Title: Adjustment of the GRACE score by 2-hour post load glucose improves prediction of long-term major adverse cardiac events in acute coronary syndrome in patients without known diabetes.

Short title: 2h post-load glucose increases the prognostic predictability of GRACE score

Authors:

Sudipta Chattopadhyay[1] MRCP Anish George[2] MRCP, Joseph John[3] FRCP, Thozhukat Sathyapalan[4] FRCP,

Affiliations:

[1]Department of Cardiology, Milton Keynes University Hospital, Milton Keynes, UK.

[2]Department of Cardiology, Scunthorpe General Hospital, Scunthorpe, UK,

[3]Department of Cardiology, Castle Hill Hospital, Kingston upon Hull, UK

[4]Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, University of Hull, Kingston upon Hull, UK

Corresponding author:

Sudipta Chattopadhyay, MBBS, MD, MRCP.

Department of Cardiology, Milton Keynes University Hospital, Standing Way, Milton Keynes, MK6 5LD. UK.

E-mail: Sudipta.Chattopadhyay@nhs.net;

Tel: 00441908660033; Fax: 00441908660023

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Abstract

Aims

Global Registry of Acute Coronary Events (GRACE) risk score (GRS), a powerful predictor of prognosis after ACE, does not include a glucometabolic measure. We investigate whether 2 hour post-load plasma glucose (2h-PG) could improve GRS based prognostic models in ACE patients without known diabetes mellitus (DM).

Methods

Retrospective cohort study of 1056 ACE survivors without known DM who had fasting (FPG) and 2h-PG measured pre-discharge. Death and non-fatal myocardial infarction (MI) were recorded as major adverse cardiac events (MACE) during follow up. GRS for discharge to 6 months was calculated. Cox proportional-hazards regression was used to identify predictors of event free survival. The predictive value of 2h-PG alone and combined with GRS was estimated using Likelihood ratio test, Akaike's Information criteria, continuous net reclassification improvement ($NRI^{>0}$) and integrated discrimination improvement (IDI).

Results

During 40.8 months follow up 235 MACEs (22.3%) occurred, more frequently in the upper 2h-PG quartiles. 2h-PG, but not FPG, adjusted for GRS independently predicted MACE (HR 1.091; 95 % CI 1.043-1.142; p=0.0002). Likelihood ratio test showed that 2h-PG significantly improved the prognostic models including GRS (χ^2=20.56, 1 df, p=0.000). Models containing GRS and 2h-PG yielded lowest corrected Akaike's Information criteria, compared to that with only GRS. 2h-PG, when added to GRS, improved net reclassification significantly ($NRIe^{>0}$ 6.4%, $NRIne^{>0}$ 24%, $NRI^{>0}$ 0.176, p = 0.017 at final follow up). 2h-PG, improved integrated discrimination of models containing GRS (IDI of 0.87%, p=0.008 at final follow up).

Conclusion

2h-PG but not FPG is an independent predictor of adverse outcome after ACE even after adjusting for the GRS. 2h-PG, but not FPG, improves the predictability of prognostic models containing GRS.

Key words:

Acute coronary syndrome, myocardial infarction, GRACE, Global Registry of Acute Coronary Events, prognosis, diabetes, oral glucose tolerance test

Introduction

The Global Registry of Acute Coronary Events (GRACE) risk score (GRS) for mortality and re-infarction up to 6 months post-discharge is a powerful predictor of short and long-term prognosis after acute coronary syndrome (ACS).[1-4] Although it is well established that post-ACS prognosis is worse in patients with known diabetes mellitus (DM) than in those without, DM is not included as a variable in the GRS model.

Several studies show that hyperglycaemia, newly diagnosed after myocardial infarction (MI) on admission plasma glucose (APG), fasting plasma glucose (FPG), admission glycosylated haemoglobin (HbA1c) and oral glucose tolerance test (OGTT), in patients without known DM adversely affects long term prognosis. None of these studies have included GRS or all of its components in their models to predict outcomes or demonstrated an independent effect of 2 hour post load glucose (2h-PG) on prognosis. A few studies that have included GRS in addition to the glycaemic indices in their prognostic models have yielded variable results.[5-16] Thus it is still unclear as to which glycaemic index best predicts prognosis after MI in patients without known diabetes and whether 2h-PG, in addition to the GRS, independently predicts post-MI prognosis.

In the present study, we investigate the value of FPG and 2h-PG in addition to GRS in predicting major adverse cardiac events (MACEs) in patients with MI but without known DM and the potential incremental prognostic value of adding FPG and 2h-PG to to models including GRS only.

Methods

We retrospectively analysed data, prospectively collected for a mandatory national audit, the Myocardial Infarction National Audit Project (MINAP), on all consecutive MI survivors without known DM, admitted between November 2005 and October 2008, who underwent pre-discharge oral glucose tolerance test (OGTT) as part of routine clinical care and were

followed up.[17] This observational study includes all patients for whom FPG, 2h-PG and the GRS were available.

Data on age, gender, risk factors for CAD, past medical history, pre-hospital and discharge medications, troponin I levels, heart rate, systolic blood pressure, creatinine level, presence of congestive heart failure, previous history of MI, revascularisation status and presence of ST-segment depression were recorded. Web-based GRS calculator was used to calculate the risk of death or MI from discharge to 6 months for each patient. Patients with pre-existing diabetes were excluded. Patients were classified as having pre-admission DM if the patient had been informed of the diagnosis by a physician or was on treatment. HbA1c was not used for diagnosing pre-hospital diabetes as it was not recommended in contemporary guidance.[18,19] FPG (after an overnight fast of ≥8 hours) and OGTT (venous plasma glucose measured 2 hours after administration of 75g glucose (2-h PG) in 200 ml water) were done on/after the third day of admission on consecutive patients without known DM. Patients who died before or did not tolerate the OGTT and were transferred to other centres before OGTT were excluded. Discharge was not delayed for the OGTT. Plasma glucose was enzymatically determined using the glucose oxidase method. Intravenous glucose solutions were not allowed, but anti-adrenergic agents were used if clinically indicated. Clinically unstable patients were tested later. The patients with impaired glucose tolerance (IGT) and new diabetes mellitus (NDM) were referred to the diabetologists for appropriate out-patients management.

Participants were followed for up to 5 years (median 3.4years) for outcomes. Completeness of follow up was ensured by manual review of hospital and general practice records. The first occurrence of a MACE defined as death or non-fatal re-infarction, the events that the GRS predicts, was obtained from patient records. Mortality data was collected from the hospital care records for patients who died in hospital. For patients who died in the community,

mortality data was obtained from the general practitioner medical records confirmed by the office of public health intelligence.

Permission was sought from the East Yorkshire and North Lincolnshire Research Ethics Committee to analyse the data. As the study retrospectively analysed routinely collected anonymised data on standard clinical practice to contribute to a National Audit database, the Committee waived the need for formal ethical approval and patient consent.[17]

Statistical analysis

Continuous variables are presented as medians (inter-quartile range) and categorical variables as counts and proportions (%). Baseline characteristics are presented as quartiles of 2h-PG. The differences were compared between groups using the one-way analysis of variance and Kruskal-Wallis test for parametric and non-parametric data respectively for continuous variables and chi-squared test for categorical variables. Event free survival was estimated in the 4 quartiles of 2h-PG from Kaplan–Meier curves that were compared using the Log-rank test. Cox proportional-hazards regression modelling was used to analyse the effect of several variables on event free survival. All covariates known to affect prognosis after MI including gender, smoking status, hypercholesterolaemia, hypertension, history of previous acute MI, diagnosis at discharge, discharge prescription of aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and statins, in-patient revascularisation status, GRS for 6 months from discharge for death and MI, FPG and 2h-PG were “entered” into the model. The GRS variables (i.e. age, resting heart rate, systolic blood pressure on arrival, creatinine, congestive heart failure, history of myocardial infarction, ST-segment depression, elevated troponin, and in-hospital revascularisation) were not entered separately. Results are reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs). Multicollinearity was examined using variance inflation factor (VIF) (MedCalc Statistical Software version 17.0.4, Ostend, Belgium) and variables with VIF<4 were included in the same model.

Nested models were compared using χ^2 likelihood ratio tests to determine whether the logistic regression model that included GRS and FPG or 2h-PG provided a significantly better fit than those with GRS alone. Comparison of nested and non-nested models including GRS, or its combination with FPG or 2h-PG was performed by calculating corrected Akaike's information criterion (AIC_c), delta-AICc ($\delta AIC)_c$, and Akaike weights (w_i), to estimate the probability that a given model is the "best" fitting model of those studied.[20]

Logistic regression models using the above covariates along with GRS, FPG and 2h-PG individually and in combination were used to generate predicted probabilities of MACE. The incremental predictive value from adding FPG and 2h-PG to models with GRS was analyzed from these predicted probabilities using several measures of improvement in discrimination: increase in the area under the receiver-operating characteristic (ROC) curve (AUC) (MedCalc Statistical Software version 17.0.4, Ostend, Belgium), category-free continuous net reclassification improvement ($cNRI^{>0}$) and integrated discrimination improvement (IDI). In the absence of clearly pre-defined clinical risk thresholds for the models including GRS, categorical NRI was not used. The event NRI (NRIe) was defined as net percentage of persons with the event of interest correctly assigned a higher predicted risk and non-event NRI (NRIne) as net percentage of persons without the event of interest correctly assigned a lower predicted risk. The overall NRI defined as sum of the net proportion of persons with and without the event of interest correctly assigned a different predicted risk is reported as a number. The IDI was equal to the increase in discrimination slope defined as the mean difference in predicted risks between those with and without events.

Results

The 1056 patients, included in the study, were divided into quartiles of 2h-PG (Q1, ≤6.5 mmol/l, Q2, 6.6-8.1 mmol/l, Q3, 8.2-10.4 mmol/l and Q4, >10.4 mmol/l) (Table 1) The patients in the upper quartiles were older, had more risk factors, were less frequently on

clopidogrel, had higher heart rate and creatinine, more frequent heart failure, ST segment depression and high-risk GRS, higher mean GRS and FPG.

Outcomes

During the median follow-up of 40.8 months (range 6-60 months) there were 235 MACEs (22.3%), 112 deaths (10.6%) and 123 non-fatal re-infarctions (11.6%). MACE was more frequent in the upper glucose quartiles (Table 1). Death and non-fatal re-infarction increased with increasing quartiles of 2h-PG even in those where the level of 2h-PG did not cross the conventional threshold for the diagnosis of DM (Fig. 1). On Cox proportional hazard regression analysis 2h-PG and GRS, but not FPG, were consistently independent predictors of MACE at the final follow up when included in the same model as GRS (Table 2). The risk of MACE increased by 9% for each mmol/l rise in 2h-PG.

Nested models were compared using likelihood ratio tests to determine whether logistic regression models that included GRS and FPG or 2h-PG provided a significantly better fit than that limited to the GRS. This showed that addition of the 2h-PG as a continuous variable significantly improved the ability of a model including GRS score to predict MACE at all time points during follow up (Table 3). Addition of FPG did not improve the model fit.

Comparing models containing GRS alone, GRS with FPG and GRS with 2h-PG, the later yielded the lowest corrected AIC, highest Akaike's weight and evidence ratio compared to that with only GRACE score (Table 3). This suggests that the model with GRACE score and 2h-PG is more likely to be the "best" fitting model compared to the other models tested.

Entering 2h-PG, but not FPG, into a logistic regression model containing GRACE score alone significantly improved the net reclassification of later model in predicting events during follow up (Table 4). Using continuous NRI ($NRI^{>0}$) 2h-PG improved reclassification by 6.4% for those with events and by 24% for those without, resulting in a significant overall

improvement in net reclassification (NRI 0.176, p = 0.017 at final follow up). The model including the GRS and 2h-PG seems to predict a lower risk of MACE than that with GRS only both in the event and non-event groups. This reduction in the predicted risk, results in 24% improvement in net reclassification in the non-event group. Addition of FPG did not improve reclassification .The addition of 2h-PG, but not FPG, to a model including GRS improved integrated discrimination at all time points during follow up (Table 4). It yielded an IDI of 0.87%, p=0.008 at final follow up.

The c-statistic was 0.746 (95% CI 0.719 to 0.772, p <0.0001) for the prognostic model containing the GRS only, 0.719 (95% CI 0.691 to 0.746, p<0.0001) for the model containing 2h-PG only and 0.754 (95% CI 0.726 to 0.779, p <0.0001) for the model including GRS and 2h-PG. The AUC for the GRS-only was better than the 2h-PG only model (δAUC 0.0274, p = 0.045). The c-statistic did not increase significantly when 2h-PG was added to the GRS only model (δAUC 0.00744, p = 0.165) but did so when GRS was added to the 2h-PG only model (δAUC 0.0348, p = 0.002). This suggests that GRS, as expected, is a more powerful predictor of events than 2h-PG.

Discussion

This study shows that 1) 2h-PG, but not FPG, independently predicts prognosis after ACS after adjusting for the GRS and 2) 2h-PG, but not FPG, improves the ability of models containing GRS to predict long-term adverse events after an ACS in patients without known DM.

The GRS is a powerful predictor of prognosis after MI at different time points up to 4 years.[1-4] Even though it is well established that patients with ACS and DM have poorer outcomes than those without; the GRS does not include DM or any of the glycaemic indices as a variable in the model. In the GRACE, DM independently predicted in-hospital[2] but not the 6-

month post-discharge mortality.[3] The initial logistic regression models developed from GRACE to predict prognosis incorporated several variables including DM as a dichotomous categorical variable. This model was reduced to include only the eight most predictive variables to make it clinically usable.[2] DM and other variables were removed as the c statistics of models with and without these variables were similar.[2,3] In the GRACE, FPG increased the risk of in-hospital mortality both when FPG was used to group patients and when used as continuous variable irrespective of a history of DM.[5] The 6 months post-discharge mortality was high only if FPG was in the diabetic range.[5]

Almost all studies suggesting that FPG, APG, HbA1c or AGT, are independent predictors of adverse prognosis after ACS have not included the GRS (or all its individual components) within their regression models. The results, in a few studies that did, are variable. When adjusted for GRS, FPG, APG and HbA1c have independently predicted outcomes in some [6,8,9,12,15] but not other[5,7,11,13,14,16] studies. APG, FPG and HbA1c improved the predictive ability of models containing GRS in some[9,12,21] but not all studies[10,13,14]. This is the only study to show that 2h-PG independently predicts prognosis after ACS after adjusting for the GRS and improves the ability of models containing GRS to predict prognosis.

In contrast to our study, Aronson et al showed that in patients without known diabetes FPG, adjusted for the GRS, predicted mortality after MI and improved the prognostic models containing GRS.[9] That study included mainly (73%) STEMI patients, measured FPG within 24 hours of admission and 2h-PG were not measured. Only 44% of our patients had STEMI and FPG and 2h-PG were measured at 3-5 days. As the troponin in the GRS is not a continuous variable it does not reflect the prognostic effect of the extent of myonecrosis. Glucose levels are higher when measured within the first 24-48 hours of MI than later and after STEMI compared to NSTEMI.[22,23] The higher FPG in these STEMI patients when combined with GRS, a variable not influenced by the volume of myonecrosis, may have affected the model favourably improving its performance. In addition, it is unclear whether

FPG would remain an independent predictor if 2h-PG was included in the models in this study. This could explain the difference in the two studies. The increased macrovascular morbidity associated with higher 2h-PG rather than FPG as seen in this study may be related to progression of atherosclerosis demonstrated with post-challenge rather than fasting hyperglycaemia.[24-28]

Without HbA1c, we do not have all the glycaemic indices to compare their effect on prognosis. HbA1c has predicted post-MI prognosis in some [8,29-31] but not all studies.[32-36] The relative ability of APG, FPG, 2h-PG and HbA1c to predict post MI prognosis in patients without previously known diabetes has rarely been studied.[32,35,37] In the EUROASPIRE IV,[35,38] neither FPG nor HbA1c predicted the primary outcome, whereas the 2h-PG did. In another study,[32] HbA1c ≥6.5%, in the same model as OGTT, did not show any significant increase in mortality. However, there was significantly increased mortality in patients with HbA1c <6.5% categorized as newly diagnosed DM by OGTT. Kowalczyk et al[37] suggest that the HbA1c may be useful in further risk stratifying patients diagnosed with IGT and NDM but do not report the effect of HbA1c on prognosis of patients without. Sattar et al[39] suggest that HbA1c and FPG are better than OGTT for cardiovascular disease risk prediction citing two studies[40,41] to argue in favour. The first,[40] specifically excluded people with history of CVD at baseline. The second,[41] DETECT-2, looks at the relation of FPG and HbA1c prevalence of retinopathy, a microangiopathy, in epidemiological setting. Thus both these studies included populations very dissimilar to our study. The EUROSPIRE IV and SWEETHEART registry[42] support the use of OGTT for predicting prognosis in these high risk patients.

The c-statistic did not change significantly when 2h-PG was added to a model containing GRS. It is unsurprising that adding GRS to the model containing 2h-PG did. The increment in the c-statistic, used to quantify the added value offered by the new biomarker, is overly conservative and the ΔAUC depends on the performance of the underlying clinical model i.e.

good clinical models are harder to improve on.[43] Improving models containing powerful variables as the GRS may be difficult. To deal with this anomaly, Pencina et al.[44,45] devised the IDI and $NRI^{>0}$, for evaluating reclassification with novel biomarkers. These matrices improved when 2h-PG is added to GRS. The larger improvement in net reclassification in the non-event group when adding 2h-PG to the GRS may suggest that the 2h-PG tempers down the risk predicted by the GRS alone in these patients.

As we aimed to evaluate whether adding FPG and/or 2h-PG improved prediction of post-MI prognosis by models containing GRS, we restricted ourselves to end-points predicted by the GRS i.e. death and non-fatal reinfarction as the only study end-points. We also entered the GRS as a composite rather than its individual covariates separately in the logistic regression analysis, as we wanted to see whether FPG and/or 2h-PG could improve the models containing GRS.

Limitations

Being an observational longitudinal cohort study using retrospective analysis of prospectively collected data from a single centre, it has its limitations. Although national death register was not consulted directly, there is no reason to doubt the accuracy of a linked general practice database used. As the study includes only the re-infarctions admitted to the local hospital, a few admitted to other hospitals may have been missed. Although every effort was made to ensure completeness of the data, information not recorded could not be used in statistical models. Exclusion of small number of patients, albeit for valid reasons, and mainly Caucasian study population could affect the generalizability of the results. The effect of random glycaemic fluctuations or stress hyperglycaemia on the results can not be excluded. As OGTT was not repeated pre- or post- discharge, it is uncertain whether random fluctuation in glycaemia or stress hyperglycaemia affected results. However, OGTT done at or after 5 days seems to reliably predict long term glucometabolic state.[46,47] As pre-discharge post-challenge hyperglycaemia, irrespective of its pathophysiological mechanism, predicted

outcomes in post-MI patients, the reproducibility of these measurements and its relation to long term glucometabolic status, though important in establishing a diagnosis of MI, may be less relevant when assessing prognostic risk.

Conclusion

This study suggests that in patients without known diabetes 2h-PG, but not FPG, is an independent predictor of adverse outcome after ACS even after adjusting for the GRS. The 2h-PG, but not FPG, improves the ability of models including GRS to predict long-term post-ACS prognosis. As the choice of diagnostic tests for detection of glycaemic abnormalities in this population is hotly debated it may be reasonable to suggest that the most important test would be the one that determines long term prognosis after ACS i.e. 2h-PG rather than the one deemed sufficient for use in the low-risk general population for epidemiological purposes even if simpler and more feasible i.e. HbA1c. This is especially so when clear evidence in favour HbA1c against 2h-PG in this high risk population is lacking. The 2h-PG should at least be considered as a marker of post-MI prognosis in these patients.

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Figure 1. The event free survival in the quartiles of 2 hour post load glucose.

Table 1. Baseline characteristics of the study population categorised by quartiles of 2h post load glucose.

	Q1 ≤6.5 (n=274)	Q2 6.6-8.1 (n=261)	Q3 8.2-10.4 (n=259)	Q4 >10.4 (n=262)	p
Male n (%)	186(67.9)	186(71.3)	193(74.5)	192(73.3)	0.344
Current smoker n (%)	114(41.6)	83(31.8)	84(32.4)	82(31.3)	0.034
Hypertension n (%)	80(29.2)	100(38.3)	110(42.5)	105(40.1)	0.009
Hypercholesterolaemia n (%)	45(16.2)	69(26.4)	57(22.0)	62(23.7)	0.039
Previous AMI n (%)	35(12.8)	45(17.2)	47(18.2)	54(20.6)	0.107
Known IHD n (%)	39(14.2)	51(19.5)	52(20.1)	58(22.1)	0.113
CVA	7(2.6)	8(3.1)	15(5.8)	22(8.5)	0.006
Normal LVEF	139(50.7)	108(41.4)	104(40.2)	108(41.2)	0.045
Diagnosis NSTEMI n (%)	163(59.5)	144(55.2)	131(50.6)	152(58.0)	0.176
Discharge medications					
Aspirin n (%)	267(97.5)	250(95.8)	241(93.1)	245(93.5)	0.070
Clopidogrel n (%)	251(91.6)	243(93.1)	220(84.9)	235(89.7)	0.013
Beta-blocker n (%)	196(71.5)	186(71.3)	190(73.4)	204(77.9)	0.287
ACEI/ARB n (%)	210(76.6)	204(78.2)	208(80.3)	214(81.7)	0.489
Statin n (%)	237(86.5)	223(85.4)	219(84.6)	228(87.0)	0.853
GRACE Variables					
Age(years; median; IQR)	59.5(18.8)	63.5(17.4)	66.3(17.5)	68.3(18.2)	<0.001
HR bpm (median, IQR)	73(24)	76(27)	74(25)	81(28)	0.005
SBP (median, IQR)	137(31)	140(38)	139(38)	140(36.5)	0.196
Creatinine µmol/l(median, IQR)	94(21)	96(23)	100(24)	102(24.5)	<0.001
HF	8(2.92)	10(3.8)	11(4.25)	23(8.8)	0.009
ST segment depression	174(63.5)	197(75.5)	195(75.3)	199(75.9)	<0.001
Troponin rise	273(99.6)	260(99.6)	256(98.8)	258(98.5)	0.369
Cardiac Arrest	6(2.2)	11(4.2)	12(4.6)	13(5.0)	0.349
GRACE score					
Admission-6m Death (Median, IQR)	103(39)	114(40)	115(37)	119(43.3)	<0.001
Admission-6m Death/MI (Median, IQR)	154(48)	166(46)	167(48)	167(54.3)	<0.001
Discharge-6m Death (Median, IQR)	104(42)	115(39)	119(38)	123(42)	<0.001
Discharge-6m Death/MI (Median, IQR)	113(37)	113(37)	113(37)	131(45)	<0.001
GRACE Risk					
High	97(35.4)	117(44.8)	131(50.6)	149(56.9)	<0.001
Intermediate	89(32.5)	95(36.4)	88(34.0)	88(33.6)	0.810
Low	88(32.1)	49(18.8)	40(15.4)	25(9.5)	<0.001
Glucometabolic category					
NGT	267(97.5)	198(75.9)	0(0)	0(0)	<0.001
IGT	0(0)	56(21.5)	253(97.7)	61(23.3)	<0.001
NDM	7(2.6)	7(2.7)	6(2.3)	209(79.8)	<0.001
FPG (mmol/l; median; IQR)	4.9(0.6)	5(0.6)	5.1(0.8)	5.5(1.13)	<0.001
2HBG (mmol/l; median; IQR)	5.6(1.3)	7.4(0.7)	9.2(1.4)	12.3(3)	<0.001
MACE	30(10.9)	64(24.5)	67(25.9)	74(28.2)	-
Deaths	14(5.1)	24(9.2)	39(15.1)	35(13.4)	-
Re-infarctions	16(5.8)	40(15.3)	28(10.8)	39(14.9)	-

Table 2. Candidate predictors of event-free survival.

Covariate	HR	95% CI	P
Grace Score	1.01	1.01-1.02	<0.0001
2h-PG	1.09	1.04-1.14	0.000
Hypercholesterolaemia	0.66	0.47-0.92	0.014
Previous MI	1.50	1.05-2.14	0.024
Discharged without BB	1.39	1.02-1.88	0.035
FPG	0.85	0.71-1.01	0.063
Discharged without clopidogrel	1.35	0.95-1.93	0.098
Hypertension	1.25	0.95-1.64	0.115
Previous Revascularisation	1.35	0.90-2.01	0.149
Discharged without ACEI	1.29	0.91-1.83	0.154
Discharged without Aspirin	1.37	0.86-2.19	0.184
Female Gender	1.14	0.85-1.51	0.379
Discharge Diagnosis of STEMI	1.13	0.86-1.49	0.381
Discharged without statin	0.90	0.58-1.38	0.619
Current Smoker	0.94	0.70-1.25	0.655

Table 3. Akaike's Information criteria and Likelihood ratio test to determine the best fitting model for predicting MACE.

Akaike's Information criteria						Likelihood ratio test			
Model	AICc	δAICc	Relative Likelihood	wi	wj/wi	Model	X^2	df	p
GRS	1006.46	8.22	0.02	0.02	2.65	GRS vs.			
GRS+2HBS	998.24	0.00	1.00	0.98	162.07	GRS+2HBS	20.56	1	0.000
GRS+FBS	1008.41	10.18	0.01	0.01	1.00	GRS+FBS	0.21	1	0.645

AICc, corrected Akaike's information criteria; δAICc, delta AICc is a measure of each model relative to the best model; wi, Akaike weights, the ratio of δAICc values for each model relative to the whole set; wj/wi, Evidence ratios compare the wi of the "best" model and competing models to test the extent to which it is better than another.

Table 4

Table 4. Net reclassification improvement for model improvement with the addition of 2h-PG or FPG to GRACE score alone.

	Grace score vs Grace score and 2h-PG				Grace score vs Grace score and FPG			
	NRIe	NRIne	Total	p	NRIe	NRIne	Total	p
UP	110	312	422		143	481	624	
DWN	125	509	634		92	340	432	
TOTAL	235	821	1056		235	821	1056	
$NRI^{>0}$	-0.064	0.240	0.176	0.017	0.217	-0.172	0.045	0.541
	IDIe	IDIne	Total	p	IDIe	IDIne	Total	p
Final	0.0067	-0.0019	0.0087	0.008	0.0000	0.0000	0.0000	0.449

Figure

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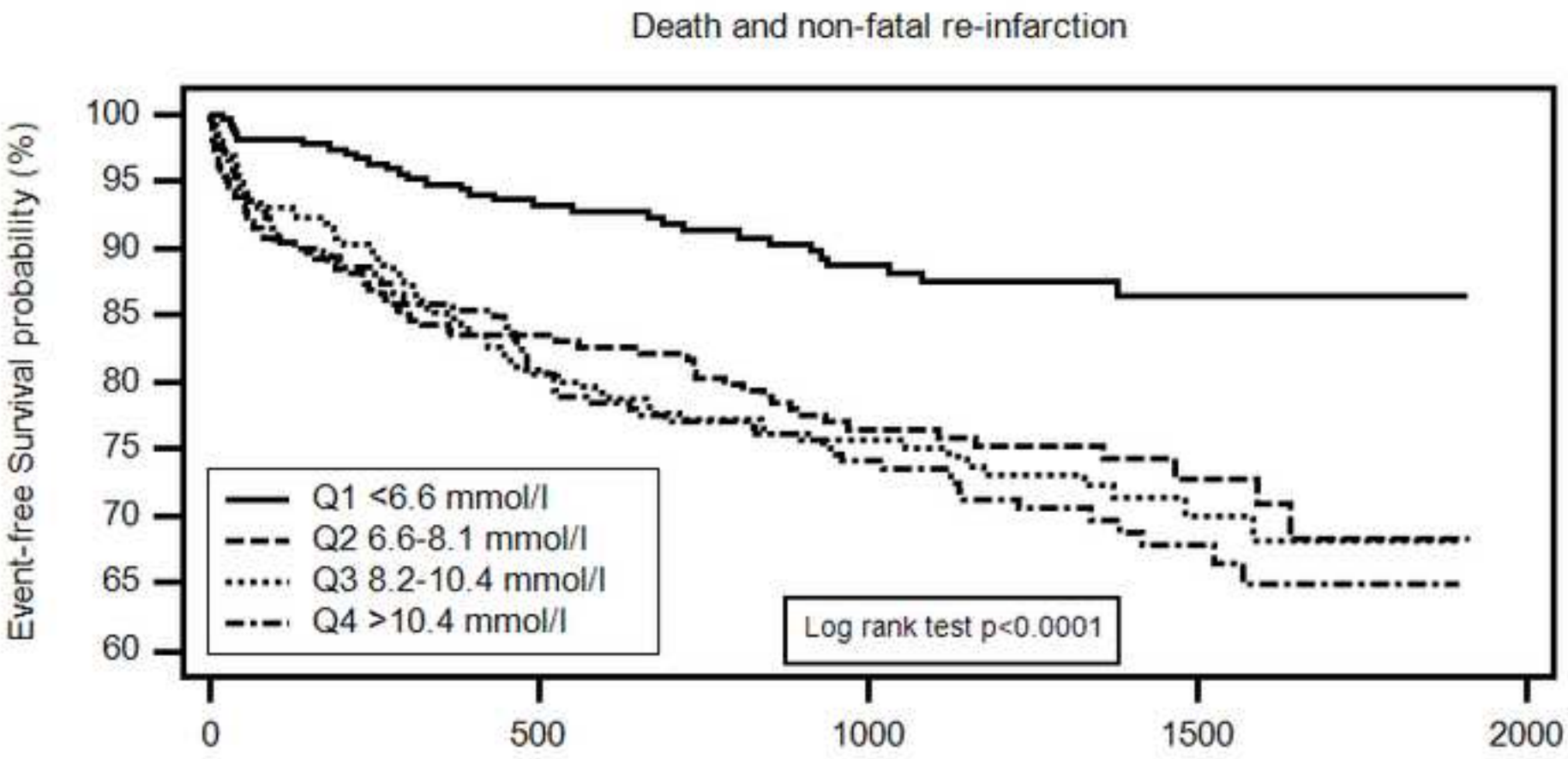

Number at risk

Group: Q1 <6.6 mmol/l				
274	223	157	59	0
Group: Q2 6.6-8.1 mmol/l				
261	202	152	47	0
Group: Q3 8.2-10.4 mmol/l				
259	185	134	50	0
Group: Q4 >10.4 mmol/l				
262	186	140	57	0

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Abstract

Aims

Global Registry of Acute Coronary Events (GRACE) risk score (GRS), a powerful predictor of prognosis after ACE, does not include a glucometabolic measure. We investigate whether 2 hour post-load plasma glucose (2h-PG) could improve GRS based prognostic models in ACE patients without known diabetes mellitus (DM).

Methods

Retrospective cohort study of 1056 ACE survivors without known DM who had fasting (FPG) and 2h-PG measured pre-discharge. Death and non-fatal myocardial infarction (MI) were recorded as major adverse cardiac events (MACE) during follow up. GRS for discharge to 6 months was calculated. Cox proportional-hazards regression was used to identify predictors of event free survival. The predictive value of 2h-PG alone and combined with GRS was estimated using Likelihood ratio test, Akaike's Information criteria, continuous net reclassification improvement ($NRI^{>0}$) and integrated discrimination improvement (IDI).

Results

During 40.8 months follow up 235 MACEs (22.3%) occurred, more frequently in the upper 2h-PG quartiles. 2h-PG, but not FPG, adjusted for GRS independently predicted MACE (HR 1.091; 95 % CI 1.043-1.142; p=0.0002). Likelihood ratio test showed that 2h-PG significantly improved the prognostic models including GRS (χ^2=20.56, 1 df, p=0.000). Models containing GRS and 2h-PG yielded lowest corrected Akaike's Information criteria, compared to that with only GRS. 2h-PG, when added to GRS, improved net reclassification significantly ($NRIe^{>0}$ 6.4%, $NRIne^{>0}$ 24%, $NRI^{>0}$ 0.176, p = 0.017 at final follow up). 2h-PG, improved integrated discrimination of models containing GRS (IDI of 0.87%, p=0.008 at final follow up).

Conclusion

2h-PG but not FPG is an independent predictor of adverse outcome after ACE even after adjusting for the GRS. 2h-PG, but not FPG, improves the predictability of prognostic models containing GRS.