

ORIGINAL ARTICLE

Clinical correlates of hypoglycaemia over 4 years in people with type 2 diabetes starting insulin: An analysis from the CREDIT study

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Aim: To identify factors associated with documented symptomatic and severe hypoglycaemia over 4 years in people with type 2 diabetes starting insulin therapy.

Materials and methods: CREDIT, a prospective international observational study, collected data over 4 years on people starting any insulin in 314 centres; 2729 and 2271 people had hypoglycaemia data during the last 6 months of years 1 and 4, respectively. Multivariable logistic regression was used to select the characteristics associated with documented symptomatic hypoglycaemia, and the model was tested against severe hypoglycaemia.

Results: The proportions of participants reporting ≥ 1 non-severe event were 18.5% and 16.6% in years 1 and 4; the corresponding proportions of those achieving a glycated haemoglobin (HbA1c) concentration $< 7.0\%$ (< 53 mmol/mol) were 24.6% and 18.3%, and 16.5% and 16.2% of those who did not. For severe hypoglycaemia, the proportions were 3.0% and 4.6% of people reaching target vs 1.5% and 1.1% of those not reaching target. Multivariable analysis showed that, for documented symptomatic hypoglycaemia at both years 1 and 4, baseline lower body mass index and more physical activity were predictors, and lower HbA1c was an explanatory variable in the respective year. Models for documented symptomatic hypoglycaemia predicted severe hypoglycaemia. Insulin regimen was a univariate explanatory variable, and was not retained in the multivariable analysis.

Conclusions: Hypoglycaemia occurred at significant rates, but was stable over 4 years despite increased insulin doses. The association with insulin regimen and with oral agent use declined over that time. Associated predictors and explanatory variables for documented symptomatic hypoglycaemia conformed to clinical impressions and could be extended to severe hypoglycaemia. Better achieved HbA1c was associated with a higher risk of hypoglycaemia.

KEYWORDS

CREDIT, documented symptomatic hypoglycaemia, multivariable analysis, severe hypoglycaemia, type 2 diabetes mellitus

1 | INTRODUCTION

Good blood glucose control can prevent microvascular complications in people with type 2 diabetes, and there is some evidence that it may prevent or slow the progression of cardiovascular diseases.^{1–4} People with type 2 diabetes can often maintain adequate glycaemic control with

appropriate lifestyle and oral glucose-lowering drugs (OGLDs), but timely introduction of injection therapy is indicated when glycaemic control is no longer maintained.^{5–7} There is often reluctance, however, to start insulin therapy on the part of both the clinician and the individual with type 2 diabetes because of the need for injections, fear of hypoglycaemia and weight gain and increased complexity of therapy.^{8–10}

The Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy (CREDIT) study aimed to evaluate both the relationship between blood glucose control and cardiovascular events prospectively over 4 years in a large cohort of people starting insulin therapy, and to provide insight into routine clinical practice in the management of people with type 2 diabetes using insulin.^{11,12} In an earlier report, we described the evolution of insulin use, associated blood glucose-related outcomes and effects on body weight and hypoglycaemia over the 4 years of the study.¹³

In the present study, we aimed to: (1) evaluate the characteristics, both at 1 year and 4 years, that were associated with documented symptomatic hypoglycaemia; (2) understand the nature of those relationships in routine care, particularly for glucose control; (3) discover if those characteristics would apply to severe hypoglycaemia; and (4) understand how the evolution of insulin regimen (and oral agents) and insulin dose affected hypoglycaemia rates. Previously, we have reported the characteristics of people in the CREDIT study that are associated with weight gain,¹⁴ and those associated with good glycaemic control,¹⁵ and described the relationship between blood glucose control and cardiovascular events.¹⁶

2 | MATERIALS AND METHODS

The CREDIT study design, participant selection criteria and participant characteristics have been reported previously.^{11,12} In brief, the study involved 314 centres in 12 countries, 10 in Europe, plus Canada and Japan. Men and women with type 2 diabetes, aged >40 years, who had started any insulin therapy within 12 months and who had a glycated haemoglobin (HbA1c) measurement ≤ 3 months before beginning insulin were eligible for inclusion. As a non-interventional 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. Ongoing data were gathered prospectively in routine clinical practice, and the treating physicians were asked to report, according to protocol, updated data every 6 months. The results presented here as the 1- and 4-year follow-up data are those provided during the 9 to 18-month and 42 to 54-month windows after starting insulin.

Hypoglycaemia data for the 6 months prior to the annual follow-up date were collected from patient records and patient recall on structured report forms. Documented symptomatic hypoglycaemia was any non-severe event with clinical symptoms resulting in hypoglycaemia confirmed by self-monitored plasma glucose concentration ≤ 3.9 mmol/L.¹⁷ Severe hypoglycaemia was any event requiring the assistance of another person and confirmed by self-monitored plasma glucose < 2.0 mmol/L or prompt recovery after oral carbohydrate, intravenous glucose or intramuscular glucagon.¹⁷ Updated mean HbA1c was the average of HbA1c measurements from 1 month after beginning insulin up to follow-up year values.

Local ethics approval was obtained for all sites, and standards of study conduct were according to the Declaration of Helsinki. Written informed consent was obtained from all participants in advance.

A statistical analysis plan was developed prior to data analysis. The principal outcome measure was the occurrence of documented

symptomatic hypoglycaemia in any participant over the 6 months before the year 1 and year 4 follow-up visits. Variables prespecified at the start of insulin therapy, as candidate predictors of documented symptomatic hypoglycaemia, were: age; gender; weight; body mass index (BMI); waist circumference; systolic blood pressure (SBP); diastolic blood pressure (DBP); diabetes duration; family history of type 2 diabetes in first-degree relatives; previous diagnosis of high blood pressure; physical activity (yes/no); micro- and macrovascular disease; family history of premature cardiovascular disease; estimated glomerular filtration rate (Cockcroft–Gault formula); urinary albumin; urinary albumin/creatinine ratio; HbA1c; fasting plasma glucose; postprandial plasma glucose; starting insulin regimen (basal insulin alone, basal plus short-acting insulin, short-acting insulin, premixed insulin, other); insulin dose; and OGLDs (none, including a sulphonylurea or no sulphonylurea). Physical activity (yes) was defined as ≥ 4 hours a week. Additional variables were: height; heart rate; lifestyle (alone/not alone); serum LDL cholesterol; HDL cholesterol; triglycerides; serum creatinine; smoking (current and stopped < 1 year/never or stopped ≥ 1 year); who advised insulin (primary care/secondary care); and whether insulin started as inpatient or not.

The following variables at years 1 or 4 were seen as potential explanatory factors: body weight; BMI; SBP; DBP; creatinine clearance; albuminuria; HbA1c; change from baseline HbA1c; fasting plasma glucose; change from baseline fasting plasma glucose; postprandial plasma glucose; change from baseline postprandial plasma glucose; insulin regimen (as above); insulin dose; and OGLD use (as above). For year 4 analyses, new microvascular disease, new macrovascular disease or both during follow-up were included, as defined previously.¹¹

2.1 | Statistical methods

Analyses were performed using SAS statistical suite version 9.2 or higher (SAS Institute, Cary, NC, USA). Descriptive statistics (hypoglycaemia incidence [proportion of population affected] and event rate) were obtained according to insulin regimen and HbA1c target achievement ($< 7.0\%$ [< 53 mmol/mol]; $\geq 7.0\%$ [≥ 53 mmol/mol]) and overall. The functional form of the continuous predictive variables was determined in logistic regression models adjusted for region (Eastern Europe: Croatia, Ukraine, Russia; Southern Europe: Italy, Portugal, Spain; France; Northern Europe: United Kingdom, Finland, Germany; Japan; Canada), by comparing the Akaike Information Criterion for models with the predictive variables in linear, \log_e and restricted cubic spline forms. The preferred model was selected from a model that only included region, with a criterion for improvement ≥ 3.84 for each step.¹⁴ No variables required transformation, except at year 4 when baseline DBP and current HbA1c and change from baseline HbA1c fitted best to restricted cubic splines.

Single variable analyses used logistic regression models, adjusted for region. For multivariable analyses, variables with $\leq 20\%$ of missing data were included in a logistic regression model with region forced into the model. Variables were selected stepwise with a significance level for entry of 20% and for removal of 5%. For restricted cubic spline variables, the whole of the restricted cubic spline together was considered, rather than considering individual terms separately, and

target values were used for the reference level. Model 1 included variables when beginning insulin, and model 2 included baseline variables retained in model 1 together with the year 1 (or year 4) explanatory variables. Model 3 included all baseline and year 1 (or year 4) explanatory variables.

To identify whether the smaller incidence of severe hypoglycaemia is consistent with the findings for documented symptomatic hypoglycaemia, a risk-factor score for year 1 (and year 4) was produced using all variables retained in the final model 1 (baseline variables) for documented symptomatic hypoglycaemia at year 1 or 4 (including region). The model prediction (fitted value) was used as a single explanatory variable for the severe hypoglycaemia model 1 at years 1 and 4, respectively. Similarly, severe hypoglycaemia models 2 and 3 used all retained variables in the documented symptomatic hypoglycaemia models 2 and 3. However, the last analysis was performed only if models 2 and 3 on documented symptomatic hypoglycaemia differed. Supportive analyses were performed for all models using region and all main variables (see above) when starting insulin for the risk factor score in model 1, all variables retained in the final model 1 plus all other explanatory variables at year 1 or 4 in model 2, and all main variables at baseline and all other explanatory variables at year 1 or 4 in model 3.

3 | RESULTS

3.1 | Glucose control and insulin regimens

Detailed core study results of glucose control and changes in insulin regimen are given elsewhere.¹³ Basal insulin and mealtime insulin usage declined over the 4 years, use of basal plus mealtime insulin increased and premixed insulin usage remained relatively constant.¹³

The mean (SD) total daily doses of insulin at years 1 and 4 were 0.43 (0.25) and 0.54 (0.31) U/kg, and the mean (SD) HbA1c concentrations were 7.7 (1.4)% (61 [15] mmol/mol) and 7.6 (1.3)% (60 [14] mmol/mol), respectively. Fasting plasma glucose concentrations were 8.0 (2.5) mmol/L at year 1 and 7.7 (2.4) mmol/L at year 4, and postprandial plasma glucose concentrations were 9.7 (3.2) and 9.4 (3.2) mmol/L, respectively. Dose and HbA1c data for individual insulin regimens are given in the Supporting Information, Table S1.

3.2 | Hypoglycaemia incidence and event rates

A total of 2729 and 2271 people had data on hypoglycaemia during the last 6 months of years 1 and 4 of follow-up, respectively. The proportions of participants (incidence) with documented symptomatic hypoglycaemia in the 6 months before the year 1 and 4 follow-up visits, respectively, were: 15.0% and 14.9% for those on basal insulin; 21.4% and 18.6% for those on basal plus mealtime insulin; 19.3% and 14.8% for those on mealtime insulin; 21.3% and 19.1% on premixed insulin; 22.4% and 15.8% on other insulin; and 8.9% and 2.5% for those who reported no insulin use.

For all insulin regimens together, the proportions of people reporting at least one documented symptomatic hypoglycaemia event were 18.5% and 16.6% for the year 1 and year 4 follow-up, and

24.6% and 18.3%, respectively, for those achieving updated mean HbA1c <7.0% (<53 mmol/mol) and 16.5% and 16.2% for those who did not. The proportions of people who reported one or more severe hypoglycaemic events for these half-yearly follow-up periods were 1.9% and 2.0% overall, 3.0% and 4.6% for those who achieved the HbA1c target, and 1.5% and 1.1% for those who did not.

Within different classifications of hypoglycaemia (documented symptomatic hypoglycaemia or severe hypoglycaemia, nocturnal or anytime), event rates were similar across years 1 to 4, and by insulin regimen (Table 1). The mean (range) rate for documented symptomatic hypoglycaemia was ~0.99 (0.85-1.05) events/person in the 6-month period, and for nocturnal documented symptomatic hypoglycaemia it was ~0.15 (0.13-0.21) events/person in the 6-month period (Table 1). The event rate for severe hypoglycaemia was less certain, with a range of 0.03 to 0.08 events/person in the 6-month period anytime, and 0.01 to 0.02 events/person in the 6-month period at night (Table 1). The rate of documented symptomatic hypoglycaemia was greater for those who achieved updated mean HbA1c <7.0% (<53 mmol/mol) than for those who did not (1.18-1.40 vs 0.75-0.96 events/person in the 6-month period), the same being true for nocturnal documented symptomatic hypoglycaemia (0.14-0.24 vs 0.12-0.20 events/person in the 6-month period). For severe hypoglycaemia there were 0.04 to 0.20 vs 0.02 to 0.04 events/person in the 6-month period for people with updated mean HbA1c <7.0% vs HbA1c ≥7.0%, while for severe hypoglycaemia at night there were 0.02 to 0.06 vs 0.00 to 0.01 events/person in the 6-month period. Severe hypoglycaemia was rare in those people who did not have a documented symptomatic hypoglycaemic event in the same period, with 3/2225 people experiencing this at 1 year and 3/1895 at 4 years.

3.3 | Predictors and explanatory factors for hypoglycaemia

Univariate analysis identified 9 variables when starting insulin and 9 variables at year 1 that were associated with documented symptomatic hypoglycaemia at year 1 (Table 2). The number of variables associated with documented symptomatic hypoglycaemia at year 4 was 8 when starting insulin and 5 at year 4 (Table 3). Baseline variables that were found in common in years 1 and 4 were body weight, BMI and physical activity. Variables in common at both visit years were change in body weight, mean HbA1c (from 6 months before to 1 month after nominal visit date), change in HbA1c and insulin regimen.

Multivariable analysis for documented symptomatic hypoglycaemia at year 1 identified the following predictor baseline variables: lower BMI; physical activity (yes); and no prior OGLDs vs sulphonylurea use (Figure 1). Model-selected explanatory variables measured at year 1 were lower HbA1c, higher total insulin dose and sulphonylurea use vs no OGLDs.

For documented symptomatic hypoglycaemia at year 4, the baseline predictor variables retained were physical activity (yes), prior macrovascular disease, lower BMI, lower HbA1c and high DBP (Figure 1). The odds ratio (OR; reference 1.00 for DBP 85 mm Hg) was increased at higher DBP (Figure 1). Additional retained variables

TABLE 1 Number and proportion of participants with hypoglycaemia and event rate (events/person in the 6-month period) over 4 years, by type of hypoglycaemia and the insulin regimen used in each year

Insulin regimen	Year 1	Year 2	Year 3	Year 4
Documented symptomatic hypoglycaemia – any time				
Basal				
n (%)	170 (15.0)	148 (15.5)	108 (13.3)	100 (14.9)
Event rate	0.82 (4.08)	0.96 (4.31)	0.81 (3.04)	1.22 (4.67)
Basal + mealtime				
n (%)	122 (21.4)	141 (21.2)	133 (18.5)	138 (18.6)
Event rate	1.38 (6.43)	1.16 (5.85)	1.00 (3.60)	1.03 (3.62)
Mealtime				
n (%)	17 (19.3)	13 (20.0)	10 (16.9)	8 (14.8)
Event rate	0.61 (1.67)	1.12 (4.09)	0.39 (0.93)	0.94 (4.25)
Premixed				
n (%)	156 (21.3)	138 (20.4)	113 (18.7)	109 (19.1)
Event rate	1.13 (4.05)	1.09 (4.53)	0.92 (3.33)	1.02 (3.57)
All ^a				
n (%)	504 (18.5)	471 (18.3)	390 (16.1)	376 (16.6)
Event rate	1.05 (4.62)	1.03 (4.76)	0.85 (3.17)	1.03 (3.88)
Documented symptomatic nocturnal hypoglycaemia				
Basal				
n (%)	66 (5.9)	52 (5.5)	49 (6.0)	47 (7.0)
Event rate	0.14 (0.94)	0.11 (0.62)	0.14 (0.71)	0.23 (1.15)
Basal + mealtime				
n (%)	34 (6.0)	47 (7.1)	39 (5.4)	58 (7.9)
Event rate	0.14 (0.73)	0.21 (1.34)	0.14 (0.78)	0.25 (1.27)
Mealtime				
n (%)	0	4 (6.2)	1 (1.7)	1 (1.9)
Event rate	0.00 (0.00)	0.31 (1.52)	0.02 (0.13)	0.28 (2.06)
Premixed				
n (%)	36 (4.9)	29 (4.3)	34 (5.6)	29 (5.1)
Event rate	0.15 (1.05)	0.10 (0.62)	0.17 (1.03)	0.18 (1.11)
All ^a				
n (%)	146 (5.4)	136 (5.3)	125 (5.2)	144 (6.4)
Event rate	0.14 (0.94)	0.13 (0.88)	0.13 (0.79)	0.21 (1.17)
Severe hypoglycaemia				
Basal				
n (%)	23 (2.0)	25 (2.6)	27 (3.3)	22 (3.3)
Event rate	0.03 (0.22)	0.05 (0.40)	0.08 (0.59)	0.15 (1.02)
Basal + mealtime				
n (%)	16 (2.8)	14 (2.1)	17 (2.4)	19 (2.6)
Event rate	0.07 (0.69)	0.04 (0.29)	0.07 (0.64)	0.09 (0.91)
Mealtime				
n (%)	0 (0.0)	1 (1.5)	1 (1.7)	3 (5.6)

(Continues)

TABLE 1 (Continued)

Insulin regimen	Year 1	Year 2	Year 3	Year 4
Event rate	0.00 (0.00)	0.02 (0.12)	0.03 (0.26)	0.22 (1.37)
Premixed				
n (%)	10 (1.4)	3 (0.4)	4 (0.7)	2 (0.3)
Event rate	0.03 (0.35)	0.00 (0.07)	0.01 (0.23)	0.00 (0.06)
All ^a				
n (%)	51 (1.9)	44 (1.7)	49 (2.0)	46 (2.0)
Event rate	0.04 (0.42)	0.03 (0.33)	0.05 (0.50)	0.08 (0.79)
Severe nocturnal hypoglycaemia				
Basal				
n (%)	11 (1.0)	9 (0.9)	11 (1.3)	15 (2.2)
Event rate	0.01 (0.12)	0.01 (0.19)	0.01 (0.13)	0.03 (0.27)
Basal + mealtime				
n (%)	7 (1.2)	9 (1.3)	8 (1.1)	9 (1.2)
Event rate	0.04 (0.64)	0.01 (0.12)	0.02 (0.22)	0.02 (0.21)
Mealtime				
n (%)	0	1 (1.5)	0	2 (3.7)
Event rate	0.00 (0.00)	0.02 (0.12)	0.00 (0.00)	0.17 (1.09)
Premixed				
n (%)	1 (0.1)	0	1 (0.2)	0
Event rate	0.00 (0.04)	0.00 (0.00)	0.00 (0.04)	0.00 (0.00)
All ^a				
n (%)	20 (0.7)	19 (0.7)	20 (0.8)	26 (1.1)
Event rate	0.01 (0.31)	0.01 (0.13)	0.01 (0.14)	0.02 (0.25)

Event rates are mean (SD). All values are for the last 6 months of the year.

^a Includes regimens included in the Table, plus other and no insulin.

from measurements at 4 years were higher total insulin dose (model 2 but not model 3, OR 1.05 [1.01; 1.10] per 0.1 U/kg/d), higher SBP, and updated HbA1c (Figure 1). The OR (reference 1.00 for HbA1c 7.0%) increased for lower HbA1c at 4 years, and substantially decreased for higher levels (Figure 1).

3.4 | Application of models to severe hypoglycaemia

The concordance (C)-statistics for severe hypoglycaemia derived from each documented symptomatic hypoglycaemia model were 0.66 for model 1 and 0.73 for model 2 at year 1 and were higher in the supportive analyses for all 3 models (0.73–0.75). This moderate predictive power was echoed at year 4, C-statistics being 0.67 in model 1, 0.76 in model 2 and 0.68 to 0.79 in the supportive analyses. The models were all highly statistically significant ($P < .0001$).

4 | DISCUSSION

This analysis of hypoglycaemia and its associations contributes data of clinical interest in 4 main areas, all derived from a large

TABLE 2 Univariate analysis^a of documented symptomatic hypoglycaemia at year 1

	With hypoglycaemia (n = 504)	Without hypoglycaemia (n = 2225)	OR ^a (95% CI)	P
Baseline variables, n (%)				
Weight, kg; per 5 kg	76.3 (18.3)	80.4 (18.9)	0.94 (0.91, 0.97)	.0002
BMI, kg/m ²	28.0 (6.1)	29.6 (6.3)	0.95 (0.94, 0.97)	<.0001
Starting total insulin dose, U/kg/d; per 0.1 U/kg/d	0.28 (0.18)	0.25 (0.17)	1.10 (1.04, 1.16)	.0009
Family history of type 2 diabetes, n (%)				
Yes (n = 1396)	277 (19.9)	1119 (80.2)	1.27 (1.04, 1.55)	.0183
No (n = 1307)	221 (16.9)	1086 (83.1)	Reference	
Prior high blood pressure, n (%)				
Yes (n = 1882)	325 (17.3)	1557 (82.7)	0.80 (0.64, 0.98)	.0345
No (n = 845)	179 (21.2)	666 (78.8)	Reference	
Physical activity, n (%)				
No (n = 1422)	221 (15.5)	1201 (84.5)	0.67 (0.55, 0.82)	.0001
Yes (n = 1296)	282 (21.8)	1014 (78.2)	Reference	
Baseline insulin regimen, n (%)				
Basal (n = 1400)	219 (15.6)	1181 (84.4)	Reference	.0024
Basal + mealtime (n = 391)	82 (21.0)	309 (79.0)	1.47 (1.09, 1.99)	
Mealtime (n = 211)	41 (19.4)	170 (80.6)	1.36 (0.90, 2.06)	
Premixed (n = 633)	140 (22.1)	493 (77.9)	1.58 (1.22, 2.04)	
Other (n = 94)	22 (23.4)	72 (76.6)	1.95 (1.15, 3.29)	
Oral agents, n (%)				
None (n = 829)	195 (23.5)	634 (76.5)	Reference	<.0001
No sulphonylurea (n = 695)	111 (16.0)	584 (84.0)	0.64 (0.49, 0.84)	
Sulphonylurea (n = 1205)	198 (16.4)	1007 (83.6)	0.60 (0.48, 0.76)	
Physician starting insulin, n (%)				
Non-primary care (n = 2394)	465 (19.4)	1929 (80.6)	1.63 (1.14, 2.34)	.0076
Primary care (n = 335)	39 (11.6)	296 (88.4)	Reference	
Variables at 1 year, mean (SD)				
Weight, kg; per 5 kg	79.1 (18.4)	82.3 (19.0)	0.96 (0.93, 0.99)	.0102
BMI, kg/m ²	28.9 (6.0)	30.3 (6.3)	0.96 (0.94, 0.98)	.0001
HbA1c, %-units	7.3 (1.2)	7.8 (1.4)	0.76 (0.70, 0.82)	<.0001
HbA1c change, %-units	-2.1 (2.2)	-1.8 (2.0)	0.93 (0.89-0.98)	.0041
Fasting plasma glucose, mmol/L	7.5 (2.2)	8.1 (2.6)	0.92 (0.87, 0.96)	.0003
Total insulin dose, U/kg/d; per 0.1 U/kg/d	0.44 (0.24)	0.42 (0.25)	1.05 (1.01, 1.09)	.0249
Insulin regimen, n (%)				
Basal (n = 1130)	170 (15.0)	960 (85.0)	Reference	.0013
Basal + mealtime (n = 569)	122 (21.4)	447 (78.6)	1.57 (1.21, 2.05)	
Mealtime (n = 88)	17 (19.3)	71 (80.7)	1.40 (0.78, 2.52)	
Premixed (n = 734)	156 (21.3)	578 (78.7)	1.52 (1.17, 1.98)	
Other (n = 152)	34 (22.4)	118 (77.6)	1.78 (1.15, 2.76)	
None (n = 56)	5 (8.9)	51 (91.1)	0.57 (0.22, 1.47)	
Oral agents (vs none), n (%)				
None (n = 986)	213 (21.6)	773 (78.4)	Reference	.0003
No sulphonylurea (n = 909)	128 (14.1)	781 (85.9)	0.60 (0.47, 0.77)	
Sulphonylurea (n = 834)	163 (19.5)	671 (80.5)	0.84 (0.66, 1.07)	
DBP, mm Hg, mean (SD)	77.8 (9.9)	79.3 (10.3)	0.85 (0.77, 0.95)	.0030

Abbreviations: BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; OR, odds ratio; SD, standard deviation. Mean (SD) or n (%).

^a Controlled for geographical region.

multinational non-interventional cohort followed for 4 years after starting insulin and collected pragmatically from usual clinical care. We describe the incidence of hypoglycaemia, predictors and in-study

explanatory factors for such events, their relationship to the trajectory of HbA1c and relationship with insulin regimen. We have previously described the evolution of individually chosen insulin regimens

and their relation to glucose control,¹³ together with analyses of predictors of weight change, glucose control and a description of the relationship of the latter to cardiovascular events.^{14–16}

The pragmatic, real-life study design may have a limitation with regard to data acquisition, as hypoglycaemia is poorly identified and recorded in usual clinical practice; however, this may mean that our analysis is focused on events more important to people with diabetes, and thus not forgotten. Accordingly we limited data collection to the 6 months before the annual clinical visits, a period similar to the 26 weeks often used in phase III clinical studies. In this context, 6-month incidence (proportion of people affected) was not high at ~16% to 19%, and with no evidence of deterioration of rate over 4 years (numerically a decrease), in contrast to what might have been expected with the move to more complex insulin regimens and with increased duration of diabetes.¹³ An explanation for this may be that individuals were actively managed to avoid hypoglycaemia; certainly, there was considerable change in individual insulin regimen.¹³ The incidence results are consistent with reviews of studies on starting insulin (17% over 6 months¹⁸) and the ORIGIN study (28% over 6 years¹⁹), but both those studies used lower glucose thresholds and would thus be expected to give somewhat lower rates. Our findings are higher than in those of some registry studies which may identify only more severe episodes,^{20,21} and much lower than the extraordinarily high rates in another study where daily recording might have led to a positive ascertainment bias.²² Severe hypoglycaemia was ~2% overall in 6 months, again did not deteriorate in incidence over 4 years, and again matches or contrasts with results from the studies just referenced.

Event rates for documented symptomatic hypoglycaemia were ~1.0 per 6 months (Table 1), implying an average > 5 events for each person having at least one episode. A similar issue pertains to severe hypoglycaemia where the average was ~2 per person experiencing at least one event, but here the event rate showed signs of rising from years 2 to 4, being ~4 events per person at 4 years, despite the unchanged incidence. Nocturnal hypoglycaemia at ~5% to 6% was ~30% of the incidence of anytime hypoglycaemia, but event rates were just one-sixth of the incidence of anytime hypoglycaemia. Interestingly, nocturnal severe hypoglycaemia was proportionately lower in incidence compared with anytime severe hypoglycaemia than was nocturnal documented symptomatic hypoglycaemia compared with anytime documented symptomatic hypoglycaemia, being ~15%, although the latter was subject to considerable uncertainties because of small numbers.

Baseline predictors of documented symptomatic hypoglycaemia were not unexpected, either in light of previous studies or clinical practice. These then included lower body weight/BMI, being more physically active and presence of micro- and/or macrovascular disease. However, renal function did not appear important, probably because of the modest levels of renal impairment found in our study population. Blood pressure (prior and SBP or DBP) was notably prominent and remained in the multivariate analyses, with the OR for SBP equivalent to a > 20% increase per 10 mm at 4 years. These may be acting as surrogates for macrovascular disease. The latter is an association reported for severe hypoglycaemia in many studies,^{23,24} and is supported by the non-linear relationship of OR, which only rises significantly at DBP >95 mm Hg on multivariable analysis. Use of renin-angiotensin system blockers may also be a factor.

Therapy-based predictors and explanatory factors (oral agents and insulin regimen type) were mainly present in the year 1 univariate analysis. Insulin regimen type at 4 years was a univariate explanatory factor for documented symptomatic hypoglycaemia, but the OR confidence intervals for the major contrasts (premixed vs basal, multiple injection vs basal) did not exclude 1.00. The explanation is again likely to be appropriate glucose control management, partly neutralizing the effects of insulin regimens (or combinations with oral agents) and/or insulin dosage giving hypoglycaemic problems. Any associations with oral agents, either at baseline or year 1, also disappeared by year 4, even though baseline use of sulphonylurea when compared with no baseline therapy was carried through on multivariable analyses and showed lower OR compared with no therapy. At first this might seem paradoxical because use of sulphonylureas with insulin has been associated with excess hypoglycaemia in 2 studies,^{18,19} and indeed documented symptomatic hypoglycaemia with oral agent use without sulphonylureas affected a numerically higher proportion of people. The explanation may be in the comparator data for no oral agent where the risk of hypoglycaemia was marginally higher than in the sulphonylurea group. It is possible that these people required more aggressive insulin dosing early on (in year 1) to achieve required glucose control, while judicious use of sulphonylureas provided some enhancement of islet β -cell function which, in turn, damped any erratic insulin action arising from varying absorption from the subcutaneous tissue depot.

The relationship of hypoglycaemia to achieved glucose control is controversial, notably after the identification in the ACCORD intensive arm of higher severe hypoglycaemia rates in those at higher HbA1c levels.²⁵ Many studies did not find any relationship,^{20,26} although the ORIGIN study (for documented symptomatic hypoglycaemia)¹⁹ and the review by Karl et al¹⁸ found more hypoglycaemia at lower attained HbA1c. There was also no relationship with current HbA1c in the standard control group in ACCORD, with a similar HbA1c to our own findings.²⁵ In the present study, we found lower attained HbA1c and higher change from baseline in HbA1c to be significant univariate associations with documented symptomatic hypoglycaemia. At year 1 this effect was retained on multivariate analysis, with odds of 25% per %-unit of HbA1c. At year 4, updated current HbA1c was also retained as a risk factor, with the OR having a non-linear relationship to HbA1c, but such that at around an HbA1c of 7.5% (58 mmol/mol) the OR was falling ~10% to 20% per %-unit. These findings and the literature can probably be reconciled. When titration is forced as in the ACCORD study, it seems vulnerable people with other medical conditions become stuck at higher levels of HbA1c with excess rates of hypoglycaemia. In more normal care, hypoglycaemia may determine attained HbA1c level ("treat-to-hypoglycaemia"), and in these circumstances hypoglycaemia rates may eventually become the same at all levels of HbA1c. The study population in CREDIT, however, appears to have been more actively managed, judged by the extensive changes to insulin regimens and increasing insulin doses,¹³ and then people managed more closely to normal levels will be at higher risk of hypoglycaemia. This may affect in particular regimens containing mealtime insulin, with selective moves away from basal + mealtime and premixed regimens accounting for the reduction in

TABLE 3 Univariate analysis^a of documented symptomatic hypoglycaemia at year 4

	With hypoglycaemia (N = 376)	Without hypoglycaemia (N = 1895)	OR ^a (95% CI)	P
Baseline variables				
Mean (SD) weight, kg; per 5 kg	77.3 (17.7)	79.8 (18.8)	0.94 (0.91, 0.98)	.0025
Mean (SD) BMI, kg/m ²	28.4 (5.8)	29.5 (6.2)	0.96 (0.94, 0.98)	.0003
Physical activity, n (%)				
No (n = 1144)	157 (13.7)	987 (86.3)	0.69 (0.55, 0.87)	.0019
Yes (n = 1118)	218 (19.5)	900 (80.5)	Reference	
Mean (SD) SBP, mm Hg; per 10 mm Hg	142.0 (20.8)	138.8 (18.8)	1.08 (1.02, 1.15)	.0079
Mean (SD) DBP, mm Hg	82.7 (12.8)	81.0 (11.3)	Non-linear	.0004
Mean (SD) HbA1c, %-units	9.3 (1.9)	9.6 (1.9)	0.90 (0.85, 0.96)	.0023
Microvascular disease, n (%)				
Yes (n = 1607)	292 (18.2)	1315 (81.8)	1.37 (1.04, 1.81)	.0234
No (n = 664)	84 (12.7)	580 (87.3)	Reference	
Macrovascular disease, n (%)				
Yes (n = 792)	160 (20.2)	632 (79.8)	1.43 (1.14, 1.80)	.0023
No (n = 1479)	216 (14.6)	1263 (85.4)	Reference	
Variables at 4 years				
Mean (SD) weight change, kg; per 5 kg	3.8 (7.6)	2.4 (7.5)	1.14 (1.05, 1.23)	.0010
Mean (SD) HbA1c, %-units	7.3 (1.0)	7.6 (1.3)	Non-linear	.0031
Mean (SD) HbA1c change, %-units	-2.0 (2.0)	-2.0 (2.2)	Non-linear	.0100
Insulin regimen, n (%)				
Basal (n = 671)	100 (14.9)	571 (85.1)	Reference	.0034
Basal + mealtime (n = 741)	138 (18.6)	603 (81.4)	1.31 (0.98, 1.75)	
Mealtime (n = 54)	8 (14.8)	46 (85.2)	1.07 (0.48, 2.38)	
Premixed (n = 571)	109 (19.1)	462 (80.9)	1.37 (1.00, 1.86)	
Other (n = 114)	18 (15.8)	96 (84.2)	1.10 (0.63, 1.94)	
None (n = 120)	3 (2.5)	117 (97.5)	0.15 (0.05, 0.49)	
Mean (SD) SBP, mm Hg; per 10 mm Hg	139.3 (17.1)	135.1 (16.2)	1.19 (1.11, 1.27)	<.0001

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; OR, odds ratio; SBP, systolic blood pressure.

^a Controlled for geographical region.

odds ratios compared with basal between years 1 and 4, indeed becoming non-statistically significant.

Lastly, dose on starting insulin was still a significant factor at year 1, as was actual insulin dose at the time, and the latter was retained as an independent factor on multivariable analyses, when the ORs suggest an increase of ~10% in risk per 0.1 U/kg/d dose difference. This decreased to ~5% at 4 years in model 2 and was not retained in model 3, and would again appear to suggest the issue was mitigated over time with appropriate clinical management.

For severe hypoglycaemia, we recognized that our data would be too sparse in people with type 2 diabetes to perform the same associative analyses, with inevitable overfitting and model optimism. We therefore examined whether the models developed from the whole dataset would perform adequately when populated with the severe hypoglycaemia data alone. This proved true of all the models developed from both the 1-year and 4-year data, with C-statistics (0.66–0.79) suggestive of moderate to good prediction. Two corollaries would appear to be that the models developed for documented symptomatic hypoglycaemia are themselves important, being verified

with a different set of data, and that occurrence of documented symptomatic hypoglycaemia is itself a useful predictor of severe hypoglycaemia. This would suggest that therapy approaches shown to reduce documented symptomatic hypoglycaemia should reduce severe hypoglycaemia, consistent with the DEVOTE study findings.²⁷

As noted above, the present study has limitations related to ascertainment, although with the incidence data matching other studies^{18,19} the problem is much smaller than found in database studies. Non-database studies do, however, inevitably involve some patient selection, consequent on-site selection. As we note above this population appears to be relatively actively managed, although not as intensively as treat-to-target or intensive therapy studies, and the findings may not be generalizable to situations where insulin therapy is less optimally managed. Furthermore, the motivators of clinical decision-making for each individual were not recorded (or indeed easy to record), so how hypoglycaemia rates were stopped from rising with increasing duration of diabetes and higher insulin doses over 4 years is unclear. Methodologically, we did define candidate variables for correlation (univariate) analysis in order to reduce risks from

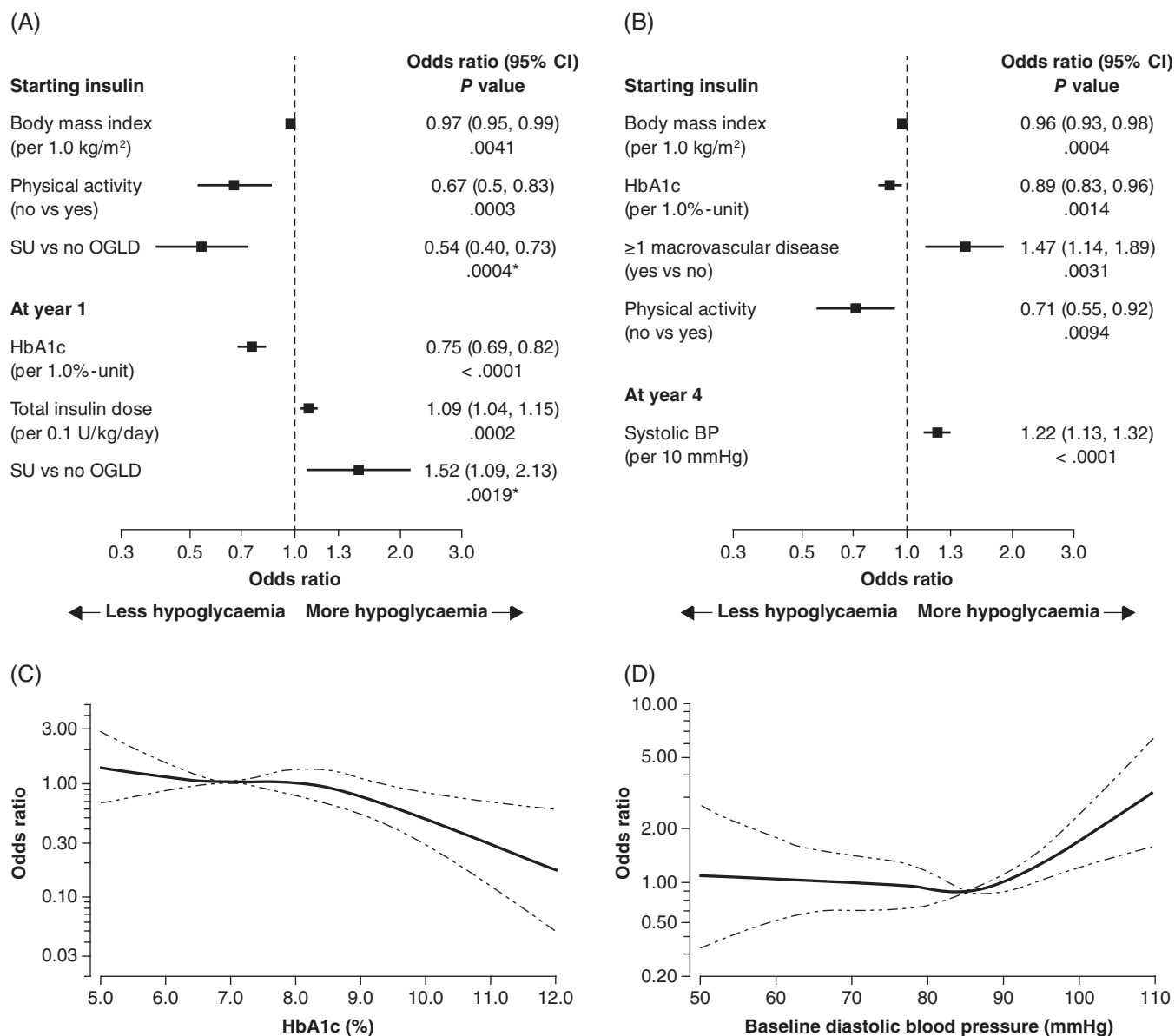


FIGURE 1 Variables retained on multivariable analysis: linear variables that influence documented symptomatic hypoglycaemia at (A) year 1 and (B) year 4, and non-linear variables that influence documented symptomatic hypoglycaemia at year 4 – cubic spline results for (C) glycated haemoglobin (HbA1c) and (D) baseline diastolic blood pressure – in people with type 2 diabetes. *P value is for oral glucose-lowering drugs (OGLDs) in 3 classes: no sulphonylurea (SU), SU, no OGLD. P values for C and D were $P = .0208$ and $.0032$, respectively. BP, blood pressure; CI, confidence interval

over-fitting, and although these included all those variables known from the literature (and others), it remains possible some factor of significance was missing. Furthermore some variables of potential interest, such as non-cardiovascular morbidities and social functioning,^{24,28} were not included nor collected for our analysis.

In conclusion, documented and severe hypoglycaemia occurred at significant but not high rates in people with type 2 diabetes who started on insulin therapy. Rates did not change over 4 years despite increased insulin dosage and duration of diabetes, and indeed the association with insulin regimen or with oral agent use declined from year 1 to year 4, perhaps suggesting the problem was addressed by active clinical management. Predictor and explanatory variables associated with hypoglycaemia were largely as expected from clinical practice and prior publications, and models identified for documented symptomatic hypoglycaemia worked well when applied to severe hypoglycaemia. However, achieved HbA1c was still quite strongly

associated with more hypoglycaemia, and this relationship did not wane with time.

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Conflict of interest

P.D.H., or institutions with which he is associated, has received funding from Antriabio, AstraZeneca, Biocron, Eli Lilly, Hanmi, Janssen, GlaxoSmithKline, Merck (MSD), Novo Nordisk, Roche Diagnostics and

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Author contributions

The idea for the current analysis came from the CREDIT Steering Committee and the current authors, and the statistical analysis was devised by them. The analyses were performed by F.C.G. at ATLANSTAT (funded by Sanofi) and N.F. All authors took part in development of the manuscript (unfunded except as above) and take responsibility for its contents.

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SUPPORTING INFORMATION

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