

ORIGINAL ARTICLE

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

Rury R. Holman, M.B., Ch.B., F.R.C.P., Kerensa I. Thorne, M.Sc.,
Andrew J. Farmer, D.M., F.R.C.G.P., Melanie J. Davies, M.D., F.R.C.P.,
Joanne F. Keenan, B.A., Sanjoy Paul, Ph.D., and Jonathan C. Levy, M.D., F.R.C.P.,
for the 4-T Study Group*

ABSTRACT

BACKGROUND

Adding insulin to oral therapy in type 2 diabetes mellitus is customary when glycemic control is suboptimal, though evidence supporting specific insulin regimens is limited.

METHODS

In an open-label, controlled, multicenter trial, we randomly assigned 708 patients with a suboptimal glycated hemoglobin level (7.0 to 10.0%) who were receiving maximally tolerated doses of metformin and sulfonylurea to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if required). Outcome measures at 1 year were the mean glycated hemoglobin level, the proportion of patients with a glycated hemoglobin level of 6.5% or less, the rate of hypoglycemia, and weight gain.

RESULTS

At 1 year, mean glycated hemoglobin levels were similar in the biphasic group (7.3%) and the prandial group (7.2%) ($P=0.08$) but higher in the basal group (7.6%, $P<0.001$ for both comparisons). The respective proportions of patients with a glycated hemoglobin level of 6.5% or less were 17.0%, 23.9%, and 8.1%; respective mean numbers of hypoglycemic events per patient per year were 5.7, 12.0, and 2.3; and respective mean weight gains were 4.7 kg, 5.7 kg, and 1.9 kg. Rates of adverse events were similar among the three groups.

CONCLUSIONS

A single analogue-insulin formulation added to metformin and sulfonylurea resulted in a glycated hemoglobin level of 6.5% or less in a minority of patients at 1 year. The addition of biphasic or prandial insulin aspart reduced levels more than the addition of basal insulin detemir but were associated with greater risks of hypoglycemia and weight gain. (Current Controlled Trials number, ISRCTN51125379.)

From the Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology, and Metabolism (R.R.H., K.I.T., A.J.F., J.F.K., S.P., J.C.L.) and the Department of Primary Health Care (A.J.F.), University of Oxford, Oxford; and the Department of Cardiovascular Sciences, University of Leicester, Leicester (M.J.D.) — all in the United Kingdom. Address reprint requests to Dr. Holman at the Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology, and Metabolism, Churchill Hospital, Headington, Oxford OX3 7LJ, United Kingdom, or at rury.holman@dtu.ox.ac.uk.

*Investigators in the Treating to Target in Type 2 Diabetes (4-T) study group are listed in the Appendix.

This article (10.1056/NEJMoa075392) was published at www.nejm.org on September 21, 2007.

N Engl J Med 2007;357.

Copyright © 2007 Massachusetts Medical Society.

TYPE 2 DIABETES MELLITUS IS A PROGRESSIVE condition in which the glycated hemoglobin level rises inexorably over time and the function of beta cells declines.^{1,2} The maintenance of nearly normal glycemic levels reduces the risk of diabetic complications³⁻⁵ but is difficult to achieve, despite the administration of escalating doses of oral antidiabetic drugs, such as metformin, sulfonylureas, and thiazolidinediones.⁶⁻⁸ Most patients eventually require insulin,⁶ which usually is added when glycemic control with a regimen of oral antidiabetic agents becomes suboptimal.⁹ The addition of insulin can result in a clinically relevant improvement in a patient's glycated hemoglobin level.¹⁰ However, many patients do not reach targets for glycated hemoglobin⁶ with conventional insulin regimens, and there is often concern regarding hypoglycemia and weight gain. Large-scale, direct comparisons of various regimens of insulin analogues in combination with oral antidiabetic agents have been lacking.

Treating to Target in Type 2 Diabetes (4-T) is a 3-year, multicenter, open-label, randomized, controlled clinical trial. We report the results of the first year, which compared the efficacy and safety of adding analogue biphasic, prandial, or basal insulin to the treatment of patients with type 2 diabetes who had suboptimal glycemic control while receiving maximally tolerated doses of metformin and sulfonylurea.

METHODS

PATIENTS

From November 1, 2004, to July 31, 2006, we recruited men and women 18 years of age or older who had had type 2 diabetes mellitus for at least 12 months and who had not been treated with insulin. Recruitment took place in 58 clinical centers in Ireland and the United Kingdom. All patients had suboptimal glycemic control (a glycated hemoglobin level of 7.0 to 10.0%) while receiving maximally tolerated doses of metformin and sulfonylurea for at least 4 months (or one agent if the other was not tolerated) and had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40.0 or less. Exclusion criteria were a history of thiazolidinedione therapy or triple oral antidiabetic treatment within the previous 6 months, sight-threatening retinopathy, a plasma creatinine level of

1.47 mg per deciliter (130 μ mol per liter) or more, cardiac disease (a history of unstable angina or myocardial infarction within the previous 6 months or New York Heart Association class III or IV congestive heart failure), hepatic disease or an alanine aminotransferase level at least two times as high as the upper limit of the normal range, unawareness of hypoglycemia or recurrent major hypoglycemia, anticipated changes in concomitant medication affecting glucose regulation, uncontrolled hypertension (systolic pressure \geq 180 mm Hg or diastolic pressure \geq 105 mm Hg), and the likelihood of pregnancy.

All patients provided written informed consent and confirmed their willingness to inject insulin and perform glucose self-monitoring. The protocol was approved by local and national ethics and regulatory agencies and was implemented in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

STUDY DESIGN

The Diabetes Trials Unit ran the study with the use of an online trial-management system, Macro, version 3 (Infermed), which was configured to validate data on entry, acquire laboratory results electronically, and track adherence to the protocol. Randomization was performed in permuted blocks of six according to center with the use of an interactive voice-response system. A total of 235 patients were assigned to receive twice-daily biphasic insulin aspart 30 (NovoMix 30), 239 to receive thrice-daily prandial insulin aspart (NovoRapid), and 234 to receive once-daily (twice if required) basal insulin detemir (Levemir). All three preparations were supplied by Novo Nordisk in 3-ml disposable-pen devices (FlexPen).

The steering committee that supervised the study consisted of five academic members who designed the trial, one lay member, and three representatives of the sponsor. Data (with the exception of data regarding safety) were held and analyzed only by the Diabetes Trials Unit. All authors had full access to the data and vouch for its accuracy and integrity.

INSULIN INITIATION AND TITRATION

The trial-management system estimated starting doses of insulin according to the following formulas¹¹: for men, [(fasting plasma glucose [mmol/liter] - 5) \times 2] \times (weight [kg] \div (14.3 \times height [m]) - height [m]); for women, [(fasting plasma

glucose [mmol/liter] $- 5) \times 2] \times (\text{weight [kg]} \div (13.2 \times \text{height [m]} - \text{height [m]}))$.

Patients injected biphasic insulin twice daily, prandial insulin immediately before meals, and basal insulin at bedtime. Visits with patients were scheduled at 2, 6, 12, 24, 38, and 52 weeks, with interim telephone contact. For each visit and telephone contact, patients were asked to perform in advance three capillary glucose profiles (Medisense Optium, Abbott) obtained before breakfast and before the evening meal for patients in the biphasic and basal groups and before meals and 2 hours after meals and at bedtime in the prandial group. Using these glucose readings and self-reported hypoglycemia, the trial-management system suggested changes in insulin doses, aiming for values before meals of 72 to 99 mg per deciliter (4.0 to 5.5 mmol per liter) and values 2 hours after meals of 90 to 126 mg per deciliter (5.0 to 7.0 mmol per liter). A morning basal dose was advised, either when glucose readings were at target before breakfast but not before the evening meal and when nocturnal hypoglycemia limited dose increases at bedtime (for details, see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Investigators and patients were encouraged to vary suggested insulin doses if such a change was deemed to be appropriate and to amend doses between visits if necessary. Hypoglycemia was categorized as grade 1 if a patient had symptoms with a self-measured capillary glucose level of 56 mg per deciliter (3.1 mmol per liter) or more, grade 2 (minor) if the patient had symptoms with a self-measured capillary glucose level of less than 56 mg per deciliter, or grade 3 (major) if third-party assistance was required.

If unacceptable hyperglycemia (a glycated hemoglobin level of more than 10.0% or two consecutive values of 8.0% or more) occurred at or after 24 weeks of therapy, a second type of insulin was added and sulfonylurea (if the patient was taking it) was discontinued. Aspart was added with the midday meal to biphasic insulin, detemir was added to prandial insulin at bedtime, and aspart was added three times daily with meals to basal insulin.

BIOCHEMICAL AND CLINICAL MEASUREMENTS

Investigators recorded any diabetic complications and race (as reported by patients) at study entry. Blood pressure was measured at baseline and at

24 and 52 weeks, waist circumference at baseline and at 52 weeks, and body weight at all visits except at week 2. Body-mass index was calculated at baseline. A quality-of-life questionnaire, the EuroQol Group 5-Dimension Self-Report Questionnaire,¹² was administered at baseline and at 12 and 52 weeks.

Glycated hemoglobin levels were measured, eight-point glucose profiles were requested, and the ratio of urinary albumin to creatinine was calculated at baseline and at 12, 24, 38, and 52 weeks; plasma creatinine levels were measured at baseline and at 2, 6, 12, 24, 38, and 52 weeks; and lipid levels and alanine aminotransferase levels were measured at baseline and at 52 weeks. Plasma samples were sent by overnight surface mail at ambient temperatures to a central laboratory. Glycated hemoglobin was measured by high-performance liquid chromatography (Biorad Variant II, Biorad) (normal range, 4.5 to 6.2%), and plasma insulin by enzyme-linked immunosorbent assay (Dako). An Olympus AU400 analyzer (Olympus Optical) was used to measure levels of low-density lipoprotein cholesterol (Genzyme kit, Biostat), high-density lipoprotein cholesterol (Olympus HDL-cholesterol kit), and triglycerides (glycerol phosphate oxidase-p-aminophenazone [GPO-PAP]); urinary albumin was measured by immunoturbidimetry, urinary creatinine by the Jaffe method, and alanine aminotransferase by a kinetic ultraviolet test.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the glycated hemoglobin level at 1 year. Secondary outcomes were the proportion of patients with a glycated hemoglobin level of 6.5% or less, the proportion of patients with a glycated hemoglobin level of 6.5% or less but without hypoglycemia (grade 2 or more) during weeks 48 to 52, the rate of hypoglycemia, weight gain, the eight-point self-measured capillary glucose profile, the proportion of patients requiring twice-daily detemir insulin, the proportion of patients with unacceptable hyperglycemia, the ratio of albumin to creatinine, and quality of life.

STATISTICAL ANALYSIS

We calculated that 198 patients per study group would need to be enrolled to detect an absolute difference of 0.4% in the achieved glycated hemoglobin level, assuming an SD of 1.1% on the basis

of trial data regarding detemir insulin,¹³ with a power of 95%. The recruitment target was 700 patients (233 per group), allowing for a discontinuation rate of 15%.

Missing data were imputed with the use of the Bayesian Markov chain Monte Carlo multiple-imputation technique.¹⁴ All analyses were adjusted according to clinical center. Mixed regression models¹⁵ were used for continuous data, with baseline values, oral antidiabetic agents, and glycated hemoglobin levels as covariates. Mixed-effect logistic models were used for the proportion of patients who had glycated hemoglobin levels of 6.5% or more or 7.0% or more, with calculations repeated for patients with baseline glycated hemoglobin levels of 8.5% or less or more than 8.5%, and with baseline values, oral antidiabetic agents, and baseline glycated hemoglobin levels as potential covariates. The proportion of patients with hypoglycemia was analyzed in a similar fashion without adjustment. Generalized mixed-effect models with Poisson and negative binomial distributions were used for rates of hypoglycemia, and an approach with unstructured correlation was used for self-measured capillary glucose profiles, with baseline values and oral antidiabetic agents as covariates. Ratios of urinary albumin to creatinine were analyzed with the use of a generalized mixed-effect model with gamma distribution, adjusted for baseline values, oral antidiabetic agents, and glycated hemoglobin levels. Quality-of-life data are presented as Winsorized means with 95% confidence intervals, with a Kruskal–Wallis analysis of variance for treatment comparisons.

A prespecified closed-test procedure allowed for a pairwise comparison of groups only if the overall treatment effect was significant. A two-sided P value of less than 0.05 was considered to indicate statistical significance; all P values are based on adjusted analyses but have not been adjusted for multiple testing.

RESULTS

PATIENTS

Of 936 patients who underwent screening, 708 were assigned randomly at baseline to the three study groups (Fig. 1). The patients had a mean (\pm SD) age of 61.7 \pm 9.8 years and a median duration of disease of 9 years; most were white and

overweight, with no significant differences in baseline variables among the groups (Table 1).

The total numbers of patients who did not complete 52 weeks did not differ significantly among the biphasic group (13 of 235, or 5.5%), the prandial group (17 of 239, or 7.1%), or the basal group (10 of 234, or 4.3%) ($P=0.40$ for all comparisons). However, of these patients, 13 in the prandial group (5.4%) withdrew from the study, as compared with 4 in the biphasic group (1.7%) and 3 in the basal group (1.3%) ($P<0.002$ for all comparisons). Demographic, anthropometric, and metabolic characteristics of the 40 patients who did not complete the study (Fig. 1) differed from those of patients who continued only in that they had a lower median triglyceride level (113 vs. 137 mg per deciliter [1.3 vs. 1.6 mmol per liter], $P=0.02$).

Starting insulin doses were 2 to 76 IU per day. In the subsequent 2 weeks, mean rates of grade 2 hypoglycemia were 0.045 event per patient per week in the biphasic group, 0.031 event in the prandial group, and 0.024 event in the basal group; there were no grade 3 episodes. During the study, the percentages of patients whose prescribed insulin doses were within $\pm 10\%$ of the recommendation of the trial-management system averaged 89.7% in the biphasic group, 80.4% in the prandial group, and 90.2% in the basal group. The median number of capillary glucose readings before visits were 9.5 (interquartile range, 6 to 12) in the biphasic group, 14 (interquartile range, 9 to 18) in the prandial group, and 9 (interquartile range, 6 to 12) in the basal group. Of patients assigned to receive basal insulin, 79 (33.8%) required additional morning injections. The number of patients with unacceptable hyperglycemia at or after 24 weeks who required injection of a second type of insulin differed according to the study group: 21 patients in the biphasic group (8.9%), 10 in the prandial group (4.2%), and 42 in the basal group (17.9%) ($P<0.001$ for all comparisons).

PRIMARY OUTCOME

The maximal reduction in the mean glycated hemoglobin level occurred by 24 weeks and then remained stable (Fig. 2A). At 52 weeks, the reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 0.8% in the basal group (Fig. 2A and 2B). At that time, the difference between the levels of 7.3% in the

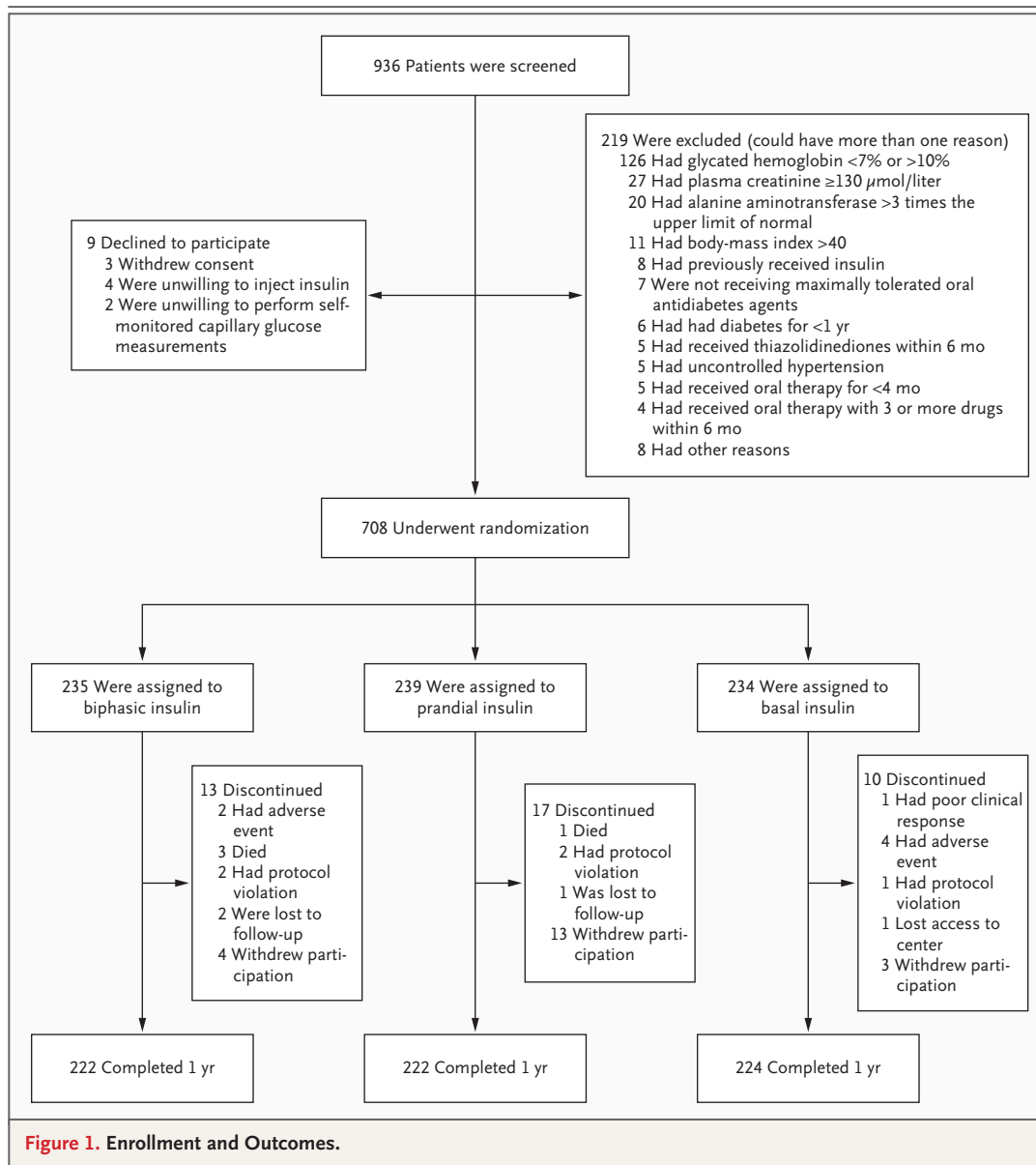


Figure 1. Enrollment and Outcomes.

biphasic group and 7.2% in the prandial group were not significant ($P=0.08$), but the level was higher (7.6%) in the basal group ($P<0.001$ for both comparisons with the basal group) (Table 2 and Fig. 2A and 3A).

SECONDARY OUTCOMES

The proportion of patients with a glycated hemoglobin level of 6.5% or less at 1 year differed among the groups ($P<0.001$ for all comparisons). The proportions of patients in the biphasic group (17.0%) and the prandial group (23.9%) did not

differ significantly ($P=0.08$), but the proportion in the basal group was lower (8.1%) than that in either other group ($P=0.001$ for the comparison with the biphasic group and $P<0.001$ for the comparison with the prandial group). The corresponding proportions of patients with a glycated hemoglobin level of 7.0% or less also differed significantly between the basal group (27.8%) and each of the two other groups (biphasic group, 41.7%; prandial group, 48.7%; $P<0.001$ for both comparisons). Among patients with a glycated hemoglobin level of 6.5% or less, proportions with-

Characteristic	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	All Patients (N=708)
Demographic				
Male sex — no. (%)	159 (67.7)	152 (63.6)	143 (61.1)	454 (64.1)
Age — yr	61.7±8.9	61.6±10.5	61.9±10.0	61.7±9.8
Duration of diabetes — yr				
Median	9	9	9	9
Interquartile range	6–12	6–14	6–12	6–13
Race — no. (%) †				
White	221 (94.0)	214 (89.5)	218 (93.2)	653 (92.2)
Mixed	1 (0.4)	4 (1.7)	2 (0.9)	7 (1.0)
Asian	11 (4.7)	15 (6.3)	9 (3.8)	35 (4.9)
Black	2 (0.9)	5 (2.1)	2 (0.9)	9 (1.3)
Other	0	1 (0.4)	3 (1.3)	4 (0.6)
Current smoker — no. (%)	33 (14.0)	43 (18.0)	33 (14.1)	109 (15.4)
Alcohol consumption (units/wk)				
Median	6	5	4	5
Interquartile range	2–12	2–12	2–12	2–12
Clinical				
Use of oral antidiabetic medication — no.				
Metformin only	4	0	2	6
Sulfonylurea only	10	12	8	30
Both metformin and sulfonylurea	221	227	224	672
Blood pressure — mm Hg				
Systolic	139±17	138±17	138±17	138±17
Diastolic	80±9	78±10	78±9	79±10
Coexisting conditions — no. (%) ‡				
Retinopathy	34 (14.5)	45 (18.8)	43 (18.4)	122 (17.2)
Neuropathy	41 (17.4)	55 (23.0)	39 (16.7)	135 (19.1)
Macroangiopathy	52 (22.1)	42 (17.6)	44 (18.8)	138 (19.5)
Nephropathy	21 (8.9)	24 (10.0)	23 (9.8)	68 (9.6)
EuroQol Group 5-Dimension Self-Report Questionnaire score§				
Winsorized mean	0.81	0.79	0.78	0.79
95% Confidence interval	0.78–0.84	0.76–0.82	0.75–0.82	0.78–0.81
Anthropometric				
Weight — kg	86.9±16.8	84.9±14.4	85.5±16.3	85.8±15.9
Body-mass index	30.2±4.8	29.6±4.5	29.7±4.6	29.8±4.6
Waist circumference — cm				
Men	104±12	102±11	104±12	103±12
Women	98±13	100±11	97±12	98±12

Table 1. (Continued.)

Variable	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	All Patients (N=708)
Biochemical				
Glycated hemoglobin — %	8.6±0.8	8.6±0.8	8.4±0.8	8.5±0.8
Self-measured capillary glucose — mg/dl				
All time points excluding 3 a.m.	202±47	200±49	196±43	200±47
Fasting plasma	175±50	173±49	171±47	173±49
Postprandial	229±54	227±56	223±50	227±54
At 3 a.m.	171±58	164±59	164±56	166±58
Cholesterol — mg/dl				
High-density lipoprotein	39.8±9.7	39.1±9.3	39.8±9.7	39.4±9.7
Low-density lipoprotein	97±27	93±27	89±27	93±27
Triglycerides — mg/dl				
Median	139	133	135	135
Interquartile range	103–189	102–201	101–195	102–196
Ratio of albumin to creatinine				
Men				
Median	13.3	18.6	10.6	13.3
Interquartile range	7.1–44.2	7.1–48.6	4.4–46.0	6.2–45.1
Women				
Median	12.4	11.5	9.7	11.5
Interquartile range	6.2–66.3	4.4–34.5	5.3–26.5	5.3–35.4
Starting insulin dose				
Recommended dose — IU/day				
Median	16	18	16	16
Interquartile range	10–26	9–24	10–24	10–24

* Plus-minus values are means ±SD. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for the ratio of albumin to creatinine to milligrams per millimole, multiply by 0.113. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Race was reported by the patient.

‡ The presence of retinopathy, neuropathy, macroangiopathy, or nephropathy was determined by the investigator.

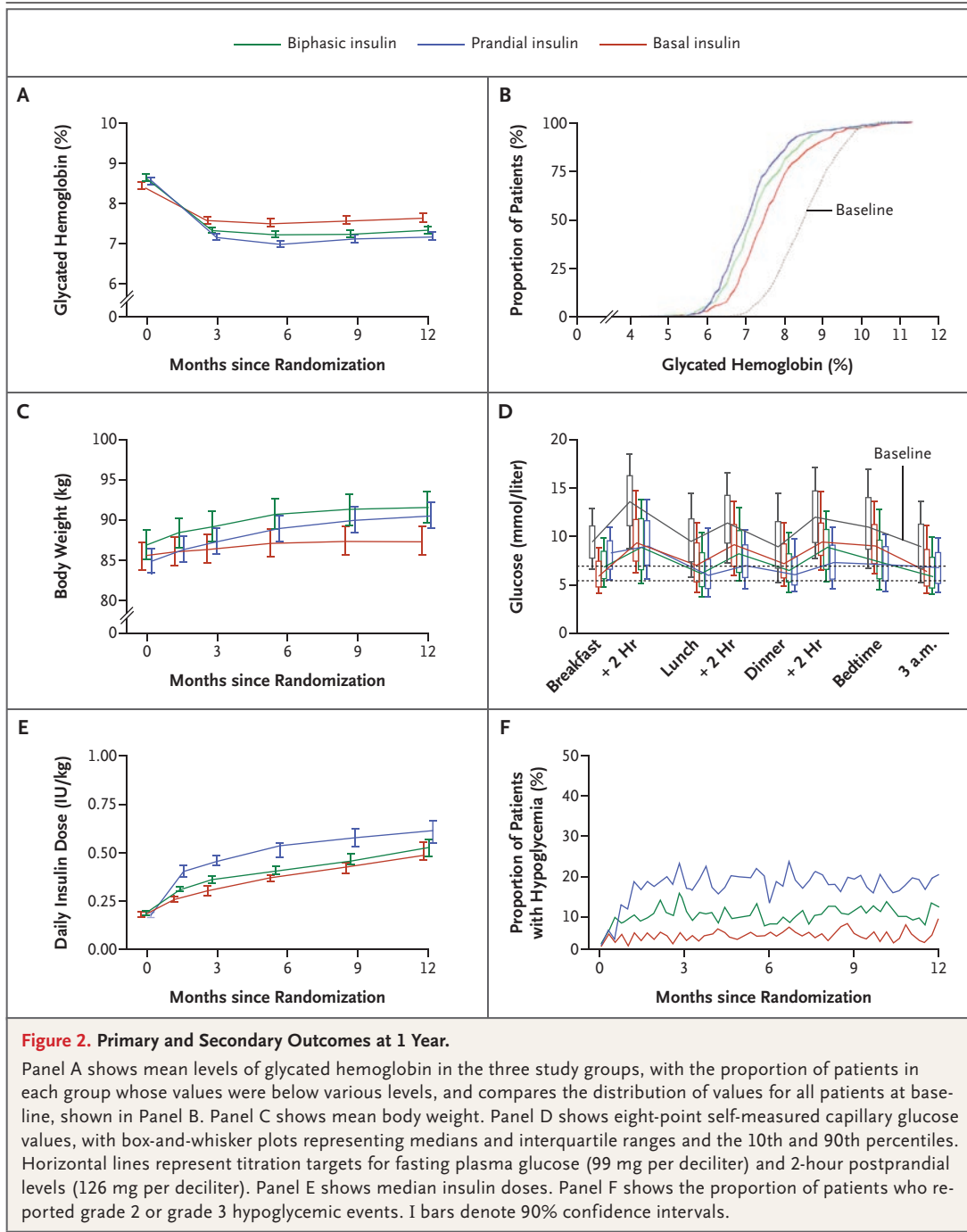
§ Scores on quality of life, as assessed by the patient, range from –0.59 to 1.00, with lower scores indicating a poorer quality of life.

out hypoglycemia (grade 2 or more) during weeks 48 to 52 were 21 of 40 (52.5%), 25 of 57 (43.9%), and 15 of 19 (78.9%) in the biphasic, prandial, and basal groups, respectively ($P=0.001$).

Among patients with a baseline glycated hemoglobin level of 8.5% or less, there was no significant difference in the likelihood of achieving values of 6.5% or less between the prandial group and the biphasic group (odds ratio for the prandial group, 1.76; 95% confidence interval [CI], 0.96 to 3.26; $P=0.07$) or between the basal

group and the biphasic group (odds ratio for the basal group, 0.50; 95% CI, 0.24 to 1.03; $P=0.06$). Patients with a baseline glycated hemoglobin level of more than 8.5% were less likely to have values of 6.5% or less in the basal group than in the biphasic group (odds ratio for the basal group, 0.21; 95% CI, 0.07 to 0.65; $P=0.007$), but patients in the prandial group did not differ significantly from those in the biphasic group (odds ratio for the prandial group, 1.24; 0.62 to 2.51; $P=0.54$).

Patients generally gained weight on all regi-



mens, with a greater increase in the prandial group than in the biphasic group and in the biphasic group than in the basal group (Fig. 2C and 3A and Table 2). Results were similar among patients with a glycated hemoglobin level of 6.5% or less at 52 weeks.

Self-measured capillary glucose profiles im-

proved on all regimens (Fig. 2D and 3A), but overall mean values and those recorded at 3 a.m. did not differ significantly (Table 2). The reduction in the mean fasting plasma glucose value was greater in the basal group than in the biphasic group and greater in the biphasic group than in the prandial group. Conversely, the reduction in

the mean postprandial glucose level was greater in the prandial group than in the biphasic group and greater in the biphasic group than in the basal group.

Median insulin doses increased steadily over the year (Fig. 2E). At 52 weeks, the doses were similar in the biphasic group and the basal group but higher in the prandial group (Table 2).

Median rates of hypoglycemia (grade 2 or more) varied little during the 52-week period but were higher in the prandial group than in the biphasic group and higher in the biphasic group than in the basal group (Fig. 2F and 3B and Table 2). The mean numbers of hypoglycemic events per patient per year were 5.7 in the biphasic group, 12.0 in the prandial group, and 2.3 in the basal group.

ADVERSE EVENTS

Four patients died during the first year of the study, three in the biphasic group (from heart failure, myocardial infarction, and ischemic heart disease) and one in the prandial group (from myocardial infarction). The proportions of patients with serious adverse events did not differ among the study groups ($P=0.25$ for all comparisons), nor did the number of adverse events ($P=0.37$) (Table 3). No clinically relevant changes occurred in levels of plasma creatinine or alanine aminotransferase, although the difference in creatinine was statistically significant (Table 2). At 1 year, elevated levels of fasting plasma insulin (more than three times the upper limit of the normal range) occurred more frequently in the biphasic group (16 of 167 patients, or 9.6%) than in either the prandial group (5 of 179 patients, or 2.8%) or the basal group (3 of 167 patients, or 1.8%) ($P=0.004$), although no discernible effects on glycemic control or hypoglycemia were observed. Two patients discontinued metformin therapy according to the study protocol after two successive measures of plasma creatinine showed values of more than 1.7 mg per deciliter (150 μmol per liter).

DISCUSSION

At 1 year, the first phase of the 3-year 4-T trial showed that three different analogue insulin regimens, when added to metformin and sulfonylurea therapy in patients with type 2 diabetes mellitus, were associated with clinically relevant and sustainable reductions in glycated hemoglobin levels. However, target levels were achieved in a

minority of patients overall, with 16% having a level of 6.5% or less and 39% having a level of 7.0% or less. Biphasic and prandial regimens lowered glycated hemoglobin to the same extent and to a greater degree than the basal regimen, although no significant differences were seen among the groups for patients with a baseline glycated hemoglobin level of 8.5% or less. Glucose lowering was achieved at the expense of weight gain and an increased risk of hypoglycemia, particularly with the biphasic and prandial regimens. Prandial insulin lowered glycated hemoglobin to the same extent as biphasic insulin but with twice the number of episodes of hypoglycemia and an increase in weight gain of 21%. This information might help clinicians choose a regimen for individual patients.

Our trial compared three distinct insulin-initiation regimens, including a prandial regimen that is popular in some countries and supported by trial evidence.^{16,17} In addition, our trial will continue for 3 years, whereas most similar studies have been of shorter duration.¹⁸⁻²⁵ Short-term trial results can be transient and misleading, as shown in the LANMET study²⁶ (comparing insulin glargine [Lantus] plus metformin with neutral protamine Hagedorn [NPH] insulin plus metformin), in which a lower hypoglycemic rate at 12 weeks was not seen at 36 weeks.

Starting insulin doses in our trial that were patient-specific and algorithm-derived were not associated with major hypoglycemia. In our study, the three regimens of single-insulin formulations showed a limited ability to achieve targets for glycated hemoglobin, though the results in the biphasic group were similar to the results in other studies.^{19,20,27} Adherence to the recommended insulin doses was uniformly good for all regimens, but the algorithm used in our study (Table 1 of the Supplementary Appendix) did not increase the insulin doses if hypoglycemia (grade 2 or more) was reported during a clinically relevant time period. However, insulin doses continued to be increased during the year, accompanied by weight gain but with no increase in hypoglycemic rates and stable glycated hemoglobin levels.

Reductions in glycated hemoglobin levels in the basal group were less favorable than those in the biphasic group and the prandial group and also than those of regimens in several similar studies. Most other trials of analogue basal in-

Table 2. Outcomes and Changes from Baseline at 1 Year.*

Variable	Biphasic Insulin (N = 235)	Prandial Insulin (N = 238) [†]	Basal Insulin (N = 234)	Overall [‡]	P Value	Biphasic vs. Prandial	Biphasic vs. Basal	Prandial vs. Basal
Primary outcome								
Glycated hemoglobin — %								
At 52 weeks	7.3±0.9	7.2±0.9	7.6±1.0	<0.001	0.08	<0.001	<0.001	<0.001
Absolute change from baseline								
	-1.3±1.1	-1.4±1.0	-0.8±1.0					
Other outcomes								
Glycated hemoglobin — no. (%)								
≤7.0%	98 (41.7)	116 (48.7)	65 (27.8)	<0.001	0.08	<0.001	<0.001	<0.001
≤6.5%	40 (17.0)	57 (23.9)	19 (8.1)	<0.001	0.08	0.001	<0.001	<0.001
Hypoglycemia — no. (%)								
Grade 1, 2, or 3	216 (91.9)	229 (96.2)	173 (73.9)	<0.001	0.08	<0.001	<0.001	<0.001
Grade 2 or 3	180 (76.6)	215 (90.3)	114 (48.7)	<0.001	<0.001	<0.001	<0.001	<0.001
Grade 3 only	11 (4.7)	16 (6.7)	4 (1.7)	0.20	NA	NA	NA	NA
Hypoglycemic events — no./patient/yr								
All patients								
Grade 1				0.22	NA	NA	NA	NA
Median	5.0	8.0	2.0					
Interquartile range	1.0 to 11.1	3.0 to 19.2	0 to 6.0					
Grade 2				0.04	0.002	0.01	<0.001	
Median	3.9	8.0	0					
Interquartile range	1.0 to 9.0	2.9 to 17.7	0 to 2.0					
Grade 3	0	0	0	0.10	NA	NA	NA	NA
Grade 2 or 3				0.04	0.002	0.01	<0.001	
Median	3.9	8.0	0					
Interquartile range	1.0 to 9.0	3.0 to 18.0	0 to 2.0					

Patients with a glycated hemoglobin level $\leq 6.5\%$						
Grade 1					0.60	NA
Median	5.4	7.8	3.9			NA
Interquartile range	1.5 to 12.8	2.0 to 21.0	0 to 5.2			
Grade 2					0.98	NA
Median	4.0	8.0	3.0			NA
Interquartile range	1.5 to 11.4	2.0 to 20.0	0 to 4.9			
Grade 3	0	0	0		0.51	NA
Grade 2 or 3					0.99	NA
Median	4.0	8.7	3.0			NA
Interquartile range	1.9 to 11.8	2.9 to 20.0	0 to 4.9			
Insulin dose						
IU/day					0.008	0.94
Median	48	56	42			0.008
Interquartile range	30 to 71	34 to 78	28 to 72			
IU/day/kg					0.04	0.49
Median	0.53	0.61	0.49			0.006
Interquartile range	0.36 to 0.70	0.37 to 0.88	0.34 to 0.73			0.006
EuroQol Group 5-Dimension Self-Report Questionnaire score§					0.48	NA
Winsorized mean	0.76	0.76	0.78			NA
95% Confidence interval	0.73 to 0.80	0.73 to 0.79	0.75 to 0.81			NA
Change in self-measured capillary glucose — mg/dl						
All time points excluding 3 a.m.	-59±54	-65±43	-43±43		0.63	NA
Fasting	-45±56	-23±49	-59±52		<0.001	<0.001
Postprandial	-68±63	-83±54	-47±54		<0.001	<0.001
At 3 a.m.	-52±70	-34±59	-40±70		0.47	NA

Table 2. (Continued.)

Variable	Biphasic Insulin (N=235)	Prandial Insulin (N=238) [‡]	Basal Insulin (N=234)	Overall [‡]	Biphasic vs. Prandial	Biphasic vs. Basal	Prandial vs. Basal	P Value
Change in weight — kg	+4.7±4.0	+5.7±4.6	+1.9±4.2	<0.001	0.005	<0.001	<0.001	
Change in waist circumference — cm	+4±5	+4±5	+2±6	<0.001	0.69	<0.001	<0.001	
Change in blood pressure — mm Hg								
Systolic	-2±18	+0±16	-4±18	0.01	0.10	0.17	0.002	
Diastolic	-2±9	+0±11	-2±10	0.01	0.10	0.21	0.004	
Change in cholesterol — mg/dl								
High-density lipoprotein	+0.4±5.0	+2.3±4.3	+0.8±4.6	0.002	<0.001	0.47	0.001	
Low-density lipoprotein	-8±23	+0±23	-4±23	0.16	NA	NA	NA	
Change in triglycerides — mg/dl				>0.05	NA	NA	NA	
Median	-9	-9	-9					
Interquartile range	-44 to 18	-35 to 27	-44 to 9					
Change in ratio of albumin to creatinine				0.07	NA	NA	NA	
Median	-0.9	-0.9	-1.8					
Interquartile range	-8.0 to 9.7	-12.4 to 6.2	-10.6 to 2.7					
Change in alanine aminotransferase — IU				0.93	NA	NA	NA	
Median	-1	-1	-1					
Interquartile range	-6 to 4	-6 to 4	-8 to 3					
Change in plasma creatinine — mg/dl	0.05±0.09	0.05±0.12	0.02±0.11	0.02	0.62	0.008	0.03	

* Plus-minus values are means ±SD. For all values given as changes from baseline to 1 year, P values were adjusted for center, baseline glycated hemoglobin level, and oral antidiabetic therapy. Missing data were imputed with the use of a multiple-imputation technique.¹⁴ To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for the ratio of albumin to creatinine to milligrams per millimole, multiply by 0.113. NA denotes not applicable.

† One patient in the prandial group had insufficient data for the imputation of missing data.

‡ P values in this category are for the overall comparisons between groups at 1 year. A prespecified closed-test procedure allowed for a pairwise comparison of groups only if the overall treatment effect was significant.

§ Scores on quality of life, as assessed by the patient, range from -0.59 to 1.00, with lower scores indicating a poorer quality of life.

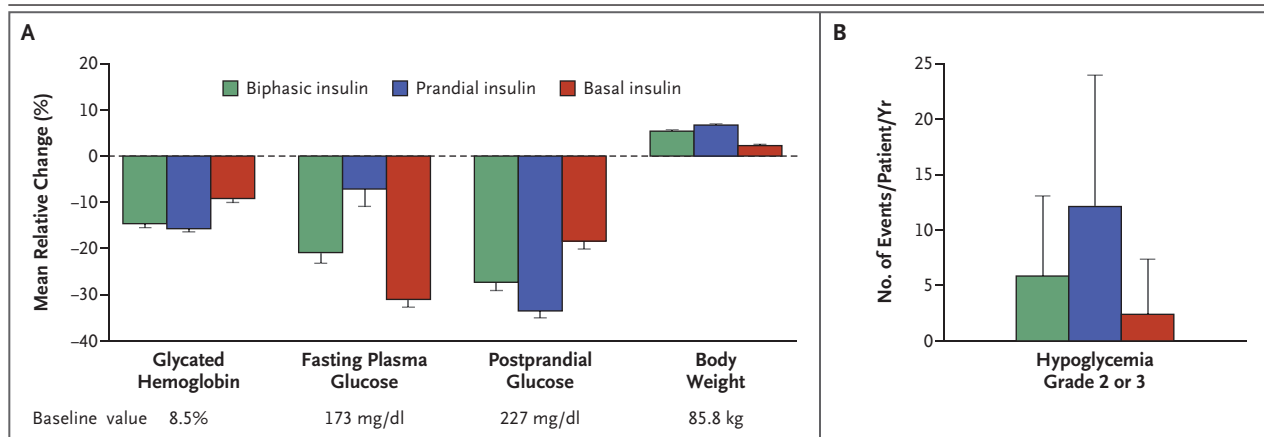


Figure 3. Mean (\pm SE) Percentage Change from Baseline to 1 Year in Glycated Hemoglobin, Fasting Plasma Glucose, Postprandial Glucose, and Body Weight (Panel A) and Mean (\pm SD) Hypoglycemic-Event Rate (Panel B).

For all measures, $P < 0.001$, with values adjusted for baseline values (except hypoglycemia), center, baseline glycated hemoglobin level, and oral antidiabetic therapy where appropriate. Missing data were imputed with the use of a multiple-imputation technique.¹⁴ To convert values for glucose to millimoles per liter, multiply by 0.05551.

Table 3. Adverse Events.*

Event	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	Overall P Value†
	<i>number (percent)</i>			
Serious adverse event	41 (17.4)	30 (12.6)	30 (12.8)	0.25
Gastrointestinal and abdominal pain	4 (1.7)	0	0	0.02
Lower respiratory tract and lung infection	4 (1.7)	0	0	0.02
Ischemic coronary-artery disorder	3 (1.3)	4 (1.7)	3 (1.3)	0.99
Abdominal and gastrointestinal infection	3 (1.3)	0	2 (0.9)	0.21
Other infection	1 (0.4)	3 (1.3)	1 (0.4)	0.63
Adverse event	209 (88.9)	203 (84.9)	207 (88.5)	0.37
Upper respiratory tract infection	81 (34.5)	74 (31.0)	91 (38.9)	0.19
Reaction at injection or infusion site	37 (15.7)	33 (13.8)	52 (22.2)	0.04
Musculoskeletal and connective-tissue symptom	43 (18.3)	37 (15.5)	35 (15.0)	0.59
Lower respiratory tract and lung infection	36 (15.3)	40 (16.7)	29 (12.4)	0.40
Nausea and vomiting	36 (15.3)	32 (13.4)	32 (13.7)	0.83
Diarrhea	27 (11.5)	26 (10.9)	34 (14.5)	0.45
Headache	16 (6.8)	27 (11.3)	20 (8.5)	0.23
Upper respiratory tract symptom	17 (7.2)	20 (8.4)	26 (11.1)	0.33
Cough	22 (9.4)	26 (10.9)	17 (7.3)	0.39

* Listed serious adverse events are those that occurred in more than 1% of patients in any of the study groups. Listed adverse events are those that occurred in more than 10% of patients in any of the study groups.

† P values are for all comparisons.

ulin have used insulin glargine,^{18,19,21,26,28,29} some using approximately double the titration frequency, as compared with our trial.^{17,19,21} Few studies to date have used detemir in type 2 diabetes.^{13,22,30} Our study was designed to evaluate

the recommended once-daily detemir regimen in type 2 diabetes mellitus but included a protocol-driven addition of a second dose when required. A recent study using twice-daily detemir from the outset achieved better glycemic outcomes,²² but

no trial has compared these two detemir regimens. The few studies that have compared a basal regimen with a biphasic regimen have shown that biphasic insulin can result in lower glycated hemoglobin levels. However, as in our study, such regimens are associated with increased episodes of hypoglycemia, more weight gain, or both.^{20,23,27,31} The addition of insulin, despite more frequent injections in the biphasic group and the prandial group, did not affect the assessed quality of life of patients in our study, as reported in previous short-term studies.³²

Our exclusion of thiazolidinediones might limit the applicability of these results. However, concern about heart failure,³³ cardiovascular risk,³⁴ increased fracture rate in women,⁸ and higher cost (as compared with a basal-insulin regimen)³⁵ would suggest that these observations may be relevant to a substantial number of patients receiving dual therapy with oral antidiabetic agents.

The three analogue-insulin regimens did not differ in glycemic efficacy for patients with a baseline glycated hemoglobin level of less than 8.5% but differed significantly for patients with values above this level, perhaps reflecting the increased influence of postprandial glycemia on

glycated hemoglobin as glycemic control worsens.³⁶ This finding, the lower rates of hypoglycemia, reduced weight gain, simplicity, and convenience might be taken to support basal insulin as a first-line add-on to dual therapy with oral antidiabetic agents in some patients. However, rapid intensification of therapy will be necessary for many of them.

The first phase of the 4-T study, which compared three alternative analogue-insulin initiation therapies, suggests that most patients are likely to need more than one type of insulin to achieve target glucose levels. The final 2 years of the trial will examine specifically the use of complex insulin regimens in these patients.

Supported by Novo Nordisk and Diabetes UK.

Dr. Holman reports receiving grant support from Novartis, Bristol-Myers Squibb, Novo Nordisk, Pfizer, GlaxoSmithKline, and Merck, consulting fees from Amylin, Novartis, Eli Lilly, Merck, and Sanofi Aventis, and lecture fees from Ajinomoto, Astellas, Servier, GlaxoSmithKline, Merck, Eli Lilly, and Sanofi-Aventis; Dr. Davies, grant support from Pfizer, Sanofi-Aventis, and Servier and consulting and lecture fees from Eli Lilly, Merck, Novo Nordisk, and Sanofi-Aventis; and Dr. Levy, consulting fees from Eli Lilly, Merck, Novartis, and Novo Nordisk and lecture fees from Eli Lilly, Merck, Novartis, and Novo Nordisk. No other potential conflict of interest relevant to this article was reported.

We thank the patients, without whom this study and these analyses would not have been possible.

APPENDIX

The following investigators participated in the 4-T trial: *Steering Committee* — R. Holman (chair), M. Davies, A. Farmer, M. Gall, J. Keenan, J. Levy, G. Nelson, A. Rosenfalck, H. Schou; *Data and Safety Monitoring Board* — R. Heine (chair), I. Campbell, R. Gray, S. Marshall, J. Scarpello; *Policy Advisory Group* — M. Davies (chair), A. Adler, P. Harvey, G. Neary, M. Bilous, J. Farmer, C. Kelly, A. Millward, D. Russell-Jones, J. Nolan; *Coordinating Center* — B. Barrow, J. Darbyshire, C. Dudley, A. Gilligan, J. Hartweg, E. Harris, R. Holman, J. Keenan, I. Kennedy, K. Macdonald, D. McLeod, S. Paul, I. Stratton, K. Thorne, A. Tse; *Central Laboratory* — R. Carter, K. Fisher, K. Islam, R. Klyne, B. Shine; *Novo Nordisk Study Team* — A. Aggarwal, C. Carrington, B. Chubb, G. Compion, L. Crawshaw, N. Dunmore, J. Fenton, M. Fitch, J. Fox, C. Gordon, J. Hauff, K. Hoppen, D. Hutchins, R. Lewis, D. Lighter, L. Lowe, S. McQuade, I. Minns, A. Monk, N. Parris, C. Pike, R. Polley, J. Shadbolt, S. Shamash, P. Snook-Smith, T. Sorensen, M. Stack, R. Taylor, E. Townshend, C. Westgarth, P. Wilkinson, S. Williams. *Investigators: England* — A. Adler, A. Akintewe, S. Atkin, T. Barnett, S. Bennett, R. Bilous, C. Bodmer, L. Borthwick, R. Davies, C. Fox, N. Furlong, I. Gallen, G. Gill, R. Gregory, P. Harvey, A. Hassey, S. Heller, P. Home, D. Hopkins, A. Johnson, E. Jude, D. Kerr, S. Kumar, J. Litchfield, J. Lorains, K. McLeod, P. McNally, M. Mansfield, D. Matthews, A. Millward, P. O'Hare, S. Page, A. Panahloo, D. Robertson, M. Rossi, R. Rowe, D. Russell-Jones, M. Sampson, I. Scobie, W. Stephens, C. Strang, J. Vora, T. Wheatley, D. Whitelaw, P. Winocour; *Ireland* — F. Dunne, B. Kinsley, J. Nolan, S. Sreenan; *Northern Ireland* — J. Andrews, W. Henry, S. Hunter; *Scotland* — P. Abraham, A. Collier, S. Gray, A. Jaap, G. Leese, D. Matthews, J. Walker.

REFERENCES

1. U.K. Prospective Diabetes Study Group. U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 1995;44:1249-58. [Erratum, *Diabetes* 1996; 45:1655.]
2. Levy J, Atkinson AB, Bell PM, McCance DR, Haddon DR. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. *Diabet Med* 1998;15:290-6.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837-53. [Erratum, *Lancet* 1999;354: 602.]
4. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28:103-17.
5. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329: 977-86.
6. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive

- requirement for multiple therapies (UKPDS 49). *JAMA* 1999;281:2005-12.
7. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes: a preliminary report. *Diabetes Care* 2004;27:17-20.
 8. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427-43. [Erratum, *N Engl J Med* 2007;356:1387-8.]
 9. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006;29:1963-72.
 10. Wright A, Burden ACF, Paisley RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002;25:330-6.
 11. Holman RR, Turner RC. A practical approach to basal and prandial insulin therapy. *Diabet Med* 1985;2:45-53.
 12. The EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
 13. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab* 2005;7:56-64.
 14. Kenward MG, Carpenter J. Multiple imputation: current perspectives. *Stat Methods Med Res* 2007;16:199-218.
 15. Demidenko E. Mixed models: theory and applications. London: Wiley-Interscience, 2004.
 16. Bastyr EJ III, Stuart CA, Brodows RG, et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. *Diabetes Care* 2000;23:1236-41.
 17. Bretzel RG, Arnolds S, Medding J, Linn T. A direct efficacy and safety comparison of insulin aspart, human soluble insulin, and human premix insulin (70/30) in patients with type 2 diabetes. *Diabetes Care* 2004;27:1023-7.
 18. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-6.
 19. Janka HU, Plewe G, Riddle MC, Klibe-Frisch C, Schweitzer MA, Yki-Jarvinen H. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 2005;28:254-9.
 20. Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28:260-5.
 21. Eliasschewitz FG, Calvo C, Valbuena H, et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. *Arch Med Res* 2006;37:495-501.
 22. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetes Care* 2006;29:1269-74.
 23. Kvapil M, Swatko A, Hilberg C, Shestakova M. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. *Diabetes Obes Metab* 2006;8:39-48.
 24. Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab* 2003;5:446-54.
 25. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J Diabetes Complications* 2003;17:307-13.
 26. Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442-51.
 27. Malone JK, Kerr LF, Campaigne BN, Sachson RA, Holcombe JH. Combined therapy with insulin lispro Mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. *Clin Ther* 2004;26:2034-44. [Erratum, *Clin Ther* 2005;27:1112.]
 28. Davies M, Storms F, Shutter S, Bianchi-Biscay M, Gomis R. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 2005;28:1282-8.
 29. Yki-Jarvinen H, Juurinen L, Alvarsson M, et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. *Diabetes Care* 2007;30:1364-9.
 30. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006;28:1569-81.
 31. Malone JK, Bai S, Campaigne BN, Reviriego J, Augendre-Ferrante B. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. *Diabet Med* 2005;22:374-81.
 32. de Grauw WJ, van de Lisdonk EH, van Gerwen WH, van den Hoogen HJ, van Weel C. Insulin therapy in poorly controlled type 2 diabetic patients: does it affect quality of life? *Br J Gen Pract* 2001;51:527-32.
 33. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89.
 34. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356:2457-71. [Erratum, *N Engl J Med* 2007;357:100.]
 35. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients. *Diabetes Care* 2006;29:554-9.
 36. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 2003;26:881-5.

Copyright © 2007 Massachusetts Medical Society.