Diabetes, Obesity and Metabolism 18: 152–158, 2016.

ORIGINAL ARTICLE

Relationship of glycaemic control and hypoglycaemic episodes to 4-year cardiovascular outcomes in people with type 2 diabetes starting insulin

N. Freemantle[1], N. Danchin[2], F. Calvi-Gries[3], M. Vincent[4] & P. D. Home[5]

[1] *Department of Primary Care and Population Health, University College London, London, UK*
[2] *Department of Medicine, University of Paris René Descartes, Paris, France*
[3] *AtlanStat, Rezé, France*
[4] *Sanofi, Paris, France*
[5] *Institute of Cellular Medicine-Diabetes, Newcastle University, Newcastle upon Tyne, UK*

Aims: To examine the relationships between glycated haemoglobin (HbA1c) and cardiovascular (CV) events in people beginning insulin in routine clinical practice in Europe, North America and Asia in a non-interventional study, the Cardiovascular Risk Evaluation in people with Type 2 Diabetes on Insulin Therapy (CREDIT) study.

Methods: Data on 2999 people were collected prospectively over 4 years from physician reports. The primary outcome was the composite of stroke or myocardial infarction (MI) or CV-specific death. Events were blindly adjudicated. The relative hazards of CV events were described from Cox proportional hazards models incorporating patient risk factors, with updated average HbA1c as a time-dependent covariate. The relationship of severe and symptomatic hypoglycaemia (collected during the 6 months before yearly ascertainment) with CV and all-cause mortality was examined.

Results: A total of 147 primary events were accrued during up to 54 months of follow-up. In all, 60 CV-specific deaths, 44 non-fatal MIs and 57 non-fatal strokes occurred, totalling 161 events. There was a significant positive relationship between updated mean HbA1c and primary outcome: hazard ratio (HR) 1.25 [95% confidence interval (CI) 1.12–1.40; $p < 0.0001$]. CV death [HR 1.31 (95% CI 1.10–1.57); $p = 0.0027$] and stroke [HR 1.36 (95% CI 1.17–1.59); $p < 0.0001$] were both strongly associated with HbA1c, while MI was not [HR 1.05 (95% CI 0.83–1.32)]. One or more severe hypoglycaemic episodes affected 175 participants, while 1508 participants experienced one or more symptomatic hypoglycaemic events. We found no relationship between severe/symptomatic hypoglycaemic events and CV-specific/all-cause death.

Conclusions: Ongoing poorer glucose control was associated with CV events; hypoglycaemia was not associated with CV-specific/all-cause death.

Keywords: cardiovascular risk, CREDIT, glycaemic control, hypoglycaemia, type 2 diabetes

Date submitted 16 March 2015; date of first decision 7 September 2015; date of final acceptance 23 October 2015

Introduction

The relationship between glycaemic control and cardiovascular (CV) outcome remains uncertain, with recent randomized trials giving contradictory results [1–4]. Observational studies can provide insights that may be generalized to clinical populations [5]. *Post hoc* analysis of the ACCORD study suggested that mortality was lowest in those with the best glycated haemoglobin (HbA1c) values [6], while a further analysis of the same study suggests that insulin was not detrimental to CV mortality over 5 years [7]. Also controversial is the relationship between hypoglycaemia and CV outcomes and death, a relationship that seems to be weakened by optimization of blood glucose control [8] and is paralleled by relationships with non-CV disease [9], prompting the authors to ask whether it is a marker of vulnerability to adverse outcomes rather than having a causal role.

The Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy (CREDIT) study, an international, 4-year, non-interventional, longitudinal study, was designed to evaluate the relationship between blood glucose control and CV events in people newly treated with insulin in routine clinical practice. Other aims were to gain insights into current clinical practice of the use of insulin in people with type 2 diabetes, and to examine factors predictive of glucose control and body weight change [10–13]. The study was conceived as an observational sibling to the ORIGIN interventional trial [14], which aimed to identify the relationship between very early insulin use and CV and oncological outcomes, with CREDIT focusing on outcomes after starting insulin in real-world practice and thus later in the course of the condition.

In the present paper we describe the association of glycaemic control with the occurrence of CV events in the CREDIT study over 4 years. Because of the interest in the potential relationship between the occurrence of hypoglycaemic events and CV-specific death or all-cause mortality [6,8,9], we also

Correspondence to: Nick Freemantle, Department of Primary Care and Population Health, Upper Third Floor, UCL Medical School (Royal Free Campus), Rowland Hill Street, London NW3 2PF, UK. E-mail: nicholas.freemantle@ucl.ac.uk

describe the relationship between hypoglycaemic events and CV-specific death or all-cause mortality. These last analyses were not part of the original focus of the CREDIT study, but were included to explore an emerging hypothesis in a novel dataset.

Materials and Methods

Objectives

The primary aim of the CREDIT study was to identify the relationship between glycaemic control during follow-up and the risk of major CV morbidity and mortality. At the same time, we examined the relationship between reported hypoglycaemic episodes and CV or all-cause mortality.

Study Design

The CREDIT study design and participant selection criteria, as well as the participant baseline characteristics, have been reported previously [10–13]. In brief, the study involved 314 recruitment centres in 12 countries: 10 in Europe, plus centres in Canada and Japan. Men and women with type 2 diabetes, aged >40 years, who had started any type of insulin therapy within 12 months and who had an HbA1c measurement <3 months before starting insulin, were eligible to participate. As this was 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. Data were gathered in routine clinical practice, and the treating physicians were asked to report updated participant data every 6 months. Ethical approval according to local regulations was obtained for all study sites. The study was conducted in accordance with 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.

Eligible Population

All people who met the study inclusion criteria and provided data for assessment of outcome events were eligible for data analysis.

Outcome Measures

Time-to-event endpoints were calculated from the date of insulin initiation and were restricted to 54 months [i.e. a participant who did not experience any event before 1644 days (inclusive) was censored at 1644 days or end of study date (latest date from date of last contact, death or last visit)].

Occurrence of CV events [myocardial infarction (MI), stable angina, severe unstable angina leading to hospitalization, heart failure leading to hospitalization, stroke, transient ischaemic attack, peripheral vascular disease, limb amputation, myocardial revascularization (coronary artery bypass grafting or percutaneous coronary intervention) and peripheral revascularization (revascularization in any arterial territory other than coronary arteries)] were to be reported by the investigator in clinical report forms at 6-month intervals. Supportive documents (e.g. ECG, biochemistry, hospital records, procedure notes, CT and/or MRI reports, medication charts) were requested by the study team and the package sent to the Adjudication Committee.

The CV events were then confirmed by decision of the Adjudication Committee (agreement of three reviewers or, if not, consensus at a formal meeting, using definitions enshrined in the Adjudication Committee charter). Deaths were adjudicated as 'CV', 'non-CV' and 'cannot classify', and all other events classified as 'event', 'no event' or 'cannot classify'. Adjudicated CV death and CV events were used to derive composite outcomes [major adverse cardiac events (MACE) and MACE+].

The primary aim was to examine the relationship between HbA1c and CV events. The principal CV event composite (MACE) was defined as time to the first experience of non-fatal MI, non-fatal stroke or CV death. The secondary CV event (MACE+) included severe unstable angina leading to hospitalization, heart failure leading to hospitalization, myocardial revascularization, peripheral revascularization, and lower limb amputation. We also describe the components of the principal outcome separately [15]. Analysis using all-cause mortality rather than CV death was added at editorial request *post hoc*.

The relationship between reports of severe or symptomatic hypoglycaemic events and subsequent CV deaths and all-cause mortality was investigated as a secondary aim as part of the statistical analysis plan. Symptomatic hypoglycaemia was predefined in the study protocol as any event with clinical symptoms resulting in hypoglycaemia, confirmed by plasma glucose ≤3.9 mmol/l. Severe hypoglycaemia was defined as an event that required the assistance of another person and confirmed by plasma glucose <2.0 mmol/l or prompt recovery after oral carbohydrate, intravenous glucose, or intramuscular glucagon. Events for the 6 months before each visit were ascertained by patient recall.

Statistical Analysis

The relationship between the hazard of CV events and glycaemic control was described using multivariable Cox models including time-dependent covariate terms [16]. The index date was the time of insulin initiation. Participant characteristics other than glycaemic control (such as HbA1c) judged *a priori* to be explanatory and likely to affect CV risk were included as candidate explanatory variables. The number of candidate explanatory variables that can be fitted without risking substantial overfitting is limited to p/10, where p is the number of events. Candidate explanatory variables describing patient status when starting insulin were age, sex, body mass index, previous diagnosis of high blood pressure (BP), family history of premature CV disease, level of physical activity, smoking status, macrovascular disease, microvascular disease, and $\log_e(1+n)$ of the number of non-insulin glucose-lowering therapy treatments. In addition, enabled by the higher number of events, the following candidate variables were assessed in the model for the MACE+ model: type of first insulin regimen, time from diagnosis of type 2 diabetes, insulin units per kg, systolic BP, diastolic BP, heart rate, antihypertensive treatment,

antiplatelet/anticoagulant treatment, and statin/fibrate treatment. HbA1c was included as a time-dependent explanatory variable, with the model updating the overall mean HbA1c each year for participants who experienced events that occurred in that period and for those remaining at risk of events (thus acting as controls to those events). Updated mean HbA1c of annual measurements of HbA1c was calculated for each individual from 1 month after insulin initiation to each year of follow-up; thus, when a patient experienced an event, the mean HbA1c for the patient up to that point was included automatically by the model as an explanatory variable, and the corresponding mean HbA1c for all other subjects who had not yet experienced an event was included for the calculation of the relationship between HbA1c level and risk of an event for that individual. Backward selection was used to remove candidate variables in turn from the statistical model on the basis of their contribution to the model, with an inclusion criterion of $p < 0.05$. Separate models were derived for MACE and MACE+.

We conducted supportive analyses comparing the updated mean HbA1c by year (the principal analyses) with models including the HbA1c for that year alone in nested statistical models. In addition to this, we examined the relationship between HbA1c by year and non-fatal MI, non-fatal stroke and CV-specific death, the individual components of the principal outcome.

In an exploratory analysis, we examined the relationship between reported symptomatic or severe hypoglycaemia with CV-specific death and with all-cause death. Terms identifying the reporting or otherwise of these events at any time during follow-up (at the yearly visits) were included in models, along with the same explanatory variables as in the MACE model.

Results

Population, Glucose Control and Event Rates

Of the 3031 people originally recruited to the CREDIT study [10–13], 2999 were available for follow-up assessment. The baseline characteristics of included participants are described in Table 1. Nine participants did not have any measure of HbA1c recorded during the study (from starting insulin up to 54 months after starting insulin), with 196 missing at least one estimation in any year. The median (quartiles 1–3) HbA1c at year 1 was 7.4 (6.7–8.4)% [57 (50–68) mmol/mol], at year 2 was 7.4 (6.7–8.3)% [57 (50–67) mmol/mol], at year 3 was 7.4 (6.7–8.2)% [57 (50–66) mmol/mol] and at year 4 was 7.3 (6.7–8.2)% [56 (50–66) mmol/mol].

During 54 months of potential follow-up, 147 people experienced a first MACE event, and 286 experienced a first MACE+ event. Contributing MACE and MACE+ events are described in Table 2. The median follow-up between starting insulin and either a first event or censorship was 4.2 (3.5–4.4) years for MACE and 4.1 (3.0–4.3) years for MACE+. MACE events were fairly evenly distributed between the three contributing events (Table 2). A small number of people with non-fatal MACE events went on to experience CV death within the 54 months of follow-up. MACE+ events, thus including events defined by a clinical intervention, amounted to >60% of qualifying events.

Table 1. Baseline characteristics at the time of starting insulin of people with type 2 diabetes included in the CREDIT study.

	n	Median (interquartile range) or %
Sex: male	1534	51.2
Age (years)	2999	61 (54–69)
HbA1c	2925	9.3 (8.1–10.7)
Duration of diabetes (years)	2985	9.0 (5.0–14.5)
Previous diagnosis of high BP	2056	68.6
Systolic BP (mmHg)	2749	138 (127–150)
Diastolic BP (mmHg)	2750	80 (72–90)
Body mass index (kg/m^2)	2796	28.6 (24.8–32.8)
Physically active, yes	1415	47.4
Smoking status		
Never smoked	1667	55.9
Stopped ≥1 year ago	758	25.4
Stopped <1 year ago	104	3.5
Currently smoke	455	15.3
Family history of premature CV disease	757	25.6
≥1 macrovascular disease	1025	34.2
≥1 microvascular disease	2085	69.5
Glucose-lowering therapies	2999	1 (0–2)
≥1 BP-lowering drug	2164	72.2
Antiplatelet/anticoagulant	1231	41.1
Statin/fibrate	1356	45.2
Region		
North America	735	24.5
Eastern Europe	647	21.6
Southern Europe	460	15.3
France	511	17.0
Northern Europe	252	8.4
Japan	394	13.1

BP, blood pressure; CV, cardiovascular; HbA1c, glycated haemoglobin. Physical activity was defined as patient involved in walking, cycling or gardening for ≥4 h a week.

Multivariable Model

The final statistical model for MACE included age, history or presence of macrovascular disease when starting insulin, and previous diagnosis of hypertension (Table 3). Updated average HbA1c was strongly related to the risk of MACE events [hazard ratio (HR) 1.25 (95% confidence interval (CI) 1.12–1.40); $p < 0.0001$]. There was thus a 25% increase in risk for each 1% unit (11 mmol/mol) higher average level of HbA1c over the 54-month period. In the supportive model where the HbA1c value considered was that in the year of the event, the magnitude of the relationship with MACE was slightly reduced, but it was still statistically significant [HR 1.23 (95% CI 1.10–1.37); $p = 0.0001$] and did not differ significantly in model fit ($p = 0.43$).

In separate models including the same explanatory risk factors, we examined the relationship between glycaemic control and stroke, non-fatal MI and CV death, which are the separate components of MACE (Table 3). Each 1% unit (11-mmol/mol) or higher average HbA1c was associated with a 31.2 (9.8–56.7)% increase in the risk of CV death ($p = 0.003$) and a 36.3 (16.8–59.1)% increase in the risk of stroke ($p < 0.0001$); however, there was no significant relationship between a 1% unit (11 mmol/mol) higher HbA1c and

Table 2. Distribution of first and subsequent composite events and individual components over 54 months of follow-up.

	Events in the composite endpoint, participants, n*	Events by 54 months, participants, n†	All events by 54 months, events, n
MACE	147	147	161
Non-fatal MI	42	42	44
Non-fatal stroke	50	50	57
CV death	55	60	60
MACE+	286	289	447
Non-fatal MI	37	42	44
Angina hospitalization	18	21	21
Heart failure hospitalization	51	62	78
Non-fatal stroke	47	50	57
Myocardial revascularization	65	101	119
Peripheral revascularization	27	34	46
Lower limb amputation	13	18	22
CV death	34	60	60

CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

*For a MACE+ event, myocardial revascularization and non-fatal MI occurring the same day are reported for each (six participants).

†The same participant may appear in different categories.

the risk of MI [HR 1.05 (95% CI 0.83–1.32)]. In the *post hoc* supportive analysis, the HR for all-cause mortality was 1.15 (95% CI 1.01–1.31; p = 0.030) per unit higher HbA1c.

The final model for MACE+ included sex, physical activity, macrovascular disease when starting insulin, duration of diabetes, and antihypertensive therapy when beginning insulin (Table 3). Updated mean HbA1c was related to the risk of MACE+ events [HR 1.16 (95% CI 1.07–1.26); p = 0.0003], a 16% increase in risk for each 1% unit (11 mmol/mol) increase in average HbA1c across the 54-month period. In the supportive model where the HbA1c value considered in the model was that in the year of the event, the magnitude of the relationship with MACE was slightly reduced, but it was still statistically significant [HR 1.14 (95% CI 1.05–1.23); p = 0.0015] and did not differ significantly in model fit (p = 0.12).

Hypoglycaemia

A total of 175 (6.6%) participants reported at least one severe hypoglycaemic event, and 1508 (53.7%) reported at least one symptomatic hypoglycaemic event. Sixty (2.0%) people died from CV disease and 148 (4.9%) from any cause over 4 years. We identified no relationship between reported hypoglycaemia and CV-specific death or all-cause mortality (Table 4).

Discussion

The CREDIT study indentified an important relationship between glycaemic control and CV risk, describing a clinically relevant lowering of the hazard of a cluster of CV events with achievable reductions in HbA1c. These results are broadly in line with the less-certain effects seen in major randomized trials, and they support the conclusion that improved glycaemic control reduces CV events [6,17,18]. Participants were newly started on insulin and generally achieved and maintained reasonable glycaemic control during follow-up in the study, with median HbA1c of 9.3% (78 mmol/mol) at baseline, declining to 7.4% (57 mmol/mol) at the end of year 1 and 7.3% (56 mmol/mol) at the end of year 4. These circumstances may have improved the power of the study by excluding both ill people who have reduced HbA1c through loss of appetite, and thus weight loss, and those stuck at higher levels of HbA1c because of concomitant disease [6], and thus judged less suitable for insulin.

The final statistical models for MACE and MACE+ did not include the specific insulin strategy used when starting insulin, indicating that for this population in this setting, it is the lower HbA1c itself (rather than the insulin regimen used to achieve it) that may be responsible for therapeutic benefits; however, we cannot exclude the possibility that good HbA1c levels for those on insulin are related to better glucose control in past years before insulin was started, and hence that it is longer-term control that is important, as noted in the UK Prospective Diabetes Study (UKPDS) [19]. It is also possible that better blood glucose control is associated with a better profile of other CV risk factors, although the statistical uncertainty arising from that putative correlation would make our fairly powerful findings unlikely, given that the number of events is not very large.

The PROactive trial found a non-significant 10% reduction in the primary outcome associated with a 0.5% reduction in HbA1c achieved with randomization to pioglitazone in a high-CV-risk population with type 2 diabetes but without heart failure [1]; this outcome is similar to our MACE+ composite. In the PROactive and CREDIT studies, the benefits of good HbA1c values with regard to CV risk were greater for MACE than MACE+ (MACE being driven only by disease status, and MACE+ also including clinical interventions). The ACCORD study also found a non-significant 10% reduction in risk of MACE, coupled with an intensive 1.1% reduction in HbA1c, but additionally found a nominally statistically significant 22% increase in CV death [3]. In a recent ACCORD substudy examining the relationship between glycaemic control and CV risk, a consistent reduction of CV events associated with better glycaemic control was reported [20]. The VADT study reported a non-significant 12% reduction in the risk of a MACE+ outcome (which differed in components from that in CREDIT) associated with a 1.5% reduction in HbA1c [2], a finding that became significant with a 17% reduction in events at 10 years in the extension phase [21]. The ADVANCE study saw a 6% non-significant reduction in MACE events associated with a 0.8% reduction in HbA1c [4]. The relationship between HbA1c reduction and CV events in the UKPDS was also suggestive, but uncertain at study end, but again significant at the end of the extension phase (MI, all-cause mortality), and in study observational analysis [17,19,22]. Accordingly, the meta-analyses of these studies also found statistically significant reductions in MI and overall CV events [18,23].

Our finding that benefits were concentrated on the MACE components of CV-specific death and non-fatal stroke was novel and unexpected; conclusions must therefore be drawn

Table 3. Hazard ratios for the measures retained in the final major adverse cardiovascular event (MACE) and MACE+ models, and for components of MACE in terms of updated mean glycated haemoglobin per 1% unit.

	HR (95% CI)	p
MACE		
Age at starting insulin (years)	1.035 (1.018–1.053)	<0.0001
Previous diagnosis of high BP (yes/no)	1.585 (1.031–2.438)	0.036
≥1 macrovascular disease when starting insulin (yes/no)	2.435 (1.731–3.425)	<0.0001
Updated average HbA1c (per 1% unit)	1.250 (1.118–1.398)	<0.0001
MACE components (per 1% unit HbA1c)*		
CV death	1.312 (1.098–1.567)	0.0027
Stroke	1.363 (1.168–1.591)	<0.0001
MI	1.047 (0.833–1.317)	0.693
MACE+		
Sex (female vs male)	0.602 (0.470–0.769)	<0.0001
Physical activity (yes vs no)	0.732 (0.578–0.928)	0.0101
≥1 macrovascular disease when starting insulin (yes/no)	2.883 (2.205–3.769)	<0.0001
Duration of diabetes when starting insulin (years)	1.018 (1.004–1.031)	0.0105
BP-lowering drug when starting insulin (yes/no)	1.652 (1.142–2.388)	0.0076
Antiplatelet/anticoagulant when starting insulin (yes/no)	1.318 (1.008–1.724)	0.0436
Updated mean HbA1c (per 1% unit)	1.161 (1.071–1.259)	0.0003

BP, blood pressure; CI, confidence interval; CV, cardiovascular; HbA1c, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.
*Including adjustment for age, prior high BP (yes/no) and history or presence of macrovascular disease (yes/no), all when starting insulin.

Table 4. Relationship between reported hypoglycaemia (yes/no) and cardiovascular-specific or all-cause mortality.

	Participants with death event, n (%)		
Event	With hypoglycaemia	Without hypoglycaemia	HR (95% CI)
CV death*			
Symptomatic hypoglycaemia	24 (49.0)	25 (51.0)	0.73 (0.41–1.27)
Severe hypoglycaemia	3 (7.5)	37 (92.5)	1.10 (0.34–3.57)
All-cause mortality*			
Symptomatic hypoglycaemia	56 (48.3)	60 (51.7)	0.71 (0.49–1.03)
Severe hypoglycaemia	8 (8.5)	86 (91.5)	1.22 (0.59–2.53)

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
*Including adjustment for age, prior high BP (yes/no) and history or presence of macrovascular disease (yes/no), all when starting insulin.

with caution. The findings on CV-specific death were confirmed in a *post hoc* sensitivity analysis for all-cause mortality, although of course the HR is closer to unity with the inclusion of deaths not expected to be influenced by blood glucose control; however, this also suggests that we are not just looking at HbA1c as a marker of ill health in general. The PROactive study found a non-significant reduction in non-fatal MI, although it included silent MI in the outcome [1]. The ACCORD study found a significant reduction in non-fatal MI associated with randomization to intensive HbA1c-lowering, although it was coupled with a significant increase in the risk of CV-specific deaths (raising the question of competing risks) [3]. While the ADVANCE study found no benefit in reduced HbA1c on the outcome of non-fatal MI, neither did it find any in non-fatal stroke [4]. Finally, the VADT study found a non-significant reduction in non-fatal MI in line with the overall (non-significant) study estimate of treatment effect [2]. The CREDIT study differs from these other studies in that all patients began insulin, which was central to the management of their blood glucose. It is possible that insulin-based strategies are specifically beneficial in reducing CV-specific death and non-fatal stroke and are not effective in reducing non-fatal MI; however, a test for heterogeneity (systematic difference over and above those expected through chance alone) indicates that differences in treatment effect estimates of at least this magnitude may be expected to occur by chance alone ~16 times in 100; this suggests we should be cautious about drawing strong conclusions.

We contrasted models in which we used the overall mean HbA1c and the mean in the previous year as time-dependent predictors, and found similar results and model fit. This may be attributable to the relative stability of glycaemic control over time, but is also supportive of the notion that the degree of glycaemic control over the proximal period has a useful predictive effect.

Because of the emerging interest in the potential relationship between hypoglycaemic events and CV-specific death [9], we included exploratory analyses to assess whether this may be supported in the CREDIT database. We found no relationship between severe hypoglycaemia and CV or all-cause mortality, but with wide CIs. Symptomatic hypoglycaemia was associated with a non-significant reduction in the risk of death (either all-cause or CV-specific). Chance is the preferred explanation of this finding; however, it is plausible that symptomatic hypoglycaemia is associated with improved glycaemic control and thus with an improved outcome. Hypoglycaemia data were collected as symptomatic reports in the previous 6 months before each visit, and thus includes only events within the time period

and those recalled by the patient; thus, patients who experienced non-symptomatic hypoglycaemia are not included in this analysis, diluting any effect seen.

The findings contrast with the design of a standard randomized controlled trial, where asymptomatic hypoglycaemic episodes may be identified through trial-based monitoring with correspondingly higher rates of events. It is not clear, however, whether this can explain the difference in results observed between previous reports and the CREDIT study, but the detailed analysis of ACCORD suggested that the association of severe hypoglycaemia with adverse outcomes was diluted by the increase in hypoglycaemia with intensification of therapy [8]. This leads to the conclusion that in non-optimized people, hypoglycaemia is a marker of adverse outcomes, but that the additional hypoglycaemia of optimized therapy must be less adverse. The CREDIT population improved glucose control markedly with the insulin therapy as above, so it is possible we are looking mainly at the comparatively benign type of hypoglycaemia associated with optimization of control with insulin, rather than the more malign type that marks concomitant illness [6,9]. Indeed, in the ORIGIN study, conducted in a very different population to that of CREDIT, and at much tighter glucose control levels, symptomatic hypoglycaemia was clearly not associated with adverse CV outcomes [24]. Severe hypoglycaemia was associated, but weakly, compared with results from ADVANCE and ACCORD, and at levels compatible with the wide CIs for hazard we establish with relatively few such events.

The CREDIT study has a number of strengths, including its rigorous real-world design and independent adjudication of CV endpoints. It also has design limitations in addition to those discussed above. Specifically, there is a trade-off between external and internal validity in any non-interventional observational study based on real-world practice, with the former maximized at the partial expense of the latter. This means that the findings are not as assured as those from a large, well-designed, randomized study, and it is possible that some other characteristic confounded with improved glycaemic control was responsible for the benefits observed. Nevertheless, the real-world design also enabled the inclusion of a variety of levels of glycaemic control in individuals over time, resulting in more precision for estimation. The glycaemic control achieved by participants in the CREDIT study reflects the best efforts of patients and clinicians in normal clinical practice in their choice of therapeutic agents. This contrasts with randomized trials where patients and clinicians are largely limited to the imposed experimental strategies. Evidence such as that from the EXPERIENCE trial shows that in the real-world setting, where changes can be made more freely than in conventional trials, larger apparent treatment effects may be observed for specific therapies than for treatments used in trials [2,25].

In conclusion, improved glycaemic control was associated with a clinically useful reduction in CV events in the CREDIT study over 54 months of follow-up. No difference was observed in the effects of different insulin regimens, suggesting that good glycaemic control is important however it is achieved, although a simple and individualized approach for should be followed where appropriate.

Acknowledgements

This study was supported by Sanofi. The authors would like to acknowledge the CREDIT investigators (File S1). Editorial support was provided by Tom Claus of PPSI (a PAREXEL Company) and funded by Sanofi.

Some of the study results were presented at the World Diabetes Congress/International Diabetes Federation meeting in 2013 and at the American Diabetes Association and the European Association for the Study of Diabetes meetings in 2014.

Conflict of Interest

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. N. D. has received research grants from AstraZeneca, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Sanofi, Servier and The Medicines Company and has received fees for speaking in industry sponsored symposia and/or consulting for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Eli Lilly, Menarini, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi, Servier and The Medicines Company. F. C.-G. is a consultant to Sanofi. M. V. is an employee 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.

N. F., N. D. and P. H. served on the CREDIT steering committee. F. C. G. undertook statistical analyses for the report. All authors contributed to the interpretation of the data and provided comments on the report at various stages in its development.

N. F. 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.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. CREDIT study investigators.

References

1. Dormandy JA, Charbonnel B, Eckland DJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; **366**: 1279–1289.
2. Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; **360**: 129–139.
3. Gerstein HC, Miller ME, Byington RP et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; **358**: 2545–2559.
4. Patel A, MacMahon S, Chalmers J et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; **358**: 2560–2572.
5. 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 A1chieve study. Diabetes Res Clin Pract 2011; **94**: 352–363.

6. Riddle MC, Ambrosius WT, Brillon DJ et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010; **33**: 983–990.
7. Siraj ES, Rubin DJ, Miller ME et al. The relationship between insulin exposure and cardiovascular mortality in the ACCORD trial. Diabetes 2013; **62** (Suppl. 1): A98.
8. Bonds DE, Miller ME, Bergenstal RM et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010; **340**: b4909.
9. Zoungas S, Patel A, Chalmers J et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010; **363**: 1410–1418.
10. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. Diabetes Care 2014; **37**: 2108–2113.
11. 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.
12. 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.
13. Home PD, Dain MP, Freemantle N et al. Four-year evolution of insulin regimens, glycaemic control, hypoglycaemia and body weight after starting insulin therapy in type 2 diabetes across three continents. Diabetes Res Clin Pract 2015; **108**: 350–359.
14. Gerstein HC, Bosch J, Dagenais GR et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012; **367**: 319–328.
15. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA 2003; **289**: 2554–2559.
16. Collett D. Modelling Survival Data in Medical Research. London: Chapman & Hall/CRC, 1994.
17. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; **321**: 405–412.
18. Turnbull FM, Abraira C, Anderson RJ et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009; **52**: 2288–2298.
19. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; **352**: 837–853.
20. Gerstein HC, Miller ME, Ismail-Beigi F et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. Lancet 2014; **384**: 1936–1941.
21. Hayward RA, Reaven PD, Wiitala WL et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015; **372**: 2197–2206.
22. 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.
23. 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.
24. Mellbin LG, Ryden L, Riddle MC et al. Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial. Eur Heart J 2013; **34**: 3137–3144.
25. Del Prato S, Blonde L, Martinez L et al. The effect of the availability of inhaled insulin on glycaemic control in patients with Type 2 diabetes failing on oral therapy: the evaluation of Exubera as a therapeutic option on insulin initiation and improvement in glycaemic control in clinical practice (EXPERIENCE) trial. Diabet Med 2008; **25**: 662–670.