This is the accepted manuscript version of an article published by S. Karger AG in Cardiology 2020;145:553–561 and available on https://doi.org/10.1159/000509180.

Title: Two hour post load plasma glucose, a biomarker to improve the GRACE score in patients without known diabetes.

Short running title: Post load glucose improves GRACE score

Authors:

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

Affiliations:

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

Sudipta.Chattopadhyay@nhs.net

[2]Department of Cardiology, Scunthorpe General Hospital, Cliff Gardens, Scunthorpe, UK.

anish26g@yahoo.com

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

Joseph.John@nhs.net

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

Thozhukat.Sathyapalan@hyms.ac.uk

Corresponding author:

Sudipta Chattopadhyay,

MBBS, MD(Med), MD(Res), FRCP, FESC.

Consultant Cardiologist. Department of Cardiology, Milton Keynes University Hospital, Standing Way, Milton Keynes MK6 5LD. United Kingdom.

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

Tel: 00441908660033

Fax: 00441908660256

Text + References: 4013

Abstract

Objective: To assess improvement of predictive performance of Global Registry of Acute Coronary Events score (GRS) by addition of a glucose matrix.

Methods: 1056 acute coronary syndrome (ACS) survivors without known diabetes had pre-discharge fasting (FPG) and 2 hour post load plasma glucose (2h-PG) measured. GRS was calculated. Major adverse cardiac events (MACE) (death and non-fatal MI) were recorded during follow up. Cox proportional-hazards regression predicted event free survival. Likelihood ratio test, Akaike's Information criteria, continuous net reclassification improvement ($NRI^{>0}$) and integrated discrimination improvement (IDI) were used to test the additional prognostic value of glycaemic indices over GRS.

Results: Median follow-up was 36.5 months. 211 MACEs (20.0%), 96 deaths (9.1%) and 115 non-fatal re-infarctions (10.9%), occurred. 2h-PG, but not FPG, independently predicted MACE-free survival at all time points (HR 1.08, 95% CI 1.03 -1.13, p=0.002, at 3 years). Risk of MACE increased by 8-11% with every mmol/l rise in 2h-PG. 2h-PG significantly improved the prognostic models containing GRS. Models containing GRS and 2h-PG yielded lowest corrected Akaike's Information criteria, compared to that with only GRS. 2h-PG, but not FPG, improved $NRI^{>0}$ ($NRI^{>0}$ 0.169, p = 0.028 at 3 years) and IDI (IDI of 0.66%, p=0.018 at 3 years) significantly at all time points during follow up.

Conclusions: 2h-PG, but not FPG, improves performance of GRS containing models in predicting post-ACS prognosis in the short to medium term.

Keywords: 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) predicts the risk of death and myocardial infarction (MI) in patients with acute coronary syndrome (ACS).[6465, 6473, 6463] The final GRACE model includes only 8 of the most prognostically significant baseline variables to make the score clinically usable. The discriminatory performance of the GRACE model leaves room for improvement. Attempts have been made to improve the model by adding multiple blood biomarkers.[6534, 6536, 6537, 6538, 6539, 6540, 6541] These are mostly emerging biomarkers that are not routinely measured. It is mostly a composite of different biomarkers rather than a single one that has provided incremental value over and above the GRACE score. Identifying a single biomarker that can be routinely measured and would not only predict prognosis but also improve the GRS would be useful.

A glycaemic matrix is notably absent in the GRACE score even though post-ACS prognosis is worse in patients with known diabetes mellitus (DM). Addition of fasting plasma glucose (FPG),[6246, 6455] admission plasma glucose (APG)[6255, 6260, 6459, 6460, 6461, 6462, 6480] and glycosylated haemoglobin (HbA1c)[6444, 6482] has been variably successful in improving the GRACE model. The GRACE model predicts post-discharge prognosis up 4 years.[6463] We investigate whether FPG and/or 2h-PG improves the performance of the GRS in predicting short to intermediate term major adverse cardiac events (MACE) in patients with MI but without known DM.

Materials and Methods

The study methods have been described previously.[6354] This analysis includes consecutive post-MI survivors without known DM who underwent routine pre-discharge oral glucose tolerance test (OGTT) with standard follow up after discharge. Information on

demographics, risk factors for coronary artery disease (CAD), past medical history including history of previous MI and revascularisation, prescribed medications, haemodynamic parameters, troponin I, renal function test, Killip class, and presence of ST-segment depression GRS for risk of death or MI from discharge to 6 months were collected from the Myocardial Infarction National Audit Project (MINAP) database. All participants underwent pre-discharge OGTT on/after the third day of admission. Venous plasma glucose was measured ≥8 hours of overnight fast and 2 hours after administration of 75g glucose in 200 ml water. Clinically unstable patients were tested later. We excluded patients who were transferred out of our centre before the OGTT or did not tolerate it. Glucose was measured using the glucose oxidase method. The patients diagnosed with impaired glucose tolerance (IGT) and new diabetes mellitus (NDM) were referred to the endocrinologists for appropriate management.

MI was defined as per the universal definition.[6276] Patients were labelled “known DM” if they were aware of the diagnosis before admission, had it documented in their medical records or was on anti-diabetic treatment. Admission HbA1c was not measured as it was not recommended in the guidelines at the time of data collection.[6275, 6328, 6329] Patients with pre-existing diabetes were excluded .The glucometabolic states were defined as normal glucose tolerance (NGT): FPG < 6.1 mmol/l and a 2-h PG < 7.8 mmol/l; impaired 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.

All participants were followed up for a median of 36 months for outcomes. Hospital and general practice records were reviewed ensuring complete follow up. The first occurrence of a major adverse cardiovascular event (MACE) defined as death or non-fatal re-infarction (the only events predicted by the GRS) was obtained from the hospital and general practice databases and confirmed by the office of public health intelligence. As routinely collected anonymised data on standard clinical practice was being retrospectively analysed, the East

Yorkshire and North Lincolnshire Research Ethics Committee waived the need for formal ethical approval and patient consent.[6354]

Statistics

Continuous variables are presented as medians (inter-quartile range, IQR) and categorical variables as counts and proportions. The baseline characteristics of the patients grouped as above and below the median 2h-PG (8.1 mmol/l) were compared using Mann-Whitney test for non-parametric continuous variables and chi-squared test for categorical variables. Event free survival was compared between groups using the Kaplan–Meier method. The dataset was censored at 6 months, 1, 2 and 3 years and analysed using multivariate Cox proportional-hazards regression (MedCalc Statistical Software version 17.0.4, Ostend, Belgium). Gender, smoking status, hypercholesterolaemia, hypertension, history of MI and revascularisation, discharge diagnosis and medications, GRS, FPG and 2h-PG were "entered" into the model. Multicollinearity was tested (MedCalc Statistical Software version 17.0.4, Ostend, Belgium) and variables with variance inflation factor <4 were included in the same model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported.

The χ^2 likelihood ratio test was used to compare nested models to determine if the logistic regression models including GRS and, FPG or 2h-PG provided a significantly better fit than those with GRS alone. Akaike's information criterion (AIC) was used to estimate the probability that a given nested or non-nested model including GRS and FPG and/or 2h-PG was the "best" fitting model of those studied.

FPG and 2h-PG were added, individually and in combination, into logistic regression models containing GRS along with other covariates to calculate the predicted probabilities of MACE at each time point. The incremental predictive value of adding 2h-PG to models with FPG was analysed from these predicted probabilities by comparing the area under the receiver-operating characteristic (ROC) curve (AUC) (MedCalc Statistical Software version

17.0.4, Ostend, Belgium), using category-free continuous net reclassification index ($NRI^{>0}$) and integrated discrimination improvement (IDI). 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

Baseline characteristics of the patients grouped as above and below the median 2h-PG (8.1 mmol/l) are shown in Table 1. OGTT was done on day on day 3 or later in 97.6% of patients. 60.3% of NSTEMI and 61.6% of STEMI patients had the glucose measured 4 days or after admission. The timing of OGTT was similar in the NSTEMI and STEMI patients (median 4.0; IQR 6-3 vs median 4.0; IQR 5-3, p = 0.420). Patients who had their OGTT on or before day 3 had lower FPG (median 5.0; IQR 5.4-4.7 vs median 5.1; IQR 5.6-4.8, p = 0.002) but similar 2h-PG (median 8.1; IQR 10.4-6.4 vs median 8.0; IQR 10.5-6.5, p = 0.762) compared to those done later. The patients with STEMI had higher FPG (median 5.1; IQR 5.6-4.8 vs median 5.05; IQR 5.5-4.7, p = 0.020) but similar 2h-PG (median 8.2; IQR 10.4-6.6 vs median 8.0; IQR 10.5-6.4, p = 0.323) than the NSTEMI patients.

Outcomes

During the median follow-up of 36.5 months there were 211 MACEs (20.0%), 96 deaths (9.1%) and 115 non-fatal re-infarctions (10.9%). Patients with 2h-PG above the median had higher MACE than those below (HR 1.53, 95% CI 1.17 to 2.01, p=0.002). The 2h-PG and GRS, but not FPG, independently predicted MACE at all time points (Table 2). The risk of MACE increased by 8-11% at various time points for each mmol/l rise in 2h-PG.

Addition of the 2h-PG, but not FPG, as a continuous variable significantly improved the ability of a model including GRS to predict MACE at all time points during follow up (Table 3).

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

2h-PG, but not FPG, significantly improved the net reclassification of model containing GRACE score alone in predicting events during follow up (Table 4). 2h-PG significantly improved $NRI^{>0}$ by 17-23% at 2 and 3 years but not at 6 months and 1 year. Addition of FPG did not change reclassification. Integrated discrimination at all time points were similarly improved by 2h-PG (Table 4). The IDI was 0.41-0.66% at the various time points.

The c-statistic for the model containing the GRS only, 2h-PG only and GRS and 2h-PG were 0.73 (95% CI 0.71 to 0.76, p <0.0001), 0.70 (95% CI 0.67 to 0.73, p<0.0001) and 0.74 (95% CI 0.71 to 0.77, p <0.0001) respectively. The AUC for the GRS-only was better than the 2h-PG only model (δAUC 0.0320, p = 0.028). Addition of 2h-PG to GRS only model did not improve the c-static (δAUC 0.0053, p = 0.295) but did so when GRS was added to the 2h-PG only model (δAUC 0.0373, p = 0.003).

Discussion/Conclusion

We show that 2h-PG, measured ≥ 3 days after the event, would improve performance of a model including the GRS in predicting post-MI prognosis in the short to intermediate term in patients without known DM. GRS accurately predicts post-MI survival in the short and long term. [6463, 6473] Multiple blood biomarkers have been added to the model to improve its performance.[6534, 6536, 6537, 6538, 6539, 6540, 6541] Its performance improves when a composite score created mostly from multiple novel biomarkers that are not routinely measured, is added. These approaches are too cumbersome to be used clinically and possibly costly with marginal gains. This study suggests that 2h-PG is single glycaemic matrix added to the GRS would improve its performance.

As the post-MI prognosis in patients with DM is inferior to those without, a glycaemic matrix would be a natural choice as an additional biomarker that could improve predictive performance of models containing GRS. The GRS model does not include history of DM or a glycaemic matrix as a variable. [6463, 6473] Although, DM as a dichotomous categorical variable independently did not predict the 6-month post-discharge events,[6473] increasing FPG increased the risk of in-hospital mortality irrespective of a history of DM.[6246] However, in the absence of OGTT, it is uncertain whether the raised FPG or undetected raised 2h-PG either in the IGT or DM range affected the outcomes in these patients. The 6-months post-ACS survival was affected by FPG only if it was above the diagnostic threshold for diabetes. [6246]

FPG, APG, HbA1c and AGT individually predicts adverse post-ACS prognosis in patients without known DM. The 2h-PG is a better predictor than both APG and FPG.[6492] FPG, APG and HbA1c, after adjusting for GRS, predicted post-MI outcomes in some [6455, 6255, 6460, 6480, 6444] but not other[6246, 6260, 6459, 6461, 6462, 6482] studies. Attempts at using APG,[6460, 6461, 6462] FPG,[6455, 6458] and HbA1c [6444] to improve the predictive ability of models containing GRS has yielded variable results. This study suggests that in patients without known DM, 2h-PG improves the performance of GRS-containing models in predicting post-MI prognosis in the short to medium term. FPG was shown to predict mortality after MI and improve the prognostic models containing GRS in one study.[6455] Most (73%) patients in this study had STEMI, FPG was measured in the first 24 hours of admission and post-load glucose was not measured.[6455] In contrast, STEMI was diagnosed in 44% of our patients and PG was measured a lot later. As a binary dichotomous variable, troponin in the GRS model does not account for the effect of the degree of myonecrosis, on prognosis. FPG is higher when measured within 24 hours of MI than when measured later and following STEMI compared to NSTEMI.[6337, 6216, 6279] The effect of FPG on the predictive performance of the model in the study by Aroson et al [6455] may be

explained by the higher levels of FPG measured early after STEMI combined with GRS unaffected by the higher volume of myonecrosis in STEMI, It is also unclear whether this effect would persist if 2h-PG was included in the models. The morbidity associated with 2h-PG rather than FPG in this study could be due to the progression of atherosclerosis seen with post-challenge but not fasting hyperglycaemia.[6424]

In the absence of HbA1c, we are unable to compare the effect of all the glycaemic matrices on prognosis. None of the patients had HbA1c measured as routine screening of the MI patients for undiagnosed diabetes using HbA1c was not recommended in the EASD Guidelines 2007.[6275] On the contrary, screening for diabetes using a non-invasive risk score, and OGTT was recommended. Whether HbA1c would be a useful biomarker to predict post-MI prognosis is debated. HbA1c has been shown to predict post-ACS prognosis in some [6336, 6443, 6444, 6449] but not all studies.[6366, 6391, 6399, 6429, 6434] The effect of APG, FPG, 2h-PG and HbA1c on post-MI prognosis in patients without known diabetes has rarely been compared. [6366, 6398, 6429, 6489] The 2h-PG, but neither FPG nor HcA1c, predicted outcome in EUROASPIRE IV.[6429] HbA1c ≥6.5%, when included in the same model as known DM did not increase mortality in another study.[6366] However, mortality increased in patients with newly diagnosed DM by OGTT even when the HbA1c was <6.5%. Kowalczyk et al suggest the usefulness of HbA1c in patients with IGT and new DM but do not report the effect of HbA1c on prognosis of patients without.[6398] [6487] There is some suggestion that HbA1c and FPG may be better than OGTT for assessing cardiovascular disease risk.[6487, 6488] Both these studies are very different from ours in that the first [6487] excludes subjects with history of CVD at baseline and the second [6488] studies the association between FPG and HbA1c and prevalence of microangiopathy, in epidemiological setting. The EUROSPIRE IV[6429] and SWEETHEART registry[6490] support the use of OGTT for predicting prognosis in these high risk patients.

The 2h-PG did not increase the c-statistic of the model containing GRS. Improving c-statistics of models containing powerful variables as GRS may be difficult as δAUC heavily depends on the strength of performance of the underlying clinical model. $NRI^{>0}$ and IDI, tests were devised to deal with this anomaly, improved when 2h-PG is added to GRS. The $NRI^{>0}$ did not change for the 6m and 1 years time points but the IDI did. The $NRI^{>0}$ counts the individuals with and without events whose calculated risk changes on addition of a variable into a model. IDI measures the amount of change in calculated risk for each individual with and without events incorporating both the direction and the extent of change in calculated risk, making it more meaningful than $NRI^{>0}$.

The study is limited by its retrospective observational nature. Deaths were recorded from the general practice database linked to national death register. Although local records are regularly updated, some re-infarctions admitted to other hospitals may have been missed. Information not available had to be excluded from statistical models. Inclusion of a mainly Caucasian population could affect its generalizability. Stress hyperglycaemia is less likely to have affected our result as the OGTT was done ≥3 days after the event. The stress response to an acute event subsides in 2-5 days with no further decrease thereafter. [6279] The effect of random fluctuation in glycaemia however can not be excluded. Although reproducibility of the OGTT results and its relation to long term glucometabolic state would be important for the diagnosis of DM, its relevance to assessing post-MI prognostic risk is less.

This study suggests that in patients without known diabetes 2h-PG, but not FPG, could be used a single biomarker to predict adverse post-ACS outcome over and above the GRACE score. It may be reasonable to choose 2h-PG as the only glycaemic matrix in post-MI survivors without known DM as it determines prognosis in favour of a one deemed sufficient for screening for epidemiological purposes even if simpler and more feasible i.e. HbA1c until clear evidence in favour HbA1c in this high risk population is establish

This study concludes that in patients without known diabetes, 2h-PG but not FPG, improves the performance of models containing GRACE score in predicting post-MI prognosis in the short to medium term. Thus 2h-PG can be used as an additional prognostic biomarker in addition to the GRACE score in these patients. There is an on-going debate as to the choice of a glucose matrix for detection of hyperglycaemia in this high risk population. It may be reasonable to choose 2h-PG, the one that minimises the risk of missing the diagnosis and is additionally capable of providing prognostic information despite it being cumbersome to measure, in favour of HbA1c that is simpler and feasible to measure, and deemed sufficient for use in the low-risk general population for epidemiological purposes especially since there is no evidence of superiority of HbA1c over 2h-PG in predicting prognosis. Thus an appropriately timed pre-discharge OGTT may be recommended for all patients without known diabetes admitted with myocardial infarction.

Acknowledgements

We thank all the nurses that helped with the collection of data. We also thank the patients whose data was utilised for this study.

Disclosure Statement

The authors have no conflicts of interest to declare

Funding Sources: None

Author Contribution:

JJ, SC conceived and designed the study. AG, SC contributed to acquisition of data. SC analysed and interpreted the 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.