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ARTICLE

Basal insulin glargine and microvascular outcomes in dysglycaemic individuals: results of the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial

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Abstract
Aims/hypothesis As glycaemia and the incidence of microvascular diabetes complications follow a log-linear relationship, it becomes increasingly difficult to demonstrate a microvascular benefit of glucose-lowering when the HbA_{1c} level is close to normal.
Methods The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomised 12,537 people with diabetes, impaired glucose tolerance or impaired fasting glucose to receive standard glycaemic care or standard care with the addition of basal insulin glargine (A21Gly,B31Arg,B32Arg human insulin), targeting a fasting plasma glucose level ≤5.3 mmol/l. Microvascular outcomes during a median follow-up of 6.2 years were examined in participants whose baseline HbA_{1c} was above or below the median of 6.4% (46.4 mmol/mol).
Results Allocation to the insulin glargine group reduced the incidence of the primary microvascular composite outcome of kidney and eye disease in participants whose baseline HbA_{1c} level was ≥6.4% (46.4 mmol/mol; HR 0.90 [95% CI 0.81, 0.99]) but not in participants with a lower baseline HbA_{1c} (HR 1.07 [95% CI 0.95, 1.20]; p value for interaction 0.031). In people whose baseline HbA_{1c} level was ≥6.4% (46.4 mmol/mol), the median post-randomisation change in HbA_{1c} was −0.65% (interquartile range −0.16, −0.91%) after allocation to insulin glargine and −0.33% (−0.83, 0.13%) after allocation to standard care (median HbA_{1c} difference 0.33%; $p<0.0001$). A smaller median difference of 0.22% was noted

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in people whose baseline HbA_{1c} was <6.4% ($p<0.0001$).
Conclusions/interpretation In patients with dysglycaemia, intervention targeting normal fasting glucose levels reduced HbA_{1c} and attenuated the risk of microvascular outcomes in participants with a baseline HbA_{1c} level ≥6.4% (46.4 mmol/mol). A neutral effect was seen in those with a lower baseline HbA_{1c} level.
Trial registration: ClinicalTrials.gov NCT00069784

Keywords Albuminuria · Diabetic nephropathy · Insulin glargine · Microvascular · Retinopathy

Abbreviations

ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blocker
IQR	Interquartile range
ORIGIN	Outcome Reduction with an Initial Glargine Intervention
UKPDS	UK Prospective Diabetes Study

Introduction

Plasma glucose concentrations are distributed over a wide range in any given population. Within this continuum, the threshold for the diagnosis of diabetes is based largely on epidemiological studies wherein a plasma glucose cut-off point largely separates individuals who are at substantial risk of diabetic retinopathy from those who are not [1]. For individuals with diabetes, numerous observational studies have indicated that the likelihood of developing both eye and kidney disease steeply increases as glucose levels rise above the diabetes threshold [2–5].

Several intervention studies have shown the effectiveness of glucose-lowering in reducing microvascular outcomes of type 2 diabetes using a range of anti-hyperglycaemic agents [6–8]. In light of these data, together with observational studies showing a log-linear relationship between HbA_{1c} and the risk of diabetes complications [4], an intervention that lowers glucose levels may be expected to have a greater effect in people with higher vs those with lower HbA_{1c} levels. We tested this possibility using data from the recently completed Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial [9], wherein 12,537 people (after exclusion of 75 individuals by the health authorities; see electronic supplementary material [ESM] Fig. 1) with a median baseline HbA_{1c} level of 6.4% (46.4 mmol/mol; interquartile range [IQR] 5.8–7.2% [39.9–55.2 mmol/mol]) were allocated to receive standard glycaemic care or standard care with the addition of basal insulin glargine (A21Gly,B31Arg,B32Arg human insulin), and followed for a median of 6.2 years (IQR 5.8–6.7 years) for the development of cardiovascular, microvascular and other clinical outcomes. Specifically, we compared the effect of the intervention on microvascular outcomes in participants within two pre-specified subgroups: those with baseline HbA_{1c} levels above and those with levels below the median.

Methods

Study design The design and main results of the ORIGIN trial have been previously reported [9–11]. Briefly, men and women aged 50 years or older with either type 2 diabetes on not more than one oral glucose-lowering drug, impaired glucose tolerance or impaired fasting glucose, and with either a prior cardiovascular event or at high risk of vascular disease were recruited. In addition to the insulin glargine vs standard care intervention, participants were randomly allocated to receive a *n*-3 fatty acid supplement or placebo according to a 2×2 factorial design. Screening, randomisation and follow-up of ORIGIN trial patients are described in ESM Fig. 1 and in further detail in the appendix to the main ORIGIN results paper [9]. Study participants provided written informed consent, with the study approved by the ethics committee at each study site.

ORIGIN intervention with insulin glargine As described in detail previously [11], participants assigned to the insulin glargine group added an evening injection to their pre-existing anti-hyperglycaemic regimen, increasing its dose to attain a self-measured fasting plasma glucose level of ≤5.3 mmol/l (95 mg/dl). Participants assigned to standard care were treated according to the investigator's discretion in alignment with local guidelines. The ORIGIN trial was designed to assess the effect of basal insulin on health outcomes, and was neither designed nor powered to assess the effect of more vs less intensive glucose-lowering. Nevertheless, the difference in insulin use led to a modest difference in fasting plasma glucose level and HbA_{1c} whereby at 2 years, the median fasting plasma glucose concentrations and HbA_{1c} were 1.6 mmol/l and 0.3% lower, respectively, in the insulin glargine group compared with the standard care group [9].

Microvascular outcomes The pre-defined composite secondary outcome of the ORIGIN trial was the first occurrence of a microvascular event defined as a doubling of serum creatinine from the baseline screening value, worsening of albuminuria category (i.e. from normoalbuminuria to either microalbuminuria or clinical proteinuria, or from microalbuminuria to clinical proteinuria), renal replacement therapy, death due to renal failure or diabetic retinopathy

requiring retinal photocoagulation or vitrectomy. All clinical outcomes were adjudicated by a committee that was blinded to treatment allocation. Participants were asked about laser eye therapy, kidney failure, dialysis, vitrectomy, photocoagulation and other serious health outcomes every 4 months, and serum creatinine was measured at baseline, 2 years and study end in local laboratories. First-voided urine samples were collected at the research sites according to the same schedule and forwarded to the Clinical Trials Laboratory at the Hamilton General Hospital (Toronto, ON, Canada) for the measurement of urine albumin and urine creatinine concentrations. Urine albumin was measured using a turbidimetric method (with the Beckman MA reagent) and urine creatinine was measured using a modified Jaffé reaction (with the Beckman CR-S reagent) on a Beckman UniCel DxC 600 Instrument (Beckman Coulter, Fullerton, CA, USA). Coefficients of variation for both albumin and creatinine at different concentrations varied from 2.4 to 4.4%.

Statistical analysis Categorical data were summarised as counts and percentages, and continuous data were summarised as either means and SDs or medians and IQRs. Medians were compared using Wilcoxon rank-sum tests, means were compared using Student's *t* tests and counts and proportions were compared using X^2 tests. The effect of allocation to the insulin glargine intervention on microvascular outcomes was assessed by constructing time-to-event curves using product-limit estimation that were compared using log-rank tests. HRs were estimated using Cox regression models that were stratified according to the factorial allocation, diabetes status at baseline and pre-randomisation cardiovascular event. Moreover, as reported in the main ORIGIN paper [9], Cox regression models with adjustment for these factors as covariates were used when there were fewer than five participants with events within any stratum. The differential effect of the intervention within the two subgroups of individuals identified according to whether the baseline HbA_{1c} level was below or at or above the median baseline value of 6.4% (46.4 mmol/mol) was assessed by including this subgroup as an independent variable as well as an interaction variable comprising the subgroup and intervention. When there was evidence of an interaction, separate HRs were estimated within each subgroup using the above approach. The subgroups were defined in this way to be consistent with the ORIGIN statistical analysis plan, which prespecified that the effect of the intervention on the primary outcome would be assessed within subgroups defined by the median baseline HbA_{1c} level.

The epidemiological relationship between baseline HbA_{1c} levels and the subsequent occurrence of microvascular outcomes (i.e. independent of treatment allocation) was assessed using a Cox proportional hazards model with adjustment for age. In a supplemental exploratory analysis, the HbA_{1c}–microvascular relationship was also assessed by dividing baseline levels into fifths using quintiles and estimating the outcome incidence during follow-up within each fifth. Two-sided Cochran–Armitage trend tests were used to test for a progressive increase in outcomes across fifths. All statistical analyses were done using SAS software (version 9.1 for Solaris, Cary, NC, USA). A nominal p value of <0.05 was pre-specified as indicating significance for tests for interactions and epidemiological relationships.

Results

Baseline characteristics and microvascular outcome Among the 12,537 participants enrolled, 2,686 (21%) experienced a microvascular outcome during the study (Table 1). These participants were older and had higher baseline BP, serum creatinine, urine albumin/creatinine ratio, fasting plasma glucose and HbA_{1c} levels than participants who did not experience a microvascular outcome. They were also more likely to have had a history of prior diabetes, laser photocoagulation or vitrectomy, or be using either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), although they were less likely to have had a prior cardiovascular event.

Effects of insulin glargine intervention on microvascular outcomes As reported previously, the incidence of the composite microvascular outcome did not differ between the glargine intervention and standard care groups overall (HR 0.97, 95% CI 0.90, 1.05; p=0.43) [9]. However, when participants were analysed within the two subgroups defined by the median HbA_{1c} of 6.4% (46.4 mmol/mol; ESM Table 1), an interaction (p=0.031) between the insulin glargine allocation and HbA_{1c} subgroup was evident for the composite microvascular outcome (Fig. 1). Specifically, allocation to insulin glargine reduced the incidence of the primary microvascular composite outcome in participants whose baseline HbA_{1c} was ≥6.4% (46.4 mmol/mol; HR 0.90 [95% CI 0.81, 0.99]) but had no effect in participants with a lower baseline HbA_{1c} (<6.4% [46.4 mmol/mol]; HR 1.07 [95% CI 0.95, 1.20]). This finding, which did not change when death was added to the composite outcome to account for the possibility of competing risk, was also apparent in the time-to-event curves for microvascular outcomes (Fig. 2). As noted in Fig. 1, no effect of allocation to insulin glargine intervention on the composite microvascular outcome was evident in other subgroups (defined by the presence or absence of hypertension, treatment with an ACE inhibitor or ARB, diabetes, baseline albuminuria or obesity).

Within the subgroup whose baseline HbA_{1c} was ≥6.4% (46.4 mmol/mol), the median (IQR) post-randomisation change in HbA_{1c} levels was −0.65% (−0.16, −0.91%) in participants allocated to the glargine group and −0.33%

Table 1 Baseline characteristics of participants who did and those who did not develop a microvascular outcome

Baseline characteristic	Incident microvascular outcome		
	Yes (*n*=2,686)	No (*n*=9,851)	*p*
Mean age, years (SD)	64.1 (7.7)	63.4 (7.8)	0.0001
Women, *n* (%)	918 (34.2)	3,468 (35.2)	0.3224
Current smoker, *n* (%)	319 (11.9)	1,233 (12.5)	0.3719
Mean systolic BP, mmHg (SD)	149.4 (22.5)	144.8 (21.5)	<0.0001
Mean diastolic BP, mmHg (SD)	84.6 (12.4)	84.0 (12.0)	0.0144
Mean BMI, kg/m^2 (SD)	29.9 (5.4)	29.8 (5.2)	0.6376
ACE inhibitor/ARB, *n* (%)	1,949 (72.6)	6,732 (68.3)	<0.0001
Prior cardiovascular disease, *n* (%)	1,512 (56.3)	5,866 (59.5)	0.0024
New or prior diabetes, *n* (%)	2,494 (92.9)	8,587 (87.2)	<0.0001
Prior laser/vitrectomy, *n* (%)	78 (2.9)	118 (1.2)	<0.0001
Median albumin/creatinine, mg/mmol (IQR)	1.12 (0.46, 2.88)	0.50 (0.25, 1.64)	<0.0001
Median HbA_{1c}, % (IQR)	6.6 (5.9, 7.4)	6.4 (5.8, 7.1)	<0.0001
Median HbA_{1c}, mmol/mol (IQR)	48.6 (41.0, 57.4)	46.4 (39.9, 54.1)	
Mean HbA_{1c}, % (SD)	6.7 (1.0)	6.5 (0.9)	<0.0001
Mean HbA_{1c}, mmol/mol	49.7	47.5	
Median FPG, mmol/l (IQR)	7.17 (6.11, 8.50)	6.90 (6.00, 8.11)	<0.0001
Mean FPG, mmol/l (SD)	7.55 (2.18)	7.27 (1.94)	<0.0001
Mean serum creatinine, μmol/l (SD)	91.57 (24.83)	88.31 (21.15)	<0.0001
Median eGFR, ml/min/1.73 m^2 (IQR)	73.38 (60.48, 88.97)	76.24 (64.14, 89.53)	<0.0001
Mean log(eGFR) (SD)	4.29 (0.30)	4.32 (0.26)	<0.0001

p values are calculated using Student's *t* tests for continuous variables, Wilcoxon rank-sum tests for medians and X^2 tests for counts

FPG, fasting plasma glucose; eGFR, estimated GFR

(−0.83, 0.13%) in participants allocated to the standard group (median HbA_{1c} difference 0.33%; $p<0.0001$). Among those whose baseline HbA_{1c} was <6.4% (46.4 mmol/mol), changes in median (IQR) HbA_{1c} levels were 0.06% (−0.21, 0.40%) and 0.27% (−0.02, 0.64%) for the glargine and standard care group, respectively (median HbA_{1c} difference 0.22%; $p<0.0001$). Changes in HbA_{1c} over time by subgroup are noted in the ESM Fig. 2, and differences in the use of glucose-lowering drugs within these two subgroups are shown in ESM Table 2.

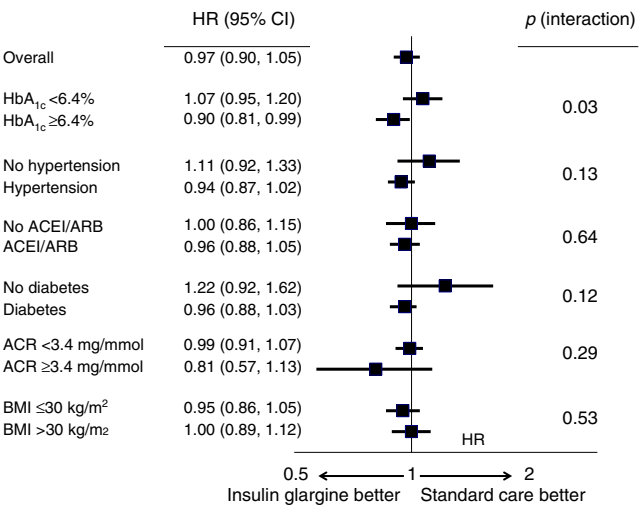

Fig. 1 Effect of allocation to insulin glargine vs standard care on microvascular outcomes overall and within subgroups; to convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929 or use the conversion calculator at www.hba1c.nu/eng/. ACEI, ACE inhibitor; ACR, albumin/creatinine ratio

Epidemiological relationship between categories of HbA_{1c} and microvascular outcomes When the effect of fifths of HbA_{1c} (defined by quintiles) was analysed in all participants, a progressive relationship was evident between the baseline HbA_{1c} and composite microvascular outcome in the entire study population (Fig. 3a, ESM Table 3). Similar trends were noted for the insulin glargine and standard care groups separately (ESM Table 3), and exploratory analyses suggested a marginally blunted rise in outcome incidence across categories in the insulin glargine vs standard care group (*p* value for interaction 0.076). In analyses of HbA_{1c} as both a categorical and continuous variable adjusted for age (Fig. 3b), the HR of the microvascular composite outcome was 1.20 (95% CI 1.16, 1.25) per 1% higher baseline HbA_{1c} ($p<0.001$). Additional adjustment for sex, diabetes status, serum creatinine, history of retinopathy and log albumin/creatinine attenuated the

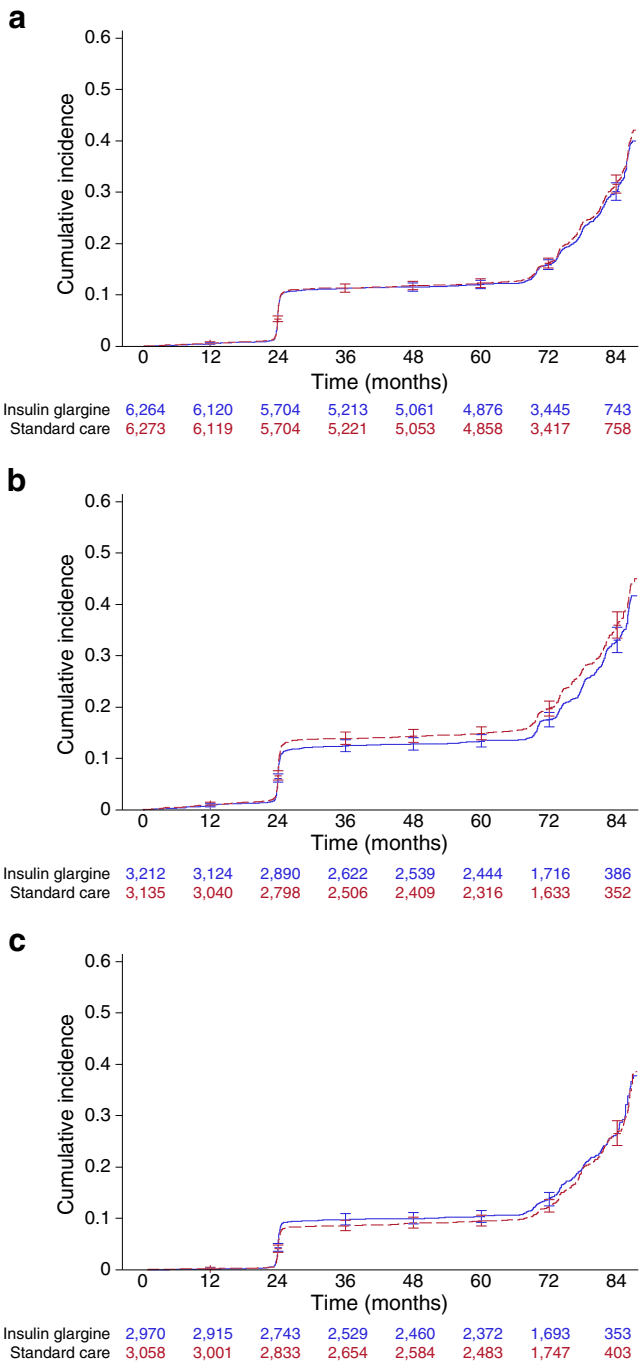

Fig. 2 Time-to-event curves for the composite microvascular outcome (doubling of serum creatinine, worsening of albuminuria, renal replacement therapy or death due to renal failure, or diabetic retinopathy requiring retinal photocoagulation or vitrectomy) in patients assigned to receive insulin glargine (blue line) or standard care (red line) in (**a**) the entire study population, (**b**) patients with baseline HbA_{1c} ≥6.4% (46.4 mmol/mol) and (**c**) those with baseline HbA_{1c} <6.4% (46.4 mmol/mol). The numbers below the graphs show the numbers of patients at each time point

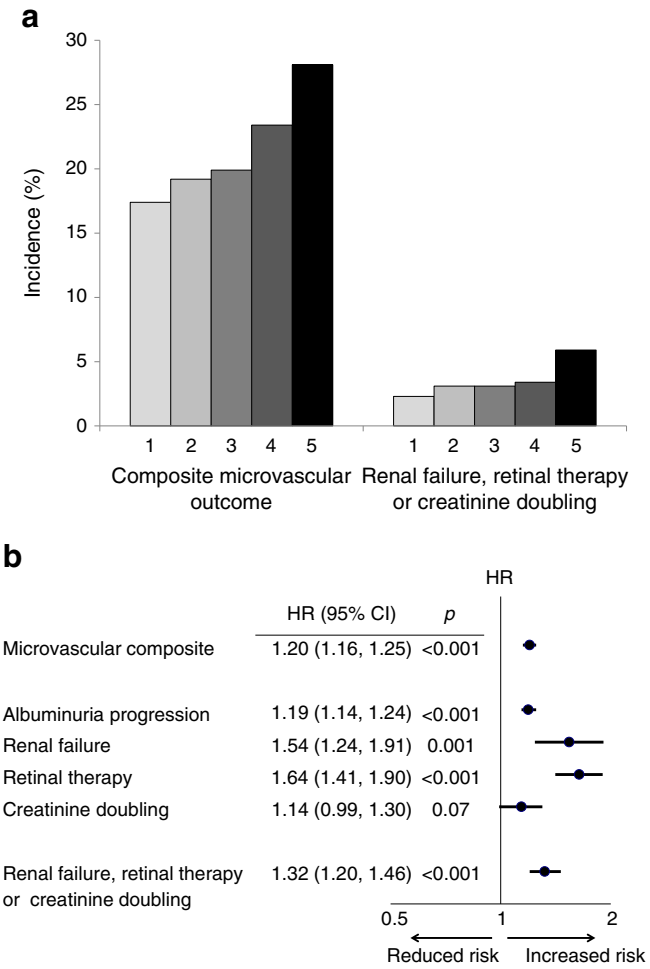

Fig. 3 (**a**) The incidence of the pre-specified microvascular composite outcome and a second clinical microvascular composite that excluded worsening albuminuria according to fifths of baseline HbA_{1c} defined by quintiles. (**b**) Age-adjusted HRs and 95% CIs of outcomes per 1% higher baseline HbA_{1c}

relationship (HR 1.12 [95% CI 1.07, 1.16]), which nevertheless remained significant ($p<0.001$). Similar relationships were noted for the individual outcomes of albuminuria progression, renal failure, retinal therapy and doubling of serum creatinine, as well as for a clinical microvascular composite outcome that excluded albuminuria progression from the pre-defined microvascular composite (ESM Table 4).

Discussion

Glycaemia and the incidence of microvascular complications follow a log-linear relationship in both type 1 and type 2 diabetes [4, 5]. As such, it may be difficult to demonstrate a microvascular benefit of further glucose-lowering when glycaemic levels are already close to normal. Accordingly, the glycaemic threshold at which intervention remains beneficial is uncertain. Similar difficulty is encountered in providing support for improved glucose control when glycaemic separation between control and intervention groups is comparatively modest. The current analysis of the ORIGIN trial addresses both issues. Here we show, first, that an intervention targeting normal fasting

glucose levels reduced microvascular outcomes in participants whose baseline HbA_{1c} was at or above 6.4% (46.4 mmol/mol; i.e. the baseline median HbA_{1c} that was pre-specified as defining a subgroup of interest prior to analysis of the ORIGIN trial results). Second, we show that this effect was evident in the setting of a modest relative reduction in median HbA_{1c} of 0.33% (i.e. a HbA_{1c} reduction of 0.65% vs 0.33% in the glargine and standard arms, respectively) over a 7-year period.

Previous studies have examined the impact of lowering blood glucose on microvascular outcomes in type 2 diabetes. In the UK Prospective Diabetes Study (UKPDS), published 20 years ago, participants assigned to the intensive therapy group experienced a 25% reduction in microvascular complications [8]. While the baseline HbA_{1c} in that study was 6.2% (44.3 mmol/mol), it rose substantially during follow-up, so that by 10 years HbA_{1c} levels were 8.7% (71.6 mmol/mol) and 8.1% (65 mmol/mol) in the standard and intensive therapy arms, respectively [8]. Thus, glycaemic control in both arms was above currently recommended targets for a large part of the UKPDS. In ORIGIN, on the other hand, the median HbA_{1c} in all participants was 6.4% (46.4 mmol/mol) at baseline, rising minimally during the 7 years of follow-up to 6.5% (47.5 mmol/mol) in those randomised to receive standard therapy and falling to 6.2% (44.3 mmol/mol) in the glargine intervention group [9].

At first glance it might seem somewhat surprising that a modest 0.33% lowering of HbA_{1c} in the ORIGIN subgroup whose baseline HbA_{1c} was ≥6.4% (46.4 mmol/mol) was associated with a 10% reduction in microvascular events. However, the findings are consistent with both the UKPDS and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study [6]. In the UKPDS, a 0.9% lowering of HbA_{1c} was associated with a 25% reduction in microvascular events and in ADVANCE a 0.6% HbA_{1c} lowering led to a 14% reduction in microvascular events [6].

Observational analyses from the Diabetes Control and Complications Trial (DCCT) and UKPDS indicate a log-linear relationship between glycaemia and the incidence of microvascular complications in both type 1 and type 2 diabetes [3–5]. These studies did not identify a glycaemic threshold below which glycaemic control was ineffective, while a threshold of 6.5% (47.5 mmol/mol) was reported in the ADVANCE trial [12]. Taking advantage of the comparatively low baseline HbA_{1c} of 6.4% (46.4 mmol/mol) in the ORIGIN trial, in conjunction with the long follow-up time and large patient numbers, we explored the relationship between fifths of glycaemia and microvascular events in ORIGIN. No HbA_{1c} threshold was evident in our analysis, with the incidence of microvascular outcomes rising progressively from the lowest fifth of <5.7% (38.8 mmol/mol) to the highest of ≥7.4% (57.4 mmol/mol), although an effect of intervention was only evident among individuals with HbA_{1c} levels >6.4%. While the number of events in the composite was largely driven by changes in albuminuria, the step-wise progression between baseline HbA_{1c} and outcome was still evident even after albuminuria-based events were excluded.

The current analysis of the ORIGIN trial has several strengths. These relate primarily to the study itself, with a duration exceeding 6 years, high rates of follow-up and treatment adherence along with the large numbers of microvascular endpoints. These factors, in addition to the prospective collection and adjudication of outcomes, provide sufficient power to detect clinically important effects. Moreover, the prospective ascertainment of data pertaining to hypoglycaemia and weight gain assists in assessing risks and benefits. Finally, although conducted after analysing the primary cardiovascular outcome, it is notable that the statistical analysis plan used in the original trial pre-specified both that the effect of the intervention on outcomes would be examined in subgroups defined by the median HbA_{1c} levels at baseline and the composite microvascular outcome as the main secondary outcome.

This study has a number of limitations. Although it is possible that the reduction in microvascular events was due to the use of insulin vs no insulin rather than to glucose-lowering, the fact that the effect was only observed in the subgroup with the higher HbA_{1c}, and that the difference in insulin use was smaller in this group than in the subgroup with a lower baseline HbA_{1c}, makes that unlikely. Thus the absence of an effect on microvascular outcomes among individuals whose HbA_{1c} was below the 6.4% (46.4 mmol/mol) median is likely to be due to the smaller glycaemic separation between the intervention and standard care groups. This lack of microvascular outcome may also have been due to the possibility that the lower absolute rate of events in people with a lower baseline HbA_{1c} reduced the power to detect a difference in this group compared with those with higher baseline HbA_{1c}. Furthermore, only clinical retinal outcomes were recorded and fundus photographs were not done, the latter potentially providing additional useful information regarding the progression of retinopathy.

In summary, the present analysis demonstrates that an insulin glargine-based intervention targeting fasting normoglycaemia in people with good glycaemic control reduces HbA_{1c} and the risk of microvascular complications in those with HbA_{1c} levels >6.4% (46.4 mmol/mol). Whether or not achieving such control with other anti-hyperglycaemic agents would also reduce microvascular complications at such low baseline HbA_{1c} levels remains unknown.

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Duality of interest REG received consulting and lecture fees from Sanofi, Merck, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and

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Contribution statement The work presented here was undertaken in collaboration between all authors. REG and HCG defined the research idea, designed the study's methodology and wrote the report. REG, HCG, JFEM, MH, GS, JB and SY contributed to the data collection, study design and discussion, review and editing of the report. All authors have seen and approved the current version of the report. HCG is responsible for the integrity of the work as a whole.

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