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Prognostic significance of the change in glucose level in the first 24 h after acute myocardial infarction: results from the CARDINAL study

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Aims In acute myocardial infarction (AMI), baseline hyperglycaemia predicts adverse outcomes, but the relation between subsequent change in glucose levels and outcomes is unclear. We evaluated the prognostic significance of baseline glucose and the change in glucose in the first 24 h following AMI.
Methods and results We analysed 1469 AMI patients with baseline and 24 h glucose data from the CARDINAL trial database. Baseline glucose and the 24 h change in glucose (24 h glucose level subtracted from baseline glucose) were included in multivariable models for 30- and 180-day mortality. By 30 and 180 days, respectively, 45 and 74 patients had died. In the multivariable 30-day mortality model, neither baseline glucose nor the 24 h change in glucose predicted mortality in diabetic patients ($n = 250$). However, in nondiabetic patients ($n = 1219$), higher baseline glucose predicted higher mortality [hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.04–1.20, per 0.6 mmol/L increase], and a greater 24 h change in glucose predicted lower mortality (HR 0.91, 95% CI 0.86–0.96, for every 0.6 mmol/L drop in glucose in the first 24 h) at 30 days. Baseline glucose and the 24 h change in glucose remained significant multivariable mortality predictors at 180 days in nondiabetic patients.
Conclusion Both higher baseline glucose and the failure of glucose levels to decrease in the first 24 h after AMI predict higher mortality in nondiabetic patients.

Introduction

In patients hospitalized with acute coronary syndromes with or without ST-segment elevation, baseline hyperglycaemia predicts adverse outcomes in patients with or without known diabetes mellitus.[1–19] Evidence supports the prognostic value of baseline glucose levels among acute myocardial infarction (AMI) patients in the reperfusion era,[5,8,10,12–17,19] but few studies have examined this relation expressing glucose as a continuous variable. In addition, it is unclear whether glucose measurements taken after hospital admission add prognostic information in AMI patients. Glucose is usually highest at baseline (upon diagnosis of AMI) and then gradually decreases as the acute stress response subsides. Guidelines from both the American College of Cardiology/American Heart Association and the American College of Endocrinology endorse treatment of hyperglycaemia in AMI patients;[20,21] however, it is unclear whether the magnitude of the decrease in glucose after AMI is of incremental prognostic significance. In the Complement and ReDuction of INfarct size after Angioplasty or Lytics (CARDINAL) trials of complement inhibition in AMI patients,[22,23] we collected serial glucose measurements. These data provide a unique opportunity to evaluate the relation between baseline and serial glucose measures and clinical outcomes. We investigated whether baseline glucose and the change in glucose level in the first 24 h after AMI add independent prognostic value to well-established predictors[24] of both 30- and 180-day mortalities following AMI.

Methods

CARDINAL trials

The CARDINAL trials investigated the effect of the in-hospital administration of pexelizumab (a complement inhibitor) in patients

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with ST-elevation myocardial infarction who were treated with primary percutaneous coronary intervention (PCI)[22] or fibrinolysis.[23] The methods and results of these studies have been reported.[22,23] Briefly, 1903 patients of 18 years or older were enrolled with AMI (defined as presentation to the hospital within 6 h of the onset of ischaemic discomfort that lasted ≥20 min and ST-segment elevation ≥2 mm in two contiguous leads or new left-bundle branch block). Patients were excluded from enrolment for the following reasons: known or suspected pregnancy during the study, serum creatinine >3.0 mg/dL, participation in another drug trial prior to being screened for CARDINAL, and any contraindication to receiving complement inhibition with pexelizumab (including haemoglobin <9.5 g/dL, platelets <100 000/mm^3, white blood cell count <3000/mm^3, known or suspected active neisserial infection, known or suspected hereditary complement deficiency, or evidence of active serious infection).[22,23] Of the 1903 patients enrolled, 960 were treated with primary PCI and 943 were treated with fibrinolysis. Patients in CARDINAL were randomly assigned to receive placebo or one of the two regimens of the complement inhibitor pexelizumab. Baseline characteristics, interventions performed during hospitalization, and vital status at 30 and 180 days were recorded.

The CARDINAL trials were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the institutional Ethics Committees at all participating hospitals. Informed consent was required for participation.

Glucose measurements and study patients

The CARDINAL protocol specified that venous chemistry measurements, including glucose, should be taken at four times: at baseline upon in-hospital diagnosis of AMI, at 24 h after baseline (and not simply the morning following baseline), at day 6 or discharge (whichever occurred first), and at day 14. All glucose values were measured in a central core laboratory. From the 1903 patients enrolled in CARDINAL, baseline glucose was measured in 1659 patients, of whom 1497 also had glucose measured at 24 h (*Figure 1*). In this study, we investigated the association between two glucose measurements and mortality: baseline glucose, and the 24 h change in glucose (which was obtained by subtracting each patient's 24 h glucose level from the baseline glucose level), in order to determine whether the change in glucose from baseline would confer additional prognostic information to the baseline glucose alone. The 24 h change in glucose could be a negative number if the glucose level actually increased during the first 24 h. We did not evaluate the effect of the additional glucose measurements (from day 6 or discharge, or from day 14) on mortality for two reasons: first, because clinicians at participating hospitals would be more likely to make risk assessments or treatment decisions on the basis of glucose measurements obtained early in the hospitalization, as opposed to measurements obtained at a later period (e.g. at discharge); secondly, because patient drop-out due to in-hospital death or missing glucose data would be minimized (e.g. 1497 patients had glucose measurements available at both baseline and 24 h, but only 1184 patients had glucose assessed at baseline, 24 h, day 6 or discharge, and day 14).

Data analysis and statistical methods

Baseline demographic and clinical characteristics were compared across groups of baseline glucose (<6.9 mmol/L, ≥6.9 but <7.8 mmol/L, ≥7.8 but <9.4 mmol/L, and ≥9.4 mmol/L) and across groups of 24 h change in glucose (≥1.7 mmol/L, indicating a large drop in glucose in the first 24 h; ≥0 but <1.7 mmol/L, indicating no change to a moderate drop in glucose; and <0 mmol/L, indicating an actual increase in glucose) by use of Pearson's χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Fisher's exact test was used in cases where the cell frequencies for categorical variables were less than five. These glucose cut points were chosen because they were easy to remember clinically (for example, 6.9 mmol/L is the fasting plasma glucose threshold for diagnosing diabetes mellitus and 7.8 mmol/L is the threshold for diagnosing diabetes mellitus following an oral glucose tolerance test[25]) and were used only for displaying baseline characteristics and raw mortality rates. For the statistical models of mortality, baseline glucose and the 24 h change in glucose were analysed as continuous variables.

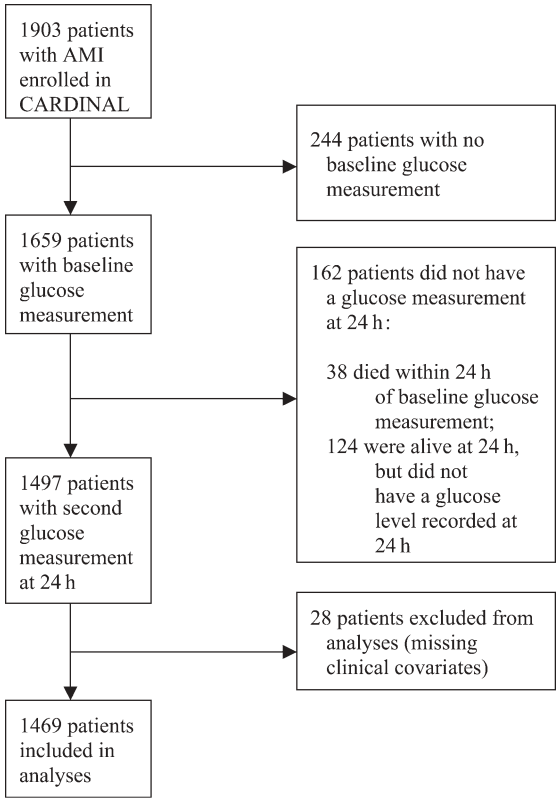

Figure 1 Patients from the CARDINAL trials with baseline and 24 h glucose measurements.

For statistical modelling, the relation between baseline glucose, 24 h change in glucose, and mortality at both 30 and 180 days was first examined using a Cox proportional hazard regression model with only baseline glucose, 24 h change in glucose, and the interaction between them as covariates. Subsequently, multivariable analysis was performed using a well-validated 30-day mortality model derived from the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO-I) trial.[26] In this model, logistic regression was applied to 40 830 GUSTO-I patients whose baseline clinical characteristics and vital status at 30 days were known.[24] Sixteen covariates in the GUSTO-I model were found to have independent prognostic value for 30-day mortality in AMI patients: age, systolic blood pressure, Killip class, heart rate, location of infarction, previous infarction, age-by-Killip class interaction, height, time to reperfusion therapy, diabetes, weight, smoking, choice of fibrinolytic therapy, previous coronary artery bypass graft surgery (CABG), hypertension, and prior cerebrovascular disease.[24] Of the 16 covariates from the original GUSTO-I model, 14 were included in both our 30-day and 180-day mortality models for the CARDINAL patients (we did not include data on baseline height and prior CABG history, as these data were not collected in CARDINAL). As only half of the CARDINAL patients received fibrinolysis (and the other half underwent primary PCI), mode of reperfusion (fibrinolysis vs. PCI) was used as a covariate instead of choice of fibrinolytic therapy. A Cox proportional hazard regression model including the 14 covariates was applied to a cohort of 1469 CARDINAL patients (28 of the 1497 patients with both baseline and 24 h glucose

measurements were excluded because of missing covariate data) (*Figure 1*). Next, the two glucose covariates, baseline glucose and 24 h change in glucose, were included in the model. We then tested for the statistical interactions between these glucose parameters and patient-reported history of diabetes. If either of these interactions was found to be statistically significant, the glucose parameters' hazard ratios (HR) with 95% confidence intervals (CI) would then be ascertained according to diabetic status. The assumption of linearity for a Cox proportional hazards model was evaluated using restricted cubic splines on each continuous variable. The model containing this transformed variable was compared with the model with a strict linear term to determine whether the variable seemed to deviate from the assumption. If so, then the plot of the transformed variable vs. the log of the HR was used to assist in determining an appropriate transformation. The proportional hazards assumption was evaluated by testing whether the HR changed with time. This was done by testing the interaction of the variable with time where this multiplicative term was used as a time-dependent covariate. If any factor had deviated from this assumption, it would have been used as a strata rather than a covariate in the modelling process, but this did not occur.

All analyses were performed using SAS® statistical software, version 8.2 (SAS Inc., Cary, NC, USA). A P-value ≤ 0.05 was considered statistically significant, bearing in mind that all analyses should be considered hypothesis-generating in the light of the observational nature of the study.

Results

Baseline characteristics and glucose levels

Figure 1 depicts the study cohort. The median glucose level was 7.9 mmol/L (interquartile range 6.7–10.0 mmol/L) at baseline and 6.7 mmol/L (5.7–8.3 mmol/L) at 24 h, and the median 24 h change in glucose (baseline glucose minus 24 h glucose) was 1.2 mmol/L (−0.1–2.7 mmol/L). All 1469 patients were stratified according to the baseline glucose level (*Table 1*). Individuals with higher baseline glucose were older, heavier, more often female, more likely to have a previous diagnosis of diabetes mellitus, and had larger infarct sizes [determined by creatine kinase (CK)-MB area under the curve]. *Table 2* shows the baseline characteristics in patients stratified by both the 24 h change in glucose and baseline glucose. Patients whose glucose levels increased during the first 24 h of AMI more often had diabetes mellitus than those individuals whose glucose level decreased during the first 24 h.

Table 1 Baseline characteristics by four groups of baseline glucose

Characteristic	Baseline glucose <6.9 mmol/L	Baseline glucose ≥6.9 but <7.8 mmol/L	Baseline glucose ≥7.8 but <9.4 mmol/L	Baseline glucose ≥9.4 mmol/L	Total population
n	438	236	353	442	1469
Baseline glucose (mmol/L)	6.2 (5.6, 6.6)	7.3 (7.1, 7.6)	8.4 (8.1, 8.8)	11.8 (10.2, 14.9)	7.9 (6.7, 10.0)
Age (years)	56 (48, 67)	57 (49, 68)	62 (53, 72)	63 (54, 72)	60 (51, 70)
Female sex (%)	24	20	27	33	27
White race (%)	85	89	92	86	88
Weight (kg)	77 (68, 88)	82 (72, 93)	78 (70, 89)	82 (72, 92)	80 (70, 90)
Baseline heart rate (b.p.m.)	77 (66, 87)	76 (65, 88)	74 (65, 86)	79 (68, 91)	76 (66, 88)
Systolic blood pressure (mmHg)	133 (120, 152)	136 (120, 151)	135 (120, 150)	135 (117, 154)	135 (120, 151)
Diastolic blood pressure (mmHg)	82 (71, 94)	82 (72, 92)	80 (70, 93)	80 (70, 90)	80 (70, 92)
Killip class (%)					
I	88	92	85	83	87
II	11	8.1	14	15	13
III	0	0	0	0	0
IV	0.9	0.4	0.9	1.4	1.0
Mode of reperfusion (%)					
Primary PCI	49	52	52	50	50
Fibrinolytic therapy	51	48	48	50	50
History of diabetes ($n = 250$) (%)	3.7	4.7	9.3	43	17
Prior MI (%)	17	15	14	21	17
Smoking status (%)					
Never smoked	23	30	32	38	31
Previous smoker	25	27	28	32	28
Current smoker	52	43	40	31	41
CK-MB on admission (ng/mL)	6.1 (2.7, 18.3)	5.6 (2.8, 16.4)	6.4 (3.1, 16.7)	5.9 (2.7, 16.0)	6.1 (2.9, 16.7)
Troponin I on admission (ng/mL)	1.2 (0.3, 6.8)	1.6 (0.3, 6.3)	1.8 (0.3, 6.4)	1.2 (0.3, 7.2)	1.4 (0.3, 6.8)
Total ST-segment elevation at baseline (mm)	8.0 (5.5, 12.0)	10.0 (6.5, 16.0)	10.5 (6.0, 17.0)	11.5 (6.5, 16.5)	10.0 (6.0, 15.5)
CK-MB AUC (assessment of infarct size)	3451 (1277, 6222)	5196 (2396, 7985)	5501 (2864, 8357)	4839 (2267, 8455)	4690 (2151, 7710)

Data are provided as median (25th, 75th) or as %, unless otherwise indicated. To convert glucose values from mmol/L to mg/dL, multiply by 18. AUC, area under the curve; b.p.m., beats per minute; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Baseline characteristics by three groups of 24 h change in glucose, stratified by baseline glucose (<7.8 or ≥7.8 mmol/L)

Characteristic	Baseline glucose <7.8 mmol/L ($n = 674$)			Baseline glucose ≥7.8 mmol/L ($n = 795$)		
	24 h change in glucose (baseline minus 24 h glucose) in mmol/L			24 h change in glucose (baseline minus 24 h glucose) in mmol/L		
	<0 mmol/L (increase in glucose)	≥0, <1.7 mmol/L (no change to moderate decrease in glucose)	≥1.7 mmol/L (large decrease in glucose)	<0 mmol/L (increase in glucose)	≥0, <1.7 mmol/L (no change to moderate decrease in glucose)	≥1.7 mmol/L (large decrease in glucose)
n	262	319	93	113	163	519
Baseline glucose (mmol/L)	6.2 (5.5, 6.8)	6.6 (6.2, 7.1)	7.3 (6.8, 7.6)	9.3 (8.3, 11.1)	8.7 (8.1, 9.7)	10.2 (8.7, 13.3)
24 h glucose (mmol/L)	7.3 (6.5, 8.3)	5.8 (5.3, 6.3)	5.1 (4.8, 5.5)	11.1 (9.8, 15.1)	7.9 (7.2, 8.9)	6.6 (5.7, 8.4)
24 h change in glucose (mmol/L)	−1.1 (−2.1, −0.4)	0.8 (0.4, 1.2)	2.0 (1.8, 2.3)	−1.5 (−2.6, −0.6)	1.0 (0.6, 1.3)	3.4 (2.6, 5.1)
Age (years)	55 (49, 67)	57 (49, 67)	58 (47, 70)	68 (55, 76)	62 (54, 72)	61 (53, 71)
Female sex (%)	24	21	25	27	30	31
Weight (kg)	78 (70, 89)	80 (70, 90)	80 (69.8, 94)	81.8 (72, 92)	80 (70, 91)	80 (70, 90)
Baseline heart rate (b.p.m.)	78 (66, 88)	76 (65, 86)	76 (66, 90)	77 (70, 90)	75 (66, 86)	77 (65, 88)
Systolic blood pressure (mmHg)	134 (120, 157)	134 (119, 150)	136 (120, 154)	135 (120, 152)	136 (120, 154)	134 (119, 151)
Killip class (%)						
I	87	91	90	80	85	85
II	13	7.9	9.7	20	14	14
III/IV	0.8	0.9	0	0	1.2	1.4
Mode of reperfusion (%)						
Primary PCI	47	51	54	55	52	50
Fibrinolytic therapy	53	49	46	45	48	50
Diabetes ($n = 250$) (%)	7.3	1.3	4.3	42	19	28
Prior MI (%)	16	16	17	19	13	19
Smoking status (%)						
Never smoked	27	24	27	37	37	34
Previous smoker	23	27	31	35	27	30
Current smoker	51	50	42	28	36	36
CK-MB on admission (ng/mL)	5.9 (2.9, 18.1)	5.6 (2.6, 16.6)	7.5 (3.0, 20.3)	8.8 (3.7, 20.3)	5.8 (3.0, 16.7)	5.9 (2.7, 15.1)
Troponin I on admission (ng/mL)	1.5 (0.3, 7.5)	1.1 (0.3, 6.3)	1.9 (0.3, 6.5)	3.3 (0.3, 10.2)	1.6 (0.3, 6.6)	1.3 (0.3, 6.0)
Total ST-segment elevation at baseline (mm)	8.5 (6.0, 13.0)	8.5 (6.0, 13.5)	9.5 (5.0, 15.0)	11.25 (6.5, 17.0)	10.0 (6.0, 16.5)	11.25 (6.5, 16.5)
CK-MB AUC (assessment of infarct size)	3695 (1305, 6420)	4414 (1856, 7285)	4462 (2360, 7080)	5658 (3247, 8471)	5150 (2492, 8452)	5043 (2385, 8391)

Data are provided as median (25th, 75th) or as %, unless otherwise indicated. To convert glucose values from mmol/L to mg/dL, multiply by 18.

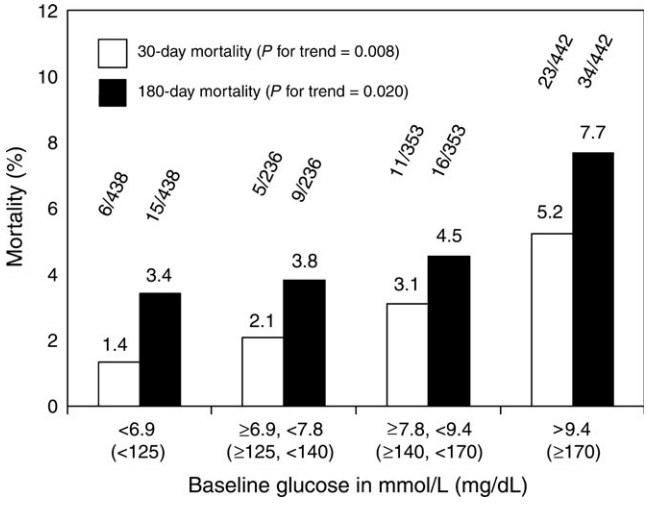

Figure 2 Relation between baseline glucose and mortality at both 30 and 180 days ($n = 1469$).

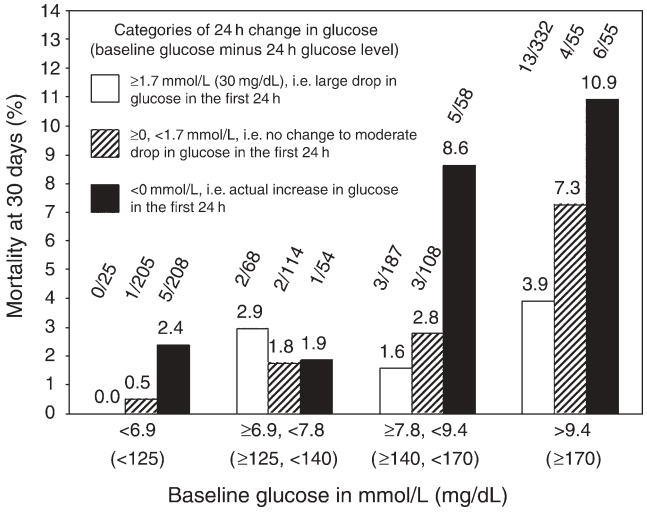

Figure 3 Relation between baseline glucose, 24 h change in glucose, and 30-day mortality ($n = 1469$). In the Cox model for 30-day mortality, both baseline glucose ($P < 0.0001$) and the 24 h change in glucose ($P = 0.0006$) independently predicted mortality. The effect of the 24 h change in glucose on 30-day mortality was independent of baseline glucose when glucose levels were assessed as continuous variables (*P*-value for interaction = 0.57); however, the relation between the 24 h change in glucose and 30-day mortality cannot be reliably interpreted from these data for the group of patients with baseline glucose less than 140 mg/dL (in which there were only 11 deaths in total at 30 days).

Relation between baseline glucose, 24 h change in glucose, and mortality

In the study cohort ($n = 1469$), there were 45 deaths at 30 days and 74 deaths at 180 days. As baseline glucose increased, there were associated increases in the mortality rates at both 30 days ($P = 0.008$) and 180 days ($P = 0.020$) (*Figure 2*). The predictive value of baseline glucose was similar when all 1659 patients with baseline glucose values (i.e. not excluding those with missing 24 h glucose data) were analysed for both 30-day and 180-day mortalities (*P* for trend <0.0001 in both cases; figure not shown). In the Cox model for 30-day mortality, both the baseline glucose [HR 1.08, 95% CI 1.05–1.12, per 0.6 mmol/L (10 mg/dL) increase; $P < 0.0001$] and the 24 h change in glucose [HR 0.93, 95% CI 0.89–0.97, per 0.6 mmol/L (10 mg/dL) drop in glucose in the first 24 h; $P = 0.0006$] predicted 30-day mortality (*Figure 3*). Similarly, at 180 days, both baseline glucose [HR 1.07, 95% CI 1.04–1.10, per 0.6 mmol/L (10 mg/dL) increase; $P < 0.0001$] and the 24 h change in glucose [HR 0.95, 95% CI 0.91–0.98, per 0.6 mmol/L (10 mg/dL) drop in glucose in the first 24 h; $P = 0.004$] predicted mortality (figure not shown).

Baseline glucose, 24 h change in glucose, and mortality rates at 30 and 180 days did not differ between patients assigned to pexelizumab (the investigational drug studied in the CARDINAL trials) and patients assigned to placebo.

Mortality models and the impact of diabetic status

Modelling for 30-day and 180-day mortalities was performed in the 1469 study patients. Results of univariable analysis showed that all of the 14 original covariates included from the GUSTO-I model except for systolic blood pressure and previous myocardial infarction were predictive of mortality at both 30 days (*Table 3*) and 180 days (table not shown). A multivariable model with only the 14 original baseline covariates (and no glucose covariates) was robust for predicting 30-day mortality (overall χ^2 112, $P < 0.0001$, *C*-index 0.89; table not shown). The overall performance of this model improved slightly (overall χ^2 125, $P < 0.0001$, *C*-index 0.90) after the addition of baseline glucose and 24 h change in glucose (*Table 4*).

In univariable analysis (*Table 3*), baseline glucose was predictive of 30-day mortality ($P = 0.0024$), as was the 24 h change in glucose adjusted only for baseline glucose ($P = 0.0006$). In the fully adjusted model (*Table 4*), there were statistical interactions between baseline glucose and history of diabetes ($P = 0.025$), and between 24 h change in glucose and history of diabetes ($P = 0.033$). In patients without diabetes, mortality at 30 days was predicted by both baseline glucose [HR 1.12, 95% CI 1.04–1.20 for every 0.6 mmol/L (10 mg/dL) increase] and 24 h change in glucose [HR 0.91, 95% CI 0.86–0.96, per 0.6 mmol/L (10 mg/dL), indicating a 9% relative decrease in mortality for every 10 mg/dL drop in glucose between baseline and 24 h] (*Table 5*). However, neither glucose covariate predicted 30-day mortality in patients with diabetes (for baseline glucose, HR 1.00, 95% CI 0.93–1.08; for 24 h change in glucose, HR 0.98, 95% CI 0.90–1.06). The prognostic value of both baseline glucose and 24 h change in glucose was independent of whether fibrinolysis or PCI was used for reperfusion (*P*-values >0.7 for the statistical interaction between the glucose covariates and mode of reperfusion).

All of the covariates that were significant predictors in the multivariable 30-day mortality model remained significant predictors in the multivariable model for 180-day mortality (table not shown). In patients without diabetes, mortality at 180 days was once again predicted by both baseline glucose [HR 1.08, 95% CI 1.02–1.15 for every 0.6 mmol/L (10 mg/dL) increase] and 24 h change in glucose [HR 0.92, 95% CI 0.88–0.97, per 0.6 mmol/L (10 mg/dL), indicating an 8% relative decrease in mortality for every 10 mg/dL drop in glucose between baseline and 24 h] (*Table 5*). However, neither glucose covariate predicted 180-day mortality in patients with diabetes (for baseline glucose, HR 1.03,

Table 3 Unadjusted covariate analysis for 30-day mortality ($n = 1469$ patients)

Variable	χ^2	*P*-value	HR	95% Confidence limits	
Age (per 10 years)	57.3	<0.0001	3.00	2.26	3.99
Systolic blood pressure (per 10 mmHg)	1.64	0.200	0.82	0.61	1.11
Killip class II, III, or IV (vs. I)	5.38	0.020	2.19	1.13	4.23
Heart rate (per 10 b.p.m.)	13.7	0.0002	1.33	1.14	1.55
MI location: anterior vs. other	5.90	0.015	5.80	1.40	23.9
Previous MI	0.27	0.604	1.21	0.58	2.52
Time to reperfusion therapy (h)	3.39	0.006	1.09	1.00	1.19
Diabetes	10.3	0.001	2.72	1.48	5.00
Weight (per 10 kg)	5.74	0.017	0.79	0.65	0.96
History of hypertension	9.48	0.002	2.82	1.46	5.47
Previous cerebrovascular disease	6.28	0.012	2.80	1.25	6.28
Mode of reperfusion (fibrinolysis vs. PCI)	5.11	0.024	2.04	1.10	3.80
Baseline glucose (per 0.6 mmol/L increase)	9.24	0.0024	1.04	1.02	1.07
24 h change in glucose (per 0.6 mmol/L drop in glucose in the first 24 h), adjusted only for baseline glucose[a]	11.9	0.0006	0.93	0.89	0.97

To convert glucose values from mmol/L to mg/dL, multiply by 18.

[a]As the 24 h change in glucose should be clinically interpreted only in the context of the baseline glucose, we report the predictive value of 24 h change in glucose adjusted only for baseline glucose.

Table 4 Adjusted covariate analysis for 30-day mortality when applied to the 1469 patients, including baseline glucose and 24 h change in glucose as covariates

Variable	χ^2	*P*-value	HR	95% Confidence limits	
Age (per 10 years)	29.8	<0.0001	3.13	2.08	4.70
Systolic blood pressure (per 10 mmHg)	1.59	0.207	0.81	0.58	1.13
Killip class II, III, or IV (vs. class I)	0.028	0.87	0.62	0.002	162.5
Heart rate (per 10 b.p.m.)	11.05	0.0009	1.29	1.11	1.49
MI location: anterior vs. other	4.66	0.03	4.85	1.16	20.31
Previous MI	0.45	0.504	0.77	0.36	1.66
Time to reperfusion therapy (h)	0.62	0.431	1.06	0.92	1.21
Diabetes[a]	0.53	0.465	1.35	0.60	3.04
Weight (per 10 kg)	0.245	0.621	1.06	0.85	1.31
History of hypertension	1.25	0.263	1.50	0.74	3.06
Previous cerebrovascular disease	3.00	0.083	2.12	0.91	4.96
Fibrinolysis (vs. PCI)	11.4	0.0007	3.10	1.61	5.99
Baseline glucose (per 0.6 mmol/L increase)[a]	1.88	0.17	1.03	0.99	1.08
24 h change in glucose (per 0.6 mmol/L drop in glucose in the first 24 h)[a]	10.10	0.002	0.91	0.86	0.96

To convert glucose values from mmol/L to mg/dL, multiply by 18.

[a]The prognostic value of diabetic status, baseline glucose, and 24 h change in glucose in the overall cohort are presented here. Because there was a statistical interaction between baseline glucose and diabetic status ($P = 0.025$) and between 24 h change in glucose and diabetic status ($P = 0.033$), the prognostic value of baseline glucose and 24 h change in glucose were also calculated separately for diabetic and nondiabetic patients and are presented in *Table 5*.

95% CI 0.97–1.10; for 24 h change in glucose, HR 0.98, 95% CI 0.91–1.05).

Discussion

This study reaffirms that higher baseline glucose levels are predictive of higher 30-day and 180-day mortalities in AMI patients undergoing reperfusion therapy. This study also extends the knowledge about glucose levels and prognosis after AMI in nondiabetic patients by demonstrating that a more substantial drop in glucose in the first 24 h after AMI is associated with improved 30-day and 180-day survival, which has potential implications for the management of elevated glucose levels following AMI. Even though glucose levels generally decrease during the first 24 h of hospitalization, which likely represents the amelioration of the acute stress response, 26% of patients in this study had glucose levels that were higher at 24 h than at baseline, suggesting that there may be an opportunity to improve in-hospital glucose control.

Baseline glucose and mortality

This study supports previous studies that have reported a direct relation between baseline glucose and mortality in AMI patients.[5,8,10,12–17,19] Many of these studies examined patients according to categories of baseline glucose, and

Table 5 Prognostic value of baseline glucose and 24 h change in glucose by diabetic status after multivariable adjustment[a], for both 30-day and 180-day mortalities

Variable	30-day mortality			180-day mortality		
	HR	95% Confidence limits		HR	95% Confidence limits	
Baseline glucose (per 0.6 mmol/L increase)						
Diabetes	1.004	0.932	1.081	1.033	0.973	1.098
No diabetes	1.119	1.041	1.202	1.082	1.020	1.148
24 h change in glucose (per 0.6 mmol/L drop in glucose in the first 24 h)						
Diabetes	0.978	0.901	1.062	0.977	0.908	1.050
No diabetes	0.905	0.857	0.957	0.920	0.877	0.965

[a]Adjusted for age, systolic blood pressure, Killip class, heart rate, location of infarction, previous infarction, age-by-Killip class interaction, time to reperfusion therapy, weight, smoking, mode of reperfusion (fibrinolysis vs. PCI), hypertension, and prior cerebrovascular disease. Each of the glucose covariates (baseline glucose and 24 h change in glucose) is also adjusted for the other glucose covariate.

this study also analysed glucose as a continuous variable, thus enabling us to quantify the risk of mortality with increasing values of baseline glucose. We found that for every 0.6 mmol/L (10 mg/dL) increase in baseline glucose, there was a 12% relative increase in the risk of death at 30 days (and an 8% increase in the risk of death at 180 days) following AMI in nondiabetic patients, even after adjustment for other important predictors of mortality. A recent study of admission glucose and mortality in over 140 000 elderly AMI patients similarly showed a graded increase in mortality for each higher quintile of baseline glucose, a finding which persisted when glucose was analysed as a continuous variable.[16]

Although higher baseline glucose levels in AMI patients (suggestive of a more exaggerated acute stress response following AMI) portends worse outcomes, recent reports have suggested that very low baseline glucose levels following AMI (perhaps suggestive of an inadequate stress response) are also predictive of adverse outcomes.[17,18] In CARDINAL, there were not enough adverse events in patients with low baseline glucose to verify this finding.

Change in glucose levels within 24 h following AMI and mortality

This study also demonstrated the prognostic value of the changes in glucose levels in the first 24 h following AMI. After adjustment for baseline glucose and other clinical predictors, we found that for every 0.6 mmol/L (10 mg/dL) drop in glucose level between baseline and 24 h, there was a 9% relative decrease in the risk of death at 30 days (and an 8% decrease in the risk of death at 180 days) in nondiabetic patients. The relation between the 24 h change in glucose and mortality appeared to be independent of baseline glucose when both parameters were analysed as continuous measures (*P*-value for interaction = 0.57 at 30 days); however, this relation could not be reliably interpreted for patients with baseline glucose less than 7.8 mmol/L (140 mg/dL), because of the small number of deaths among patients in this group (*Figure 3*). A larger study would be required to determine whether a greater decrease in glucose in the first 24 h after AMI predicts improved survival for subjects without elevated baseline glucose.

A recent study reported that the fasting glucose level obtained within 24 h of AMI adds independent prognostic value to baseline glucose.[14] However, that study did not evaluate the prognostic value of the change in glucose level for each patient within 24 h following AMI. Our study showed the prognostic value of both elevated baseline glucose and the degree of the change in glucose in the first 24 h of AMI. However, these observational studies (including ours) cannot distinguish whether glucose levels are merely risk markers or direct mediators of outcome following AMI. Both the American College of Cardiology[20] and the American College of Endocrinology[21] endorse intensive glycaemic control in hospitalized patients, which is largely based on a single randomized trial that demonstrated that intensive glycaemic control with insulin infusion reduced mortality by 42% compared with standard glycaemic control in surgical intensive care unit patients.[27] The Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial of 620 diabetic AMI patients is often quoted as a study of insulin therapy to achieve short-term glycaemic control following AMI,[28] but the mean blood glucose level achieved 24 h after the initiation of insulin therapy was 9.6 mmol/L (173 mg/dL), which is substantially higher than the normoglycaemic range that is recommended in critically ill hospitalized patients.[21] However, the achieved glucose level of 9.6 mmol/L in the intervention arm in DIGAMI was significantly lower than the glucose level of 11.7 mmol/L (211 mg/dL) achieved in the control arm and led to a 29% lower 1 year mortality in the insulin arm compared with the control arm. These results were not reproduced in the DIGAMI 2 study that utilized the same insulin protocol in diabetic patients and achieved a similar glucose level in the treatment group, but a much smaller difference (0.9 mmol/L) relative to the control group.[29] Thus, the degree of glucose control *per se* may have a direct bearing on outcomes following AMI in diabetic patients. However, no randomized controlled trials have been conducted to determine the efficacy and safety of intensive insulin therapy targeting normoglycaemia in nondiabetic AMI patients. In the absence of such randomized controlled trial data, our observational study should not be interpreted to suggest that intentional glucose lowering is either safe or efficacious in improving outcomes in nondiabetic AMI patients.

Interaction between glucose levels and diabetic status

In this study, the prognostic value of baseline glucose and 24 h change in glucose was observed in patients without a history of diabetes, but not in individuals with previously diagnosed diabetes. Several studies have examined whether elevated baseline glucose predicts mortality in diabetic AMI patients,[3,4,11–13,16,17] but to our knowledge, only three studies reported a positive relation.[3,12,16] Our study may have failed to find a prognostic value of glucose measurements in diabetic AMI patients because of the small number of diabetic (relative to nondiabetic) patients in our study.

In clinical practice, attention is often directed at reducing blood sugars in diabetic patients with hyperglycaemia. Consequently, elevated glucose levels may be less likely to be treated in patients without a prior diagnosis of diabetes. Our analysis suggests, however, that the potential harm of persistently elevated glucose levels after AMI is at least as great (if not greater) in nondiabetic patients as in diabetic patients, a finding which has been observed previously.[16]

Limitations

First, there was an unavoidable selection bias in this study, because we could not include in our multivariable mortality model (in which 24 h change in glucose was a covariate) the 38 subjects who died within the first 24 h of AMI diagnosis or he 124 other patients who were alive at 24 h but were otherwise missing a 24 h glucose value (*Figure 1*). Secondly, our study was a retrospective investigation of a prospectively acquired database and was not prespecified in the protocol of the CARDINAL trials. However, our clinical and laboratory data capture was robust enough to allow the application of a validated mortality model to almost 80% of the CARDINAL population, and we were able to demonstrate that the addition of baseline glucose and the 24 h change in glucose as covariates improved the prognostic ability of mortality models in our cohort. Thirdly, a previous diagnosis of diabetes was determined only by medical history and not by objective testing. It is likely that some 'nondiabetic' patients had unrecognized diabetes, a limitation that is common in studies of AMI patients due to the inability to diagnose diabetes mellitus in acutely ill patients. Next, data on the use of diabetes medications were not systematically collected in the CARDINAL trials, and hence, we were unable to adjust for this variable in our multivariable mortality models or account for the impact of diabetes medications on the 24 h change in glucose. However, we found that baseline glucose and the 24 h change in glucose had prognostic significance only in nondiabetic patients. Kosiborod *et al.*[16] reported that the rates of insulin administration among AMI patients without diabetes were very low at only 5.6% [among patients with a baseline glucose level 9.4–13.3 mmol/L (170–240 mg/dL)] and 21.8% [for baseline glucose >13.3 mmol/L (240 mg/dL)], compared with insulin administration rates of 49% and 73%, respectively, for patients with diabetes. On the basis of these data, it is unlikely that many nondiabetic AMI patients in our study were treated with insulin during their hospitalization, and therefore, our results would likely not have changed substantially had we been able to account for diabetes medications in our modelling. Finally, the high *C*-index values ($C = 0.90$) obtained for the 30-day mortality model should be interpreted with caution, bearing in mind the small number of events at 30 days. However, our primary purpose was not to validate the predictive value of the GUSTO-I mortality model in a separate population, but was to demonstrate the prognostic value of baseline glucose and the 24 h change in glucose independent of other well-established mortality predictors. In this regard, we do not believe that overfitting of the data was a significant limitation in our analyses.

Conclusions

Both baseline glucose and the 24 h change in glucose level add independent prognostic value following AMI in nondiabetic patients, even in addition to a highly predictive set of variables. Despite the growing body of evidence of the prognostic value of glucose levels in AMI, glycaemic control is often not a focus of care in the management of AMI patients. Glucose levels are easy to obtain, inexpensive to monitor, and relatively easy to manage when elevated. Our data reinforce the importance of baseline glucose and its change over the first 24 h following AMI as independent risk markers. These findings support the need for further research into how glucose control might impact outcomes in patients with AMI.

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Conflict of interest: T.G.T. is an employee of Procter & Gamble Pharmaceuticals and C.F.M. is an employee of Alexion Pharmaceuticals. Both companies supported the CARDINAL study. K.W.M., C.B.G., and P.T. have received research grant support from and served as consultants for both companies. J.S.H. has served as a consultant for Procter & Gamble Pharmaceuticals. A.G., J.G., J.C.N., W.D.W., G.B.F.O., and P.W.A. have no conflicts of interest to declare in relation to this study.

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