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Mean HbA_{1c} and mortality in diabetic individuals with heart failure: a population cohort study

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Aims Controversy exists regarding the importance of glycaemic control in patients with type 2 diabetes mellitus (T2DM) and chronic heart failure (CHF) based on conflicting reports using single baseline glycosyated haemoglobin (HbA_{1c}). Using the time-weighted mean of serial HbA_{1c} measurements has been found to be a better predictor of diabetic complications as it reflects the glycaemic burden for that individual over time. We therefore sought to confirm this in a large cohort of patients with T2DM and incident CHF.

Methods and results A time-weighted mean HbA_{1c} was calculated using all HbA_{1c} measurements following CHF diagnosis. Patients were grouped into five categories of HbA_{1c} (≤6.0%, 6.1–7.0%, 7.1–8.0%, 8.1–9.0%, and >9.0%). The relationship between time-weighted mean HbA_{1c} and all-cause death after CHF diagnosis was assessed. A total of 1447 patients with T2DM met the study criteria. During a median follow-up of 2.8 years, there were 826 (57.1%) deaths, with a crude death rate of 155 deaths per 1000 person-years [95% confidence interval (CI) 144–166]. A Cox regression model, adjusted for all significant predictors, with the middle HbA_{1c} category (7.1–8.0%) as the reference, showed a U-shaped relationship between HbA_{1c} and outcome [HbA_{1c} <6.0%, hazard ratio (HR) 2.5, 95% CI 1.8–3.4; HbA_{1c} 6.1–7.0%, HR 1.4, 95% 1.1–1.7; HbA_{1c} 8.1–9.0%, HR 1.3, 95% CI 1.0–1.6; and HbA_{1c} >9.0%, HR 1.8, 95% CI 1.4–2.3]. Further analysis revealed a protective effect of insulin sensitizers (i.e. metformin) (HR 0.7, 95% CI 0.61–0.93) but not other drug classes.

Conclusions In patients with T2DM and CHF, our study shows a U-shaped relationship between HbA_{1c} and mortality, with the lowest risk in patients with modest glycaemic control (HbA_{1c} 7.1–8.0%) and those treated with insulin sensitizers.

Keywords Heart failure • Outcomes • Diabetes • HbA_{1c} • Metformin

Introduction

Chronic heart failure (CHF) and type 2 diabetes mellitus (T2DM) frequently co-exist. In population-based studies and in CHF trials, the prevalence of T2DM is estimated to be between 11% and 28%. Among all patients hospitalized for CHF, it has been reported that 25–30% have T2DM.[1] This association can be lethal since T2DM has consistently been shown to be an independent predictor of increased morbidity and mortality in patients with CHF.[2]

The question arises of whether glycaemic control matters in T2DM patients with CHF. The benefit of improved glycaemic control on microvascular complications in T2DM is well established. Trials have attempted to clarify the role of glycaemic control in macrovascular outcomes.[3,4] These data suggest that improved

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glycaemic control has the potential to reduce significantly the risk of both micro- and macrovascular disease when instigated early in the disease course, but, in more advanced T2DM, the benefits of improved control appear to be less evident.[5] Furthermore, studies suggest that tight glycaemic control can sometimes be associated with a poorer macrovascular outcome.[6,7] In patients with co-existing CHF and T2DM, the relevance of good glycaemic control is a critical issue not only as the combination may be associated with a significantly poorer outcome but also as the choice of drugs available to manage the hyperglycaemia in CHF is perhaps more limited.[8,9] There have been conflicting reports regarding the importance of glycaemic control in patients with T2DM and CHF.[10–14] The level of glycosylated haemoglobin (HbA_{1c}) provides a measure of the glycaemic control of patients with T2DM during the previous 2–3 months.[15] Studies that assessed the importance of glycaemic control in diabetic patients with CHF[10–14] have usually used a single measurement of HbA_{1c} which has been shown to underestimate the importance of glycaemic control.[16] Calculation of a mean of serial HbA_{1c} measurements has been found to be a better predictor of diabetic complications,[2,15,17] and this may be due to the fact that it incorporates multiple measurements over time[2,16] and therefore better reflects the glycaemic burden for that individual. However, this variable may also result in underestimation of the importance of glycaemic control, as the updated mean value of HbA_{1c} gives equal weight to all historical HbA_{1c} measurements. However, a more accurate assessment of the effects of HbA_{1c} would be one that incorporates not only the HbA_{1c} value itself but also the length of time that the patient has been at that level, thus accounting for the natural fluctuation of HbA_{1c} as well as its temporal effects on outcomes. This time-weighted mean HbA_{1c} method has been shown to be superior to the updated mean.[18] We therefore sought to determine the relationship between the time-weighted mean HbA_{1c} and outcomes in a large cohort of patients with T2DM and incident CHF.

Methods

Data sources

We exploited the established regional clinical informatics systems developed in partnership between the University of Dundee and NHS Tayside which makes use of a unique health record identifier, the Community Health Index (CHI) number, to link multiple clinical data sets deterministically through established and robust anonymization protocols within the Health Informatics Centre (HIC) and the University of Dundee at an individual level with high accuracy. The clinical data sets include the following (i) Echocardiography Database: this contains information on all clinically requested outpatient echocardiograms performed in Ninewells Hospital, Dundee and is maintained by the Department of Cardiology, Ninewells Hospital. All echocardiograms are performed in a standardized protocol by accredited echo cardiographers. (ii) Scottish Care Information–Diabetes Collaboration: the SCI-DC data set contains detailed clinical information on every patient diagnosed with DM in Tayside. Clinical information is collected according to the national clinical data set for the care of diabetic patients in Scotland and includes diabetes type and date of diagnosis. (iii) Other HIC data sets: other data sets utilized were the dispensed prescribing data set which contains detailed information of all prescription drugs that are dispensed for essentially all individuals in Tayside over the past 20 years. Hospital discharge data comprising the Scottish Morbidity Record (SMR01) containing International Classification of Diseases (ICD) 9 and 10 classification codes, data on death from the General Registrar's Office (GRO), and finally laboratory data containing information on all biochemical tests on all individuals historically. Access to the anonymized data sets was approved by the East of Scotland Ethics Committee.

Study design

We performed a retrospective observational cohort study between 1 January 1993 and 31 March 2010 in Tayside Scotland (population 400 000) to examine the relationship between HbA_{1c} and all-cause death in patients with T2DM who subsequently develop CHF. Therefore, to be eligible for the study, patients had to develop incident CHF after being diagnosed with T2DM. The patients also had to have at least one HbA_{1c} measurement recorded after CHF diagnosis.

Definition of chronic heart failure

Chronic heart failure was defined as a record of an echocardiogram with evidence of LV systolic dysfunction and, either a prescription for a loop diuretic (British National Formulary code 2.2.2; provided not greater than 1 year prior to echocardiogram) or an admission to hospital with an associated CHF diagnostic code (ICD9 428, ICD10 I50). We used these ICD CHF diagnostic codes based on previous work that had demonstrated their validity in identifying HF from electronic records.[19–21] With respect to the CHF definition based on the prescription of a loop diuretic, a previous case validation exercise found 91% concordance between a clinical diagnosis of HF from case note review and definition of HF based on echocardiographic evidence of LV systolic dysfunction requiring prescription of loop diuretics.[22]

Definition of study period

Immortal time bias can affect observational cohort studies when improper design or analysis methods are used.[23] In order to account for immortal time, we only considered each individual to be at risk at the time when they met all the CHF diagnostic criteria and had their first HbA_{1c} measurement. We adjusted for the time between initial CHF diagnosis (baseline) and first Hba_{1c} measurement in our model.

Calculation of mean glycosylate haemoglobin

A time-weighted mean HbA_{1c} was calculated using all available HbA_{1c} measurements during the 'at-risk' period. The mean was weighted by time between measurements and was then used to group patients into five categories of HbA_{1c} (≤6.0%, 6.1–7.0%, 7.1–8.0%, 8.1–9.0, and >9.0%).

Covariates

In the models, the following covariates were considered in addition to mean study HbA_{1c}: age at T2DM diagnosis, sex, and social deprivation; and the following baseline measures: age, weighted mean of available HbA_{1c} measurements from DM diagnosis to baseline, smoking status,

and prior hospitalization with myocardial infarction (MI) (defined as ICD9 410–414, ICD10 I21–I25). For mean body mass index (BMI), mean arterial pressure (MAP), and estimated glomerular filtration rate (eGFR), we utilized all available measurements up to 2 years prior to baseline. Any prescriptions up to 6 months prior to baseline for DM treatment grouped by diet alone, insulin sensitizers, insulin secretagogues, and insulin, and cardiovascular medication [aspirin, statins, thiazide diuretics, beta-blockers, ACE inhibitors or ARBs, and calcium channel blockers (CCBs) (split by rate-limiting and all others)] were used to define drug use at baseline. During the study period, hospitalization with MI, and prescriptions for DM and cardiovascular medication were entered into the model time dependently.

Statistical analysis

A Cox proportional hazards model with delayed entry was used to model time to death.[18,24] Time from CHF diagnosis was assessed, with patients entering the risk set at the date of their first HbA_{1c} after CHF diagnosis. For each model, all covariates were entered, then backward elimination was performed with any covariates with a significance of $P > 0.05$ excluded from the final model. Time-dependent covariates were modelled by splitting the follow-up into 56-day intervals, which corresponded to the median duration of drug prescription. This method allows us to observe any changes in the patient's circumstances in every interval, updating the changes in all the covariates during that same period. Any HbA_{1c} reading that was detected was then weighted to the time duration from the previous reading. Unadjusted models are also presented. In the analysis split by diet and drug treatment, to enable the inclusion of all patients, drug treatment was defined as any treatment between date of T2DM diagnosis and study end. All tests were two-sided, with a *P*-value of <0.05 considered significant. All statistical analysis were performed using R for windows (v3.2.0)

Results

From an initial 2035 T2DM subjects in the echocardiographic database with evidence of LV systolic dysfunction following DM diagnosis, 1933 (95%) had a post-DM diagnosis hospitalization for CHF and/or valid loop diuretic prescription. Of those, 1447 had an HbA_{1c} measurement during their observable study period.

Characteristics of the 1447 patients in the study population are provided in *Table 1* split by HbA_{1c} category. Patients in the lowest HbA_{1c} category had shorter study duration and therefore fewer HbA_{1c} measurements, were diagnosed with CHF and T2DM at an older age, and had a lower BMI and eGFR at baseline. In addition, although not statistically significant, they tended to be more likely to smoke and were prescribed less aspirin but had fewer MI events prior to baseline. With respect to diabetes therapy, there were relatively more diet-treated and fewer insulin-treated patients.

In contrast, patients in the highest HbA_{1c} category were diagnosed with CHF and T2DM at a younger age, had a higher BMI and eGFR, relatively more MI events at baseline, and comprised the smallest proportion of diet- and the largest proportion of insulin-treated patients. In addition, they were more likely to be prescribed aspirin at baseline.

Glycosylated haemoglobin and mortality

Over a median follow-up of 2.8 years, there were 826 (57%) all-cause deaths, with a crude death rate of 155 deaths per 1000 person-years. In a Cox regression model, adjusted for all other significant predictors, with the middle HbA_{1c} category (7.1–8%) as the reference, we found a U-shaped relationship between HbA_{1c} and outcome, with the two lowest and the highest HbA_{1c} categories significantly associated with a higher risk of death: HbA_{1c} <6.0%, hazard ratio (HR) 2.5, 95% confidence interval (CI) 1.8–3.4; HbA_{1c} 6.1–7.0%, HR 1.4, 95% CI 1.1–1.7; HbA_{1c} 8.1–9.0%, HR 1.3, 95% CI 1.0–1.6; and HbA_{1c} >9.0%, HR 1.8, 95% CI 1.4–2.3 (*Figure 1*). (The full model is included in the Supplementary material online, *Table S1*.)

Glycosylated haemoglobin and mortality: diet- and drug-treated type 2 diabetes

To explore this U-shaped association more carefully, we limited our analysis to the lower two categories of HbA_{1c} <6.0% and 6.1–7.0% (i.e. HbA_{1c} ≤7%) comparing patients on diet and drug treatment (*Table 2*). We made two observations in the analysis of this subgroup. First, when comparing HbA_{1c} levels before and after CHF diagnosis, there was no difference in the diet-treated group (mean ± SD, 6.11 ± 0.81 vs. 6.11 ± 0.55, $P = 0.29$) but in the drug-treated group the HbA_{1c} was significantly lower after CHF diagnosis (7.27 ± 1.1 vs. 6.33 ± 0.49, $P < 0.0001$), indicating an intensification of treatment following the diagnosis of CHF (*Table 2*). Secondly, we, unexpectedly, found patients on diabetic medications to have higher mortality than those who were not (HR 1.5, 95% CI 1.2–2.0).

We then studied the relationship between HbA_{1c} and death (for the entire study population) in the diet- and drug-treated groups separately. As the number of patients in each group became smaller, we reduced the number of HbA_{1c} categories to three (≤7%, 7.1–9%, and >9%). The adjusted and unadjusted Cox regression models are presented in *Table 3* (full models included in the Supplementary material online, *Tables S2–S4*). The U-shaped association observed in the overall study population remained in the drug-treated group, but was lost in the diet-controlled group (*Figure 2A* and *B*) This, once again, suggested the increased mortality of patients at low HbA_{1c} levels seen in the overall model to be the result of diabetic drug therapy. Finally, we developed an adjusted model for the drug-treated group alone and saw a significant protective effect of exposure to metformin (HR 0.75, 95% CI 0.61–0.93), but not in patients on insulin secretagogues (such as sulphonylureas) or insulin.

Discussion

This study had two main findings. First, in our cohort of T2DM patients with incident CHF, we observed a U-shaped relationship between mortality and glycaemic control, as assessed by a time-weighted mean HbA_{1c}. Secondly, additional analysis showed that this U-shaped relationship was present in drug-treated but not in diet-treated T2DM patients. A closer inspection of the

Table 1 Clinical characteristics by glycosylated haemoglobin category

	All	HbA_{1c} category (%)					*P*-value
		<6	6.1–7.0	7.1–8.0	8.1–9.0	>9	
Number of subjects (%)	1447 (100.0)	171 (11.8)	411 (28.4)	415 (28.7)	237 (16.4)	213 (14.7)	
Age (years)	71.8(9.95)	73.5 (9.52)	73.6 (9.84)	72 (9.49)	70.6 (9.69)	68.1 (10.5)	0.078[b]
Females (%)	551 (38.1)	64 (37.4)	142 (34.5)	169 (40.7)	96 (40.5)	80 (37.6)	0.399[a]
Total follow up time (person-years)	5334	459	1385	1750	1010	729	
Deaths (%)	826 (57.1)	109 (63.7)	214 (52.1)	242(58.3)	140 (59.1)	121 (56.8)	
Death rate/1000 person-years (95% CI)	155 (144–166)	237 (195–286)	154 (134–177)	138 (121–157)	139 (117–164)	166 (138–198)	
Age at DM diagnosis	62.5 (11.8)	65.6 (11.2)	66.2 (10.8)	62.3 (11.3)	59.0 (11.9)	57.1 (11.7)	0.002[b]
Duration of diabetes (years)	7.7 (3.5, 13.2)	5.4 (2.4, 10.6)	5.7 (2.35, 10.6)	8.1 (3.72, 14)	10.1 (5.9, 15.6)	9.9 (5.4, 15.6)	0.001[c]
MAP (mmHg)	96.3 (50)	94.6 (13)	96.3 (14)	95.7 (13)	97.6 (5)	97.4 (5)	0.385[b]
BMI	29.1 (25.7, 33)	26.8 (24, 31.6)	28.7 (25.5, 32.3)	28.9 (25.8, 33)	29.5 (26.4, 33.1)	31 (27.1, 34.8)	0.003[c]
eGFR (ml/min/1.72 m^2)	58.6 (12)	53.9 (1)	59.3 (3)	57.5 (5)	59.3 (2)	62.3 (1)	0.107[b]
Number of post-CHF HbA_{1c} measurements	8 (3–16)	4 (2–9)	7 (2–14)	9 (4–19)	9 (4–21)	8 (4–15)	<0.0001[c]
Mean HbA_{1c} prior to CHF diagnosis	7.57 (1.43)	6.52 (1.27)	7.03 (1.06)	7.69 (1.36)	8.16 (1.44)	8.56 (1.3)	<0.0001[c]
Mean HbA_{1c} after CHF diagnosis	7.53 (1.43)	5.59 (0.329)	6.53 (0.277)	7.47 (0.285)	8.47 (0.289)	10.1 (1.01)	<0.0001[c]
Ever smoked	791 (54.7)	92 (53.8)	245 (59.6)	221 (53.3)	123 (51.9)	110 (51.6)	0.166[a]
Previous MI	703 (48.6)	74 (43.3)	205 (49.9)	193 (46.5)	124 (52.3)	107 (50.2)	0.345[a]
Social deprivation:							0.495[a]
1 (most)	362 (25)	44 (25.7)	93 (22.6)	106 (25.5)	59 (24.9)	60 (28.2)	
2	256 (17.7)	30 (17.5)	66 (16.1)	73 (17.6)	48 (20.3)	39 (18.3)	
3	254 (17.6)	37 (21.6)	73 (17.8)	64 (15.4)	37 (15.6)	43 (20.2)	
4	358 (24.7)	40 (23.4)	104 (25.3)	108 (26)	63 (26.6)	43 (20.2)	
5 (least)	199 (13.8)	17 (9.9)	69 (16.8)	58 (14)	28 (11.8)	27 (12.7)	.
Diabetic therapy							
Diet control	355 (24.5)	82 (48.0)	124 (30.2)	98 (23.6)	30 (12.7)	21 (9.9)	<0.0001[a]
Insulin sensitizers	524 (36.2)	37 (21.6)	153 (37.2)	153 (36.9)	90 (38)	91 (42.7)	<0.0001[a]
Insulin secretagogues	554 (38.3)	45 (26.3)	150 (36.5)	163 (39.3)	111 (46.8)	85 (39.9)	<0.0001[a]
Insulin	354 (24.5)	19 (11.1)	55 (13.4)	98 (23.6)	88 (37.1)	94 (44.1)	<0.0001[a]
Cardiovascular drugs							
ACE-I / ARB	843 (58.3)	98 (57.3)	236 (57.4)	242 (58.3)	132 (55.7)	13 5 (63.4)	0.538[a]
Beta-blockers	527 (36.4)	59 (34.5)	164 (39.9)	143 (34.5)	77 (32.5)	84 (39.4)	0.237[a]
Thiazide diuretics	131 (9.1)	15 (8.8)	46 (11.2)	34 (8.2)	12 (5.1)	24 (11.3)	0.074[a]
Statins	744 (51.4)	84 (49.1)	216 (52.6)	213 (51.3)	114 (48.1)	117 (54.9)	0.615[a]
Aspirin	787 (54.4)	83 (48.5)	236 (57.4)	214 (51.6)	134 (56.5)	120 (56.3)	0.200[a]
Rate-limiting CCB	155 (10.7)	19 (11.1)	42 (10.2)	47 (11.3)	23 (9.7)	24 (11.3)	0.961[a]
Non-rate-limiting CCB	347 (24)	44 (25.7)	90 (21.9)	97 (23.4)	66 (27.8)	50 (23.5)	0.505[a]

BMI, body mass index; CCB, calcium channel blocker; CHF, chronic heart failure; CI, confidence interval; DM diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; MAP, mean arterial pressure; MI, myocardial infarction.
[a].Chi-square;
[b].ANOVA;
[c].Mann-Whitney test.

drug-treated group revealed a clear difference in the outcomes driven by the type of antidiabetic therapy; patients on 'low hypoglycaemia risk' medications had fewer outcomes than those on 'high hypoglycaemia risk' medications (insulin secreatagougues or insulin).

The relationship between glycaemic control and outcome in patients with CHF and T2DM has previously been studied in at least four retrospective studies, with different conclusions reported.[11–14] The relationship between glycaemic control and outcome has been reported to be 'U' shaped,[14], 'J' shaped,[13] linear,[12] and even inverse.[11] In the most recent analysis, Aguilar *et al.*[14] performed a retrospective analysis of 5815 veterans (94% male) with T2DM and CHF defined by clinic coding, 45.5% of which had significantly impaired LV function. Over a 2-year follow-up

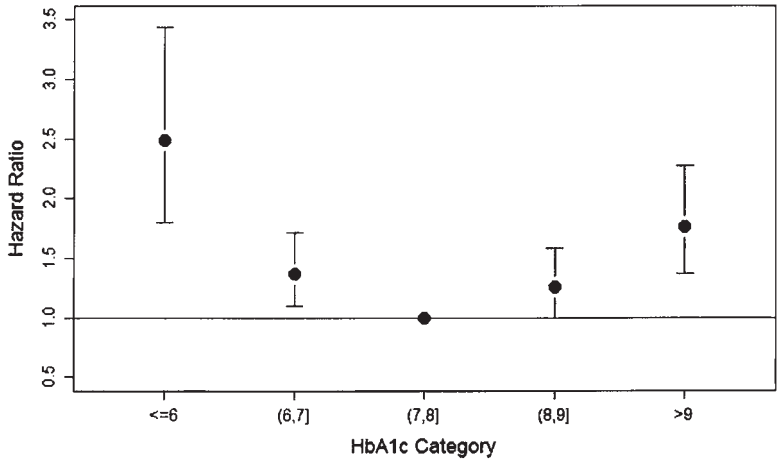

Figure 1 Hazard ratios for death by categories of glycosylated haemoglobin (HbA_{1c}).

they observed a U-shaped relationship between HbA_{1c} and mortality, with a 'sweet spot' seen with individuals in quintile 3 (HbA_{1c} 7.1–7.8 %). Compared with quintile 3, all other quintiles had significantly elevated risk of death at 2 years, with those in the lowest and highest quintiles faring worst. Our data would support these findings. It should be noted that, like most of the previous studies, Aguilar's study used only a single HbA_{1c} measurement to assess glycaemic control. However, a single HbA_{1c} may not be reliable, especially if sampled at the time of the diagnosis of CHF when it is potentially influenced by recent alterations in therapy. Individuals may consult physicians with symptoms prior to diagnosis, leading to alterations in oral hypoglycaemic agents or initiation of diuretic therapy that may affect the single HbA_{1c} measurement recorded in the specialist clinic at the time of CHF diagnosis. This effect was clearly demonstrated in our cohort when we observed a significant improvement in HbA_{1c} levels among drug-treated patients following the diagnosis of CHF, indicating an intensification of therapy at the time of diagnosis. In addition to that, studies have also shown that HbA_{1c} levels have a persistent association with complications several years after their measurement.[25,26] Our data are unique as we were able to utilize all HbA_{1c} measurements recorded for each individual, enabling us to consider the importance of longer term glycaemic control over a long period of time in a large patient cohort. In this study, we used a time-weighted mean to examine the impact of glycaemic control on outcome. This method of HbA_{1c} analysis has been shown to offer superior predictive power over time when compared with a single baseline measurement which, as we have shown, can result in underestimations of the impact of glycaemic control.[2,16,27] It should be noted that others have attempted to achieve the same effect by using techniques such as simple mean, logarithm of updated means, annual average change slope, and change between baseline and final measures, none of which has been shown to be superior to the time-weighted mean.[17,28] Although they may appear to incorporate multiple measurements of HbA_{1c}, they all discount the important component of time weightage. Multiple studies have shown a legacy effect of HbA_{1c} where it can have an influence on outcomes remote from the time of measurement.[29,30] Merely accounting for fluctuations in HbA_{1c} without factoring in its temporal relationship to outcomes is too simplistic and has been shown to result in suboptimal analysis.[31,32] Accordingly, the use of time-weighted mean HbA_{1c} coupled with a median follow-up of 2.8 years enhances the ability of this study to determine accurately the relationship between HbA_{1c} and mortality, as the predictive power of mean HbA_{1c} is known to increase with longer study length.[25–27]

The finding of a higher mortality risk in patients in the lower HbA_{1c} categories (HbA_{1c} ≤6% and HbA_{1c} 6.1–7%) deserves some consideration. In our study, patients in these low HbA_{1c} categories had both favourable and less favourable clinical characteristics. On the one hand, these patients had fewer previous MIs and had less intensive DM treatment with less use of insulin. On the other hand, these patients were older when they developed their CHF and they had a lower eGFR. Interpretation of these findings is always going to be limited by a lack of information on the underlying cause of death. However, our finding that this U-shaped relationship was present in drug-treated but not in diet-treated T2DM patients may suggest that the outcomes observed in the low HbA_{1c} categories may be related to the response of patients to the DM medications. It should be noted that the current findings are concordant with the ACCORD[5] study which demonstrated that very tight control of glucose in patients with T2DM may not be beneficial in those with existing cardiovascular disease and a longer duration of T2DM. Besides that, further analysis of the results from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial also revealed a similar finding of poorer outcomes among patients with hypoglycaemia complicating HF post-MI (HR 1.38, 95% CI 1.06–1.81).[33] There are multiple pathophysiological mechanisms that are implicated in hypoglycaemia-induced cardiovascular events. A key mechanism revolves around the profound sympatho-adrenal system activation resulting in a surge in catecholamines. In an

Table 2 Clinical characteristics of glycosylated haemoglobin ≤7% split by diabetes treatment

	All	Diet control	Anti-DM drugs	*P*-value
Number of subjects (%)	582 (100)	206 (35.4)	376 (64.6)	.
Age	73.6 (9.74)	74.2 (9.95)	73.3 (9.62)	0.316[b]
Females	206 (35.4)	77 (37.4)	129 (34.3)	0.516[a]
Total follow up time (person-years)	1844	737	1107	.
Deaths (%)	323 (55.5)	116 (56.3)	207 (55.0)	
Death rate/1000 person-years (95% CI)	175 (156–195)	157 (130–189)	187 (162–214)	
Age at DM diagnosis	66.2 (2)	69 (1)	64.6 (1)	<0.0001[b]
Duration of diabetes (years)	5.6 (2.4, 10.6)	3.15 (1.52, 6.45)	7.3 (3.45, 12.2)	<0.0001[c]
MAP (mmHg)	95.8 (14.1)	96.4 (14.1)	95.5 (14.1)	0.511[b]
BMI	28.9 (5.7)	27.7 (5.5)	29.5 (5.7)	0.001[b]
eGFR (ml/min/1.72 m^2)	57.7 (23.8)	55.9 (23.1)	58.7 (24.2)	0.169[b]
Mean HbA_{1c} prior to CHF diagnosis	6.88 (1.15)	6.11 (0.81)	7.27 (1.1)	<0.0001[c]
Mean HbA_{1c} after CHF diagnosis	6.25 (0.52)	6.11 (0.55)	6.33 (0.49)	<0.0001[b]
Ever smoked	337 (57.9)	121 (58.7)	216 (57.4)	0.892[a]
Previous MI	279 (47.9)	98 (47.6)	181 (48.1)	0.965[a]
Social deprivation				
1 (most)	137 (23.5)	45 (21.8)	92 (24.5)	0.922[a]
2	96 (16.5)	37 (18)	59 (15.7)	
3	110 (18.9)	39 (18.9)	71 (18.9)	
4	144 (24.7)	51 (24.8)	93 (24.7)	
5 (least)	86 (14.8)	32 (15.5)	54 (14.4)	
Cardiovascular drugs				
ACE-I / ARB	334 (57.4)	102 (49.5)	232 (61.7)	0.006[a]
Beta-blockers	223 (38.3)	78 (37.9)	145 (38.6)	0.939[a]
Thiazide diuretics	61 (10.5)	17 (8.3)	44 (11.7)	0.247[a]
Statins	300 (51.5)	100 (48.5)	200 (53.2)	0.324[a]
Aspirin	319 (54.8)	107 (51.9)	212 (56.4)	0.346[a]
Rate-limiting CCB	61 (10.5)	19 (9.2)	42 (11.2)	0.554[a]
Non-rate-limiting CCB	134 (23)	45 (21.8)	89 (23.7)	0.691[a]

ACE-I, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CHF, chronic heart failure; CI, confidence interval; DM diabetes mellitus; eGFR, esti8mated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; MAP, mean arterial pressure; MI, myocardial infarction. Data are mean (standard deviation), median (interquartile range) or n(%).
[a].Chi-square;
[b].ANOVA;
[c].Mann-Whitney test.

Table 3 Cox models analysing glycosylated haemoglobin by three categories

HbA_{1c} category	All ($n = 1447$)		Diet only ($n = 328$)		DM drug ($n = 1119$)	
	Adjusted HR (95% CI)	Unadjusted HR	Adjusted HR (95% CI)	Unadjusted HR	Adjusted HR (95% CI)	Unadjusted HR
≤7.0	1.4 (1.2–1.7)	1.2 (1.1–1.4)	1.09 (0.76–1.58)	1.2 (0.84–1.6)	1.5 (1.2–1.8)	1.3 (1.1–1.6)
7.1–9.0	1	1	1	1	1	1
>9.0	1.6 (1.3–2.0)	1.7 (1.4–2.0)	6.5 (2.8–14.8)	2.1 (1.1–4.1)	1.7 (1.3–2.1)	1.6 (1.2–2.0)

CI, confidence interval; HbA_{1c}, glycosylated haemoglobin; HR, hazard ratio; DM, diabetes mellitus.

attempt to preserve the glucose supply to critical organs such as the brain, blood is diverted cephalically and to the splanchnic system (for gluconeogenesis in the liver) by increasing peripheral vascular resistance and augmenting cardiac contractility and rate.[34] Additionally there is also evidence of increased occurrence of myocardial ischaemia[35] and prolonged QT[36] intervals during states of hypoglycaemia among patients with T2DM. All of these may be tolerated by diabetic patients without cardiovascular disease but not those with concomitant CHF. These cardiac stressors, even though transient, will only serve to accelerate decline in cardiac function. All or a combination of these cardiac abnormalities associated with hypoglycaemia could very well be the reason

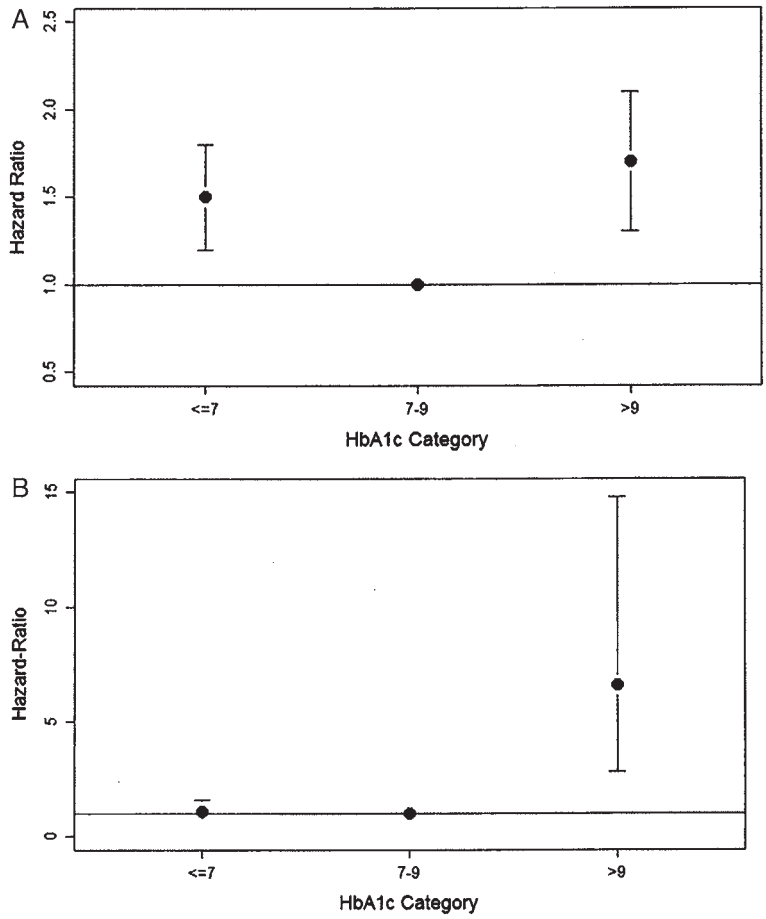

Figure 2 Hazard ratios for death by categories of glycosylated haemoglobin (HbA_{1c}) among patients (*A*) on antidiabetic therapy and (*B*) on diet control only.

behind our findings, indeed even those of larger trials such as ADVANCE[7], VADT,[37] and ACCORD[5].

In our study, we also observed a poor outcome in CHF patients with the highest HbA_{1c}. In a sense, this was not unexpected. These patients had more previous MIs at baseline, had more aggressive DM therapy, with the largest proportion of insulin-treated patients. These findings of worse outcomes among patients with poor glycaemic control has been well described in the contemporary literature[38] and is concordant with previous experimental work.[39,40] Obviously, the mechanisms for reduced survival associated both with very tight glycaemic as well with poor glycaemic control in CHF must remain speculative and cannot be inferred directly from this study.

We also made some expected observations regarding the effects of medications on outcomes in this cohort of patients. Reassuringly, we found patients on insulin sensitizers such as metformin to have a lower mortality risk than those who were not. This echoes previous findings by our group on the beneficial effects of metformin on a host of cardiovascular outcomes such as exercise capacity[41] and mortality,[42] as well as ongoing work on its effects on LV mass.[43] There is also a large body of work that clearly demonstrates the beneficial effects of metformin in a heterogeneous group of patients with high cardiovascular risk.[44–46] These findings underscore not only the safety but also the efficacy of metformin use in diabetic patients with concomitant CHF. With respect to insulin use in CHF patients, there are conflicting outcome data. Although patients with T2DM on insulin had a higher risk of death in CHF trials,[12,47] the UKPDS 33 study[48] as well as a retrospective cohort study of 16 000 Medicare diabetic beneficiaries with CHF, showed that insulin use did not predict mortality.[49] A potentially revealing analysis would have been to determine if there were any differences in the outcomes of patients treated with metformin vs. sulphonylurea/insulin therapies within the lower HbA_{1c} categories (i.e. HbA_{1c} <7%). We were unable to perform such an analysis in our cohort due to the small numbers in this group ($n = 376$, before subdivision into treatment categories); however, we believe future research in this area should consider studying this.

Limitations

We recognize the limitations of our study that are inherent with any retrospective, non-randomized, observational data. However,

the current study reflects the true population and a 'real world scenario' and adds to previous studies by selecting a large number of patients with T2DM and CHF with a long follow-up period. In common with all observational studies, it was impossible in our study to account for all confounding influences that may have biased the observed differences between the groups considered. We have sought to minimize these as far as practicable by utilizing multivariate models and incorporating data on drug prescribing, laboratory blood tests, and smoking status. Additionally, because of the observational nature of this study, we were unable to include patients with asymptomatic LV systolic dysfunction (Stage B heart failure), as these patients would not have been routinely referred for echocardiographic assessment, and therefore would be grossly under-represented. This study was also unable to account for patients with HFpEF because of the inherent difficulties in diagnosing HFpEF, supported by the lack of uniformity between guidelines.[50] Furthermore, we utilized multiple HbA_{1c} measurements for each individual, and as these were not sampled at specified intervals this may potentially result in bias for those who have a greater number of measures; in turn this was minimized by utilizing a mean HbA_{1c} weighted for time. Due to the frequency of recording of renal function and BMI, we utilized a mean value in our model. We were also unable to use contemporary biomarkers to diagnose and prognosticate HF such as BNP because it is not a routinely available test in Tayside. The study has considerable strengths, including the large number of subjects, the large number of HbA_{1c} measurements available, the high event rate (62% mortality), and the reliable and comprehensive data which were available with which to build the statistical model.

Conclusion

In patients with T2DM and CHF, our observational study shows that there is a U-shaped relationship between HbA_{1c} and mortality, with the lowest mortality risk in patients with modest glycaemic control (HbA_{1c}, 7.1–8.0%). We also demonstrated low hypoglycaemia risk medications such as metformin to be safe and efficacious in this cohort. These observational data add support to the growing concern that we need to redefine the optimal HbA_{1c} level and treatment choices in this high-risk group of patients with co-existing T2DM and CHF.

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Supplementary Information

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

Table S1 Entire population.
Table S2 Entire population with three HbA_{1c} categories.
Table S3 Drug treated only split into three HbA_{1c} categories.
Table S4 Diet control only split into three HbA_{1c} categories.

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