Admission blood glucose concentration; A more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001596
Article Type:	Research
Date Submitted by the Author:	06-Jul-2012
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Myocardial infarction < CARDIOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Coronary heart disease < CARDIOLOGY

Admission blood glucose concentration; A more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis

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Keywords: Acute myocardial infarction, diabetes, glucose

Word count: 3029

ABSTRACT:

Objective: To explore the relative impact of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with ST elevation myocardial infarction (STEMI) and non-STEMI.

Design: Retrospective cohort study based on the Myocardial Ischaemia National Audit Project dataset.

Setting: Tertiary care centre.

Participants: 4111 (20.3% known diabetes) consecutive patients admitted with acute myocardial infarction (58.3% STEMI) between October 2002 and September 2008.

Primary and secondary outcome measures: All-cause mortality at 30-days and 1-year. The relative association of admission blood glucose and of antecedent diabetes with mortality was assessed using multivariate Cox regression analysis. Furthermore we compared these relationships in patients with STEMI to those with NSTEMI.

Results: By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) of patients died. After adjusting for covariates, diabetes did not show independent association with mortality at any time point, in the entire cohort (HR 30 days 0.93 (CI 0.63 – 1.38); 1-year 1.00 (0.77 – 1.30)) or in subgroups of STEMI (HR 30days 1.03 (0.65 – 1.64); 1 year 1.08 (0.77 – 1.51)) and non-STEMI (HR 30-days 0.62 (0.26-1.50); 1-year 0.87(0.56 – 1.36)). In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR: 30 days 1.07 (1.04 – 1.10); 1-year 1.05 (1.03 – 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03 – 1.10); 1-year 1.07 (1.04 – 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 - 1.14); 1-year 1.02 (0.97 - 1.06)).

Conclusion: Admission glucose is strongly associated with mortality in all presentations of acute myocardial infarction (AMI), irrespective of established diabetes diagnosis. The increased risk is

maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.

INTRODUCTION

For patients with acute myocardial infarction (AMI) the risk of adverse outcome is increased by the concomitant diagnosis of diabetes mellitus (diabetes).(1, 2) In addition, elevated blood glucose concentration, a common finding at admission in patients with AMI, is also associated with increased risk of adverse outcome, irrespective of prior diabetes.(1-8). In some studies (4, 9) the association between admission blood glucose concentration and adverse outcome was more powerful in patients without, compared to those with, prior diabetes. Indeed we previously reported more powerful association with 30-day and 1-year mortality after STEMI for admission blood glucose concentration, compared to the diagnosis of diabetes.(9)

While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which hyperglycaemia may impart toxicity during myocardial ischaemia.(10, 11) Indeed, observational data suggest that elevated blood glucose may contribute directly to adverse outcome after AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 hours after AMI compared to those in whom blood glucose normalises.(12, 13) In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with improved prognosis.(14, 15) Further, in randomised, controlled trials (RCTs) of intensive, insulin-based blood glucose management during admission with AMI, survival benefit was evident only when intervention effectively lowered blood glucose concentration.(16, 17)

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of acute coronary syndromes in contemporary practice are non-ST elevation AMI (NSTEMI). The aim of the current analysis was to compare the relative strength of association with 30-day, and 1-year mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with STEMI and with NSTEMI, and in those with and without a history of diabetes, in a multi-ethnic population. We also assessed the relevance

of blood glucose concentration, recorded soon after admission to hospital with AMI, to mortality in patients surviving to discharge.

METHODS

Data were from consecutive admissions between 1st October 2002 – 30th September 2008, to the two coronary care units (CCU) of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). For all patients, as part of the hospital's mandatory commitment to the Myocardial Ischaemia National Audit Project (MINAP),(18) we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), electrocardiographic (ECG) site of infarct, medical history, coronary heart disease risk-factors, and prescribed medication. Data are record-linked to mortality information (19) and include self reported coding for ethnicity, for which local coverage is thorough. Approximately 10% of the local population are of South Asian ethnic origin, over twice the UK national average.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient, or on the basis of medication prescribed prior to admission. The blood glucose measurement used for the analysis was the first recorded at the time of the index admission, assayed in the hospital laboratory as part of routine investigations. All diagnoses of AMI were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACCF/AHA/WHF definition.(20) Patients were categorised as STEMI or NSTEMI, according to the final discharge diagnosis recorded in the MINAP database. For patients with multiple AMI admissions during the study period, we considered only the first event.

Survival was measured from the date of first admission to the date of death or of censoring at 30th September 2009. Mortality data are supplied to the hospital on a monthly basis via the UK Office for

National Statistics. The pre-defined primary outcome measure was 30-day, and 1-year, all-cause mortality..

The study was approved by the local research ethics committee. The data used in this analysis were gathered during routine care and as part of the MINAP (18) mandatory requirement for all acute hospitals in England and Wales to collect data pertaining to admission with AMI.

Statistical analysis

Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Mortality at 30 days and at 1 year, in the entire cohort, and in those patients surviving to discharge, was calculated.

We calculated mortality proportions for patients admitted from 1st October 2002 to 30th September 2008 with follow-up censored at 30th September 2009. Survival probabilities were calculated using Kaplan-Meier [KM] analyses and patient groups compared using survival analysis log rank test. Relative risk of mortality, as a function of clinical variables, was examined using Cox proportional hazards techniques. We initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity (white European, South Asian), smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary revascularisation during index admission, pre-admission and discharge drug therapy (anti-platelet, beta-blocker, statin, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker), and index loop diuretic use. An interaction term representing calendar year of admission was included to adjust for potential temporal changes in the management of acute coronary artery disease.

Demographic and clinical covariates with univariate association (p<0.10) with mortality at 30 days, or 1 year were entered into multivariate models (Cox proportional hazards). Statistical significance for all comparisons was set at p<0.05 (2 sided). Data are presented as hazard ratio (HR) and 95% confidence intervals (CI). We used fractional polynominals to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS version 18.

RESULTS

The study population was the 4111 patients admitted between 1st October 2002 – 30th September 2008 with discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow up was 912 days (range 0 to 2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow up was 1031 (range 1 to 2556) days.

Demographic details of the study population are presented in Table 1. Prior diabetes was recorded in 835 (20.3%) patients: compared to those without, patients with antecedent diabetes were on average older (68.6 vs 65.8 years, p<0.005), more likely to be female (33.9% vs 28.9%, p = 0.022) and to have prior cardiovascular co-morbidities. Presentation with NSTEMI was more prevalent in cases with (50.1%), compared to those without (39.6%), prior diabetes (p <0.005). Mean plasma glucose was higher in patients with diabetes (12.0 ± 5.5 mmol/L) compared to those without (7.9 ± 3.3 mmol/L) (p <0.005). Mean peak CK was lower in patients with diabetes.

During the index admission administration of loop diuretic was more frequent (52.7% vs 33.4%, p<0.005) and, for patients with STEMI, coronary reperfusion therapy less frequent (50.2% vs 60.9%, <0.005), in patients with diabetes. Other than for slightly less use of beta-blockers and aspirin in

patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

Mortality – Univariate analysis

Deaths during hospitalisation, over 30-days, 1-year and the entire period of follow-up numbered 319 (7.8%), 409 (9.9%), 677 (16.5%) and 1041 (25.3%) respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (Table 2). Loop diuretic was associated with a 3-4 fold increase in mortality during follow-up. Survival improved over the period of observation.

Prior diabetes showed strong univariate association with mortality risk over all time periods: HR 30 days 1.40 (1.12 - 1.75); 1 year 1.58 (1.33 - 1.86); all follow-up 1.66 (1.44 , 1.90)) (Table 2). The strength of association between glucose and mortality was consistent at 30-days and at 1-year, each mmol/L increase in admission glucose concentration being associated with a 6-7% increase in hazard of mortality over all time periods.

Post-discharge mortality

In those surviving to discharge (N=3792), 106 (2.8%), 363 (9.6%) and 726 (19.1%) died by 30-days, 1-year and over all follow-up (Table 2A, Supplementary data). Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, (0.87 - 2.12)). For admission glucose, the strength of association with post-discharge mortality was very similar to that in the entire cohort, with 5-7% increase risk per mmol/L increase in glucose. (Table 2A, Supplementary Data).

Mortality – Multivariate analysis

Table 3 shows the results of multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of loop diuretic, and STEMI (compared to NSTEMI) each retained independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain independent association with mortality at any time. In contrast, adjustment for covariates had little impact upon the risk of mortality associated with admission glucose concentration.

Post-discharge mortality

For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort (Table 3A, Supplementary data). While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 – 1.300); 1 year 0.91 (0.66 – 1.26); all follow-up 1.08 (0.86 – 1.36)), blood glucose retained powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/L 1.10, 95% CI 1.05 – 1.15), 1 year (1.05, 1.02 – 1.08), and over all follow-up (1.04, 1.02 – 1.06)).

Admission glucose concentration – influence on mortality in patients with or without diabetes

We repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (Figure 1), there was no conventional statistically significant difference in the association between mortality and admission blood glucose for patients with and without diabetes (30 days HR 1.00, (CI 0.97 – 1.03, p=0.95; 1 year 0.99, (0.97 – 1.02), p=0.66; entire follow-up 0.99, (0.97 – 1.01, p=0.42)).

Diabetes and glucose after AMI – influence on mortality in STEMI and NSTEMI

After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period, either for STEMI or NSTEMI (Table 4). The strength of association

between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only after NSTEMI.

DISCUSSION

It is well known that, both prior diabetes diagnosis, and admission blood glucose concentration, are associated with adverse outcome after AMI. In this report we compared the relative association of these two measures of dysglycaemia with survival after STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55-65% thereafter) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In our previous report of over 4000 patients with STEMI, admitted in 1993-2004,(9) the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and removed completely when admission blood glucose concentration was included in the analysis. The current report confirms these observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI, in whom the strength of association between admission blood glucose concentration and 30-day mortality risk was similar, and concentration dependent. Importantly, the excess risk, around 7% for each 1mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Further, this phenomenon was attenuated with time only for patients with NSTEMI, and was evident even in those patients who survived to discharge from hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association between admission glucose and mortality to be confined to in-hospital deaths following either

STEMI or NSTEMI.(8) They are however in keeping with the vast majority of reports in this area.(1-7, 9, 11)

In contrast to most previous reports,(1-9, 11) we observed no independent association between diabetes and mortality risk after AMI. However, to our knowledge and unlike the present report, none of these studies adjusted for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis (1, 2, 4, 8) or blood glucose concentration.(3-8, 11-13, 21) The current analysis and our previous study (9) are the only reports to compare the relative association with outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose, and the loss of association between mortality and diabetes when blood glucose is considered.

These observations are of potential clinical significance. While admission blood glucose concentration after AMI is on average higher in patients with, compared to those without, known diabetes,(4, 8, 9) there is considerable overlap, as seen in the current report (Figure 1). While many patients presenting with AMI will have previously undiagnosed diabetes,(22) blood glucose at the time of admission with AMI is not a reliable indicator of the subsequent diagnosis of diabetes.(23, 24) In routine practice, the management of hyperglycaemia after AMI is influenced by the presence of prior diabetes diagnosis.(5) In both European(14) and North American(6) settings, the majority (>65%) of patients presenting with hyperglycaemia in the context of AMI, and not previously known to have diabetes, do not receive active management of blood glucose. In the presence of a true, direct toxic effect upon prognosis of elevated blood glucose, failure to correct hyperglycaemia may represent suboptimal clinical care, and patients without known diabetes may be particularly disadvantaged. In particular, our demonstration that the relationship between glucose concentration and subsequent outcome is evident in NSTEMI as well as STEMI is of clear clinical relevance in terms of the overall management of patients presenting with AMI.

The strength of association between diabetes and mortality risk after AMI has been reported to increase with time from the event.(25) While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate. A previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcome.(4) While we could not demonstrate formal statistical evidence of such a phenomenon, our data show convincingly that the relationship between glucose and outcome is at least as powerful in patients without known diabetes. Blood glucose soon after admission represents an easily identified, clinically relevant marker of risk after AMI, which should be assessed routinely irrespective of diabetes status.

An important observation from this study is the persisting association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTEMI and STEMI. While in keeping with the possibility that blood glucose concentration at admission reflects the degree of individual physiological stress, or is a marker of the extent of infarction, our findings are as much in keeping with a direct, adverse influence on prognosis of acute hyperglycaemia. The mechanisms by which elevated glucose may be directly cardiotoxic have been summarised elsewhere (10) and include attenuation of ischaemic preconditioning, QT prolongation, increased thrombophilia, and endothelial dysfunction. Furthermore, clinical studies overwhelmingly support a possible causal link between hyperglycaemia and adverse prognosis after AMI. Hyperglycaemia persisting at 24 hours after admission is associated with adverse outcome,(12, 13, 17).

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent.(16,17) However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis.(16) The guidelines from professional societies in this area differ in their recommendations.(27,28) In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant

hyperglycaemia (blood glucose levels > 10.0 mmol/L) admitted in an intensive care unit.(28) In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with acute coronary syndrome.(27) The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Our report is subject to the limitations inherent in all observational cohort studies. Blood glucose concentration used in this analysis was that first recorded for the index admission, and is likely to have varied in timing relative to symptom onset. Our database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure, and a number of other potentially relevant variables. Further, we have no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status. Thus we suggest the first recorded blood glucose concentration to be highly relevant to guiding appropriate management in individual patients, irrespective of residual LV function. While we have no information on interventions or changes to therapy after discharge, it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. After adjustment for admission blood glucose, known diabetes is not associated with adverse outcome. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTEMI as well as STEMI, and persists beyond 1 year from the index event, including in patients surviving to discharge. Future studies are merited of the impact of active management of blood glucose in patients with all presentations of acute coronary artery disease, irrespective of diabetes diagnosis.

ARTICLE SUMMARY

Article focus

- Robust associations is seen for both measures of glycaemia - the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).
- We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with STEMI and NSTEMI.

Key Messages:

- In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.
- The increased risk associated with admission glucose is evident during the index admission, at 30 days, one year and beyond and is apparent in those surviving to discharge.
- Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study

- This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.
- A statistically robust association was seen for admission glucose with both short and loner term mortality after adjusting for many important confounders.

- Our data lacks information on glucose lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

Table 1: Baseline characteristics at admission stratified by diabetes status

	All n=4111	Known DM n= 835 (20.3%)	Not Known DM n=3276 (79.7%)	P Value*	Missing Value (%)
Demography					
Age (years)	66.4 (13.3)	68.6 (11.8)	65.8 (13.6)	<0.005	0.0
Women (%)	1224 (29.8)	276 (33.1)	948 (28.9)	0.022	0.0
Ethnicity (%)					
White European	3381 (82.2%)	545 (16.1)	2836 (86.6)	<0.005	0.0
South Asian	730 (17.8%)	290 (39.7%)	440 (60.3%)		0.0
Medical History (%)					
Hypertension	2048 (50.3)	584 (70.0)	1464 (45.0)	<0.005	1.0
Current/Ex Smoker	1366 (35.7)	282 (36.8)	1084 (35.5)	0.527	7.1
Coronary Heart Disease§	491 (12.1)	149 (17.9)	342 (10.6)	<0.005	0.9
CVA	254 (6.3)	86 (10.3)	168 (5.2)	<0.005	1.2
PVD	154 (3.8)	42 (5.0)	112 (3.5)	0.041	1.2
Heart Failure	190 (4.7)	76 (9.1)	114 (3.5)	<0.005	1.2
Type of Infarction (%)					
STEMI	2397 (58.3)	417 (49.9)	1980 (60.4)	<0.005	0.0
nSTEMI	1714 (41.7)	418 (50.1)	1296 (39.6)		
Physical Examination					
Heart Rate (beats/min)	81.1 (24.3)	85.5 (25.3)	80.0 (24.0)	<0.005	1.5
SBP (mmHg)	136.5 (28.4)	137.7 (30.7)	136.2 (27.8)	0.202	1.0
Biochemical Data					
Peak CK (IU/L, Normal range < 200)	1113.5 (1810.4)	939.9 (1279.3)	1156.4 (1917)	<0.005	7.6
Creatinine (µmol/L)	116.4 (63.8)	128.8 (76.1)	113.1 (59.8)	<0.005	16.8
eGFR (mL/min)	63.0 (22.2)	57.7 (23.6)	64.4 (21.7)	<0.005	16.6
Total cholesterol (mmol/L)	5.1 (1.3)	4.4 (1.2)	5.2 (1.3)	<0.005	16.6
Haemoglobin (g/L)	13.7 (1.9)	13.0 (1.9)	13.9 (1.8)	<0.005	66.6
Plasma glucose (mmol/L)	8.8 (4.2)	12.0 (5.5)	7.9 (3.3)	<0.005	14.9
Therapies (%)					
Prior to index admission					
Aspirin	2671 (65.0)	622 (74.5)	2049 (62.5)	<0.005	0.0
Beta blocker	990 (25.6)	265 (33.2)	725 (23.6)	<0.005	6.0
ACEI or ARB	1097 (28.3)	407 (51.0)	690 (22.5)	<0.005	5.8
Statins	1083 (28.0)	389 (48.7)	694 (22.6)	<0.005	5.8
In-hospital					
Reperfusion therapy #	2414 (58.7)	419 (50.2)	1995 (60.9)	<0.005	0.0
Loop diuretics	1502 (37.4)	436 (52.7)	1066 (33.4)	<0.005	2.3
At discharge					
Aspirin	2701 (68.1)	529 (65.3)	2172 (68.8)	0.057	3.5
Beta blocker	2513 (63.3)	483 (59.6)	2030 (64.3)	0.013	3.5
ACEI or ARB	2493 (62.9)	495 (61.0)	1998 (63.4)	0.222	3.6
Statin	2704 (67.7)	537 (65.6)	2167 (68.2)	0.167	2.8

All values are mean (SD) or number (%). * known diabetes vs not known diabetes. DM, Diabetes Mellitus; CVA, Cerebrovascular accidents; PVD, Peripheral Vascular Disease; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; SBP, Systolic blood pressure; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

thrombolysis or coronary intervention (PCI or CABG) or both

Table 2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.47)	**All (Median 912 days)** 1041 (25.32)
Admission Demographic Variable			
Gender (Female vs Male)	0.535 (0.439 , 0.650)	0.515 (0.443 , 0.600)	0.554 (0.490 , 0.627)
Age (year)	1.068 (1.059 , 1.078)	1.077 (1.069 , 1.084)	1.084 (1.077 , 1.090)
SBP (mmHg)	0.979 (0.976 , 0.983)	0.987 (0.984 , 0.990)	0.992 (0.990 , 0.994)
Heart Rate (beat/min)	1.010 (1.006 , 1.013)	1.012 (1.009 , 1.014)	1.012 (1.010 , 1.014)
Total Cholesterol (mmol/L)	0.732 (0.666 , 0.806)	0.765 (0.712 , 0.821)	0.744 (0.703 , 0.788)
Admission plasma glucose (mmol/L)	1.072 (1.052 , 1.084)	1.065 (1.055 , 1.076)	1.059 (1.050 , 1.068)
eGFR (mL/min)	0.956 (0.951 , 0.961)	0.955 (0.951 , 0.959)	0.959 (0.956 , 0.962)
NSTEMI vs STEMI	0.504 (0.405 , 0.627)	0.736 (0.629 , 0.862)	0.939 (0.830 , 1.063)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.909 (0.688 , 1.200)	0.846 (0.681 , 1.052)	0.919 (0.780 , 1.082)
2005	0.591 (0.402 , 0.870)	0.652 (0.491 , 0.865)	0.702 (0.564 , 0.873)
2006	0.830 (0.592 , 1.164)	0.696 (0.529 , 0.917)	0.716 (0.572 , 0.897)
2007	0.759 (0.570 , 1.010)	0.678 (0.541 , 0.849)	0.679 (0.558 , 0.826)
2008	0.485 (0.338 , 0.696)	0.551 (0.424 , 0.716)	0.531 (0.415 , 0.680)
Test for Linear Trend (p-value)	<0.001	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.013 (0.786 , 1.304)	0.909 (0.741 , 1.114)	0.856 (0.725 , 1.012)
Medical History (Yes vs No)			
Smoking	1.016 (0.819 , 1.259)	1.049 (0.891 , 1.235)	1.160 (1.019 , 1.320)
Prior Diabetes	1.400 (1.121 , 1.750)	1.576 (1.331 , 1.865)	1.655 (1.445 , 1.896)
Prior Coronary Heart Disease §	0.862 (0.628 , 1.182)	0.998 (0.791 , 1.258)	1.113 (0.931 , 1.330)
Prior Hypertension	1.286 (1.056 , 1.567)	1.437 (1.232 , 1.676)	1.472 (1.300 , 1.666)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.746 (0.613 , 0.909)	0.869 (0.744 , 1.015)	0.913 (0.804 , 1.036)
Beta Blocker	1.385 (1.116 , 1.719)	1.577 (1.338 , 1.859)	1.489 (1.301 , 1.703)
Statin	0.994 (0.795 , 1.245)	1.129 (0.953 , 1.338)	1.194 (1.041 , 1.370)
ACEI or ARB	1.242 (1.002 , 1.540)	1.467 (1.247 , 1.726)	1.621 (1.423 , 1.847)
Admission treatment (Yes vs No)			
Initial Reperfusion	0.616 (0.507 , 0.749)	0.540 (0.464 , 0.629)	0.466 (0.411 , 0.527)
Loop Diuretic	3.457 (2.807 , 4.256)	4.348 (3.681 , 5.136)	4.052 (3.556 , 4.618)
Discharge Medication (Yes vs No)			
Aspirin	0.043 (0.029 , 0.062)	0.227 (0.192 , 0.269)	0.439 (0.386 , 0.499)
Beta Blocker	0.038 (0.025 , 0.058)	0.237 (0.199 , 0.282)	0.406 (0.357 , 0.461)
Statin	0.043 (0.029 , 0.062)	0.196 (0.165 , 0.233)	0.344 (0.303 , 0.390)
ACEI or ARB	0.047 (0.031 , 0.700)	0.236 (0.198 , 0.281)	0.469 (0.412 , 0.533)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 3: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals).

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.5)	**All (Median 912 days)** 1041 (25.3)
Admission Demographics			
Gender (Female vs Male)	1.268 (0.885, 1.819)	1.094 (0.865, 1.383)	1.114 (0.931, 1.332)
Age (year)	1.059 (1.040, 1.078)	1.062 (1.048, 1.075)	1.073 (1.062, 1.083)
SBP (mmHg)	0.987 (0.981, 0.992)	0.991 (0.987, 0.995)	0.993 (0.990, 0.996)
Heart Rate (beat/min)	1.007 (1.001, 1.013)	1.006 (1.002, 1.010)	1.007 (1.005, 1.010)
Admission plasma glucose (mmol/L)	1.072 (1.042, 1.104)	1.059 (1.037, 1.081)	1.053 (1.036, 1.071)
eGFR (mL/min)	0.987 (0.978, 0.996)	0.983 (0.977, 0.990)	0.988 (0.983, 0.993)
NSTEMI vs STEMI	0.411 (0.282, 0.597)	0.558 (0.443, 0.704)	0.700 (0.587, 0.834)
Ethnicity (South Asian vs White European)	1.355 (0.893, 2.057)	1.155 (0.851, 1.568)	0.996 (0.779, 1.273)
Medical History (Yes vs No)			
Smoking	1.125 (0.788, 1.607)	0.953 (0.749, 1.213)	0.942 (0.786, 1.130)
Prior Diabetes	0.934 (0.631, 1.382)	1.001 (0.770, 1.300)	1.134 (0.927, 1.386)
Prior Coronary Heart Disease§	0.717 (0.402, 1.278)	0.898 (0.632, 1.277)	1.111 (0.864, 1.428)
Prior Hypertension	1.291 (0.903, 1.846)	1.155 (0.913, 1.461)	1.133 (0.949, 1.353)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.944 (0.667, 1.335)	0.989 (0.781, 1.252)	1.010 (0.842, 1.213)
Beta Blocker	1.288 (0.898, 1.849)	1.363 (1.067, 1.742)	1.173 (0.970, 1.418)
Statin	0.863 (0.579, 1.286)	0.877 (0.668, 1.150)	0.918 (0.743, 1.135)
ACEI or ARB	0.719 (0.497, 1.042)	0.932 (0.728, 1.194)	1.017 (0.840, 1.232)
Admission treatment (Yes vs No)			
Loop Diuretic	1.416 (0.993, 2.019)	1.703 (1.322, 2.195)	1.532 (1.268, 1.851)
Discharge Medication (Yes vs No)			
Aspirin	0.297 (0.157, 0.562)	0.656 (0.479, 0.897)	0.861 (0.676, 1.097)
Beta Blocker	0.257 (0.133, 0.494)	0.564 (0.423, 0.753)	0.671 (0.544, 0.828)
Statin	0.628 (0.295, 1.339)	0.683 (0.484, 0.963)	0.629 (0.490, 0.808)
ACEI or ARB	0.470 (0.229, 0.968)	0.610 (0.443, 0.839)	0.850 (0.668, 1.081)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 4: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the subgroups of patients with STEMI and NSTEMI. Data are hazard ratio (95% confidence intervals)

N=4111		Mortality, N (%)					
STEMI	NSTEMI	30 days		1 Year		All	
2397	1714	STEMI	NSTEMI	STEMI	NSTEMI	STEMI	NSTEMI
Admission Demographics							
Age (year)		1.055 (1.033 - 1.077)	1.073 (1.031 - 1.116)	1.061 (1.044 - 1.078)	1.056 (1.035 - 1.079)	1.077 (1.062 - 1.091)	1.061 (1.046 - 1.077)
SBP (mmHg)		0.988 (0.982 - 0.994)	0.983 (0.970 - 0.995)	0.992 (0.987 - 0.997)	0.988 (0.982 - 0.995)	0.993 (0.989 - 0.997)	0.994 (0.990 - 0.998)
Heart Rate (beat/min)		1.008 (1.001 - 1.015)	1.008 (0.997 - 1.02)	1.008 (1.002 - 1.013)	1.007 (1.001 - 1.013)	1.008 (1.004 - 1.012)	1.007 (1.002 - 1.011)
eGFR (mL/min)		0.986 (0.975 - 0.997)	0.987 (0.969 - 1.005)	0.982 (0.974 - 0.991)	0.978 (0.968 - 0.989)	0.986 (0.979 – 0.993)	0.987 (0.979 - 0.995)
Admission plasma glucose		1.070 (1.034 – 1.107)	1.074 (1.005 - 1.148)	1.071 (1.042 - 1.10)	1.021 (0.979 - 1.066)	1.076 (1.051 - 1.10)	1.014 (0.983 – 1.047)
Prior Diabetes		1.035 (0.652 - 1.641)	0.629 (0.264 - 1.502)	1.083 (0.772 - 1.518)	0.878 (0.566 – 1.36)	1.189 (0.907 -1.559)	1.055 (0.773 – 1.44)
Admission treatment (Yes vs No)							
Loop Diuretic		1.330 (0.890 - 1.989)	1.66 (0.759 - 3.629)	1.706 (1.248 (2.333)	1.988 (1.283 - 3.081)	1.365 (1.068 - 1.745)	2.03 (1.496 - 2.756)
Discharge Medication (Yes vs No)							
Aspirin		0.301 (0.135 - 0.672)	0.308 (0.088 - 1.076)	0.499 (0.322 - 0.773)	0.869 (0.523 - 1.433)	0.697 (0.501 - 0.970)	1.052 (0.711 - 1.557)
Beta Blocker		0.208 (0.095 - 0.455)	0.337 (0.094 - 1.207)	0.469 (0.320 - 0.687)	0.77(0.485 - 1.222)	0.520 (0.393 - 0.698)	0.939 (0.674 - 1.308)
Statin		1.046 (0.375 - 2.918)	0.255 (0.066 - 0.992)	0.551 (0.334 - 0.908)	0.745 (0.449 - 1.237)	0.615 (0.429 - 0.880)	0.65 (0.444 - 0.951)
ACEI or ARB		0.392 (0.153 - 1.006)	0.451 (0.121 - 1.673)	0.903 (0.545 - 1.496)	0.541 (0.348 - 0.841)	1.041 (0.712 - 1.523)	0.857 (0.616 - 1.194)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Contributors: NG, IS, KK conceived the idea of the study and were responsible for the design of the study. NG, RM were responsible for undertaking for the data analysis and produced the tables and graphs. IS, KK, MJD provided input into the data analysis. The initial draft of the manuscript was prepared by NG and IS and then circulated repeatedly amongst all authors for critical revision. IS was responsible for the acquisition of the data and IS, NG, RM, KK and MJD contributed to the interpretation of the results.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The work in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. NG has received support by the National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care - Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC for LNR) project for a PhD.

Competing interests: None

Ethical approval: The study was approved by the local research ethics committee.

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FIGURE LEGENDS

Figure 1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes.

The bars represent the number of people at various glucose levels. Solid lines indicate odds ratios while **dotted lines** indicate 95% confidence intervals. **Solid bars and black lines** indicate patients with diabetes. **Clear bars** and **red lines** indicate patients without Diabetes.

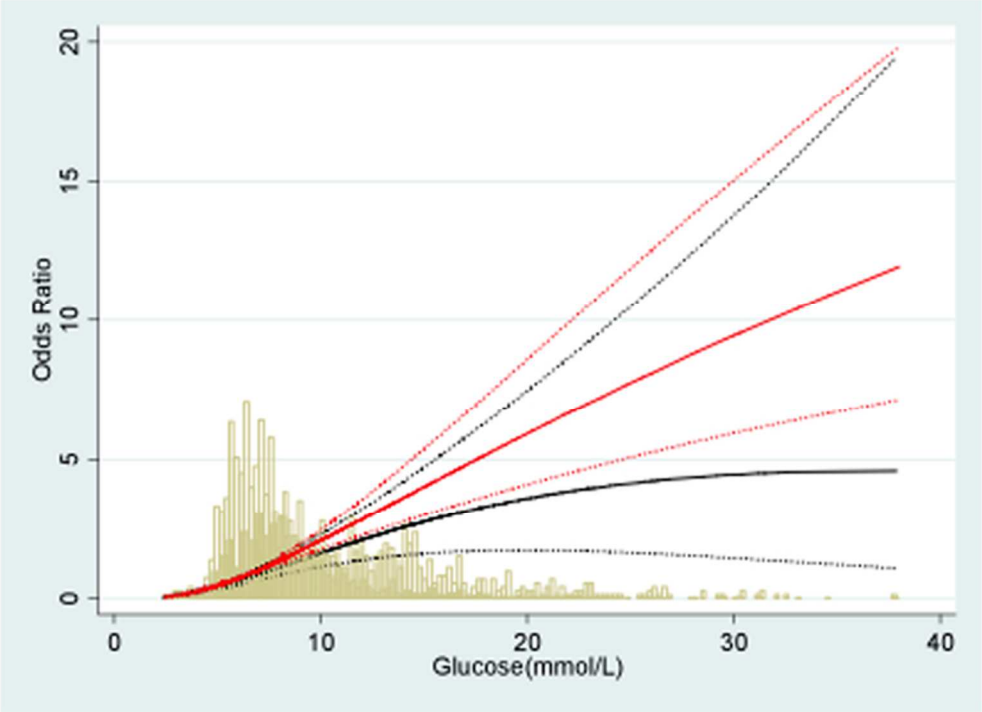

Figure 1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes.

The **bars** represent the number of people at various glucose levels. **Solid lines** indicate odds ratios while **dotted** lines indicate 95% confidence intervals. **Solid bars** and **black lines** indicate patients with diabetes. **Clear bars** and **red lines** indicate patients without Diabetes.
70x51mm (300 x 300 DPI)

Supplementary Table 2A: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the survivors at discharge cohort. Data are hazard ratio (95% confidence intervals)

	Mortality N(%)		
N= 3790	**30 days** 106(2.80)	**1 Year** 363(9.60)	**All** 726(19.10)
Admission Demographics Variables			
Gender (Female vs Male)	0.585 (0.395 , 0.865)	0.520 (0.422 , 0.640)	0.577 (0.497 , 0.670)
Age (year)	1.059 (1.041 , 1.077)	1.080 (1.069 , 1.090)	1.088 (1.080 , 1.096)
SBP (mmHg)	0.985 (0.978 , 0.992)	0.995 (0.991 , 0.999)	0.998 (0.996 , 1.001)
Heart Rate (beats/min)	1.002 (0.994 , 1.010)	1.012 (1.008 , 1.015)	1.012 (1.010 , 1.015)
Total Cholesterol (mmol/L)	0.772 (0.646 , 0.922)	0.801 (0.730 , 0.879)	0.752 (0.703 , 0.803)
Admission plasma glucose (mmol/L)	1.069 (1.044 , 1.095)	1.060 (1.045 , 1.076)	1.054 (1.042 , 1.065)
eGFR (mL/min)	0.957 (0.947 , 0.967)	0.954 (0.949 , 0.959)	0.959 (0.955 , 0.963)
nSTEMI vs STEMI	0.558 (0.367 , 0.850)	1.015 (0.824 , 1.250)	1.213 (1.048 , 1.403)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.907 (0.551 , 1.494)	0.789 (0.590 , 1.054)	0.915 (0.757 , 1.105)
2005	0.490 (0.234 , 1.024)	0.670 (0.465 , 0.964)	0.727 (0.567 , 0.934)
2006	0.647 (0.334 , 1.252)	0.562 (0.382 , 0.827)	0.645 (0.489 , 0.850)
2007	0.402 (0.215 , 0.751)	0.517 (0.376 , 0.712)	0.560 (0.435 , 0.721)
2008	0.261 (0.115 , 0.589)	0.477 (0.333 , 0.682)	0.460 (0.331 , 0.639)
Test for Linear Trend (p-value)	0.002	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.172 (0.726, 1.891)	0.881 (0.665, 1.167)	0.824 (0.673, 1.008)
Medical History (Yes vs No)			
Smoking	1.417 (0.945 , 2.124)	1.179 (0.950 , 1.464)	1.281 (1.101 , 1.491)
Prior Diabetes	1.363 (0.874 , 2.124)	1.736 (1.384 , 2.177)	1.782 (1.516 , 2.093)
Prior Coronary Heart Disease §	1.427 (0.848 , 2.402)	1.289 (0.965 , 1.722)	1.309 (1.071 , 1.601)
Prior Hypertension	1.987 (1.315 , 3.002)	1.752 (1.413 , 2.172)	1.646 (1.417 , 1.912)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.945 (0.633 , 1.412)	1.078 (0.865 , 1.344)	1.038 (0.889 , 1.211)
Beta Blocker	1.966 (1.306 , 2.960)	1.850 (1.484 , 2.305)	1.582 (1.348 , 1.857)
Statin	1.169 (0.759 , 1.799)	1.306 (1.042 , 1.638)	1.323 (1.125 , 1.556)
ACEI or ARB	1.174 (0.762 , 1.807)	1.708 (1.373 , 2.124)	1.833 (1.570 , 2.140)
Admission treatment (Yes vs No)			
Initial Reperfusion	1.154 (0.774 , 1.720)	0.570 (0.464 , 0.701)	0.449 (0.387 , 0.521)
Loop Diuretic	3.199 (2.129 , 4.806)	4.940 (3.922 , 6.221)	4.174 (3.573 , 4.877)
Discharge Medication (Yes vs No)			
Aspirin	0.165 (0.107 , 0.253)	0.582 (0.469 , 0.723)	0.908 (0.771 , 1.069)
Beta Blocker	0.138 (0.086 , 0.221)	0.557 (0.451 , 0.688)	0.729 (0.626 , 0.848)
Statin	0.166 (0.108 , 0.255)	0.458 (0.371 , 0.566)	0.624 (0.536 , 0.726)
ACEI or ARB	0.176 (0.112 , 0.276)	0.545 (0.441 , 0.673)	0.886 (0.759 , 1.036)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Supplementary Table 3A: Multivariate association of clinical variables with 30-day, 1-year, and total mortality subject to survival to discharge. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N= 3792	**30 days** 106(2.80)	**1 Year** 363(9.60)	**All** 726(19.10)
Admission Demographics			
Gender (Female vs Male)	0.848 (0.467, 1.538)	1.026 (0.774, 1.360)	1.113 (0.912, 1.358)
Age (year)	1.077 (1.040,1.115)	1.058 (1.042, 1.075)	1.071 (1.059, 1.083)
SBP (mmHg)	0.981(0.971, 0.990)	0.994 (0.989, 0.998)	0.996 (0.993, 0.999)
Heart Rate (beat/min)	0.998 (0.987,1.008)	1.004 (1.000, 1.009)	1.007 (1.004, 1.010)
Admission plasma glucose (mmol/L)	1.095 (1.047,1.146)	1.046 (1.017,1.077)	1.042 (1.021, 1.064)
eGFR (mL/min)	0.994 (0.977, 1.011)	0.978 (0.970, 0.987)	0.985 (0.980, 0.991)
nSTEMI vs STEMI	0.253 (0.125, 0.512)	0.643 (0.486, 0.852)	0.826 (0.679, 1.005)
Year of Admission	0.826 (0.701, 0.974)	0.956 (0.887, 1.030)	0.926 (0.873, 0.981)
Ethnicity			
(South Asian vs White European)	2.021 (0.932, 4.384)	1.118 (0.760, 1.643)	0.950 (0.718, 1.258)
Medical History (Yes vs No)			
Smoking	1.722 (0.934, 3.177)	0.949 (0.710, 1.270)	0.920 (0.752, 1.124)
Prior Diabetes	0.638 (0.313, 1.303)	0.907 (0.656, 1.255)	1.080 (0.860, 1.356)
Prior Coronary Heart Disease §	1.093 (0.467, 2.560)	1.117 (0.751, 1.661)	1.328 (1.015, 1.738)
Prior Hypertension	1.836 (0.985, 3.421)	1.152 (0.868, 1.529)	1.112 (0.914, 1.354)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.951 (0.509, 1.778)	1.088 (0.810, 1.462)	1.086 (0.883, 1.336)
Beta Blocker	1.707 (0.929, 3.136)	1.403 (1.045, 1.883)	1.127 (0.913, 1.392)
Statin	0.961 (0.463, 1.997)	0.974 (0.699, 1.358)	0.992 (0.782, 1.258)
ACEI or ARB	0.685 (0.351, 1.339)	1.059 (0.784, 1.429)	1.093 (0.883, 1.353)
Admission treatment (Yes vs No)			
Loop Diuretic	1.029 (0.568,1.867)	1.598 (1.172, 2.179)	1.484 (1.203, 1.830)
Discharge Medication (Yes vs No)			
Aspirin	0.543 (0.235,1.256)	1.027 (0.702, 1.503)	1.228 (0.925, 1.631)
Beta Blocker	0.357 (0.167, 0.763)	0.730 (0.529, 1.007)	0.795 (0.633, 0.997)
Statin	1.191 (0.448, 3.170)	0.844 (0.574, 1.240)	0.712 (0.542, 0.935)
ACEI or ARB	0.425 (0.176, 1.027)	0.673 (0.475, 0.955)	0.955 (0.734, 1.243)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Admission blood glucose concentration; A more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis

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Keywords: Acute myocardial infarction, diabetes, glucose

Word count: 3029~~2938~~

ABSTRACT:

Objective: To explore the relative impact of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with ST elevation myocardial infarction (STEMI) and non-STEMI.

Design: Retrospective cohort study based on the Myocardial Ischaemia National Audit Project dataset.

Setting: Tertiary care centre.

Participants: 4111 (20.3% known diabetes) consecutive patients admitted with acute myocardial infarction (58.3% STEMI) between October 2002 and September 2008.

Primary and secondary outcome measures: All-cause mortality at 30-days and 1-year. The relative association of admission blood glucose and of antecedent diabetes with mortality was assessed using multivariate Cox regression analysis. Furthermore we compared these relationships in patients with STEMI to those with NSTEMI.

Results: By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) of patients died. After adjusting for covariates, diabetes did not show independent association with mortality at any time point, in the entire cohort (HR 30 days 0.93 (CI 0.63 – 1.38); 1-year 1.00 (0.77 – 1.30)) or in subgroups of STEMI (HR 30days 1.03 (0.65 – 1.64); 1 year 1.08 (0.77 – 1.51)) and non-STEMI (HR 30-days 0.62 (0.26-1.50); 1-year 0.87(0.56 – 1.36)). In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR ~~per mmol/L increase;~~ 30 days 1.07 (1.04 – 1.10); 1-year 1.05 (1.03 – 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03 – 1.10); 1-year 1.07 (1.04 – 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 - 1.14); 1-year 1.02 (0.97 - 1.06)).

Conclusion: Admission glucose is strongly associated with mortality in all presentations of acute myocardial infarction (AMI), irrespective of established diabetes diagnosis. The increased risk is maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.

INTRODUCTION

For patients with acute myocardial infarction (AMI) the risk of adverse outcome is increased by the concomitant diagnosis of diabetes mellitus (diabetes).(1, 2) In addition, elevated blood glucose concentration, a common finding at admission in patients with AMI, is also associated with increased risk of adverse outcome, irrespective of prior diabetes.(1-8). In some studies (4, 9) the association between admission blood glucose concentration and adverse outcome was more powerful in patients without, compared to those with, prior diabetes. Indeed we previously reported more powerful association with 30-day and 1-year mortality after STEMI for admission blood glucose concentration, compared to the diagnosis of diabetes.(9)

While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which hyperglycaemia may impart toxicity during myocardial ischaemia.(10, 11) Indeed, observational data suggest that elevated blood glucose may contribute directly to adverse outcome after AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 hours after AMI compared to those in whom blood glucose normalises.(12, 13) In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with improved prognosis.(14, 15) Further, in randomised, controlled trials (RCTs) of intensive, insulin-based blood glucose management during admission with AMI, survival benefit was evident only when intervention effectively lowered blood glucose concentration.(16, 17)

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of acute coronary syndromes in contemporary practice are non-ST elevation AMI (NSTEMI). The aim of the current analysis was to compare the relative strength of association with 30-day, and 1-year mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with STEMI and with NSTEMI, and in those

with and without a history of diabetes, in a multi-ethnic population. We also assessed the relevance of blood glucose concentration, recorded soon after admission to hospital with AMI, to mortality in patients surviving to discharge.

METHODS

Data were from consecutive admissions between 1st October 2002 – 30th September 2008, to the two coronary care units (CCU) of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). For all patients, as part of the hospital's mandatory commitment to the Myocardial Ischaemia National Audit Projectgramme (MINAP),(18) we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), electrocardiographic (ECG) site of infarct, medical history, coronary heart disease risk-factors, and prescribed medication. Data are record-linked to mortality information (19) and include self reported coding for ethnicity, for which local coverage is thorough. Approximately 10% of the local population are of South Asian ethnic origin, over twice the UK national average.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient, or on the basis of medication prescribed prior to admission. The blood glucose measurement used for the analysis was the first recorded at the time of the index admission, assayed in the hospital laboratory as part of routine investigations. All diagnoses of AMI were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACCF/AHA/WHF definition.(20) Patients were categorised as STEMI or NSTEMI, according to the final discharge diagnosis recorded in the MINAP database. For patients with multiple AMI admissions during the study period, we considered only the first event.

Survival was measured from the date of first admission to the date of death or of censoring at 30th September 2009. Mortality data are supplied to the hospital on a monthly basis via the UK Office for

National Statistics. The pre-defined primary outcome measure was ~~the relative strength of association with~~ 30-day, and 1-year, all-cause mortality~~. for diabetes diagnosis and for admission blood glucose concentration~~.

The study was approved by the local research ethics committee. The data used in this analysis were gathered during routine care and as part of the MINAP (18) mandatory requirement for all acute hospitals in England and Wales to collect data pertaining to admission with AMI.

Statistical analysis

Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Mortality at 30 days and at 1 year, in the entire cohort, and in those patients surviving to discharge, was calculated.

We calculated mortality proportions for patients admitted from 1st October 2002 to 30th September 2008 with follow-up censored at 30th September 2009. Survival probabilities were calculated using Kaplan-Meier [KM] analyses and patient groups compared using survival analysis log rank test. Relative risk of mortality, as a function of ~~explanatory~~clinical variables, was examined using Cox proportional hazards techniques. We initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity (white European, South Asian), smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary revascularisation during index admission, pre-admission and discharge drug therapy (anti-platelet, beta-blocker, statin, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker), and index loop diuretic use. An interaction term representing calendar year of admission was included to adjust for potential temporal changes in the management of acute coronary artery disease.

Demographic and clinical covariates with univariate association (p<0.10) with mortality at 30 days, or 1 year were entered into multivariate models (Cox proportional hazards). Statistical significance for all comparisons was set at p<0.05 (2 sided). Data are presented as hazard ratio (HR) and 95% confidence intervals (CI). We used fractional polynominals to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS version 18.

RESULTS

~~Between 1st October 2002 – 30th September 2009, we recorded 4640 admissions with discharge diagnosis of AMI.~~ The study population was the 4111 ~~(STEMI 2397, 58.3%)~~ patients admitted between 1st October 2002 – 30th September 2008 with discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow up was 912 days (range 0 to 2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow up was 1031 (range 1 to 2556) days.

Demographic details of the study population are presented in Table 1. Prior diabetes was recorded in 835 (20.3%) patients: compared to those without, patients with antecedent diabetes were on average older (68.6 vs 65.8 years, p<0.005), more likely to be female (33.9% vs 28.9%, p = 0.022) and to have prior cardiovascular co-morbidities. Presentation with NSTEMI was more prevalent in cases with (50.1%), compared to those without (39.6%), prior diabetes (p <0.005). Mean plasma glucose was higher in patients with diabetes (12.0 ± 5.5 mmol/L) compared to those without (7.9 ± 3.3 mmol/L) (p <0.005). Mean peak CK was lower in patients with diabetes.

During the index admission administration of loop diuretic was more frequent (52.7% vs 33.4%, p<0.005) and, for patients with STEMI, coronary reperfusion therapy less frequent (50.2% vs 60.9%, <0.005), in patients with diabetes. Other than for slightly less use of beta-blockers and aspirin in

patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

Mortality – Univariate analysis

Deaths during hospitalisation, over 30-days, 1-year and the entire period of follow-up numbered 319 (7.8%), 409 (9.9%), 677 (16.5%) and 1041 (25.3%) respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (Table 2). Loop diuretic was associated with a 3-4 fold increase in mortality during follow-up. Survival improved over the period of observation.

Prior diabetes showed strong univariate association with mortality risk over all time periods: HR 30 days 1.40 (1.12 - 1.75); 1 year 1.58 (1.33 - 1.86); all follow-up 1.66 (1.44 , 1.90)) (Table 2). The strength of association between glucose and mortality was consistent at 30-days and at 1-year, each mmol/L increase in admission glucose concentration being associated with a 6-7% increase in hazard of mortality over all time periods.

Post-discharge mortality

In those surviving to discharge (N=3792), 106 (2.8%), 363 (9.6%) and 726 (19.1%) died by 30-days, 1-year and over all follow-up (Table 2A, Supplementary data). Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, (0.87 - 2.12)). For admission glucose, the strength of association with post-discharge mortality was very similar to that in the entire cohort, with 5-7% increase risk per mmol/L increase in glucose. (Table 2A, Supplementary Data).

Mortality – Multivariate analysis

Table 3 shows the results of multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of loop diuretic, and STEMI (compared to NSTEMI) each retained independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain independent association with mortality at any time. In contrast, adjustment for covariates had little impact upon the risk of mortality associated with admission glucose concentration.

Post-discharge mortality

For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort (Table 3A, Supplementary data). While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 – 1.300); 1 year 0.91 (0.66 – 1.26); all follow-up 1.08 (0.86 – 1.36)), blood glucose retained powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/L 1.10, 95% CI 1.05 – 1.15), 1 year (1.05, 1.02 – 1.08), and over all follow-up (1.04, 1.02 – 1.06)).

Admission glucose concentration – influence on mortality in patients with or without diabetes

We repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (Figure 1), there was no conventional statistically significant difference in the association between mortality and admission blood glucose for patients with and without diabetes (30 days HR 1.00, (CI 0.97 – 1.03, p=0.95; 1 year 0.99, (0.97 – 1.02), p=0.66; entire follow-up 0.99, (0.97 – 1.01, p=0.42)).

Diabetes and glucose after AMI – influence on mortality in STEMI and NSTEMI

After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period, either for STEMI or NSTEMI (Table 4). The strength of association

between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only after NSTEMI.

DISCUSSION

It is well known that, both prior diabetes diagnosis, and admission blood glucose concentration, are associated~~both have well-recognised association~~ with adverse outcome after AMI. In this ~~This is the first~~ report we~~to~~ compared the relative association of these two measures of dysglycaemia with survival after ~~AMI in a population of~~ STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55-65% thereafter) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In our previous report of over 4000 patients with STEMI, admitted in 1993-2004,(9) the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and removed completely when admission blood glucose concentration was included in the analysis. The current report confirms these observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI, in whom the strength of association between admission blood glucose concentration and 30-day mortality risk was similar, and concentration dependent. Importantly, the excess risk, around 7% for each 1mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Further, this phenomenon was attenuated with time only for patients with NSTEMI, and was evident even in those patients who survived to discharge from hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association

between admission glucose and mortality to be confined to in-hospital deaths following either STEMI or NSTEMI.(8) They are however in keeping with the vast majority of reports in this area.(1-7, 9, 11)

In contrast to most previous reports,(1-9, 11) we observed no independent association between diabetes and mortality risk after AMI. However, to our knowledge and unlike the present report, none of these studies adjusted for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis (1, 2, 4, 8) or blood glucose concentration.(3-8, 11-13, 21) The current analysis and our previous study (9) are the only reports to compare the relative association with outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose, and the loss of association between mortality and diabetes when blood glucose is considered.

These observations are of potential clinical significance. While admission blood glucose concentration after AMI is on average higher in patients with, compared to those without, known diabetes,(4, 8, 9) there is considerable overlap, as seen in the current report (Figure 1). While many patients presenting with AMI will have previously undiagnosed diabetes,(22) blood glucose at the time of admission with AMI is not a reliable indicator of the subsequent diagnosis of diabetes.(23, 24) In routine practice, the management of hyperglycaemia after AMI is influenced by the presence of prior diabetes diagnosis.(5) In both European(14) and North American(6) settings, the majority (>65%) of patients presenting with hyperglycaemia in the context of AMI, and not previously known to have diabetes, do not receive active management of blood glucose. In the presence of a true, direct toxic effect upon prognosis of elevated blood glucose, failure to correct hyperglycaemia may represent suboptimal clinical care, and patients without known diabetes may be particularly disadvantaged. In particular, our demonstration that the relationship between glucose concentration and subsequent outcome is evident in NSTEMI as well as STEMI is of clear clinical relevance in terms of the overall management of patients presenting with AMI.

The strength of association between diabetes and mortality risk after AMI has been reported to increase with time from the event.(25) ~~We observed no such trend, an observation which may relate to methodological differences among studies, including our inclusion of blood glucose as a covariate~~ While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate. A previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcome.(4) While we could not demonstrate formal statistical evidence of such a phenomenon, our data show convincingly that the relationship between glucose and outcome is at least as powerful in patients without known diabetes. Blood glucose soon after admission represents an easily identified, clinically relevant marker of risk after AMI, which should be assessed routinely irrespective of diabetes status.

An important observation from this study is the persisting association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTEMI and STEMI. While in keeping with the possibility that blood glucose concentration at admission reflects the degree of individual physiological stress, or is a marker of the extent of infarction, our findings are as much in keeping with a direct, adverse influence on prognosis of acute hyperglycaemia. The mechanisms by which elevated glucose may be directly cardiotoxic have been summarised elsewhere (10) and include attenuation of ischaemic preconditioning, QT prolongation, increased thrombophilia, and endothelial dysfunction. Furthermore, clinical studies overwhelmingly support a possible causal link between hyperglycaemia and adverse prognosis after AMI. ~~, and also the benefit of active lowering of glucose in this setting.~~ Hyperglycaemia persisting at 24 hours after admission is associated with adverse outcome,(12, 13, 17). ~~and in controlled trials of the active management of blood glucose effective reduction in blood glucose after AMI was associated with improved prognosis.(16, 17)~~

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent.(16,17) However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis.(16) The guidelines from professional societies in this area differ in their recommendations.(27,28) In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels > 10.0 mmol/L) admitted in an intensive care unit.(28) In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with acute coronary syndrome.(27) The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Our report is subject to the limitations inherent in all observational cohort studies. Blood glucose concentration used in this analysis was that first recorded for the index admission, and is likely to have varied in timing relative to symptom onset. Our database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure, and a number of other potentially relevant variables. Further, we have no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status. Thus we suggest the first recorded blood glucose concentration to be highly relevant to guiding appropriate management in individual patients, irrespective of residual LV function. While we have no information on interventions or changes to therapy after discharge, it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. After adjustment for admission blood glucose, known diabetes is not

associated with adverse outcome. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTEMI as well as STEMI, and persists beyond 1 year from the index event, including in patients surviving to discharge. Future studies are merited of the impact of active management of blood glucose in patients with all presentations of acute coronary artery disease, irrespective of diabetes diagnosis.

ARTICLE SUMMARY

Article focus

- Robust associations is seen for both measures of glycaemia - the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).
- We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with STEMI and NSTEMI.

Key Messages:

- In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.
- The increased risk associated with admission glucose is evident during the index admission, at 30 days, one year and beyond and is apparent in those surviving to discharge.
- Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study

- This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.
- A statistically robust association was seen for admission glucose with both short and loner term mortality after adjusting for many important confounders.
- Our data lacks information on glucose lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

Table 1: Baseline characteristics at admission stratified by diabetes status

	All n=4111	Known DM n= 835 (20.3%)	Not Known DM n=3276 (79.7%)	P Value*	Missing Value (%)
Demography					
Age (years)	66.4 (13.3)	68.6 (11.8)	65.8 (13.6)	<0.005	0.0
Women (%)	1224 (29.8)	276 (33.1)	948 (28.9)	0.022	0.0
Ethnicity (%)					
White European	3381 (82.2%)	545 (16.1)	2836 (86.6)	<0.005	0.0
South Asian	730 (17.8%)	290 (39.7%)	440 (60.3%)		0.0
Medical History (%)					
Hypertension	2048 (50.3)	584 (70.0)	1464 (45.0)	<0.005	1.0
Current/Ex Smoker	1366 (35.7)	282 (36.8)	1084 (35.5)	0.527	7.1
Coronary Heart Disease§	491 (12.1)	149 (17.9)	342 (10.6)	<0.005	0.9
CVA	254 (6.3)	86 (10.3)	168 (5.2)	<0.005	1.2
PVD	154 (3.8)	42 (5.0)	112 (3.5)	0.041	1.2
Heart Failure	190 (4.7)	76 (9.1)	114 (3.5)	<0.005	1.2
Type of Infarction (%)					
STEMI	2397 (58.3)	417 (49.9)	1980 (60.4)	<0.005	0.0
nSTEMI	1714 (41.7)	418 (50.1)	1296 (39.6)		
Physical Examination					
Heart Rate (beats/min)	81.1 (24.3)	85.5 (25.3)	80.0 (24.0)	<0.005	1.5
SBP (mmHg)	136.5 (28.4)	137.7 (30.7)	136.2 (27.8)	0.202	1.0
Biochemical Data					
Peak CK (IU/L, Normal range < 200)	1113.5 (1810.4)	939.9 (1279.3)	1156.4 (1917)	<0.005	7.6
Creatinine (µmol/L)	116.4 (63.8)	128.8 (76.1)	113.1 (59.8)	<0.005	16.8
eGFR (mL/min)	63.0 (22.2)	57.7 (23.6)	64.4 (21.7)	<0.005	16.6
Total cholesterol (mmol/L)	5.1 (1.3)	4.4 (1.2)	5.2 (1.3)	<0.005	16.6
Haemoglobin (g/L)	13.7 (1.9)	13.0 (1.9)	13.9 (1.8)	<0.005	66.6
Plasma glucose (mmol/L)	8.8 (4.2)	12.0 (5.5)	7.9 (3.3)	<0.005	14.9
Therapies (%)					
Prior to index admission					
Aspirin	2671 (65.0)	622 (74.5)	2049 (62.5)	<0.005	0.0
Beta blocker	990 (25.6)	265 (33.2)	725 (23.6)	<0.005	6.0
ACEI or ARB	1097 (28.3)	407 (51.0)	690 (22.5)	<0.005	5.8
Statins	1083 (28.0)	389 (48.7)	694 (22.6)	<0.005	5.8
In-hospital					
Reperfusion therapy #	2414 (58.7)	419 (50.2)	1995 (60.9)	<0.005	0.0
Loop diuretics	1502 (37.4)	436 (52.7)	1066 (33.4)	<0.005	2.3
At discharge					
Aspirin	2701 (68.1)	529 (65.3)	2172 (68.8)	0.057	3.5
Beta blocker	2513 (63.3)	483 (59.6)	2030 (64.3)	0.013	3.5
ACEI or ARB	2493 (62.9)	495 (61.0)	1998 (63.4)	0.222	3.6
Statin	2704 (67.7)	537 (65.6)	2167 (68.2)	0.167	2.8

All values are mean (SD) or number (%). * known diabetes vs not known diabetes. DM, Diabetes Mellitus; CVA, Cerebrovascular accidents; PVD, Peripheral Vascular Disease; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; SBP, Systolic blood pressure; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

thrombolysis or coronary intervention (PCI or CABG) or both

Table 2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.47)	**All (Median 912 days)** 1041 (25.32)
Admission Demographic Variable			
Gender (Female vs Male)	0.535 (0.439 , 0.650)	0.515 (0.443 , 0.600)	0.554 (0.490 , 0.627)
Age (year)	1.068 (1.059 , 1.078)	1.077 (1.069 , 1.084)	1.084 (1.077 , 1.090)
SBP (mmHg)	0.979 (0.976 , 0.983)	0.987 (0.984 , 0.990)	0.992 (0.990 , 0.994)
Heart Rate (beat/min)	1.010 (1.006 , 1.013)	1.012 (1.009 , 1.014)	1.012 (1.010 , 1.014)
Total Cholesterol (mmol/L)	0.732 (0.666 , 0.806)	0.765 (0.712 , 0.821)	0.744 (0.703 , 0.788)
Admission plasma glucose (mmol/L)	1.072 (1.052 , 1.084)	1.065 (1.055 , 1.076)	1.059 (1.050 , 1.068)
eGFR (mL/min)	0.956 (0.951 , 0.961)	0.955 (0.951 , 0.959)	0.959 (0.956 , 0.962)
NSTEMI vs STEMI	0.504 (0.405 , 0.627)	0.736 (0.629 , 0.862)	0.939 (0.830 , 1.063)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.909 (0.688 , 1.200)	0.846 (0.681 , 1.052)	0.919 (0.780 , 1.082)
2005	0.591 (0.402 , 0.870)	0.652 (0.491 , 0.865)	0.702 (0.564 , 0.873)
2006	0.830 (0.592 , 1.164)	0.696 (0.529 , 0.917)	0.716 (0.572 , 0.897)
2007	0.759 (0.570 , 1.010)	0.678 (0.541 , 0.849)	0.679 (0.558 , 0.826)
2008	0.485 (0.338 , 0.696)	0.551 (0.424 , 0.716)	0.531 (0.415 , 0.680)
Test for Linear Trend (p-value)	<0.001	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.013 (0.786 , 1.304)	0.909 (0.741 , 1.114)	0.856 (0.725 , 1.012)
Medical History (Yes vs No)			
Smoking	1.016 (0.819 , 1.259)	1.049 (0.891 , 1.235)	1.160 (1.019 , 1.320)
Prior Diabetes	1.400 (1.121 , 1.750)	1.576 (1.331 , 1.865)	1.655 (1.445 , 1.896)
Prior Coronary Heart Disease §	0.862 (0.628 , 1.182)	0.998 (0.791 , 1.258)	1.113 (0.931 , 1.330)
Prior Hypertension	1.286 (1.056 , 1.567)	1.437 (1.232 , 1.676)	1.472 (1.300 , 1.666)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.746 (0.613 , 0.909)	0.869 (0.744 , 1.015)	0.913 (0.804 , 1.036)
Beta Blocker	1.385 (1.116 , 1.719)	1.577 (1.338 , 1.859)	1.489 (1.301 , 1.703)
Statin	0.994 (0.795 , 1.245)	1.129 (0.953 , 1.338)	1.194 (1.041 , 1.370)
ACEI or ARB	1.242 (1.002 , 1.540)	1.467 (1.247 , 1.726)	1.621 (1.423 , 1.847)
Admission treatment (Yes vs No)			
Initial Reperfusion	0.616 (0.507 , 0.749)	0.540 (0.464 , 0.629)	0.466 (0.411 , 0.527)
Loop Diuretic	3.457 (2.807 , 4.256)	4.348 (3.681 , 5.136)	4.052 (3.556 , 4.618)
Discharge Medication (Yes vs No)			
Aspirin	0.043 (0.029 , 0.062)	0.227 (0.192 , 0.269)	0.439 (0.386 , 0.499)
Beta Blocker	0.038 (0.025 , 0.058)	0.237 (0.199 , 0.282)	0.406 (0.357 , 0.461)
Statin	0.043 (0.029 , 0.062)	0.196 (0.165 , 0.233)	0.344 (0.303 , 0.390)
ACEI or ARB	0.047 (0.031 , 0.700)	0.236 (0.198 , 0.281)	0.469 (0.412 , 0.533)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 3: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals).

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.5)	**All (Median 912 days)** 1041 (25.3)
Admission Demographics			
Gender (Female vs Male)	1.268 (0.885, 1.819)	1.094 (0.865, 1.383)	1.114 (0.931, 1.332)
Age (year)	1.059 (1.040, 1.078)	1.062 (1.048, 1.075)	1.073 (1.062, 1.083)
SBP (mmHg)	0.987 (0.981, 0.992)	0.991 (0.987, 0.995)	0.993 (0.990, 0.996)
Heart Rate (beat/min)	1.007 (1.001, 1.013)	1.006 (1.002, 1.010)	1.007 (1.005, 1.010)
Admission plasma glucose (mmol/L)	1.072 (1.042, 1.104)	1.059 (1.037, 1.081)	1.053 (1.036, 1.071)
eGFR (mL/min)	0.987 (0.978, 0.996)	0.983 (0.977, 0.990)	0.988 (0.983, 0.993)
NSTEMI vs STEMI	0.411 (0.282, 0.597)	0.558 (0.443, 0.704)	0.700 (0.587, 0.834)
Ethnicity (South Asian vs White European)	1.355 (0.893, 2.057)	1.155 (0.851, 1.568)	0.996 (0.779, 1.273)
Medical History (Yes vs No)			
Smoking	1.125 (0.788, 1.607)	0.953 (0.749, 1.213)	0.942 (0.786, 1.130)
Prior Diabetes	0.934 (0.631, 1.382)	1.001 (0.770, 1.300)	1.134 (0.927, 1.386)
Prior Coronary Heart Disease§	0.717 (0.402, 1.278)	0.898 (0.632, 1.277)	1.111 (0.864, 1.428)
Prior Hypertension	1.291 (0.903, 1.846)	1.155 (0.913, 1.461)	1.133 (0.949, 1.353)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.944 (0.667, 1.335)	0.989 (0.781, 1.252)	1.010 (0.842, 1.213)
Beta Blocker	1.288 (0.898, 1.849)	1.363 (1.067, 1.742)	1.173 (0.970, 1.418)
Statin	0.863 (0.579, 1.286)	0.877 (0.668, 1.150)	0.918 (0.743, 1.135)
ACEI or ARB	0.719 (0.497, 1.042)	0.932 (0.728, 1.194)	1.017 (0.840, 1.232)
Admission treatment (Yes vs No)			
Loop Diuretic	1.416 (0.993, 2.019)	1.703 (1.322, 2.195)	1.532 (1.268, 1.851)
Discharge Medication (Yes vs No)			
Aspirin	0.297 (0.157, 0.562)	0.656 (0.479, 0.897)	0.861 (0.676, 1.097)
Beta Blocker	0.257 (0.133, 0.494)	0.564 (0.423, 0.753)	0.671 (0.544, 0.828)
Statin	0.628 (0.295, 1.339)	0.683 (0.484, 0.963)	0.629 (0.490, 0.808)
ACEI or ARB	0.470 (0.229, 0.968)	0.610 (0.443, 0.839)	0.850 (0.668, 1.081)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 4: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the subgroups of patients with STEMI and NSTEMI. Data are hazard ratio (95% confidence intervals)

N=4111		Mortality, N (%)					
STEMI	NSTEMI	30 days		1 Year		All	
2397	1714	STEMI	NSTEMI	STEMI	NSTEMI	STEMI	NSTEMI
Admission Demographics							
Age (year)		1.055 (1.033 - 1.077)	1.073 (1.031 - 1.116)	1.061 (1.044 - 1.078)	1.056 (1.035 - 1.079)	1.077 (1.062 - 1.091)	1.061 (1.046 - 1.077)
SBP (mmHg)		0.988 (0.982 - 0.994)	0.983 (0.970 - 0.995)	0.992 (0.987 - 0.997)	0.988 (0.982 - 0.995)	0.993 (0.989 - 0.997)	0.994 (0.990 - 0.998)
Heart Rate (beat/min)		1.008 (1.001 - 1.015)	1.008 (0.997 - 1.02)	1.008 (1.002 - 1.013)	1.007 (1.001 - 1.013)	1.008 (1.004 - 1.012)	1.007 (1.002 - 1.011)
eGFR (mL/min)		0.986 (0.975 - 0.997)	0.987 (0.969 - 1.005)	0.982 (0.974 - 0.991)	0.978 (0.968 - 0.989)	0.986 (0.979 – 0.993)	0.987 (0.979 - 0.995)
Admission plasma glucose		1.070 (1.034 – 1.107)	1.074 (1.005 - 1.148)	1.071 (1.042 - 1.10)	1.021 (0.979 - 1.066)	1.076 (1.051 - 1.10)	1.014 (0.983 – 1.047)
Prior Diabetes		1.035 (0.652 - 1.641)	0.629 (0.264 - 1.502)	1.083 (0.772 - 1.518)	0.878 (0.566 – 1.36)	1.189 (0.907 -1.559)	1.055 (0.773 – 1.44)
Admission treatment (Yes vs No)							
Loop Diuretic		1.330 (0.890 - 1.989)	1.66 (0.759 - 3.629)	1.706 (1.248 (2.333)	1.988 (1.283 - 3.081)	1.365 (1.068 - 1.745)	2.03 (1.496 - 2.756)
Discharge Medication (Yes vs No)							
Aspirin		0.301 (0.135 - 0.672)	0.308 (0.088 - 1.076)	0.499 (0.322 - 0.773)	0.869 (0.523 - 1.433)	0.697 (0.501 - 0.970)	1.052 (0.711 - 1.557)
Beta Blocker		0.208 (0.095 - 0.455)	0.337 (0.094 - 1.207)	0.469 (0.320 - 0.687)	0.77(0.485 - 1.222)	0.520 (0.393 - 0.698)	0.939 (0.674 - 1.308)
Statin		1.046 (0.375 - 2.918)	0.255 (0.066 - 0.992)	0.551 (0.334 - 0.908)	0.745 (0.449 - 1.237)	0.615 (0.429 - 0.880)	0.65 (0.444 - 0.951)
ACEI or ARB		0.392 (0.153 - 1.006)	0.451 (0.121 - 1.673)	0.903 (0.545 - 1.496)	0.541 (0.348 - 0.841)	1.041 (0.712 - 1.523)	0.857 (0.616 - 1.194)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Contributors: NG, IS, KK conceived the idea of the study and were responsible for the design of the study. NG, RM were responsible for undertaking for the data analysis and produced the tables and graphs. IS, KK, MJD provided input into the data analysis. The initial draft of the manuscript was prepared by NG and IS and then circulated repeatedly amongst all authors for critical revision. IS was responsible for the acquisition of the data and IS, NG, RM, KK and MJD contributed to the interpretation of the results.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The work in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. NG has received support by the National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care - Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC for LNR) project for a PhD .

Competing interests: None

Ethical approval: The study was approved by the local research ethics committee.

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FIGURE LEGENDS

Figure 1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes.

The bars represent the number of people at various glucose levels. Solid lines indicate odds ratios while **dotted lines** indicate 95% confidence intervals. **Solid bars and black lines** indicate patients with diabetes. **Clear bars** and **red lines** indicate patients without Diabetes. ~~**Solid lines** indicate odds ratios while **dotted lines** indicate 95% confidence intervals.~~

Is blood glucose concentration a more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis? A retrospective cohort study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001596.R1
Article Type:	Research
Date Submitted by the Author:	27-Jul-2012
Complete List of Authors:	Gholap, Nitin; University Hospitals of Leicester, Diabetes Research; University Of Leicester, Health Sciences Mehta, Rajnikant; University Of Leicester, Health Sciences Ng, Leong; University of Leicester, Cardiovascular Sciences Davies, Melanie; University of Leicester, Cardiovascular sciences Khunti, Kamlesh; University Of Leicester, Health Sciences Squire, Iain; Leicester Royal Infirmary, Cardiovascular Sciences
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diabetes and endocrinology
Keywords:	Myocardial infarction < CARDIOLOGY, Diabetic nephropathy & vascular disease < DIABETES & ENDOCRINOLOGY, Coronary heart disease < CARDIOLOGY

Is admission blood glucose concentration a more powerful predictor of mortality after myocardial infarction than diabetes diagnosis? : A retrospective cohort study.

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Keywords: Acute myocardial infarction, diabetes, glucose

Word count: 3277

ABSTRACT:

Objective: To explore the relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with ST elevation myocardial infarction (STEMI) and non-STEMI.

Design: Retrospective cohort study based on the Myocardial Ischaemia National Audit Project dataset.

Setting: Tertiary care centre.

Participants: 4111 (20.3% known diabetes) consecutive patients admitted with acute myocardial infarction (58.3% STEMI) between October 2002 and September 2008.

Primary and secondary outcome measures: All-cause mortality at 30-days and 1-year. The relative association of admission blood glucose and of antecedent diabetes with mortality was assessed using multivariate Cox regression analysis. Furthermore we compared these relationships in patients with STEMI to those with NSTEMI.

Results: By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) of patients died. After adjusting for covariates, diabetes did not show independent association with mortality at any time point, in the entire cohort (HR 30 days 0.93 (CI 0.63 – 1.38); 1-year 1.00 (0.77 – 1.30)) or in subgroups of STEMI (HR 30days 1.03 (0.65 – 1.64); 1 year 1.08 (0.77 – 1.51)) and non-STEMI (HR 30-days 0.62 (0.26-1.50); 1-year 0.87(0.56 – 1.36)). In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR: 30 days 1.07 (1.04 – 1.10); 1-year 1.05 (1.03 – 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03 – 1.10); 1-year 1.07 (1.04 – 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 - 1.14); 1-year 1.02 (0.97 - 1.06)).

Conclusion: Admission glucose is strongly associated with mortality in all presentations of acute myocardial infarction (AMI), irrespective of established diabetes diagnosis. The increased risk is

maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.

ARTICLE SUMMARY

Article focus

• Robust associations is seen for both measures of glycaemia - the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).

• We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with STEMI and NSTEMI.

Key Messages:

• In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.

• The increased risk associated with admission glucose is evident during the index admission, at 30 days, one year and beyond and is apparent in those surviving to discharge.

• Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study

• This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.

• A statistically robust association was seen for admission glucose with both short and loner term mortality after adjusting for many important confounders.

• Our data lacks information on glucose lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

INTRODUCTION

For patients with acute myocardial infarction (AMI) the risk of adverse outcome is increased by the concomitant diagnosis of diabetes mellitus (diabetes).(1, 2) In addition, elevated blood glucose concentration, a common finding at admission in patients with AMI, is also associated with increased

risk of adverse outcome, irrespective of prior diabetes.(1-8). In some studies (4, 9) the association between admission blood glucose concentration and adverse outcome was more powerful in patients without, compared to those with, prior diabetes. Indeed we previously reported more powerful association with 30-day and 1-year mortality after STEMI for admission blood glucose concentration, compared to the diagnosis of diabetes.(9)

While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which hyperglycaemia may impart toxicity during myocardial ischaemia.(10, 11) Indeed, observational data suggest that elevated blood glucose may contribute directly to adverse outcome after AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 hours after AMI compared to those in whom blood glucose normalises.(12, 13) In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with improved prognosis.(14, 15) Further, in randomised, controlled trials (RCTs) of intensive, insulin-based blood glucose management during admission with AMI, survival benefit was evident only when intervention effectively lowered blood glucose concentration.(16, 17)

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of acute coronary syndromes in contemporary practice are non-ST elevation AMI (NSTEMI). The aim of the current analysis was to compare the relative strength of association with 30-day, and 1-year mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with STEMI and with NSTEMI, and in those with and without a history of diabetes, in a multi-ethnic population. We also assessed the relevance of blood glucose concentration, recorded soon after admission to hospital with AMI, to mortality in patients surviving to discharge.

METHODS

Data were from consecutive admissions between 1st October 2002 – 30th September 2008, to the two coronary care units (CCU) of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). For all patients, as part of the hospital's mandatory commitment to the Myocardial Ischaemia National Audit Project (MINAP),(18) we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), electrocardiographic (ECG) site of infarct, medical history, coronary heart disease risk-factors, and prescribed medication. Data are record-linked to mortality information (19) and include self reported coding for ethnicity, for which local coverage is thorough. Approximately 10% of the local population are of South Asian ethnic origin, over twice the UK national average.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient, or on the basis of medication prescribed prior to admission. All patients with AMI routinely underwent blood glucose measurement, in most cases within first 12 hours after admission with their blood samples assayed in the hospital laboratory. We used such first recorded admission glucose levels for this analysis. All diagnoses of AMI were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACCF/AHA/WHF definition.(20) Patients were categorised as STEMI or NSTEMI, according to the final discharge diagnosis recorded in the MINAP database. For patients with multiple AMI admissions during the study period, we considered only the first event. The number of cases admitted with AMI during the study period determined the sample size.

Survival was measured from the date of first admission to the date of death or of censoring at 30th September 2009. Mortality data are supplied to the hospital on a monthly basis via the UK Office for National Statistics. Follow-up data on mortality was available for all the patients. The pre-defined primary outcome measure was 30-day, and 1-year, all-cause mortality..

The study was approved by the local research ethics committee (LNR Research Ethics Committee 1, Ref 09/H0406/71 for database analysis study). The data used in this analysis were gathered during routine care and as part of the MINAP (18) mandatory requirement for all acute hospitals in England and Wales to collect data pertaining to admission with AMI.

Statistical analysis

Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Mortality at 30 days and at 1 year, in the entire cohort, and in those patients surviving to discharge, was calculated.

We calculated mortality proportions for patients admitted from 1st October 2002 to 30th September 2008 with follow-up censored at 30th September 2009. Survival probabilities were calculated using Kaplan-Meier [KM] analyses and patient groups compared using survival analysis log rank test. Relative risk of mortality, as a function of clinical variables, was examined using Cox proportional hazards techniques. We initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity (white European, South Asian), smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary revascularisation during index admission, pre-admission and discharge drug therapy (anti-platelet, beta-blocker, statin, angiotensin converting enzyme inhibitor/ angiotensin receptor blocker), and index loop diuretic use. An interaction term representing calendar year of admission was included to adjust for potential temporal changes in the management of acute coronary artery disease.

Demographic and clinical covariates with univariate association ($p<0.10$) with mortality at 30 days, or 1 year were entered into multivariate models (Cox proportional hazards). All quantitative variables

were entered as continues variables into the model. Patients with missing data (Table 1) were not excluded but there values were set as missing. Statistical significance for all comparisons was set at p<0.05 (2 sided). Data are presented as hazard ratio (HR) and 95% confidence intervals (CI). We used fractional polynominals to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS version 18.

RESULTS

The study population was the 4111 patients admitted between 1st October 2002 – 30th September 2008 with discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow up was 912 days (range 0 to 2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow up was 1031 (range 1 to 2556) days.

Demographic details of the study population are presented in Table 1. Prior diabetes was recorded in 835 (20.3%) patients: compared to those without, patients with antecedent diabetes were on average older (68.6 vs 65.8 years, p<0.005), more likely to be female (33.9% vs 28.9%, p = 0.022) and to have prior cardiovascular co-morbidities. Presentation with NSTEMI was more prevalent in cases with (50.1%), compared to those without (39.6%), prior diabetes (p <0.005). Mean plasma glucose was higher in patients with diabetes (12.0 ± 5.5 mmol/L) compared to those without (7.9 ± 3.3 mmol/L) (p <0.005). Mean peak CK was lower in patients with diabetes.

During the index admission administration of loop diuretic was more frequent (52.7% vs 33.4%, p<0.005) and, for patients with STEMI, coronary reperfusion therapy less frequent (50.2% vs 60.9%, <0.005), in patients with diabetes. Other than for slightly less use of beta-blockers and aspirin in

patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

Mortality – Univariate analysis

Deaths during hospitalisation, over 30-days, 1-year and the entire period of follow-up numbered 319 (7.8%), 409 (9.9%), 677 (16.5%) and 1041 (25.3%) respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (Table 2). Loop diuretic was associated with a 3-4 fold increase in mortality during follow-up. Survival improved over the period of observation.

Prior diabetes showed strong univariate association with mortality risk over all time periods: HR 30 days 1.40 (1.12 - 1.75); 1 year 1.58 (1.33 - 1.86); all follow-up 1.66 (1.44, 1.90)) (Table 2). The strength of association between glucose and mortality was consistent at 30-days and at 1-year, each mmol/L increase in admission glucose concentration being associated with a 6-7% increase in hazard of mortality over all time periods.

Post-discharge mortality

In those surviving to discharge (N=3792), 106 (2.8%), 363 (9.6%) and 726 (19.1%) died by 30-days, 1-year and over all follow-up (Table 2A, Supplementary data). Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, (0.87 - 2.12)). For admission glucose, the strength of association with post-discharge mortality was very similar to that in the entire cohort, with 5-7% increase risk per mmol/L increase in glucose. (Table 2A, Supplementary Data).

Mortality – Multivariate analysis

Table 3 shows the results of multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of loop diuretic, and STEMI (compared to NSTEMI) each retained independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain independent association with mortality at any time. In contrast, adjustment for covariates had little impact upon the risk of mortality associated with admission glucose concentration.

Post-discharge mortality

For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort (Table 3A, Supplementary data). While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 – 1.300); 1 year 0.91 (0.66 – 1.26); all follow-up 1.08 (0.86 – 1.36)), blood glucose retained powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/L 1.10, 95% CI 1.05 – 1.15), 1 year (1.05, 1.02 – 1.08), and over all follow-up (1.04, 1.02 – 1.06)).

Admission glucose concentration – influence on mortality in patients with or without diabetes

We repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (Figure 1), there was no conventional statistically significant difference in the association between mortality and admission blood glucose for patients with and without diabetes (30 days HR 1.00, (CI 0.97 – 1.03, p=0.95; 1 year 0.99, (0.97 – 1.02), p=0.66; entire follow-up 0.99, (0.97 – 1.01, p=0.42)).

Diabetes and glucose after AMI – influence on mortality in STEMI and NSTEMI

After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period, either for STEMI or NSTEMI (Table 4). The strength of association

between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only after NSTEMI.

DISCUSSION

It is well known that, both prior diabetes diagnosis, and admission blood glucose concentration, are associated with adverse outcome after AMI. In this report we compared the relative association of these two measures of dysglycaemia with survival after STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55-65% thereafter) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In our previous report of over 4000 patients with STEMI, admitted in 1993-2004,(9) the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and removed completely when admission blood glucose concentration was included in the analysis. The current report confirms these observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI, in whom the strength of association between admission blood glucose concentration and 30-day mortality risk was similar, and concentration dependent. Importantly, the excess risk, around 7% for each 1mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Further, this phenomenon was attenuated with time only for patients with NSTEMI, and was evident even in those patients who survived to discharge from hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association between admission glucose and mortality to be confined to in-hospital deaths following either

STEMI or NSTEMI.(8) They are however in keeping with the vast majority of reports in this area.(1-7, 9, 11)

In contrast to most previous reports,(1-9, 11) we observed no independent association between diabetes and mortality risk after AMI. However, to our knowledge and unlike the present report, none of these studies adjusted for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis (1, 2, 4, 8) or blood glucose concentration.(3-8, 11-13, 21) The current analysis and our previous study (9) are the only reports to compare the relative association with outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose, and the loss of association between mortality and diabetes when blood glucose is considered. Due to incomplete data and lack of power, we could not assess whether outcomes varied by diabetes therapies. However previous studies have reported an independent association of admission blood glucose with mortality regardless of diabetic therapy used.(2,5,7)

These observations are of potential clinical significance. While admission blood glucose concentration after AMI is on average higher in patients with, compared to those without, known diabetes,(4, 8, 9) there is considerable overlap, as seen in the current report (Figure 1). While many patients presenting with AMI will have previously undiagnosed diabetes,(22) blood glucose at the time of admission with AMI is not a reliable indicator of the subsequent diagnosis of diabetes.(23, 24) In routine practice, the management of hyperglycaemia after AMI is influenced by the presence of prior diabetes diagnosis.(5) In both European(14) and North American(6) settings, the majority (>65%) of patients presenting with hyperglycaemia in the context of AMI, and not previously known to have diabetes, do not receive active management of blood glucose. In the presence of a true, direct toxic effect upon prognosis of elevated blood glucose, failure to correct hyperglycaemia may represent suboptimal clinical care, and patients without known diabetes may be particularly disadvantaged. In particular, our demonstration that the relationship between glucose

concentration and subsequent outcome is evident in NSTEMI as well as STEMI is of clear clinical relevance in terms of the overall management of patients presenting with AMI.

The strength of association between diabetes and mortality risk after AMI has been reported to increase with time from the event.(25) While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate. A previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcome.(4) While we could not demonstrate formal statistical evidence of such a phenomenon, our data show convincingly that the relationship between glucose and outcome is at least as powerful in patients without known diabetes. Blood glucose soon after admission represents an easily identified, clinically relevant marker of risk after AMI, which should be assessed routinely irrespective of diabetes status.

An important observation from this study is the persisting association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTEMI and STEMI. While in keeping with the possibility that blood glucose concentration at admission reflects the degree of individual physiological stress, or is a marker of the extent of infarction, our findings are as much in keeping with a direct, adverse influence on prognosis of acute hyperglycaemia. The mechanisms by which elevated glucose may be directly cardiotoxic have been summarised elsewhere (10) and include attenuation of ischaemic preconditioning, QT prolongation, increased thrombophilia, and endothelial dysfunction. Furthermore, clinical studies overwhelmingly support a possible causal link between hyperglycaemia and adverse prognosis after AMI. Hyperglycaemia persisting at 24 hours after admission is associated with adverse outcome,(12, 13, 17).

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent.(16,17) However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis.(16) The guidelines from

professional societies in this area differ in their recommendations.(27,28) In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels > 10.0 mmol/L) admitted in an intensive care unit.(28) In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with acute coronary syndrome.(27) The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Our report is subject to the limitations inherent in all observational cohort studies. Our results are from a single-centre study. In the early years of the MINAP project, data on only STEMI were collected. Furthermore, data collected for MINAP was gathered mainly from a setting of coronary care unit. Selection bias could be the reason behind the overall low numbers of AMI cases (4111) recruited in our study over a six year period in a catchment population of 1 million. However baseline and clinical outcome parameters in our study are similar to previous studies. Selection bias could also explain relatively high proportion of patients with STEMI (58.4%) compared to NSTEMI in our cohort. We therefore conducted subgroup analysis for people with STEMI and NSTEMI and compared their outcomes. Blood glucose concentration used in this analysis was that first recorded for the index admission, and is likely to have varied in timing relative to symptom onset. Our database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure, and a number of other potentially relevant variables. Information on body mass index, an indicator of underlying metabolic syndrome and associated dysglycaemia, was not available. Further, we have no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status. Thus we suggest the first recorded blood glucose concentration to be highly relevant to guiding appropriate management in individual patients, irrespective of residual LV function. While we have no information on interventions or changes to

therapy after discharge, it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days. Findings of our study based on real-life practice are applicable to other populations treated in similar setting.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. After adjustment for admission blood glucose, known diabetes is not associated with adverse outcome. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTEMI as well as STEMI, and persists beyond 1 year from the index event, including in patients surviving to discharge. Future studies are merited of the impact of active management of blood glucose in patients with all presentations of acute coronary artery disease, irrespective of diabetes diagnosis.

ARTICLE SUMMARY

Article focus

- Robust associations is seen for both measures of glycaemia - the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).
- We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with STEMI and NSTEMI.

Key Messages:

- In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.

- The increased risk associated with admission glucose is evident during the index admission, at 30 days, one year and beyond and is apparent in those surviving to discharge.

- Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study

- This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.

- A statistically robust association was seen for admission glucose with both short and loner term mortality after adjusting for many important confounders.

- Our data lacks information on glucose lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

Table 1: Baseline characteristics at admission stratified by diabetes status

	All n=4111	Known DM n= 835 (20.3%)	Not Known DM n=3276 (79.7%)	P Value*	Missing Value (%)
Demography					
Age (years)	66.4 (13.3)	68.6 (11.8)	65.8 (13.6)	<0.005	0.0
Women (%)	1224 (29.8)	276 (33.1)	948 (28.9)	0.022	0.0
Ethnicity (%)					
White European	3381 (82.2%)	545 (16.1)	2836 (86.6)	<0.005	0.0
South Asian	730 (17.8%)	290 (39.7%)	440 (60.3%)		0.0
Medical History (%)					
Hypertension	2048 (50.3)	584 (70.0)	1464 (45.0)	<0.005	1.0
Current/Ex Smoker	1366 (35.7)	282 (36.8)	1084 (35.5)	0.527	7.1
Coronary Heart Disease§	491 (12.1)	149 (17.9)	342 (10.6)	<0.005	0.9
CVA	254 (6.3)	86 (10.3)	168 (5.2)	<0.005	1.2
PVD	154 (3.8)	42 (5.0)	112 (3.5)	0.041	1.2
Heart Failure	190 (4.7)	76 (9.1)	114 (3.5)	<0.005	1.2
Type of Infarction (%)					
STEMI	2397 (58.3)	417 (49.9)	1980 (60.4)	<0.005	0.0
nSTEMI	1714 (41.7)	418 (50.1)	1296 (39.6)		
Physical Examination					
Heart Rate (beats/min)	81.1 (24.3)	85.5 (25.3)	80.0 (24.0)	<0.005	1.5
SBP (mmHg)	136.5 (28.4)	137.7 (30.7)	136.2 (27.8)	0.202	1.0
Biochemical Data					
Peak CK (IU/L, Normal range < 200)	1113.5 (1810.4)	939.9 (1279.3)	1156.4 (1917)	<0.005	7.6
Creatinine (µmol/L)	116.4 (63.8)	128.8 (76.1)	113.1 (59.8)	<0.005	16.8
eGFR (mL/min)	63.0 (22.2)	57.7 (23.6)	64.4 (21.7)	<0.005	16.6
Total cholesterol (mmol/L)	5.1 (1.3)	4.4 (1.2)	5.2 (1.3)	<0.005	16.6
Haemoglobin (g/L)	13.7 (1.9)	13.0 (1.9)	13.9 (1.8)	<0.005	66.6
Plasma glucose (mmol/L)	8.8 (4.2)	12.0 (5.5)	7.9 (3.3)	<0.005	14.9
Therapies (%)					
Prior to index admission					
Aspirin	2671 (65.0)	622 (74.5)	2049 (62.5)	<0.005	0.0
Beta blocker	990 (25.6)	265 (33.2)	725 (23.6)	<0.005	6.0
ACEI or ARB	1097 (28.3)	407 (51.0)	690 (22.5)	<0.005	5.8
Statins	1083 (28.0)	389 (48.7)	694 (22.6)	<0.005	5.8
In-hospital					
Reperfusion therapy #	2414 (58.7)	419 (50.2)	1995 (60.9)	<0.005	0.0
Loop diuretics	1502 (37.4)	436 (52.7)	1066 (33.4)	<0.005	2.3
At discharge					
Aspirin	2701 (68.1)	529 (65.3)	2172 (68.8)	0.057	3.5
Beta blocker	2513 (63.3)	483 (59.6)	2030 (64.3)	0.013	3.5
ACEI or ARB	2493 (62.9)	495 (61.0)	1998 (63.4)	0.222	3.6
Statin	2704 (67.7)	537 (65.6)	2167 (68.2)	0.167	2.8

All values are mean (SD) or number (%). * known diabetes vs not known diabetes. DM, Diabetes Mellitus; CVA, Cerebrovascular accidents; PVD, Peripheral Vascular Disease; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; SBP, Systolic blood pressure; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

thrombolysis or coronary intervention (PCI or CABG) or both

Table 2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.47)	**All (Median 912 days)** 1041 (25.32)
Admission Demographic Variable			
Gender (Female vs Male)	0.535 (0.439 , 0.650)	0.515 (0.443 , 0.600)	0.554 (0.490 , 0.627)
Age (year)	1.068 (1.059 , 1.078)	1.077 (1.069 , 1.084)	1.084 (1.077 , 1.090)
SBP (mmHg)	0.979 (0.976 , 0.983)	0.987 (0.984 , 0.990)	0.992 (0.990 , 0.994)
Heart Rate (beat/min)	1.010 (1.006 , 1.013)	1.012 (1.009 , 1.014)	1.012 (1.010 , 1.014)
Total Cholesterol (mmol/L)	0.732 (0.666 , 0.806)	0.765 (0.712 , 0.821)	0.744 (0.703 , 0.788)
Admission plasma glucose (mmol/L)	1.072 (1.052 , 1.084)	1.065 (1.055 , 1.076)	1.059 (1.050 , 1.068)
eGFR (mL/min)	0.956 (0.951 , 0.961)	0.955 (0.951 , 0.959)	0.959 (0.956 , 0.962)
NSTEMI vs STEMI	0.504 (0.405 , 0.627)	0.736 (0.629 , 0.862)	0.939 (0.830 , 1.063)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.909 (0.688 , 1.200)	0.846 (0.681 , 1.052)	0.919 (0.780 , 1.082)
2005	0.591 (0.402 , 0.870)	0.652 (0.491 , 0.865)	0.702 (0.564 , 0.873)
2006	0.830 (0.592 , 1.164)	0.696 (0.529 , 0.917)	0.716 (0.572 , 0.897)
2007	0.759 (0.570 , 1.010)	0.678 (0.541 , 0.849)	0.679 (0.558 , 0.826)
2008	0.485 (0.338 , 0.696)	0.551 (0.424 , 0.716)	0.531 (0.415 , 0.680)
Test for Linear Trend (p-value)	<0.001	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.013 (0.786 , 1.304)	0.909 (0.741 , 1.114)	0.856 (0.725 , 1.012)
Medical History (Yes vs No)			
Smoking	1.016 (0.819 , 1.259)	1.049 (0.891 , 1.235)	1.160 (1.019 , 1.320)
Prior Diabetes	1.400 (1.121 , 1.750)	1.576 (1.331 , 1.865)	1.655 (1.445 , 1.896)
Prior Coronary Heart Disease §	0.862 (0.628 , 1.182)	0.998 (0.791 , 1.258)	1.113 (0.931 , 1.330)
Prior Hypertension	1.286 (1.056 , 1.567)	1.437 (1.232 , 1.676)	1.472 (1.300 , 1.666)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.746 (0.613 , 0.909)	0.869 (0.744 , 1.015)	0.913 (0.804 , 1.036)
Beta Blocker	1.385 (1.116 , 1.719)	1.577 (1.338 , 1.859)	1.489 (1.301 , 1.703)
Statin	0.994 (0.795 , 1.245)	1.129 (0.953 , 1.338)	1.194 (1.041 , 1.370)
ACEI or ARB	1.242 (1.002 , 1.540)	1.467 (1.247 , 1.726)	1.621 (1.423 , 1.847)
Admission treatment (Yes vs No)			
Initial Reperfusion	0.616 (0.507 , 0.749)	0.540 (0.464 , 0.629)	0.466 (0.411 , 0.527)
Loop Diuretic	3.457 (2.807 , 4.256)	4.348 (3.681 , 5.136)	4.052 (3.556 , 4.618)
Discharge Medication (Yes vs No)			
Aspirin	0.043 (0.029 , 0.062)	0.227 (0.192 , 0.269)	0.439 (0.386 , 0.499)
Beta Blocker	0.038 (0.025 , 0.058)	0.237 (0.199 , 0.282)	0.406 (0.357 , 0.461)
Statin	0.043 (0.029 , 0.062)	0.196 (0.165 , 0.233)	0.344 (0.303 , 0.390)
ACEI or ARB	0.047 (0.031 , 0.700)	0.236 (0.198 , 0.281)	0.469 (0.412 , 0.533)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 3: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals).

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.5)	**All (Median 912 days)** 1041 (25.3)
Admission Demographics			
Gender (Female vs Male)	1.268 (0.885, 1.819)	1.094 (0.865, 1.383)	1.114 (0.931, 1.332)
Age (year)	1.059 (1.040, 1.078)	1.062 (1.048, 1.075)	1.073 (1.062, 1.083)
SBP (mmHg)	0.987 (0.981, 0.992)	0.991 (0.987, 0.995)	0.993 (0.990, 0.996)
Heart Rate (beat/min)	1.007 (1.001, 1.013)	1.006 (1.002, 1.010)	1.007 (1.005, 1.010)
Admission plasma glucose (mmol/L)	1.072 (1.042, 1.104)	1.059 (1.037, 1.081)	1.053 (1.036, 1.071)
eGFR (mL/min)	0.987 (0.978, 0.996)	0.983 (0.977, 0.990)	0.988 (0.983, 0.993)
NSTEMI vs STEMI	0.411 (0.282, 0.597)	0.558 (0.443, 0.704)	0.700 (0.587, 0.834)
Ethnicity (South Asian vs White European)	1.355 (0.893, 2.057)	1.155 (0.851, 1.568)	0.996 (0.779, 1.273)
Medical History (Yes vs No)			
Smoking	1.125 (0.788, 1.607)	0.953 (0.749, 1.213)	0.942 (0.786, 1.130)
Prior Diabetes	0.934 (0.631, 1.382)	1.001 (0.770, 1.300)	1.134 (0.927, 1.386)
Prior Coronary Heart Disease§	0.717 (0.402, 1.278)	0.898 (0.632, 1.277)	1.111 (0.864, 1.428)
Prior Hypertension	1.291 (0.903, 1.846)	1.155 (0.913, 1.461)	1.133 (0.949, 1.353)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.944 (0.667, 1.335)	0.989 (0.781, 1.252)	1.010 (0.842, 1.213)
Beta Blocker	1.288 (0.898, 1.849)	1.363 (1.067, 1.742)	1.173 (0.970, 1.418)
Statin	0.863 (0.579, 1.286)	0.877 (0.668, 1.150)	0.918 (0.743, 1.135)
ACEI or ARB	0.719 (0.497, 1.042)	0.932 (0.728, 1.194)	1.017 (0.840, 1.232)
Admission treatment (Yes vs No)			
Loop Diuretic	1.416 (0.993, 2.019)	1.703 (1.322, 2.195)	1.532 (1.268, 1.851)
Discharge Medication (Yes vs No)			
Aspirin	0.297 (0.157, 0.562)	0.656 (0.479, 0.897)	0.861 (0.676, 1.097)
Beta Blocker	0.257 (0.133, 0.494)	0.564 (0.423, 0.753)	0.671 (0.544, 0.828)
Statin	0.628 (0.295, 1.339)	0.683 (0.484, 0.963)	0.629 (0.490, 0.808)
ACEI or ARB	0.470 (0.229, 0.968)	0.610 (0.443, 0.839)	0.850 (0.668, 1.081)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 4: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the subgroups of patients with STEMI and NSTEMI. Data are hazard ratio (95% confidence intervals)

N=4111		Mortality, N (%)					
STEMI	NSTEMI	30 days		1 Year		All	
2397	1714	STEMI	NSTEMI	STEMI	NSTEMI	STEMI	NSTEMI
Admission Demographics							
Age (year)		1.055 (1.033 - 1.077)	1.073 (1.031 - 1.116)	1.061 (1.044 - 1.078)	1.056 (1.035 - 1.079)	1.077 (1.062 - 1.091)	1.061 (1.046 - 1.077)
SBP (mmHg)		0.988 (0.982 - 0.994)	0.983 (0.970 - 0.995)	0.992 (0.987 - 0.997)	0.988 (0.982 - 0.995)	0.993 (0.989 - 0.997)	0.994 (0.990 - 0.998)
Heart Rate (beat/min)		1.008 (1.001 - 1.015)	1.008 (0.997 - 1.02)	1.008 (1.002 - 1.013)	1.007 (1.001 - 1.013)	1.008 (1.004 - 1.012)	1.007 (1.002 - 1.011)
eGFR (mL/min)		0.986 (0.975 - 0.997)	0.987 (0.969 - 1.005)	0.982 (0.974 - 0.991)	0.978 (0.968 - 0.989)	0.986 (0.979 – 0.993)	0.987 (0.979 - 0.995)
Admission plasma glucose		1.070 (1.034 – 1.107)	1.074 (1.005 - 1.148)	1.071 (1.042 - 1.10)	1.021 (0.979 - 1.066)	1.076 (1.051 - 1.10)	1.014 (0.983 – 1.047)
Prior Diabetes		1.035 (0.652 - 1.641)	0.629 (0.264 - 1.502)	1.083 (0.772 - 1.518)	0.878 (0.566 – 1.36)	1.189 (0.907 -1.559)	1.055 (0.773 – 1.44)
Admission treatment (Yes vs No)							
Loop Diuretic		1.330 (0.890 - 1.989)	1.66 (0.759 - 3.629)	1.706 (1.248 (2.333)	1.988 (1.283 - 3.081)	1.365 (1.068 - 1.745)	2.03 (1.496 - 2.756)
Discharge Medication (Yes vs No)							
Aspirin		0.301 (0.135 - 0.672)	0.308 (0.088 - 1.076)	0.499 (0.322 - 0.773)	0.869 (0.523 - 1.433)	0.697 (0.501 - 0.970)	1.052 (0.711 - 1.557)
Beta Blocker		0.208 (0.095 - 0.455)	0.337 (0.094 - 1.207)	0.469 (0.320 - 0.687)	0.77(0.485 - 1.222)	0.520 (0.393 - 0.698)	0.939 (0.674 - 1.308)
Statin		1.046 (0.375 - 2.918)	0.255 (0.066 - 0.992)	0.551 (0.334 - 0.908)	0.745 (0.449 - 1.237)	0.615 (0.429 - 0.880)	0.65 (0.444 - 0.951)
ACEI or ARB		0.392 (0.153 - 1.006)	0.451 (0.121 - 1.673)	0.903 (0.545 - 1.496)	0.541 (0.348 - 0.841)	1.041 (0.712 - 1.523)	0.857 (0.616 - 1.194)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Contributors: NG, IS, KK conceived the idea of the study and were responsible for the design of the study. NG, RM were responsible for undertaking for the data analysis and produced the tables and graphs. IS, KK, MJD provided input into the data analysis. The initial draft of the manuscript was prepared by NG and IS and then circulated repeatedly amongst all authors for critical revision. IS was responsible for the acquisition of the data and IS, NG, RM, KK and MJD contributed to the interpretation of the results.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The work in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. NG has received support by the National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care - Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC for LNR) project for a PhD.

Competing interests: None

Ethical approval: The study was approved by the local research ethics committee (LNR Research Ethics Committee 1, Ref 09/H0406/71 for database analysis study).

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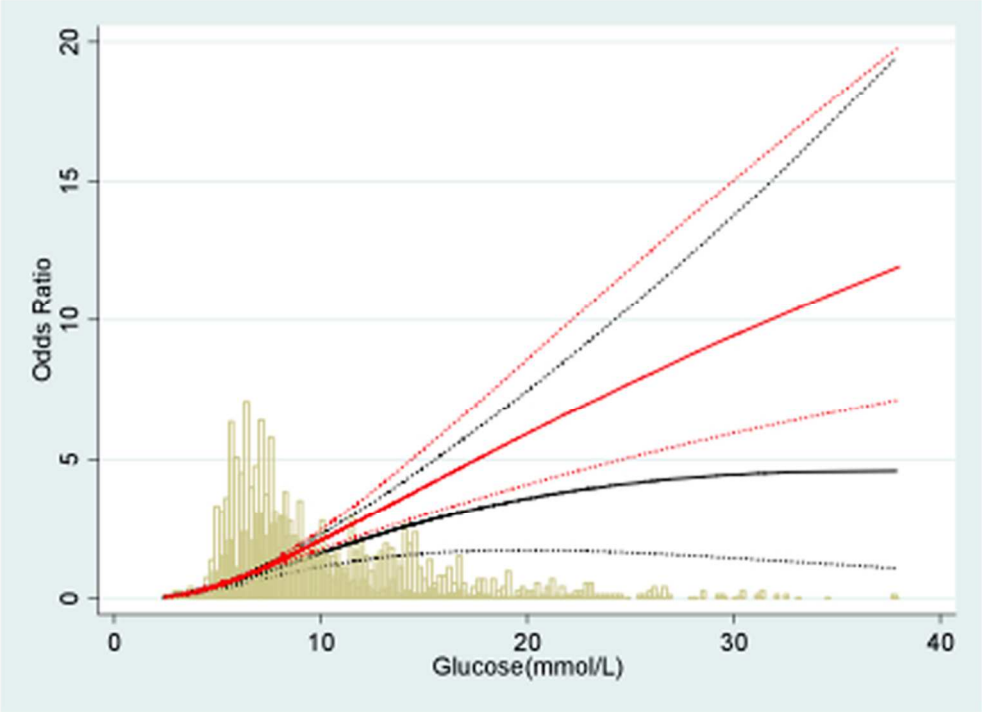
FIGURE LEGENDS

Figure 1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes.

The bars represent the number of people at various glucose levels. Solid lines indicate odds ratios while **dotted lines** indicate 95% confidence intervals. **Solid bars and black lines** indicate patients with diabetes. **Clear bars** and **red lines** indicate patients without Diabetes.



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70x51mm (300 x 300 DPI)

Supplementary Table 2A: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the survivors at discharge cohort. Data are hazard ratio (95% confidence intervals)

	Mortality N(%)		
N= 3790	**30 days** 106(2.80)	**1 Year** 363(9.60)	**All** 726(19.10)
Admission Demographics Variables			
Gender (Female vs Male)	0.585 (0.395 , 0.865)	0.520 (0.422 , 0.640)	0.577 (0.497 , 0.670)
Age (year)	1.059 (1.041 , 1.077)	1.080 (1.069 , 1.090)	1.088 (1.080 , 1.096)
SBP (mmHg)	0.985 (0.978 , 0.992)	0.995 (0.991 , 0.999)	0.998 (0.996 , 1.001)
Heart Rate (beats/min)	1.002 (0.994 , 1.010)	1.012 (1.008 , 1.015)	1.012 (1.010 , 1.015)
Total Cholesterol (mmol/L)	0.772 (0.646 , 0.922)	0.801 (0.730 , 0.879)	0.752 (0.703 , 0.803)
Admission plasma glucose (mmol/L)	1.069 (1.044 , 1.095)	1.060 (1.045 , 1.076)	1.054 (1.042 , 1.065)
eGFR (mL/min)	0.957 (0.947 , 0.967)	0.954 (0.949 , 0.959)	0.959 (0.955 , 0.963)
nSTEMI vs STEMI	0.558 (0.367 , 0.850)	1.015 (0.824 , 1.250)	1.213 (1.048 , 1.403)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.907 (0.551 , 1.494)	0.789 (0.590 , 1.054)	0.915 (0.757 , 1.105)
2005	0.490 (0.234 , 1.024)	0.670 (0.465 , 0.964)	0.727 (0.567 , 0.934)
2006	0.647 (0.334 , 1.252)	0.562 (0.382 , 0.827)	0.645 (0.489 , 0.850)
2007	0.402 (0.215 , 0.751)	0.517 (0.376 , 0.712)	0.560 (0.435 , 0.721)
2008	0.261 (0.115 , 0.589)	0.477 (0.333 , 0.682)	0.460 (0.331 , 0.639)
Test for Linear Trend (p-value)	0.002	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.172 (0.726, 1.891)	0.881 (0.665, 1.167)	0.824 (0.673, 1.008)
Medical History (Yes vs No)			
Smoking	1.417 (0.945 , 2.124)	1.179 (0.950 , 1.464)	1.281 (1.101 , 1.491)
Prior Diabetes	1.363 (0.874 , 2.124)	1.736 (1.384 , 2.177)	1.782 (1.516 , 2.093)
Prior Coronary Heart Disease §	1.427 (0.848 , 2.402)	1.289 (0.965 , 1.722)	1.309 (1.071 , 1.601)
Prior Hypertension	1.987 (1.315 , 3.002)	1.752 (1.413 , 2.172)	1.646 (1.417 , 1.912)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.945 (0.633 , 1.412)	1.078 (0.865 , 1.344)	1.038 (0.889 , 1.211)
Beta Blocker	1.966 (1.306 , 2.960)	1.850 (1.484 , 2.305)	1.582 (1.348 , 1.857)
Statin	1.169 (0.759 , 1.799)	1.306 (1.042 , 1.638)	1.323 (1.125 , 1.556)
ACEI or ARB	1.174 (0.762 , 1.807)	1.708 (1.373 , 2.124)	1.833 (1.570 , 2.140)
Admission treatment (Yes vs No)			
Initial Reperfusion	1.154 (0.774 , 1.720)	0.570 (0.464 , 0.701)	0.449 (0.387 , 0.521)
Loop Diuretic	3.199 (2.129 , 4.806)	4.940 (3.922 , 6.221)	4.174 (3.573 , 4.877)
Discharge Medication (Yes vs No)			
Aspirin	0.165 (0.107 , 0.253)	0.582 (0.469 , 0.723)	0.908 (0.771 , 1.069)
Beta Blocker	0.138 (0.086 , 0.221)	0.557 (0.451 , 0.688)	0.729 (0.626 , 0.848)
Statin	0.166 (0.108 , 0.255)	0.458 (0.371 , 0.566)	0.624 (0.536 , 0.726)
ACEI or ARB	0.176 (0.112 , 0.276)	0.545 (0.441 , 0.673)	0.886 (0.759 , 1.036)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Supplementary Table 3A: Multivariate association of clinical variables with 30-day, 1-year, and total mortality subject to survival to discharge. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N= 3792	**30 days** 106(2.80)	**1 Year** 363(9.60)	**All** 726(19.10)
Admission Demographics			
Gender (Female vs Male)	0.848 (0.467, 1.538)	1.026 (0.774, 1.360)	1.113 (0.912, 1.358)
Age (year)	1.077 (1.040,1.115)	1.058 (1.042, 1.075)	1.071 (1.059, 1.083)
SBP (mmHg)	0.981(0.971, 0.990)	0.994 (0.989, 0.998)	0.996 (0.993, 0.999)
Heart Rate (beat/min)	0.998 (0.987,1.008)	1.004 (1.000, 1.009)	1.007 (1.004, 1.010)
Admission plasma glucose (mmol/L)	1.095 (1.047,1.146)	1.046 (1.017,1.077)	1.042 (1.021, 1.064)
eGFR (mL/min)	0.994 (0.977, 1.011)	0.978 (0.970, 0.987)	0.985 (0.980, 0.991)
nSTEMI vs STEMI	0.253 (0.125, 0.512)	0.643 (0.486, 0.852)	0.826 (0.679, 1.005)
Year of Admission	0.826 (0.701, 0.974)	0.956 (0.887, 1.030)	0.926 (0.873, 0.981)
Ethnicity			
(South Asian vs White European)	2.021 (0.932, 4.384)	1.118 (0.760, 1.643)	0.950 (0.718, 1.258)
Medical History (Yes vs No)			
Smoking	1.722 (0.934, 3.177)	0.949 (0.710, 1.270)	0.920 (0.752, 1.124)
Prior Diabetes	0.638 (0.313, 1.303)	0.907 (0.656, 1.255)	1.080 (0.860, 1.356)
Prior Coronary Heart Disease §	1.093 (0.467, 2.560)	1.117 (0.751, 1.661)	1.328 (1.015, 1.738)
Prior Hypertension	1.836 (0.985, 3.421)	1.152 (0.868, 1.529)	1.112 (0.914, 1.354)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.951 (0.509, 1.778)	1.088 (0.810, 1.462)	1.086 (0.883, 1.336)
Beta Blocker	1.707 (0.929, 3.136)	1.403 (1.045, 1.883)	1.127 (0.913, 1.392)
Statin	0.961 (0.463, 1.997)	0.974 (0.699, 1.358)	0.992 (0.782, 1.258)
ACEI or ARB	0.685 (0.351, 1.339)	1.059 (0.784, 1.429)	1.093 (0.883, 1.353)
Admission treatment (Yes vs No)			
Loop Diuretic	1.029 (0.568,1.867)	1.598 (1.172, 2.179)	1.484 (1.203, 1.830)
Discharge Medication (Yes vs No)			
Aspirin	0.543 (0.235,1.256)	1.027 (0.702, 1.503)	1.228 (0.925, 1.631)
Beta Blocker	0.357 (0.167, 0.763)	0.730 (0.529, 1.007)	0.795 (0.633, 0.997)
Statin	1.191 (0.448, 3.170)	0.844 (0.574, 1.240)	0.712 (0.542, 0.935)
ACEI or ARB	0.425 (0.176, 1.027)	0.673 (0.475, 0.955)	0.955 (0.734, 1.243)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Is ~~A~~admission blood glucose concentration a ~~;A~~ more powerful predictor of mortality after myocardial infarction than diabetes diagnosis? : A retrospective cohort study.

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Keywords: Acute myocardial infarction, diabetes, glucose

Word count: 3~~029~~277

ABSTRACT:

Objective: To explore the relative ~~impact~~association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with ST elevation myocardial infarction (STEMI) and non-STEMI.

Design: Retrospective cohort study based on the Myocardial Ischaemia National Audit Project dataset.

Setting: Tertiary care centre.

Participants: 4111 (20.3% known diabetes) consecutive patients admitted with acute myocardial infarction (58.3% STEMI) between October 2002 and September 2008.

Primary and secondary outcome measures: All-cause mortality at 30-days and 1-year. The relative association of admission blood glucose and of antecedent diabetes with mortality was assessed using multivariate Cox regression analysis. Furthermore we compared these relationships in patients with STEMI to those with NSTEMI.

Results: By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) of patients died. After adjusting for covariates, diabetes did not show independent association with mortality at any time point, in the entire cohort (HR 30 days 0.93 (CI 0.63 – 1.38); 1-year 1.00 (0.77 – 1.30)) or in subgroups of STEMI (HR 30days 1.03 (0.65 – 1.64); 1 year 1.08 (0.77 – 1.51)) and non-STEMI (HR 30-days 0.62 (0.26-1.50); 1-year 0.87(0.56 – 1.36)). In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR: 30 days 1.07 (1.04 – 1.10); 1-year 1.05 (1.03 – 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03 – 1.10); 1-year 1.07 (1.04 – 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 - 1.14); 1-year 1.02 (0.97 - 1.06)).

Conclusion: Admission glucose is strongly associated with mortality in all presentations of acute myocardial infarction (AMI), irrespective of established diabetes diagnosis. The increased risk is

maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.

INTRODUCTION

For patients with acute myocardial infarction (AMI) the risk of adverse outcome is increased by the concomitant diagnosis of diabetes mellitus (diabetes).(1, 2) In addition, elevated blood glucose concentration, a common finding at admission in patients with AMI, is also associated with increased risk of adverse outcome, irrespective of prior diabetes.(1-8). In some studies (4, 9) the association between admission blood glucose concentration and adverse outcome was more powerful in patients without, compared to those with, prior diabetes. Indeed we previously reported more powerful association with 30-day and 1-year mortality after STEMI for admission blood glucose concentration, compared to the diagnosis of diabetes.(9)

While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which hyperglycaemia may impart toxicity during myocardial ischaemia.(10, 11) Indeed, observational data suggest that elevated blood glucose may contribute directly to adverse outcome after AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 hours after AMI compared to those in whom blood glucose normalises.(12, 13) In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with improved prognosis.(14, 15) Further, in randomised, controlled trials (RCTs) of intensive, insulin-based blood glucose management during admission with AMI, survival benefit was evident only when intervention effectively lowered blood glucose concentration.(16, 17)

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of acute coronary syndromes in contemporary practice are non-ST elevation AMI (NSTEMI). The aim of the current analysis was to compare the relative strength of association with 30-day, and 1-year mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with STEMI and with NSTEMI, and in those with and without a history of diabetes, in a multi-ethnic population. We also assessed the relevance

of blood glucose concentration, recorded soon after admission to hospital with AMI, to mortality in patients surviving to discharge.

METHODS

Data were from consecutive admissions between 1st October 2002 – 30th September 2008, to the two coronary care units (CCU) of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). For all patients, as part of the hospital's mandatory commitment to the Myocardial Ischaemia National Audit Project (MINAP),(18) we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), electrocardiographic (ECG) site of infarct, medical history, coronary heart disease risk-factors, and prescribed medication. Data are record-linked to mortality information (19) and include self reported coding for ethnicity, for which local coverage is thorough. Approximately 10% of the local population are of South Asian ethnic origin, over twice the UK national average.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient, or on the basis of medication prescribed prior to admission. All patients with AMI routinely underwent blood glucose measurement, in most cases within first 12 hours after admission with their blood samples assayed in the hospital laboratory. We used such first recorded admission glucose levels for this analysis. ~~The blood glucose measurement used for the analysis was the first recorded at the time of the index admission, assayed in the hospital laboratory as part of routine investigations.~~ All diagnoses of AMI were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACCF/AHA/WHF definition.(20) Patients were categorised as STEMI or NSTEMI, according to the final discharge diagnosis recorded in the MINAP database. For patients with multiple AMI admissions during the study period, we

considered only the first event. The number of cases admitted with AMI during the study period determined the sample size.

Survival was measured from the date of first admission to the date of death or of censoring at 30th September 2009. Mortality data are supplied to the hospital on a monthly basis via the UK Office for National Statistics. Follow-up data on mortality was available for all the patients. The pre-defined primary outcome measure was 30-day, and 1-year, all-cause mortality..

The study was approved by the local research ethics committee. The data used in this analysis were gathered during routine care and as part of the MINAP (18) mandatory requirement for all acute hospitals in England and Wales to collect data pertaining to admission with AMI.

Statistical analysis

Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Mortality at 30 days and at 1 year, in the entire cohort, and in those patients surviving to discharge, was calculated.

We calculated mortality proportions for patients admitted from 1st October 2002 to 30th September 2008 with follow-up censored at 30th September 2009. Survival probabilities were calculated using Kaplan-Meier [KM] analyses and patient groups compared using survival analysis log rank test. Relative risk of mortality, as a function of clinical variables, was examined using Cox proportional hazards techniques. We initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity (white European, South Asian), smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary revascularisation during index admission, pre-admission and discharge drug therapy (anti-platelet, beta-blocker, statin, angiotensin converting enzyme inhibitor/

angiotensin receptor blocker), and index loop diuretic use. An interaction term representing calendar year of admission was included to adjust for potential temporal changes in the management of acute coronary artery disease.

Demographic and clinical covariates with univariate association (p<0.10) with mortality at 30 days, or 1 year were entered into multivariate models (Cox proportional hazards). All quantitative variables were entered as continues variables into the model. Patients with missing data (Table 1) were not excluded but there values were set as missing. Statistical significance for all comparisons was set at p<0.05 (2 sided). Data are presented as hazard ratio (HR) and 95% confidence intervals (CI). We used fractional polynominals to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS version 18.

RESULTS

The study population was the 4111 patients admitted between 1st October 2002 – 30th September 2008 with discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow up was 912 days (range 0 to 2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow up was 1031 (range 1 to 2556) days.

Demographic details of the study population are presented in Table 1. Prior diabetes was recorded in 835 (20.3%) patients: compared to those without, patients with antecedent diabetes were on average older (68.6 vs 65.8 years, p<0.005), more likely to be female (33.9% vs 28.9%, p = 0.022) and to have prior cardiovascular co-morbidities. Presentation with NSTEMI was more prevalent in cases with (50.1%), compared to those without (39.6%), prior diabetes (p <0.005). Mean plasma glucose

was higher in patients with diabetes (12.0 ± 5.5 mmol/L) compared to those without (7.9 ± 3.3 mmol/L) (p <0.005). Mean peak CK was lower in patients with diabetes.

During the index admission administration of loop diuretic was more frequent (52.7% vs 33.4%, p<0.005) and, for patients with STEMI, coronary reperfusion therapy less frequent (50.2% vs 60.9%, <0.005), in patients with diabetes. Other than for slightly less use of beta-blockers and aspirin in patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

Mortality – Univariate analysis

Deaths during hospitalisation, over 30-days, 1-year and the entire period of follow-up numbered 319 (7.8%), 409 (9.9%), 677 (16.5%) and 1041 (25.3%) respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (Table 2). Loop diuretic was associated with a 3-4 fold increase in mortality during follow-up. Survival improved over the period of observation.

Prior diabetes showed strong univariate association with mortality risk over all time periods: HR 30 days 1.40 (1.12 - 1.75); 1 year 1.58 (1.33 - 1.86); all follow-up 1.66 (1.44 , 1.90)) (Table 2). The strength of association between glucose and mortality was consistent at 30-days and at 1-year, each mmol/L increase in admission glucose concentration being associated with a 6-7% increase in hazard of mortality over all time periods.

Post-discharge mortality

In those surviving to discharge (N=3792), 106 (2.8%), 363 (9.6%) and 726 (19.1%) died by 30-days, 1-year and over all follow-up (Table 2A, Supplementary data). Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with

increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, (0.87 - 2.12)). For admission glucose, the strength of association with post-discharge mortality was very similar to that in the entire cohort, with 5-7% increase risk per mmol/L increase in glucose. (Table 2A, Supplementary Data).

Mortality – Multivariate analysis

Table 3 shows the results of multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of loop diuretic, and STEMI (compared to NSTEMI) each retained independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain independent association with mortality at any time. In contrast, adjustment for covariates had little impact upon the risk of mortality associated with admission glucose concentration.

Post-discharge mortality

For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort (Table 3A, Supplementary data). While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 – 1.300); 1 year 0.91 (0.66 – 1.26); all follow-up 1.08 (0.86 – 1.36)), blood glucose retained powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/L 1.10, 95% CI 1.05 – 1.15), 1 year (1.05, 1.02 – 1.08), and over all follow-up (1.04, 1.02 – 1.06)).

Admission glucose concentration – influence on mortality in patients with or without diabetes

We repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (Figure 1), there was no conventional statistically significant difference in the association between mortality

and admission blood glucose for patients with and without diabetes (30 days HR 1.00, (CI 0.97 – 1.03, p=0.95; 1 year 0.99, (0.97 – 1.02), p=0.66; entire follow-up 0.99, (0.97 – 1.01, p=0.42)).

Diabetes and glucose after AMI – influence on mortality in STEMI and NSTEMI

After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period, either for STEMI or NSTEMI (Table 4). The strength of association between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only after NSTEMI.

DISCUSSION

It is well known that, both prior diabetes diagnosis, and admission blood glucose concentration, are associated with adverse outcome after AMI. In this report we compared the relative association of these two measures of dysglycaemia with survival after STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55-65% thereafter) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In our previous report of over 4000 patients with STEMI, admitted in 1993-2004,(9) the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and removed completely when admission blood glucose concentration was included in the analysis. The current report confirms these observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI, in whom the strength of association between admission blood glucose concentration and 30-day mortality risk was similar,

and concentration dependent. Importantly, the excess risk, around 7% for each 1mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Further, this phenomenon was attenuated with time only for patients with NSTEMI, and was evident even in those patients who survived to discharge from hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association between admission glucose and mortality to be confined to in-hospital deaths following either STEMI or NSTEMI.(8) They are however in keeping with the vast majority of reports in this area.(1-7, 9, 11)

In contrast to most previous reports,(1-9, 11) we observed no independent association between diabetes and mortality risk after AMI. However, to our knowledge and unlike the present report, none of these studies adjusted for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis (1, 2, 4, 8) or blood glucose concentration.(3-8, 11-13, 21) The current analysis and our previous study (9) are the only reports to compare the relative association with outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose, and the loss of association between mortality and diabetes when blood glucose is considered. Due to incomplete data and lack of power, we could not assess whether outcomes varied by diabetes therapies. However previous studies have reported an independent association of admission blood glucose with mortality regardless of diabetic therapy used.(2,5,7)

These observations are of potential clinical significance. While admission blood glucose concentration after AMI is on average higher in patients with, compared to those without, known diabetes,(4, 8, 9) there is considerable overlap, as seen in the current report (Figure 1). While many patients presenting with AMI will have previously undiagnosed diabetes,(22) blood glucose at the time of admission with AMI is not a reliable indicator of the subsequent diagnosis of diabetes.(23, 24) In routine practice, the management of hyperglycaemia after AMI is influenced by the presence

of prior diabetes diagnosis.(5) In both European(14) and North American(6) settings, the majority (>65%) of patients presenting with hyperglycaemia in the context of AMI, and not previously known to have diabetes, do not receive active management of blood glucose. In the presence of a true, direct toxic effect upon prognosis of elevated blood glucose, failure to correct hyperglycaemia may represent suboptimal clinical care, and patients without known diabetes may be particularly disadvantaged. In particular, our demonstration that the relationship between glucose concentration and subsequent outcome is evident in NSTEMI as well as STEMI is of clear clinical relevance in terms of the overall management of patients presenting with AMI.

The strength of association between diabetes and mortality risk after AMI has been reported to increase with time from the event.(25) While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate. A previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcome.(4) While we could not demonstrate formal statistical evidence of such a phenomenon, our data show convincingly that the relationship between glucose and outcome is at least as powerful in patients without known diabetes. Blood glucose soon after admission represents an easily identified, clinically relevant marker of risk after AMI, which should be assessed routinely irrespective of diabetes status.

An important observation from this study is the persisting association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTEMI and STEMI. While in keeping with the possibility that blood glucose concentration at admission reflects the degree of individual physiological stress, or is a marker of the extent of infarction, our findings are as much in keeping with a direct, adverse influence on prognosis of acute hyperglycaemia. The mechanisms by which elevated glucose may be directly cardiotoxic have been summarised elsewhere (10) and include attenuation of ischaemic preconditioning, QT prolongation, increased thrombophilia, and endothelial dysfunction. Furthermore, clinical studies overwhelmingly support a

possible causal link between hyperglycaemia and adverse prognosis after AMI. Hyperglycaemia persisting at 24 hours after admission is associated with adverse outcome,(12, 13, 17).

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent.(16,17) However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis.(16) The guidelines from professional societies in this area differ in their recommendations.(27,28) In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels > 10.0 mmol/L) admitted in an intensive care unit.(28) In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with acute coronary syndrome.(27) The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Our report is subject to the limitations inherent in all observational cohort studies. Our results are from a single-centre study. In the early years of the MINAP project, data on only STEMI were collected. Furthermore, data collected for MINAP was gathered mainly from a setting of coronary care unit. Selection bias could be the reason behind the overall low numbers of AMI cases (4111) recruited in our study over a six year period in a catchment population of 1 million. However baseline and clinical outcome parameters in our study are similar to previous studies. Selection bias could also explain relatively high proportion of patients with STEMI (58.4%) compared to NSTEMI in our cohort. We therefore conducted subgroup analysis for people with STEMI and NSTEMI and compared their outcomes. Blood glucose concentration used in this analysis was that first recorded for the index admission, and is likely to have varied in timing relative to symptom onset. Our database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure, and a number of other potentially relevant variables. Information on body mass index, an indicator of

underlying metabolic syndrome and associated dysglycaemia, was not available. Further, we have no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status. Thus we suggest the first recorded blood glucose concentration to be highly relevant to guiding appropriate management in individual patients, irrespective of residual LV function. While we have no information on interventions or changes to therapy after discharge, it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days. Findings of our study based on real-life practice are applicable to other populations treated in similar setting.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. After adjustment for admission blood glucose, known diabetes is not associated with adverse outcome. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTEMI as well as STEMI, and persists beyond 1 year from the index event, including in patients surviving to discharge. Future studies are merited of the impact of active management of blood glucose in patients with all presentations of acute coronary artery disease, irrespective of diabetes diagnosis.

ARTICLE SUMMARY

Article focus

- Robust associations is seen for both measures of glycaemia - the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).

- We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long term survival in a contemporary UK population of patients with STEMI and NSTEMI.

Key Messages:

- In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.
- The increased risk associated with admission glucose is evident during the index admission, at 30 days, one year and beyond and is apparent in those surviving to discharge.
- Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study

- This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.
- A statistically robust association was seen for admission glucose with both short and loner term mortality after adjusting for many important confounders.
- Our data lacks information on glucose lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

Table 1: Baseline characteristics at admission stratified by diabetes status

	All n=4111	Known DM n= 835 (20.3%)	Not Known DM n=3276 (79.7%)	P Value*	Missing Value (%)
Demography					
Age (years)	66.4 (13.3)	68.6 (11.8)	65.8 (13.6)	<0.005	0.0
Women (%)	1224 (29.8)	276 (33.1)	948 (28.9)	0.022	0.0
Ethnicity (%)					
White European	3381 (82.2%)	545 (16.1)	2836 (86.6)	<0.005	0.0
South Asian	730 (17.8%)	290 (39.7%)	440 (60.3%)		0.0
Medical History (%)					
Hypertension	2048 (50.3)	584 (70.0)	1464 (45.0)	<0.005	1.0
Current/Ex Smoker	1366 (35.7)	282 (36.8)	1084 (35.5)	0.527	7.1
Coronary Heart Disease§	491 (12.1)	149 (17.9)	342 (10.6)	<0.005	0.9
CVA	254 (6.3)	86 (10.3)	168 (5.2)	<0.005	1.2
PVD	154 (3.8)	42 (5.0)	112 (3.5)	0.041	1.2
Heart Failure	190 (4.7)	76 (9.1)	114 (3.5)	<0.005	1.2
Type of Infarction (%)					
STEMI	2397 (58.3)	417 (49.9)	1980 (60.4)	<0.005	0.0
nSTEMI	1714 (41.7)	418 (50.1)	1296 (39.6)		
Physical Examination					
Heart Rate (beats/min)	81.1 (24.3)	85.5 (25.3)	80.0 (24.0)	<0.005	1.5
SBP (mmHg)	136.5 (28.4)	137.7 (30.7)	136.2 (27.8)	0.202	1.0
Biochemical Data					
Peak CK (IU/L, Normal range < 200)	1113.5 (1810.4)	939.9 (1279.3)	1156.4 (1917)	<0.005	7.6
Creatinine (µmol/L)	116.4 (63.8)	128.8 (76.1)	113.1 (59.8)	<0.005	16.8
eGFR (mL/min)	63.0 (22.2)	57.7 (23.6)	64.4 (21.7)	<0.005	16.6
Total cholesterol (mmol/L)	5.1 (1.3)	4.4 (1.2)	5.2 (1.3)	<0.005	16.6
Haemoglobin (g/L)	13.7 (1.9)	13.0 (1.9)	13.9 (1.8)	<0.005	66.6
Plasma glucose (mmol/L)	8.8 (4.2)	12.0 (5.5)	7.9 (3.3)	<0.005	14.9
Therapies (%)					
Prior to index admission					
Aspirin	2671 (65.0)	622 (74.5)	2049 (62.5)	<0.005	0.0
Beta blocker	990 (25.6)	265 (33.2)	725 (23.6)	<0.005	6.0
ACEI or ARB	1097 (28.3)	407 (51.0)	690 (22.5)	<0.005	5.8
Statins	1083 (28.0)	389 (48.7)	694 (22.6)	<0.005	5.8
In-hospital					
Reperfusion therapy #	2414 (58.7)	419 (50.2)	1995 (60.9)	<0.005	0.0

Loop diuretics	1502 (37.4)	436 (52.7)	1066 (33.4)	<0.005	2.3
At discharge					
Aspirin	2701 (68.1)	529 (65.3)	2172 (68.8)	0.057	3.5
Beta blocker	2513 (63.3)	483 (59.6)	2030 (64.3)	0.013	3.5
ACEI or ARB	2493 (62.9)	495 (61.0)	1998 (63.4)	0.222	3.6
Statin	2704 (67.7)	537 (65.6)	2167 (68.2)	0.167	2.8

All values are mean (SD) or number (%). * known diabetes vs not known diabetes. DM, Diabetes Mellitus; CVA, Cerebrovascular accidents; PVD, Peripheral Vascular Disease; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; SBP, Systolic blood pressure; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

thrombolysis or coronary intervention (PCI or CABG) or both

Table 2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals)

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.47)	**All (Median 912 days)** 1041 (25.32)
Admission Demographic Variable			
Gender (Female vs Male)	0.535 (0.439 , 0.650)	0.515 (0.443 , 0.600)	0.554 (0.490 , 0.627)
Age (year)	1.068 (1.059 , 1.078)	1.077 (1.069 , 1.084)	1.084 (1.077 , 1.090)
SBP (mmHg)	0.979 (0.976 , 0.983)	0.987 (0.984 , 0.990)	0.992 (0.990 , 0.994)
Heart Rate (beat/min)	1.010 (1.006 , 1.013)	1.012 (1.009 , 1.014)	1.012 (1.010 , 1.014)
Total Cholesterol (mmol/L)	0.732 (0.666 , 0.806)	0.765 (0.712 , 0.821)	0.744 (0.703 , 0.788)
Admission plasma glucose (mmol/L)	1.072 (1.052 , 1.084)	1.065 (1.055 , 1.076)	1.059 (1.050 , 1.068)
eGFR (mL/min)	0.956 (0.951 , 0.961)	0.955 (0.951 , 0.959)	0.959 (0.956 , 0.962)
NSTEMI vs STEMI	0.504 (0.405 , 0.627)	0.736 (0.629 , 0.862)	0.939 (0.830 , 1.063)
Year of Admission			
Oct 2002-Dec 2003	1	1	1
2004	0.909 (0.688 , 1.200)	0.846 (0.681 , 1.052)	0.919 (0.780 , 1.082)
2005	0.591 (0.402 , 0.870)	0.652 (0.491 , 0.865)	0.702 (0.564 , 0.873)
2006	0.830 (0.592 , 1.164)	0.696 (0.529 , 0.917)	0.716 (0.572 , 0.897)
2007	0.759 (0.570 , 1.010)	0.678 (0.541 , 0.849)	0.679 (0.558 , 0.826)
2008	0.485 (0.338 , 0.696)	0.551 (0.424 , 0.716)	0.531 (0.415 , 0.680)
Test for Linear Trend (p-value)	<0.001	<0.001	<0.001
Ethnicity (South Asian vs. White European)	1.013 (0.786 , 1.304)	0.909 (0.741 , 1.114)	0.856 (0.725 , 1.012)
Medical History (Yes vs No)			
Smoking	1.016 (0.819 , 1.259)	1.049 (0.891 , 1.235)	1.160 (1.019 , 1.320)
Prior Diabetes	1.400 (1.121 , 1.750)	1.576 (1.331 , 1.865)	1.655 (1.445 , 1.896)
Prior Coronary Heart Disease §	0.862 (0.628 , 1.182)	0.998 (0.791 , 1.258)	1.113 (0.931 , 1.330)
Prior Hypertension	1.286 (1.056 , 1.567)	1.437 (1.232 , 1.676)	1.472 (1.300 , 1.666)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.746 (0.613 , 0.909)	0.869 (0.744 , 1.015)	0.913 (0.804 , 1.036)
Beta Blocker	1.385 (1.116 , 1.719)	1.577 (1.338 , 1.859)	1.489 (1.301 , 1.703)
Statin	0.994 (0.795 , 1.245)	1.129 (0.953 , 1.338)	1.194 (1.041 , 1.370)
ACEI or ARB	1.242 (1.002 , 1.540)	1.467 (1.247 , 1.726)	1.621 (1.423 , 1.847)
Admission treatment (Yes vs No)			

Initial Reperfusion	0.616 (0.507 , 0.749)	0.540 (0.464 , 0.629)	0.466 (0.411 , 0.527)
Loop Diuretic	3.457 (2.807 , 4.256)	4.348 (3.681 , 5.136)	4.052 (3.556 , 4.618)
Discharge Medication (Yes vs No)			
Aspirin	0.043 (0.029 , 0.062)	0.227 (0.192 , 0.269)	0.439 (0.386 , 0.499)
Beta Blocker	0.038 (0.025 , 0.058)	0.237 (0.199 , 0.282)	0.406 (0.357 , 0.461)
Statin	0.043 (0.029 , 0.062)	0.196 (0.165 , 0.233)	0.344 (0.303 , 0.390)
ACEI or ARB	0.047 (0.031 , 0.700)	0.236 (0.198 , 0.281)	0.469 (0.412 , 0.533)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 3: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals).

	Mortality, N (%)		
N=4111	**30 days** 409 (9.95)	**1 Year** 677 (16.5)	**All (Median 912 days)** 1041 (25.3)
Admission Demographics			
Gender (Female vs Male)	1.268 (0.885, 1.819)	1.094 (0.865, 1.383)	1.114 (0.931, 1.332)
Age (year)	1.059 (1.040, 1.078)	1.062 (1.048, 1.075)	1.073 (1.062, 1.083)
SBP (mmHg)	0.987 (0.981, 0.992)	0.991 (0.987, 0.995)	0.993 (0.990, 0.996)
Heart Rate (beat/min)	1.007 (1.001, 1.013)	1.006 (1.002, 1.010)	1.007 (1.005, 1.010)
Admission plasma glucose (mmol/L)	1.072 (1.042, 1.104)	1.059 (1.037, 1.081)	1.053 (1.036, 1.071)
eGFR (mL/min)	0.987 (0.978, 0.996)	0.983 (0.977, 0.990)	0.988 (0.983, 0.993)
NSTEMI vs STEMI	0.411 (0.282, 0.597)	0.558 (0.443, 0.704)	0.700 (0.587, 0.834)
Ethnicity (South Asian vs White European)	1.355 (0.893, 2.057)	1.155 (0.851, 1.568)	0.996 (0.779, 1.273)
Medical History (Yes vs No)			
Smoking	1.125 (0.788, 1.607)	0.953 (0.749, 1.213)	0.942 (0.786, 1.130)
Prior Diabetes	0.934 (0.631, 1.382)	1.001 (0.770, 1.300)	1.134 (0.927, 1.386)
Prior Coronary Heart Disease§	0.717 (0.402, 1.278)	0.898 (0.632, 1.277)	1.111 (0.864, 1.428)
Prior Hypertension	1.291 (0.903, 1.846)	1.155 (0.913, 1.461)	1.133 (0.949, 1.353)
Pre -Admission Medication (Yes vs No)			
Aspirin	0.944 (0.667, 1.335)	0.989 (0.781, 1.252)	1.010 (0.842, 1.213)
Beta Blocker	1.288 (0.898, 1.849)	1.363 (1.067, 1.742)	1.173 (0.970, 1.418)
Statin	0.863 (0.579, 1.286)	0.877 (0.668, 1.150)	0.918 (0.743, 1.135)
ACEI or ARB	0.719 (0.497, 1.042)	0.932 (0.728, 1.194)	1.017 (0.840, 1.232)
Admission treatment (Yes vs No)			
Loop Diuretic	1.416 (0.993, 2.019)	1.703 (1.322, 2.195)	1.532 (1.268, 1.851)
Discharge Medication (Yes vs No)			
Aspirin	0.297 (0.157, 0.562)	0.656 (0.479, 0.897)	0.861 (0.676, 1.097)
Beta Blocker	0.257 (0.133, 0.494)	0.564 (0.423, 0.753)	0.671 (0.544, 0.828)
Statin	0.628 (0.295, 1.339)	0.683 (0.484, 0.963)	0.629 (0.490, 0.808)
ACEI or ARB	0.470 (0.229, 0.968)	0.610 (0.443, 0.839)	0.850 (0.668, 1.081)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

Table 4: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the subgroups of patients with STEMI and NSTEMI. Data are hazard ratio (95% confidence intervals)

N=4111		Mortality, N (%)					
STEMI	NSTEMI	30 days		1 Year		All	
2397	1714	STEMI	NSTEMI	STEMI	NSTEMI	STEMI	NSTEMI
Admission Demographics							
Age (year)		1.055 (1.033 - 1.077)	1.073 (1.031 - 1.116)	1.061 (1.044 - 1.078)	1.056 (1.035 - 1.079)	1.077 (1.062 - 1.091)	1.061 (1.046 - 1.077)
SBP (mmHg)		0.988 (0.982 - 0.994)	0.983 (0.970 - 0.995)	0.992 (0.987 - 0.997)	0.988 (0.982 - 0.995)	0.993 (0.989 - 0.997)	0.994 (0.990 - 0.998)
Heart Rate (beat/min)		1.008 (1.001 - 1.015)	1.008 (0.997 - 1.02)	1.008 (1.002 - 1.013)	1.007 (1.001 - 1.013)	1.008 (1.004 - 1.012)	1.007 (1.002 - 1.011)
eGFR (mL/min)		0.986 (0.975 - 0.997)	0.987 (0.969 - 1.005)	0.982 (0.974 - 0.991)	0.978 (0.968 - 0.989)	0.986 (0.979 – 0.993)	0.987 (0.979 - 0.995)
Admission plasma glucose		1.070 (1.034 – 1.107)	1.074 (1.005 - 1.148)	1.071 (1.042 - 1.10)	1.021 (0.979 - 1.066)	1.076 (1.051 - 1.10)	1.014 (0.983 – 1.047)
Prior Diabetes		1.035 (0.652 - 1.641)	0.629 (0.264 - 1.502)	1.083 (0.772 - 1.518)	0.878 (0.566 – 1.36)	1.189 (0.907 -1.559)	1.055 (0.773 – 1.44)
Admission treatment (Yes vs No)							
Loop Diuretic		1.330 (0.890 - 1.989)	1.66 (0.759 - 3.629)	1.706 (1.248 (2.333)	1.988 (1.283 - 3.081)	1.365 (1.068 - 1.745)	2.03 (1.496 - 2.756)
Discharge Medication (Yes vs No)							
Aspirin		0.301 (0.135 - 0.672)	0.308 (0.088 - 1.076)	0.499 (0.322 - 0.773)	0.869 (0.523 - 1.433)	0.697 (0.501 - 0.970)	1.052 (0.711 - 1.557)
Beta Blocker		0.208 (0.095 - 0.455)	0.337 (0.094 - 1.207)	0.469 (0.320 - 0.687)	0.77(0.485 - 1.222)	0.520 (0.393 - 0.698)	0.939 (0.674 - 1.308)
Statin		1.046 (0.375 - 2.918)	0.255 (0.066 - 0.992)	0.551 (0.334 - 0.908)	0.745 (0.449 - 1.237)	0.615 (0.429 - 0.880)	0.65 (0.444 - 0.951)
ACEI or ARB		0.392 (0.153 - 1.006)	0.451 (0.121 - 1.673)	0.903 (0.545 - 1.496)	0.541 (0.348 - 0.841)	1.041 (0.712 - 1.523)	0.857 (0.616 - 1.194)

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Contributors: NG, IS, KK conceived the idea of the study and were responsible for the design of the study. NG, RM were responsible for undertaking for the data analysis and produced the tables and graphs. IS, KK, MJD provided input into the data analysis. The initial draft of the manuscript was prepared by NG and IS and then circulated repeatedly amongst all authors for critical revision. IS was responsible for the acquisition of the data and IS, NG, RM, KK and MJD contributed to the interpretation of the results.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The work in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease. NG has received support by the National Institute for Health Research, Collaboration for Leadership in Applied Health Research and Care - Leicestershire, Northamptonshire and Rutland (NIHR CLAHRC for LNR) project for a PhD.

Competing interests: None

Ethical approval: The study was approved by the local research ethics committee.

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FIGURE LEGENDS

Figure 1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes.

The bars represent the number of people at various glucose levels. Solid lines indicate odds ratios while **dotted lines** indicate 95% confidence intervals. **Solid bars and black lines** indicate patients with diabetes. **Clear bars** and **red lines** indicate patients without Diabetes.