Predictive and Explanatory Factors of Change in HbA_{1c} in a 24-Week Observational Study of 66,726 People With Type 2 Diabetes Starting Insulin Analogs

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OBJECTIVE

Individualization of therapy choices requires the prediction of likely response. Predictor and explanatory factors of change in HbA_{1c} were studied using data from a large observational study of starting insulin analog therapy (the A_1chieve study).

RESEARCH DESIGN AND METHODS

Univariate analyses were performed for insulin-naive people and prior insulin users in the A_1chieve study. Statistically significant factors were carried forward to baseline factor–only multivariate analyses ("predictor" analysis), and separately using all significant factors ("explanatory" analysis). Power was considered in terms of the variance explained.

RESULTS

Geographical region, baseline HbA_{1c} level, lipid levels, and baseline insulin dose were the most powerful predictors of HbA_{1c} change (mean change −2.1% [−23 mmol/mol]) observed in the univariate analysis ($r^2 > 0.010$, $P < 0.001$). However, although the predictor and explanatory multivariate models explained 62–82% of the variance in HbA_{1c} change, this was mainly associated with baseline HbA_{1c} (r^2 = 0.544–0.701) and region (r^2 = 0.014–0.037). Other factors were statistically significant but had low predictive power ($r^2 < 0.010$); in the explanatory analysis, this included end-of-study hypoglycemia (insulin-naive group), insulin dose, and health-related quality of life ($r^2 < 0.001$–0.006, $P \leq 0.007$).

CONCLUSIONS

Many factors can guide clinicians in predicting the response to starting therapy with insulin analogs, but many are interdependent and thus of poor utility. The factor explaining most of the variance in HbA_{1c} change is baseline HbA_{1c} level, with each increase of 1.0%-units (11 mmol/mol) providing a 0.7–0.8%-units (8–9 mmol/mol) greater fall. Other factors do not explain much of the remaining variance, even when including all end-of-trial measures.

Diabetes Care 2014;37:1237–1245 | DOI: 10.2337/dc13-2413

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Received 17 October 2013 and accepted 6 January 2014.

Clinical trial reg. no. NCT00869908, clinicaltrials.gov.

Maintaining control of blood glucose to target levels in people with diabetes can delay the development and progression of diabetes-related complications in type 2 diabetes, emphasizing the importance of effectively managing glucose levels in this population (1–3). Because of the progressive nature of type 2 diabetes, obtaining optimal glucose levels with lifestyle changes and/or oral glucose-lowering drugs (OGLDs) becomes increasingly difficult over time from diagnosis, and other glucose-lowering strategies may need to be considered (4,5).

A number of randomized controlled trials provide evidence of improved glycemic control without an increase in hypoglycemia when insulin analogs are added to therapy with OGLDs in insulin-naive people, or when they are used to replace human insulin in insulin users (6–8). Observational studies, including the A_1chieve study, have provided support for this from routine clinical practice (9–12).

It is generally agreed that individualizing therapies can help in achieving blood glucose level targets in people with type 2 diabetes (13,14). Accordingly, if possible, it would be useful to be able to predict responses to insulin therapy, both when beginning insulin therapy and when adapting insulin regimens. Additionally, it would be scientifically useful to examine explanatory factors to try to understand what determines a better response to insulin when therapy is begun or enhanced.

A few studies have looked at factors potentially linked to good glycemic control in individuals with type 2 diabetes, but these are mostly local and relatively small studies, often with no therapy change and with low power (15–20). A_1chieve studied 66,726 people in 28 countries across four continents (12); thus, despite the limitations of observational data, this study population provides an opportunity for higher power and global relevance compared with smaller studies. Furthermore, glucose control improved to a clinically relevant degree, providing a robust outcome with which to look at predictors and explanatory factors, a wide range of measures being collected both at baseline and within-study, including health-related quality of life (HRQOL) (12,21). The large numbers studied suggest that, in addition to identifying which factors are predictive of improved glucose control, it may be possible to gain an estimate of the power of prediction, and therefore potential clinical and scientific utility.

RESEARCH DESIGN AND METHODS

Study Design

A total of 66,726 people were enrolled in the A_1chieve study, as fully described elsewhere (12). Briefly, this was a 24-week, international, prospective, multicenter, noninterventional, observational study examining the safety and effectiveness of basal insulin detemir (Levemir; Novo Nordisk, Bagsvaerd, Denmark), meal-time insulin aspart (NovoRapid; Novo Nordisk), and biphasic insulin aspart 30 (aspart premix) (NovoMix 30; Novo Nordisk), alone or in combination, in routine clinical use in people with type 2 diabetes. There were no restrictions otherwise on entry into the study, in particular for baseline HbA_{1c} levels, except pregnancy, intended pregnancy, or breast feeding. The study was carried out in 3,166 centers in 28 countries. The countries were grouped into the following seven geographical regions: China; South Asia; East Asia; North Africa; Middle East/Gulf; Latin America; and Russia. The participants and advising physicians decided on which insulin to use, the starting dose, administration frequency, and any later changes to either dose or frequency. There were no defined study-related procedures, except measurement of HRQOL; other measurements were made by the treating physician as part of their normal clinical practice. Study data were extracted at baseline, and at 12 and 24 weeks. Baseline characteristics for insulin-naive and insulin-experienced participants enrolled in the A_1chieve study are shown in Table 1.

Statistical Methods

For the current study, the dependent (outcome) variable was change in HbA_{1c} level from baseline to week 24 (continuous variable). Independent factors included the demographic and biomedical characteristics listed in Table 1, but also, for the explanatory factors, the repeated measures at the end of trial included plasma glucose measurements, HRQOL, blood lipid levels, blood pressure, hypoglycemia, insulin dose, and OGLD use. These factors were first examined using a univariate analysis model, followed by a stepwise multivariate analysis model including only factors that were statistically significant ($P < 0.05$) in the univariate analysis. For the predictor analysis, only baseline measures were included as predictors (Table 1). For the explanatory analysis, both baseline and end-of-trial measurements (including the change in parameter from baseline values) were included as predictors.

The generalized linear model procedure in SAS (version 9.3; SAS Institute, Cary, NC) was used for univariate analysis, and a stepwise generalized linear model procedure was used for multivariate analysis. All analyses were conducted separately in insulin-naive and insulin-experienced participants, since these groups differ in stage and duration of diabetes, and in insulin dose titration needs. Forcing-in region and baseline HbA_{1c} level as factors in the multivariate model were considered, but, since both were statistically significant in both univariate analyses, this proved unnecessary. In judging predictive or explanatory power, $r^2 \geq 0.010$ was chosen as being minimally useful, as r values <0.10 on correlation are conventionally taken as inconsequential. However, the r^2 value is given in the tables for all statistically significant factors in all models.

RESULTS

Predictive Analysis

In insulin-naive participants, the mean change in HbA_{1c} level was −23 mmol/mol (SD 19 mmol/mol) [−2.1% (SD 1.7%)]. A large number of baseline factors examined in the univariate analysis showed a statistically significant association with change in HbA_{1c} level after 24 weeks (all $P \leq 0.01$), while body weight and measures of prior hypoglycemia did not (Table 2). However, most measures had an $r^2 < 0.010$ and were thus of poor predictive power, with only geographical region ($r^2 = 0.028$), greater use of OGLDs prestudy ($r^2 = 0.015$), measures of

Table 1—Baseline characteristics for insulin-naive and insulin-experienced people enrolled in the A_1chieve study

Characteristics	Entire cohort, *n* = 66,726 (100%)	Insulin-naive, *n* = 44,872 (67.2%)	Insulin-experienced, *n* = 21,854 (32.8%)
Sex (%)			
Male	55.6	57.3	51.9
Female	44.4	42.7	48.1
Age (years)	54.0 (12.0)	53.2 (11.6)	55.6 (12.5)
Body weight (kg)	72.9 (15.0)	71.7 (14.4)	75.3 (15.9)
BMI (kg/m^2)	27.1 (5.0)	26.7 (4.7)	27.9 (5.5)
Diabetes duration (years)	8.0 (6.2)	6.6 (5.4)	10.8 (6.8)
Geographic region, *n* (%)			
China	11,020 (16.5)	8,206 (12.3)	2,814 (4.2)
East Asia	10,032 (15.0)	6,594 (9.9)	3,438 (5.2)
Latin America	1,138 (1.7)	636 (1.0)	502 (0.8)
Middle East and Gulf	14,976 (22.4)	7,501 (11.2)	7,475 (11.2)
North Africa	4,039 (6.1)	1,969 (3.0)	2,070 (3.1)
Russia	3,074 (4.6)	1,899 (2.8)	1,175 (1.8)
South Asia	22,447 (33.6)	18,067 (27.1)	4,380 (6.6)
Prior OGLDs, *n* (%)			
One	16,193 (29.6)	8,519 (21.9)	7,674 (48.6)
Two	27,466 (50.3)	21,372 (55.0)	6,094 (38.6)
Two or more	10,981 (20.1)	8,971 (23.1)	2,010 (12.7)
HbA_{1c} (%, mmol/mol)	9.5 (1.7); 80 (19)	9.5 (1.7); 80 (19)	9.4 (1.8); 79 (20)
FPG (mg/dL)	197 (64)	201 (62)	189 (67)
PPG (mg/dL)	273 (79)	280 (78)	256 (81)
Hypoglycemia (events/person-year)			
Overall	3.11	1.07	7.31
Minor	2.79	0.98	6.50
Nocturnal	0.93	0.28	2.24
Major	0.33	0.09	0.81
EQ-5D HRQOL score (VAS score)	63.4 (16.9)	62.8 (17.0)	64.8 (16.6)
SBP (mmHg)	134.2 (17.8)	134.0 (17.7)	134.7 (18.0)
Microvascular complications, *n* (%)	35,078 (53.5)	20,753 (47.5)	14,325 (65.7)
Macrovascular complications, *n* (%)	17,806 (27.2)	10,321 (23.6)	7,485 (34.3)
Insulin dose (units/kg)	0.44 (0.24)	0.38 (0.20)	0.55 (0.27)
Total cholesterol (mmol/L)	5.3 (1.3)	5.4 (1.3)	5.2 (1.3)
Triglycerides (mmol/L)	2.1 (1.1)	2.1 (1.1)	2.0 (1.1)
HDL cholesterol (mmol/L)	1.1 (0.4)	1.2 (0.4)	1.1 (0.4)
LDL cholesterol (mmol/L)	3.1 (1.0)	3.2 (1.0)	3.1 (1.1)
Creatinine (μmol/L)	80.5 (32.3)	79.3 (32.7)	82.3 (31.6)

Data are mean (SD), unless otherwise stated. SBP, systolic blood pressure; VAS, visual analog scale (1–100).

baseline blood glucose control (fasting plasma glucose [FPG] level r^2 = 0.116; postprandial plasma glucose [PPG] level r^2 = 0.079), aspects of blood lipid control (r^2 = 0.011), and initial insulin dose (r^2 = 0.031) each accounting for >1.0% of the variance in change in HbA_{1c} level ($r^2 \geq$ 0.010). The strongest association with HbA_{1c} level change in this univariate analysis was for baseline HbA_{1c} level (r^2 = 0.676).

Among insulin users, the mean change in HbA_{1c} level was −19 (SD 19) mmol/mol [−1.8 (SD 1.7) %]. Only sex, baseline HRQOL, and serum creatinine level were not significantly associated with the extent of improvement of HbA_{1c} level. However, relatively few factors had predictive power, these again being geographical region (r^2 = 0.024), prior glucose control (FPG level r^2 = 0.105; PPG level r^2 = 0.094), baseline insulin dose (r^2 = 0.015), and measures of serum lipids (r^2 = 0.023), but here also including duration of diabetes (r^2 = 0.012). Baseline HbA_{1c} level had the greatest predictive power (r^2 = 0.568). Measures of hypoglycemia during prior insulin therapy were statistically significant ($P \leq$ 0.026), but had weak predictive power ($r^2 \leq$ 0.002) (Table 2). Baseline insulin regimen had limited predictive power in both insulin-naive people (r^2 = 0.007) and prior insulin users (r^2 = 0.004).

In the multivariate analysis, the model predicted 74% of the variance in HbA_{1c} level change for insulin-naive people and 62% for prior insulin users. Predictors of HbA_{1c} level change that displayed considerable predictive power ($r^2 \geq$ 0.010) were HbA_{1c} level at baseline (r^2 = 0.701) and geographical region (r^2 = 0.037) in the insulin-naive group, and similarly (r^2 = 0.576 and r^2 = 0.034, respectively) for prior insulin users (Table 3). In both insulin-naive people and prior insulin users, baseline BMI, LDL cholesterol level, microvascular complications, and prestudy OGLD number were also statistically significant, but all had r^2 value ≤0.003 and were thus of low predictive power. In addition, age, body weight, duration of diabetes, PPG level, systolic blood pressure, total cholesterol level, triglyceride level, macrovascular complications, and major hypoglycemia while receiving prestudy insulin therapy were similarly statistically significant but of low predictive power (all $r^2 \leq$ 0.003) for prior insulin users (Table 3).

Explanatory Analysis

In insulin-naive participants, a large number of within-study and end-of-trial measures showed a statistically significant association with change in HbA_{1c} level after 24 weeks (Table 4). Indeed, this included within-study biochemical measures, body weight, HRQOL, measures of hypoglycemia, and measures such as insulin dose and use of OGLDs related to treatment. Several of these factors returned an r^2 value of ≥0.010, and thus showed some useful explanatory power, including measures of plasma glucose (r^2 = 0.010–0.169) and lipid control (r^2 = 0.016–0.019), insulin dose at end of trial (r^2 = 0.019), OGLD number at end of trial (r^2 = 0.011), and HRQOL at end of trial (r^2 = 0.029).

Table 2—Univariate analysis of baseline measures used for predictive analysis for both insulin-naive and insulin-experienced populations

	Insulin-naive population			Insulin-experienced population		
Factor	Estimate*	*P*	r^2	Estimate*	*P*	r^2
Region (vs. Russia)†	−0.345 to 0.417	NS to <0.001	0.028	−0.018 to 0.780	NS to <0.001	0.024
Age (years)	0.008	<0.001	0.003	0.007	<0.001	0.003
Sex (male vs. female)	−0.065	0.001	<0.001	−0.015	NS	—
Duration of diabetes (years)	0.017	<0.001	0.003	0.029	<0.001	0.012
Body weight (kg)	−0.001	NS	—	−0.005	<0.001	0.002
BMI (kg/m^2)	0.005	0.011	<0.001	−0.012	<0.001	0.002
HbA_{1c} (%)	−0.814	<0.001	0.676	−0.739	<0.001	0.568
FPG (mmol/L)	−0.171	<0.001	0.116	−0.158	<0.001	0.105
PPG (mmol/L)	−0.110	<0.001	0.079	−0.119	<0.001	0.094
SBP (mmHg)	−0.005	<0.001	0.003	−0.004	0.007	0.001
Creatinine (μmol/L)	0.003	<0.001	0.004	−0.001	NS	—
Total cholesterol (mmol/L)	−0.153	<0.001	0.011	−0.212	<0.001	0.023
LDL cholesterol (mmol/L)	−0.186	<0.001	0.012	−0.144	<0.001	0.008
HDL cholesterol (mmol/L)	−0.194	<0.001	0.002	−0.117	0.007	0.001
Triglycerides (mmol/L)	−0.034	0.011	<0.001	−0.173	<0.001	0.011
Complications (yes vs. no)						
Microvascular	−0.150	<0.001	0.002	0.089	0.005	0.001
Macrovascular	−0.071	0.001	<0.001	−0.072	0.018	<0.001
QOL (0–100 score)	−0.005	<0.001	0.002	0.001	NS	—
Hypoglycemia (yes vs. no)						
All	0.005	NS	—	0.178	<0.001	0.002
Minor	0.048	NS	—	0.191	<0.001	0.002
Major	−0.199	NS	—	−0.168	0.026	<0.001
Baseline insulin regimen (vs. basal)†	−0.495 to 0.193	0.001 to <0.001	0.007	−0.426 to 0.095	NS to <0.001	0.004
Dose at baseline (units/day)	−0.021	<0.001	0.031	−0.010	<0.001	0.015
OGLD number prestudy (yes vs. no)	0.673 to 0.696	<0.001	0.015	−0.089 to 0.127	NS to <0.001	0.002

QOL, quality of life; SBP, systolic blood pressure. *A negative estimate implies a greater reduction in HbA_{1c} level. †For region and insulin regimen, multiple contrasts were tested; the choice of reference comparator was random and does not affect the r^2 estimates.

Among insulin users transferring from another insulin, the patterns of explanatory variables were similar (Table 4). Again, metabolic measures of blood glucose and lipids had some explanatory power ($r^2 \geq 0.010$), but here insulin dose at end of trial and OGLD number at end of trial carried only a weak explanation for the change in HbA_{1c} level ($r^2 \leq 0.008$), although HRQOL at end of trial had similar power to the insulin-naive group ($r^2 = 0.022$). In insulin-naive people and insulin users, the greatest additional explanatory association for the change in HbA_{1c} level after 24 weeks was observed with the change in FPG level ($r^2 = 0.169$ and $r^2 = 0.191$, respectively), followed closely by change in PPG level ($r^2 = 0.134$ and $r^2 = 0.179$, respectively).

In the multivariate analysis, the model explained 82% of the variance in HbA_{1c} change for insulin-naive people and 71% for prior insulin users (Table 3). Of baseline factors, only HbA_{1c} level itself remained in the model with useful explanatory power for both the insulin-naive and insulin user groups ($r^2 = 0.687$ and $r^2 = 0.544$). Geographical region presented minimally useful explanatory power ($r^2 = 0.028$ and $r^2 = 0.014$), while other baseline and demographic factors that were statistically significant had very little explanatory power. Of the within-study factors, a similar pattern emerged in the insulin-naive and insulin user groups. Measures of glucose control such as FPG level at end of trial had some explanatory power in both groups ($r^2 = 0.088$ and $r^2 = 0.110$, respectively). However, in the insulin user group, there was no independent association between end-of-trial minor hypoglycemia, creatinine level, and systolic blood pressure with the change in HbA_{1c} level, while in the insulin-naive group these factors still had a significant association but with minimal explanatory power ($r^2 < 0.010$). Total cholesterol change, end-of-trial HRQOL score, and insulin dose also had significant association but with very low explanatory power in both participant groups.

CONCLUSIONS

The large size (~67,000 people) and wide geographical distribution (outside western nations) of the A_1chieve study should provide the most robust estimates yet of predictors and explanatory factors of improvement in HbA_{1c} level when starting or changing insulin therapy, albeit limited here to three preparations of insulin analogs. Because of the power of the study, many factors were highly statistically significant in the univariate analysis (Tables 2 and 4) for both the predictive (baseline factors) and explanatory (including within-study measures) analyses, and, indeed, for factors that

Table 3—Multivariate predictor and explanatory analysis of change in HbA_{1c} in insulin-naive people and insulin users starting therapy with insulin analogs

	Insulin-naive people			Insulin-experienced people		
Analyses	Estimate*	*P*	Adjusted r^2	Estimate*	*P*	Adjusted r^2
Predictor analysis						
Region (vs. Russia)†	−0.046 to 0.861	<0.001	0.037	−0.142 to 0.616	<0.001	0.034
Age (years)	—	—	—	−0.003	0.032	<0.001
Duration of diabetes (years)	—	—	—	0.012	<0.001	<0.001
Body weight (kg)	—	—	—	−0.004	0.037	<0.001
BMI (kg/m^2)	0.015	<0.001	0.001	0.021	<0.001	0.001
HbA_{1c} at baseline (%)	−0.799	<0.001	0.701	−0.743	<0.001	0.576
PPG at baseline (mmol/L)	—	—	—	0.009	0.012	<0.001
SBP (mmHg)	—	—	—	−0.003	<0.001	0.001
Total cholesterol (mmol/L)	—	—	—	−0.112	<0.001	0.003
LDL cholesterol (mmol/L)	−0.052	<0.001	0.001	0.038	0.044	<0.001
Triglycerides (mmol/L)	—	—	—	0.035	0.041	<0.001
Complications						
Microvascular (yes vs. no)	0.122	<0.001	0.001	0.211	<0.001	0.003
Macrovascular (yes vs. no)	—	—	—	−0.070	0.011	<0.001
Hypoglycemia, yes vs. no						
Major	—	—	—	−0.167	0.028	<0.001
OGLDs prestudy (yes vs. no)	0.155 to −0.171	0.001	0.001	0.097 to −0.196	0.003	0.001
Explanatory analysis						
Baseline factors						
Region (vs. Russia)†	−0.212 to 0.434	<0.001	0.028	−0.222 to 0.483	<0.001	0.014
Sex (male vs. female)	−0.071	0.022	<0.001	—	—	—
Duration of diabetes (years)	—	—	—	0.008	0.005	0.001
HbA_{1c} (%)	−0.799	<0.001	0.687	−0.720	<0.001	0.544
FPG (mmol/L)	−0.016	0.016	<0.001	−0.034	<0.001	0.007
Insulin dose (units/day)	−0.003	0.040	<0.001	—	—	—
OGLDs prestudy (yes vs. no)†	—	—	—	−0.035 to 0.144	0.036	0.001
Insulin regimen at baseline (vs. basa)l†	—	—	—	−0.209 to 0.183	0.042	0.001
Within-study factors						
FPG at EoT (mmol/L)	0.192	<0.001	0.088	0.152	<0.001	0.110
PPG at EoT (mmol/L)	0.080	<0.001	0.009	0.070	<0.001	0.024
PPG change (mmol/L)	0.013	<0.001	0.002	0.017	0.010	0.001
SBP at EoT (mmHg)	0.003	0.034	<0.001	—	—	—
Total cholesterol change (mmol/L)	0.036	0.009	<0.001	0.042	0.025	0.001
Creatinine at EoT (μmol/L)	0.002	<0.001	0.001	—	—	—
Hypoglycemia at EoT (yes vs. no)						
Minor	0.171	0.002	0.001	—	—	—
Insulin dose at EoT (units/day)	0.004	0.007	<0.001	0.003	0.043	<0.001
QOL at EoT (0–100 score)	−0.006	<0.001	0.002	−0.007	<0.001	0.006
QOL change, 0–100 score	—	—	—	−0.005	0.001	0.001

EoT, end of trial; QOL, quality of life; SBP, systolic blood pressure. *A negative estimate implies a greater reduction in HbA_{1c} level. †For region, OGLDs and insulin regimen multiple contrasts were tested; the choice of reference comparator was random and does not affect the r^2 estimates.

proved independent in the multivariate analysis (Table 3). However, the variance explained by many factors is poor, providing a reminder that *P* values are not good measures of clinical significance when sample size figures are large.

The strongest predictive factor was baseline HbA_{1c} level, both for individuals starting insulin therapy and for those switching insulin therapy to these insulin analogs. Indeed, the estimate is such that baseline HbA_{1c} level in the univariate analysis accounted for approximately half or more of the improvement in HbA_{1c} levels when starting therapy with insulin analogs, strengthening on multivariate analysis to around two-thirds. Other measures of baseline glucose control (fasting and postprandial) also correlated with change in HbA_{1c} level, but these either disappeared (fasting) or were markedly reduced in power (postprandial) in the multivariate analysis, presumably through being related to HbA_{1c} itself. It is likely that, if baseline HbA_{1c} level were excluded from the factors considered, FPG and PPG levels would be the strongest factors remaining on multivariate analysis. Others have noted that, between studies, baseline HbA_{1c} level is a predictor of response to glucose-lowering agents (22,23), and, indeed, the effect was readily seen in some single studies (24,25). A question arises as to whether this predictive power of baseline HbA_{1c} level is a property of the insulin or medication itself, or of associated factors (e.g., education given at the time, study effect, regression to the mean). In the A_1chieve study, it was noted that weight gain and hypoglycemia were not problems when

Table 4—Univariate explanatory analysis of additional within-study factors correlating with change in HbA_{1c} level from both insulin-naive people and insulin users starting therapy with insulin analogs

	Insulin-naive people			Insulin-experienced people		
Factors	Estimate*	*P*	r^2	Estimate*	*P*	r^2
Body weight at EoT (kg)	−0.001	0.073	<0.001	−0.004	<0.001	0.001
Body weight change (kg)	−0.002	NS	—	0.0164	<0.001	0.001
HbA_{1c} at EoT (%)	0.473	<0.001	0.081	0.461	<0.001	0.107
FPG at EoT (mmol/L)	0.096	<0.001	0.010	0.171	<0.001	0.044
FPG change (mmol/L)	0.216	<0.001	0.169	0.207	<0.001	0.191
PPG at EoT (mmol/L)	0.078	<0.001	0.017	0.113	<0.001	0.037
PPG change (mmol/L)	0.143	<0.001	0.134	0.162	<0.001	0.179
SBP at EoT (mmHg)	0.002	0.014	<0.001	0.009	<0.001	0.005
SBP change (mmHg)	0.007	<0.001	0.005	0.012	<0.001	0.012
Total cholesterol at EoT (mmol/L)	0.007	NS	—	−0.010	NS	—
Total cholesterol change (mmol/L)	0.214	<0.001	0.019	0.286	<0.001	0.037
LDL cholesterol at EoT (mmol/L)	0.017	NS	—	−0.066	0.005	0.001
LDL cholesterol change (mmol/L)	0.217	<0.001	0.016	0.093	<0.001	0.003
HDL cholesterol at EoT (mmol/L)	−0.345	<0.001	0.006	0.200	<0.001	0.002
HDL cholesterol change (mmol/L)	−0.168	<0.001	0.001	0.018	NS	—
Triglycerides at EoT (mmol/L)	0.121	<0.001	0.003	0.055	0.031	0.001
Triglycerides change (mmol/L)	0.141	<0.001	0.006	0.340	<0.001	0.031
Creatinine at EoT (μmol/L)	0.002	<0.001	0.002	−0.000	NS	—
Creatinine change (μmol/L)	−0.001	NS	—	0.001	NS	—
Hypoglycemia at EoT (yes vs. no)						
Total	−0.263	<0.001	0.001	0.101	0.044	<0.001
Minor	−0.267	<0.001	0.001	0.103	0.042	<0.001
Major	0.434	NS	—	−0.748	NS	—
Dose at EoT (units/day)	−0.013	<0.001	0.019	−0.006	<0.001	0.008
Dose change in dose (units/day)	0.001	NS	—	0.004	0.001	0.001
OGLD number (yes at day 1 vs. no OGLD)	0.126 to 0.317	0.005 to <0.001	0.005	−0.059 to −0.171	NS to 0.006	0.001
OGLD number (yes at EoT vs. no OGLD)	0.021 to 0.383	NS to <0.001	0.011	0.065 to 0.170	NS to <0.001	0.001
QOL at EoT (0–100 score)	−0.027	<0.001	0.029	−0.021	<0.001	0.022
QOL change (0–100 score)	−0.007	<0.001	0.005	−0.013	<0.001	0.015

*A negative estimate implies a greater reduction in HbA_{1c}. EoT, end of trial; QOL, quality of life; SBP, systolic blood pressure.

starting therapy with an insulin analog, while systolic blood pressure also improved, and it was therefore suggested that some combination of these factors together with the insulin was of importance (12).

Other metabolic factors such as lipid measures also had some predictive power, but largely dropped out or had very low power in the multivariate analysis. It may be presumed that they were either related to the poor blood glucose control or also responded to lifestyle measures (and perhaps other therapy) introduced in this observational study at the time of starting therapy with the insulin analog. Therapeutic factors such as starting insulin dose and use of OGLDs were also moderately predictive but, again, dropped out or became very poorly predictive ($r^2 \leq 0.001$) in the multivariate analysis. OGLD use at end of study similarly had low-to-moderate explanatory power in the univariate analysis but disappeared in the multivariate analysis. All three of these factors are possibly clinicians' responses to levels of blood glucose control, and may not have been independent of baseline HbA_{1c} level.

Measures of the status of diabetes such as duration from diagnosis, and microvascular and macrovascular complications, do appear as predictive factors, but disappear in the multivariate analysis, apart from microvascular complications (predictive analysis) and duration of diabetes (explanatory analysis), but, again, the predictive power is very low in both cases.

Important clinically, and often seemingly interrelated, factors are body weight, quality of life, and hypoglycemia. The first factor is poorly predictive of final HbA_{1c} level even in the univariate analysis, and not at all in the insulin-naive population or in the explanatory analysis, although the effect in insulin users is preserved very weakly in the predictor multivariate analysis. In the A_1chieve study, people did not gain weight with insulin analog therapy in routine clinical practice (indeed, they lost it with insulin detemir therapy), perhaps obviating the clinical experience that weight gain sometimes limits insulin dose titration and thus attainment of improved glucose control. Indeed, we have presented subanalysis data that HbA_{1c} change did not differ by baseline BMI with insulin detemir

treatment, and that body weight change was inversely related to baseline BMI (26). Hypoglycemia (no vs. yes in the last 4 weeks of study) does have some power as an explanatory factor for final HbA_{1c} level; however, very low rates of hypoglycemia were recorded in the A_1chieve study (12), which in turn could have reduced the power of this explanatory association between hypoglycemia and final HbA_{1c} level. This explanatory power effectively disappeared in the multivariate analysis. Since end-of-study glucose control (fasting and postprandial) remained in the explanatory model, it is possible that the rather unstable hypoglycemia measures were related to these, and were driven out by them. Last, quality of life, measured by the EQ-5D questionnaire, which changed markedly in the study, was poorly predictive at baseline, but somewhat more related to HbA_{1c} level change at end of study, an effect that remained with low power, in the multivariate analysis.

The subject of this study is relatively novel, and related articles generally do not specifically address predictors of control on starting or changing insulin therapy. Evidently, a few studies comparing insulin regimens do compare outcomes of glucose control between regimens, finding, as we do, that these outcomes are not major predictor or explanatory factors (27,28). The IMPROVE study results section comments that duration of diabetes and baseline HbA_{1c} level are predictors of control change at 26 weeks using a multivariate analysis when starting biphasic insulin aspart therapy, but no details as to what variables were included in the analysis are given (20). However, it can be inferred that baseline HbA_{1c} level was again a powerful predictor, while duration of diabetes had a smaller effect (20). Similar observations were made by Nichols et al. (29) in a retrospective analysis of medical records from Kaiser Permanente Northwest (Hillsboro, OR), where baseline HbA_{1c} level accounted for 96% of the explainable variance in HbA_{1c} level change in patients with type 2 diabetes. The other studies on prediction of HbA_{1c} are either cross-sectional or deal with no particular intervention, and are mainly concerned with the influence of patterns of care and population characteristics rather than therapy interventions (15–20).

Our study has its limitations. The duration of the study was relatively short at 24 weeks, and from routine care data we had no measures of factors that might affect longer-term trends in control, such as C-peptide levels or patient adherence and resources (30). Indeed, the diverse regional coverage of the study is both a strength and a weakness, increasing overall generalizability but carrying the risk that regional variations could have diluted the power of associations that might be locally relevant. In the A_1chieve study, individuals receiving routine care were treated with different insulin analogs; therefore, the reported associations were generated using data from a mixture of different interventions. It is not necessarily the case that different analogs, and indeed different insulins, would yield similar results if they resulted in different changes in HbA_{1c} levels. Also, any unique properties of a studied analog, such as those regarding hypoglycemia or weight change, and which might putatively affect HbA_{1c} level change, would limit generalizability, probably to a small but unknowable extent. In addition, given the global scope of the A_1chieve study, potential variation in data collection methods across different regions may confound the prediction analysis. Set against these limitations is the sheer size of the study, thus delivering high power of correlation for the univariate analysis, and thus the power to enter with validity a large number of possible variables into the discriminatory analyses. Indeed, our models were able to predict 63–82% of the overall variance in change in HbA_{1c} levels, suggesting that we are capturing most of the important influences, although perhaps data on adherence to therapy and lifestyle might have improved overall power further (15,19,31).

Clinically, it seems that physicians can expect from these results that all markers of poor metabolic control may predict that larger improvements in glucose control can be achieved when starting insulin therapy, although, ultimately, it is enough to look at HbA_{1c} level. However, it may be reassuring to the person contemplating starting or switching insulin therapy that there is an opportunity for improvement in multiple risk factors, and to the payer that the package of changes is cost-effective (12,32). Of clinical importance, neither baseline body weight nor prior hypoglycemia are strong predictors of failure to achieve change in HbA_{1c} level. This is equally true of factors associated with long duration of diabetes such as the presence of complications.

Unfortunately, we know from the ACCORD epidemiological analysis that people who fail to improve control with intensification of therapy (including insulin presumably) have poor outcomes (33), but it appears from our analysis that the factors measured here, including macrovascular complications and prior hypoglycemia, had little power to predict who those people might be. Indeed, although those failing to improve control in the ACCORD study had higher rates of hypoglycemia during the study (after intensification), this effect is not seen in our data. One explanation may be that, while the ACCORD study was using high-intensity therapy with the aim of achieving HbA_{1c} levels of ~6.0% (42 mmol/mol), our investigators were delivering routine care and may have backed off from further dose titration once hypoglycemia occurred.

In conclusion, in routine clinical care around the world, when starting or switching to therapy with an insulin analog, the major determinant of change in HbA_{1c} is baseline HbA_{1c} level. While other factors do contribute statistically to predictive models, their power is very low, considering both baseline factors alone and explanatory factors measured during the follow-up period or at end of study.

Acknowledgments. The authors thank the people with diabetes and investigators across the globe who contributed time and effort to the underlying study.

Duality of Interest. This study was funded by Novo Nordisk. Writing assistance was provided by Steven Barberini of Watermeadow Medical, funded by Novo Nordisk. P.D.H., M.I.H., Z.A.L., and G.G.G. have received funding from Novo

Nordisk (and in some cases from other insulin manufacturers) for themselves or their institutions for research, educational, and advisory activities. C.S. and J.-W.C. are employees of Novo Nordisk.

Author Contributions. P.D.H. and C.S. researched the data, contributed to the analysis, and contributed to critical revision of the manuscript. M.I.H., Z.A.L., J.-W.C., and G.G.G. contributed to critical revision of the manuscript. P.D.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, IL, 21–25 June 2013.

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