Survival as a function of HbA$_{1c}$ in people with type 2 diabetes: a retrospective cohort study

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Summary

Background Results of intervention studies in patients with type 2 diabetes have led to concerns about the safety of aiming for normal blood glucose concentrations. We assessed survival as a function of HbA$_{1c}$ in people with type 2 diabetes.

Methods Two cohorts of patients aged 50 years and older with type 2 diabetes were generated from the UK General Practice Research Database from November 1986 to November 2008. We identified 27 965 patients whose treatment had been intensified from oral monotherapy to combination therapy with oral blood-glucose lowering agents, and 20 005 who had changed to regimens that included insulin. Those with diabetes secondary to other causes were excluded. All-cause mortality was the primary outcome. Age, sex, smoking status, cholesterol, cardiovascular risk, and general morbidity were identified as important confounding factors, and Cox survival models were adjusted for these factors accordingly.

Findings For combined cohorts, compared with the glycated haemoglobin (HbA$_{1c}$) decile with the lowest hazard (median HbA$_{1c}$ 7·5%, IQR 7·5–7·6%), the adjusted hazard ratio (HR) of all-cause mortality in the lowest HbA$_{1c}$ decile (6·4%, 6·1–6·6) was 1·52 (95% CI 1·32–1·76), and in the highest HbA$_{1c}$ decile (median 10·5%, IQR 10·1–11·2%) was 1·79 (95% CI 1·56–2·06). Results showed a general U-shaped association, with the lowest HR at an HbA$_{1c}$ of about 7·5%. HR for all-cause mortality in people given insulin-based regimens (2834 deaths) versus those given combination oral agents (2035) was 1·49 (95% CI 1·39–1·59).

Interpretation Low and high mean HbA$_{1c}$ values were associated with increased all-cause mortality and cardiac events. If confirmed, diabetes guidelines might need revision to include a minimum HbA$_{1c}$ value.

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Introduction

The main objective for care of patients with diabetes mellitus is to keep the risk of microvasular and macrovascular complications to a minimum by returning blood pressure, lipid profiles, and glycaemia to normal.[1] The specific goal for control of glycaemia is to return glycated haemoglobin (HbA$_{1c}$) to a normal range, because good glycaemic control is known to reduce risk of long-term microvascular complications in both type 1[2] and type 2 diabetes.[3,4] Researchers of the ADVANCE trial[5] and the ACCORD study[6] investigated the effect of targeted type 2 diabetes glycaemic control on macrovascular outcomes in patients with diabetes and microvascular or macrovascular disease. Both studies failed to show that achievement of good glycaemic control was associated with reduction of cardiovascular risk.

Reports of potentially raised mortality rates associated with intensive glycaemic control have triggered discussion about recommendations for treatment of type 2 diabetes, specifically relating to the optimum target for HbA$_{1c}$. Researchers have suggested that hypoglycaemia contributes to a heightened risk of mortality in patients with diabetes. Because intensive glycaemic control increases risk of hypoglycaemia with some drugs more than with others, assessment of risks associated with the different blood glucose-lowering regimens is important.

In two meta-analyses,[7,8] researchers combined data from several important trials[5,6,9] and concluded that intensive glycaemic control has positive effects on cardiovascular endpoints. However, these meta-studies were constrained by inherent limitations of the clinical trials that were analysed.

In this retrospective cohort study, our aim was to assess the association between all-cause mortality and HbA$_{1c}$ in patients with type 2 diabetes in a primary-care setting, and establish whether any evident association was independent of the diabetes treatment regimen.

Methods
Sample selection

We obtained data from routine general practice in the UK from a proprietary health data resource: the General Practice Research Database (GPRD).[10,11] GPRD was established in 1987, and contains data derived from computerised records. A detailed description of GPRD is available elsewhere.[12] GPRD data are gathered in a non-interventional way from the daily record keeping of general practitioners. Records are anonymised at the time that they are obtained. They contain the following information: demographic information, medical history (diagnoses), test results, and additional health-related data such as smoking status, drug treatments, and mortality.[13] Data

	HbA₁c deciles										All (n=27 965)
	1 (n=3513)	2 (n=3501)	3 (n=3374)	4 (n=3136)	5 (n=2884)	6 (n=2684)	7 (n=2437)	8 (n=2334)	9 (n=2133)	10 (n=1969)	
HbA₁c post index* (% total haemoglobin)	6·42% (3·30–6·72)	6·94% (6·73–7·11)	7·27% (7·12–7·40)	7·54% (7·41–7·68)	7·82% (7·69–7·96)	8·11% (7·97–8·26)	8·44% (8·27–8·63)	8·85% (8·64–9·11)	9·41% (9·12–9·84)	10·47% (9·85–16·20)	7·73% (3·30–16·20)
Men	1973 (56%)	1939 (55%)	1928 (57%)	1824 (58%)	1699 (59%)	1596 (60%)	1410 (58%)	1370 (59%)	1254 (59%)	1055 (54%)	16 048 (57%)
Age† (years)	67·4	66·3	65·5	64·7	64·0	63·7	62·7	62·1	61·0	59·7	64·1
Previous SBP‡ (mm Hg)	145 (17)	144 (16)	144 (16)	144 (16)	144 (17)	143 (17)	144 (17)	144 (17)	144 (17)	145 (18)	144 (17)
Smoked ever (%)	2178 (62%)	2240 (64%)	2159 (64%)	1976 (63%)	1846 (64%)	1745 (65%)	1487 (61%)	1447 (62%)	1322 (62%)	1201 (61%)	17 618 (63%)
Previous total cholesterol‡ (mmol/L)	5·2 (1·0)	5·3 (1·0)	5·3 (1·0)	5·4 (1·1)	5·4 (1·0)	5·5 (1·1)	5·6 (1·1)	5·6 (1·1)	5·7 (1·2)	5·8 (1·3)	5·4 (1·1)
Male weight (kg)	90 (16)	89 (16)	88 (15)	89 (16)	90 (16)	90 (16)	91 (17)	91 (17)	92 (18)	93 (19)	90 (16)
Female weight (kg)	79 (17)	79 (16)	78 (16)	78 (16)	78 (16)	79 (17)	79 (17)	81 (17)	81 (18)	84 (19)	79 (17)
Previous LVD§	892 (25%)	846 (24%)	760 (23%)	702 (22%)	629 (22%)	620 (23%)	552 (23%)	466 (20%)	403 (19%)	360 (18%)	6230 (22%)
Diabetes duration¶ (years)											
Mean (SD)	5·3 (4·2)	5·3 (4·1)	5·5 (4·1)	5·4 (3·9)	5·4 (3·9)	5·6 (4·1)	5·6 (4·0)	5·5 (4·0)	5·2 (3·7)	5·4 (3·9)	5·4 (4·0)
Median (IQR)	4·2 (2·2–7·3)	4·2 (2·3–7·1)	4·5 (2·4–7·4)	4·5 (2·4–7·4)	4·4 (2·4–7·4)	4·6 (2·4–7·4)	4·8 (2·5–7·8)	4·6 (2·5–7·5)	4·3 (2·4–7·0)	4·4 (2·3–7·6)	4·4 (2·4–7·4)
Previous vision problem	502 (14%)	486 (14%)	509 (15%)	424 (14%)	351 (12%)	343 (13%)	278 (11%)	246 (11%)	253 (12%)	212 (11%)	3604 (13%)
Creatinine >130 μmol/L‖	243 (7%)	204 (6%)	184 (6%)	167 (5%)	133 (5%)	111 (4%)	110 (5%)	86 (4%)	71 (3%)	57 (3%)	1366 (5%)
Deaths	301 (9%)	238 (7%)	231 (7%)	207 (7%)	190 (7%)	179 (7%)	175 (7·%)	168 (7%)	161 (8%)	185 (9%)	2035 (7%)

Achieved HbA₁c was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR) unless otherwise stated. HbA₁c=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA₁c recorded between study index date and event or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 μmol/L before index date.

Table 1: Baseline characteristics of cohort 1 (oral hypoglycaemic agents) by baseline, stratified by mean HbA₁c decile group

were obtained from November, 1986, to November, 2008, inclusively.

We identified all patients who had a diagnosis of type 2 diabetes and whose treatment history included evidence of a specific escalation of their diabetes treatment. We included in the analysis those who had received oral blood-glucose lowering drugs or a prescription of insulin, and were older than 50 years. Patients also needed to have a case history of more than 6 months before they were eligible for classification into one of two treatment groups for analysis. We excluded those who had a record of diabetes secondary to other causes (eg, gestational or drug-induced diabetes) and those who did not have at least 12 months of exposure after their respective index date—ie, the date at which they were started with either specific regimen. Ethics approval was given by the Scientific and Ethics Advisory Group at GPRD on Aug 1, 2008; protocol number 08-049R.

Procedures

We classified patients into two groups that were dependent on broad treatment regimens. Cohort 1 was defined as patients with a newly identified switch from oral blood-glucose lowering monotherapy to a combination oral regimen with a sulphonylurea plus metformin. Those included in cohort 2 were initiated on insulin with or without concomitant oral hypoglycaemic agents—their diabetes having previously been treated with oral agents alone. This two-cohort approach was intended to establish whether any emergent patterns were independent of diabetes treatment regimen.

Large-vessel disease was defined as any record of myocardial infarction, stroke, coronary revascularisation, carotid or peripheral arterial revascularisation, or angina of cardiac origin; it was used as a covariate in the survival models, and independently as a secondary endpoint if an event was recorded for the first time after the index date. We used post-index mean HbA₁c to express glycaemic control, calculated as the mean of all observations recorded between the index date (first prescription of intensified diabetes therapy) and the respective outcome event (death or large-vessel event) or the censoring point (further switching of treatment or the last recorded database observation). To account for individual changes in HbA₁c over time and to avoid violation of an assumption of the survival analysis, we undertook a sensitivity analysis[14] of the way in which the HbA₁c parameter was introduced into the Cox model in two alternative, time-dependent ways. First, it was introduced as a yearly mean value with the last observation carried forward for missing data, and second as an updated, cumulative, yearly mean value. Cohorts were divided into deciles by the rank of the mean of all post-index HbA₁c values or yearly values where appropriate.

The primary outcome measure was all-cause mortality. The secondary outcome measure was occurrence of a major cardiovascular event, but only in those patients with no record of cardiovascular disease before the index date.

	HbA₁c deciles										All (n=20005)
	1 (n=1289)	2 (n=1291)	3 (n=1424)	4 (n=1661)	5 (n=1878)	6 (n=2148)	7 (n=2354)	8 (n=2463)	9 (n=2660)	10 (n=2837)	
HbA₁c post index* (% total haemoglobin)	6·38% (3·97–6·72)	6·95% (6·73–7·11)	7·28% (7·12–7·40)	7·55% (7·41–7·68)	7·83% (7·69–7·96)	8·11% (7·97–8·26)	8·45% (8·27–8·63)	8·87% (8·64–9·11)	9·42% (9·12–9·84)	10·56% (9·85–18·80)	8·31% (3·97–18·80)
Men	680 (53%)	726 (56%)	780 (55%)	911 (55%)	1035 (55%)	1128 (53%)	1262 (54%)	1315 (53)	1320 (50%)	1409 (50%)	10566 (53%)
Age† (years)	65·9 (11·2)	66·3 (10·3)	65·5 (10·0)	64·9 (10·5)	64·4 (10·5)	64·7 (10·5)	63·4 (10·6)	63·1 (10·9)	62·3 (11·3)	60·3 (11·5)	63·6 (11·0)
Previoius SBP‡ (mmHg)	145 (19)	145 (18)	145 (18)	144 (18)	144 (18)	144 (18)	143 (17)	143 (18)	143 (18)	142 (18)	143 (18)
Smoked ever (%)	786 (61%)	852 (66%)	897 (63%)	1030 (62%)	1202 (64%)	1332 (62%)	1483 (63%)	1527 (62%)	1649 (62%)	1731 (61%)	12603 (63%)
Total cholesterol‡ (mmol/L)	5·3 (1·2)	5·3 (1·1)	5·3 (1·1)	5·3 (1·0)	5·4 (1·1)	5·4 (1·1)	5·4 (1·1)	5·5 (1·2)	5·6 (1·2)	5·6 (1·2)	5·5 (1·2)
Male weight‡ (kg)	88 (17)	87 (16)	86 (16)	88 (16)	86 (16)	86 (16)	87 (16)	87 (17)	88 (17)	90 (19)	88 (17)
Female weight‡ (kg)	77 (18)	79 (17)	79 (18)	77 (17)	79 (17)	77 (16)	78 (17)	79 (17)	79 (19)	81 (19)	79 (18)
Previous LVD§	459 (36%)	435 (34%)	411 (29%)	505 (30%)	569 (30%)	625 (29%)	733 (31%)	711 (29%)	766 (29%)	723 (26%)	5937 (30%)
Diabetes duration¶ (years)											
Mean (SD)	6·8 (5·2)	7·5 (5·1)	8·1 (5·4)	7·8 (5·3)	8·0 (5·1)	8·2 (5·1)	8·0 (5·0)	7·9 (5·1)	7·9 (5·0)	7·3 (4·9)	7·8 (5·1)
Median (IQR)	5·9 (2·6–9·9)	6·9 (3·4–10·8)	7·4 (3·8–11·5)	7·1 (3·5–11·1)	7·2 (4·0–11·3)	7·4 (4·3–11·4)	7·4 (4·0–11·2)	7·2 (3·8–11·2)	7·2 (4·0–11·2)	6·5 (3·4–10·4)	7·1 (3·7–11·0)
Previous vision problems	251 (20%)	272 (21%)	320 (23%)	341 (21%)	380 (20%)	501 (23%)	524 (22%)	523 (21%)	557 (21%)	556 (20%)	4225 (21%)
Creatinine >130 μmol/L‖	205 (16%)	185 (14%)	182 (13%)	215 (13%)	203 (11%)	248 (12%)	213 (9%)	251 (10%)	257 (10%)	250 (9%)	2209 (11%)
Deaths	232 (18%)	204 (16%)	209 (15%)	192 (12%)	211 (11%)	271 (13%)	305 (13%)	334 (14%)	404 (15%)	472 (17%)	2834 (14%)

Achieved HbA₁c was the mean of any values recorded between the index date and death or censor. Data are median (range), n (%), mean (SD), or median (IQR). HbA₁c=glycated haemoglobin. SBP=systolic blood pressure. LVD=large-vessel disease. *Mean HbA₁c recorded between study index date and event date or censor date. †At index date. ‡Mean of all observations in year before index date. §Clinically emergent large-vessel disease before index date (defined by ACCORD[6] trial criteria). ¶Duration of diabetes before index date from first relevant clinical event. ‖Any record of serum creatinine test result >130 μmol/L before index date.

Table 2: Baseline characteristics of cohort 2 (insulin treated) at baseline, stratified by mean HbA₁c decile group

Statistical methods

Survival was assessed with Cox proportional hazards models, with use of SPSS version 15. In addition to the HbA₁c decile, the following covariates were included in the base case model: age at index date, sex, smoking status, mean post-index total cholesterol, baseline body-mass index, and general comorbidity. Three measures of the level of baseline morbidity were generated: (1) a record of any large-vessel disease event before the index date, (2) the total number of contacts with the general practitioner in the year before the index date (log transformed), and (3) the Charlson index (both unadjusted and adjusted for age).[15] The Charlson comorbidity index predicts the relative likelihood of 1-year mortality for a patient who might have any of 22 comorbid disorders, such as heart disease or cancer.[16] All these risk factors showed significant differences at baseline between HbA₁c deciles. We used a manual forward-inclusion method, in which the p value for every parameter was p=0·05 or less, to specify the final adjusted Cox models.

We tested the proportional hazards assumption for the Cox models by examination of the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that progressed to an event (censored cases were excluded).[17] The p values were two-sided, and 95% CIs were calculated for HRs. For cases whose duration of follow-up was sufficient to allow them to be included in both cohorts, the values from the first cohort membership (almost always cohort 1) were censored at the start of membership of the second cohort.

Survival was assessed in two ways. First, we measured survival with all data by separate stratification of the two treatment cohorts. Second, we compared the two cohorts in one model, controlling for other variables. In modelling of the combined cohorts, patients with dual cohort membership (n=5588) were included in the model twice on the basis that the two constructed treatment cohorts represent real-life options in a strategy to escalate treatment for type 2 diabetes to meet glycaemic goals. To test the effect of dual cohort membership on the assumption of independent observations, we did a sensitivity analysis by fitting the model with single-cohort cases only. Results from this model were similar to those from the model with all patients included.

Role of the funding source

The sponsors of the study had a role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication. The sponsor provided the proprietary GPRD data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 27965 patients who met the criteria for cohort 1. Table 1 shows baseline characteristics of this cohort and provides baseline characteristics by HbA₁c decile. Baseline mean HbA₁c (before treatment escalation

	Model 1: all patients		Model 2: cohort 1 (met plus sulph)		Model 3: cohort 2 (insulin-based regimens)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Age at baseline (years)	1·08 (1·08–1·09)	<0·0001	1·10 (1·09–1·11)	<0·0001	1·07 (1·07–1·08)	<0·0001
Sex (men *vs* women)	1·34 (1·26–1·43)	<0·0001	1·25 (1·12–1·38)	<0·0001	1·41 (1·29–1·54)	<0·0001
Smoking status (ever *vs* never)	1·10 (1·03–1·18)	0·0063	1·18 (1·06–1·31)	0·0019	1·05 (0·96–1·15)	0·2760
Mean total cholesterol (mmol/L)	1·30 (1·26–1·35)	<0·0001	1·40 (1·33–1·47)	<0·0001	1·23 (1·17–1·28)	<0·0001
Previous LVD (yes *vs* no)	1·21 (1·13–1·30)	<0·0001	1·28 (1·15–1·43)	<0·0001	1·18 (1·08–1·29)	<0·004
Cohort (insulin *vs* OHA combination)	1·49 (1·39–1·59)	<0·0001		NA		NA
Age adjusted Charlson (C) index, C 1 (reference)						
C 2	1·52 (1·40–1·64)	<0·0001	1·55 (1·38–1·74)	<0·0001	1·51 (1·35–1·68)	<0·0001
C 3	2·06 (1·88–2·26)	<0·0001	1·86 (1·61–2·15)	<0·0001	2·17 (1·92–2·45)	<0·0001
C 4	2·79 (2·48–3·14)	<0·0001	2·57 (2·12–3·13)	<0·0001	2·88 (2·48–3·34)	<0·0001
C 5	3·66 (3·11–4·3)	<0·0001	2·15 (1·52–3·03)	<0·0001	4·31 (3·57–5·21)	<0·0001
C 6	3·16 (2·42–4·13)	<0·0001	1·83 (1·03–3·26)	0·0405	3·72 (2·74–5·04)	<0·0001
C 7	4·71 (3·28–6·76)	<0·0001	5·67 (2·34–13·75)	<0·0001	4·62 (3·10–6·88)	<0·0001
C 8	8·17 (4·61–14·49)	<0·0001	7·39 (2·36–23·09)	0·0006	8·97 (4·61–17·45)	<0·0001
C 9	3·10 (1·29–7·46)	0·0117	7·06 (2·27–22·01)	0·0007	1·95 (0·49–7·81)	0·3480
HbA1c as mean of values by decile*						
D 1 (mp 6·4%)	1·52 (1·32–1·76)	<0·0001	1·30 (1·07–1·58)	0·0072	1·79 (1·45–2·22)	<0·0001
D 2 (mp 6·9%)	1·24 (1·07–1·44)	0·0036	1·07 (0·88–1·31)	0·4882	1·45 (1·17–1·80)	0·0007
D 3 (mp 7·3%)	1·18 (1·02–1·37)	0·0234	1·03 (0·85–1·26)	0·7716	1·35 (1·09–1·67)	0·0001
Reference D 4 (mp 7·5%)	..	..	..	..	..	..
D 5 (mp 7·8%)	1·01 (0·87–1·17)	0·8809	1·06 (0·86–1·3)	0·5872	0·98 (0·79–1·21)	0·8564
D 6 (mp 8·1%)	1·07 (0·93–1·24)	0·3586	0·99 (0·80–1·23)	0·9162	1·15 (0·95–1·41)	0·1608
D 7 (mp 8·4%)	1·17 (1·01–1·35)	0·0349	1·12 (0·90–1·39)	0·3067	1·21 (1·00–1·48)	0·0544
D 8 (mp 8·9%)	1·14 (0·99–1·32)	0·0707	1·09 (0·87–1·37)	0·4368	1·21 (0·99–1·47)	0·0577
D 9 (mp 9·4%)	1·36 (1·18–1·57)	<0·0001	1·23 (0·98–1·55)	0·0733	1·46 (1·21–1·77)	<0·0001
D 10 (mp 10·6%)	1·79 (1·56–2·06)	<0·0001	1·93 (1·55–2·42)	<0·0001	1·80 (1·49–2·17)	<0·0001

Cohort 1=26 866 people and 1699 events (6·1%), cohort 2=18 994 cases and 2404 events (12%). Cases with any missing covariate data were automatically excluded from the Cox models; thus, total cases analysed are slightly reduced from the initial cohort data. Met=metformin. Sulph=sulphonylurea. LVD=large-vessel disease. OHA=oral hypoglycaemic agents. D=decile. mp=median point. *From index date to event or censor.

*Table 3:* Cox proportional hazard models for progression to all-cause mortality

index date) was 9·0% (SD 1·5). The age and proportion of patients with a previous diagnosis of large-vessel disease were highest in the group with the lowest post-index mean HbA1c.

We identified 20 005 patients who met criteria for cohort 2. Table 2 shows baseline characteristics of this cohort and provides baseline characteristics by HbA1c decile. Baseline mean HbA1c (before the index date) was 10·0% (1·9). 30% of patients had previous large-vessel disease. The proportion of patients with previous large-vessel disease was highest in the group that had the lowest post-index mean HbA1c. Mean and median diabetes duration were longer in cohort 2 than in cohort 1 (tables 1 and 2). As expected with a long duration of type 2 diabetes, more patients from cohort 2 than from cohort 1 had vision problems and creatinine concentrations higher than 130 μmol/L.

Mean follow-up was 4·5 years (SD 2·7) and median follow-up 3·9 years (IQR 2·5–5·9) in cohort 1 and 5·2 years (3·6) and 4·4 years (2·6–7·2) in cohort 2. This follow-up equated to 125 968 person-years of treatment in cohort 1 and 104 106 person-years in cohort 2. Fewer deaths were recorded in cohort 1 than in cohort 2. Unadjusted mortality rates were 16·2 deaths per 1000 person-years of follow-up in cohort 1 and 27·2 deaths in cohort 2. Mortality varied by post-index HbA1c decile in both cohorts, with increased unadjusted mortality in the lowest and highest HbA1c deciles (tables 1 and 2). Patients included in decile 4 (median HbA1c of 7·5%, IQR 7·5–7·6%), the reference group, had the lowest hazard of death across the range of HbA1c deciles.

HbA1c values in the lowest decile (median 6·4%; IQR 6·2–6·6 in cohort 1 and 6·4%; 6·1–6·6 in cohort 2) were associated with a heightened risk of all-cause mortality for all patients. Furthermore, mean HbA1c in the highest decile (median HbA1c 10·5%, 10·1–11·2) was associated with an increased risk of all-cause mortality. Higher mortality HRs associated with lowest and highest adjusted mean HbA1c were evident for the lowest and highest mean HbA1c deciles in both cohorts (table 3 and figure 1). Compared with the reference decile, the only deciles in cohort 1 for which HRs were significantly different were deciles 1 and 10, whereas for cohort 2 significant differences were evident for deciles 1, 2, 3, 9,
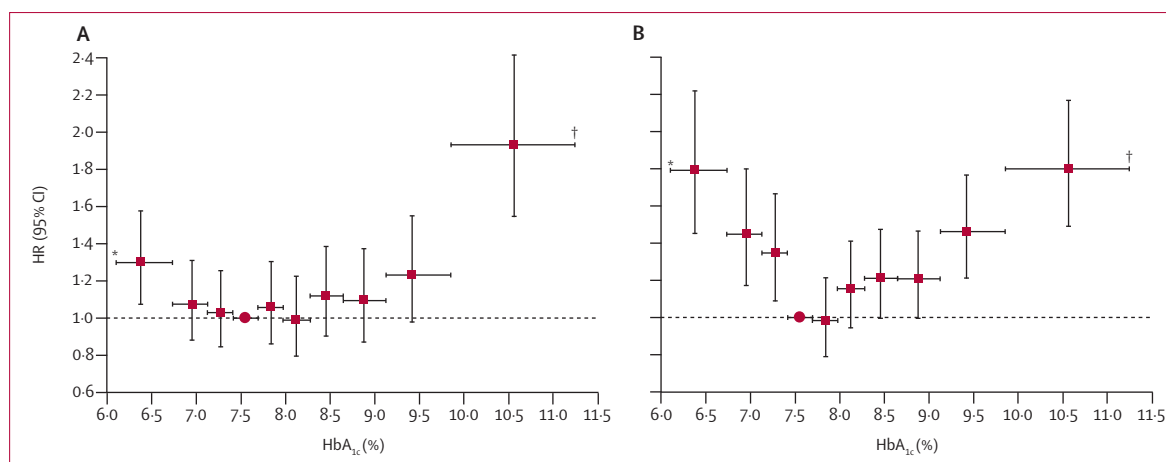
Figure 1: Adjusted hazard ratios for all-cause mortality by HbA$_{1c}$ deciles in people given oral combination and insulin-based therapies
Cox proportional hazards models were used, with the HbA$_{1c}$ base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA$_{1c}$ range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

and 10. Table 3 shows the complete survival models. These findings were consistent when high-risk patients with previous large-vessel disease at baseline were excluded from Cox analysis—eg, decile 1, HR 1·54, 95% CI 1·28–1·84; and decile 10, 1·36, 1·14–1·61.

This U-shaped pattern of association remained similar when HbA$_{1c}$ was introduced into the Cox model with two time-dependent methods (figure 2). With respect to decile 4, HRs for the time-dependent analysis of yearly mean HbA$_{1c}$ values (with last observation carried forward in cases of missing data) were 1·65 (95% CI 1·44–1·90) for decile 1 and 1·34 (1·15–1·55) for decile 10. With updated, cumulative, yearly mean values HbA$_{1c}$ values, the HRs were 1·25 (1·09–1·44) for decile 1 and 1·61 (1·40–1·85) for decile 10 (figure 2).

Table 3 lists the covariates that were included in the Cox models. We identified increased risk of all-cause mortality in people given insulin-based regimens compared with those given combination oral blood-glucose lowering agents. Furthermore, in sensitivity analysis, after exclusion of patients with high cardiovascular risk (record of previous large-vessel disease) or renal impairment, the HR for insulin-based therapy versus oral combination therapy with oral hypoglycaemic agents was 1·46 (1·34–1·59).

After the index date, we recorded large-vessel disease events in 1707 of 20 817 (8·2%) patients with no previous large-vessel disease in cohort 1, and in 1608 of 13 475 (11·9%) patients in cohort 2. The crude event rate was 18·8 per 1000 person-years in cohort 1, and 24·1 in cohort 2. With introduction of mean HbA$_{1c}$ as a time-fixed covariate into the Cox model, the adjusted risk of progression to overt large-vessel disease for all patients had the same general U-shaped association as that for all-cause mortality (figure 3). Relative to the referent HbA$_{1c}$ category (decile 4), the HR for adjusted risk of progression to a large-vessel disease event in decile 1 was 1·54 (1·28–

1·84). In decile 10, the HR was 1·36 (1·14–1·61). Consistent with all-cause mortality, insulin treatment (cohort 2 vs cohort 1) was associated with an increased likelihood of progression to first large-vessel disease event (adjusted HR 1·31, 1·22–1·42).

Discussion

We have shown that an HbA$_{1c}$ of approximately 7·5% was associated with lowest all-cause mortality and lowest progression to large-vessel disease events. An increase or decrease from this mean HbA$_{1c}$ value was associated with heightened risk of adverse outcomes. The U-shaped pattern of risk association was sufficiently similar in the two treatment cohorts to suggest that risk of mortality with respect to HbA$_{1c}$ was independent of treatment regimen. Furthermore, we noted that mortality risk between the two treatment cohorts differed, showing that insulin treatment was associated with increased mortality. This general pattern of association remained consistent with time-dependent HbA$_{1c}$ as a covariate.

Our results lend support to findings of the ACCORD trial.[6,18] In this trial, results showed that patients with cardiovascular disease or at least two risk factors for cardiovascular disease or severe atherosclerosis, and an HbA$_{1c}$ of 7·5% who were submitted to intensive glycaemic control (target HbA$_{1c}$<6·0% vs 7·0–7·9%), had increased mortality (HR 1·22, 95% CI 1·01–1·46). However, our data are at variance with the UKPDS follow-up data,[19] which showed that intensive treatment was associated with a reduced risk for all diabetes-related endpoints. However, less than 15% of patients in the UKPDS[20] trial achieved an HbA$_{1c}$ of less than 6·5%. Results from the initial randomised phase of UKPDS showed a non-significant 14% relative-risk reduction in myocardial infarctions per 1% reduction in HbA$_{1c}$.[21] Results from our analysis confirm a weak association between HbA$_{1c}$ and reduced risk of large-vessel disease
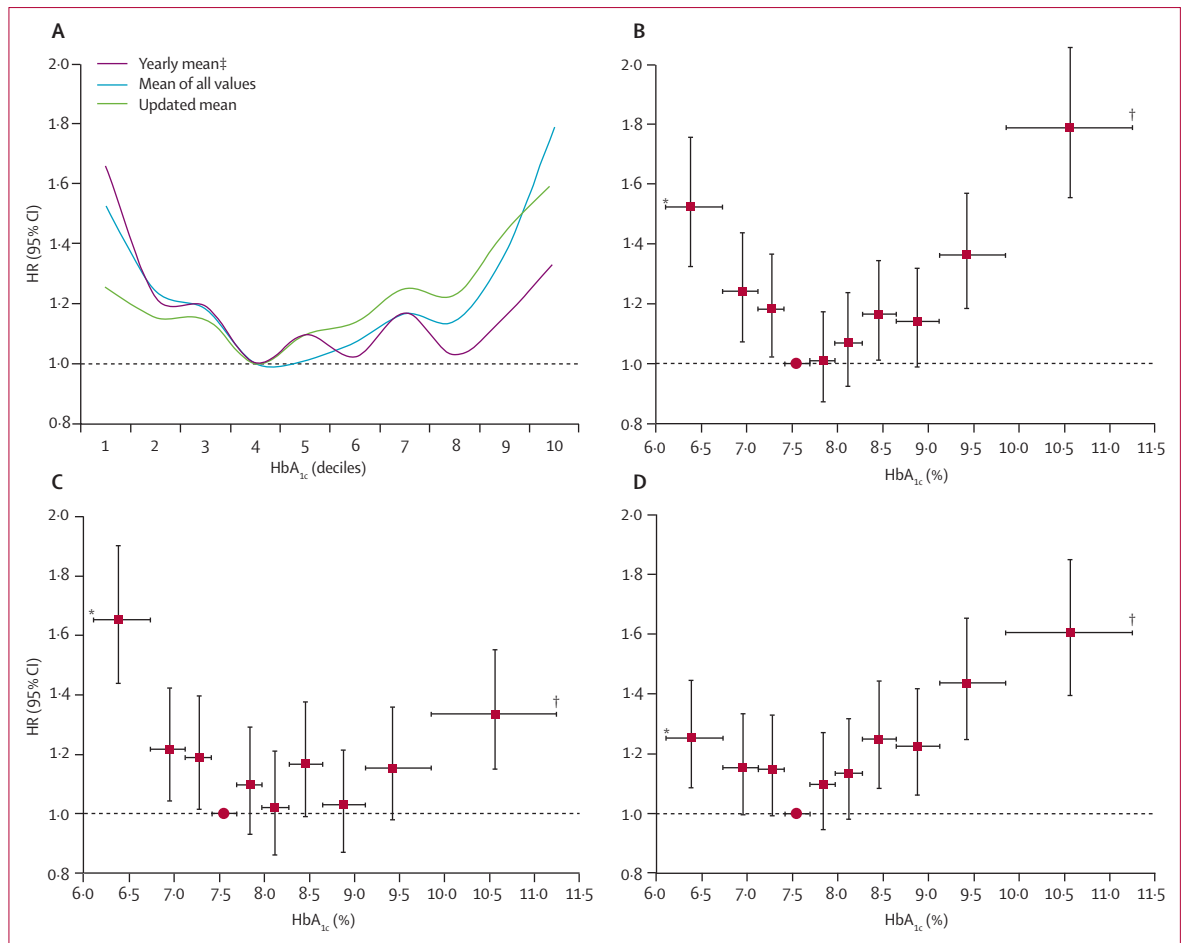
Figure 2: Adjusted hazard ratios for all-cause mortality introducing HbA_{1c} (%) into Cox proportional hazards model as a time-fixed or time-dependent covariate
Consists of two time-dependent covariates with data from combined cohorts. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. All three methods compared (A); mean of all HBA_{1c} values (B); yearly mean, last observation carried forward‡ (C); updated mean (D).

events at an HbA_{1c} higher than 7·5%, but, unlike the UKPDS, showed a rise in mortality at an HbA_{1c} of less than 6·5% in patients both with and without recorded large-vessel disease.

The ADVANCE study[5] assessed effects of intensive blood pressure and blood glucose control (target HbA_{1c}<7·5%) on microvascular and macrovascular complications in patients given oral blood-glucose lowering regimens. Good glycaemic control was associated with a reduced frequency of microvascular but not macrovascular events after a median of 5 years of follow-up. Improved glycaemic control was not associated with increased mortality. The difference between observations from ADVANCE and our findings might be partly related to issues of statistical power, a low cardiovascular risk profile in ADVANCE, or our findings being unrepresentative.

Both the ACCORD trial and the Veterans Affairs trial[22] raised concerns about safety for patients with type 2 diabetes who were given intensive insulin therapy. Furthermore, researchers in the EDIC study[23] of patients

with type 1 diabetes reported cardiovascular benefits associated with intensive glycaemic control, but not in those with an HbA_{1c} lower than 6·5%. The potential mechanisms that might account for this finding are unknown. Early reports from the ACCORD trial could not identify differences in cause of death between study groups—mortality rates were raised in the two extreme HbA_{1c} categories, independent of treatment regimen and some cardiovascular risk factors. Decreased survival in patients achieving low mean percentages of HbA_{1c} might be related to hypoglycaemia—a common complication of intensive blood-glucose control.[24] In this study, mortality was three times higher in patients in either the conventional or intensive treatment groups who had severe hypoglycaemia than in those who did not have severe hypoglycaemia. Furthermore, in the Veterans Affairs study,[7] more than one episode of severe hypoglycaemia was associated with an 88% rise in relative risk for sudden death.

Hypoglycaemia is associated with various sequelae that could increase mortality. For example, a link exists

between the sympathomimetic (adrenergic) or hypo-kalaemic manifestations of hypoglycaemia and the onset of cardiac arrhythmia, including a protracted QTc in patients who have diabetes with established cardio-vascular disease.[25] Intensive glycaemic control with associated hypoglycaemia might potentiate glucose variability, contributing to raised oxidative stress and vascular inflammation.[26] This outcome might predispose patients to atherosclerotic plaque destabilisation and vascular dysfunction.[27]

Lower survival reported in the group given insulin than in the group not given insulin could suggest that insulin might heighten mortality risk in patients with type 2 diabetes. Margolis and co-workers[28] reported that insulin use is associated with heightened risk of serious ischaemic cardiac outcomes. A possible explanation is that insulin-treated patients were older and had more comorbidities and a longer diabetes duration than those not given insulin, as suggested by results of an assessment[29] study of patients with diabetes who underwent surgery for a coronary artery bypass graft. In this study, frequency of baseline comorbidities, including renal failure, was higher in those who used insulin than in those given oral blood-glucose lowering drugs. No evidence exists to support the idea that insulin has a direct cardiotoxic effect in type 2 diabetes patients who do not have cardiovascular or autonomic disease; however, a link between use of insulin and cancer progression[30] and mortality[31] has been reported in this disorder.

Differences between cohorts at baseline might have affected our findings. More patients from cohort 2 than from cohort 1 had had a previous cardiovascular event and creatinine concentrations higher than 130 µmol/L. Previous cardiovascular events and early renal in-sufficiency are risk factors for poor cardiovascular outcomes in those with atherosclerosis or diabetes.[32–34] However, when patients with no documented large-vessel disease were excluded from the Cox analysis, those given insulin therapy were at higher risk of progression to large-vessel disease than those given oral combined therapy. In our study, we adjusted for differences in morbidity between cohorts, and undertook detailed sensitivity analyses when comparing the two cohorts, such as adjustment for diabetes duration (some data not shown). Differences in survival and frequency of large-vessel disease events between cohorts persisted with all analytical conditions. Another plausible idea is that causes of death and underlying pathology in the high and low HbA$_{1c}$ categories differ.

Our study had several limitations. GPRD collates data from routine practice; thus, some data are missing, coding imperfections might have occurred, and measures such as HbA$_{1c}$ have not been standardised. Normal ranges for HbA$_{1c}$ would have varied between biochemical test centres, and measurements would have been taken with varying periodicity. After considering the
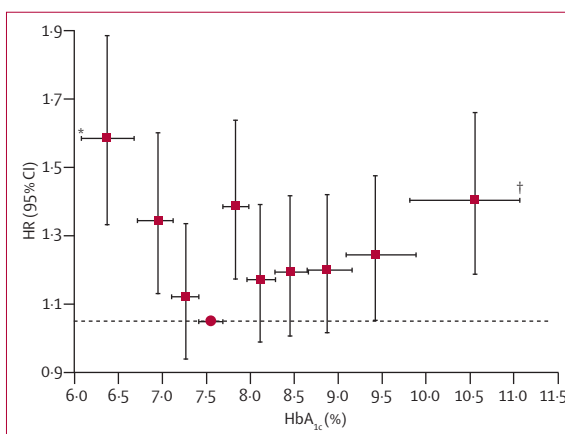
Figure 3: Hazard ratios for progression to first large-vessel disease event by HbA$_{1c}$ decile, with Cox proportional hazards model
Vertical error bars show 95% CIs, horizontal bars show HbA$_{1c}$ range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Model specification, for people with no previous cardiovascular disease only: age, sex, Charlson index (age unadjusted), total cholesterol, smoking status history, and cohort membership.

appropriateness of use of techniques such as linear interpolation of values,[35] we deemed measurement of total exposure to the risk parameter unreliable. Variability in the frequency of HbA$_{1c}$ measurement might have introduced bias. However, we tested for bias with three different methods (time-fixed mean of all observations, time-varying yearly mean with last observation carried forward, and time-varying yearly updated mean with last observation carried forward) and findings remained the same. Furthermore, our study was not randomised. Although, when possible, we have standardised for recognised confounding factors, some effects might still be unaccounted for. Unmeasured confounding could have arisen, because other variables that might have been important were not recorded and could not be included in the model. Additionally, the HbA$_{1c}$ groups differed systematically, although survival models would account for some of these differences.

We decided that details of cause of death were too intermittent and imprecise to inform this study. No data were available to characterise ethnic origin. Additional significant limitations were that we did not undertake a separate case-control analysis to assess duration-response effect, or assess the effect of severe hypoglycaemia on mortality because of data limitations. A possible source of confounding was differences in rates of prescribing for cardiovascular prophylaxis throughout HbA$_{1c}$ deciles. Although these data are not shown, we investigated this effect in some detail and identified it to be unimportant with respect to the objectives of our study, although we noted some evidence that people with a high HbA$_{1c}$ received fewer prophylactic drugs than did others.

Our decision to include cases with dual cohort membership is contentious—arguments both for and

against exist. Although this factor could have introduced bias into the study, we tested for this bias in sensitivity analysis by introduction of a covariate indicating dual cohort membership into the insulin regimen parameter—this parameter was not significant. These data, therefore, still need cautious interpretation. However, our data were from a large number of patients and represented what actually took place in clinical practice. Allowing for these limitations, we believe that the resulting strength of our evidence suggests that this association is reliable, although these findings need independent confirmation.

Our study, combined with evidence from ACCORD, might have important implications for care of people with type 2 diabetes. Whether our data and findings from the ACCORD study apply to patients with type 1 diabetes is unclear and needs to be investigated. These data imply for oral combination therapy that a wide HbA_{1c} range is safe with respect to all-cause mortality and large-vessel events, but for insulin-based therapy, a more narrow range might be desirable. This implication does not mean that there is unquestionable value in achievement of present glycaemic targets for reduction of microvascular disease.[36] Whether intensification of glucose control with insulin therapy alone further heightens risk of death in patients with diabetes needs further investigation and assessment of the overall risk balance. Our findings suggest that diabetes guidelines might need revision to include a definition of an HbA_{1c} minimum value.

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