Post-load glucose spike but not fasting glucose determines prognosis after myocardial infarction in patients without known or newly diagnosed diabetes.

Running Title: Post-load glucose spike and post-MI prognosis

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Abstract
Background: Effect of post- load glucose spike (PGS), the difference between 2-hour post-load (2h-PG) and fasting plasma glucose (FPG), on post-MI prognosis in non-diabetic patients is unexplored.
Method: Retrospective cohort analysis of 847 non-diabetic post-MI survivors who underwent pre-discharge oral glucose tolerance test (median PGS: 2.4 mmol/l). Patients, divided into unmatched Groups 1 and 2 (PGS ≤ and >2.4 mmol/l) and propensity score matched Groups 1M and 2M (355 pairs assembled from the overall cohort) were compared. Major adverse cardiac events (MACE: death and non-fatal reinfarction) were recorded during follow up (median: 3.4 yrs). Event freesurvival was compared by Kaplan–Meier method. Multivariate Cox proportional hazard regression determined predictors of MACE. C-statistics (δAUC), continuous net reclassification improvement ($NRI_{>0}$) and integrated discrimination index (IDI) were used to compare models.
Results: MACE was higher in Groups 2 (27.3% v 14.2%, p<0.001) and 2M (24.5% v 15.5%, p<0.001). Event free survival was worse in Groups 2 (HR 2.01, 95% CI 1.49 to 2.71, p<0.001) and 2M (HR 1.63, 95% CI 1.17 to 2.27, p=0.004). PGS independently predicted MACE free survival in the whole (HR 1.16, 95% CI 1.06 to 1.26, p=0.002) and matched cohort (HR 1.12, 95% CI 1.02 to 1.24, p=0.021). PGS, but not FPG or 2h-PG, improved the predictive performance of base model (δAUC 0.013, p=0.046) with greater improvement seen when PGS was added compared to 2h-PG (δAUC 0.005, p=0.034, $NRI_{>0}$ 0.2107, p=0.013, IDI 0.0042, p=0.046).
Conclusion: PGS is better predictor of post-MI prognosis than 2h-PG in non-diabetic patients.

Highlights

1. The first study to suggest that post-load glucose spike (PGS) defined as the difference between 2 hour post-load and fasting glucose measured after MI is robust enough to predict post MI prognosis in patients without known or newly diagnosed diabetes.
2. In patients without diabetes, PGS is a stronger determinant of post-MI prognosis than 2-hour post-load glucose.

Keywords:
Diabetes mellitus, Oral glucose tolerance test, Myocardial infarction, Acute coronary syndrome, Glucose spike, Glucose excursion

Background

The adverse effect of post-load glucose on post-MI prognosis in patients with newly diagnosed diabetes mellitus (NDM) or pre-DM (pDM) is well established.[1-16]However, the effect of post- load glucose spike (PGS), defined as the difference between fasting (FPG) and 2-hour post-load plasma glucose (2h-PG), on post-MI prognosis in non-diabetic patients has not been studied. The adverse prognostic effect of PGS in non-diabetic population was suggested in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE)study[17] where the number of deaths in patients increased as the difference between the fasting and 2h-PG increased. PGS, but not FPG or HbA1c, in non-diabetic subjects is positively associated with extent and progression of atherosclerosis [18-22], coronary plaque and plaque vulnerability. [23-27]

Glycaemic variability (GV), that has been used to characterise hyperglycaemic spikes or 'excursions' especially following meals using continuous glucose monitoring (CGM) or self monitoring of blood glucose (SMBG) adversely affected post-ACS prognosis in some [28-31] but not other studies.[32-34] A third to two-thirds of the patients included in these studies had diabetes mellitus (DM), a group where post-ACS prognosis is already known to be worse than in those without. GV is not identical to PGS, measuring it is cumbersome; requiring specialised equipment for CGM or frequent needle pricks for SMBG and denotes relative variability in blood glucose and not the absolute magnitude of glycaemic spikes. Such monitoring can only be justified in patients with known DM or at least admission hyperglycaemia to assist clinicians in titrating therapies and where monitoring hypoglycaemia is as important as hyperglycaemia. Its use only to determine post-ACS prognosis in patients without diabetes is difficult to argue for. We undertake this study to assess whether a single measure of post-challenge glucose spike is robust enough to predict post-ACS prognosis in patients without known or newly diagnosed diabetes.

Methods

Study Population

We retrospectively analysed data on consecutive MI survivors not known to have DM discharged from our institution between November 2005 and October 2008 who underwent pre-discharge oral glucose tolerance test (OGTT), collected for the Myocardial Infarction National Audit Project. A standardised dataset that included age, gender, risk factors for coronary artery disease (CAD), past medical history including history of previous MI and revascularisation, all medications, troponin I, haemodynamic status, creatinine level, presence of heart failure and ECG changeswas analysed. The Global Registry of Acute Coronary Events (GRACE) risk score (GRS) for mortality and re-infarction up to 6months post-discharge was calculated using a web-based calculator. Patients underwent routine OGTT on or after 3 days of admission. FPG was measured after ≥8 hours of overnight

fasting and 2h-PGwas measured 2 hours after administration of 75g glucose in 200 ml water. Patients who did not tolerate or refused OGTT and those transferred to others centres before OGTT were not considered for the study. Patients with pre-DM were advised lifestyle changes in the cardiac rehabilitation clinic and flagged up for surveillance with their family physicians.

Definitions

MI was defined according to the universal definition.[35] Diabetes was labelled as “known” if the patient gave a history, it was recorded in there medical notes or was on treatment. Patients without “known diabetes” were not screened with HbA1c as not recommended at the time of data collection.[36-38] All the patients with NDM (FPG ≥ 7.0 and/or 2-h PG ≥ 11.1 mmol/l) were excluded from the analysis. The rest of the patients with NGT: FPG <6.1 mmol/l and 2-h PG <7.8 mmol/l, IFG: FPG 6.1-6.9 mmol/l and 2h-PG <7.8 mmol/l and IGT: FPG <5.6 mmol/l and 2h-PG 7.8-11 mmol/l patients were included in the study. The post-glucose spike (PGS) was defined as the difference between the 2h-PG and FPG. The study population was divided into two groups; Group 1: PGS ≤ median PGS (2.4 mmol/l) and Group 2: PGS > 2.4 mmol/l. To mitigate the differences in the baseline characteristics that are likely to affect prognosis of the patients, propensity score matching was used to assemble a paired cohort of patients in the two groups (Group1M and Group2M) with similar baseline characteristics.

Follow up

Hospital and general practice patient records were manually checked for the first occurrence of major adverse cardiovascular events (MACE) defined as death or non-fatal re-infarction, over the follow up period of 5 years (median 3.4 years). Completeness of follow up was carefully ensured by manual review of hospital and general practice records. Mortality data was verified from the general practice records linked to the national death registry. The East Yorkshire and North Lincolnshire Research Ethics Committee waived the need for formal ethical approval and patient consent as this was a retrospective analysis of routine data collected for the national audit.[9]

Statistics

Continuous variables are presented as medians (inter-quartile range, IQR) and categorical variables as counts and proportions. The baseline characteristics in the patients in the Groups were compared with Mann-Whitney test for continuous variables and chi-squared test for categorical variables. Kaplan–Meier method and log-rank test was used to compare the event free survival. Regression models were adjusted for covariates in the conventional fashion for the “overall” analysis for the whole cohort. Logistic regression was used to compare the incidence of MACE in the two groups. Multivariate Cox proportional hazard regression modelling was used to analyse the effect of several variables on event free survival. The base modelincluded the following co-variates: 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, inpatient revascularization status and GRS for 6months from discharge for death and MI. Variables already included in the GRS were not included separately. Hazard ratios with associated 95% confidence intervals (CIs) are reported. Any covariate with variance inflation factor (VIF) >4 (MedCalc Statistical Software version 17.0.4, Ostend, Belgium), were not included in the same model to avoid the effect of multicollinearity. 2h-PG and PGS (VIF 9.8 in the whole cohort) were not included in the same model.

Logistic regression models, created by adding PGS, 2h-PG and FPG individually and in combinations to the base model, were used to calculate predicted probabilities of MACE for each subject. Improvement in the predictive performance of the restricted models on addition of a covariate was examined from these predicted probabilities using different tests of improvement in discrimination: increase in the area under the receiver operating

characteristic curve (AUC) (MedCalc Statistical Software version 17.0.4, Ostend, Belgium), category-free continuous net reclassification index ($cNRI_{>0}$) and integrated discrimination improvement (IDI). Without pre-defined clinical risk thresholds for the models categorical NRI was not used. The event (NRIe) and non-event NRI (NRIne) are the net percentage of patients with and without MACE correctly assigned a higher and lower predicted risk by the newer model with the added covariate, respectively. The overall NRI is the sum of the net proportions of individuals with and without MACE correctly assigned a different predicted risk and is reported as a number. The IDI is defined as the mean difference in predicted risks between those with and without events.

Propensity-matching was done for the matched part only. Propensity scores were computed for the whole cohort from above logistic regression models using all the covariates included in the base models except the glycaemic matrices. Bipartite matching with 1:1 ratio was performed using greedy algorithm with a fixed calliper to construct a paired cohort of patients from Group 1 and 2. The outcomes in these two matched groups were compared.

Results

Baseline characteristics

After exclusion of 206 patients with newly diagnosed DM, 847 patients were included in the study, of which 469(55.4%) had NGT, 6 IFG, 23 IFG combined with IGT and 349 isolated IGT. PGS was 1.5 (IQR 0.8 to 2.1) in the NGT group, and 4.0 (IQR 3.3 to 5.0) in the pDM group. The median PGS for the entire cohort was 2.4 mmol/l (95% CI 2.3 to 2.6). There were 430 patients in Group 1 (PGS≤2.4 mmol/l) and 417 in Group 2 (PGS>2.4 mmol/l). The matched groups had 355 patients each with PGS ≤2.4 mmol/l (Group 1M) and PGS >2.4 mmol/l (Group 2M). The median PGS for Group1M was 1.3 mmol/l and Group 2M was 3.9 mmol/l. The baseline characteristics of the whole and the matched cohort are presented in Table 1.

Outcomes

During a median follow up of 3.4 years, MACE was higher in Group 2 compared to Group 1, both in the unmatched and matched groups (Table 1). Event free survival was lower in group 2 and 2M than in group 1 and 1M respectively (Fig 1). Group 2 (HR 1.75, 95% CI 1.26 to 2.42, p<0.001) and 2M (HR 1.70, 95% CI 1.21 to 2.41, p=0.003) independently predicted MACE. PGS, as a continuous variable was a predictor of MACE free survival when adjusted for several covariates for the unmatched and matched groups (Table 2). With every mmol/l increase in PGS, there would be a 16% and 12% increase in the probability of MACE (Table 2).

The c-statistic of the base model increased from 0.744 (95% CI 0.713 to 0.773) to 0.757 (95% CI 0.727 to 0.786) on addition of PGS, δAUC 0.013, p=0.046 but not on addition of FPG 0.747, (95% CI 0.716 to 0.776), δAUC 0.003, p=0.143 or 2h-PG 0.752 (95% CI 0.722 to 0.781), δAUC=0.008, p=0.146.The c-statistics was higher when PGS was added to the base model compared to when 2h-PG was added, δAUC 0.005, p=0.034. Addition of PGS to models containing only GRS or GRS and FPG, in association with other co-variates improved their predictive performance as measured by $NRI_{>0}$ and IDI (Table 3). Within the whole cohort, PGS improved net reclassification by 28% when added to the model containing GRS only. Addition of PGS to the model containing GRS and FPG resulted in net reclassification improvement of 25.5%. Discrimination improved in a similar pattern. These improvements were not seen with addition of FPG. There was a greater improvement in the predictive performance of the base model when PGS was added to it compared to when 2h-PG was added ($NRI_{>0}$ 0.2107, p=0.013, IDI 0.0042, p=0.046). This suggests that PGS is a more powerful indicator of post-MI prognosis that 2h-PG itself.

Discussion

Several studies report worse post-MI prognosis in patients with newly diagnosed DM and pre-diabetes[1-16] with the 2h-PG being a better predictor than FPG.[9;12;15;16]The relation between post-challenge glucose spike and post-MI prognosis in patients without known or newly diagnosed DM had not been studied. This is the first study to suggest that post-load blood glucose spike is an independent determinant and a better predictor of post-MI prognosis in these patients.

The effect of post-glucose spike defined as the difference between the fasting and 2 hour post-challenge glucose levels on prognosis in non-diabetic population was suggested in the DECODE study.[17] The largest number of excess deaths occurred in individuals with FPG ≤6.1 mmol/l and high glucose spike in terms of increase from baseline to 2−h glucose value. The number of deaths in patients without newlydiagnosed DM increased as the difference between the fasting and 2h-PG increased. This is the first study to suggest this in a post-MI population. In the Diabetes Control and Complications Trial diabetic patients with similar HbA1c treated conventionally had a higher risk of complications than those treated intensively.[39] Although extent of postprandial glycaemic excursions was speculated as a possible cause, subsequent reanalysis explained the results by the differences in mean HbA1c between treatment groups over time.[40] In our patients PGS as a continuous variable was a stronger predictor of prognosis than 2h-PG itself.

The effect of post-MI stress on glycaemic status makes the timing of OGTT relevant. Glucometabolic abnormalities are overestimated when measured within the first 24 hours after STEMI.[5;41;42] However, the stress response subsidesbetween 2-5 days with no further decrease thereafter.[43] OGTT results are more reproducible in patients with subendocardial rather than transmural infarctions.[44]OGTT in this study was done ≥ 3 days after admission and 55% of our patients had NSTEMI. Thus the glucose measurements are likely to be reproducible. More importantly, as PGS is the difference between 2h-PG and FPG, both of which are increased by stress, PGS unlikely to have been overestimated. This may be an advantage of measuring PGS rather than 2h-PG to mitigate the effect of stress on the glycaemic matrices.

Glycaemic variability (GV) has variably been implicated in adverse post-MI outcomes. MAGE during the first 72 hours of admission predicted MACE in anelderly ACS population 54% of whom had DM.[28] In STEMI patients with and without DM undergoing primary PCI, MAGE was associated with short term MACE.[29;30] in another study, MAGE predicted post-ACS events only by marginal significance driven solely by its effect on events in patients with DM and did not improve the predictive performance of models not containing MAGE.[31] In a large cohort of STEMI and NSTEMI patients, 38% of whom had DM, none of the GV matrices during first 48 hours of hospital admission was associated with overall adjusted in-hospital mortality. GV was associated with mortality in STEMI but not NSTEMI patients.[32] In the Diabetic Patients With Acute Myocardial Infarction study, prognsis did not relate to GV in DM patients with AMI treated with insulin infusion.[33] In patients with DM, GV did not predict post-MI mortality.[34]

GV is not identical to PGS. GV refers to fluctuation in glucose levels, typically characterized by hyperglycaemic spikes or ‘excursions’ following meals and quantified, as the standard deviation of plasma glucose levels, the interquartile range, or the mean amplitude of glycaemic excursion (MAGE). Measuring GV is cumbersome; requiring specialised equipment for continuous glucose monitoring (CGM) or frequent needle pricks for self monitoring of blood glucose (SMBG). This may be justified in the patients with DM where therapy tailored to the daily variations in blood glucose is required. This is not an appropriate test in patients without DM to assess their post-MI prognosis. MAGE only yield data about relative variability in blood glucose and not the absolute magnitude of glycaemic spikes. Our data suggests that in patients with known or newly diagnosed DM, the amplitude of a single

post-load glucose spike is sufficient to predict post-MI prognosis negating the need for GV measurements.

PGS, defined as the difference between the 2 hour post-load and fasting glucose level during OGTT, adversely affects atherosclerosis. PGS, but not FPG or HbA1c, is positively associated with carotid intima-media thickness, after adjustment for other co-variates, both in patients without [19-22] and with DM.[45] Progression of coronary atherosclerosis in non-diabetic, non-glucose-intolerant patients with coronary artery disease is associated with 2-hour post challenge glucose peak but not fasting glucose.[18] Glucose spikes can accelerate atherosclerotic lesion formation in non-diabetic mice model exposed to repetitive glucose infusion.[46;47]High GV, after ACS, has been associated with progression of coronary plaque and plaque vulnerability.[23-27] PGS is likely to affect the post-MI prognosis via these pathophysiological mechanisms.

Limitation

The study is limited by its retrospective observational design. This has been partially mitigated by comparing matched groups. Although every effort was made to ensure completeness of the data from hospital and general practice databases informationrecorded incompletely could not be used. Exclusion of a small number of patientsthat could not have the OGTT and mainly Caucasian study population could affect the generalizability of the results. All patients with known or newly diagnosed DM were excluded. Even without the use of admission HbA1c, undiagnosed DM is unlikely to have been missed using OGTT. Thus it is certain that the study cohort does not inadvertently include DM patients. Indicators of metabolic syndrome e.g. anthropometric measurements, assessment of insulin resistance etc. were not available and could have changed during the follow-up. OGTT was not repeated post-discharge. There is a possibility that patients may have crossed over between the two compared groups. However, the KM curves remain uniformly separated throughout follow up suggesting that the hazard assumption for the Cox analysis was proportional and therefore this is unlikely to have affected the results. As pre-DM is associated frequently with metabolic syndrome, in the absence of anthropometric measurements and other risk factors, it is unclear whether this affected outcomes.

Conclusion

In patients without known or newly diagnosed DM, post-load glucose spike is a determinant of post-MI. The post-load glucose spike is a stronger determinant of prognosis than 2-hour post-load glucose. This has important clinical implications. Firstly, to adequately prognosticate post-MI patients without diabetes, FPG alone is inadequate and 2h-PG is needed. Secondly, a single post-load glucose spike may obviate the need for cumbersome measurement of glycaemic variability that is very difficult to justify in non-diabetic patients. Thirdly, lifestyle interventions may have to be implemented in patients with high PGS even with normal glucose tolerance to prevent the development of diabetes. And finally, trials of SGLT2 inhibitors and GLP-1 receptor agonist may be needed to assess where blunting the PGS would improve post-MI prognosis.

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Figure Legend
Figure 1. Kaplan-Meier curves showing survival free of MACE in the unmatched (A) and matched (B) Groups divided by the median post-load glucose spike in each cohort. Group 1 ≤ median, Group 2 > median.

Table 1. Baseline characteristics of patients.

	Group 1 PGS≤2.4 n=430	Group 2 PGS>2.4 n=417	p	Group 1M PGS≤2.4 n=355	Group 2M PGS>2.4 n=355	p
Male n (%)	294(68.4)	311(74.6)	0.046	237(66.8)	269(75.8)	0.008
Current smoker n (%)	166(38.6)	134(32.1)	0.049	126(35.5)	121(34.1)	0.693
Hypertension n (%)	141(32.8)	171(41.0)	0.013	127(35.8)	133(37.5)	0.640
Hypercholesterolaemia n (%)	87(20.2)	101(24.2)	0.163	71(20.0)	82(23.1)	0.315
Previous AMI n (%)	58(13.5)	86(20.6)	0.006	52(14.7)	52(14.7)	1.000
Previous revascularisation n (%)	29(6.7)	41(9.8)	0.103	23(6.5)	25(7.0)	0.765
Previous PVD n (%)	16(3.7)	14(3.4)	0.775	11(3.1)	12(3.4)	0.832
Previous CVA n (%)	13(3.0)	20(4.8)	0.183	9(2.5)	13(3.7)	0.386
Normal LVEF	364(84.6)	341(81.8)	0.262	299(84.2)	295(83.1)	0.685
Diagnosis NSTEMI n (%)	249(57.9)	218(52.3)	0.099	205(57.7)	185(52.1)	0.131
Discharge Medications						

Aspirin n (%)	418(97.2)	393(94.2)	0.033	345(97.2)	338(95.2)	0.169
Clopidogrel n (%)	396(92.1)	367(88.0)	0.047	283(79.7)	284(80.0)	0.925
Beta-blocker n (%)	310(72.1)	311(74.5)	0.413	254(71.6)	270(76.1)	0.172
ACEI/ARB n (%)	332(77.2)	335(80.3)	0.266	274(77.2)	288(81.1)	0.196
Statin n (%)	373(86.7)	357(85.6)	0.633	309(87.0)	304(85.6)	0.585
GRACE variables						
Age years (median, IQR)	60.4(18.5)	66.9(17.4)	<0.001	62.0(18.7)	64.7(16.3)	0.070
Heart rate bpm (median, IQR)	75(25)	74(26)	0.707	76(25)	74(25)	0.427
SBP mmHg (median, IQR)	139(32)	138(39)	0.506	139(32.0)	138(38.0)	0.477
Creatinine µmol/l (median, IQR)	94(22)	99(24.5)	<0.001	93(21.8)	98(21.0)	<0.001
Heart failure n (%)	15(3.5)	20(4.8)	0.339	12(3.4)	10(2.8)	0.665
ST segment depression n (%)	295(68.6)	307(73.6)	0.108	245(69.0)	266(74.9)	0.079
Troponin rise n (%)	429(99.8)	413(99.0)	0.168	355(100.0)	352(99.2)	0.083
Cardiac Arrest n (%)	14(3.3)	18(4.3)	0.418	11(3.1)	17(4.8)	0.247
GRACE Score						
Admission-6m Death (median, IQR)	105(39.0)	116(39.0)	<0.001	109(39.3)	113(35.7)	0.196
Admission-6m Death/MI (median, IQR)	157(47.0)	167(50.0)	<0.001	157(44.5)	164(28.0)	0.148
Discharge-6m Death (median, IQR)	108(41.0)	119(38.0)	<0.001	112(40.0)	116(35.0)	0.0138
Discharge-6m Death/MI (median, IQR)	113(37.0)	123(48.0)	<0.001	113(37.0)	113(37.0)	0.250
Glucose levels						
FPG (mmol/l) (median, IQR)	4.9(0.6)	5.0(0.7)	0.003	4.9(0.6)	5.0(0.7)	0.122
2h-PG (mmol/l) (median, IQR)	6.25 (1.5)	9.0(2.0)	<0.001	6.3(1.4)	8.9(2.0)	<0.001
Post load glucose spike (mmol/l)	1.3(1.2)	3.9(1.9)	<0.001	1.3(1.1)	3.9(1.9)	<0.001
NGT n (%)	408(94.9)	61(14.6)	<0.001	337(94.9)	51(14.4)	<0.001
MACE n (%)	61(14.2)	114(27.3)	<0.001	55(15.5)	87(24.5)	0.003
Deaths n (%)	25(5.8)	60(14.4)	<0.001	32(9.0)	44(12.4)	0.145
Re-infarctions n (%)	36(8.4)	54(12.9)	0.031	23(6.5)	43(12.1)	0.010

AMI, Acute myocardial infarction; PVD, peripheral vascular disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; NSTEMI' non-ST elevation myocardial infarction; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; HR, heart rate; SBP, systolic blood pressure; FPG, fasting plasma glucose; 2HBG, 2 hour plasma glucose; NGT, normal glucose tolerance; MACE, major adverse cardiovascular events.

Table 2.. Predictors of major adverse cardiovascular events.

	Whole Cohort			Matched Cohort		
Covariate	HR	95% CI	P	HR	95% CI	P
Discharged without Aspirin	1.77	1.02 to 3.06	0.043	1.56	0.81 to 3.03	0.182
Discharged without clopidogrel	1.58	1.03 to 2.42	0.035	1.98	1.17 to 3.34	0.012
GRACE Score	1.01	1.01 to 1.01	<0.001	1.01	1.01 to 1.02	<0.001
Previous AMI	1.95	1.29 to 2.94	0.001	1.88	1.16 to 3.05	0.010

Hypercholesterolaemia	0.67	0.45 to 0.99	0.043	0.66	0.43 to 1.02	0.063
Post load glucose spike	1.16	1.06 to 1.26	0.002	1.12	1.02 to 1.24	0.021

The full model included 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, inpatient revascularization status and GRACE risk score, fasting plasma glucose. Abbreviations as in the text.

Table 3. Net reclassification index and integrated discrimination index for model improvement with the addition of PGS or FPG to the model with only GRACE score.

	All patients			
	EVENT	NONEVENT	TOTAL	p
GRS v GRS+FPG				
UP	93	331	424	
DOWN	82	341	423	
TOTAL	175	672	847	
NRI	0.0628	0.0149	0.0777	0.3597
GRS v GRS+PGS				
UP	93	263	356	
DOWN	82	409	491	
TOTAL	175	672	847	
NRI	0.0628	0.2173	0.2801	<0.0001
GRS+FPG v GRS+FPG+PGS				
UP	90	260	350	
DOWN	85	412	497	
TOTAL	175	672	847	
NRI	0.0286	0.2262	0.2548	0.0027
	IDIe	IDIne	IDI	p
GRS v GRS+FPG				
	0.00022	-0.00004	0.00026	0.8143
GRS v GRS+PGS				
	0.00736	-0.00189	0.00925	0.0299
GRS+FPG v GRS+FPG+PGS				
	0.00766	-0.00197	0.00964	0.0260

NRI, net reclassification index; UP, number of patients with and without event whose probability of MACE increased with adding a variable to the restricted model; DOWN, number of patients with and without event whose probability of MACE decreased with adding a variable to the restricted model; IDIe, integrated discrimination index event; IDIne, integrated discrimination index non-event.