The impact of metabolic control and QTc prolongation on all-cause mortality in patients with type 2 diabetes and foot ulcers

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Abstract

Aims/hypothesis The increased all-cause mortality in patients with chronic diabetic foot ulcers cannot fully be explained by traditional cardiovascular risk factors. The significance of heart-rate-corrected QT (QTc) prolongation, a finding often seen in these patients, is unknown. Recently, the importance of metabolic control and hypoglycaemia has been discussed. The aim of this study was to evaluate the impact of different HbA_{1c} levels and QTc prolongation on all-cause mortality in the high-risk population of patients with type 2 diabetes mellitus and foot ulcers.

Methods All patients with type 2 diabetes, younger than 80 years, visiting our diabetes foot unit, with a foot ulcer duration >4 weeks, were screened for participation. Patients on dialysis were excluded. Patients were grouped according to HbA_{1c} level and QTc time ≤ or >440 ms.

Results Patients (*n*=214, median age 69.1 years) were grouped according to HbA_{1c} level (HbA_{1c}<7.5% [*<*58 mmol/mol] *n*=81, 7.5–8.9% [58–74 mmol/mol] *n*=70, >8.9% [*>*74 mmol/mol] *n*=63). Baseline characteristics, including use of potential hypoglycaemic drugs, were similar between groups. During the 8 years of follow-up 151 patients died (70.6%) and HbA_{1c}<7.5% (<58 mmol/mol) was strongly associated with increased mortality. The highest mortality was seen in patients with a combination of HbA_{1c}<7.5% (<58 mmol/mol) and

QTc prolongation, with an 8 year mortality of 92.1% as compared with 48.8% in those with HbA_{1c}<7.5% (<58 mmol/mol) but without QTc prolongation.

Conclusion/interpretations HbA_{1c}<7.5% (<58 mmol/mol) in a high-risk population of patients with type 2 diabetes and foot ulcers is associated with a significantly higher mortality, particularly in patients with QTc prolongation.

Keywords Diabetes · Foot ulcers · HbA_{1c} · Metabolic control · Mortality · QTc prolongation

Abbreviations

ABI	Ankle brachial index
ACCORD	Action to Control Cardiovascular Risk in Diabetes
CAN	Cardiac autonomic neuropathy
CVD	Cardiovascular disease
DFU	Diabetic foot unit
eGFR	Estimated glomerular filtration rate
IQR	Interquartile range
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation
PVD	Peripheral vascular disease
QTc interval	Heart-rate-corrected QT interval

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Introduction

Patients with a history of diabetic foot ulcers are considered to be a high-risk population for cardiovascular disease (CVD) and increased all-cause mortality [1, 2]. This risk increment can not fully be explained by traditional CVD risk factors, such as peripheral arterial disease, history of myocardial

infarction (MI) or renal dysfunction [2]. The importance of other diabetic complications, including microvascular disease and neuropathy, needs to be further evaluated.

In patients with type 2 diabetes, prospective studies have shown an association between the degree of hyperglycaemia, measured as HbA_{1c}, and incidence of cardiovascular events [3–6]. Based on these studies, EASD and ADA recommend a strict metabolic control with HbA_{1c} <7.0% (<52 mmol/mol) for most adults with diabetes [7, 8]. However, when the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study was published, showing an increased mortality among patients randomised to receive intensive glycaemic control, a less stringent HbA_{1c} goal was suggested for patients with a history of severe hypoglycaemia, a limited life expectancy or advanced diabetic complications [9]. The importance of hypoglycaemia has frequently been discussed as a plausible factor or mediator of this increased mortality, although no study has been able to show causality [10–12]. Hypoglycaemia alters several risk factors for mortality, including vasoconstriction and cytokine responses, and increases the likelihood of lethal arrhythmias [13–17].

It has been demonstrated that patients with diabetes mellitus have a more frequent occurrence of heart-rate-corrected QT (QTc) interval prolongation than non-diabetic patients [18]. Prolonged QTc time is associated with an increased risk of both cardiovascular and all-cause mortality in the general population [19, 20]. Long QTc time is related to several factors—older age, coronary heart disease, intake of certain drugs and presence of cardiac autonomic neuropathy (CAN, a serious complication of diabetes), as well as hypoglycaemia [18, 21, 22].

The aim of our study was to evaluate the impact of different HbA_{1c} levels and QTc prolongation on all-cause mortality in a predefined high-risk population consisting of patients with type 2 diabetes mellitus and a history of hard-to-heal foot ulcers.

Methods

Patient characteristics and measurement of variables All patients with type 2 diabetes mellitus and age below 80 years, visiting our Diabetic Foot Unit (DFU; Skåne University Hospital, Lund, Sweden) during two consecutive years were screened for study participation. Those with an ulcer that did not heal within 4 weeks of treatment were included in this study. Patients with ongoing dialysis and those without an HbA_{1c} or ECG registration within a 4 month period following the first visit to the DFU were excluded.

Patients were grouped according to HbA_{1c} level: group 1, HbA_{1c} <7.5% (<58 mmol/mol); group 2, HbA_{1c} 7.5–8.9% (58–74 mmol/mol) and group 3, HbA_{1c} >8.9% (>74 mmol/mol).

HbA_{1c}, creatinine, cholesterol, HDL-cholesterol, LDL-cholesterol and triacylglycerol were analysed in our local certified laboratory. Estimated glomerular filtration rate (eGFR) was derived from plasma creatinine level using the modification of diet in renal disease (MDRD) equation [23]. An eGFR ≥60 mlmin⁻¹ 1.73 m⁻² was considered to indicate normal renal function. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or current use of blood-pressure-lowering drugs. Hyperlipidaemia was considered present if total cholesterol was >5.0 mmol/l, LDL-cholesterol was >2.5 mmol/l or the patient was prescribed a cholesterol-lowering drug. Peripheral vascular disease (PVD) was defined by the presence of an abnormal ankle brachial index (ABI) value (≤0.9 or ≥1.4) or a history of previously performed vascular surgery including percutaneous transluminal angioplasty [24]. The ABI was measured as the ratio of systolic ankle pressure divided by arm blood pressure. Systolic ankle pressure was analysed with a pen doppler over the dorsal pedal or posterior tibial arteries.

A standard 12-lead resting ECG was taken during a regular visit to the clinic, using a Siemens ECG machine (Siemens Elema, Solna, Sweden). The QT interval was calculated from the beginning of the QRS complex to the end of the T wave, using the validated Sicard 440/740 ECG computer-analysis programme (Megacart version 3 V4, 7/2.38/23; Siemens Elema) [25, 26]. The QT intervals were then corrected for heart rate to obtain the QTc value using Bazett's formula [27]. A QTc value greater than 440 ms was considered abnormal and patients in each HbA_{1c} group were divided according to QTc time ≤ or >440 ms [28]. Mortality data was obtained from the Swedish National Death Registry. This study was approved by the Local Ethics Committee in Lund, Sweden and was carried out in accordance with the Declaration of Helsinki, as revised in 2000. All patients have given their consent.

Statistical analysis Patient characteristics are summarised by descriptive statistics. Continuous variables are expressed as median and interquartile range (IQR; 25–75 percentile) and categorical variables are presented as percentages. Continuous data were compared using Mann–Whitney *U* test and categorical variables using Fisher's exact test. Univariate survival analysis was performed by Kaplan–Meier analysis and overall significance was calculated by the Gehan–Wilcoxon test.

Cox proportional hazard regression models were applied to study the independent association between HbA_{1c} level, QTc prolongation and mortality. Initial analyses included the following basal characteristics with plausible impact on mortality: sex, previous MI, heart failure, PVD, hyperlipidaemia,

renal impairment (eGFR ≥ 60 , 45–59, 30–44, <30 mlmin⁻¹ min 1.73 m⁻²), diabetes duration (decades), smoking, age (grouped according to decade of age) and usage of insulin, insulin-releasing agents or beta blockers. Potential confounding factors with a p value <0.10 were entered in the final analyses. The results of these Cox proportional hazards models are presented as HR with 95% CI.

All statistical analyses were performed using Statistica software version 10 (Statsoft, Tulsa, OK, USA) and statistical significance was assessed at the two-tailed 0.05 threshold.

Results

Baseline characteristics Of the initial sample of 224 patients with type 2 diabetes and foot ulcers, ten were excluded from the study due to lack of HbA_{1c} data. Thus, 214 patients (37.9% women) with type 2 diabetes mellitus were grouped according to their HbA_{1c} level (HbA_{1c} $<7.5\%$ [<58 mmol/mol] $n=81$, 7.5–8.9% [58–74 mmol/mol] $n=70$, $>8.9\%$ [>74 mmol/mol] $n=63$).

The median age in the whole study population was 69.1 years (range 63–76) and did not differ between groups. As shown in Table 1, QTc prolongation and PVD was most prevalent in patients with HbA_{1c} $<7.5\%$ (<58 mmol/mol). There were no differences between groups in the usage of drugs with potential hypoglycaemic effect, although insulin therapy was most frequently used in the group of patients with the highest HbA_{1c} levels. Prescription of beta blockers, as well as other drugs with potential effect on the QT interval (tricyclic antidepressants, certain antibiotics [e.g. macrolides and quinolones]) did not differ between groups and did not affect the outcome of this study.

Survival analysis During a follow-up period of 8 years, 151 patients died (70.6% of total). As shown in Fig. 1, an HbA_{1c} level $<7.5\%$ (<58 mmol/mol) was strongly associated with increased mortality.

In a Cox hazard model including the following possible confounding factors: HbA_{1c} level, age, sex, diabetes duration, hyperlipidaemia, renal impairment, smoking habits, presence of heart failure, previous MI, PVD, usage of insulin or insulin-releasing drugs, usage of beta blockers and QTc prolongation, only age, sex, HbA_{1c} level and QTc prolongation were associated ($p<0.10$) with mortality and thus included in the final analysis. The outcome of this analysis showed that both HbA_{1c} $<7.5\%$ (<58 mmol/mol) and presence of QTc prolongation were independently associated with a higher mortality (Table 2).

In a subgroup analysis evaluating the impact of QTc prolongation at different HbA_{1c} levels, highest mortality was found in patients with HbA_{1c} $<7.5\%$ (<58 mmol/mol)

and QTc time >440 ms (Fig. 2). In these patients 8 year mortality was 92.1% as compared with 48.8% in those with HbA_{1c} $<7.5\%$ (<58 mmol/mol) but without QTc prolongation ($p<0.00001$). A statistically non-significant trend towards worse outcome in patients with QTc prolongation was seen in the other two HbA_{1c} groups (Fig. 2). In a Cox hazard model adjusted for the same plausible confounding factors as used in the previous analysis, HbA_{1c}/QTc (patients with both HbA_{1c} $<7.5\%$ [<58 mmol/mol] and QTc prolongation vs all other patients), age and sex was associated ($p<0.10$) with an increased 2, 4, 6 and 8 year mortality and thus included in the final analysis. Presence of hyperlipidaemia was associated with 2 year mortality in the initial but not in the final analysis ($p=0.16$). Patients with the combination of QTc time >440 ms and HbA_{1c} $<7.5\%$ (<58 mmol/mol) were at highest mortality risk in our study (Table 3).

A statistically significant correlation ($r=0.23$, $p=0.034$) was present between HbA_{1c} level and QTc time in the groups of patients not using any potentially QTc-prolonging drug (beta blockers, selective serotonin re-uptake inhibitors, macrolides, quinolones, proton-pump inhibitors or tricyclic antidepressants), whereas this was not the case in patients prescribed any of these drugs.

Discussion

It is well documented that improved metabolic control reduces microvascular complications in patients with type 2 diabetes mellitus, although it is not clear whether patients with type 2 diabetes mellitus and hard-to-heal foot ulcers benefit from strict glycaemic control. In our 8 year follow-up study evaluating survival in type 2 diabetes patients with hard-to-heal foot ulcers, short- as well as long-term all-cause mortality was higher in patients with HbA_{1c} levels below 7.5% (58 mmol/mol). Our finding is in accordance with the increased mortality in the intensively treated arm in the ACCORD trial and with the outcome of a large British cohort study including 47,970 patients with type 2 diabetes [9, 29]. The outcome of this latter study by Currie and co-workers showed a U-formed association between HbA_{1c} and all-cause mortality, with the lowest HR at an HbA_{1c} level of about 7.5% (58 mmol/mol). The adjusted HR of all-cause mortality for patients with the lowest HbA_{1c} decile was 1.59 [29]. Similar outcomes have been seen in studies evaluating the impact of HbA_{1c} levels in diabetic patients with severe renal complications [30, 31]. In a large cohort study including all diabetic patients with stage 3 and 4 chronic kidney disease in Alberta, Canada, the association between all-cause mortality and HbA_{1c} was J-shaped [30]. In a smaller study prospectively evaluating all-cause mortality in diabetic patients beginning dialysis treatment, a decreased mortality risk was observed with increasing

Table 1 Baseline characteristics of patients with different HbA_{1c} levels

Characteristic	HbA _{1c} <7.5% (<58 mmol/mol)	HbA _{1c} 7.5–8.9% (58–74 mmol/mol)	HbA _{1c} >8.9% (>75 mmol/mol)	<i>p</i> value
<i>n</i>	81	70	63	
Age (years)	72 (67–77)	71 (65–76)	67 (61–75)	NS
Diabetes duration (years)	11 (5–16)	11 (8–15)	12 (8–20)	NS
HbA _{1c} (%)	6.8 (6.3–7.2)	8.2 (7.8–8.5)	9.9 (9.2–10.8)	0.00000
HbA _{1c} (mmol/mol)	51 (45–55)	66 (62–69)	85 (77–95)	
QTc>440 ms (%)	46.9	30.0	30.7	0.019 ^a
Creatinine (μmol/l)	82 (68–100)	85 (66–103)	73 (56–97)	NS
eGFR<60 mlmin ⁻¹ (1.73 m) ⁻² (%)	28.4	34.8	27.0	NS
Sex, female/male (%)	32.1/67.9	38.6/61.4	44.4/55.6	NS
Previous MI (%)	33.3	28.9	22.2	NS
Heart failure (%)	24.7	28.6	19.1	NS
Hypertension (%)	75.3	68.6	68.3	NS
Hyperlipidaemia (%)	39.5	37.1	36.5	NS
Smoking (ever) (%)	56.8	51.4	54.0	NS
PVD (%)	58.0	42.9	25.4	0.07 ^b
				<0.01 ^c
				0.04 ^d
Previous vascular surgical intervention in a lower limb	34.6	20.0	12.7	0.07 ^b
				<0.01 ^c
				0.35 ^d
Glucose-lowering treatment				
Diet only (%)	11.1	1.4	1.6	NS
Metformin only (%)	6.2	11.4	4.8	NS
Sulfonylurea only (%)	19.8	14.3	11.1	NS
Metformin + sulfonylurea (%)	11.1	17.1	9.5	NS
Insulin alone or in combination (%)	51.9	55.7	73.0	NS ^b
				0.01 ^c
				<0.05 ^d
Insulin or sulfonylurea alone or in combination (%)	82.7	87.1	93.7	NS
Beta blocker (%)	27.2	30.0	33.3	NS
Digoxin (%)	9.9	15.7	9.5	NS
Tricyclic antidepressant (%)	4.9	1.4	3.2	NS
Selective serotonin re-uptake inhibitor (%)	6.2	13.0	9.7	NS
Macrolide (%)	0	0	0	NS
Quinolone (%)	8.8	17.4	9.7	NS
Proton-pump inhibitor (%)	13.6	10.0	6.3	NS

Data are given as percentage or median (IQR)

^a HbA_{1c}<7.5% (<58 mmol/mol) vs ≥7.5% (≥58 mmol/mol)

^b HbA_{1c}<7.5% (<58 mmol/mol) vs 7.5–8.9% (58–74 mmol/mol)

^c HbA_{1c}<7.5% (<58 mmol/mol) vs >8.9% (>75 mmol/mol)

^d HbA_{1c}7.5–8.9% (58–74 mmol/mol) vs >8.9% (>75 mmol/mol)

HbA_{1c} [31]. The follow-up time in these studies was 46 and 32 months, respectively. Contrarily, in-hospital mortality following acute MI was not associated with HbA_{1c} levels in an American study using data from a nationwide voluntary register [32].

A plausible explanation for this increased mortality might be a higher frequency of hypoglycaemic episodes in patients with a lower HbA_{1c}. It is well proven that the use of insulin or insulin secretagogues can cause severe and fatal hypoglycaemia. In type 1 diabetes mellitus, 6–10% of all

Fig. 1 Kaplan–Meier survival curve showing 8 year mortality in patients grouped according to HbA_{1c} levels, $p < 0.01$ for pooled comparison. For separate comparisons: HbA_{1c} $< 7.5\%$ (< 58 mmol/mol) vs HbA_{1c} $7.5\text{--}8.9\%$ ($58\text{--}74$ mmol/mol), $p = 0.06$. HbA_{1c} $< 7.5\%$ (< 58 mmol/mol vs HbA_{1c} $> 8.9\%$ (> 74 mmol/mol)), $p = 0.02$. HbA_{1c} $7.5\text{--}8.9\%$ ($58\text{--}74$ mmol/mol) vs HbA_{1c} $> 8.9\%$ (> 74 mmol/mol), NS. Solid line, HbA_{1c} $< 7.5\%$ (< 58 mmol/mol); dotted line, HbA_{1c} $7.5\text{--}8.9\%$ ($58\text{--}74$ mmol/mol); dashed line, HbA_{1c} $> 8.9\%$ (> 74 mmol/mol)

mortality is estimated to be associated with hypoglycaemia [33–35]. In addition, in the Normoglycemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study a strong association between hypoglycaemia and all-cause mortality was seen [11]. The follow-up period in NICE-SUGAR was 90 days and the median time from the first episode of hypoglycaemia to death was 7 days. A causal relationship between hypoglycaemia and mortality is likely for several reasons. Cardiac arrhythmias occurring during hypoglycaemia were first described in psychiatric patients treated with insulin shock in the 1930s [36]. Several case reports have also described an

association between arrhythmia and spontaneous hypoglycaemia [37, 38]. Further, hypoglycaemia triggers an array of counter-regulatory responses that would normally return blood glucose to non-pathological levels. Glucagon, adrenaline (epinephrine), noradrenaline (norepinephrine), cortisol, growth hormone, corticotropin, pancreatic polypeptide and the autonomic nervous system are all activated, leading to alterations in blood flow and blood composition, vasoconstriction, white-cell activation and a release of inflammatory mediators and cytokines [13–15, 17]. Several studies have also shown an association between hypoglycaemia and QTc prolongation in type 1 as well as type 2 diabetes mellitus [39, 40]. In our study QTc prolongation might be linked to hypoglycaemia, as it was more frequently present in the group of patients with the lowest HbA_{1c} levels (47 vs 30% in the other two groups), wherein 83% were prescribed drugs with hypoglycaemic effects (insulin or sulfonylurea). Further, a negative correlation between QTc time and HbA_{1c} was present in our patients without QTc-prolonging drugs, suggesting a plausible association between these two risk factors.

QTc prolongation, a condition known to be associated with CAN, has been shown to increase the risk of arrhythmia and sudden death in diabetic patients [41, 42]. In the ACCORD trial, the presence of CAN, defined as a combination of pathological QT index and abnormal heart-rate variability, was associated with increased mortality risk [43]. The highest mortality rate in our study was among patients with both QTc prolongation and HbA_{1c} $< 7.5\%$ (< 58 mmol/mol). In this group 8 year mortality was 92% as compared with 49% in those patients with similar HbA_{1c} but normal QTc time.

Although a causal relationship between these two factors and mortality is plausible, it will be difficult (and perhaps impossible) to sort out the true determinants of our outcome. However, the increased mortality in the group of patients with prolonged QTc time and the lowest HbA_{1c} level could not be explained by differences in traditional cardiovascular risk factors, such as MI, heart failure, hypertension or smoking habits, and our findings were sustained after being

Table 2 Predictors of all-cause mortality in patients with type 2 diabetes mellitus and hard-to-heal ulcers based on Cox proportional analyses adjusted for plausible confounders

All-cause mortality	HbA _{1c} $< 7.5\%$ vs $\geq 7.5\%$ ^a	p value	Age, risk per decade	p value	Female sex	p value	QTc prolongation	p value
2 year mortality	1.88 (1.05, 3.36)	0.033	1.72 (1.07, 2.75)	0.025	0.61 (0.32, 1.16)	NS	1.74 (0.98, 3.12)	0.060
4 year mortality	1.78 (1.16, 2.73)	0.009	1.56 (1.12, 2.17)	0.008	0.61 (0.37, 0.98)	0.042	2.08 (1.35, 3.22)	0.001
6 year mortality	1.47 (1.01, 2.14)	0.045	1.63 (1.22, 2.17)	0.001	0.64 (0.42, 0.97)	0.035	1.96 (1.34, 2.86)	0.001
8 year mortality	1.41 (1.00, 2.00)	0.052	1.51 (1.17, 1.95)	0.001	0.63 (0.43, 0.93)	0.019	2.00 (1.40, 2.85)	0.000

Data are given as HR (95% CI)

^a < 58 mmol/mol vs ≥ 58 mmol/mol

Fig. 2 Kaplan–Meier survival curve showing 8 year mortality in patients grouped according to HbA_{1c} levels and presence of QTc prolongation, defined as QTc time >440 ms. $p<0.0001$ for pooled comparison. For separate comparisons: QTc prolongation and HbA_{1c}<7.5% (<58 mmol/mol) vs all three groups with normal QTc-time separately $p<0.0001$; vs group with QTc prolongation and HbA_{1c} 7.5–8.9% (58–74 mmol/mol) $p=0.023$; and vs group with QTc prolongation and HbA_{1c}>8.9% (>74 mmol/mol) $p=0.015$. QTc prolongation and HbA_{1c} 7.5–8.9% (58–74 mmol/mol) vs normal QTc time and HbA_{1c}>8.9% (>74 mmol/mol), $p=0.025$. All other comparisons NS. Blue lines, patients with QTc prolongation; red lines, patients without QTc prolongation; solid line, HbA_{1c}<7.5% (<58 mmol/mol); dotted line, HbA_{1c} 7.5–8.9% (58–74 mmol/mol); dashed line, HbA_{1c}>8.9% (>74 mmol/mol)

adjusted for possible confounders. PVD, as well as a history of previous vascular surgical intervention in the lower limb, was more frequently present in the group of patients with the lowest HbA_{1c}. The 8 year mortality rate was higher in patients with a history of vascular intervention in a lower limb than in those without such intervention (74.1 vs 58.6%,

$p=0.032$); however, in the Cox proportional hazard model neither this intervention nor presence of PVD were independently associated with mortality. This outcome is in accordance with the result of a UK study evaluating factors associated with mortality in diabetic patients with novel foot ulcers [44]. In this study presence of PVD was associated with a higher mortality rate but after adjustment for confounding factors only older age turned out to be a significant predictor of mortality.

Autonomic neuropathy, which might not only lead to decreased adrenergic awareness of hypoglycaemia but also to increased risk of cardiac arrhythmia, may have been more frequently present in those patients with prolonged QTc time[45]. An alternative explanation is that QTc prolongation in combination with a low HbA_{1c} level, occurs as a result of disease processes that confer a predisposition to death, and that this cluster of risk factors represents a marker, rather than a cause, of an increased risk of death.

Possible limitations of this study include selection bias, although this is not a critical issue as all patients with diabetic foot problems in our catchment area are, with few exceptions, referred to our clinic. Our registry, including all patients visiting our clinic, as well as all charts from the years of inclusion, was carefully monitored. Mortality data are robust as the Swedish National Death Registry capture data on 100% of all deaths. The fact that we only included baseline clinical variables and did not account for time-varying covariates, might affect outcome. Further, QTc time might be influenced by several factors, including drugs and acute heart disease. All ECGs at our clinic were taken during non-acute, resting conditions, which limits (although does not exclude) biases such as myocardial ischaemia or acute heart failure. Neither could we identify any significant differences in prescription patterns of the most commonly used drugs with plausible QTc-prolonging actions (including beta blockers, tricyclic antidepressants, macrolides and quinolones) between groups. We did not collect data on the frequency of hypoglycaemia, so we can therefore only

Table 3 Importance of the combination of QTc prolongation and HbA_{1c}<7.5% (58 mmol/mol) on all-cause mortality in patients with type 2 diabetes mellitus and hard-to-heal ulcers based on Cox proportional analyses adjusted for plausible confounders

All-cause mortality	HbA _{1c} <7.5% ^a +long QTc time vs HbA _{1c} <7.5% ^a +QTc ≤440 ms and HbA _{1c} ≥7.5% ^a	<i>p</i> value	Age, risk per decade	<i>p</i> value	Female sex	<i>p</i> value
2 year mortality	2.80 (1.54, 5.09)	<0.001	1.76 (1.10, 2.82)	0.019	0.56 (0.29, 1.07)	0.079
4 year mortality	2.65 (1.66, 4.24)	<0.000	1.63 (1.18, 2.27)	0.003	0.54 (0.34, 0.87)	0.012
6 year mortality	2.55 (1.67, 3.87)	<0.000	1.69 (1.27, 2.25)	<0.000	0.58 (0.39, 0.87)	0.09
8 year mortality	2.76 (1.86, 4.09)	<0.0000	1.57 (1.21, 2.02)	0.001	0.57 (0.39, 0.84)	0.004

Data are given as HRs (95% CI)

All statistically significant risk factors are presented in the table

^a<58 mmol/mol

speculate on its importance as a possible cause or mediator of the increased mortality seen in patients with low HbA_{1c} level and prolonged QTc interval. Still, a causal relationship is plausible, and in the EURODIAB insulin dependent diabetes mellitus (IDDM) complications trial an annual occurrence of at least three severe hypoglycaemic events was, independently of confounders, associated with presence of QTc prolongation [46]. Another confounder might be that HbA_{1c} may decrease with older age, as well as being associated with terminal disease, but in our study no differences in age, medications or comorbidities were seen between HbA_{1c} groups. In this study we have neither evaluated cause of death nor autonomic nervous function, which limits our opportunity to identify any relationship between QTc time, autonomic function and cause of death. Despite these limitations we identified a group of patients with clinically and statistically significant increased mortality. However, to fully evaluate the importance of metabolic control and QTc time on mortality in this high-risk population a larger prospective multicentre study needs to be initiated.

In conclusion, in this high-risk population of patients with type 2 diabetes mellitus and hard-to-heal foot ulcers, an HbA_{1c} level below 7.5% (58 mmol/mol) was associated with higher mortality, particularly in the presence of QTc prolongation. This finding indicates the clinical importance of ECG screening and suggests that, in patients with prolonged QT intervals, drugs which are known to affect QT interval and hypoglycaemia should be avoided.

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