men or women aged 30–70 years, with diabetes for ≥2 years, and treated with stable doses of one or two oral antihyperglycemic agents (sulfonylureas, metformin, pioglitazone, or rosiglitazone) for ≥3 months. Inclusion criteria included BMI between 26 and 40 kg/m^2, HbA_{1c} between 7.5 and 10.0%, and FPG ≥140 mg/dl (7.8 mmol/l) at screening. Exclusion criteria included prior use of insulin except for gestational diabetes or for <1 week, current use of an α-glucosidase inhibitor or a rapid-acting insulin secretagogue, use of other agents affecting glycemic control (including systemic glucocorticoids, nonselective β-sympathetic blockers, and weight-loss drugs), history of ketoacidosis or self-reported inability to recognize hypoglycemia, serum alanine aminotransferase or aspartate aminotransferase more than twofold above the upper limit of normal or serum creatinine (≥1.5 mg/dl for men and ≥1.4 mg/dl for women), and a history of drug or alcohol abuse or inability to provide informed consent. To minimize the likelihood of including patients with late-onset type 1 diabetes, candidates with a positive test for anti-GAD antibody (Northwest Clinical Research, Seattle, WA) or with fasting plasma C-peptide ≤0.25 pmol/ml (Clinical Reference Laboratory, Lenexa, KS) were excluded.

Study design

This multicenter, open-label, randomized, parallel, 24-week comparative study was performed at 80 sites in the U.S. and Canada between 7 January 2000 and 22 October 2001. It was conducted in accordance with the Declaration of Helsinki and approved by local ethical review committees. All subjects provided informed consent. A randomization schedule generated by Quintiles (Kansas City, MO) linked sequential numbers to random treatment codes and assured an ~1:1 ratio at each site. Randomization was performed in the order in which subjects qualified, using a centralized telephone system.

Study protocol and treatment

Patients were randomized to either glargine (Lantus; Aventis) or human NPH insulin (Novolin; Novo Nordisk) to be administered subcutaneously at bedtime, at a site preferred by the individual (usually the abdomen), using a pen injector (OptiPen Pro 1 for glargine or NovoPen 3 for NPH) for 24 weeks. Oral antihyperglycemic agents were continued at prestudy dosages. No dietary advice was given beyond reinforcement of standard guidelines (15). The starting dose of both insulins was 10 IU, and dosage was titrated weekly according to daily self-monitored capillary fasting blood glucose measurements using meters (Accu-Chek Advantage; Roche Diagnostics) that provide values corresponding closely to laboratory measurements of plasma glucose. A forced titration schedule was used, seeking a target FPG of ≤100 mg/dl (≤5.6 mmol/l) (Table 1).

Table 1—*Forced weekly insulin titration schedule*

Start with 10 IU/day bedtime basal insulin and adjust weekly	
Mean of self-monitored FPG values from preceding 2 days	Increase of insulin dosage (IU/day)
≥180 mg/dl (10 mmol/l)	8
140–180 mg/dl (7.8–10.0 mmol/l)	6
120–140 mg/dl (6.7–7.8 mmol/l)	4
100–120 mg/dl (5.6–6.7 mmol/l)	2

The treat-to-target FPG was ≤100 mg/dl. Exceptions to this algorithm were *1*) no increase in dosage if plasma-referenced glucose <72 mg/dl was documented at any time in the preceding week, and *2*) in addition to no increase, small insulin dose decreases (2–4 IU/day per adjustment) were allowed if severe hypoglycemia (requiring assistance) or plasma-referenced glucose <56 mg/dl were documented in the preceding week.

Subjects visited the research site at baseline and 2, 4, 8, 12, 18, and 24 weeks and were contacted by telephone at 1, 3, 5, 6, 7, 10, 15, and 21 weeks to discuss dosage changes. Glucose values and insulin changes were transmitted to a central coordinating center. Failure to follow the algorithm was investigated by coordinating center personnel or members of a titration monitoring committee. Subjects were asked to test glucose whenever they experienced symptoms that might be related to hypoglycemia and to record the results. Hypoglycemia documented by glucose levels ≤72 mg/dl (4 mmol/l) or requiring assistance called for cessation of titration for a week, but subjects were asked to resume upward titration the next week if hypoglycemia did not recur. When mean glucose values in the 100–120 mg/dl (5.6–6.7 mmol/l) range were obtained, investigators were allowed to stop titration or temporarily reduce dosage when they believed further titration would be hazardous. In addition to glucose tests to guide titration and document hypoglycemia, subjects performed morning fasting tests for 7 consecutive days and 1-day eight-point glucose profiles (before and 2 h after breakfast, lunch, and dinner, and at bedtime and 5 h after bedtime) before each clinic visit.

Weight was measured, and venous blood for FPG was collected between 0700 and 0900 h at each visit. Blood for HbA_{1c} was collected at baseline and 8, 12, 18, and 24 weeks. Glucose and HbA_{1c} (Diabetes Control and Complications Trial referenced, normal range 4–6%) were measured at the Diabetes Diagnostic Laboratory, University of Missouri-Columbia, Columbia, Missouri. Results of these tests were not disclosed to the investigators until completion of the trial.

Outcome measures

The primary outcome measure was the percentage of subjects achieving HbA_{1c} ≤7.0% without a single instance of symptomatic nocturnal hypoglycemia confirmed by plasma-referenced glucose ≤72 mg/dl (4 mmol/l) and/or meeting criteria for severe hypoglycemia. This glucose threshold was chosen because lower levels can induce hypoglycemia unawareness (16). Severe hypoglycemia was defined as symptoms consistent with hypoglycemia during which the subject required the assistance of another person and was associated with either a glucose level <56 mg/dl (3.1 mmol/l) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon. Nocturnal hypoglycemia was defined as occurring after the bedtime injection and before the measurement of glucose, eating breakfast, or administration of any oral antihyperglycemic agent in the morning.

Other measures included changes from baseline for HbA_{1c}, FPG, and weight; percentage of subjects achieving

HbA_{1c} ≤7% or FPG ≤100 mg/dl (5.6 mmol/l) independent of the occurrence of hypoglycemia; the percentage of subjects achieving FPG ≤100 mg/dl (5.6 mmol/l) without confirmed hypoglycemia; within-subject variability between seven sequential fasting glucose measures; and overall rates of symptomatic hypoglycemia including unconfirmed, confirmed, and severe hypoglycemia.

Statistical analyses

Based on previous data (17), randomization of 750 subjects had the power to provide an 85% chance of detecting, with $\alpha = 5\%$, a 10% treatment effect for the primary outcome measure. The intent-to-treat (ITT) population included all subjects randomized who received at least one dose of study medication. The last measurement before discontinuation or completion of the protocol was considered the end point measurement (last observation carried forward). For all center-stratified analyses, centers with <24 randomized and treated subjects were pooled on a geographical basis, independently of treatment identification. Between-treatment differences in the percentages of subjects achieving the primary end point or other HbA_{1c} or FPG targets or experiencing hypoglycemia were assessed by the Cochran-Mantel-Haenszel test stratified by pooled center. For the continuous variables, the change from baseline was examined by ANCOVA with treatment and pooled center as fixed effects and the corresponding baseline as a covariate. All statistical tests were two sided, and results are presented as means and SE unless otherwise specified.

Table 2—*Baseline characteristics of subjects in the study*

	Glargine	NPH
n	367	389
Sex (F/M) (%)	45/55	44/56
Age (years)	55 ± 9.5	56 ± 8.9
Duration of diabetes (years)	8.4 ± 5.55	9.0 ± 5.57
BMI (kg/m^2)	32.5 ± 4.64	32.2 ± 4.80
FPG (mg/dl [mmol/l])	198 (11.0) ± 49 (2.71)	194 (10.8) ± 47 (2.61)
HbA_{1c} (%)	8.61 ± 0.9	8.56 ± 0.9
Ethnicity (%)		
White	84	83
Black	11	13
Asian	3	3
Multiracial	1	1
Hispanic heritage (%)	10	6
Prior therapy (%)		
SU + metformin	71	74
SU only	11	10
Metformin only	8	7
SU + TZD	6	5
Metformin + TZD	3	3
TZD only	<1	<1

Data are means ± SD, unless otherwise noted. SU, sulfonylurea; TZD, thiazolidinedione.

RESULTS — In total, 1,381 subjects were screened. After a 4-week run-in period, 764 qualifying subjects were randomized to either glargine or NPH. Eight (five glargine and three NPH) withdrew before receiving an insulin injection. The remaining 756 subjects comprised the ITT population. Equivalent numbers withdrew from the two groups during the trial: 33 of 367 (9.0%) from glargine and 32 of 389 (8.2%) from NPH. Reasons for withdrawal included subject preference (glargine 15, NPH 3); investigator's discretion, poor adherence, or lack of efficacy (glargine 3, NPH 14); hypoglycemia (glargine 1, NPH 3); adverse events other than hypoglycemia (glargine 6, NPH 4); and protocol violation, loss to follow-up, or other reasons (glargine 6, NPH 6).

No between-treatment differences were apparent at baseline in the ITT population (Table 2), except that slightly more subjects in the glargine group were of Hispanic descent. Over 70% were taking both a sulfonylurea and metformin. Initial HbA_{1c} averaged 8.6%.

Glycemic response, insulin dosage, and weight

Fasting glucose decreased smoothly in both groups, reaching a plateau by 12 weeks. Mean FPG at end point was 117 mg/dl (6.5 mmol/l) for glargine and 120 mg/dl (6.7 mmol/l) for NPH (P = NS; between-treatment difference −3.6 mg/dl [−0.2 mmol/l] [95% CI −8.82 to 1.62]) (Fig. 1*A*). HbA_{1c} declined at a predictably slower rate, stabilizing after 18 weeks (Fig. 1*B*). Mean HbA_{1c} at end point was 6.96% with glargine and 6.97% with NPH (P = NS; between-treatment difference −0.03%; [−0.13 to 0.08]).

Insulin dosage increased in similar patterns in both groups, but was higher with glargine than with NPH from week 2 until the study's end ($P < 0.05$–0.001). Mean daily dosages at end point were 47.2 ± 1.3 IU for glargine vs. 41.8 ± 1.3 for NPH ($P < 0.005$; between-treatment difference 5.3 IU [95% CI 1.8–8.9]). Mean daily dosages at end point adjusted for body weight were 0.48 ± 0.01 IU/kg for glargine vs. 0.42 ± 0.01 IU/kg for NPH ($P < 0.001$; between-treatment difference 0.06 IU/kg [0.02–0.09]). Weight increased similarly from baseline to end point in both groups: 3.0 ± 0.2 kg with glargine and 2.8 ± 0.2 kg with NPH (P = NS; between-treatment difference 0.2 kg [−0.24 to 0.68]).

Self-measured glycemic patterns

Eight-point glucose profiles were compared at baseline and end point. Mean values at all times of day declined after addition of insulin, without alteration of the postmeal increments and without differences between treatments. Although population mean values for fasting glucose were similar, with glargine there was less within-subject variability between seven sequential fasting measurements over the course of treatment. At 24 weeks, the mean deviation from the median of fasting values for individual subjects was greater with NPH than glargine (20.36 mg/dl [1.13 mmol/l] vs. 18.38 mg/dl [1.02 mmol/l]; between-treatment P = 0.013, after adjustment for baseline).

Rates of hypoglycemia

Figure 2 shows the cumulative incidence of hypoglycemic events. Fewer events oc-

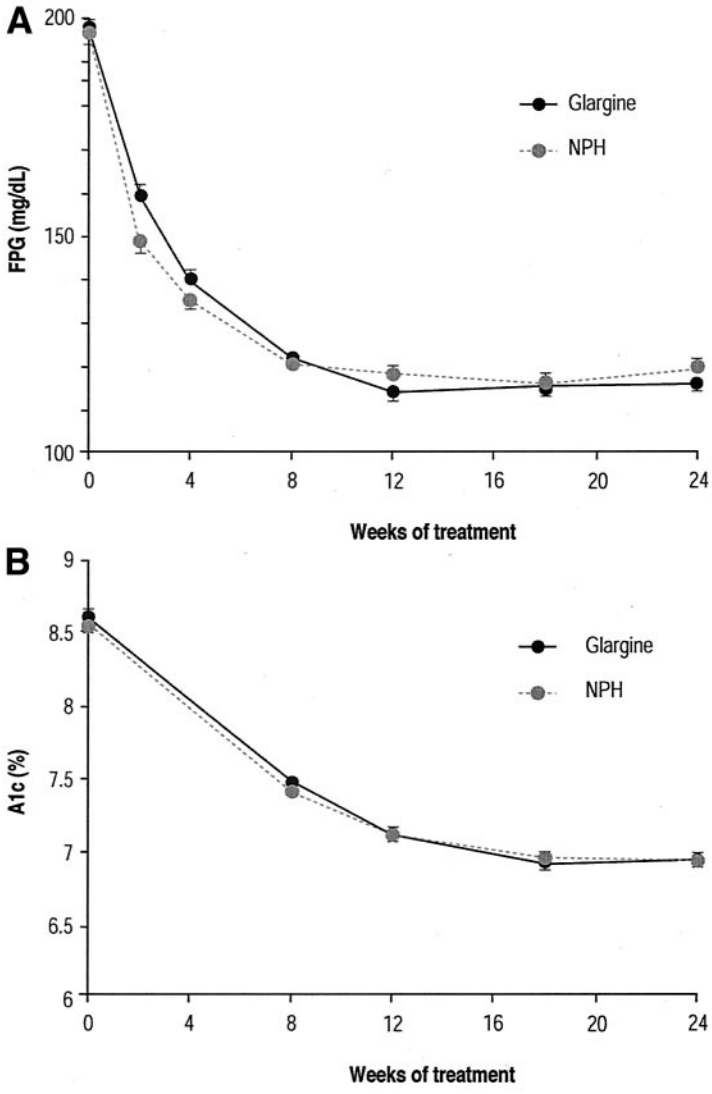

Figure 1—*FPG (A) and HbA_{1c} (B) during the study. Values in both figures are means; error bars indicate SE.*

curred with glargine than NPH, especially those confirmed by glucose tests (Fig. 2*A* and *B*), with no tendency for the between-treatment difference to decline over time.

Expressed as events per patient year, the rates of hypoglycemia with glargine versus NPH were 13.9 vs. 17.7 ($P < 0.02$) for all symptomatic events, 9.2 vs. 12.9 ($P < 0.005$) for confirmed events of ≤72 mg/dl (4.0 mmol/l), and 3.0 vs. 5.1 ($P < 0.003$) for confirmed events of ≤56 mg/dl (3.1 mmol/l). These *P* values were derived from an analysis of ranks due to the skew in distribution of the observed values. The risk reduction with glargine relative to NPH for these categories of hypoglycemia was 21, 29, and 41%, respectively. Severe hypoglycemia was similarly uncommon with the two treatments. Nine patients taking glargine (2.5%) reported 14 severe events and seven taking NPH (1.8%) reported 9 severe events. None of these episodes resulted in unconsciousness or seizures. Severe hypoglycemia was the only serious adverse event considered possibly related to treatment.

Daily pattern of hypoglycemia

Significantly more patients experienced hypoglycemia at night with NPH, but there were no between-treatment differences in the percentage of patients with symptomatic hypoglycemia confirmed by a measurement of glucose ≤72 mg/dl (4.0 mmol/l) through the day and early evening (Fig. 3*A*). Similar patterns were evident for the rates of confirmed hypoglycemic events per patient-year (Fig. 3*B*) except for slightly more events at a single daytime time point (11.00–12.00 h) with glargine. With either way of displaying the temporal distribution of hypoglycemia, a peak was evident in the early morning for NPH. Expressed as events per patient year, the rates of nocturnal hypoglycemia with glargine versus NPH were 4.0 vs. 6.9 ($P < 0.001$) for all reported events, 3.1 vs. 5.5 ($P < 0.001$) for confirmed events of ≤72 mg/dl (4.0 mmol/l), and 1.3 vs. 2.5 ($P < 0.002$) for confirmed events of ≤56 mg/dl (3.1 mmol/l). The risk reduction with glargine for these categories of hypoglycemia was 42, 44, and 48%, respectively.

Treatment success

The two insulins were equally effective in achieving target levels of glycemic control. The ≤7% HbA_{1c} target was reached by 58.0% of subjects with glargine and 57.3% with NPH. However, complete treatment success, rigorously defined as reaching target HbA_{1c} without an episode of documented nocturnal hypoglycemia, was achieved by more subjects with glargine (33.2 vs. 26.7%, $P < 0.05$). The 100-mg/dl (5.6-mmol/l) FPG titration target was reached by 36.2% of subjects with glargine and 34.4% with NPH. However, this target was more often achieved without hypoglycemia using glargine. With glargine, 22.1% of patients reached FPG ≤100 mg/dl and 33.2% reached FPG ≤120 mg/dl without documented nocturnal hypoglycemia compared with 15.9% and 25.7% with NPH, respectively (both $P < 0.03$).

CONCLUSIONS — This trial was designed to clarify two issues. First, it was a proof-of-concept trial testing the hypothesis that supplementing oral therapy with a bedtime injection of basal insulin can routinely achieve the recommended 7% HbA_{1c} target in this population. Second, it tested whether glargine is better suited than NPH to provide this supplement.

In support of our first hypothesis, both insulins reduced mean HbA_{1c} from 8.6% at baseline to 7% at end point, with nearly 60% of patients reaching 7% or less. This exceptional success exceeded the results of other trials in which basal or premixed insulin was added to oral therapy when mean HbA_{1c} was >8% (17–21), and several factors probably

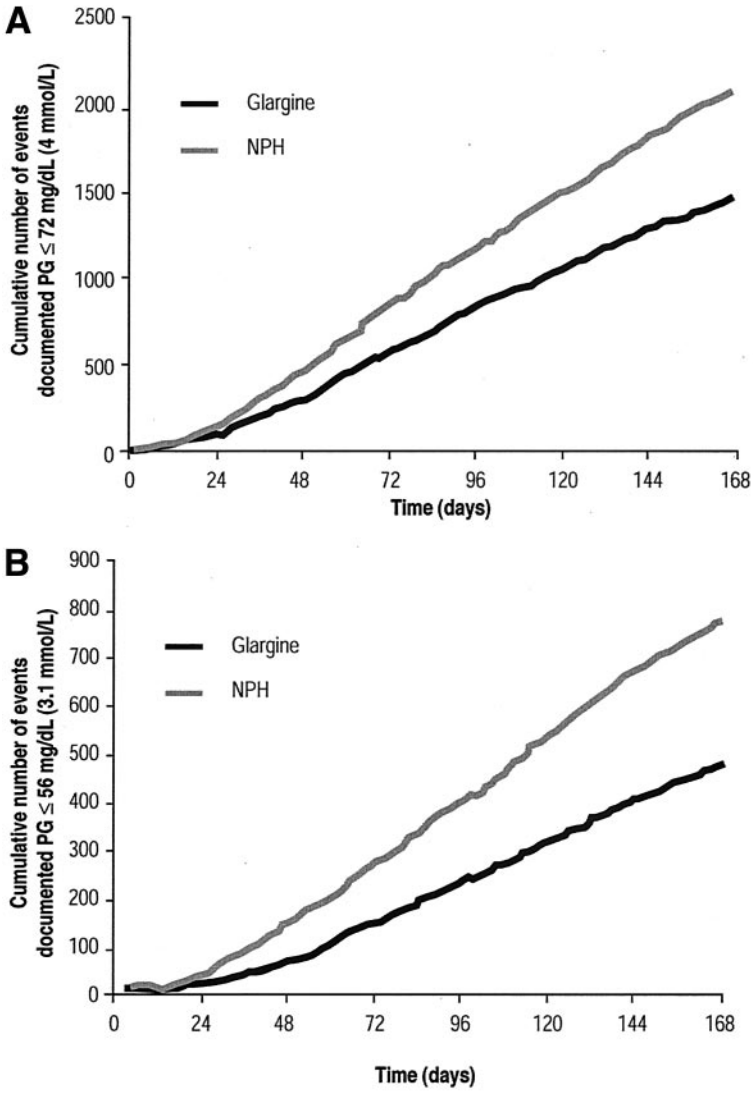

Figure 2—*Cumulative number of hypoglycemia events. Events with plasma-referenced glucose (PG) ≤72 mg/dl (4.0 mmol/l)* (A) *and with PG ≤56 mg/dl (3.1 mmol/l)* (B) *are depicted.*

contributed. First, baseline HbA_{1c} was lower in this study than in most other studies. Second, over two-thirds of the subjects were taking two oral agents, and although poor control on two agents suggests advanced diabetes, potentially requiring multiple injections of insulin, continuation of these agents probably enhanced the effects of remaining endogenous insulin. Third, the titration target was ambitiously low (100 mg/dl [5.6 mmol/l] using a plasma-referenced system, corresponding to ~90 mg/dl [5.0 mmol/l] with a whole-blood system). Finally, insulin dosage was systematically titrated to target. The reported levels of patient adherence to the treatment protocol exceeded 90%, suggesting that this regimen was easy to follow.

The comparison of glargine with NPH added important information about hypoglycemia occurrence and timing. Although the two insulins achieved similar FPG and HbA_{1c} levels, glargine did so with considerably less symptomatic hypoglycemia. This indicates the success of the effort devoted to titration but reveals that the equivalent success with NPH came with more risk and inconvenience related to this side effect. The lower rates of hypoglycemia with glargine were accompanied by less variability of FPG, which presumably contributed to this advantage. Nocturnal hypoglycemia was especially more common with NPH. The rates of hypoglycemia by clock time, following a bedtime injection of NPH (Fig. 3), closely resembled the action profile of NPH in pharmacodynamic studies (22), highlighting the main limitation of this insulin as a basal supplement—its characteristic peak of glucose-lowering activity between 4 and 8 h after injection. The 42–48% reduction of nocturnal hypoglycemia with glargine provides clinical support for the theoretical superiority of glargine, based on its flatter action profile (23). Rates of daytime hypoglycemia were reassuringly low, showing that the reduction of nocturnal hypoglycemia with glargine did not come at the expense of more hypoglycemia throughout the day. Severe hypoglycemia was similarly infrequent with the two insulins. These hypoglycemia data confirm the hypothesis that glargine is better suited to this basal insulin regimen than NPH by allowing patients to reach recommended levels of glycemic control more safely.

Some important questions are not addressed by these findings. For example, which subgroups of patients are most likely to reach target with this regimen, and which will have the greatest relative benefit from glargine? If patients are less strongly encouraged to increase insulin after mild hypoglycemia, will they have higher HbA_{1c} values when NPH is used than with glargine? How clinically important is the 3-kg weight gain after starting insulin, which was not reduced in the glargine group, and how can it be minimized? How should patients not reaching or maintaining the HbA_{1c} target with a single basal insulin injection subsequently advance to intensified therapy including mealtime rapid-acting insulin? What approach should be used for categories of patients who were not included in this trial, such as those with late-onset type 1 diabetes or with HbA_{1c} values >10%, many of whom may need additional injections of short-acting insulin if levels of HbA_{1c} remain above target despite optimization of basal insulin? Further analyses and more studies are clearly needed.

Despite these limitations, the Treat-to-Target Trial offers the basis for a simple, standardized way to initiate basal insulin in routine practice for an important group of patients, those overweight patients with type 2 diabetes who have HbA_{1c} between 7.5 and 10% despite us-

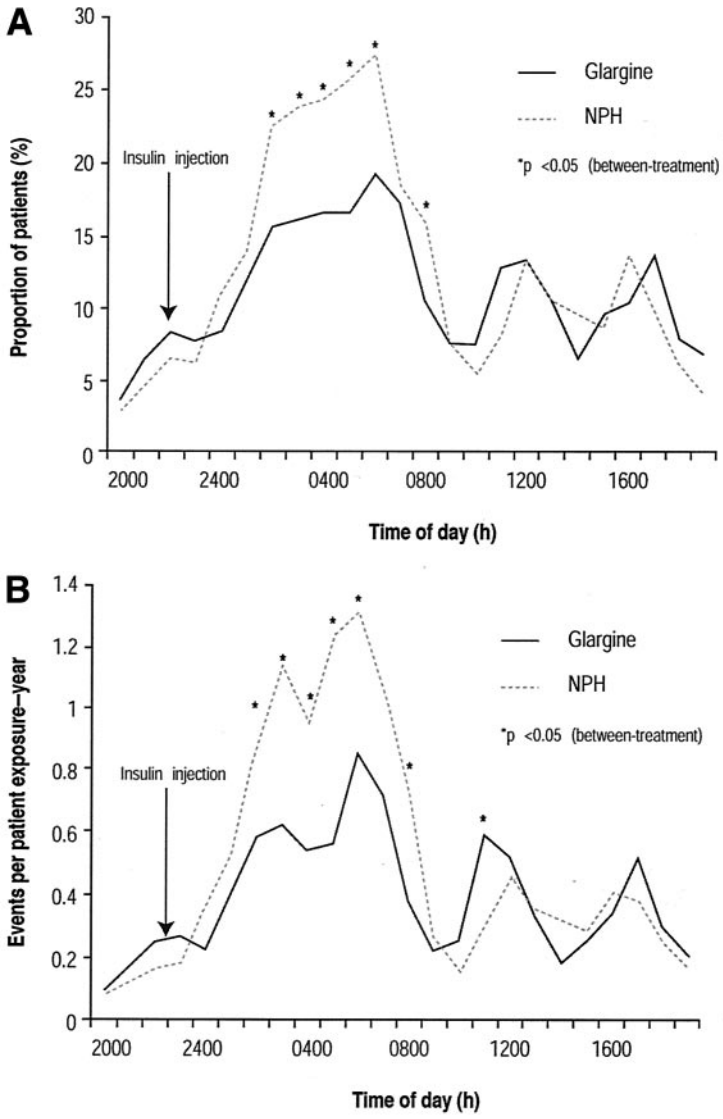

Figure 3—*Distribution of hypoglycemia by time of day*. A*: The proportion of patients experiencing at least one episode of hypoglycemia documented with plasma-referenced glucose ≤72 mg/dl (4.0 mmol/l)*. B*: The hourly hypoglycemia rates, expressed as events per patient-year at the same plasma-referenced glucose cutoff.*

ing one or two oral agents. The regimen requires just one daily injection added to oral therapy and one daily fasting glucose test to guide adjustment of dosage. In this trial, it achieved the 7% HbA_{1c} target for a majority of patients. Furthermore, the lower risk of nocturnal hypoglycemia with glargine relative to NPH reduces the leading barrier to starting insulin therapy: the fear of hypoglycemia. This study brings us one step closer to a widely applicable clinical algorithm.

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Data from this study have been previously published in abstract form (in *Diabetes* 50 [Suppl. 2]:A129, 2001; *Diabetes* 51 [Suppl. 2]:A113, A482, 2002; *Diabetologia* 45 [Suppl. 2]:A52, A259, 2002) and presented at the 2002 congresses for the American Diabetes Association and the European Association for the Study of Diabetes.

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APPENDIX

Investigators in the Insulin Glargine 4002 Study Group

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