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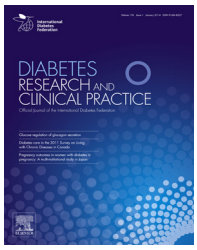

Predictors of HbA1c over 4 years in people with type 2 diabetes starting insulin therapies: The CREDIT study

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ABSTRACT

Aims: To identify factors associated with glucose control, as measured by HbA1c over 4 years, in people with type 2 diabetes starting insulin therapy.
Methods: CREDIT, an observational cohort study, collected data semi-annually over 4 years, on people with type 2 diabetes starting any insulin, in 311 centres in 12 countries; 2803 people had data on HbA1c during follow-up. Multivariable backward regression analysis selected characteristics associated with glycaemic control from a limited number of candidate variables.
Results: Before starting insulin therapy, HbA1c was 9.3% (78 mmol/mol) and decreased to 7.6% (60 mmol/mol) after 1 year, and changed little after that. Insulin dose increased from 0.21 U/kg to 0.36 U/kg at 1 year, and then by 0.10 U/kg over the next 3 years. Body weight increased by 2.0 kg in the first year and increased little thereafter. Poorer glycaemic control over the 4 years was mainly determined by the HbA1c before starting therapy, after accounting for the other statistically significant associated variables in multivariable analysis: higher BMI, younger age, longer diabetes duration, more glucose-lowering drugs, using basal insulin alone, higher insulin dose and female sex. At 4 years, a higher current insulin dose was the characteristic most strongly associated with a higher concurrent HbA1c.
Conclusions: HbA1c at the start of insulin therapy was the characteristic most predictive of later HbA1c, after accounting for other variables associated with HbA1c. This may provide some justification for earlier insulin introduction to improve glucose control to target.

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1. Introduction

Blood glucose control is well recognised as a factor associated with microvascular complications in people with type 2 diabetes, and there is some evidence that it may slow the progression of cardiovascular diseases [1,2]. People with type 2 diabetes can often maintain adequate glycaemic control with appropriate lifestyle and oral glucose-lowering agents, but timely introduction of insulin therapy is indicated when glycaemic control is no longer maintained [3]. However, there is often reluctance to start insulin therapy on the part of both the physician and the individual with type 2 diabetes, because of the need for injections, fear of hypoglycaemia and weight gain [4–6].

Clinical trials have provided invaluable information about glycaemic control following therapy by differing insulin therapies. However, the people in clinical trials are highly selected according to the trial protocol, advised by the more motivated clinicians who agree to participate in trials, while participants are closely monitored in line with a trial protocol. There is less published information about the outcomes of insulin therapy in current clinical practice, and it is often only very short term [7].

The Cardiovascular Risk Evaluation in people with Type 2 Diabetes on Insulin Therapy (CREDIT) study was designed in 2006 [8] and aimed to evaluate both the relationship between blood glucose control and cardiovascular events over 4 years in people starting insulin therapy, and to provide insight into current, real-world practices in the management of people with type 2 diabetes using insulin. In this report, we evaluate the characteristics, both when starting insulin and at 4 years, that are associated with glycaemic control during the 4 years of follow-up and at 4 years.

2. Subjects, materials and methods

2.1. Study design and participants

The CREDIT study design and selection of the people with type 2 diabetes have been reported previously [8]. Briefly, people were recruited in 311 centres in 12 countries in North America, Europe and Asia (see Supplementary Table S1) for this non-interventional, observational, 4-year study. After baseline, data were collected prospectively. The participants were over 40 years of age, newly started on insulin therapies ($\leq$12 months), and with an HbA1c measurement in the 3 months before starting insulin. While follow-up was over 4 years, there was no fixed study schedule, and physicians were asked to record data at the usual visits to the clinic, every 6 months. The starting insulin regimen and dose were at the discretion of the treating physician, as were any changes of therapy.

The study was approved by recruiting centre ethics committees, and informed written consent was obtained from each participant. The study was conducted according to the principles of the Declaration of Helsinki.

The principal outcome measure for this report is the average 1–4 year HbA1c, the average at years 1, 2, 3 and 4 after starting insulin; the HbA1c data used for the 1 year time point was the blood sample with a date closest to 1 year, within the time window 9–18 months after inclusion in the study; similar windows were used for the 2, 3 and 4-year HbA1c values. The average of the available yearly values was then used.

The secondary outcome measure is the HbA1c at year 4, at the end of the study, after 4 years of insulin therapy.

The main variables studied at the start of insulin therapy, as predictors of the two HbA1c outcome measures, were: sex, age, physical activity (recorded as some physical activity or none), smoking status (currently smokes or stopped $<$1 year; never smoked or stopped $\geq$1 year), family history of premature cardiovascular disease, micro- or macrovascular disease, other comorbidities, body mass index (BMI), duration of diabetes, HbA1c (normalised according to local laboratory values), number of oral glucose-lowering drugs, diagnosis of high blood pressure, number of blood pressure-lowering drugs, insulin regimen (basal alone, basal and short acting, short acting alone, premix insulin alone, other), total dose of insulin. At the end of 4 years the following additional variables were included as potential explanatory factors for HbA1c at 4 years: micro- and/or macrovascular disease or other comorbidities during follow-up; number of oral glucose-lowering drugs, insulin regimen and total insulin dose at 4 years; change in weight over 4 years; and symptomatic hypoglycaemia in the 6 months prior to the 4-year evaluation.

2.2. Statistical analyses

SAS statistical programme version 9.2 (Cary, NC, USA) was used for all analyses.

The characteristics of participants are described by percentages and by medians (quartile 1, quartile 4), geometric means and percentiles. Those with and without the two HbA1c outcome measures were compared by chi-square and Student *t*-tests. The percentage (95% confidence interval [CI]) achieving an HbA1c target of 7.0% at each year is shown graphically.

Both HbA1c outcome measures were $\log_e$ transformed for statistical analysis, as they were right-skewed. The functional form of the continuous predictive variables was determined in linear models adjusted for region (six regions – Eastern Europe: Croatia, Ukraine and Russia; Southern Europe: Italy, Portugal, Spain; France; Northern Europe: United Kingdom, Finland, Germany; Japan; Canada) and for random centre effects (to allow for physician characteristics), by comparing the Akaike Information Criterion for models with the predictive variables in linear, $\log_e$ and restricted cubic spline forms; all continuous variables (excepting change in weight) were $\log_e$ transformed.

Univariate analyses of variables predicting the two HbA1c outcome measures used linear models, adjusted for region, as a fixed factor and recruiting centres as random effects. For the multivariable models, variables were selected by a backwards procedure, limited to effects significant at the conventional 0.05 level. For the HbA1c outcome measure at 4 years, an additional multivariable model included variables already selected at starting insulin, along with those measured at 4 years listed above, using a similar backwards selection procedure.

Predictors of the two HbA1c outcome measures above the 7.0% units HbA1c target were studied using univariate and

multivariable mixed effects logistic regression models and backwards variable selection methods, similar to those above.

3. Results

3.1. *Baseline characteristics of people followed for glycaemic control*

Of the 3060 people with type 2 diabetes who were started on insulin therapy and included in the CREDIT study, 2803 had HbA1c levels recorded at and after entry (principal outcome: average 1–4 year HbA1c), of whom 2212 had HbA1c at year 4 (secondary outcome) (Supplementary Fig. S1). The people with the principal HbA1c outcome available had similar baseline characteristics to those who were not followed, except for small but statistically significant differences: more physically active, fewer smoked, more micro- or macrovascular disease, and more high blood pressure; for the secondary HbA1c outcome measure, those studied were more often women, more physically active, fewer smoked, more family history of premature CVD, more microvascular disease, fewer comorbidities, and more treated with short-acting insulin (23% vs. 18%). The people studied were distributed across 12 countries (Supplementary Table S1), with Russia and Japan recruiting the largest numbers of people.

The characteristics of the populations with the principal and secondary HbA1c outcomes were very similar (Table 1): men and women were equally represented, and they were aged 61 years (median), with a BMI of 28.6–28.7 kg/m^2. At the start of insulin therapy, HbA1c was 9.2–9.3% (77–78 mmol/mol),

Table 1 – Characteristics[a] of the people with type 2 diabetes started on insulin therapy, for the population with data on the principal outcome: average 1–4 year HbA1c (n = 2803), and for the population with the secondary outcome: HbA1c data at 4 years (n = 2212). The CREDIT study.

	Population with principal outcome: Average 1–4 y HbA1c (n = 2803)	Population with secondary outcome: HbA1c at year 4 (n = 2212)
At start of insulin therapy		
Men (%)	51	49
Age (y)	61 (54–69)	61 (54–68)
Physically active (%)	48	50
Currently smokes or stopped <1 y (%)	18	16
Family history of premature CVD (%)	26	27
Microvascular disease (%)	60	62
Macrovascular disease (%)	35	34
Other comorbidities (%)	30	29
BMI (kg/m^2)	28.7 (24.9, 21.9)	28.6 (24.9, 32.8)
Duration of diabetes (y)	9.0 (5.0, 14.3)	8.9 (5.0, 14.0)
HbA1c (%)	9.2 (8.1, 10.7)	9.3 (8.1, 10.7)
Glucose-lowering drugs (%)	70	70
Diagnosed high blood pressure (%)	69	69
Blood pressure-lowering drugs (%)	73	72
Insulin regimen		
Basal only (%)	52	52
Basal and short-acting (%)	14	15
Short-acting alone (%)	8	8
Premix insulin alone (%)	23	23
Other (%)	3	3
Insulin dose at starting insulin (U/kg)	0.20 (0.13, 0.36)	0.20 (0.13, 0.34)
At 4 years or during follow-up		
Microvascular disease (%)		50
Macrovascular disease (%)		15
Other comorbidities (%)		16
Glucose-lowering drugs (%)		64
Insulin regimen		
Basal alone (%)		30
Basal and short acting (%)		32
Short acting alone (%)		2
Premix insulin alone (%)		25
Other (%)		5
No insulin (%)		6
Insulin dose (U/kg)		0.50 (0.32, 0.69)
Symptomatic hypoglycaemia[b] (%)		17
Severe hypoglycaemia[b] (%)		2
Weight change (kg)		2.0 (−1.0, 7.0)

[a] Data shown are median (quartile 1, quartile 3), or percentage of population.
[b] Hypoglycaemia is for the 6 months before the 4-year visit.

with 25% having an HbA1c >10.7% units (93 mmol/mol); 52% were started on basal insulin alone, 23% with premix alone, while the median starting insulin dose was 0.20 U/kg; 70% were additionally treated with oral glucose-lowering drugs when starting insulin therapy.

3.2. Characteristics over the 4 years after starting insulin therapy

The principal HbA1c outcome measure had a skewed distribution, with a geometric mean of 7.6% (60 mmol/mol), an upper quartile of 8.2% (66 mmol/mol), and 4.4% of people had an HbA1c >10.0% (86 mmol/mol) (Supplementary Fig. S2). After 1 year, HbA1c was 7.6% (60 mmol/mol) and was fairly constant thereafter, being 7.5% (58 mmol/mol) at year 4 [9]. While 94% of people had an HbA1c ≥7.0% (≥53 mmol/mol) when starting insulin, this was 67% at year 1 and 65% at year 4 (Supplemental Fig. S3).

The insulin dose increased from 0.21 U/kg (geometric mean) at starting insulin to 0.36, 0.40, 0.43, and 0.46 U/kg at years 1–4, respectively [9]. For 46% of people, the insulin regimen changed over the 4-year time period. At 4 years, fewer people were treated with basal insulin alone (30% vs. 52% at baseline), while more were treated with basal plus mealtime insulin (32% vs. 14%), fewer with short-acting alone (2% vs. 8%), similar percentages with premix insulin (25% vs. 23%) and with other insulins (5% vs. 3%) (Table 1); 6% were no longer treated with insulin. Glucose-lowering drugs were recorded in 70% of people at starting insulin and in 64% at 4 years. Body weight increased over the first year of insulin therapy [9], but little over the three subsequent years; the median (quartiles) of weight change over 4 years was 2.0 kg (−1.0, 7.0), highly variable.

3.3. Characteristics associated with the average 1–4 year HbA1c, the principal outcome measure

The baseline characteristics associated with a higher HbA1c outcome (Tables 2 and 3) were: absence of other comorbidities (other than micro- or macrovascular complications, neither of which showed an association), more glucose-lowering drugs, a younger age, a higher BMI and a higher baseline HbA1c (all $P < 0.0001$); other variables associated with a higher HbA1c outcome were female sex, a family history of premature CVD, the insulin regimen (in particular basal insulin alone and premix insulin alone) and a longer duration of diabetes (all $P < 0.01$).

The multivariable analysis predicting higher average 1–4-year HbA1c, after a backwards selection of baseline characteristics, included eight predictors (Table 4): baseline HbA1c was by far the strongest predictor, followed by BMI, age and diabetes duration (all $P < 0.0001$); other predictors were a higher number of glucose-lowering drugs, insulin regimen (specifically basal insulin alone and short-acting alone), and a higher insulin dose. Similar characteristics were also predictive of an average 1–4-year HbA1c of ≥7.0% units in a multivariable analysis (Table 4). However, the starting insulin dose was only predictive of the continuous HbA1c variable, while men were more likely than women to achieve the HbA1c target.

3.4. Characteristics associated with HbA1c at year 4, the secondary outcome measure

The baseline characteristics associated with a higher HbA1c at year 4 (Tables 2 and 3) were: younger age, higher BMI and higher baseline HbA1c (all $P < 0.0001$); fewer non-vascular comorbidities and more glucose-lowering drugs (both $P < 0.005$). Year 4 characteristics associated with a higher HbA1c were a higher insulin dose, a greater increase in weight, the insulin regimen (in particular basal and short-acting insulin) (all $P < 0.0001$); microvascular disease and fewer comorbidities during the follow-up, more glucose-lowering drugs, and lack of hypoglycaemia (all $P < 0.02$).

After backwards selection of variables, and accounting for all other variables included as predictors in the multivariable analysis, baseline HbA1c was again the strongest predictor of HbA1c at year 4, followed by age (both $P < 0.0001$), then BMI diabetes duration and other glucose-lowering drugs, in order of significance (Table 5). Considering also possible explanatory variables at year 4, a higher insulin dose at year 4 was the most significant predictor, with a higher baseline HbA1c, a greater number of glucose-lowering drugs at year 4, less hypoglycaemia in the 6 months before the year 4 visit, as well as younger age, and a higher BMI at baseline. Furthermore, the 4-year increase in weight was associated with a higher HbA1c at year 4, but the effect was minimal after adjusting for the other variables shown in Table 5: a 5-kg increase in weight over the 4 years was associated with a 0.01% unit increase in HbA1c. Characteristics associated with being above the 7.0% unit target for HbA1c were similar to those above: a higher baseline HbA1c, being younger, a longer duration of diabetes and more glucose-lowering drugs. The 4-year data were more explanatory (Supplementary Table S2): significant factors at 4 years were a higher insulin dose, more glucose-lowering drugs with an increase in weight, no microvascular disease during the 4 years of follow-up, as well at baseline, a higher HbA1c and a longer duration of diabetes. Of note, for the analyses to target, baseline BMI was not retained in the multivariable models, but weight change was still statistically significant.

4. Discussion

In this study of people with type 2 diabetes starting insulin therapy in routine clinical practice, there was a marked improvement in glycaemic control at 1 year, which remained stable over the remaining 3 years of the study. However, at 4 years after starting insulin therapy, only 35% of the participants had an HbA1c below the general glycaemic target of 7.0% (53 mmol/mol), with 13% having an HbA1c ≥9.0% (75 mmol/mol). The main baseline characteristics associated with poorer glycaemic control over the 4 years were higher values of baseline HbA1c, age, BMI, duration of diabetes, number of other glucose-lowering drugs, insulin regimen (specifically basal or premix insulins vs. multiple injection regimens), and finally a higher insulin dose and female sex. For glycaemic control at the end of the 4 years, a higher concomitant insulin dose was the most predictive factor, with more glucose-lowering drugs, weight gain, lack of hypoglycaemia and new

Table 2 – Geometric means (95% CI)[a] of the principal outcome: average 1–4 year HbA1c, and the secondary outcome: HbA1c at year 4, according to categorical characteristics at baseline and at 4 years or during follow-up, by univariate regression analysis (adjusted for region and centre). The CREDIT study.

	Average 1–4 years HbA1c (n = 2803)		HbA1c at year 4 (n = 2212)	
	Geometric mean (95% CI)	Overall P	Geometric mean (95% CI)	Overall P
At start of insulin therapy				
Sex				
Men	7.5 (7.4, 7.6)	0.003	7.5 (7.4, 7.7)	0.5
Women	7.6 (7.5, 7.8)		7.5 (7.4, 7.7)	
Physically active				
No	7.6 (7.5, 7.7)	0.2	7.5 (7.4, 7.7)	0.8
Yes	7.5 (7.4, 7.7)		7.5 (7.4, 7.7)	
Smoking				
Current or stopped <1 year	7.6 (7.4, 7.7)	0.08	7.5 (7.4, 7.7)	0.9
Non-smoker	7.6 (7.5, 7.8)		7.5 (7.4, 7.7)	
Family history premature CVD				
No	7.5 (7.4, 7.7)	0.009	7.5 (7.4, 7.6)	0.2
Yes	7.7 (7.5, 7.8)		7.6 (7.4, 7.8)	
Microvascular disease				
No	7.6 (7.4, 7.7)	0.9	7.6 (7.4, 7.7)	0.5
Yes	7.6 (7.4, 7.7)		7.5 (7.4, 7.7)	
Macrovascular disease				
No	7.6 (7.5, 7.7)	0.2	7.5 (7.4, 7.7)	0.3
Yes	7.5 (7.4, 7.7)		7.5 (7.3, 7.6)	
Other comorbidities				
No	7.6 (7.5, 7.8)	<0.0001	7.6 (7.5, 7.7)	0.0004
Yes	7.4 (7.3, 7.6)		7.4 (7.2, 7.6)	
Glucose-lowering drugs				
None	7.4 (7.3, 7.6)	<0.0001	7.4 (7.3, 7.6)	0.004
One	7.5 (7.4, 7.7)		7.5 (7.3, 7.6)	
Two	7.7 (7.5, 7.8)		7.6 (7.5, 7.8)	
Three or more	7.7 (7.5, 8.0)		7.7 (7.4, 7.9)	
Diagnosed high blood pressure				
No	7.6 (7.4, 7.7)	0.5	7.6 (7.4, 7.8)	0.07
Yes	7.6 (7.4, 7.7)		7.5 (7.4, 7.6)	
Blood pressure drugs				
None	7.6 (7.5, 7.8)	0.4	7.6 (7.4, 7.8)	0.2
One	7.6 (7.4, 7.7)		7.5 (7.4, 7.7)	
Two	7.5 (7.4, 7.7)		7.5 (7.3, 7.7)	
Three or more	7.5 (7.4, 7.7)		7.4 (7.3, 7.6)	
Insulin regimen				
Basal alone	7.6 (7.5, 7.8)	0.0008	7.6 (7.4, 7.7)	0.09
Basal and short acting	7.4 (7.3, 7.6)		7.4 (7.3, 7.7)	
Short acting alone	7.3 (7.1, 7.5)		7.3 (7.1, 7.5)	
Premix insulin alone	7.6 (7.5, 7.8)		7.5 (7.3, 7.7)	
Other	7.4 (7.2, 7.7)		7.7 (7.3, 8.0)	
At 4 years or during follow-up				
Microvascular disease[b]				
No			7.4 (7.3, 7.6)	0.02
Yes			7.6 (7.5, 7.7)	
Macrovascular disease[b]				
No			7.5 (7.4, 7.7)	0.6
Yes			7.6 (7.4, 7.8)	
Other comorbidities[b]				
No			7.6 (7.4, 7.6)	0.02
Yes			7.4 (7.2, 7.6)	
Glucose-lowering drugs				
None			7.4 (7.3, 7.6)	0.004
One			7.6 (7.4, 7.7)	
Two			7.5 (7.3, 7.7)	
Three or more			7.8 (7.6, 8.1)	
Insulin regimen				
Basal alone			7.4 (7.3, 7.6)	<0.0001
Basal and short acting			7.7 (7.6, 7.9)	
Short acting alone			7.2 (6.9, 7.6)	
Premix insulin alone			7.5 (7.4, 7.7)	
Other			7.4 (7.2, 7.7)	

Table 2 (*Continued*)

	Average 1–4 years HbA1c (n = 2803)		HbA1c at year 4 (n = 2212)	
	Geometric mean (95% CI)	Overall P	Geometric mean (95% CI)	Overall P
None			7.2 (7.0, 7.5)	
Hypoglycaemia[c]				
No			7.6 (7.4, 7.7)	0.0002
Yes			7.3 (7.1, 7.5)	

[a] Data shown are geometric means (95% confidence intervals) from linear regression models.
[b] Microvascular, macrovascular diseases and other comorbidities were during the 4-year follow-up.
[c] Hypoglycaemia is defined as confirmed hypoglycaemia within the 6 months prior to 4-year visit.

microvascular disease over the follow-up also associated with poorer control; baseline HbA1c and age remained predictive.

While at first sight it might seem clinically sensible that in the years after starting insulin therapy, a higher baseline HbA1c should be a co-predictor of HbA1c, along with BMI and the starting insulin dose, these variables were retained in multivariable analysis, so it cannot simply be that they are co-associated with later poor control due to investigators starting insulin later in the more obese, and then at higher doses, in conjunction with more oral agents. Similarly, it is tempting to attribute both high baseline HbA1c and duration of diabetes to a relative deficiency of endogenous insulin secretion; again these characteristics were both retained on multivariable analysis, suggesting that there may not be a single underlying unmeasured explanatory factor for predicting poorer blood glucose control. The independent association of BMI with later HbA1c could reflect a reluctance of clinicians to titrate the insulin dose in the more obese (although a higher concomitant insulin dose at the end of the study was an independent explanatory factor), or perhaps it is simply a marker of difficulty in harnessing self-motivation to improve measures of health status.

The associations of insulin regimen with glucose control over the 4 years, but not at the end of the study, need a more complex explanation. It might be expected that basal insulin alone and premix insulin would be selected for those with earlier and easier to treat blood glucose control, and thus that attained HbA1c might be lower. However, for the CREDIT study, we have already shown that the HbA1c at start of insulin therapy was not a factor associated with the choice between basal insulin and insulin regimens other than premix [8], and indeed basal insulin was more frequent in those taking more oral glucose-lowering therapies. It appears that at baseline, basal insulin is chosen for those who have more difficulty in managing their diabetes. Accordingly, on multivariable analysis, neither initial nor current insulin regimen was predictive of control at 4 years, but their role may be played out through the concurrent insulin dose.

Hypoglycaemia might a priori be expected to be a factor explanatory for HbA1c. Clinicians appear to expect lower HbA1c to be associated with more hypoglycaemia, contrary to the findings of the ACCORD study for either intensive or standard therapy [10]. In the CREDIT study, we have found that an episode of hypoglycaemia in the last 6 months of follow-up is associated with lower HbA1c at year 4 on multivariable analysis, although by a modest average of 0.08% units. However, hypoglycaemia was not experienced by a majority of people studied, at least in the 6 months before the year 4 visit, and severe hypoglycaemia was uncommon. This must limit its ability to modulate insulin dose, insulin regimen, or patient behaviour.

Other publications have addressed this issue in randomised controlled trials of insulin regimens [11–13], in retrospective studies from electronic prescriber databases [14–16] and in observational studies with features in common with our own [7,17,18]. Randomised clinical trials however, are generally restricted to their planned comparison, and are often of short duration. The 4-T study did suggest that insulin regimen had

Table 3 – Univariate regression coefficients (SE)[a,b] for continuous variables associated with the principal outcome: average 1–4 year HbA1c and the secondary outcome: HbA1c at year 4, according to continuous characteristics at baseline and 4 years or during follow-up (adjusted for region and centre). The CREDIT study.

	Average 1–4 year HbA1c (n = 2803)			HbA1c at year 4 (n = 2212)		
	Beta (SE)	Beta/SE	P	Beta (SE)	Beta/SE	P
At start of insulin therapy						
Age (y)	−0.143 (0.016)	−9.0	<0.0001	−0.137 (0.020)	−6.9	<0.0001
BMI (kg/m^2)	0.114 (0.014)	8.0	<0.0001	0.086 (0.018)	4.7	<0.0001
Duration of diabetes (y)	0.007 (0.003)	2.4	0.01	0.003 (0.004)	0.8	0.4
HbA1c (%)	0.193 (0.014)	13.91	<0.0001	0.122 (0.018)	6.9	<0.0001
Insulin dose (U/kg)	−0.000 (0.005)	−0.02	1	0.002 (0.006)	0.4	0.7
At 4 years or during follow-up						
Insulin dose (U/kg)				0.074 (0.006)	12.7	<0.0001
Weight change (kg)				0.002 (0.001)	4.0	<0.0001

[a] Data shown are beta coefficients (standard errors) from linear regression models.
[b] HbA1c and continuous variables all $\log_e$ transformed, except weight change.

Table 4 – Multivariable linear and logistic regression coefficients (SE)[a,b] and odds ratios (95% confidence intervals) of variables at the start of insulin therapy associated with the principal outcome: average 1–4 year HbA1c after backwards selection of variables. The CREDIT study.

	Predicting $\log_e$ HbA1c			Predicting HbA1c ≥7.0%	
	Beta (SE)	Beta/SE	P	Odds ratio (95% CI)	P
HbA1c (%)	0.187 (0.015)	12.8	<0.0001	8.33 (4.55, 14.29)	<0.0001
BMI (kg/m^2)	0.098 (0.015)	6.7	<0.0001	2.27 (1.32, 4.00)	0.003
Age (y)	−0.110 (0.017)	−6.5	<0.0001	0.37 (0.19, 0.69)	0.002
Duration of diabetes (y)	0.016 (0.003)	5.4	<0.0001	1.27 (1.12, 1.41)	<0.0001
Glucose-lowering drugs			0.007		0.02
One vs. none	0.008 (0.007)	1.0	0.3	0.84 (0.64, 1.10)	0.2
Two vs. none	0.025 (0.008)	3.0	0.003	1.18 (0.87, 1.61)	0.3
Three or more vs. none	0.032 (0.013)	2.5	0.01	1.43 (0.88, 2.33)	0.2
Insulin regimen			0.001		0.0006
Basal + short-acting vs. basal alone	−0.043 (0.011)	−3.9	<0.0001	0.55 (0.39, 0.78)	0.0006
Short-acting alone vs. basal alone	−0.028 (0.012)	−2.3	0.02	0.84 (0.55, 1.28)	0.4
Premix alone vs. basal alone	−0.005 (0.008)	−0.6	0.6	1.22 (0.90, 1.64)	0.2
Other vs. basal alone	−0.026 (0.017)	−1.5	0.1	0.81 (0.45, 1.47)	0.5
Insulin dose (U/kg)	0.013 (0.006)	2.2	0.03		
Sex (women vs. men)				1.41 (1.15, 1.75)	0.0008

[a] Data shown are beta coefficients (standard errors) from linear regression models to predict HbA1c and odds ratios (95% confidence intervals) to predict HbA1c <7%, from logistic regression; both regression analyses adjusted for region and centre.
[b] HbA1c and continuous variables all $\log_e$ transformed.

an effect on achieved glucose control at 1 year, with those on basal insulin having worse glucose control but a better hypoglycaemia experience than those on premix or mealtime insulins alone [11]. Regimens in the 4-T study were intensified over the next 2 years and the contrast changed so that fewer people on premix insulin achieved a 6.5% (48 mmol/mol) HbA1c target than those on either basal or mealtime insulin regimens, although the median HbA1c levels at year 3 were very similar: 6.9–7.1% units (42–54 mmol/mol) [12]. Riddle et al. [13] analysed 12 mostly short-term clinical trials, all using structured titration of glargine. They found that baseline factors predictive of HbA1c <7.0% (<53 mmol/mol) were male sex, white race, shorter duration of diabetes, lower baseline HbA1c, metformin use, and no sulphonylurea use. For the studies from electronic prescribers and databases and from observational studies [7,14–18], baseline factors predictive of HbA1c <7.0% (<53 mmol/mol) identified in at least one study were lower HbA1c (noted in almost all studies), shorter duration of diabetes, being older, male sex, white race, no oral glucose-lowering drugs before starting insulin, a lower

Table 5 – Multivariable linear regression coefficients (SE)[a,b] of variables associated with the secondary outcome: HbA1c at year 4, after backwards selection of variables. The CREDIT study.

	Baseline predictors			Baseline predictors and explanatory variables		
	Beta (SE)	Beta/SE	P	Beta (SE)	Beta/SE	P
At starting insulin therapy						
HbA1c (%)	0.115 (0.018)	6.3	<0.0001	0.074 (0.018)	4.0	<0.0001
Age (y)	−0.105 (0.021)	−4.9	<0.0001	−0.076 (0.021)	−3.6	0.0003
BMI (kg/m^2)	0.062 (0.018)	3.4	0.0008	0.058 (0.019)	3.0	0.003
Duration of diabetes (y)	0.012 (0.004)	3.3	0.0009			
Glucose-lowering drugs			0.03			
One vs. none	0.002 (0.009)	0.3	0.8			
Two vs. none	0.023 (0.009)	2.4	0.02			
Three or more vs. none	0.024 (0.015)	1.6	0.1			
At 4 years or during follow-up						
Insulin dose (U/kg)				0.068 (0.006)	10.9	<0.0001
Glucose-lowering drugs						<0.0001
One vs. none				0.019 (0.008)	2.4	0.02
Two vs. none				0.037 (0.010)	3.6	0.0003
Three or more vs. none				0.075 (0.018)	4.3	<0.0001
Hypoglycaemia[c]				−0.031 (0.009)	−3.4	0.0007
Weight change (kg)				0.001 (0.000)	2.1	0.04

[a] Data shown are beta coefficients (standard errors) from linear regression models, after adjusting for region and centre.
[b] HbA1c and all continuous variables were $\log_e$ transformed excepting weight change.
[c] Hypoglycaemia is occurrence of an event in the last 6 months before the 4-year visit.

insulin dose, short-acting or premix insulin in comparison to other regimens, lower family income, presence of comorbidities (peripheral vascular disease, cancer, obesity, kidney disease; however, there was no association with other micro- or macrovascular diseases, or with hypertension), less hypoglycaemia before the start of insulin, and a lower BMI. At the end of the observation periods, a lower insulin dose, a better quality of life, no change in oral therapy, and less hypoglycaemia were associated with a greater reduction of HbA1c. The findings from these studies taken together are consistent with our longer-duration study.

A previous report from the CREDIT study compared insulin regimens using a propensity score of baseline characteristics to try to overcome the probable confounding factors in the allocation of specific insulin regimens [19]. Insulin regimens were compared in sub-populations matched by propensity scores. After 1 year of insulin therapy, and adjusting for baseline HbA1c and random recruitment-centre effects, the only differences between regimens were that people initially treated with short-acting insulin alone had a higher 1-year HbA1c than those treated with premix or basal insulin alone; note that short-acting insulin alone was used by only 8% of our study population. From the analyses shown here, after adjusting for other predictive factors, those treated with basal insulin had on average a higher HbA1c over years 1–4 than those treated with either basal plus short-acting or short-acting alone. In contrast, HbA1c at year 4 was strongly associated with the insulin regimen at year 4 in univariate analysis; in the multivariable analysis, insulin regimen was no longer associated, and any effect of the insulin regimen appears to be played by other more highly associated variables in the model, including the insulin dose. A likely explanation for this is the prospective evolution of insulin regimens, as ~30% of people begun on basal insulin added a mealtime insulin during the study, presumably to achieve improved control [9].

Our study has its limitations. While the participating physicians were chosen to represent those prescribing insulin in a given country [8], not all of the physicians invited actually participated in the study, and those participating are likely to be the physicians who are more motivated for treating and controlling glycaemia in people with type 2 diabetes and with better organised practice. For the insulin therapy, we have no information on whether insulin analogue or human insulin was used, nor details of the types of insulin used. As with all observational studies, we are limited by missing data from people who were not able to be followed up for the entire duration of the study. However, the differences in characteristics of the population studied and the initial population were minor.

With regard to the strengths of this study, it was prospective and longitudinal with findings over a 4-year follow-up–much longer than in many other reports. The results were generally consistent from year 1. The physicians were free to choose the insulin regimen and its dose when initiating insulin therapy; as there were no study recommendations on either, it is expected that physicians would have followed normal practice, both when starting insulin and with any changes during follow-up. This differs from the prospective observational studies discussed above, which were limited to specific insulin analogues, and of shorter duration [7,17,18]. Our data are those collected and recorded in routine practice, while the large number of participants and participating physicians provide a wide range of clinical practices from the developed world. Accordingly each of the study variables would have a wide range, thus enhancing the chance of showing variables with a statistically significant association (or not) with glycaemic control. However, the large sample size may also mean that small effects that are clinically insignificant, and perhaps clinically undetectable, may be statistically significant. This is the case for weight gain at the end of the study, where a 1 kg weight gain was associated with only a 0.003% unit (0.03 mmol/mol) increase in HbA1c that was statistically significantly in multivariable analysis.

The principal characteristics for glycaemic control after starting insulin therapy thus appear to be a lower starting HbA1c, a shorter duration of diabetes, a lower number of oral glucose-lowering drugs, and a lower insulin dose. Together, these variables seem to point to an advantage in beginning insulin earlier. Some studies have addressed this point directly, and while the advantages of very early use of insulin over oral agents can be disputed, these studies do not suggest much in the way of detriment either [20,21]. Using the CORE Diabetes Model, Goodall et al. [22] using data specific to the UK, suggested that starting insulin rather than continuing oral agents for a further 8 years would increase lifespan by 7.5 months on average, as well as improving quality of life. However, individualised and more patient-centred approaches have been emphasised in recent recommendations [3,20,23]. While older patients are usually considered more fragile, it would appear that they are able to achieve better glycaemic control than their younger counterparts, perhaps suggesting a cautious but optimistic approach to insulin provided other comorbidities are not present.

In conclusion, the glycaemic control of these people with type 2 diabetes starting on insulin therapy, improved markedly by the end of the first year, and this level was maintained over the three subsequent years. However, the major determinant of success was a low baseline HbA1c, supported by lower BMI, higher age, lower starting insulin dose, and a shorter duration of diabetes. At the 4-year follow-up the predictive characteristics were similar, but concurrent low insulin dose was highly predictive, as well as a lower number of oral glucose-lowering drugs. Given the impact of HbA1c at starting insulin therapy, and also the duration of diabetes, it would appear that the timing of starting insulin therapy may be crucial in the longer-term maintenance of good glycaemic control.

Conflict of interest

B.B. has served on advisory bureaus for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Novo Nordisk and Sanofi. F.C.G. is a consultant to Sanofi. N.F. has received research grants and served as consultant to Eli Lilly, Medtronic, Novo Nordisk, Pfizer, and Sanofi and has served on speaker bureaus for Novo Nordisk and Sanofi. M.V. and V.P. are employees of Sanofi. P.D.H, either personally or through institutions with which he is associated, receives funding for research, advisory, and educational activities from most insulin and other glucose-lowering medication manufacturers, including Sanofi, Novo Nordisk, and Eli Lilly.

Authors contribution

B.B., N.F., V.P. and P.D.H. contributed to study design, study conduct/data collection, data analysis, and writing. F.C.G. and M.V. contributed to data analysis and writing. 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. All authors have approved the final article. These results were presented orally at the IDF World Diabetes Congress, Melbourne, Australia, December 2013 and as a poster at the French Speaking Society for Diabetes, Paris, France, March 2014.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2015.02.034.

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