Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events

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Aims The study evaluated the associations between glycometabolic parameters at admission and during hospitalization and 2 year all-cause mortality risk in an unselected cohort of consecutive patients with diabetes admitted for unstable angina or non-Q-wave myocardial infarction to a university hospital during 1988–98.

Methods and results A total of 713 consecutive patients with diabetes were included. During 2 years of follow-up, 242 (34%) patients died. All analyses were retrospective using prospectively collected clinical data. The primary study endpoint was 2 year all-cause mortality collected from the Swedish cause-specific mortality register. In unadjusted analyses, high admission blood glucose (highest vs. lowest quartile: hazard ratio (HR) 2.66; 95% confidence interval (CI) 1.83, 3.86) and hypoglycaemia recorded during hospitalization (hypoglycaemia vs. normal: HR 1.77; 95% CI 1.09, 2.86) were both significantly associated with increased 2 year all-cause mortality risk. These associations remained significant after multivariable adjustment.

Conclusion In the setting of acute coronary syndromes (ACS) among patients with diabetes, hyperglycaemia on arrival and hypoglycaemia during hospitalization are both independently associated with worse adjusted all-cause 2 year mortality risk. These observations suggest that the avoidance of both hyper- and hypoglycaemia during ACS events may be of similar importance, and glucose modulation remains an important objective to address in future randomized trials.

Introduction

The global incidence and prevalence of diabetes, especially type 2 diabetes, are rapidly increasing,[1] and a parallel increase in the proportion of patients suffering from acute coronary ischaemic events with diabetes has been reported.[2] The association between diabetes and cardiovascular risk has been well described,[3,4] including observational analyses from cohort studies and large-scale clinical trials demonstrating worse short- and intermediate-term clinical outcomes following ACS events among the population of patients with diabetes.[5–8]

Few studies have directly evaluated the relationship between admission hyperglycaemia and clinical outcomes among diabetic patients with acute coronary syndromes (ACS).[8–11] Regardless of diabetes status, hyperglycaemia on arrival for patients presenting with ACS has been associated with adverse outcomes,[9,10] with higher reported incidence of congestive heart failure,[11] cardiogenic shock, and death.[12] Less is known regarding the association between hypoglycaemic events during hospitalization for ACS and clinical outcomes.

The purpose of the present study was to investigate the associations between glycometabolic state at admission and during hospitalization and 2 year all-cause mortality risk among a cohort of patients with diabetes admitted with ACS using data from a single-centre consecutive patient registry collected during 1988–98.

Methods

Patient population

Data were analysed from consecutive patients with diabetes admitted with a diagnosis of unstable angina or non-Q-wave myocardial infarction (MI) during 1988–98 to the Östra Hospital in Göteborg, Sweden. This hospital serves the northern and eastern parts of the city, which include a population of about 250 000 inhabitants. During the study period, clinical data on all admissions to either an 8-bed coronary care unit or a 14-bed cardiac step-down unit, excluding only those patients who were not residents of Sweden (<1%), were prospectively entered into a computerized clinical database approved by the Swedish National Board of Data

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Protection. Data collection included detailed information on clinical history and hospital course, treatments received, and discharge diagnosis and prescription.[13] For patients with multiple admissions, only data from the sentinel presentation were included. During this time period, there were 10 742 admissions recorded, of which 4341 patients met study criteria for ACS, including 713 patients with previously documented diabetes mellitus who comprise the present analysis cohort. For these patients, manual chart review was undertaken to abstract additional data regarding blood glucose measurements at the time of admission and throughout the hospitalization. All analyses were retrospective using prospectively collected clinical data.

Data definitions

The diagnosis of unstable angina or non-Q-wave MI was determined at the time of discharge. Non-Q-wave MI was defined by typical enzyme changes (serial creatine kinase > 3.3 μkat/L = 180 U/L or serial creatine kinase MB subunit mass concentration > 15 μg/L) and either a clinical syndrome consistent with ACS (chest pain, shock, syncope, or pulmonary oedema) or ischaemic electrocardiographic (ECG) changes without the development of Q-waves. Unstable angina was defined by at least one of the following: worsening of previous stable pattern of angina, chest pain at rest or minimal effort with transient ST-segment elevation or depression on ECG, or elevation of cardiac enzymes not reaching the criteria for MI. Diabetes was defined by clinical history recorded at the time of admission and classified according to previous treatment with insulin and/or oral hypoglycaemic agents and/or diet. Information regarding hypoglycaemic drug use and duration of diabetes was abstracted from medical records.

Blood samples

As this was a retrospective analysis of prospectively collected data, only standard clinical measures of blood glucose were available. Blood glucose was measured on admission for all patients before any treatments were initiated and routinely throughout the hospitalization according to usual clinical practice. Glucose values abstracted for the present analyses included the admission, highest, lowest, and last blood glucose measurements. At least three evaluable glucose measurements were available in 599 (84%) of 713 patients, with 23 patients (3%) having only one measurement of glucose recorded. A total of 65 patients died during index hospitalization and of these, 47 (72%) had at least three evaluable glucose measurements. Nine patients died so early in the course that only one glucose measurement was available. Before January 1998, whole blood glucose was measured routinely, but after 1998 plasma glucose came into routine use. For 67 patients included during 1998, plasma glucose values were converted to blood glucose using a constant of 0.9. Hypoglycaemia was defined as any episode of recorded blood glucose ≤3.0 mmol/L (55 mg/dL) any time during hospitalization with or without associated clinical symptoms or intervention.[14] Serum creatinine on admission was categorized into three groups: normal ≤120 μmol/L (≤1.36 mg/dL), elevated 121–150 μmol/L (1.37–1.70 mg/dL), and high ≥151 μmol/L (≥1.71 mg/dL). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in metres.

Outcome measures

The primary study outcome was 2-year all-cause mortality collected from the Swedish cause-specific mortality registry. Mortality was also assessed during the sentinel hospitalization using chart review and at 30 days following presentation with ACS using mortality registry data. All Swedish citizens have a unique personal identification number (PIN), which was used to link Swedish population records from 1988 to 1998 with data from the national Cause of Death Register.

Statistical methods

The mean values and proportions of baseline variables were compared among subgroups according to glucose status using ANOVA or Pearson's χ^2 tests as appropriate. Univariable and multivariable Cox proportional hazard modelling was used to analyse the association between admission glucose measurements, lowest recorded glucose measurements and clinical outcomes with on-arrival glucose values analysed both as a continuous and categorical variable. For categorical analysis, patients were divided into quartiles on the basis of blood glucose level at admission. In addition, patients were categorized on the basis of the lowest glucose measurement recorded during hospitalization into three groups: low (i.e. hypoglycaemic) [≤3.0 mmol/L (≤55 mg/dL)], intermediate [3.1–6.5 mmol/L (56–119 mg/dL)] and high (i.e. persistently hyperglycaemic) [≥6.6 mmol/L (≥120 mg/dL)]. For the multivariable modelling, covariates previously demonstrated to be independently associated with 2 year mortality following ACS were included in the model,[5] and included age, sex, and previous MI, hypertension, peripheral vascular disease, congestive heart failure, and PTCA/PCI. In addition, the final multivariable model included covariates with strong univariable associations in the present dataset, including duration of diabetes, year of registry entry, ACS type, elevated s-creatinine, treated hyperlipidaemia, smoking status, and β-blockers prescribed at discharge. Results are reported as HR with associated 95% CI and P-values. A two-tailed P-value <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 11.5 software package.

Results

Baseline

During the interval 1988–98, 713 consecutive patients with diabetes were admitted with unstable angina or non-Q-wave MI. In the overall cohort, the average patient age was 70.1 ±10.2 years, and 38% of patients were female. Baseline clinical and demographic characteristics are presented in *Table 1* according to on-arrival glucose quartiles. Glucose control strategies among these patients included 105 treated with diet alone, 204 treated with insulin monotherapy, 254 treated with sulfonylurea monotherapy, 8 treated with metformin monotherapy, and the remaining 115 patients treated with combinations of these strategies.

Association with baseline clinical variables

In univariate analyses, higher blood glucose levels at admission were associated with female sex, increased duration of diabetes, more congestive heart failure at admission, and elevated creatinine and more likely to have non-Q-wave MI as the qualifying ACS event; the level of blood glucose was inversely associated with the use of lipid-lowering drugs (*Table 1*).

Outcome during prospective follow-up

Follow-up data through 2 years post-event were available on 100% of patients in the Swedish cause-specific mortality registry. During this period 242 patients (34%) died.

Association between glucose parameters and 2 year mortality

Admission blood glucose analysed as a continuous variable (per mmol/L) was associated with 2 year all-cause mortality in unadjusted (HR = 1.07; 95% CI 1.05–1.10) and adjusted

Table 1 Baseline clinical characteristics according to the quartile of blood glucose level at admission

Characteristics[a]	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-value for trend
mmol/L	≤8.5	8.6–11.5	11.6–15.2	≥15.3	
mg/dL	≤153	154–208	209–274	≥275	
No. of patients (*n*)	177	168	169	172	
Age, mean (SD)	69.0 ±10.1	70.5 ±10.0	69.2 ±11.0	71.3 ±9.5	0.119
Female, *n* (%)	61 (34.5)	61 (36.3)	64 (37.9)	75 (44.8)	0.049
Smoker or previous smoker, *n* (%)	59 (33.3)	42 (25.0)	49 (29.0)	46 (26.7)	0.293
BMI (kg/m²), mean ±SD	27.0 ±4.5	27.0 ±4.0	27.0 ±5.2	26.9 ±4.9	0.995
Diabetes duration, >10 year, *n* (%)	52 (30.2)	39 (25.0)	64 (39.0)	60 (37.5)	0.031
Previous MI, *n* (%)	75 (42.4)	80 (47.6)	69 (40.8)	62 (36.0)	0.129
Hypertension, *n* (%)	81 (45.8)	80 (47.6)	76 (45.0)	69 (40.1)	0.250
Peripheral vascular disease, *n* (%)	22 (12.4)	17 (10.1)	15 (8.9)	25 (14.5)	0.647
CHF at admission, *n* (%)	12 (6.8)	17 (10.1)	28 (16.6)	40 (23.3)	<0.001
Treated hyperlipidemia, *n* (%)	23 (13.0)	15 (8.9)	17 (10.1)	10 (5.8)	0.038
Previous coronary revascularization (CABG or PCI), *n* (%)	14 (7.9)	6 (3.6)	9 (5.3)	10 (5.8)	0.548
Non-Q-wave MI, *n* (%)	86 (48.6)	110 (65.5)	113 (66.9)	142 (82.6)	<0.001
Creatinine at admission					
Elevated ≥121 μmol/L/ ≥ 1.37 mg/dL, *n* (%)	54 (30.5)	38 (22.8)	51 (30.4)	80 (47.3)	<0.001

CHF, congestive heart failure; CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

[a]For each variable, the percentages reflect the total number of patients for whom data were available. In some instances, this number was less than total number of patients in the quartile.

analyses (HR = 1.03; 95% CI 1.01–1.06). Using receiver–operator characteristic (ROC) curve methods to analyse admission blood glucose as a continuous variable, the optimized glucose cutpoint for prediction of 2 year all-cause mortality risk was 11.6 mmol/L (209 mg/dL), with an area under the ROC curve of 0.626.

For clarity of presentation and interpretation, after demonstrating the significant adjusted association between admission glucose as a continuous variable and 2 year mortality, the remaining analyses were conducted using admission glucose as a categorical variable, defined by quartiles. Increased admission blood glucose across quartiles was associated with increased mortality during initial hospitalization, after 30 days and at 2 years (unadjusted *P* for trend <0.0001 for all timepoints) (*Table 2, Figure 1*). Using the lowest glucose quartile as the referent, the unadjusted 2 year mortality risk was found to be significantly higher in the highest glucose quartiles (HR 2.66; 95% CI 1.83–3.86), an association that remained significant after adjusting for age and all baseline differences (HR 1.69; 95% CI 1.14–2.51) (*Table 2*).

During hospitalization, the mean lowest blood glucose in the overall cohort was 6.5 (±3.1) mmol/L. For the 684 patients with blood glucose data during hospitalization available, 44 patients had at least one documented hypoglycaemic event with glucose documented ≤3.0 mmol/L, 364 had an intermediate lowest glucose value (3.1–6.5 mmol/L), and 276 had persistent hyperglycaemia with the lowest glucose documented ≥6.6 mmol/L. Baseline characteristics according to the categories of lowest measured blood glucose are presented in *Table 3*. Compared with the intermediate group, both the lowest and the highest groups had significantly higher adjusted 2 year mortality using a model that included on-arrival blood glucose as a covariate (HR 1.93, 95% CI 1.18, 3.17; HR 1.48, 95% CI 1.09, 1.99, respectively) (*Table 4, Figure 2*).

Discussion

This is one of the largest studies reported to date evaluating the prognostic correlates of hyper- and hypoglycaemia, comprising an unselected, consecutive series of patients with diabetes and representing a broad spectrum of unstable coronary syndromes. These analyses demonstrate a clear association between hyperglycaemia, both at the time of presentation with ACS and during hospitalization, and long-term adverse clinical outcomes. In addition, the novel observation of the association between recorded hypoglycaemia and adverse clinical outcomes underscores the importance of judicious glycaemic management in this high-risk clinical setting. Our study included patients with the spectrum of comorbidities frequently seen in clinical practice, and as long as objective criteria were met for acute coronary event, no exclusion was made on the basis of duration of symptoms, glycometabolic parameters, or risk factors.

Hyperglycaemia

The large number of diabetes patients in this study allowed us to explore the relation between admission blood glucose and outcomes across a broad range of glucose concentrations. The increased cardiovascular risk associated with diabetes in the setting of ACS is only partially understood. Some of this increased risk may be caused by a direct effect of hyperglycaemia, or by the diabetic state itself, though the mechanism is not yet completely understood.

The present data demonstrate an independent graded association between increasing levels of admission glucose and adverse clinical outcomes, with a linear association observed between admission blood glucose and death. The results from the analyses of admission glucose with outcomes using categories provide the advantage of demonstrating the graded relationship between glucose levels

Table 2 Adjusted all-cause mortality risk according to the quartile of blood glucose level at admission

n (%)	Quartile 1 (n = 177)	Quartile 2 (n = 168)	Quartile 3 (n = 169)	Quartile 4 (n = 172)	P-trend χ^2	Adjusted-HR[a] (95% CI)
Blood glucose, mmol/L	≤ 8.5	8.6–11.5	11.6–15.2	≥15.3		
Blood glucose, mg/dL	≤153	154–208	209–274	≥275		
Deaths during hospital stay	8 (4.5)	7 (4.2)	15 (8.9)	35 (20.3)	<0.0001	2.46 (1.12, 5.42)
Deaths within 30 days	11 (6.2)	13 (7.7)	16 (9.5)	45 (26.2)	<0.0001	2.41 (1.22, 4.77)
Deaths within 2 years	42 (23.7)	42 (25.0)	62 (36.7)	82 (48.8)	<0.0001	1.69 (1.14, 2.51)

[a]Quartile 4 vs. Quartile 1; multivariable Cox proportional hazard models adjusted for age, sex, diabetes duration > 10 years, CHF, elevated creatinine, non-Q-wave MI, and treated hyperlipidaemia.
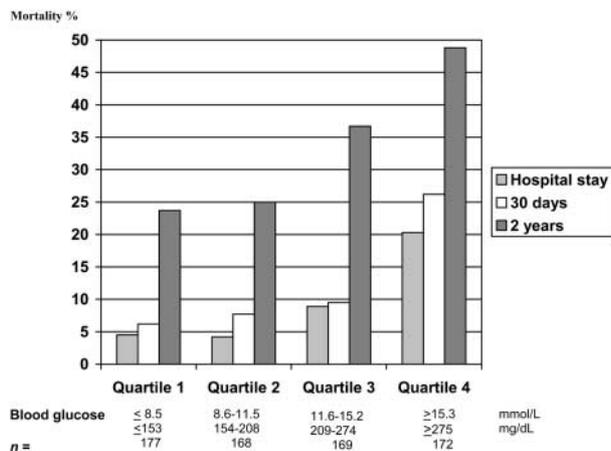

Figure 1 Crude mortality according to blood glucose at admission in quartiles.

and mortality rate, compared with reporting the similar association using on-arrival glucose analysed as a continuous variable, which was also statistically significant. The risk was greatest for patients with admission concentrations ≥15.3 mmol/L, consistent with previous observations.[10] Possibly there is a continuous association between on-arrival glucose and mortality risk. We therefore performed ROC analysis evaluating glucose continuously. We did not observe a threshold at the lower end below which no mortality gradient existed. Because of this, and importantly, because of the observational nature of the analyses precluding assumptions of causality, we are unable, in this study, to identify an 'ideal' glucose to propose as a therapeutic target. On the basis of our hypoglycaemia data, we would assume a U-shaped relationship would exist if we had more representation of lower blood glucose values on arrival, but this dataset is simply not informative in that regard.

Hyperglycaemia in diabetes patients is strongly associated with risk for coronary vascular disease and its progression, including increased mortality risk,[15,16] as demonstrated in a recent meta-analysis that included data from more than 95 000 patients.[17] Hyperglycaemia is also a common finding in patients with acute MI and likewise has been found to be an independent predictor of early cardiovascular death.[18–20] As suggested by significant trend analyses in *Table 1*, hyperglycaemia is associated with more advanced diseases such as MI (compared with unstable angina), more congestive heart failure, and longer duration of diabetes,

all of which perhaps contribute to the observed association, possibly due in part to more adverse neurohormonal activity in the setting of ACS associated with these conditions. Whether the association between hyperglycaemia and adverse outcomes is causally linked or is a reflection of severity of underlying disease (or both) remains to be determined.

Although improved metabolic control and insulin–glucose infusion followed by multi-dose insulin were shown to reduce mortality after MI in the DIGAMI study,[21] the recent negative results from the DIGAMI-2 study surprisingly demonstrated no benefit associated with an acute insulin–glucose infusion (identical to the DIGAMI protocol) with or without chronic intensive insulin therapy compared with usual care (EASD presentation: European Association for the Study of Diabetes 40th Annual Scientific Sessions 2004, Berlin). On the basis of the persistent uncertainties, randomized clinical trials are needed to better define the optimal glycaemic control targets and therapeutic strategies for patients with diabetes suffering from acute coronary ischaemic complications, including those with unstable angina pectoris or non-Q-wave MI. Mechanisms of the adverse effects of hyperglycaemia cannot be deduced from our data, although there were clear independent associations between both increasing admission blood glucose and persistent hyperglycaemia during hospitalization with poor outcomes.

Hypoglycaemia

Hypoglycaemia is a frequent side effect of diabetes treatment, having potential serious consequences and can be a frightening experience for patients. Low blood glucose [≤3.0 mmol/L (≤55 mg/dL)] during hospitalization was an independent predictor for death within 2 years compared with patients with normal glucose values throughout hospitalization, with an adjusted hazard of 2 year mortality of 1.93 (95% CI 1.18–3.17). Our results encourage further exploration of the importance of hypoglycaemic events during hospitalization as a possible useful marker for identification of diabetes patients with poor prognosis, and suggest that more careful management of plasma glucose in order to avoid hypoglycaemia may translate into mortality benefit. In the DIGAMI study,[14] which randomized patients with acute coronary events and hyperglycaemia at hospital presentation to acute insulin–glucose infusion followed by long-term treatment with subcutaneous insulin vs. usual care, 28 (18%) of the patients randomized to insulin treatment had documented hypoglycaemic episodes during hospitalization. In that

Table 3 Baseline clinical characteristics according to lowest blood glucose recorded during hospital stay

Characteristics[a]				P-value for trend
mmol/L	≤ 3.0	3.1–6.5	≥6.6	
mg/dL	≤ 55	56–119	≥120	
No. of patients	44	364	276	
Age, mean (SD)	68.8 ± 12.5	69.9 ± 10.0	70.3 ± 10.0	0.424
Female, n (%)	14 (31.8)	134 (36.8)	112 (40.6)	0.187
Smoker or previous smoker, n (%)	17 (38.6)	107 (29.3)	71 (25.7)	0.086
BMI kg/m^2, mean (SD)	25.5 (4.3)	26.6 (4.3)	27.8 (5.1)	0.001
Diabetes duration, >10 years, n (%)	25 (58.1)	116 (33.2)	72 (27.8)	<0.01
Previous MI, n (%)	14 (31.8)	158 (43.4)	115 (41.7)	0.620
Hypertension, n (%)	13 (29.5)	159 (43.6)	134 (48.6)	0.024
Peripheral vascular disease, n (%)	5 (11.4)	43 (11.8)	30 (10.9)	0.774
CHF at admission, n (%)	5 (11.4)	52 (14.2)	39 (14.1)	0.783
Treated hyperlipidemia, n (%)	3 (6.8)	35 (9.6)	27 (9.8)	0.663
Previous coronary revascularization, (CABG or PCI), n (%)	1 (2.3)	22 (6.0)	16 (5.8)	0.619
Non-Q-wave MI, n (%)	33 (75.0)	224 (61.4)	192 (69.6)	0.348
Elevated creatinine at admission[b], n (%)	16 (36.4)	121 (33.3)	86 (31.4)	0.465
Admission blood glucose, mmol/dL mean (SD)	11.7 (7.6)	11.2 (5.0)	13.6 (4.7)	<0.0001

[a]For each variable, the percentages reflect the total number of patients for whom data were available. In some instances, this number was less than total number of patients in the subgroup.
[b]Elevated creatinine defined as ≥121 µmol/L (≥1.37 mg/dL).

study, there was no evidence of adverse clinical outcomes in the hypoglycaemic group. However, with only 28 evaluable patients, this analysis has insufficient statistical power to definitively evaluate the possible association.

Whether the association between documented hypoglycaemia and adverse intermediate and long-term outcomes is causally linked remains unclear. Hypoglycaemia may be a marker of severity of underlying disease, such as type 1 or insulin-requiring type 2 diabetes, renal insufficiency, diagnosed or occult malignancy, or other clinical conditions that adversely affect outcomes.[22] However, as shown in *Table 3*, there were no obvious comorbidities that were over-represented in the group with hypoglycaemia. In addition, the association remained significant after adjusting for many of the imbalances in patient characteristics among the groups.

Although it may not be inherently evident how in-hospital hypoglycaemia may be associated with long-term risk for adverse outcomes following acute coronary events, some plausible mechanistic links are supported by prior reports. For example, among six diabetic patients without known coronary disease intentionally subjected to insulin-induced hypoglycaemia,[23] ischaemic ECG changes were associated with hypoglycaemia in five of the six subjects. These observations are supported by a more recent study that correlated hypoglycaemia, detected by continuous glucose monitoring, with symptoms of angina and ischaemic changes recorded with ambulatory ECG among 19 diabetic subjects.[24] These observations suggest that hypoglycaemia may precipitate or exacerbate cardiac ischaemia. In addition, in the study by Lindstrom *et al.*,[23] significant elevations of catecholamines and declines in serum potassium were observed during hypoglycaemia, each of which may be associated with adverse cardiac consequences in the post-ACS period. In a similar study of seven patients with type 2 diabetes and seven controls, Spyer *et al.*[25] demonstrated similar counter-regulatory hormone responses

to insulin-induced hypoglycaemia, with the catecholamine responses exaggerated among the diabetic subjects and occurring at higher glucose thresholds in the low-normal range (3.8 mmol/L).

In addition to the acute ramifications of hypoglycaemia in the ACS setting, it also remains possible that the subset of patients with documented hypoglycaemia during hospitalization were at above-average risk for subsequent hypoglycaemic events throughout the follow-up period, with increased exposure to the associated adverse cardiovascular conditions discussed earlier. Our observation of increased mortality risk among those patients with hypoglycaemia following ACS in the context of the reported cardiovascular and counter-regulatory consequences of hypoglycaemia warrants further investigation to define optimal acute and long-term glycaemic control strategies for patients with diabetes following ACS events.

Limitations

The study has number of notable limitations. Our study included only 713 patients from a single centre. It is a retrospective subanalysis; however, the inclusion of a consecutive patient cohort, the prospective collection of data, the large sample size, and the completeness of the follow-up data acquisition counter this limitation. Blood glucose was not measured systematically during hospitalization, with only standard clinical measures of blood glucose available. Therefore, we may have missed some nadir glucose values, but this limitation should tend to bias the results towards the null hypothesis. As a limitation of observational data analyses, the use of multivariable modelling using a broad array of covariates adjusts for much of the imbalance in patient mix, but may not completely adjust for unmeasured and immeasurable parameters that could influence outcomes, such as differences in other comorbidities and in

Table 4 Association of cardiovascular risk factors with 2 year mortality (*n* = 713)

Variable	Unadjusted[a] HR (95% CI)	Adjusted[a] HR (95% CI)
Age, risk per 10 years	1.87 (1.61–2.16)	1.59 (1.32–1.93)
Diabetes duration, risk per 10 years	1.60 (1.21–2.09)	1.55 (1.16–2.07)
Non-Q-wave MI vs. unstable angina pectoris	2.98 (2.13–4.15)	2.02 (1.38–2.70)
S-creatinine elevation, admission[b]	1.96 (1.68–2.29)	1.53 (1.27–1.84)
Quartile blood glucose elevation, admission[c]	1.42 (1.26–1.60)	1.17 (1.02–1.34)
Lowest blood glucose, during hospital stay		
$\leq$ 3.0 vs. 3.1–6.5 mmol/L/$\leq$ 55 vs. 56–119 mg/dL	1.77 (1.09–2.86)	1.93 (1.18–3.17)
$\geq$ 6.6 vs. 3.1–6.5 mmol/L/ $\geq$ 120 vs. 56–119 mg/dL	1.60 (1.22–2.11)	1.48 (1.09–1.99)
Year of admission, risk per year	0.93 (0.89–0.97)	0.91 (0.87–0.96)
Treated hyperlipidemia	0.40 (0.22–0.74)	0.38 (0.19–0.76)
β-blockers prescribed at discharge	0.44 (0.34–0.57)	0.58 (0.43–0.78)
Female sex	1.21 (0.94–1.56)	1.05 (0.78–1.41)
Smoker or previous smoker	0.70 (0.52–0.95)	1.19 (0.84–1.68)
Previous myocardial Infarction	1.17 (0.91–1.50)	1.23 (0.93–1.63)
Previous hypertension	1.03 (0.80–1.33)	1.04 (0.78–1.39)
Peripheral vascular disease	1.74 (1.24–2.43)	1.36 (0.94–1.97)
Congestive heart failure at admission	2.23 (1.65–3.02)	1.33 (0.95–1.87)
Previous coronary revascularization (CABG or PCI)	0.75 (0.40–1.37)	1.35 (0.67–2.74)

[a]Cox proportional hazard model, adjusted for all in the list.
[b]Categorized $\leq$120; ($\leq$1.36 mg/dL); 121–150 (1.37–1.70 mg/dL), and $\geq$151 μmol/L ($\geq$1.71 mg/dL).
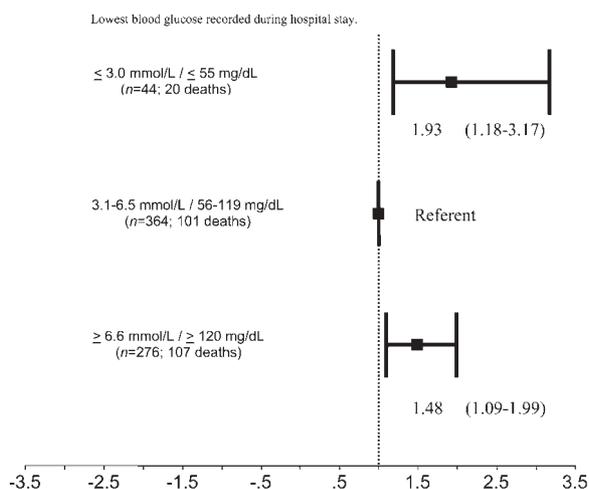[c]Per quartile.

Figure 2 Association between lowest recorded blood glucose during hospitalization and incidence of death within 2 years. The values are HR and 95% CI.

treatments received among the glucose categories. Similarly, we are unable to distinguish whether hyper- and hypoglycaemia are causally linked to adverse outcomes, are simply markers of more severe underlying disease state, or both. As we relied on death registry data, which lack information on other important parameters of health outcome, our study is limited by the exclusive evaluation of all-cause mortality endpoints. However, it does reflect the 'real world' population in that it includes all consecutive patients hospitalized with ACS in a self-contained health care system and thus provides important insights into treatment and outcome of such patients when stratified according to their glycaemic status.

Conclusions

Admission glucose level and persistent hyperglycaemia throughout hospitalization independently predicted short and 2 year mortality risk among patients with diabetes and ACS. Regardless of admission hyperglycaemia, documented hypoglycaemia during hospitalization was also associated with increased mortality risk and may be a useful adjunctive marker for identification of diabetes patients with poor prognosis. In addition, the important associations of both hyper- and hypoglycaemia with post-ACS mortality risk underscore the importance of continued investigation to define the optimal glycaemic control strategies during and after ACS events.

Acknowledgements

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