ORIGINAL ARTICLE

Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes

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ABSTRACT

BACKGROUND

Evidence supporting the addition of specific insulin regimens to oral therapy in patients with type 2 diabetes mellitus is limited.

METHODS

In this 3-year open-label, multicenter trial, we evaluated 708 patients who had suboptimal glycated hemoglobin levels while taking metformin and sulfonylurea therapy. Patients were randomly assigned to receive biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (twice if required). Sulfonylurea therapy was replaced by a second type of insulin if hyperglycemia became unacceptable during the first year of the study or subsequently if glycated hemoglobin levels were more than 6.5%. Outcome measures were glycated hemoglobin levels, the proportion of patients with a glycated hemoglobin level of 6.5% or less, the rate of hypoglycemia, and weight gain.

RESULTS

Median glycated hemoglobin levels were similar for patients receiving biphasic (7.1%), prandial (6.8%), and basal (6.9%) insulin-based regimens ($P=0.28$). However, fewer patients had a level of 6.5% or less in the biphasic group (31.9%) than in the prandial group (44.7%, $P=0.006$) or in the basal group (43.2%, $P=0.03$), with 67.7%, 73.6%, and 81.6%, respectively, taking a second type of insulin ($P=0.002$). Median rates of hypoglycemia per patient per year were lowest in the basal group (1.7), higher in the biphasic group (3.0), and highest in the prandial group (5.7) ($P<0.001$ for the overall comparison). The mean weight gain was higher in the prandial group than in either the biphasic group or the basal group. Other adverse event rates were similar in the three groups.

CONCLUSIONS

Patients who added a basal or prandial insulin-based regimen to oral therapy had better glycated hemoglobin control than patients who added a biphasic insulin-based regimen. Fewer hypoglycemic episodes and less weight gain occurred in patients adding basal insulin. (Current Controlled Trials number, ISRCTN51125379.)

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Most patients with type 2 diabetes require insulin therapy when oral antidiabetic agents provide suboptimal glycemic control, since long-term glycemic improvement reduces the risks of both microvascular[1] and macrovascular[1,2] complications. However, different insulin regimens have varying effects on glycemic control, weight gain, and the risk of hypoglycemia.[3]

In the first phase of the Treating to Target in Type 2 Diabetes (4-T) study, we evaluated patients with type 2 diabetes who had suboptimal glycemic control despite maximally tolerated doses of metformin and sulfonylurea to see whether the randomized addition of a biphasic, prandial, or basal analogue insulin would lead to clinically relevant improvement in glycated hemoglobin levels during a 1-year period.[4] Although the intensification of insulin therapy reduces glycated hemoglobin levels,[5] it is not clear which complex regimen best achieves the glycemic targets.[6] The choice of insulin regimen varies widely according to country, but large-scale direct comparisons of complex insulin regimens have not been performed. Here we report 3-year results comparing the three insulin regimens in which sulfonylurea therapy was replaced by a second type of insulin if glycated hemoglobin levels of 6.5% or less were not achieved with a single type of insulin.

METHODS

PATIENTS

The study design and 1-year results have been reported previously.[4] Briefly, men and women 18 years of age or older who had at least a 12-month history of type 2 diabetes mellitus and who had not been treated with insulin were recruited in 58 clinical centers in the United Kingdom and Ireland. All patients had glycated hemoglobin levels of 7.0 to 10.0% while receiving maximally tolerated doses of metformin and sulfonylurea for at least 4 months; 5% of the patients were taking only one of these drugs, since the other was not tolerated. All patients had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 40 or less. Exclusion criteria included a history of thiazolidinedione therapy or triple oral antidiabetic therapy.

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 the provisions of the Declaration of Helsinki[7] and Good Clinical Practice guidelines.[8]

STUDY DESIGN

Patients were randomly assigned to receive twice-daily biphasic insulin aspart (NovoMix 30), three-times-daily prandial insulin aspart (NovoRapid), or once-daily (twice if required) basal insulin detemir (Levemir). Patients injected doses of biphasic and prandial insulin immediately before meals and basal insulin at bedtime. All three preparations were supplied by Novo Nordisk in 3-ml disposable-pen devices (FlexPen).

During the first year of the study, sulfonylurea therapy was replaced by a second type of insulin if hyperglycemia became unacceptable (a glycated hemoglobin level of >10.0% or two consecutive values of ≥8.0% at or after 24 weeks of therapy) or subsequently if glycated hemoglobin levels were more than 6.5%.[4] For the biphasic-based regimen, midday prandial insulin was added, starting with 10% of the current total daily biphasic insulin dose and limited to a minimum of 4 units and a maximum of 6 units. For the prandial-based regimen, basal insulin (10 units) was added at bedtime. For the basal-based regimen, prandial insulin was added at breakfast, lunch, and dinner, starting with 10% of the current total daily dose of basal insulin at each time point and limited to a minimum of 4 units and a maximum of 6 units.

First-year visits with patients were scheduled at 2, 6, 12, 24, 38, and 52 weeks, with interim telephone contact. After the first year, visits were scheduled every 3 months, with patients asked in advance to perform three daily capillary glucose profiles (Medisense Optium, Abbott).[4] Using these profiles and data regarding self-reported hypoglycemia, the trial-management system[4] suggested changes in the insulin dose, aiming for glucose 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). Investigators and patients were encouraged to vary suggested insulin doses, as clinically appropriate, and to amend the doses between visits. Hypoglycemia was categorized as grade 1 (symptoms only) 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.[4]

The trial steering committee consisted of five academic members, one lay member, and three representatives of Novo Nordisk, the sponsor. Only academic members had access to the nonsafety data. All authors vouch for the accuracy, integrity, and completeness of the reported data, which were collected and analyzed by the Diabetes Trials Unit.

BIOCHEMICAL AND CLINICAL MEASUREMENTS

Glycated hemoglobin levels were measured at baseline; at 12, 24, 38, and 52 weeks; and then every 12 weeks. Plasma creatinine was measured at baseline; at 2, 6, and 12 weeks; and then every 12 weeks. Blood pressure was measured and the ratio of urinary albumin to creatinine was determined at baseline and then every 26 weeks. Plasma lipid and alanine aminotransferase levels were measured and a health-status questionnaire (EuroQol Group 5-Dimension Self-Report Questionnaire) was administered at baseline, at 12 and 52 weeks, and then annually.[9]

PRIMARY AND SECONDARY OUTCOMES

The primary 3-year outcome was the glycated hemoglobin level. 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 of grade 2 or more, weight gain, self-measured capillary glucose profiles, the proportion of patients requiring a second type of insulin, the ratio of albumin to creatinine, and quality of life.

STATISTICAL ANALYSIS

Five imputations for missing data were performed with the use of the Bayesian Markov chain Monte Carlo multiple-imputation technique.[10] To account for center-level clustering, the study center was included as a random effect in all regression models. For normal continuous variables, mixed linear regression models[11] were used, with respective baseline values, type of baseline oral antidiabetic therapy, study group, and baseline glycated hemoglobin level as covariates. Mixed-effect logistic models were used for patients with glycated hemoglobin levels of 6.5% or less or 7.0% or less. Calculations were repeated for patients with baseline glycated hemoglobin levels of 8.5% or less, with the type of oral antidiabetic therapy and glycated hemoglobin level at baseline as potential covariates. The proportion of patients with hypoglycemia was analyzed with the use of a generalized binomial model without adjustment for covariates. For hypoglycemia rates, generalized mixed models with negative binomial distributions were used. Repeatedly observed, self-measured capillary glucose profiles were analyzed with the use of an unstructured covariance matrix and random study-center effects, with the usual covariates.

The ratio of urinary albumin to creatinine and insulin doses were analyzed with the use of generalized mixed-effect models with gamma distribution, adjusted for baseline values, including glycated hemoglobin level, and type of oral antidiabetic therapy. Quality-of-life data are presented as Winsorized means with 95% confidence intervals, with treatment comparisons at median levels based on quantile regression. For skewed data, the median with 95% confidence intervals is presented.[12]

A prespecified closed-test procedure allowed for a pairwise comparison between groups. 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

From November 1, 2004, to July 31, 2006, we recruited 708 patients and randomly assigned 235 to the biphasic group, 239 to the prandial group, and 234 to the basal group (Fig. 1). The patients' mean (±SD) age was 61.7±9.8 years, and the median duration of disease was 9 years. Most of the patients were white and overweight, without significant differences in baseline variables among the groups.[4] Overall 130 patients (18.4%) did not complete the 3-year evaluation, with no significant between-group differences in the biphasic group (14.5%), the prandial group (21.3%), and the basal group (19.2%) (P=0.15 for the overall comparison). However, the proportions of patients who withdrew from the study differed significantly among the groups (5.1%, 11.7%, and 8.5% respectively; P=0.04). There were no significant differences in baseline variables between patients

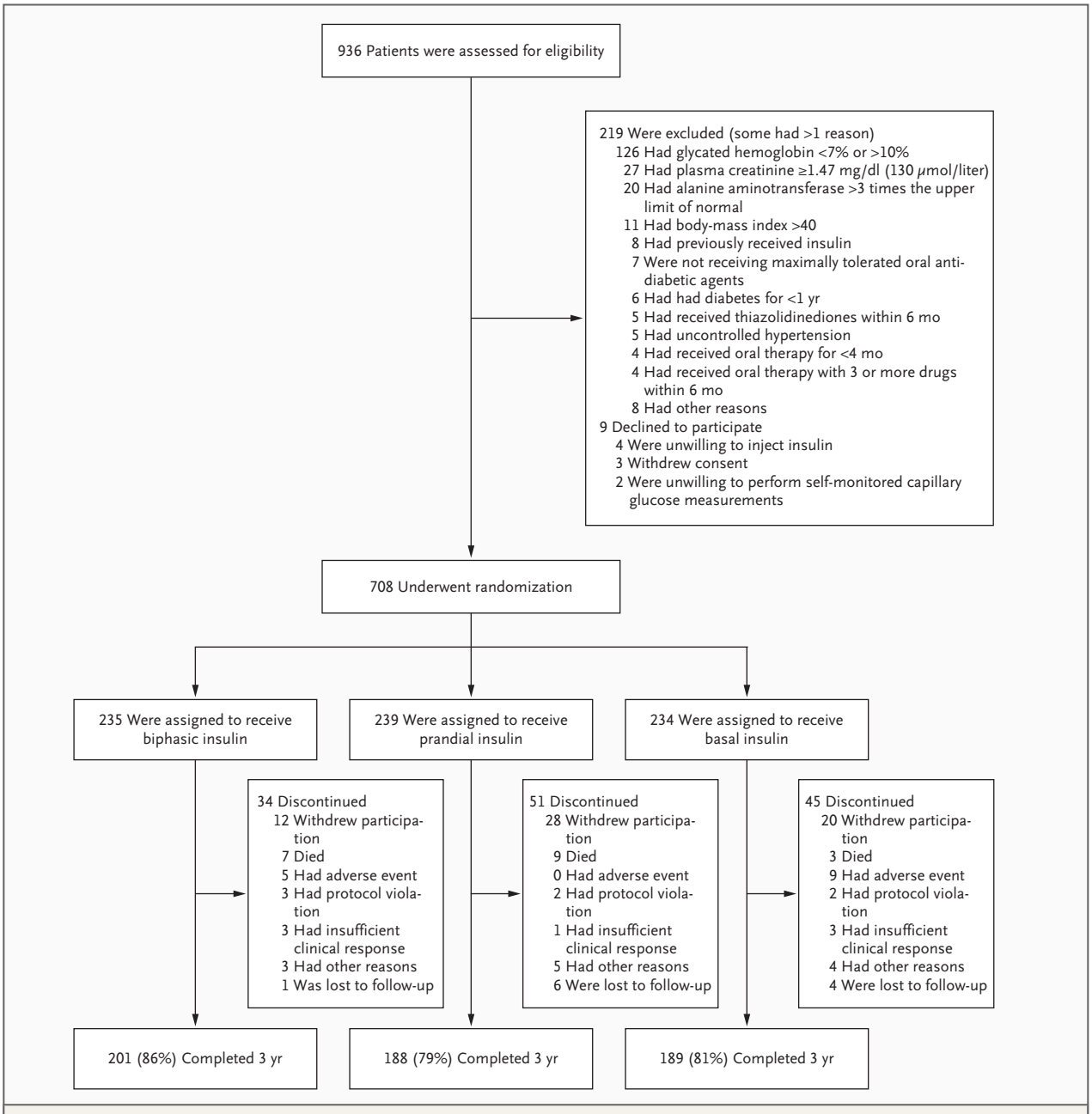

Figure 1. Enrollment and Outcomes.

who withdrew from the study and those who completed the study.

PRIMARY OUTCOME

The median glycated hemoglobin levels converged after 1 year and remained stable in all groups, with an overall value at 3 years of 6.9% (95% confidence interval [CI], 6.8 to 7.1); these values did not differ significantly in the three groups ($P=0.28$ for the overall comparison) (Table 1 and Fig. 2A). At 3 years, the mean reduction from baseline was 1.3% in the biphasic group, 1.4% in the prandial group, and 1.2% in the basal group (Fig. 2A and 2B).

SECONDARY OUTCOMES

Fewer patients in the biphasic group (31.9%) achieved glycated hemoglobin levels of 6.5% or

Table 1. Outcomes and Changes from Baseline at 3 Years.*

Variable	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	P Value			
				Overall†	Biphasic vs. Prandial	Biphasic vs. Basal	Prandial vs. Basal
Primary outcome							
Glycated hemoglobin — %							
Median at 3 yr (95% CI)	7.1 (6.9 to 7.3)	6.8 (6.6 to 7.0)	6.9 (6.6 to 7.1)	0.28	0.28	0.67	0.52
Absolute change from baseline	−1.3±0.1	−1.4±0.1	−1.2±0.1				
Other outcomes							
Glycated hemoglobin — no. (%)							
≤6.5%	75 (31.9)	107 (44.8)	101 (43.2)	0.006	0.006	0.03	0.55
≤7.0%	116 (49.4)	161 (67.4)	148 (63.2)	<0.001	<0.001	0.02	0.22
Patients with a baseline glycated hemoglobin of ≤8.5% — no. (%)							
No. of patients	115 (48.9)	118 (49.4)	125 (53.4)				
Patients achieving target glycated hemoglobin of ≤6.5%	40 (34.8)	62 (52.5)	67 (53.6)	0.008	0.007	0.004	0.86
Change in self-measured capillary glucose — mg/dl							
All time points excluding 3 a.m.	−56±47	−67±47	−58±43	0.001	0.001	0.06	0.10
Fasting	−50±47	−49±45	−47±49	0.83	0.83	0.91	0.93
Postprandial	−61±58	−85±59	−67±50	<0.001	<0.001	0.04	0.007
At 3 a.m.	−38±77	−27±70	−45±77	0.46	0.50	0.13	0.02
Increase in weight — kg	5.7±0.5	6.4±0.5	3.6±0.5	0.20	0.21	0.005	<0.001
Increase in waist circumference — cm	6.0±0.5	6.6±0.6	4.2±0.5	0.44	0.45	0.04	0.007
Insulin dose							
All patients							
Dose — IU/day							
Median (95% CI)	70 (58 to 82)	86 (73 to 99)	88 (74 to 102)	0.05	0.09	0.008	0.19
Dose — IU/day/kg							
Median (95% CI)	0.78 (0.67 to 0.90)	0.94 (0.82 to 1.06)	1.03 (0.90 to 1.16)	0.02	0.05	<0.001	0.07
Patients taking two types of insulin							
No. (%)	159 (67.7)	176 (73.6)	191 (81.6)	0.002	0.15	<0.001	0.04
Dose — IU/day							
Median (95% CI)	79 (64 to 94)	105 (91 to 119)	105.5 (90 to 121)	0.04	0.07	0.007	0.26
Dose — IU/day/kg							
Median (95% CI)	0.86 (0.71 to 1.01)	1.14 (1.01 to 1.28)	1.21 (1.08 to 1.34)	0.02	0.04	0.001	0.15

Ratio of prandial to total insulin							
Median (95% CI)	0.40 (0.39 to 0.41)	0.72 (0.71 to 0.77)	0.58 (0.56 to 0.59)	<0.001	<0.001	0.001	<0.001
Hypoglycemia — no. (%)							
Grade 1, 2, or 3	116 (49.4)	122 (51.0)	103 (44.0)	0.67	0.68	0.29	0.14
Grade 2 or 3	86 (36.6)	105 (43.9)	79 (33.8)	0.09	0.09	0.56	0.03
Grade 3 only	6 (2.6)	5 (2.1)	2 (0.9)	NA	NA	NA	NA
Hypoglycemic events — no./patient/yr							
All patients							
Grade 1, median (95% CI)	3.8 (3.3 to 4.3)	5.7 (4.3 to 7.2)	2.7 (2.3 to 3.0)	0.002	0.002	0.01	<0.001
Grade 2, median (95% CI)	3.0 (2.3 to 4.0)	5.5 (4.3 to 6.9)	1.7 (1.3 to 2.0)	<0.001	<0.001	<0.001	<0.001
Grade 3, median (95% CI)	0	0	0	NA	NA	NA	NA
Grade 2 or 3, median (95% CI)	3.0 (2.3 to 4.0)	5.7 (4.3 to 7.0)	1.7 (1.3 to 2.0)	<0.001	<0.001	<0.001	<0.001
Patients with a glycated hemoglobin level of ≤6.5%							
Grade 1, median (95% CI)	3.0 (1.7 to 3.9)	5.7 (3.5 to 7.7)	3.0 (1.7 to 3.7)	0.006	0.01	0.64	0.001
Grade 2, median (95% CI)	2.7 (1.7 to 5.2)	5.3 (3.8 to 8.0)	2.0 (1.3 to 2.7)	<0.001	0.002	0.07	<0.001
Grade 3, median (95% CI)	0	0	0	NA	NA	NA	NA
Grade 2 or 3, median (95% CI)	3.0 (1.7 to 5.3)	5.5 (4.0 to 8.0)	2.0 (1.3 to 2.7)	<0.001	0.002	0.06	<0.001
Change in blood pressure — mm Hg							
Systolic	−0.2±1.4	+0.5±1.3	+0.5±1.2	0.68	0.68	0.66	0.98
Diastolic	−2.4±0.7	−1.5±0.7	−2.4±0.7	0.35	0.35	0.96	0.38
Change in cholesterol — mg/dl							
High-density lipoprotein	+1.2±0.4	+2.3±0.4	+2.3±0.4	0.03	0.03	0.06	0.81
Low-density lipoprotein	−9±2	−5±2	−7±2	0.13	0.13	0.47	0.45
Change in triglycerides — mg/dl							
Median (95% CI)	−12 (−20 to −3)	−7 (−14 to 0)	−5 (−12 to 2)	0.14	0.14	0.13	0.75
Change in ratio of urinary albumin to creatinine‡							
Median (95% CI)	−1.15 (−2.21 to −0.04)	+1.15 (−0.09 to 2.34)	−0.97 (−2.04 to −0.02)	0.79	0.79	0.99	0.76
EuroQol Group 5-Dimension Self-Report Questionnaire score§							
Winsorized mean (95% CI)	0.76 (0.71 to 0.80)	0.77 (0.73 to 0.81)	0.80 (0.77 to 0.83)	0.72	0.73	0.86	0.86
Change in alanine aminotransferase — IU/liter							
Median (95% CI)	−1 (−3 to 0)	−1 (−2 to 0)	0 (−2 to 1)	0.33	0.82	0.46	0.002
Change in plasma creatinine — mg/dl							
Median (95% CI)	0.08 (0.06 to 0.10)	0.08 (0.06 to 0.10)	0.07 (0.05 to 0.08)	0.42	0.42	0.73	0.78

* Plus–minus values are means ±SE. For all values given as changes from baseline to 1 year, P values were adjusted for study center, baseline glycated hemoglobin level, and type of baseline oral antidiabetic therapy. Missing data were imputed with the use of a multiple-imputation technique.[10] 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. CI denotes confidence interval, and NA not applicable.

† P values in this category are for the overall comparisons between groups at 3 years. A prespecified closed-test procedure allowed for a pairwise comparison of groups.

‡ For the ratio of albumin to creatinine, albumin was measured in milligrams per deciliter, and creatinine was measured in grams per deciliter.

§ Quality-of-life scores, as assessed by the patient, ranged from −0.35 to 1.00, with lower scores indicating a poorer quality of life.

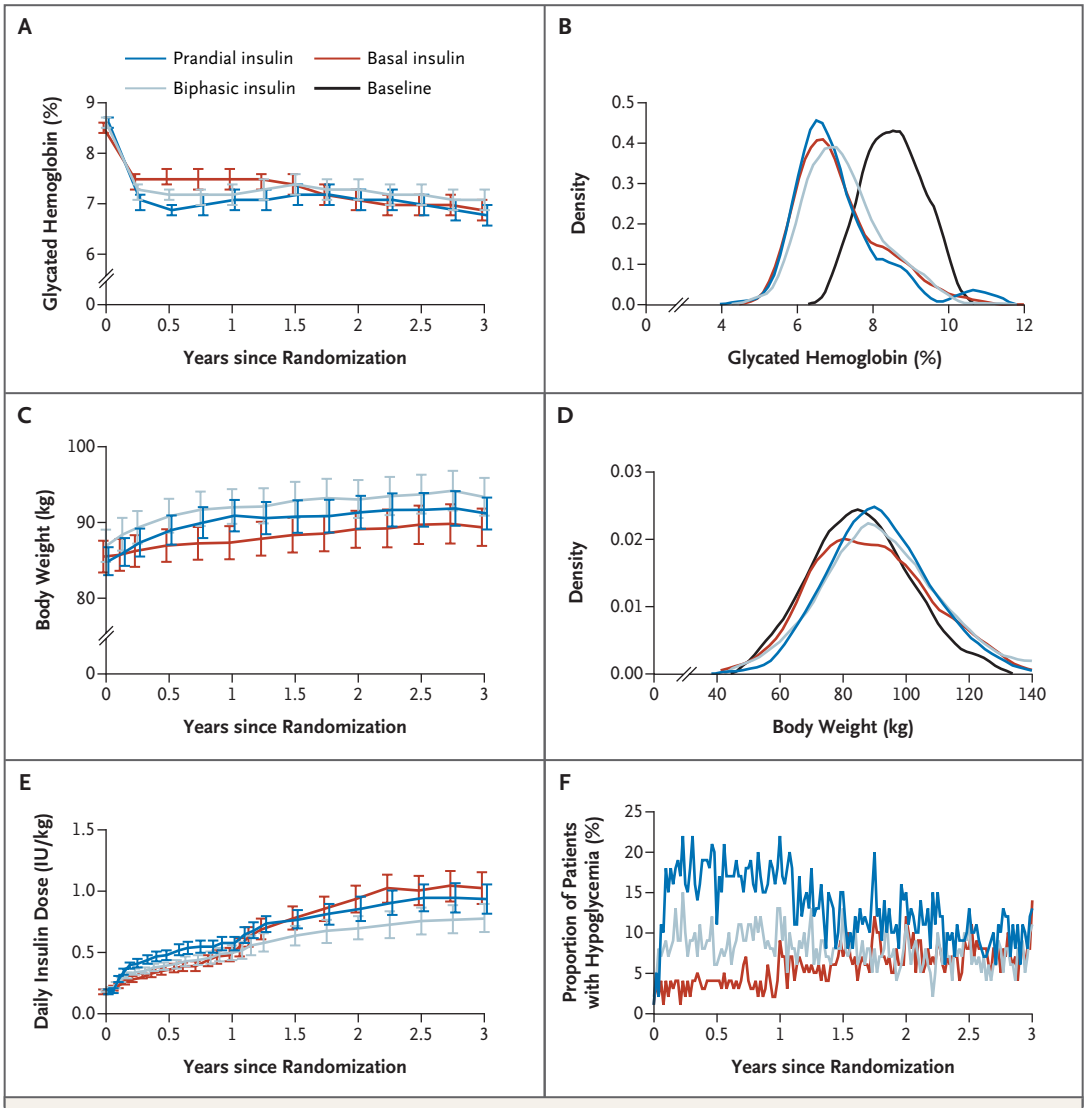

Figure 2. Primary and Secondary Outcomes at 3 Years.

Panel A shows median levels of glycated hemoglobin in the three study groups, with a kernel-density plot of the distribution of values for patients in each group at 3 years, as compared with the distribution of values for all patients at baseline, shown in Panel B. Panel C shows mean body weight, with a kernel-density plot of the distribution of values for patients in each group at 3 years, as compared with the distribution of values for all patients at baseline, shown in Panel D. Panel E shows median insulin doses. Panel F shows the proportions of patients in the three study groups reporting grade 2 or grade 3 hypoglycemic events over time. The I bars indicate 95% confidence intervals.

less than in either the prandial group (44.7%, P=0.006) or the basal group (43.2%, P=0.03) (Table 1). The corresponding proportions of patients with a glycated hemoglobin level of 7.0% or less also differed significantly between the biphasic group (49.4%) and each of the two other groups, with 67.4% in the prandial group (P<0.001) and 63.2% in the basal group (P=0.02).

Among patients with a baseline glycated hemoglobin level of 8.5% or less, those in the biphasic group were less likely to achieve values of 6.5% or less, as compared with either the prandial group (odds ratio, 0.48; 95% CI, 0.28 to 0.82; P=0.007) or with the basal group (odds ratio, 0.46; 95% CI, 0.27 to 0.78; P=0.004).

The proportions of patients who replaced sulfonylurea with a second type of insulin differed significantly among the three groups, with 67.7%

in the biphasic group, 73.6% in the prandial group, and 81.6% in the basal group (P=0.002 for the overall comparison).

Self-measured capillary glucose levels at all time points except 3 a.m. were significantly lower in the prandial group than in the biphasic group (P=0.001) but were not significantly lower than in the basal group (P=0.06). No significant differences were seen in fasting glucose values in the three groups (Fig. 3A). However, a greater mean reduction in postprandial glucose values was seen in the prandial group than in either the biphasic group (P<0.001) or the basal group (P=0.007), with a greater reduction in the basal group than in the biphasic group (P=0.04). The reduction in 3 a.m. glucose values was significantly greater in the basal group than in the prandial group (P=0.02)

Patients gained weight in all three groups; increases in the biphasic group and the prandial group were similar and were more than those in the basal group (Fig. 2C and 2D and 3A). Waist circumference increased less in the basal group than in either the biphasic group or the prandial group.

The median daily insulin dose per kilogram of body weight increased steadily during the second and third years of the study (Fig. 2E). The dose was similar at 3 years in the prandial group and the basal group but lower in the biphasic group (P=0.02 for the overall comparison). Patients who required a second type of insulin had higher median daily insulin doses, with a similar pattern but substantially different ratios of prandial insulin to total insulin.

Rates of hypoglycemia of grade 2 or more converged among the groups during the second and third years of the study and did not differ significantly in the third year (P=0.44) (Fig. 2F). However, the overall hypoglycemia rates remained highest in the prandial group and lowest in the basal group (Fig. 3B). The median number of hypoglycemic events per patient per year during the trial was 3.0 in the biphasic group, 5.5 in the prandial group, and 1.7 in the basal group; among patients with a glycated hemoglobin level of 6.5% or less, the corresponding numbers were similar, with 3.0, 5.5, and 2.0 events, respectively (P<0.001 for the overall comparison).

At 3 years, no clinically relevant between-group differences were seen in changes from baseline in either systolic or diastolic blood pressure, high-density lipoprotein or low-density lipoprotein cholesterol, triglycerides, or the ratio of urinary albumin to creatinine, although the differences in high-density lipoprotein cholesterol were significant (P=0.03). In addition, no significant differences were seen in changes from baseline with respect to Winsorized mean scores on the EuroQol Group 5-Dimension Self-Report Questionnaire.

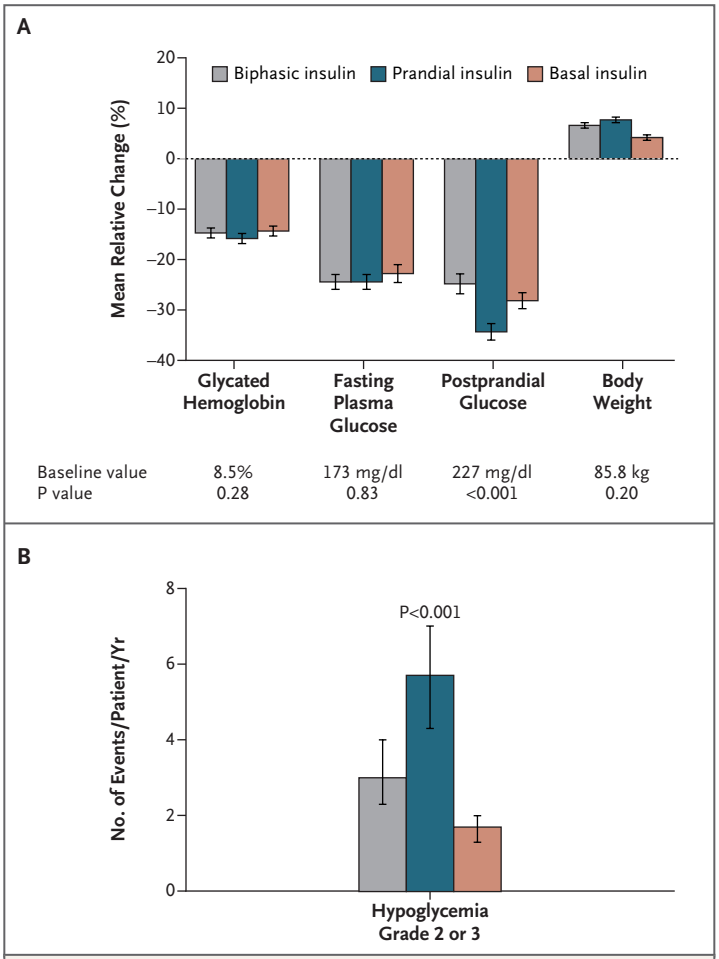

Figure 3. Changes from Baseline to 3 Years in Glycated Hemoglobin, Fasting Plasma Glucose, Postprandial Glucose, and Body Weight and the Rate of Hypoglycemia.

Panel A shows the mean (±SE) percentage changes in key outcome measures, with P values adjusted for baseline values (except hypoglycemia), study center, baseline glycated hemoglobin level, and type of oral antidiabetic therapy, where appropriate. Missing data were imputed with the use of a multiple-imputation technique.[10] To convert values for glucose to millimoles per liter, multiply by 0.05551. Panel B shows the median number of hypoglycemic events per patient per year in the three groups. The I bars indicate 95% confidence intervals.

Table 2. Adverse Events.*

Event	Biphasic Insulin (N=235)	Prandial Insulin (N=239)	Basal Insulin (N=234)	Overall P Value†
		number (percent)		
Serious adverse event	105 (44.7)	79 (33.1)	78 (33.3)	0.01
Abdominal pain	5 (2.1)	1 (0.4)	1 (0.4)	0.10
Accidental overdose of any kind	0	0	3 (1.3)	NA
Angina				
Pectoris	8 (3.4)	2 (0.8)	4 (1.7)	0.13
Unstable	0	1 (0.4)	3 (1.3)	0.37
Cardiac failure				
Any	2 (0.9)	3 (1.3)	1 (0.4)	0.88
Congestive	4 (1.7)	1 (0.4)	3 (1.3)	0.37
Carpal tunnel syndrome	3 (1.3)	1 (0.4)	0	0.37
Cellulitis	6 (2.6)	1 (0.4)	0	0.05
Stroke	3 (1.3)	0	2 (0.9)	1.00
Chest pain	3 (1.3)	1 (0.4)	5 (2.1)	0.25
Circulatory collapse	0	4 (1.7)	0	NA
Dyspnea	3 (1.3)	3 (1.3)	3 (1.3)	1.00
Femoral-neck fracture	3 (1.3)	1 (0.4)	1 (0.4)	0.54
Gastroenteritis	4 (1.7)	0	2 (0.9)	0.69
Hypoglycemia				
Any	12 (5.1)	13 (5.4)	5 (2.1)	0.15
With loss of consciousness	1 (0.4)	0	3 (1.3)	0.37
Iron deficiency anemia	4 (1.7)	1 (0.4)	0	0.21
Lower respiratory tract infection	3 (1.3)	2 (0.8)	0	0.68
Myocardial infarction	2 (0.9)	4 (1.7)	6 (2.6)	0.36
Myocardial ischemia	2 (0.9)	4 (1.7)	1 (0.4)	0.52
Osteoarthritis	6 (2.6)	1 (0.4)	4 (1.7)	0.17
Pulmonary edema	0	2 (0.8)	3 (1.3)	0.68
Urinary tract infection	3 (1.3)	1 (0.4)	1 (0.4)	0.54
Adverse event	228 (97.0)	235 (98.3)	227 (97.0)	0.58
Abdominal discomfort	27 (11.5)	16 (6.7)	14 (6.0)	0.06
Arthralgia	26 (11.1)	24 (10.0)	16 (6.8)	0.26
Back pain	30 (12.8)	38 (15.9)	31 (13.2)	0.57
Cough	38 (16.2)	51 (21.3)	49 (20.9)	0.29
Diarrhea	47 (20.0)	55 (23.0)	62 (26.5)	0.25
Headache	26 (11.1)	36 (15.1)	32 (13.7)	0.43
Hypertension	28 (11.9)	24 (10.0)	28 (12.0)	0.75
Infection	59 (25.1)	55 (23.0)	50 (21.4)	0.63
Influenza	33 (14.0)	30 (12.6)	38 (16.2)	0.51
Injection-site hematoma	34 (14.5)	34 (14.2)	39 (16.7)	0.72
Nasopharyngitis	99 (42.1)	97 (40.6)	108 (46.2)	0.45
Nausea	37 (15.7)	35 (14.6)	28 (12.0)	0.48
Oropharyngeal pain	27 (11.5)	31 (13.0)	35 (15.0)	0.54
Limb pain	38 (16.2)	31 (13.0)	31 (13.2)	0.54
Upper respiratory tract infection	27 (11.5)	28 (11.7)	33 (14.1)	0.64
Urinary tract infection	32 (13.6)	26 (10.9)	32 (13.7)	0.58
Vomiting	43 (18.3)	45 (18.8)	45 (19.2)	0.97

* The listed serious adverse events occurred in more than 1% of patients in any study group. Listed adverse events occurred in more than 10% of patients in any study group. NA denotes not applicable.
† P values are for all comparisons.

ADVERSE EVENTS

During the study period, 19 patients died (7 in the biphasic group, 9 in the prandial group, and 3 in the basal group; P=0.23); of these patients, 14 died from cardiovascular disease (4 in the biphasic group, 9 in the prandial group, and 1 in the basal group; P=0.002). The proportion of patients with any type of serious adverse event differed among the groups, with the highest proportion in the biphasic group (P=0.01). No significant between-group differences were seen in the proportion of patients with individual serious adverse events or in the numbers of nonserious adverse events (Table 2).

No clinically relevant changes occurred in levels of plasma creatinine or alanine aminotransferase in any group. According to the protocol, 14 patients discontinued metformin therapy (4 in the biphasic group, 6 in the prandial group, and 4 in the basal group) after two successive plasma creatinine measurements of more than 1.7 mg per deciliter (150 μmol per liter).[13]

DISCUSSION

In our 3-year evaluation of three different analogue insulin regimens, the median achieved glycated hemoglobin was similar in all three groups, but the distributions differed, with fewer patients achieving glycemic targets in the biphasic group than in either the prandial group or the basal group. The substantially improved glycated hemoglobin levels that were achieved at the beginning of the trial were generally maintained, although a majority of patients required intensification to a more complex insulin regimen.

There were important clinical differences among the three strategies. There was less weight gain and a smaller increase in waist circumference in the basal group than in either the biphasic group or the prandial group. Rates of hypoglycemia also differed and were lowest in the basal group and highest in the prandial group.

We used a clinically relevant, pragmatic protocol with clinic visits every 3 months, a schedule that was commensurate with routine management in primary care; the 3-year retention rate was 82%. Insulin titration to glycemic targets, which was guided by a computerized algorithm on the basis of self-monitored glucose profiles, was consistent among the three groups. We believe that our findings may be generalizable, since short- and long-acting analogues have efficacies similar to those of human insulin,[14-17] and meta-analysis has demonstrated only a minor benefit for short-acting analogues.[18]

A strength of our trial was its long duration, with overall maintenance of glycemic control with low rates of hypoglycemia. In routine clinical practice, even moderate glycemic control remains an elusive goal, characterized by delays in intensifying oral therapies and in the initiation of insulin, as evidenced by a retrospective study between 1995 and 2005.[19]

The results of our trial support current guidelines, which suggest that basal and prandial insulin regimens should be considered if adequate glycemic control is not achieved with initial regimens.[20,21] Although there is evidence for the advantages of the present approach in patients with type 1 diabetes, data supporting such a strategy in those with type 2 diabetes have been sparse, apart from a recent nonrandomized subgroup observational analysis of the effects of transferring from a biphasic regimen to various basal–prandial regimens.[22]

The achieved glycated hemoglobin level[5] and the proportions of patients who had glycated hemoglobin levels of 7.0% or less and those who had levels of 6.5% or less[23] are consistent with previous trials of complex insulin regimens. Approximately two thirds of patients in the two groups in which intensification led to a basal–prandial regimen reached the 7.0% glycated hemoglobin target, which showed that the tight glycemic control that was achieved in short-term studies of treat-to-target insulin initiation[15,24] can be maintained. The lower success rate for the biphasic-based regimen and the lower median insulin dose achieved may reflect the decreased flexibility of a fixed-ratio insulin formulation, as compared with a basal–prandial regimen.

During a 3-year period, the median daily insulin doses rose progressively to become higher than those reported in short-term insulin trials[24,25] and greater in the basal and prandial regimens than in the biphasic regimen. Although daily insulin doses were similar in the basal and prandial groups, our findings suggest that the initiation of insulin with a basal formulation, as compared with a prandial formulation, is of benefit before intensification to a basal–prandial regimen. It is likely that the greater ratio of prandial to total insulin in the prandial group explains the great-

er reduction in postprandial glucose levels and the higher rate of hypoglycemia than in the basal group. The lower weight gain in the basal group may be persistence of the difference observed at 1 year or may reflect a continuing need to correct the higher rates of hypoglycemia, as seen in the biphasic and prandial groups, with a higher carbohydrate intake. The higher rate of hypoglycemia and weight gain in the prandial group than in the basal group was consistent with the findings in other trials.[3,25]

Recent trials of intensive glycemic control have shown risks of severe hypoglycemia.[26,27] In our trial, we found that reasonable levels of glycemic control could be achieved with a low rate of major hypoglycemia, particularly when therapy was initiated with basal insulin. However, the possible association between hypoglycemia and death from cardiovascular causes supports continuing research in this area. Reassuringly, the rate of hypoglycemia in our study was no greater in patients reaching the 6.5% target than in those who did not reach this target.

Future research will need to explore the relative inability of a minority of patients to achieve an adequate reduction in glycated hemoglobin levels, regardless of the insulin regimen used, and to examine whether this outcome is associated with physiological or behavioral factors in either patients or health care professionals.[28]

In conclusion, our findings comparing three different insulin strategies provide an evidence base to guide the addition of insulin to oral antidiabetic therapy and its intensification in clinical practice. The results support the initial addition of basal insulin to oral therapy, with subsequent intensification to a basal–prandial regimen, consistent with consensus recommendations.[21] Using this approach, a majority of patients were able to achieve glycemic targets safely, with rates of hypoglycemia and weight gain that were lower than those in either the biphasic group or the prandial group.

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APPENDIX

The following investigators participated in the 4-T trial (asterisks indicate employees of Novo Nordisk): **Steering Committee** — R. Holman (chair), J. Darbyshire, M. Davies, A. Dyer Toft,* A. Farmer, M. Gall,* J. Levy, G. Nelson, H. Schou.* **Data and Safety Monitoring Board** — S. del Prato (chair), I. Campbell, R. Gray, R. Hills, S. Marshall, J. Scarpello. **Policy Advisory Group** — M. Davies (chair), A. Adler, P. Harvey, G. Neary, M. Bilous, J. Farmer, S. Gray, R. Jones, C. Kelly, D. Mellor, A. Millward, D. Moore, D. Russell-Jones, J. Nolan. **Coordinating Center** — B. Barrow, J. Darbyshire, Z. Doran, C. Dudley, A. Gilligan, V. Gregory, J. Hartweg, E. Harris, R. Holman, J. Keenan, I. Kennedy, K. Macdonald, D. McLeod, S. Motupally, R. Roberts, S. Paul, I. Stratton, K. Thorne, A. Tse, L. Tucker, M. Usman. **Central Laboratory** — J. Carpenter, R. Carter, K. Fisher, K. Islam, R. Klyne, L. Mansfield, A. Platt, B. Shine, A. Tse, T. Waknell. **Novo Nordisk Study Team*** — A. Aggarwal, J. Blakemore, A. Brown, N. Bryant, M. Budwal, C. Carrington, F. Chambers, B. Chubb, L. Clemente, L. Crawshaw, N. Dunmore, M. du Preez, J. Fenton, M. Fitch, J. Fox, C. Gordon, J. Hauff, K. Hoppen, D. Hutchins, R. Lewis, D. Lighter, L. Lowe, S. McQuade, S. Mansfield, I. Minns, A. Monk, N. Griffiths, M. Patterson, S. Peck, C. Pike, R. Meakin, A. Rosenfalck, J. Shadbolt, S. Shamash, T. Sorensen, M. Stack, P. Stella, R. Taylor, E. Townshend, P. Wilkinson, S. Williams, R. Young. **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. Wiles, 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, I. Malik, D. Matthews, J. Walker.

REFERENCES

1. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
2. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009 August 5 (Epub ahead of print).
3. Lasserson DS, Glasziou P, Perera R, Holman RR, Farmer AJ. Optimal insulin regimens in type 2 diabetes mellitus: systematic review and meta-analyses. Diabetologia 2009;52:1990-2000.
4. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357:1716-30.
5. 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.
6. McMahon GT, Dluhy RG. Intention to treat — initiating insulin and the 4-T study. N Engl J Med 2007;357:1759-61.
7. Declaration of Helsinki: ethical principles for medical research involving human subjects. Last amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Ferney-Voltaire, France: World Medical Association. (Accessed October 2, 2009, at http://www.wma.net/e/policy/b3.htm.)
8. International Conference on Harmonisation. ICH harmonised tripartite guideline: Good Clinical Practice. Geneva: International Conference on Harmonisation, May 1, 1996.
9. EuroQol Group. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.
10. Kenward MG, Carpenter J. Multiple imputation: current perspectives. Stat Methods Med Res 2007;16:199-218.
11. Demidenko E. Mixed models: theory and applications. London: Wiley-Interscience; 2004.
12. Bonett DG, Price RM. Statistical inference for a linear function of medians: confidence intervals, hypothesis testing, and sample size requirements. Psychol Methods 2002;7:370-83.
13. Jones GC, Macklin JP, Alexander WD. Contraindications to the use of metformin: evidence suggests that it is time to amend the list. BMJ 2003;326:4-5.
14. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007;2:CD005613.
15. 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.
16. 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-naive people with type 2 diabetes. Diabetes Care 2006;29:1269-74. [Erratum, Diabetes Care 2007;30:1035.]
17. Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005;28:950-5.
18. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database Syst Rev 2006;2:CD003287.
19. Calvert MJ, McManus RJ, Freemantle N. The management of people with type 2 diabetes with hypoglycaemic agents in primary care: retrospective cohort study. Fam Pract 2007;24:224-9.
20. Type 2 diabetes: the management of type 2 diabetes (update). London: National Institute for Health and Clinical Excellence, 2009.
21. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193-203.
22. Davies M, Lavalle-Gonzalez F, Storms F, Gomis R. Initiation of insulin glargine therapy in type 2 diabetes subjects suboptimally controlled on oral antidiabetic agents: results from the AT.LANTUS trial. Diabetes Obes Metab 2008;10:387-99.
23. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. Diabetes Care 2008;31:20-5.
24. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49:442-51.
25. Bretzel RG, Nuber U, Landgraf W, Owens DR, Bradley C, Linn T. Once-daily basal insulin glargine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral hypoglycaemic agents (APOLLO): an open randomised controlled trial. Lancet 2008;371:1073-84. [Erratum, Lancet 2008;372:718.]
26. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-59.
27. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129-39. [Errata, N Engl J Med 2009;361:1024-5, 1028.]
28. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care 2005;28:2673-9.