Factors Associated With Weight Gain in People With Type 2 Diabetes Starting on Insulin

Beverley Balkau,[1,2] Philip D. Home,[3] Maya Vincent,[4] Michel Marre,[5] and Nick Freemantle[6]

Diabetes Care 2014;37:2108–2113 | DOI: 10.2337/dc13-3010

OBJECTIVE

Moderate weight gain is usual after starting insulin therapy. The identification and quantification of factors associated with weight gain may help target strategies for avoidance of weight gain.

RESEARCH DESIGN AND METHODS

The noninterventional CREDIT (Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy) study included data from people with type 2 diabetes starting any insulin in 314 centers, in 12 countries. From a number of predefined candidate explanatory variables, analyses identified factors associated with weight gain 1 year after starting insulin treatment, after adjusting for investigational site as a random factor. A multivariable backward regression analysis selected a subset of these factors associated with weight gain.

RESULTS

We studied the 2,179 people with data for body weight change at 1 year and for potential predictive factors. The mean weight gain was 1.78 kg, and 24% gained ≥5.0 kg. Baseline factors associated with weight gain were BMI, A1C, insulin regimen, insulin dose, other glucose-lowering therapies, and hypertension; at 1 year, additional factors were A1C, insulin regimen, insulin dose, and use of other glucose-lowering therapies. In multivariable analysis, weight gain at 1 year was associated with a higher A1C at baseline, a higher insulin dose at baseline and at 1 year, and a lower baseline BMI.

CONCLUSIONS

By the time insulin was started, a high baseline A1C and insulin dose requirements were independently associated with greater weight gain, as was lower baseline BMI. Insulin regimen per se was not a predictive factor.

Good glycemic control in people with type 2 diabetes can prevent long-term microvascular complications and may also prevent or slow progression of the macrovascular disease associated with diabetes (1–3). Insulin therapy is an effective method to attain and maintain appropriate glycemic control (4,5). However, along with the improvement in blood glucose control, weight gain is usual after starting insulin therapy (6–8).

Guidelines are needed in clinical practice on the appropriate time and means of beginning insulin therapy, according to individual characteristics and desires. Weight gain is an important factor in this choice, and often the start of insulin treatment is delayed in the obese person with diabetes. A meta-analysis of

[1]INSERM Centre for Research in Epidemiology and Population Health, U1018, Villejuif, France
[2]University Paris-Sud, URMS 1018, Villejuif, France
[3]Newcastle University, Newcastle upon Tyne, U.K.
[4]Sanofi, Paris, France
[5]INSERM U695, University of Paris 7, Paris, France
[6]University College London, London, U.K.

Corresponding author: Beverley Balkau, beverley.balkau@inserm.fr.

Received 23 December 2013 and accepted 29 March 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-3010/-/DC1.

A slide set summarizing this article is available online.

randomized clinical trials indicated that weight gain was less at 1 year in those treated by basal insulin rather than by two injections a day or prandially, with no differences between the latter two regimens (7).

The CREDIT (Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy) study, an international, 4-year, noninterventional, longitudinal study, was designed to evaluate, in routine clinical practice, the relationship between blood glucose control and cardiovascular events in people newly treated with insulin and to provide insight into current clinical practice of the use of insulin in people with type 2 diabetes (9,10). In this report, we study the factors associated with weight gain in the CREDIT study after 1 year of insulin treatment.

RESEARCH DESIGN AND METHODS

The CREDIT study design and participant selection criteria, as well as participant baseline characteristics, have been reported previously (9,10). In brief, the study involved 314 recruitment centers in 12 countries, 10 in Europe, plus centers in Canada and Japan. Men and women with type 2 diabetes, age >40 years, who had started any type of insulin therapy within 12 months and who had an A1C measurement within the 3 months prior to beginning insulin were eligible to participate in the study. As this was a noninterventional study, there was no fixed study visit schedule, and insulin choice, dosage, titration, medical costs, and concomitant oral agent therapy were according to usual local practice. Data were gathered in routine clinical practice, and the treating physicians were asked to report updated participant data every 6 months. Data presented as the 1-year follow-up data are those provided during the 9–18-month window after starting insulin treatment. Ethical approval according to local regulations was obtained for all study sites. Conduct of the study adhered to standards of data collection for clinical trials, according to the Declaration of Helsinki. Written informed consent was obtained from all participants before commencement of data collation.

Statistical Analyses

Patient characteristics are presented by weight change group: for continuous variables by the mean (SD) or median (quartile 1, quartile 3) and for categorical variables by *n* (%).

To identify factors associated with weight gain at the start of insulin therapy and after 1 year, univariate mixed models studied a predefined number of candidate explanatory variables, with adjustment for recruitment centers as random effects, to allow for differences between patients in different settings. The functional form of each continuous variable in the univariable analyses was determined by contrasting the Akaike Information Criteria for the model with the untransformed variable, and a model with the $\log_e$ transformed variable, and the transformed variable was used if the Akaike Information Criteria differed by more than –3.84 (χ^2, 1 df criteria). If transformation was favored, a restricted cubic spline was planned in models if the Akaike Information Criteria improved by a further 3.84. Relations were linear for age, BMI, and for both $\log_e$(A1C) and $\log_e$(insulin dose) at baseline and after 1 year. Interactions were tested ($P < 0.05$) between explanatory variables both at baseline and at 1 year.

A multivariable stepwise mixed model added or removed explanatory variables from the model, based on minimizing the Schwarz Bayesian information criterion. Predictive factors were studied before the start of insulin treatment and separately after 1 year, when factors predictive at baseline or at 1 year were studied. Analyses used SAS statistical software, version 9.2 or above (SAS Institute, Cary, NC).

RESULTS

Characteristics and Univariable Analysis

The CREDIT study included 3,061 participants at baseline, of whom 2,179 had data on body weight change at 1 year and on the prespecified explanatory variables (Supplementary Fig. 1). The 882 participants with missing data for body weight change, or other candidate explanatory variables, differed from the 2,179 participants included in the analyses on several characteristics: more were men, more came from North America and Northern Europe and fewer from Eastern Europe, fewer were taking sulfonylureas and biguanides, fewer had a medical history of macrovascular disease, more smoked, and more were taking mealtime insulin.

For the 2,179 participants studied, mean weight gain was 1.78 kg (median 2.0 kg), and this differed across countries (Supplementary Table 1), with the highest weight gain being in Portugal, averaging 4.26 kg with 40% of the participants gaining at least 5.0 kg. Germany had the lowest average weight gain, 0.95 kg, with 15% gaining 5.0 kg or more. The distribution of weight gain is shown separately for the 1,077 men and 1,102 women (Supplementary Fig. 2), and although the median values for men (2.00 kg) and women (1.95 kg) were similar, the weight gain was less variable in women.

Characteristics of the participants and their treatment when starting insulin therapy (Table 1) and after 1 year of insulin therapy (Table 2) are shown according to classes of weight gain at 1 year. When starting insulin therapy, after accounting for recruitment site, those who gained more weight over 1 year had a lower BMI, a higher A1C, fewer had diagnosed hypertension, fewer used basal insulin alone, more used basal + mealtime insulin, and fewer used biguanides or sulfonylureas, while they had a higher insulin dose (Table 1). After 1 year of insulin therapy, those who had gained more weight had a higher A1C at 1 year, fewer were on basal insulin therapy but more were on basal + mealtime therapy, fewer were using biguanides or sulfonylureas, and they had a higher insulin dose (Table 2). There were no significant interactions between these explanatory variables.

Multivariable Analysis

When factors before the start of insulin were combined in a multivariable analysis, the stepwise procedure selected higher A1C and lower BMI as predictors of weight gain, after accounting for recruitment center (Table 3). For example, the model predicted a weight gain 0.5 kg higher in a person with an A1C of 8.0% (64 mmol/mol) in comparison with 7.0% (53 mmol/mol) after adjusting for baseline BMI, with a 0.5 kg lower weight gain for a 4.0 kg/m^2 higher baseline BMI, after adjusting for baseline A1C.

From among factors at the start of insulin treatment and after 1 year of treatment, the stepwise procedure selected

Table 1—Characteristics (median [quartile 1, quartile 3]) or *n* (%) of the people studied when starting insulin, according to their weight gain at 12 months, and β coefficients from linear models adjusted for the investigational site as a random factor

	Weight gain at 12 months (kg)						
Item	<2.0 *n* = 1,087	2.0–4.9 *n* = 581	5.0–9.9 *n* = 405	≥10 *n* = 106	β coefficient*	(95% CI)	*P*
Age (years)	62 (55, 69)	61 (55, 68)	60 (53, 69)	58 (53, 67)	−0.013	(–0.032 to 0.007)	0.204
Men	536 (49%)	282 (48%)	202 (50%)	57 (54%)	0.123	(–0.274 to 0.520)	0.543
Women	551 (51%)	299 (52%)	203 (50%)	49 (46%)			
Smoking							0.153
Never smoked	637 (59%)	345 (59%)	232 (57%)	48 (45%)	Reference		
Stopped ≥1 year	272 (25%)	131 (23%)	97 (24%)	28 (26%)	−0.302	(–0.776 to 0.171)	0.211
Stopped <1 year	30 (3%)	16 (3%)	18 (4%)	8 (8%)	0.735	(–0.357 to 1.828)	0.187
Currently smokes	148 (14%)	89 (15%)	58 (14%)	22 (21%)	0.277	(–0.291 to 0.846)	0.339
BMI (kg/m^2)	29.1 (25.9, 33.5)	29.1 (25.9, 33.5)	27.5 (24.0, 31.6)	28.4 (23.7, 33.5)	−0.124	(–0.156 to –0.091)	<0.001
Duration of diabetes (years)	9 (5, 14)	9 (5, 15)	10 (5, 15)	9 (5, 14)	0.007	(–0.018 to 0.033)	0.579
A1C (%)†	9.0 (8.0, 10.2)	9.2 (8.1, 10.4)	9.9 (8.6, 11.4)	10.1 (8.8, 11.7)	1.346	(1.034 to 1.659)	<0.001
A1C (mmol/mol)†	75 (64, 88)	77 (65, 90)	85 (70, 101)	87 (73, 104)	0.123	(0.095 to 0.152)	<0.001
Diagnosed hypertension	792 (73%)	389 (67%)	268 (66%)	68 (64%)	−0.755	(–1.183 to –0.328)	0.001
Microvascular disease	825 (76%)	453 (78%)	307 (76%)	87 (82%)	−0.259	(–0.748 to 0.231)	0.300
Macrovascular disease	370 (34%)	207 (36%)	141 (35%)	44 (42%)	−0.022	(–0.437 to 0.392)	0.916
Insulin regimen							<0.001
Basal insulin alone	599 (56%)	304 (53%)	169 (42%)	42 (40%)	Reference		
Basal + mealtime	132 (12%)	92 (16%)	74 (19%)	25 (24%)	1.376	(0.776 to 1.974)	<0.001
Mealtime alone	74 (7%)	34 (6%)	37 (25%)	4 (4%)	0.093	(–0.745 to 0.933)	0.827
Premix	243 (23%)	121 (21%)	101 (25%)	29 (28%)	0.774	(0.253 to 1.295)	0.004
Other	28 (3%)	21 (4%)	18 (4%)	5 (5%)	1.766	(0.609 to 2.922)	0.003
Other diabetes drugs							0.004
None	325 (30%)	198 (34%)	172 (42%)	44 (42%)	Reference		
One	428 (39%)	190 (33%)	149 (37%)	40 (38%)	−0.615	(–1.084 to –0.147)	0.010
Two	282 (26%)	163 (28%)	70 (17%)	19 (18%)	−0.909	(–1.446 to –0.372)	0.001
Three or more	52 (5%)	30 (5%)	14 (4%)	3 (3%)	−1.054	(–2.042 to –0.066)	0.037
Biguanides	553 (51%)	280 (48%)	169 (42%)	50 (47%)	−0.513	(–0.914 to – 0.111)	0.012
Sulfonylureas	385 (35%)	213 (34%)	89 (22%)	26 (24%)	−0.554	(–0.990 to – 0.118)	0.013
Daily insulin dose (IU/kg)†	0.18 (0.12, 0.31)	0.20 (0.13, 0.33)	0.27 (0.15, 0.42)	0.31 (0.20, 0.47)	4.814	(3.673 to 5.955)	<0.0001

*For categorical measures, β coefficients are given for yes vs. no, or against the reference group stated. †Data were $\log_e$ transformed for analysis, so the β coefficients are for $\log_e$ of a unit difference.

the following factors predicting weight gain: a higher baseline A1C, a higher insulin dose at both baseline and at 1 year, and a lower baseline BMI, after accounting for recruitment center (Table 3). After adjusting for other factors, an insulin dose at 1 year of 0.6 compared with 0.4 IU/kg/day (a 50% increase) was associated with a 0.5 kg higher weight gain. There was no association with A1C at 1 year, or with the change in A1C, in the multivariable analysis.

CONCLUSIONS

In this multivariable analysis of routinely started insulin therapy in developed nations, four factors were found to be independent predictors of weight gain. The level of A1C before starting insulin treatment was relatively strongly predictive of weight gain over the subsequent 12-month period. However, a higher BMI was associated with a lesser weight gain. For both of these factors, a difference in weight gain could be predicted for a difference in baseline clinical characteristics of an order commonly seen in clinical practice. The same can be said of insulin dose, both at baseline and at 1 year, for although the difference in insulin dose required to predict a 0.5-kg difference in weight gain was large, such large differences are commonly encountered in clinical practice. Interestingly, when including these factors in the multivariable model, insulin regimen per se was not a predictive factor, suggesting its presence in the univariable analysis was associated with factors that remained on multivariable analysis.

In a propensity score analysis that we have already published on the CREDIT study, treatment regimens were compared in pairs (9). This method of analysis accounts for the baseline characteristics of the individuals that could influence the regimen chosen by the prescribing physician. Comparing basal and premix insulin, with 343 people treated by each insulin type and matched on baseline characteristics, the difference in weight gain, after adjusting for recruitment centers and initial weight, was 1.3 kg lower with basal than premix insulin ($P < 0.001$). However, those treated with premix had a significantly higher daily insulin dose at baseline than those treated with basal insulin, 39 vs. 30 units/day, respectively ($P < 0.001$). Comparing treatment by basal and

Table 2—Characteristics (median [quartile 1, quartile 3]) or *n* (%) of the people and their treatment after 12 months of insulin treatment, according to their weight gain at 12 months, and β coefficients from linear models adjusted for the investigational site as a random factor

	Weight gain at 12 months (kg)						
Item	<2.0 *n* = 1,087	2.0–4.9 *n* = 581	5.0–9.9 *n* = 405	≥10 *n* = 106	β coefficient*	(95% CI)	*P*
A1C (%)†	7.3 (6.7, 8.3)	7.6 (6.9, 8.4)	7.6 (6.9, 8.5)	7.7 (6.8, 8.6)	1.968*	(0.794 to 3.141)	0.001
A1C (mmol/mol)†	56 (50, 67)	60 (52, 68)	60 (52, 69)	61 (51, 70)	0.180	(0.073 to 0.287)	0.001
Insulin regimen							<0.001
Basal insulin alone	531 (49%)	256 (44%)	104 (26%)	30 (28%)	Reference		
Basal + mealtime	192 (18%)	129 (22%)	119 (29%)	37 (35%)	1.964	(1.441 to 2.487)	<0.001
Mealtime alone	39 (4%)	16 (2%)	10 (2%)	1 (1%)	−0.268	(–1.443 to 0.908)	0.665
Premix	276 (25%)	146 (25%)	137 (34%)	32 (30%)	1.269	(0.770 to 1.767)	<0.001
Other	49 (4%)	34 (6%)	35 (9%)	6 (6%)	1.686	(0.796 to 2.576)	<0.001
Other diabetes drugs							0.008
None	360 (33%)	215 (37%)	175 (43%)	49 (46%)	Reference		
One	410 (38%)	182 (31%)	147 (36%)	37 (35%)	−0.522	(–0.987 to 60.058)	0.027
Two	267 (25%)	155 (27%)	70 (17%)	17 (16%)	−0.878	(–1.415 to –0.342)	0.001
Three or more	50 (5%)	29 (5%)	13 (3%)	3 (3%)	−0.948	(–1.949 to 0.053)	0.063
Biguanides	532 (49%)	267 (46%)	167 (41%)	46 (43%)	−0.504	(–0.907 to –0.101)	0.014
Sulfonylureas	365 (34%)	201 (35%)	87 (22%)	23 (22%)	−0.584	(–1.026 to –0.142)	0.010
Daily insulin dose (IU/kg)†	0.33 (0.21, 0.52)	0.40 (0.26, 0.56)	0.46 (0.33, 0.63)	0.51 (0.33, 0.64)	1.529	(1.202 to 1.856)	<0.001

*For categorical measures, β coefficients are given for yes vs. no, or against the reference group stated. †Data were $\log_e$ transformed for analysis, so the β coefficients are for $\log_e$ of a unit difference.

basal + mealtime insulin, for the 200 matched patients, those treated with basal insulin had a 1.4 kg lower weight gain ($P < 0.016$), as well as a lower insulin dose, 30 vs. 46 units/day ($P < 0.001$). For the remaining comparisons of the six possible pairs of regimens, we did not find significant differences in the weight gain between regimens, even when the insulin dose differed, but some of the sample sizes were much smaller. The effect of the insulin regimen, however, may be being played out through the insulin dose.

We can compare our results with those from the UK Prospective Diabetes Study (UKPDS): after 1 year of insulin treatment, the median weight gain was 2 kg (11) or a mean weight gain of ~2.5 kg (12) in people with newly diagnosed diabetes; the median weight gain was identical to that found in our observational study. A recent meta-analysis of 46 randomized controlled trials (7) studied the increase of body weight over the 1st year of insulin treatment, a difficulty here being the selected and not necessarily clinically representative nature of the populations studied in randomized clinical trials. When all regimens were pooled, insulin dose was positively correlated with weight gain except for basal insulin alone, where weight gain was negatively correlated with insulin dose (6). In our study, we found no such interaction between insulin dose and insulin regimen on weight gain. In the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once-Weekly (DURATION)-3 trial (13), after 26 weeks of treatment with basal insulin treatment, glargine, the weight gain was 1.4 kg. More recent data from the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial (14), in people at a high risk of cardiovascular disease, and with impaired fasting glucose, impaired glucose tolerance, or new or established diabetes (zero or one oral glucose-lowering drug), weight gain on insulin glargine was 1.6 kg, over 6.2 years.

Although clinical trials provide a head-to-head comparison between different drugs in a highly selected study population, observational studies provide information about how drugs are used more generally in the population. Published observational studies on weight gain are few. Our results are consistent with those of a retrospective study from a single center (15). The noninterventional A_1chieve study in a different group of countries around the world compared insulin analog treatments in people with type 2 diabetes (4). For the population treated with detemir, weight gain over 24 weeks was not associated with insulin dose (16). In the large UK

Table 3—β coefficients to predict weight gain from multivariable linear models, after stepwise selection of variables measured at baseline before prescription of insulin, and when including measures at 1 year, both adjusted for the investigational site as a random factor

	β coefficient	(95% CI)	*P*
Baseline variables only			
A1C, per $\log_e$ %*	4.371	(3.365 to 5.377)	<0.0001
BMI, per 10.0 kg/m^2	−1.198	(–1.516 to –0.880)	<0.0001
Baseline variables and variables after 1 year			
A1C at baseline, per $\log_e$ %*	3.397	(2.379 to 4.414)	<0.0001
Daily insulin dose at baseline, per $\log_e$ IU/kg	0.415	(0.062 to 0.768)	0.021
Daily insulin dose at 1 year, per $\log_e$ IU/kg	1.143	(0.783 to 1.504)	<0.0001
BMI at baseline, per 10.0 kg/m^2	−1.121	(–1.444 to –0.799)	<0.0001

*For mmol/mol, the β coefficient is for a $\log_e$ 10.9 mmol/mol change.

General Practice Research Database (17), in people with type 2 diabetes newly treated with insulin, weight gain was greater on premixed insulin than on other regimens, but there is no information provided on insulin dose. The Health Improvement Network database studied 1,492 people newly diagnosed with diabetes >18 years of age who required insulin treatment within the first 6 months after diagnosis, and who responded to insulin treatment (A1C <7.5% [<58 mmol/mol]) within the first 18 months of treatment (18). These people would probably be classified as having latent autoimmune diabetes of adults or slow-onset type 1 diabetes. However, average weight gain over the 18 months was 2.4 kg, but the initial insulin regimen was not a predictive factor; information on insulin dose was not provided. The relationship between these factors appears to merit further investigation in larger databases.

After adjusting for insulin dose (inherent in multivariable analysis) as well as recruitment centers, lower BMI was predictive of weight gain. This is a clear finding in a large population but may seem contrary to some clinical perceptions of likely runaway weight gain in more obese people. However, there are explanations for the findings. First, as baseline BMI is highly correlated with baseline body weight, and the calculation of the difference in weight (the weight gain) includes baseline weight, it would be expected that change in weight would be negatively correlated with baseline BMI. Second, there could be some regression to the mean for BMI over time, in particular if prior weight loss due to very poor glucose control and baseline A1C 9.5% (80 mmol/mol) was reversed by the insulin therapy (15). Third, the adverse clinical perception may be being colored by a small group of people at the higher end of the BMI spectrum; nevertheless, those with more extreme weight gain did not differ notably in baseline BMI in our study. One of the reasons for a lower BMI at starting insulin therapy might be particular conditions such as type 1 diabetes, diabetes secondary to pancreatitis, or pancreatic cancer, but although some people were initially included with these conditions, they were excluded from the study. It remains possible that due to investigator misattribution or uncertainty of diabetes type, a small number of people with latent autoimmune diabetes of adults or type 1 diabetes or secondary pancreatic diabetes may have been included.

In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, 19% of the type 2 diabetic patients were newly treated with insulin during the 5-year trial (19). For all glucose-lowering treatments and their combinations, oral or injected, those who gained the most weight tended to have a lower mean baseline BMI. One of the initial hypotheses of the report by Watson et al. (17) from the UK General Practice Research Database was that higher baseline BMI was correlated with weight gain in patients newly treated with insulin. However, their data showed the opposite, that weight gain was negatively correlated with BMI class, at all times of follow-up up to 24 months, and this relation remained significant after multivariable adjustment in the 2,042 patients studied. In agreement with our study, they also found that baseline A1C was associated with weight gain. In the Health Improvement Network database study, the average weight gain over the 18 months was 2.4 kg, again with a greater weight gain in those with lower BMI (18).

Our large observational study has limitations. We were not able to study the reasons why some people may not have been given insulin treatment, e.g., fear of insulin treatment or fear of weight gain in the obese. The physicians' treatment targets for individual patients were not available. The study provides information on "real-life" use of insulin and its consequences on weight gain, in contrast to clinical trials in often highly selected groups of people. However, in this international study, a number of countries were studied, along with their different dietary habits and diabetes treatment protocols. Further, the recruitment centers included may not be representative of those in a given country, and the countries studied are not representative of all countries. Statistically, we have accounted for recruitment site, and this should condition for some of these differences, and so make the results more generalizable. We do not have information on analog and nonanalog insulins and thus have had to assume they have similar effects. Further, almost 30% of those people initially enrolled in the study did not have sufficient information collected in routine clinical practice on the key variables within the time windows and so were not included in the analysis; given their mixed characteristics, it is difficult to conclude whether and how this might have biased our results.

The main factors associated with weight gain in this international study were higher insulin dose, not the actual insulin regimen, higher baseline A1C, and lower baseline BMI. Taken together, the clinical message from this appears to be that if higher weight gain is to be avoided, then insulin should be started before A1C rises to more extreme levels and body weight is lost through poor glucose control. Given that islet β-cell function deteriorates with time (20), insulin dose is then likely to be lower, also assuaging the risk of weight gain according to our study. Furthermore, these findings should reassure physicians that starting insulin therapy in the more obese has no more risk of weight gain than in the less obese. Nevertheless, there is some weight gain in clinical practice with insulin therapy, although it appears that lifestyle measures can minimize weight gain in routine care (4).

Acknowledgments. Editorial support was provided by Tom Claus of PPSI (a PAREXEL company).

Duality of Interest. This study was supported by Sanofi. B.B. is on advisory boards for Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly and Company, and Sanofi and has received a research grant from Servier. P.D.H. and institutions with which he is associated receive funding for his research, advisory, and lecturing activities from all major insulin manufacturers, including Sanofi. M.V. is an employee of Sanofi. N.F. has received research grants and served as consultant to Eli Lilly and Company, Medtronic, Novo Nordisk, Pfizer, and Sanofi and has served on speaker bureaus for Novo Nordisk and Sanofi. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. B.B. and P.D.H. conceived and designed the main study and this substudy, supervised the study during implementation, advised on data interpretation, and were part of the writing team. M.V. contributed to analysis and wrote the manuscript. M.M. contributed to the design of the main study and wrote the manuscript. N.F. contributed to the study design, study conduct, and data analysis and wrote the manuscript. B.B. 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. These results were presented at the European Association for the Study of Diabetes meeting in 2010 and at the American Diabetes Association Middle East Congress in 2012.

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;359:1577–1589
2. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373:1765–1772
3. The Control Group. Intensive glucose control and macrovascular outcomes in type 2 diabetes [published correction appears in Diabetologia 2009;52:2470]. Diabetologia 2009;52:2288–2298
4. Home P, Naggar NE, Khamseh M, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A_1chieve study. Diabetes Res Clin Pract 2011;94:352–363
5. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
6. Holman RR, Thorne KI, Farmer AJ, et al.; 4-T Study Group. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357:1716–1730
7. Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metab 2011;13:1008–1019
8. Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26:3080–3086
9. Freemantle N, Balkau B, Home PD. A propensity score matched comparison of different insulin regimens 1 year after beginning insulin in people with type 2 diabetes. Diabetes Obes Metab 2013;15:1120–1127
10. Freemantle N, Balkau B, Danchin N, et al. Factors influencing initial choice of insulin therapy in a large international non-interventional study of people with type 2 diabetes. Diabetes Obes Metab 2012;14:901–909
11. UK Prospective Study of Therapies of Maturity-Onset Diabetes. UK prospective study of therapies of maturity-onset diabetes. I. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. Diabetologia 1983;24:404–411
12. 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;352:837–853
13. Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 2010;375:2234–2243
14. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
15. Larger E, Rufat P, Dubois-Laforgue D, Ledoux S. Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. Diabetes Care 2001;24:1849–1850
16. Home P, Malek R, Prusty V, Latif ZA, Haddad J. Impact of insulin detemir on weight change in relation to baseline BMI: observations from the A_1chieve Study (Abstract). Diabetes 2013;62:A246
17. Watson L, Wilson BP, Alsop J, Kumar S. Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? Diabetes Obes Metab 2011;13:823–831
18. Idris I, Pillai A, Fernando DJ, Thomson G, Tate H. Responders to insulin therapy at 18 months in adults with newly diagnosed diabetes: which insulin regimen? Diabet Med 2013;30:e95–e100
19. van Dieren S, Czernichow S, Chalmers J, et al. Weight changes and their predictors amongst 11 140 patients with type 2 diabetes in the ADVANCE trial. Diabetes Obes Metab 2012;14:464–469
20. 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;44:1249–1258