Title: Two hour post-challenge glucose is a better predictor of adverse outcome after myocardial infarction than fasting or admission glucose in patients without diabetes.

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Abstract

Background: We evaluate prevalence of new abnormal glucose tolerance (AGT) in post MI survivors without known DM if guidelines are followed and compare the ability of admission (APG),fasting (FPG) and 2 hour post-load plasma glucose (2h-PG) to predict prognosis.

Methods: 674 patients were followed up of 4 years for incidence of major adverse cardiovascular events (MACE) of cardiovascular death, non-fatal re-infarction or non-haemorrhagic stroke. Ability of logistic regression models including APG, FPG and 2h-PG alone or in combination to predict MACE were compared.

Results: 93-96% of impaired glucose tolerance and 64-75% of DM on OGTT would be missed with current guidelines. 134 MACEs recorded, higher in the upper quartiles of 2h-PG. The 2h-PG and FPG included individually into Cox proportional hazard regression models, predicted MACE. When included simultaneously, only 2h-PG predicted MACE (HR 1.12, CI 1.04-1.20, p=0.0012), all cause mortality (HR 1.17, CI 1.05 - 1.30, p=0.0039), cardiovascular mortality (HR 1.17, CI 1.02 - 1.33, p=0.0205) and non-fatal MI (HR 1.10, CI 1.01 - 1.20, p=0.0291). Adding 2h-PG significantly improved ability of models including FPG ($\chi 2$ = 16.01, df = 1, p = 0.0001) or FPG and APG ($\chi 2$ = 17.36, df = 1, p = 0.000) to predict MACE. Addition FPG or APG to models including 2h-PG did not improve its predictability. Model including 2h-PG only with other covariates had the lowest Akaike's information criteria and highest Akaike weights suggesting that this was the best in predicting events. Adding 2h-PG to models including FPG or APG with other co-variates yielded continuous net reclassification improvement of 0.22 (p = 0.026) and 0.27 (p = 0.005) and categorical net reclassification improvement of 0.09 (p = 0.032) and 0.12 (p = 0.014) respectively. Neither FPG nor APG improved net reclassification of model including 2h-PG. Adding 2h-PG to models including only FPG, only RPG and both yielded integrated discrimination improvement of 0.012 (p= 0.015), 0.022 (p = 0.001) and 0.013 (p = 0.014) respectively.

Conclusion: AGT is under-diagnosed on current guidelines. FPG and APG are not predictors of prognosis when considered with 2h-PG. 2h-PG is seemingly a better predictor of prognosis compared to APG and FPG.

Keywords: diabetes, myocardial infarction, acute coronary syndrome, oral glucose tolerance, impaired glucose tolerance, prognosis, glycated haemoglobin, glycosylated haemoglobin,

Background

Current guidelines [1,2] do not recommend routine use of oral glucose tolerance test (OGTT) to identify abnormal glucose tolerance (AGT) in patients without known diabetes mellitus (DM) admitted with acute coronary syndromes (ACS). These guidelines are not based on prognostic studies.[3-7]. It is reasonable to suggest that the most important measure of the glucometabolic state would be the one that determines long term prognosis after ACS.

Elevated admission (APG), [8-13] fasting plasma glucose (FPG), [14-21] admission glycosylated haemoglobin (HbA1c)[22-26] and newly diagnosed AGT [27-31] after myocardial infarction (MI) and ACS in patients without known DM adversely affect prognosis. However, the ability of APG, FPG and 2 hours post-load plasma glucose (2h-PG) to predict post-ACS prognosis in same group of patients without known DM has not been evaluated. Studies exploring relationship between abnormal APG, FPG or 2h-PG and prognosis, have done so using dichotomous groupings e.g. those above and below a cut-off point [27] or conventional classifications of normal (NGT) or impaired glucose tolerance (IGT) and new DM (NDM)[28-35] rather than through a study of the predictability of these measurements as continuous variables. Furthermore, information on the independent effect of 2h-PG on prognosis is limited.[28,29,33]

In the present study, we evaluate the effect of the current guidelines on the prevalence of new AGT in patients with ACS and compare the predictive value of APG, FPG and 2h-PG on prognosis after MI in patients without known DM.

Methods

As reported,[31] we retrospectively analysed standard dataset collected locally for the Myocardial Infarction National Audit Project (MINAP) on 768 consecutive post MI [36] survivors admitted between November 2005 and October 2008 without known DM who

underwent pre-discharge OGTT. This study includes patients for whom APG, FPG and 2h-PG were available.

"Known DM" was diagnosed from history i.e. the patient had been informed of the diagnosis by a physician before the admission or was on anti-diabetic treatment. HbA1c was not used in diagnosing pre-hospital diabetes as it was not recommended in contemporary guidance. [37-39] FPG and OGTT were done on/after the third day of admission. We defined admission hyperglycaemia (AH) as APG ≥7.8 mmol/l [5] and DM as APG >11.1 mmol/l.[40] The patients were classified as normal glucose tolerance (NGT), impaired fasting glucose (IFG), IGT and NDM as follows: normal glucose tolerance (NGT): FPG <6·1 mmol/l and a 2-h PG <7·8 mmol/l; imapired fasting glucose (IFG): FPG 6·1–6·9 mmol/l and 2-h PG <7·8 mmol/l; IGT: FPG <7 mmol/l and 2-h PG 7·8–11 mmol/l. NDM: FPG ≥7·0 and/or 2-h PG ≥11·1 mmol/l. The patients were divided into quartiles of 2h-PG. The patients with IGT and NDM were advised lifestyle modification including diet, physical activity and referred to the diabetologists for appropriate out-patients management.

All participants were followed up for a median of 48 months for outcomes. Completeness of follow up was ensured by manual review of hospital and general practice records. The first occurrence of an adverse event was obtained from hospital and general practice records and confirmed by the office of public health intelligence. The major adverse cardiovascular event (MACE) was defined as cardiovascular death, non-fatal re-infarction or non-haemorrhagic stroke. Cardiovascular death was defined as death from MI, heart failure or sudden death. A non-fatal re-infarction was a non-fatal MI occurring later than 72 h after the index infarction. Stroke was defined as a neurological deficit persisting >24 hours as observed by a physician with radiological confirmation. As this study retrospectively analysed routinely collected anonymised data on standard clinical practice for MINAP, the East Yorkshire and North Lincolnshire Research Ethics Committee confirmed that formal patient consent and ethical approval was not required. [31]

Statistics

Continuous variables are presented as mean±SD and median (interquartile range, IR) and categorical variables as counts and proportions (%). The baseline characteristics of quartiles were compared using 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. Correlations were assessed with Spearman's rank correlation coefficient (ρ). Event-free survival curves were estimated by the Kaplan-Meier method compared using the Log-rank test. Cox proportional-hazards regression was used to analyse the effect of several variables on event free survival. Age, gender, smoking status, hypercholesterolemia, hypertension, history of previous MI, diagnosis at discharge, discharge prescription of aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and statins, revascularisation status, and glucometabolic status were "entered" into the model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported. 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 models including APG, FPG and 2h PG provided a significantly better fit than those with variables individually, in pairs and vice versa. Nested and non-nested models containing one of either APG, FPG, 2h-PG or a combination were compared using the corrected Akaike's information criterion (AIC_c), δAIC_c, Akaike weights (w_i) and evidence ratios to estimate of the probability that a given model is the best fitting model of those studied. [41,42]

Logistic regression analysis of models including APG, FPG and 2h-PG, individually and in combination, along with the other above covariates was used to compute the predicted

probabilities of MACE. The incremental predictive value of adding 2h-PG to models with APG and FPG was analyzed from these predicted probabilities using several measures: categorical (cNRI) and category-free continuous net reclassification improvement ($NRI^{>0}$) and integrated discrimination improvement (IDI). In the absence of clearly pre-defined clinical risk thresholds for the models, we opted not to use arbitrary cut-offs for risk. Instead, the predicted probabilities for the most restricted model were divided into quartiles to define the risk categories for calculating categorical NRI. The event (NRIe) and non-event NRI (NRIne) were defined as net percentage of persons with and without the event of interest correctly assigned a higher and lower predicted risk respectively. The overall NRI is the sum of NRIe and NRIne reported as a number. The IDI was defined as the mean difference in predicted risks between those with and without events.

Results

Of the 674 patients included, 70.3% had normal APG (Figure 1). Of those without AH 35.0% had IGT and 15.2% had NDM. Of those with AH, 79.0% had normal FPG, of which 47.5% and 18.4% had IGT and NDM respectively. AGT would be missed in 52.0% patients with AH without OGTT. If AH was not considered, 89.3% had normal FPG. Of these, 38.6% and 14.3% had IGT and NDM respectively. Thus IGT and NDM would be diagnosed only in 1.3% and 4.9% patients on following CG130[1] and 2.5% and 7.1% patients on following ESC Guidance[2] respectively. The clinical characteristics of patients in each 2h-PG quartiles are shown in Table 1. All the patients in the 1st quartile and 78.7% in the 2nd quartile had NGT; 21.3% in the 2nd quartile. All patients in the 3rd quartile and 22.7% in the 4th quartile had IGT. The rest in the 4th quartile had NDM. FPG was <6.1 mmol/l in 83.3% patients with 2h-PG ≥7.8 mmol/l

MACE and non-fatal MIs were higher in the upper glucose quartiles (Table 2). Event-free survival significantly reduced with increasing quartiles of 2h-PG even below the conventional

threshold for DM (Figure 2). There was only a moderate correlation between FPG and 2h-PG (ρ, 0.39, p<0.0001), FPG and RPG (ρ 0.33, p<0.0001) and RPG and 2h-PG (ρ 0.32, p<0.0001). The multicollinearity between these variables was low (VIF: FPG 1.56, 2h-PG 1.50 and APG 1.32). Thus they were included into Cox proportional hazard regression models individually and in combinations. When APG, FPG or 2h-PG were included individually with other covariates (Table 3), 2h-PG independently predicted all, FPG predicted some but APG did not predict any outcomes. The risk of adverse events increased by 9-19% for each mmol/l rise in 2h-PG and by 18-44% for each increasing quartile of 2h-PG. In a model including FPG, 2h-PG and APG, 2h-PG consistently remained an independent predictor of survival (Table 4) free of MACE (HR 1.12, CI 1.04-1.20, p=0.0012), all cause mortality (HR 1.17, CI 1.05 - 1.30, p=0.0039), cardiovascular mortality (HR 1.17, CI 1.02 - 1.33, p=0.0205) and non-fatal MI (HR 1.10, CI 1.01 - 1.20, p=0.0291) but neither FPG nor APG predicted events.

Nested models were compared using likelihood ratio tests to determine whether logistic regression models that included 2h-PG provided a significantly better fit than that limited to the APG, FPG or its combination (Table 5). This showed that addition of the 2h-PG significantly improved the ability of a model including FPG to predict MACE ($\chi 2$ = 16.01, df = 1, p = 0.0001), all deaths ($\chi 2$ = 7.75, df = 1, p = 0.005), cardiovascular deaths ($\chi 2$ = 4.90, df = 1, p = 0.027) and myocardial infarction ($\chi 2$ = 8.64, df = 1, p = 0.003). Addition of 2h-PG to models including FPG and APG improved the ability of the later to predict MACE ($\chi 2$ = 17.36, df = 1, p = 0.000), all deaths ($\chi 2$ = 7.85,, df = 1, p = 0.005), cardiovascular death ($\chi 2$ = 6.04, df = 1, p = 0.014) and MI ($\chi 2$ = 8.57, df = 1, p = 0.003). However, addition of FPG or APG to a model including 2h-PG did not improve its predictability.

The model including 2h-PG as the only measure of the glucometabolic state with other covariates had the lowest AICc and the highest w_i suggesting that these models were the best in predicting all events (Table 6). The δAICc suggests that addition of FPG or RPG to

these models worsen the AICc. Models with FPG or APG alone or in combination are inadequate. On comparing non-nested models (Table 7) containing FPG, APG and 2h-PG, the later consistently had the lowest AICc. It also has a 98% , 71%, 66% and 82% chance of being the “best” model among these for predicting MACE, all deaths, cardiovascular deaths and MI respectively.

The addition of 2h-PG to a logistic regression models including FPG or RPG with other co-variates to calculate risk of MACE at the end of follow up led to a continuous net reclassification improvement of 0.22 (p = 0.026) and 0.27 (p = 0.005) respectively. Adding 2h-PG to a model including FPG and RPG led to a $NRI^{>0}$ of 0.19 (p = 0.046). Addition of either FPG or RPG to a model including 2h-PG did not significantly improve net reclassification. Similarly addition of 2h-PG to models including FPG or RPG led to a categorical net reclassification improvement of 0.09 (p = 0.032) and 0.12 (p = 0.014) respectively. Addition of either FPG or RPG to a model including 2h-PG did not significantly improve net reclassification. Adding 2h-PG to models including only FPG, only RPG and both yielded IDI of 0.012 (p= 0.015), 0.022 (p = 0.001) and 0.013 (p = 0.014) respectively.

Discussion

Our study suggests that 1) AGT after an MI is under-diagnosed if current guidelines are followed, 2) FPG, but not APG, when considered alone independently predicts post-MI prognosis, 3) FPG ceases to be an independent predictor when included with 2h-PG in the same model and 4) 2h-PG may be a better independent predictor of prognosis compared to APG and FPG.

The prevalence of AGT resembles Euro Heart Survey[43] suggesting a true estimate. AGT is underestimated without OGTT.[5,28,31,44,45] If CG130[1] is followed, 70% of our patients would not have further tests. This proportion would increase if higher threshold of APG was used for AH. As plasma glucose is overestimated early after MI,[30,46] it is likely that

number of patients with abnormal FPG would decrease if more patients were tested later thus reducing the number of patients undergoing OGTT even further. If ESC Guidance[2] is followed, 89% of our patients would not have OGTT. HbA1c is unlikely to be raised in all of these patients with normal FPG. Thus a large proportion of these patients with normal HbA1c and FPG would not be offered further testing. Thus AGT after an MI would be substantially under-diagnosed if current guidelines are followed.

Current Guidelines are not based on prognostic studies.[3-7] This is the first study to assess the relative importance of APG, FPG and 2h-PG in determining post-MI prognosis in the same patients. Studies suggesting adverse post-MI prognosis in newly diagnosed AGT,[27-31,33,34] have not shown 2h-PG to be independent predictor of event-free survival. Moreover, the cut-offs defining glucometabolic categories suggested by WHO and ADA for epidemiological purposes may be somewhat arbitrary soon after an MI. As increasing plasma glucose is likely to affect post-MI prognosis as a continuum, it was important to test the relative ability of these measurements as continuous variables in predicting outcomes. Increasing tertiles of FPG even below conventional levels of abnormality independently affects prognosis.[15] The risk of events increase with each increasing quartiles of 2h-PG in our study. The 2h-PG independently affected outcomes even when included in the same model as the FPG and APG.

Epidemiological studies suggest that 2h-PG is better than FPG alone at identifying increased prognostic risk.[45,47,48] The relative value of FPG, APG and 2h-PG in predicting post-MI prognosis in the same population of patients had not been tested. Tamita et al[28,33] showed that neither APG nor FPG independently predicted MACE; the effect of 2h-PG was not reported. FPG may be a better predictor of prognosis than APG.[14,15] Ravid et al[20] suggested FPG was more important in predicting the course of the MI, than the results of OGTT. In our study, adding 2h-PG to models including APG and/or FPG significantly improved their ability to predict prognosis. The models containing 2h-PG yielded best AIC

and demonstrated a very high probability of representing the best model. Adding 2h-PG to logistic regression models containing FPG significantly improved the net reclassification and the integrated discrimination of these models. Thus 2h-PG may be a more powerful predictor of event-free survival than FPG or APG. The increased macrovascular morbidity associated with higher 2h-PG rather than FPG seen here may be related to progression of atherosclerosis demonstrated with post-challenge rather than fasting hyperglycaemia.[49-53]

Whether OGTT after MI reflects “true” glucometabolic state is debated. The pre-discharge glucometabolic category may[30,34,46] or may not[54,55] change with time. The infarct size and timing of OGTT may influence its ability to predict long term glucometabolic status.[30,46,54-56] The accuracy of pre-discharge OGTT in diagnosing NDM or IGT is pertinent for studies using OGTT to categorise patients to these groups.[27-31,33,34] As pre-discharge 2h-PG much below the conventional abnormal thresholds predicted risk of MACE irrespective of the categorisation of patients, the long term reproducibility of these categorisations may be less relevant when assessing prognostic risk. OGTT was done at least three days after the index event and 60% patients had NSTEMI. These two opposing influences may have limited the effect of stress dysglycaemia on our results.

HbA1c was not measured as per guidance.[37-39] Prevalence of HbA1c ≥ 6.5% is 5-7% in similar populations.[6,7,23,24] Thus most of our patients with normal FPG and HbA1c would not qualify for OGTT.[1,2] Consequently, a large proportion of AGT would be missed. HbA1c has predicted post-MI prognosis in some [23,57-59] but not all studies.[24,60-63] The 2h-PG, but not HbA1c, predicted prognosis in studies comparing the two [24,62] Kowalczyk et al suggest that the HbA1c may be useful in further risk stratifying patients diagnosed with new AGT but do not report the effect of HbA1c on prognosis of patients without AGT.[64] This suggests that usefulness of HbA1c in determining post-MI prognosis is seemingly unclear. HbA1c <6.5%, would leave many patients with undiagnosed AGT and unidentified

risk of future adverse events according to current guideline. HbA1c ≥6.5% may not predict risk. Under both conditions an OGTT may be useful to determine prognosis.

This study has the limitations of an observational study using retrospective analysis of data collected from a single centre. Although national death register was not consulted directly, a linked general practice database was used. Information recorded incompletely 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. However, as pre-discharge 2h-PG predicted post-MI outcomes, the reproducibility of these measurements and its relation to long term glucometabolic status may be less relevant when assessing prognostic risk.

Conclusion

New AGT after an MI is under-diagnosed on following current guidelines. 2h-PG is likely to be a better predictor of long term prognosis than FPG or APG, Although FPG may on its own independently predict long term prognosis, it ceases to be an independent predictor when considered with 2h-PG. An appropriately timed OGTT may be useful to determine long term prognosis in post-MI patients without known diabetes.

List of abbreviations

OGTT = oral glucose tolerance test

AGT = abnormal glucose tolerance

DM = diabetes mellitus

ACS = acute coronary syndromes

APG = admission plasma glucose

FPG = fasting plasma glucose

HbA1c = glycosylated haemoglobin

MI = myocardial infarction

2h-PG = 2 hours post-load plasma glucose

NGT = normal glucose tolerance

IGT = impaired glucose tolerance

NDM = new DM

MINAP = Myocardial Infarction National Audit Project

AH = admission hyperglycaemia

IFG = impaired fasting glucose

MACE = major adverse cardiovascular event

HR = Hazard ratios

CI = confidence intervals

VIF = variance inflation factor

AIC = Akaike's information criterion

AIC_c = corrected Akaike's information criterion

$\delta AIC_{c,}$ = delta corrected Akaike's information criterion

w_i = Akaike weights

cNRI = categorical net reclassification improvement

$NRI^{>0}$ = category-free continuous net reclassification improvement

NRIe = event net reclassification improvement

NRIne = non-event net reclassification improvement

IDI = integrated discrimination improvement

Declarations:

Ethics approval and consent to participate

The need for approval was waived.

Consent for publication

Not Applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

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Author Contribution:

JJ, SC conceived or designed the study. AG, SC contributed to acquisition, analysis, or interpretation of data. AG, SC drafted the manuscript. JJ, SC, TS critically revised the manuscript. AG, JJ, SC, TS gave final approval. AG, JJ, SC, TS agree to be accountable for all aspects of work ensuring integrity and accuracy..

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

	Q1,<6.6 (n=165)	Q2,6.6-8.1 (n=160)	Q3,8.2-10.5 (n=177)	Q4,>10.5 (n=172)	p
Age(years; median; IQR)	61(13)	64(17)	67(18)	69(20)	0.00
Male n (%)	120(72.7)	109(68.1)	131(74.0)	122(70.9)	0.66
Non-smoker n (%)	41(24.9)	48(30.0)	50(28.3)	57(33.1)	0.40
Hypertension n (%)	43(26.1)	69(43.1)	73(41.2)	79(45.9)	0.00
Hypercholesterolaemia n (%)	73(44.2)	86(53.8)	82(46.3)	79(45.9)	0.32
Previous AMI n (%)	22(13.3)	27(16.9)	39(22.0)	36(20.9)	0.15
Known IHD n (%)	36(21.8)	48(30.0)	55(31.1)	60(34.9)	0.06
Diagnosis STEMI n (%)	67(40.6)	70(43.8)	82(46.3)	70(40.7)	0.66
Discharge medications					
Aspirin n (%)	155(93.9)	144(90.0)	163(92.1)	156(90.7)	0.58
Clopidogrel n (%)	132(80.0)	136(85.0)	137(77.4)	147(85.5)	0.15
Dual anti-platelet n (%)	126(76.4)	128(80.0)	129(72.9)	136(79.1)	0.40
Beta-blocker n (%)	132(80.0)	118(73.8)	136(76.8)	134(77.9)	0.60
ACEI/ARB n (%)	128(77.6)	133(83.1)	148(83.6)	144(83.7)	0.39
Statin n (%)	159(96.4)	155(96.9)	165(93.2)	163(94.8)	0.38
Revascularised n (%)	74(44.9)	70(43.8)	70(39.6)	66(38.4)	0.56
Troponin I (µg/l; median; IQR)	2.5(13.7)	3.2(14.5)	3.5(15.7)	3.1(14.4)	0.90
FPG (mmol/l; median; IQR)	4.9(0.5)	5.0(0.6)	5.2(0.8)	5.6(1.1)	0.00
RBG (mmol/l; median; IQR)	5.9(1.93)	6.4(1.75)	6.8(2.4)	7.7(2.8)	0.00
2HBG (mmol/l; median; IQR)	5.6(1.4)	7.4(0.8)	9.3(1.33)	12.3(3.0)	0.00

Table 2. Adverse cardiovascular events in each quartile of 2 hour post load plasma glucose.

	Q1 n(%) (n=165)	Q2 n(%) (n=160)	Q3 n(%) (n=177)	Q4 n(%) (n=172)	p	Total n(%) (n=674)
Death	9(5.5)	12(7.5)	23(13.0)	21(12.2)	0.052	65(9.6)
Non-cardiovascular	4(2.4)	7(4.4)	9(5.1)	7(4.1)	0.644	27(4.0)
Cardiovascular	5(3.0)	5(3.1)	14(7.9)	14(8.1)	0.051	38(5.6)
Non-fatal MI	13(7.9)	23(14.4)	19(10.7)	32(18.6)	0.021	87(12.9)
Non-hgic stroke	1(0.61)	0(0.00)	4(2.3)	4(2.3)	0.153	9(1.3)
MACE	19(11.5)	28(17.5)	37(20.9)	50(29.1)	0.001	134(19.9)

Table 3: Adjusted** Risk of adverse events as predicted by APG, FPG and 2h-PG using the Cox proportional hazard

	MACE		All cause mortality		Cardiovascular mortality		Non-fatal MI	
	HR 95% CI	P	HR 95% CI	P	HR 95% CI	P	HR 95% CI	P
2h-PG	1.12 (1.06-1.19)	0.00	1.13 (1.04-1.23)	0.00	1.19 (1.08-1.33)	0.00	1.09 (1.02-1.17)	0.01
FPG	1.28 (1.07-1.53)	0.01	1.13 (0.82-1.54)	0.46	1.51 (1.11-2.04)	0.01	1.15 (0.90-1.48)	0.26
APG	1.03 (0.95-1.12)	0.42	1.05 (0.94-1.16)	0.42	1.01 (0.87-1.17)	0.90	1.03 (0.93-1.14)	0.55
2h-PG Quartile*	1.29 (1.09-1.53)	0.00	1.29 (1.00-1.66)	0.04	1.44 (1.03-2.02)	0.03	1.18 (0.95-1.45)	0.13

* for each higher quartile. **The final model was adjusted for age, gender, history of previous myocardial infarction, hypertension and hypercholesterolaemia, discharge diagnosis of STEMI or NSTEMI, discharge medication, use of reperfusion therapy and smoking status.
APG, FPG, 2h-PG are continuous variables

Table 4. Candidate predictors affecting end-points for the entire population using Cox proportional-hazards regression modelling.

	MACE			All cause deaths		
Covariate	HR	95% CI	P	HR	95% CI	P
Age	1.03	1.01-1.05	0.0003	1.07	1.04-1.10	0.0001
2h-PG	1.12	1.04-1.20	0.0012	1.17	1.05-1.30	0.0039
Previous MI	2.49	1.71-3.62	0.0001	0.98	0.54-1.76	0.9406
Discharged without beta-blockers	1.60	1.09-2.34	0.0160	1.86	1.08-3.19	0.0241
Revascularised	1.50	1.05-2.15	0.0273	0.65	0.35-1.21	0.1774
Hypercholesterolaemia	0.69	0.48-0.99	0.0459	0.79	0.46-1.35	0.3873
Discharged without clopidogrel	1.51	1.00-2.27	0.0495	2.15	1.25-3.70	0.0055
Hypertension	1.35	0.94-1.92	0.1007	1.53	0.91-2.56	0.1088
Discharged without Aspirin	1.29	0.76-2.18	0.3486	1.22	0.58-2.60	0.6012
Discharge Diagnosis of STEMI	1.18	0.83-1.69	0.3563	1.23	0.72-2.09	0.4426
Discharged without ACEI/ARB	1.21	0.78-1.86	0.3937	1.78	1.01-3.16	0.0479
Discharged without Statin	1.27	0.64-2.50	0.4962	1.98	0.90-4.36	0.0904
Current smoker	0.87	0.56-1.33	0.5062	0.93	0.51-1.68	0.8129
APG	0.97	0.88-1.06	0.5193	1.01	0.90-1.13	0.9209
Female gender	0.90	0.60-1.34	0.6030	0.65	0.35-1.19	0.1654
FPG	1.06	0.84-1.35	0.6186	0.83	0.56-1.22	0.3350
	Cardiovascular Deaths			Myocardial infarction		
	HR	95% CI	P	HR	95% CI	P
Age	1.05	1.02-1.09	0.0045	1.02	1.00-1.04	0.0420
2h-PG	1.17	1.02-1.33	0.0205	1.10	1.01-1.20	0.0291
Previous MI	1.86	0.91-3.81	0.0911	2.68	1.68-4.23	0.0001
Discharged without beta-blockers	1.60	0.78-3.27	0.1993	1.71	1.07-2.75	0.0259
Revascularised	0.82	0.38-1.77	0.6111	1.85	1.19-2.87	0.0064
Hypercholesterolaemia	0.78	0.39-1.56	0.4808	0.72	0.46-1.12	0.1437
Discharged without clopidogrel	2.81	1.38-5.72	0.0043	1.08	0.62-1.87	0.7917
Hypertension	1.30	0.66-2.56	0.4526	1.32	0.85-2.04	0.2204
Discharged without Aspirin	1.27	0.48-3.38	0.6300	1.45	0.75-2.79	0.2655
Discharge Diagnosis of STEMI	1.16	0.58-2.30	0.6788	1.23	0.79-1.93	0.3565
Discharged without ACEI/ARB	2.03	0.99-4.17	0.0541	0.76	0.40-1.42	0.3830
Discharged without Statin	2.55	0.97-6.67	0.0570	0.83	0.29-2.35	0.7210
Current smoker	0.72	0.32-1.63	0.4285	1.16	0.68-1.98	0.5789
APG	0.91	0.78-1.07	0.2644	1.00	0.88-1.12	0.9343
Female gender	0.80	0.36-1.75	0.5727	0.99	0.61-1.62	0.9782
FPG	1.25	0.82-1.91	0.2910	0.97	0.71-1.33	0.8332

Table 5: Likelihood ratio test comparing nested models containing APG, FPG and 2h-PG individually and in combinations.

MODELS			MACE		All Deaths		CVS Death		MI		CVS Deaths + MI	
1	2	3	χ^2	P	χ^2	P	χ^2	P	χ^2	P	χ^2	P
FPG	FPG 2h-PG		16.01	0.000	7.75	0.005	4.90	0.027	8.64	0.003	15.75	0.000
FPG	APG FPG		0.76	0.383	0.01	0.938	3.62	0.057	0.08	0.780	0.72	0.395
2h-PG	FPG 2h-PG		0.64	0.425	1.52	0.218	1.98	0.159	0.22	0.641	0.13	0.721
2h-PG	APG 2h-PG		1.28	0.258	0.38	0.538	2.80	0.094	0.06	0.806	1.52	0.217
APG	APG FPG		13.82	0.000	0.08	0.783	13.91	0.000	1.16	0.281	10.15	0.001
APG	APG 2h-PG		29.71	0.000	6.68	0.010	16.01	0.000	9.57	0.002	26.58	0.000
	FPG 2h-PG	APG FPG 2h-PG	2.11	0.146	0.10	0.747	4.76	0.029	0.01	0.929	2.01	0.156
	APG FPG	APG FPG 2h-PG	17.36	0.000	7.85	0.005	6.04	0.014	8.57	0.003	17.04	0.000
	FPG 2h-PG	APG FPG 2h-PG	1.47	0.225	1.24	0.265	3.94	0.047	0.17	0.684	0.62	0.432

Table 6: Akaike's Information Criterion for nested and non-nested models for each end point.

Desc of Model	AICc	δAICc	RelLikelihood	wi	wj/wi
MACE					
FPG	605.69	7.69	0.02	0.01	26.18
2HPG	598.00	0.00	1.00	0.52	1222.31
APG	612.22	14.22	0.00	0.00	1.00
FPG 2HPG	599.79	1.79	0.41	0.21	500.22
APG FPG	607.42	9.41	0.01	0.00	11.05
APG 2HPG	599.47	1.47	0.48	0.25	587.30
All Cause Deaths					
FPG	374.14	3.12	0.21	0.09	2.86
2HPG	371.02	0.00	1.00	0.42	13.59
APG	374.18	3.15	0.21	0.09	2.81
FPG 2HPG	372.37	1.35	0.51	0.21	6.93
APG FPG	376.24	5.22	0.07	0.03	1.00
APG 2HPG	372.94	1.91	0.38	0.16	5.22
Cardiovascular Deaths					
FPG	275.00	1.46	0.48	0.15	13.11
2HPG	273.54	0.00	1.00	0.31	27.21
APG	280.14	6.61	0.04	0.01	1.00
FPG 2HPG	274.65	1.11	0.57	0.18	15.58
APG FPG	275.29	1.75	0.42	0.13	11.31
APG 2HPG	274.24	0.70	0.70	0.22	19.13
Myocardial Infarction					
FPG	499.61	4.21	0.12	0.06	2.81
2HPG	495.40	0.00	1.00	0.50	23.09
APG	500.15	4.76	0.09	0.05	2.14
FPG 2HPG	497.39	2.00	0.37	0.19	8.51
APG FPG	501.67	6.28	0.04	0.02	1.00
APG 2HPG	497.47	2.07	0.35	0.18	8.18
Cardiovascular Deaths and Myocardial Infarction					
FPG	586.12	7.81	0.02	0.01	10.57
2HPG	578.31	0.00	1.00	0.53	525.05
APG	590.84	12.53	0.00	0.00	1.00
FPG 2HPG	580.35	2.04	0.36	0.19	189.24
APG FPG	587.87	9.55	0.01	0.00	4.42
APG 2HPG	579.65	1.34	0.51	0.27	268.28

AICc=Corrected Akaike's Information Criterion; δAICc= difference between AICc value for a model and minimum AICc i.e. AIC value of the "best" model. w_i = Akaike weights, the ratio of δAICc values for each model relative to the whole set of candidate models; w_j/w_i = Evidence ratios, ratio of AICc of the "best" model and competing models. All models included age, gender, history of previous myocardial infarction, hypertension and hypercholesterolaemia, discharge diagnosis of STEMI or NSTEMI, discharge medication, use of reperfusion therapy and smoking status.

Table 7: Akaike's Information Criterion for different non-nested models for each end point.

Desc of Model	AICc	DeltaAICc	RelLikelihood	AkaikeWt	EvidenceRatio
MACE					
FPG	605.69	7.69	0.02	0.02	26.18
2HPG	598.00	0.00	1.00	0.98	1,222.31
APG	612.22	14.22	0.00	0.00	1.00
All Cause Deaths					
FPG	374.14	3.12	0.21	0.15	1.02
2HPG	371.02	0.00	1.00	0.71	4.84
APG	374.18	3.15	0.21	0.15	1.00
Cardiovascular Deaths					
FPG	275.00	1.46	0.48	0.32	13.11
2HPG	273.54	0.00	1.00	0.66	27.21
APG	280.14	6.61	0.04	0.02	1.00
Myocardial Infarction					
FPG	499.61	4.21	0.12	0.10	1.31
2HPG	495.40	0.00	1.00	0.82	10.78
APG	500.15	4.76	0.09	0.08	1.00
Cardiovascular Deaths and Myocardial Infarction					
FPG	586.12	7.81	0.02	0.02	10.57
2HPG	578.31	0.00	1.00	0.98	525.05
APG	590.84	12.53	0.00	0.00	1.00

Table 8. Continuous Net Reclassification Improvement for MACE.

	Add FPG				Add 2h-PG				Add APG			
FPG						E	NE	TOTAL		E	NE	TOTAL
					UP	67	212		UP	83	307	
					DWN	67	328		DWN	51	233	
					TOTAL	134	540		TOTAL	134	540	
					NRI	0	21.481	0.215	NRI	0.239	-0.137	0.102
					SE			0.097	SE			0.097
					Z statistic			2.226	Z statistic			1.054
					p-Value			0.026	p-Value			0.292
2h-PG		E	NE	TOTAL						E	NE	TOTAL
	UP	66	258						UP	81	312	
	DWN	68	282						DWN	53	228	
	TOTAL	134	540						TOTAL	134	540	
	NRI	-1.493	4.444	0.03					NRI	0.209	-0.156	0.053
	SE			0.097					SE			0.097
	Z statistic			0.306					Z statistic			0.553
	p-Value			0.76					p-Value			0.58
RPG		E	NE	TOTAL		E	NE	TOTAL				
	UP	67	199		UP	70	209					
	DWN	67	341		DWN	64	331					
	TOTAL	134	540		TOTAL	134	540					
	NRI	0	26.296	0.263	NRI	4.478	22.593	0.271				
	SE			0.097	SE			0.097				
	Z statistic			2.725	Z statistic			2.805				
	p-Value			0.006	p-Value			0.005				
FPG						E	NE	TOTAL				
+APG					UP	66	214					
					DWN	68	326					
					TOTAL	134	540					
					NRI	-1.493	20.741	0.192				
					SE			0.097				
					Z statistic			1.994				
					p-Value			0.046				
APG		E	NE	TOTAL								
+2hPG	UP	69	256									
	DWN	65	284									
	TOTAL	134	540									
	NRI	2.985	5.185	0.082								
	SE			0.097								
	Z statistic			0.847								
	p-Value			0.397								
FPG										E	NE	TOTAL
+2hPG									UP	82	308	
									DWN	52	232	
									TOTAL	134	540	
									NRI	22.388	-14.074	0.083
									SE			0.097
									Z statistic			0.861
									p-Value			0.389

Table 9. Categorical Net Reclassification Improvement for MACE.

	Add FPG				Add 2h-PG				Add APG			
FPG						E	NE	TOTAL		E	NE	
					UP	13	57		UP	4	12	
					DWN	8	84		DWN	2	17	
					TOTAL	134	540		TOTAL	134	540	
					NRI	3.7	5.0	0.087	NRI	1.5	0.9	0.024
					SE			0.041	SE			0.021
					Z statistic			2.148	Z statistic			1.161
					p-Value			0.032	p-Value			0.245
2h-PG		E	NE	TOTAL						E	NE	
	UP	2	17						UP	3	19	
	DWN	7	10						DWN	5	18	
	TOTAL	134	540						TOTAL	134	540	
	NRI	-3.7	-1.3	-0.050					NRI	-1.5	-0.2	-0.017
	SE			0.024					SE			0.024
	Z statistic			-2.063					Z statistic			-0.701
	p-Value			0.039					p-Value			0.483
RPG		E	NE	TOTAL		E	NE	TOTAL				
	UP	10	45		UP	20	76					
	DWN	8	64		DWN	13	114					
	TOTAL	134	540		TOTAL	134	540					
	NRI	1.5	3.5	0.050	NRI	5.2	7.0	0.123				
	SE			0.037	SE			0.050				
	Z statistic			1.351	Z statistic			2.457				
	p-Value			0.177	p-Value			0.014				
FPG						E	NE	TOTAL				
+RPG					UP	12	67					
					DWN	9	88					
					TOTAL	134	540					
					NRI	2.2	3.9	0.061				
					SE			0.041				
					Z statistic			1.486				
					p-Value			0.137				
RPG		E	NE	TOTAL								
+2hPG	UP	3	18									
	DWN	1	17									
	TOTAL	134	540									
	NRI	1.5	-0.2	0.013								
	SE			0.019								
	Z statistic			0.706								
	p-Value			0.480								
FPG										E	NE	TOTAL
+2hPG									UP	6	20	
									DWN	1	23	
									TOTAL	134	540	
									NRI	3.7	0.6	0.043
									SE			0.023
									Z statistic			1.849
									p-Value			0.064

Table 10. Integrated Discrimination Improvement for MACE.

		Add FPG			Add 2h-PG			Add APG		
		IDI	zIDI	P	IDI	zIDI	P	IDI	zIDI	P
FPG	E				0.009			0.000		
	NE				-0.002			0.000		
	TOTAL				0.012	2.175	0.015	0.000	0.126	0.450
2h-PG	E	0.001						0.000		
	NE	0.000						0.000		
	TOTAL	0.001	0.847	0.199				0.000	0.105	0.458
RPG	E	0.009			0.018					
	NE	-0.002			-0.004					
	TOTAL	0.011	2.258	0.012	0.022	3.018	0.001			
FPG+RPG	E				0.010					
	NE				-0.002					
	TOTAL				0.013	2.192	0.014			
RPG+2hPG	E	0.001								
	NE	0.000								
	TOTAL	0.002	0.941	0.173						
FPG+2hPG	E							0.001		
	NE							0.000		
	TOTAL							0.001	0.372	0.355

Figure legends:

Figure 1. The distribution of glucometabolic abnormalities according to the NICE (CG130) and ESC guidelines.

Figure 2. Kaplan–Meier curves showing the survival free of major cardiovascular adverse events, all cause mortality, cardiovascular mortality and non-fatal myocardial infarction in the four quartiles of 2h-PG.