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ARTICLE

Association of HbA_{1c} levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds

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Abstract
Aims/hypothesis There is conflicting evidence regarding appropriate glycaemic targets for patients with type 2 diabetes. Here, we investigate the relationship between HbA_{1c} and the risks of vascular complications and death in such patients.
Methods Eleven thousand one hundred and forty patients were randomised to intensive or standard glucose control in the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. Glycaemic exposure was assessed as the mean of HbA_{1c} measurements during follow-up and prior to the first event. Adjusted risks for each HbA_{1c} decile were estimated using Cox models. Possible differences in the association between HbA_{1c} and risks at different levels of HbA_{1c} were explored using linear spline models.
Results There was a non-linear relationship between mean HbA_{1c} during follow-up and the risks of macrovascular events, microvascular events and death. Within the range of HbA_{1c} studied (5.5–10.5%), there was evidence of 'thresholds', such that below HbA_{1c} levels of 7.0% for macrovascular events and death, and 6.5% for microvascular events, there was no significant change in risks (all $p>0.8$). Above these thresholds, the risks increased significantly: every 1% higher HbA_{1c} level was associated with a 38% higher risk of a macrovascular event, a 40% higher risk of a microvascular event and a 38% higher risk of death (all $p<0.0001$).

To convert values for HbA_{1c} in % into mmol/mol subtract 2.15 and multiply by 10.929.

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Conclusions/interpretation In patients with type 2 diabetes, HbA_{1c} levels were associated with lower risks of macrovascular events and death down to a threshold of 7.0% and microvascular events down to a threshold of 6.5%. There was no evidence of lower risks below these levels but neither was there clear evidence of harm.

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Keywords Glycaemic control · Macrovascular disease · Microvascular disease · Mortality · Type 2 diabetes

Abbreviations

ADVANCE	Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation
ARIC	Atherosclerosis Risk in Communities
eGFR	Estimated glomerular filtration rate
MR	Modified release
SBP	Systolic blood pressure
UACR	Urinary albumin/creatinine ratio
UKPDS	UK Prospective Diabetes Study

Introduction

Previous observational studies in patients with and without type 2 diabetes have reported a progressive linear relationship between glycaemic exposure and the risks of vascular complications and death [1–5]. In the landmark UK Prospective Diabetes Study (UKPDS), published over a decade ago, every 1% lower level of mean HbA_{1c} was associated with a 14% lower risk of myocardial infarction, 37% lower risk of microvascular disease and 14% lower risk of death [4]. Moreover, for all the clinical outcomes studied there was no threshold of glycaemia below which the risks no longer fell with lower levels of HbA_{1c}, suggesting that HbA_{1c} targets should be as near to the normal range as possible [4]. In contrast, three recent large studies, examining the risks of macrovascular disease and mortality by fasting blood glucose concentrations and HbA_{1c} levels, have described a non-linear relationship [6–8], with one study suggesting that both low and high HbA_{1c} levels were associated with increased risks [7].

Translation of the clinical benefits expected from epidemiological associations assumes that the associations remain constant over time, are similar across different populations and are not modified by other risk factors or therapies. This may not be the case. A prior meta-analysis examining the effects of glycaemic exposure on major cardiovascular events in patients with type 2 diabetes reported a pooled greater risk of 18% for every 1% higher level of HbA_{1c} (95% CI 10, 26%) [3]. However, the authors also found significant heterogeneity in the effects among the studies included (with some reporting increases in risk of between 3% and 156%). Identification of the source of the heterogeneity was not possible, highlighting the limitations of pooling tabular data from different studies (varying in size from 94 to 3,642 persons) and settings. Moreover, the generalisability of these findings remains unclear due to changes in the current management of patients with type 2 diabetes. Although a number of individual large-scale clinical trials aiming for near-normal HbA_{1c} targets have separately failed to demonstrate significant benefits on major cardiovascular events or death [9–11], a meta-analysis pooling data from these trials and the UKPDS trial, did show a modest benefit for cardiovascular events but not mortality [12]. Thus, the need to re-examine these associations in contemporary populations has become imperative.

The recent Action in Diabetes and Vascular disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study, examined the effects of intensive glucose control on vascular outcomes and death in a broad range of people with type 2 diabetes from around the world [11]. The purpose of the present post hoc analyses was to quantify macrovascular, microvascular and mortality risks associated with HbA_{1c} level in a contemporary cohort with established type 2 diabetes.

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Methods

Study design and participants ADVANCE was a factorial randomised controlled trial evaluating the effects of blood pressure-lowering and intensive blood glucose control on vascular outcomes. A detailed description of the design has been published previously [11, 13]. In brief, 11,140 individuals with type 2 diabetes aged 55 years and older, with at least one additional risk factor for cardiovascular disease were enrolled from 215 centres in 20 countries. There were no participant inclusion or exclusion criteria based on prior levels of glycaemic control. Eligible participants were randomly assigned to either a gliclazide modified release (MR)-based intensive glucose control regimen, aiming for an HbA_{1c} level of 6.5% or lower or to standard glucose control based on local guidelines of participating countries. In a factorial design, participants were also randomised to either a fixed combination of perindopril and indapamide (4 mg/1.25 mg) or matching placebo, after a 6 week active run-in period. Approval for the trial was obtained from each centre's institutional review board and all participants provided written informed consent.

Follow-up and assessments Follow-up data used here come from study visits common to all participants (3, 4 and 6 months after randomisation and every 6 months thereafter). At each of these visits, information was collected on adherence to, and tolerability of, study treatments and occurrence of study outcomes. Blood glucose and HbA_{1c} were measured at baseline, 6 months and annually thereafter. All measurements were performed in local laboratories, and each HbA_{1c} assay was standardised, as reported previously [14].

Glycaemic exposure Glycaemic levels over time were assessed as the mean HbA_{1c} of measurements taken at baseline, 6 months and every 12 months for each individual. The average HbA_{1c} for an individual was the mean as obtained by weighting each measurement for the individual by the time intervals between measurements during follow-up and prior to the first event. For example, someone with HbA_{1c} values of 9.0% at baseline, 8.5% at 6 months, 8.0% at 12 months, 7.5% at 24 months and who died at 32 months would have a mean HbA_{1c} of $(9\times6+8.5\times6+8\times12+7.5\times8)/32=8.16\%$.

Outcomes The main outcomes for this study were macrovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), death from any cause, cardiovascular death and microvascular events (new or worsening nephropathy that is, development of macroalbuminuria, defined as a urinary albumin/creatinine ratio [UACR] of more than 33.9 mg albumin/mmol creatinine, or doubling of the serum creatinine level to at least 200 μmol/l, the need for renal-replacement therapy, or death due to renal disease; or retinopathy that is, development of proliferative retinopathy, macular oedema or diabetes-related blindness or the use of retinal photocoagulation therapy). Only the first event of the relevant outcome type was included in each analysis. All these events were reviewed and validated by an independent endpoint adjudication committee. The other outcomes studied were coronary events (death due to coronary heart disease and non-fatal myocardial infarct), cerebrovascular events (death due to cerebrovascular disease or non-fatal stroke), new or worsening nephropathy, new or worsening retinopathy and peripheral vascular events.

Statistical analysis For all outcomes, unadjusted and adjusted HRs for each mean HbA_{1c} decile were estimated using Cox proportional hazards models, overall and separately for the intensive and standard treatment groups. The floating absolute risk approach was used to find 95% CI [15]. Adjustments were made for baseline age, sex, mean UACR, mean estimated glomerular filtration rate (eGFR), mean systolic blood pressure (SBP), currently treated hypertension, history of macrovascular disease, mean triacylglycerols, mean LDL cholesterol, mean HDL cholesterol, mean BMI, smoking, drinking, ECG abnormality (left ventricular hypertrophy, Q-wave, atrial fibrillation), duration of diabetes and randomised treatment allocation. The mean HbA_{1c} group closest to the target HbA_{1c} level for intensive glucose control in ADVANCE (6.5%) was chosen as the reference category. Locally weighted scatterplot smoothing [16] was applied to the HR by decile to describe the shape of the relationship between HbA_{1c} and the HR. This was used to decide on appropriate spline models to fit in order to quantify the continuous effects of HbA_{1c} for the three main outcomes in the entire dataset [17]. As this indicated that binary spline models were always appropriate, unadjusted and adjusted HRs per 1% change in mean HbA_{1c} level were then estimated above and below the knots. For each of the three main outcomes, the nadir of the HbA_{1c}-risk association, i.e. the point at which the association changes direction, was estimated by fitting a quadratic regression model in HbA_{1c} within the range of 0–8%. Bias and acceleration-corrected 95% CI for each threshold was obtained from 10,000 bootstrap samples.

Three sets of sensitivity analyses were performed for the three main outcomes. First, binary spline models for the overall dataset were repeated using other potential knots, chosen to lie within the range for HbA_{1c} of 6.0% to 7.5%. This also presented an objective method for choosing the 'best' knot within this range, as the knot after which the slope in the HbA_{1c} range below the knot changed direction. Second, the primary spline models, with the 'best' knot, were repeated within pre-specified subgroups defined by treatment allocation (intensive versus standard glucose control), median age (<65 versus ≥65 years), sex, median duration of diabetes (<7 versus ≥7 years) and each of prevalent macrovascular and microvacular disease at study entry (yes

versus no). The heterogeneity in the relationships was tested by adding, to the relevant model, an interaction term between the HbA_{1c} variable taken as a continuous variable and subgroup. Third, the primary spline models were refitted to analyse the relationship between the single baseline HbA_{1c} (rather than the mean follow-up HbA_{1c}) and the hazards for the three outcomes.

All analyses were performed with SAS version 9.1 (SAS, Cary, NC, USA) or Stata version 11 (Statacorp, College Station, TX, USA). All p values were calculated using two-tailed tests.

Results

Study population and baseline characteristics In total, 11,086 participants were included in the observational analyses after the exclusion of 54 participants for whom levels of HbA_{1c} at baseline were not available. The mean HbA_{1c} was 7.5% (standard deviation 1.6%), with no difference between the treatment arms (Table 1). There were 4,112 participants included who were from Asia (China, India, Philippines and Malaysia) and 6,974 from the other regions of Europe, North America and Australia/New Zealand.

Association between glycaemic exposure and risks of major vascular outcomes and mortality The mean HbA_{1c} of participants during follow-up was 7.1% (SD 1.1%) with a range from 4.6% to 14.8%. There was a non-linear relationship between glycaemic exposure assessed as mean HbA_{1c} level and the risk of the three main outcomes, with clear evidence of a threshold above which risk increased (Fig. 1). The HRs for the three main outcomes above and below varying HbA_{1c} knots are given in Electronic supplementary material (ESM) Table 1. Estimates and bootstrap 95% CI for the quadratic nadirs of the three risk associations were: macrovascular disease 6.57 (5.19, 7.26), death 6.54 (6.16, 6.75) and microvascular disease 6.14 (4.33, 6.51). From all these analyses combined, we concluded that the threshold is in the range of 6.5% to 7.0% for macrovascular disease and death, and in the range of 6.0% to 6.5% for microvascular disease. The lower threshold for microvascular disease is supported by the results of the 10,000 bootstrap samples in which 87% of samples had a lower quadratic nadir for microvascular compared with macrovascular disease, and 94% had a lower quadratic nadir for microvascular disease compared with death.

Accordingly, in round terms and erring on the side of caution, the most appropriate risk thresholds for HbA_{1c} were 7.0% for macrovascular disease and death, and 6.5% for microvascular disease. Above the thresholds, there was a log-linear relationship such that the risks of the three main outcomes significantly increased with each higher HbA_{1c} level (ESM Fig. 1, all $p<0.0001$). Every 1% higher mean HbA_{1c} level above these thresholds was associated with a 38% higher risk of a macrovascular event, a 40% higher risk of a microvascular event and a 38% higher risk of death

Table 1 Baseline clinical characteristics of ADVANCE patients included in the observational HbA_{1c} analyses

Characteristic	Overall (n=11,086)
Age (years)	66±6
Female, *n* (%)	4,703 (42.4)
Duration of diabetes (years), median (IQR)	7 (3–11)
Blood glucose control	
HbA_{1c} (%)	7.51±1.56
Fasting blood glucose (mmol/l)	8.49±2.77
Blood pressure control	
Systolic blood pressure (mmHg)	145.0±21.5
Systolic blood pressure (mmHg)	80.6±10.9
Currently treated hypertension, *n* (%)	7,623 (68.8)
Other risk factors	
Serum creatinine (μmol/l)	87±25
UACR (mg/mmol), median (IQR)	1.7 (0.8–4.5)
Serum LDL-cholesterol (mmol/l)	3.11±1.03
Serum HDL-cholesterol (mmol/l)	1.26±0.35
Serum triacylglycerol (μmol/l), median (IQR)	1.60 (1.2–2.3)
BMI (kg/m^2)	28±5
History of macrovascular disease, *n* (%)	3,572 (32.2)
History of microvascular disease, *n* (%)	1,153 (10.4)
ECG abnormalities (Q-wave, LVH or AF), *n* (%)	1,972 (17.8)
Current smoking, *n* (%)	1,544 (13.9)
Current drinking, *n* (%)	3,379 (30.5)
Glucose-lowering drug, *n* (%)	
Gliclazide	861 (7.8)
Other sulfonylurea	7,056 (63.7)
Metformin	6,718 (60.6)
Thiazolidinedione	405 (3.7)
Acarbose	958 (8.6)
Glinide	185 (1.7)
Any glucose-lowering drug	10,082 (90.9)
Insulin	155 (1.4)
Other drug, *n* (%)	
Statins	3,134 (28.3)
Other lipid-modifying drug	929 (8.4)
Aspirin	4,876 (44)
Other anti-platelet agent	504 (4.5)
Any blood pressure-lowering drug	8,333 (75.2)
Study treatment, *n* (%)	
Randomised blood pressure treatment	5,536 (49.9)
Randomised glucose treatment	5,543 (50.0)

Values are mean±SD unless stated otherwise

AF, atrial fibrillation; LVH, left ventricular hypertrophy

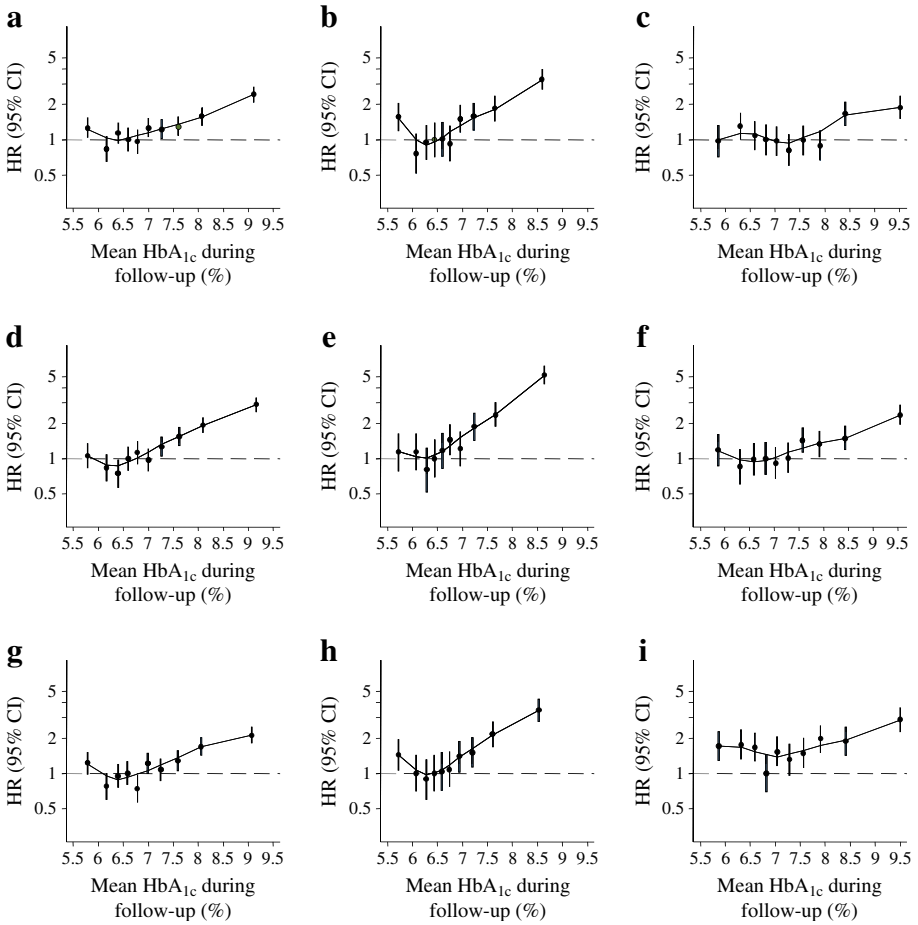

Fig. 1 Adjusted HRs for major macrovascular events (**a**) overall, (**b**) intensive group, (**c**) standard group; major microvascular events (**d**) overall, (**e**) intensive group, (**f**) standard group; and all-cause death (**g**) overall, (**h**) intensive group, (**i**) standard group, by decile of mean HbA_{1c} levels during follow-up with locally weighted scatterplot smoothing lines. The deciles are <6.00%, 6.01–6.29%, 6.30–6.49%, 6.50–6.69%, 6.70–6.89%, 6.90–7.11%, 7.12–7.39%, 7.40–7.79%, 7.80–8.49% and >8.5%. The centres of the squares are placed at the point estimates and vertical lines represent the corresponding 95% CI. The area of each square is proportional to the inverse variance of each estimate. The estimates are adjusted for baseline and time-dependent age, sex, mean UACR, mean eGFR, mean SBP, currently treated hypertension, history of macrovascular disease, mean triacylglycerol, mean LDL-cholesterol, mean HDL-cholesterol, mean BMI, smoking, drinking, ECG abnormality (left ventricular hypertrophy, Q-wave, atrial fibrillation), duration of diabetes and randomised treatment allocation. The HbA_{1c} reference group for all outcomes was 6.50–6.69%. CIs were estimated using the floating absolute risk method

(Table 2). Below these thresholds, there was no clear relationship between mean HbA_{1c} levels and the risks of the three main outcomes (all $p>0.40$, Table 2).

When the associations were examined by allocation to intensive or standard glucose control, the relationship between mean HbA_{1c} and the three main outcomes was qualitatively similar. Above the thresholds, the magnitude of these associations was always larger in the intensive than the standard control group (p for interaction <0.001, Table 2). However, the overall variation in mean HbA_{1c} levels was always less in the intensive than the standard control group (mean of standard deviation of HbA_{1c} levels, 0.63% and 0.73% respectively, ESM Table 2). Below these thresholds, there was no clear relationship between mean HbA_{1c} levels and the risks of the three main outcomes in either the intensive or standard control groups (all $p>0.80$, Table 2).

Similar non-linear relationships were observed for the secondary outcomes of coronary events, cerebrovascular events, peripheral vascular events, cardiovascular death, new onset retinopathy and new onset nephropathy (Fig. 2).

When the relationships were examined in subgroups defined by baseline age, sex, duration of diabetes, history of macrovascular or microvascular disease, the associations were similar with the magnitude of the effects only slightly greater for women than men and for those with longer rather than shorter duration of diabetes (ESM Table 3). When baseline HbA_{1c} level replaced mean HbA_{1c} level in the spline models, similar relationships were observed, although

Table 2 Unadjusted and adjusted hazards of adverse outcomes associated with a 1% higher mean HbA_{1c} level above and below specified knots

Endpoints	HR (95% CI) per 1% higher mean HbA_{1c} level							
	Knots	Overall population				Intensive glucose control	Standard glucose control	*p* value (intensive vs standard)
		Unadjusted	*p* value	Adjusted[a]	*p* value	Adjusted[a]	Adjusted[a]	
Macrovascular events	Below 7.0	1.07 (0.91, 1.26)	0.4117	1.02 (0.86, 1.21)	0.8310	1.13 (0.89, 1.43)	0.82 (0.65, 1.04)	0.7362
	Above 7.0	1.43 (1.35, 1.51)	<0.0001	1.38 (1.30, 1.47)	<0.0001	1.58 (1.43, 1.75)	1.31 (1.21, 1.42)	0.0974
Microvascular events	Below 6.5	1.06 (0.79, 1.42)	0.7012	1.02 (0.76, 1.39)	0.8744	1.06 (0.69, 1.63)	0.82 (0.54, 1.25)	0.9016
	Above 6.5	1.58 (1.51, 1.65)	<0.0001	1.40 (1.33, 1.47)	<0.0001	1.72 (1.59, 1.87)	1.26 (1.18, 1.35)	<0.0001
All-cause death	Below 7.0	1.04 (0.88, 1.23)	0.6246	1.01 (0.85, 1.21)	0.9158	1.12 (0.87, 1.44)	0.81 (0.64, 1.04)	0.9008
	Above 7.0	1.42 (1.34, 1.51)	<0.0001	1.38 (1.29, 1.48)	<0.0001	1.67 (1.50, 1.86)	1.29 (1.18, 1.41)	0.0080

[a] Adjusted for age, sex, randomised BP and glucose treatment (excluded in randomised treatment subgroup analyses), mean UACR, mean eGFR, mean SBP, mean triacylglycerol, mean LDL-cholesterol, mean HDL-cholesterol, mean BMI and the additional baseline covariates of currently treated hypertension, history of macrovascular disease, history of microvasular disease, smoking, drinking, ECG abnormality (left ventricular hypertrophy, Q-wave, atrial fibrillation) and duration of diabetes

the magnitude of the association was attenuated (ESM Table 4).

Discussion

In people with established type 2 diabetes in the ADVANCE trial, the risks of vascular complications and death were strongly associated with glycaemic exposure. For all outcomes, there was a non-linear relationship between HbA_{1c} level and risk of events with evidence of HbA_{1c} 'thresholds' at which the lowest event rates were observed. Above these thresholds, a higher level of HbA_{1c} was significantly associated with higher risks of macrovascular, microvascular events and death in a log-linear manner. Below these thresholds, there was no significant relationship between mean HbA_{1c} level and risks. For macrovascular events and death the apparent threshold HbA_{1c} level was 7.0%, and for microvascular events the level was 6.5%. The relationships were similar among participants allocated to intensive or

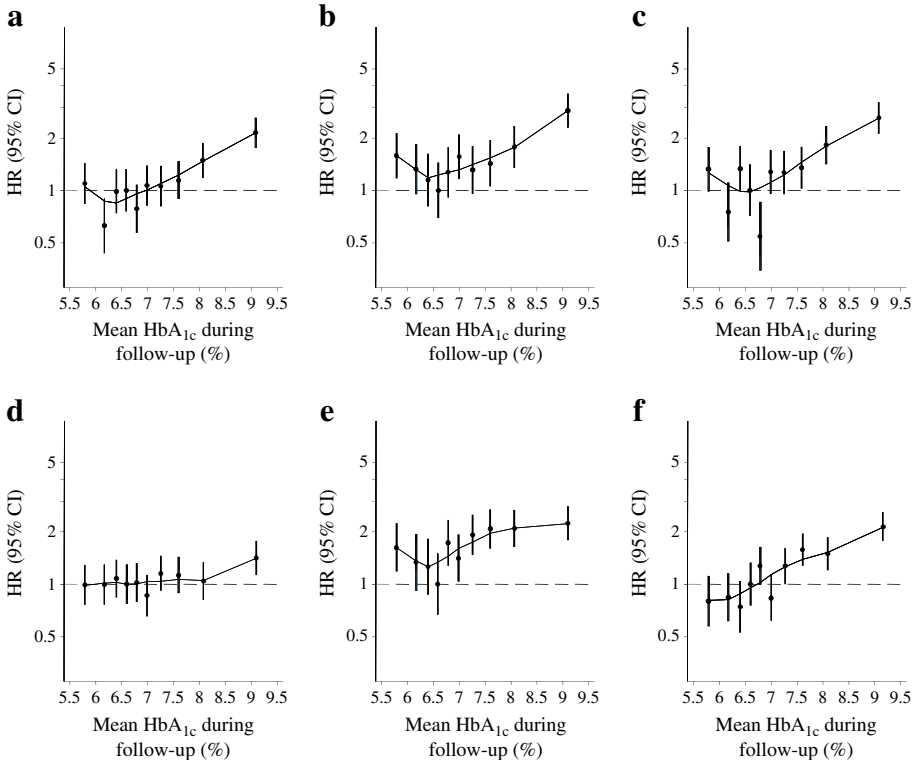

Fig. 2 Adjusted HRs for (**a**) major coronary events, (**b**) major cerebrovascular events, (**c**) cardiovascular death, (**d**) peripheral vascular events, (**e**) new or worsening nephropathy and (**f**) new or worsening retinopathy by decile of mean HbA_{1c} levels during follow-up with locally weighted scatterplot smoothing lines. For explanations see Fig. 1

standard glucose control, although the thresholds were always lower and the magnitude of the associations larger in the intensive control group. The relationships did not differ by baseline age, sex or prior history of macrovascular or microvascular disease.

The present results are in contrast to those of the UKPDS that reported no threshold effect of lower levels of HbA_{1c} on risks of macrovascular events, microvascular events or death in people with type 2 diabetes, as well as stronger associations for microvascular events than myocardial infarction [4]. This may be due to differences in the populations studied and the effects of concomitant use of other cardiovascular preventive therapies. First, ADVANCE studied patients with established diabetes, whereas the UKPDS studied patients with newly diagnosed diabetes. Second, ADVANCE included many more patients on other preventive therapies such as cholesterol-lowering, blood pressure-lowering and antiplatelet therapies. Third, as ADVANCE included higher risk patients, the number of events accumulated in the lower HbA_{1c} categories was much greater than in the UKPDS, allowing us to study the effects at these levels with greater precision. Finally, the UKPDS may have had less power to detect threshold effects as it had relatively fewer patients with mean HbA_{1c} levels less than 7.0%.

The association between HbA_{1c} level and risk of microvascular events above the HbA_{1c} threshold of 6.5% was similar to that reported by the UKPDS [4]. The benefits of aiming for near-normal HbA_{1c} levels to prevent microvascular complications therefore remain unequivocal. On the other hand, the absence of any significant association between the risks of macrovascular outcomes and death and the level of HbA_{1c} below the threshold of 7%, suggest that achieving near-normal levels of HbA_{1c} in patients with established type 2 diabetes receiving contemporary preventive care will produce little additional benefit for these outcomes within the time frame of most clinical trials.

In support of a threshold for macrovascular and mortality risks at HbA_{1c} levels of around 7%, another prospective observational study of patients from Norway has recently demonstrated the lowest risks of mortality from ischaemic heart disease in those achieving mean HbA_{1c} levels of 7.2% or less [18]. By contrast, a study of general practice patients from the UK receiving treatment for diabetes has demonstrated heightened risks of all-cause mortality and cardiac events in those with mean HbA_{1c} values less than 7.5% and called for an increase in the minimum HbA_{1c} target recommended [7]. Our data would not support a call for a higher HbA_{1c} target. Moreover, the Emerging Risk Factors Collaboration and the Atherosclerosis Risk in Communities (ARIC) study has also described non-linear relationships between fasting blood glucose levels or HbA_{1c} levels and vascular risks or mortality in populations without known diabetes with risk thresholds much lower than those observed here [6, 8]. Combining individual participant data from 102 prospective studies, the Emerging Risk Factors Collaboration report that fasting blood glucose levels of 3.8–5.6 mmol/l (in the normal range) were not related to vascular risk and that fasting blood glucose levels of 5.6–6.9 mmol/l (in the impaired fasting glucose range) were only associated with a small increase in vascular risk that did not significantly improve prediction of cardiovascular risk [6]. In contrast, the ARIC study reports increased cardiovascular and mortality risks at HbA_{1c} levels greater than 5.5%, implying that the relationship between HbA_{1c} and risks is altered by commencement of agents to lower glucose levels [8].

In the intensive and standard glucose control groups, the relationships between HbA_{1c} and risks of the major outcomes were qualitatively similar; however, the magnitude of the risks for each 1% higher HbA_{1c} level above the thresholds was consistently larger in the intensive group. This is likely to be attributable, at least in part, to more within-participant variability in the HbA_{1c} levels or regression dilution in the standard care group; over an average of six observations per participant in each group, the mean standard deviation in the standard care group was 0.73% and in the intensive control group 0.63%. (ESM Table 2). This is an expected finding as only the intervention group was treated to a target. In addition, this may reflect greater residual confounding in those who have failed to safely achieve better glycaemic control despite intensification of therapy due to worse disease severity in the context of resistant hyperglycaemia.

Strengths and weaknesses These data, in a contemporary cohort of people with type 2 diabetes, add to the existing body of evidence linking long-term glycaemia to increased risks of vascular outcomes and death. This is one of the largest studies to evaluate the association between HbA_{1c} and adverse outcomes in patients with long-standing diabetes. It demonstrates the impact of glycaemic exposure on prognosis in subgroups defined by age, sex, and prevalent macrovascular or microvascular disease. Due to the trial's liberal HbA_{1c} inclusion criteria and the degree of glucose control achieved in the intensive group participants, these analyses benefit from having a large number of individuals dispersed across a broad range of HbA_{1c} levels, including many with levels less than 7%. The analyses also have limitations. The results will not necessarily be applicable to populations without diabetes or with glucometabolic disturbances other than type 2 diabetes. There were relatively few events observed at HbA_{1c} levels less than 6.5% making the estimates of the associations at these HbA_{1c} levels less precise than at higher levels. Moreover, the selective nature of trial participants and the potential influence of randomised treatments may affect the generalisability of the findings, although the ADVANCE participants are fairly typical of

current populations with type 2 diabetes managed in the community [19]. Finally, despite extensive multiple variable adjustment, these analyses may be unable to completely eliminate the effects of residual confounding attributable to disease severity.

Conclusions

In conclusion, the risks of vascular complications and death were strongly associated with glycaemic exposure. However, although the risks of microvascular events were clearly progressively lower down to HbA_{1c} levels of 6.5%, the risks of macrovascular events and death were only clearly lower down to levels of 7.0%. This observation is consistent with the lack of clear macrovascular and mortality benefits observed in the recent clinical trials targeting HbA_{1c} levels of less than 6% or 6.5%.

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