Development of a Predictive Model to Identify Patients with Suspected Acute Coronary Syndromes at High Risk of Cardiac Arrest or In-Hospital Mortality: A Sub-study of the IMMEDIATE Trial

A thesis

Submitted by

Madhab Ray, MD

In partial fulfillment of the requirements

For the degree of

Master of Science

In Clinical and Translational Science

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

February, 2014

ADVISER: Harry Selker, MD, MSPH

ABSTRACT

Background: Intravenous glucose insulin potassium (GIK) solution has been shown to have a protective role in preventing myocardial damage from ischemic insult in laboratory animals. Its effectiveness in human subjects has long been debated and clinical studies have produced divergent results. The recently completed IMMEDIATE Trial showed benefit of GIK in the composite outcome of cardiac arrest or in-hospital mortality in patients with suspected acute coronary syndrome (ACS). To aid the identification of patients most likely to experience this benefit, this ancillary analysis of the IMMEDIATE Trial was performed to develop a predictive model that could facilitate recognition of these high-risk patients for prioritization for GIK therapy.

Methods: Multivariable logistic regression was used to develop a predictive model for the composite endpoint cardiac arrest or in-hospital mortality using patients of the control arm of the IMMEDIATE Trial, i.e., patients not treated with GIK. Tertiles of predicted risk categories then were created for all patients in the trial (treated and not treated) using the developed predictive model and risk categories were tested for interactions with GIK on the outcome.

Results: Four variables were significantly associated with the study endpoint: advanced age, low systolic blood pressure, ST elevation in the presenting electrocardiogram (ECG), and duration of symptoms from the onset. The model developed using these variables predicted cardiac arrest or death with good performance, corresponding to a C statistic of 0.75. Calibration of the predictive instrument for observed and predicted rates of cardiac arrest or in-hospital mortality was very good.

No significant interaction on the odds ratio scale with GIK was identified for any candidate variables or the predicted risk categories in the study population. However, based on constant

odds ratio (OR) across the risk categories there was an absolute risk reduction of 8.6% with GIK in high-risk tertile with the corresponding number needed to treat (NNT) of 12 to prevent one cardiac arrest or in-hospital mortality. The corresponding figures for the low-risk tertile were 0.8% and 125 respectively. Thus there appears to be a pronounced benefit of GIK in the high-risk group compared to the low-risk group when absolute risk reduction was used to measure the effect of treatment with GIK compared to placebo.

Conclusions: A multivariable predictive model was developed that identifies patients at high risk of cardiac arrest or death. When classified by the predictive model, the greatest benefit of GIK is demonstrated in the high-risk tertile.

ACKOWLEDGEMENTS

This work was supported by National Center for Research Resources Grant Number UL1RR025752, now the National Center for Advancing Translational Sciences, National Institutes of Health (NIH) Grant Number Ul1 TR000073.

The IMMEDIATE Trial was funded by the National Institutes of Health cooperative agreement from National Heart, Lung and Blood Institute (U01HL077821, U01HL077823, and U01HL077826). The IMMEDIATE Trial is registered at www.ClinicalTrials.gov (NCT00091507).

Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACS - Acute coronary syndrome

STEMI - ST segment elevation myocardial infarction

EMS - Emergency medical services

ECG - Electrocardiogram

IMMEDIATE - Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care

GIK - Glucose Insulin Potassium

ACI-TIPI - Acute cardiac ischemia time-insensitive predictive instrument

TPI - Thrombolytic predictive instrument

PCI - Percutaneous coronary intervention

NNT- Number needed to treat

INTRODUCTION

Studies in animals suggest that intravenous glucose-insulin-potassium (GIK) solution, when administered early during the course of cardiac ischemia, reduces ischemia-induced arrhythmias and myocardial injury.[1] Clinical trials in humans, however, have produced conflicting results,[2-5] and one of the reasons for the inconsistency in results among trials has been postulated to be the variable delay in the administration of GIK after the onset of ischemia. The IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care) Trial, which examined the benefits of very early administration of GIK in patients with an acute coronary syndrome (ACS), showed benefits in the composite endpoint of cardiac arrest and in-hospital mortality.[6] As the treatment of ACS evolved from the pre-thrombolytic era to the present day when primary percutaneous coronary intervention is the standard of care, there has been significant reduction in mortality rates related to this diagnosis. However, in the early emergency evaluation, there is a need to be able to identify patients with suspected ACS who are at high risk for cardiac arrest or death. Among all patients with a clinical presentation of chest pain or equivalent, only about a quarter have true ACS. Among those with ACS, identification of high risk patients by EMS and ED physicians is crucial for giving prompt, appropriate treatment and for allocating valuable resources.

To address the need for identifying the most at-risk patients, using data from the IMMEDIATE Trial, we used logistic regression to develop a predictive model for risk stratification of patients presenting with suspected ACS. We also examined the effect of GIK across the different risk groups.

MATERIALS & METHODS

Dataset

This study used data from the IMMEDIATE Trial. Details of the study protocol and inclusion and exclusion criteria have been published elsewhere.[6, 7] It was a randomized, placebo-controlled, double-blind, multicenter clinical effectiveness trial conducted in the United States that assessed the effect of intravenous GIK infusion initiated in the out-of-hospital setting for patients with suspected ACS. The trial included 871 patients who were randomized for this study. The predictive model was developed using the data from the control (placebo) group of the IMMEDIATE Trial. Thereby the model was intended to represent the clinical course where the outcome was not influenced by administration of GIK.

IMMEDIATE Trial Inclusion and Exclusion Criteria

Screened patients included those transported by EMS who were 30 years of age or older and had an out-of-hospital electrocardiogram (ECG) performed for symptoms suggestive of ACS. *To be included in the study*, the patient's out-of-hospital ECG had to meet at least one of the following criteria: prediction of ACS by the acute ischemia time insensitive predictive instrument (ACI-TIPI) of 75% or higher, generation by the thrombolytic predictive instrument (TPI) of a statement recognizing ST elevation myocardial infarction (STEMI), or judgment by the paramedic that the ECG showed definite STEMI. Patients who met any of the following criteria were *excluded:* having a language barrier or impaired reasoning, being a prisoner, being a pregnant woman, or having clinically significant rales (heart failure Killip class 3 or 4).

STATISTICAL ANALYSIS

Presenting Clinical Variables

Our main independent variables were demographic, clinical and electrocardiographic. These included age, sex, body mass index, time of initiation of study drug (GIK or placebo) after the onset of symptoms, vital signs obtained in the out-of-hospital setting and in the emergency department (pulse, and systolic and diastolic blood pressures), medical histories of coronary artery disease (myocardial infarction, coronary artery revascularization, heart failure, and stroke), cardiovascular risk factors (diabetes mellitus, hypertension, and hyperlipidemia), history of hemodialysis, previous use of aspirin, and treatment with beta blocker.

Electrocardiographic variables included ST elevation, PR interval, QRS duration, corrected QT interval (QTc), and axes of the P, T, and QRS waves. We also used the probability of ACS as computed by the ACI-TIPI.[8, 9] In addition, for use in the QTc variable, we used the categories from the cardiac arrest model by Selker, et al,[10] and for heart rate and blood pressure, we explored the variables previously used in predictive models of cardiac arrest and in-hospital mortality.[11-13].

Clinical Outcome to be Predicted

The study outcome of interest was the composite of cardiac arrest or in-hospital mortality, which was adjudicated as described in the IMMEDIATE Trial.[6, 7] This composite outcome was chosen based on the clinical and experimental evidence that a combination of left ventricular dysfunction and cardiac arrhythmias are the major determinants of immediate outcome in the patients with acute coronary syndromes and also to investigate the possible protective role of GIK in this clinical condition.[14, 15]

Development of Predictive Model

A post hoc analysis of the data from the IMMEDIATE Trial compared the baseline characteristics of patients with and without the composite outcome of interest among patients admitted with suspected ACS. Between group differences were assessed by logistic regression based on demographic, clinical, and ECG variables. A predictive model was developed using the data from the placebo group. Variables that were significant at the p value level <0.01 were included in the multivariable model building process to identify those patients at highest risk for the composite outcome (who thereby might benefit most by early administration of GIK). Collinearity was tested by examining variance inflation factor (vif). If the square root of vif was found to be more than 2, collinearity was suspected and the variable with lowest p value was used in further analysis.

Stepwise multivariable logistic regression analysis was performed using the variables that proved promising in the univariate analyses. The Akaike Information Criteria (AIC) and clinical coherence were used as measures for model performance, resulting in a model with four variables described below.

The final model was tested for discrimination by C statistic (the equivalent of the area under the receiver-operating characteristic [ROC] curve). Based on the predicted value from the final model, a risk score was developed and then was used to stratify risk into tertiles of equal numbers of patients. The event rates in each risk category were calculated and compared between the GIK and placebo groups. We checked for interactions of GIK with different covariates in the model and also with the different risk categories. Finally, efforts were made to identify the clinical characteristics of patients in the highest risk group and to formulate a risk scoring system to prioritize these patients for consideration for early GIK therapy.

RESULTS

Table 1 shows the baseline characteristics of the study population and their event rates, i.e., the composite outcome of cardiac arrest or in-hospital mortality.

Of the 871 patients enrolled in the study (411 in the GIK group and 460 in the placebo group) 58 had the outcome of interest, i.e., out-of-hospital or in-hospital cardiac arrest or death during the index hospitalization. In the control group the total number of outcomes was 40 (cardiac arrest 29, in-hospital mortality 23 and both 12) while in the treatment group the total number of outcomes was 18 (cardiac arrest 15, in-hospital mortality 13 and both 10). To construct the risk prediction model, we used the data from the placebo group (n=460). Among the patients in the placebo group those with the event were slightly older and included a greater proportion of women. These patients presented late, had a systolic blood pressure about 10 mm Hg lower and pulse about 10 beats per minute higher than those patients without events. In addition, they frequently had histories of previous coronary artery disease and their presenting ECG more often showed ST elevation and higher ACI-TIPI probabilities of having ACS. These differences in clinical presentation indicate the possible role of advanced age, low systolic blood pressure, tachycardia, history of coronary artery disease, ST elevation on presentation and higher ACI-TIPI score as important variables in the development of the predictive model for the outcome under study.

Among 34 candidate variables, 11 were found to be statistically significant and one was found to be borderline when a threshold of significance was taken as <0.1. Age and gender were tested among the demographic variables; age was significant and gender was not. None of the traditional cardiovascular risk factors, nor history of previous coronary artery disease, heart failure, stroke, prior use of aspirin, nor beta blocker, were significant in predicting the outcomes. Further characterization of the age variable by restricted cubic spline demonstrated nonlinear

relationship of age with the outcome of interest, i.e., cardiac arrest or in-hospital mortality. Two nodes were noted at 60 and 85 years of age. Graphically there was no obvious difference in the outcome rates below 60 and above 85 years of age. Thus the age variable was truncated at 60 and 85 years, and age between 60 and 85 years was treated as a continuous variable. This resulted in a small degree of further improvement of the model performance.

Similarly, univariate analyses of systolic blood pressure suggested a non-linear relationship with the outcome of interest; systolic blood pressure less than 105 mm Hg was adversely related to the outcome. Therefore we dichotomized the systolic blood pressure variable using a cut-off point at 105 mm Hg.

Duration of time from onset of chest pain at presentation as a continuous linear variable was not found to be predictive of outcome. Considering the potential relationship of the variable with the outcome, further analysis was performed with duration of symptoms divided into two categories: early (within one hour), and late (beyond one hour). We found the odds of the outcome were four times higher in those who received the treatment (placebo) within an hour of symptom onset.

Previous investigators[10] have suggested a predictive role of QTc as a function of time since onset of symptoms suggestive of ACS. Arguably prolonged ischemia can cause myocardial injury and prolongation of QTc (and thereby QT dispersion)[16, 17] and in combination they form a pathophysiological substrate for ventricular arrhythmia and cardiac arrest. Although univariate analyses did not demonstrate significant predictive value of QTc or duration of symptoms, a composite variable of QTc and duration of chest pain since onset was created ("QTcChestpaincategory") as described in the literature:[10] QTcChestpaincategory1: QTc<0.44; QTcChestpaincategory2: QTc≥0.44 & onset of chest pain to ECG ≤0.75 hrs.; QTcChestpaincategory3: QTC≥0.44 & onset of chest pain to ECG >0.75 & <1.25 hrs.; QTcChestpaincategory4: QTc≥0.44 & onset of chest pain to ECG ≥1.25 hrs. This derived

variable was tested in the multivariable model. No improvement in model performance was noted.

It is well-established in the literature that the hemodynamic state of the patient presenting with ACS is a major determinant of the clinical outcome.[18] In our model based on the univariate analyses, we used both heart rate and systolic blood pressure to account for the hemodynamic state of the patient. To investigate whether a composite variable of heart rate and systolic blood pressure on presentation performed better than the components, a composite variable was created as suggested in the literature. No further improvement was noted in the model performance as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate, whereas respiratory rate was of borderline significance. When the vital signs recorded in the emergency department were analyzed, systolic and diastolic blood pressure, heart rate, and respiratory rate were significant. Higher serum potassium level had a significant protective role, whereas glucose and C-reactive protein (CRP) levels did not show predictive significance. However, blood tests were felt to be less attractive as presenting clinical variables and were not used for the predictive model. Among ECG-based variables, ST elevation on the presenting ECG and a high ACI-TIPI score were significant predictors in the univariate models tested.

A combination of different multivariable logistic regression methods was used for model development. In each step of model development test of collinearity was performed using variance inflation factor (vif) with a plan to select the more meaningful predictor if any collinearity was found. A stepwise selection process resulted in a model with four covariates: age (truncated at 60 and 85 years), systolic blood pressure (dichotomized at 105 mm Hg), presence of ST elevation in the initial ECG, and duration of time from symptom onset until initiation of the study drug (dichotomized at one hour). The final model is shown in Table 2.

Figure 1 shows the ROC curve and Table 3 shows the data for calibration. There is good discrimination, with a C statistic 0.75. The calibration table suggests good agreement of the observed outcome with the predicted values.

Based on the final model, we calculated a predicted risk score as a continuous variable. For clinical use, tertiles of risk categories were created and the event rate calculated in each risk category. In the predictive model developed from the placebo group (Table 4) the event rate is 3.4% in the low-risk category, 5.6% in the moderate-risk category and 17.6% in high-risk category.

Finally, we applied the model to the entire dataset (both arms) and examined the effect of GIK on the different risk categories by introducing an interaction term. No significant interaction was found in the effect of GIK when patients with suspected ACS were studied across the risk categories. In the entire cohort, the odds of cardiac arrest or in-hospital mortality for the main effect of GIK in the treatment group was 0.45 (CI 0.24, 0.83, p value 0.01) relative to the odds in the placebo arm. Assuming constant OR across the spectrum of calculated risk the predicted absolute risk reduction was more pronounced (8.6% vs. 0.8%) for the high-risk group compared to the low-risk group, with corresponding numbers needed to treat being 12 and 125 respectively for the high- and low-risk tertiles. Table 5 and corresponding Figure 2 demonstrate the effect of GIK on the composite outcome of cardiac arrest and death by comparing the observed outcome rate with the predicted outcome rate, based on our model developed on patients who received placebo.

We studied the clinical profile of the patients in different risk groups and compared it to the overall group in the IMMEDIATE Trial. Table 6 summarizes the differences in the study groups. The high-risk group is about four years older than the entire cohort, has a mean systolic blood pressure on presentation about 11 mm Hg lower, with a much higher proportion of patients

having systolic blood pressure below 105 mm Hg. More often patients in the high-risk group presented within one hour of onset of symptoms, and they had ST elevation in the initial ECG twice as often as the other groups. The presence of these clinical characteristics in high risk patients is reflected in our predictive model and was considered reinforcing of the potential of the model to help select the most at-risk patients for expedited treatment.

DISCUSSION

Using the placebo group of the IMMEDIATE Trial, we developed a predictive model for the composite outcome of cardiac arrest or in-hospital mortality using four variables: age, systolic blood pressure, ST elevation in the presenting ECG, and duration of symptoms being within an hour of onset. Its predictive accuracy was good, reflected by a C statistic of 0.75, and it had very good calibration represented by the degree of agreement between the observed and predicted outcome rates. The overall OR for the entire cohort in our study was 0.45 (p value 0.01). In the scale of absolute risk reduction there is noticeable difference between the risk tertiles. This difference was most pronounced when the high-risk group was compared to the low risk group (absolute risk reduction 8.6% vs. 0.8%; NNT 12 vs. 125 respectively)

Treatment of ACS has evolved substantially over the last three decades, resulting in significant reductions in morbidity and mortality. Nonetheless, despite advances in thrombolysis and catheter based interventions, early mortality remains high.[19] To help address this, there have been efforts to develop predictive models and risk stratification methods to support evidence-based treatment that parallel advances in thrombolysis, antiplatelet therapy, and coronary interventions. Major contributions in this area of risk assessment came from the works of Killip[20] (1967), Forrester and Chatterjee[18] (1976) and Selker et al[9, 21-23] (1988-2002).

Pozen et al (1984)[24] developed a predictive model using seven variables that could reduce the proportion of hospitalizations among patients with chest pain but not having ACS from 44 to 33%. For the purpose of real-time clinical decision-making and using six variables as predictors and mortality as outcome the predictive model by Selker et al (1991) had a discriminative capacity of 0.80.[13] In another study, these investigators (1997) developed a predictive model for decision support for the treatment of patients with STEMI with thrombolysis. The model included 13 variables and had a discriminative capacity of 0.77-0.84 for 30-day mortality.[10] A seven-variable person-time interval model by Schmid et al (1997)[11] using time dependent treatment variable in the setting of MI to predict sudden cardiac arrest within 48 hours could achieve a C statistic of 0.79.

To represent the underlying risk of patients with suspected ACS, our predictive model for the composite outcome of cardiac arrest or mortality was developed using data from the placebo group of the IMMEDIATE Trial. In the overall study the total number of patients was 871 with total number of events 58; however, the predictive model was developed using the data from the placebo group (n=460, events=40). This model is simpler with four variables: age, duration of symptoms, systolic blood pressure, and presence of ST elevation in the presenting ECG. These variables are clinically sensible and easy to collect in real time. The model showed good discrimination reflected by a C statistic of 0.75, in line with those of previously developed models. Using variables readily obtainable in emergency medical service (EMS) settings, once validated on other data, the model should be applicable to use in the field. Moreover, our finding that the high-risk patients benefit most from administration of GIK by the EMS could help focus this treatment on those patients.

Although antiplatelet agents, thrombolytic therapy, and percutaneous coronary interventions remain the mainstays of treatment of ACS, there has been interest in finding added benefit from other pharmacological agents, such as GIK. Ever since the experiments in baboons by Opie et al[1]

in 1975, GIK has generated interest in research and clinical practice. Its low cost and availability make it appealing, but its exact benefits in humans have been unclear. Early studies in humans, such as DIGAMI[2, 3] demonstrated promise, but a subsequent large clinical trial by Mehta, et al concluded that high-dose GIK infusion had a neutral effect on mortality, cardiac arrest and cardiogenic shock in patients with STEMI.[5]

The effect of GIK in our study was independent of other patient-level variables, e.g., duration of chest pain, age, gender, traditional cardiovascular risk factors, etc. However, even assuming constant odds ratio across the risk-spectrum, the absolute risk reduction in the high risk group was 8.6% compared to 0.8% in the low risk group with the corresponding NNT being 12 and 125 respectively. If validated in an independent group of patients our model may help identify the high risk patients who may be prioritized for treatment with GIK, and potentially other important treatments.

Strengths of our study come from data used for the analysis. The IMMEDIATE Trial is a double-blinded, placebo-controlled, NIH-sponsored clinical effectiveness trial of 871 participants. Other strengths include the use of few and readily recognizable clinical predictors (age, SBP, duration from symptom onset, and ST elevation in ECG on presentation) and its discrimination performance reflected by a C statistic of 0.75. Also, its identification of the high-risk patients with more pronounced benefit of GIK makes the model potentially attractive for application in varied clinical settings.

There are a number of limitations to this study. The number of clinical outcome events of interest is relatively small (40 in the placebo group) compared to the candidate number of variables explored. Also, missing data limited investigation of some variables, such as duration of symptoms at the time of EMS initiation of treatment with the study drug. However, sensitivity analysis with the missing data made no significant change in the overall performance of the

predictive model. Data were not collected for traditional cardiovascular risk factors such as smoking and family history of premature coronary artery disease and from a practical perspective, reliable collection of these data was seen as challenging in the acute EMS setting. It would be interesting to see if laboratory parameters like CRP, initial glucose level or potassium levels could have played any role in the predictive model. Only a small number of patients had data collected for these variables and, because these tests are not uniformly available in all EMS settings, collecting data for them was not practical for this predictive model.

Finally, for validation of our findings and prior to general clinical use, the predictive model must be tested on other datasets. This also applies to the finding of greater benefit from GIK in the high-risk group, although such an effect is consistent with other studies of intervention that find more effect with higher risk patients. We encourage such testing on analogous data sets, understanding that extant data on very early treatment with GIK in a placebo-controlled trial are still hard to find.

Our predictive model achieved good accuracy in identifying patients with suspected ACS at high risk of cardiac arrest or death. The results of our analysis of the IMMEDIATE Trial placebo and treatment groups provide understanding of the potentially enhanced impact of GIK in high-risk patients. The fact that the model's risk includes earliness of treatment reinforces understanding that earlier treatment with GIK is more efficacious. Once the model and the GIK results are validated on other datasets, these results could be helpful in identifying patients most likely to deserve most immediate attention and acute interventions for ACS, including very early out-of-hospital GIK

Table 1 Baseline Characteristics of Participants by Outcome Groups (N =460)

Characteristics	*Participants with cardiac arrest or in-hospital mortality N=40, n=(#) when n<N*	*Participants without cardiac arrest or in-hospital mortality N=420, n=(#) when n<N*	*P value (logistic regression Chi square)*
Age *(mean ± SD, years)*	68.4 ± 13.74	62.84 ± 14.11	0.019
Gender, % male	65%	70%	0.512
BMI	28.48 ± 5.9 (n=27)	29.17 ± 7.04 (n=385)	0.614
Time from onset of symptoms to treatment (minutes)			
Mean ± SD	140.2 ± 192.63 (n=32)	154.2 ± 184.45 (n=356)	0.684
median <IQR>	54.5 <43.0 to 151.8>	85 <51.75 to 166.75>	
Vital Signs, (mean ± SD, years)			
Out-of-Hospital			
Systolic BP (mm Hg)	126.2 ± 34.66	145.1 ± 34.64 (n=417)	<0.001
Diastolic BP (mm Hg)	78.66 ± 22.14 (n=38)	85.55 ± 25.27 (n=413)	0.103
Pulse Rate (beats/m)	86.05 ± 27.34	86.65 ± 25.43 (n=417)	0.887
Respiration rate/m	20.1 ± 5.52 (n=39)	19.41 ± 4.42 (n=403)	0.346
In Emergency Department			
Systolic BP (mm Hg)	122.8 ± 26.87	138.4 ± 27.2	<0.001
Diastolic BP (mm Hg)	71.13 ± 22.77 (n=39)	81.46 ± 17.62 (n=418)	0.001
Pulse Rate (beats/m)	90.58 ± 23.94	83.08 ± 22.62	0.048
Respiration rate/min	19.41 ± 4.10 (n=39)	19.06 ± 4.07 (n=412)	0.605
Medical History, % (n)			
MI	40.0% (16)	34.1% (143)	0.45
CABG	22.5% (9)	13.3% (56)	0.117
PCI	42.5% (17)	25.7% (108)	0.025
CHF	17.5% (7)	16.7% (70)	0.893
Stroke	7.5% (3)	8.6% (36)	0.816
DM	30.0% (12)	26.0% (109)	0.579
Hypertension	72.5% (29)	66.9% (281)	0.472
Hyperlipidemia	47.5% (19)	50.0% (210)	0.763
Previous Aspirin	60.0% (24)	50.24% (211)	0.24
Previous Beta blocker	37.5% (15)	39.05% (164)	0.848
Initial in-hospital laboratory values			
Glucose (mg/dl)	231.8 ± 137.6 (n=39)	164.1 ± 89.33 (n=415)	0.004
Potassium (mEq/L)	4.09 ± 0.81 (n=39)	3.93 ± 0.53 (n=410)	0.094
Out-of-hospital ECG			
ST segment elevation	70.0% (28)	39.52% (166)	<0.001
ACI-TIPI score, (Mean ± SD)	85.26 ± 9.33 (n=25)	76.09 ± 21.22 (n=314)	0.011
PR interval (ms)	138.7 ± 84.45 (n=25)	135.8 ± 74.28 (n=314)	0.852
QTc duration (ms)	430.3 ± 31.45 (n=25)	431.3 ± 74.28 (n=314)	0.937
QRS axis (degrees)	43.68 ± 45.47 (n=25)	24.92 ± 57.40 (n=314)	0.112
T wave axis (degrees)	80.6 ± 81.89 (n=25)	73.3 ± 68.92 (n=314)	0.614
P wave axis (degrees)	58.24 ± 53.60 (n=25)	50.9 ± 47.17 (n=314)	0.458

Table 2 Final Model

Variable	Estimate	95% CI		OR	95% CI		P value
(Intercept)	-6.95	-9.78	-4.24	0.00	0.00	0.01	0.000
Age truncated	0.06	0.02	0.10	1.06	1.02	1.10	0.002
STEMI	1.44	0.71	2.22	4.22	2.04	9.24	<0.001
BPcat (Below105)	0.99	0.14	1.78	2.68	1.15	5.96	0.02
CPCat (<60 mins)	1.97	1.05	4.06	1.97	0.95	4.06	0.07

N= 457, missing: BPcat 3, Age truncated 0, STEMI 0, CPCat 0.

Residual deviance 238.28 on 452 degrees of freedom AIC 248.28, C statistic 74.6 Age<60 treated as 60 and age >85 treated as 85 year.

Table 3 Calibration in the Developmental Data *(Placebo Group of IMMEDIATE Trial)*

Risk Tertile	Total	Mean Predicted Risk	Predicted Number	Observed Number
Low	153	2.3%	3.57	5
Moderate	152	6.2%	9.44	8
High	152	17.8%	26.98	27

Table 4 Event Rates by Risk Tertiles and Treatment Groups

Risk Tertiles	**Observed Event Rates n (%)**		**Predicted**		
	GIK (n=408)	**Placebo** (n=457)	**OR**	**ARR**	**NNT**
Total N=865, missing=6	17 (4.2)	40 (8.8)	0.45 (0.23, 0.83)		
Low N=290 (34%)	2 (1.4)	5 (3.4)	-	0.8%	125
Moderate N=288 (33%)	8 (6.2)	9 (5.6)	-	3.3%	30
High N=287 (33%)	7 (5.1)	26 (17.6)	-	8.6%	12

P value for overall OR of GIK vs. placebo = 0.01; OR= Odds ratio; ARR=Absolute risk reduction; NNT=Number needed to treat.

P value for test of interaction (risk tertile: treatment) = 0.12. There is no significant interaction between GIK and risk tertile for the outcome.

Table 5 Observed and Predicted Risk in Treatment Groups

Risk Tertile	**Total**	**Mean Predicted Risk** % (n)	**Mean Observed Risk** % (n)
Low	136	2.3% (3.09)	1.5% (2)
Moderate	137	6.1% (8.4)	5.8% (8)
High	135	17.6% (23.78)	5.2% (7)

Table 6 Clinical Characteristics of Participants in Different Risk Tertiles

Group	Age (year)	Systolic Blood Pressure (mm Hg)	Systolic Blood Pressure < 105 mm Hg (%)	Presentation ≤ 1 hour (%)	ST elevation (%)
Overall	63.6	143	12%	37%	41%
High Risk	67.9	132	28%	63%	82%
Moderate Risk	67.6	144	7%	16%	41%
Low Risk	55.5	153	0%	28%	0%

Figure 1 ROC Curve for the Final Model

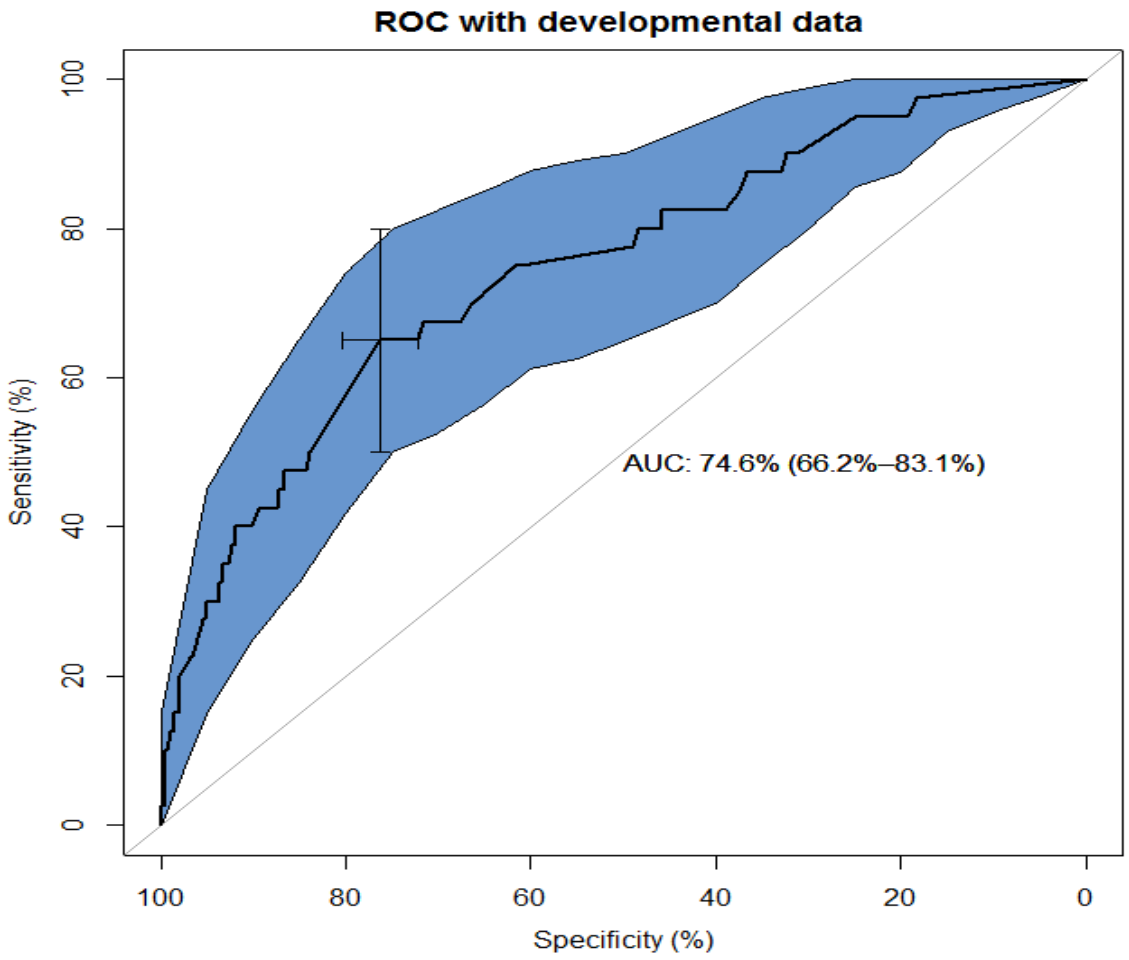
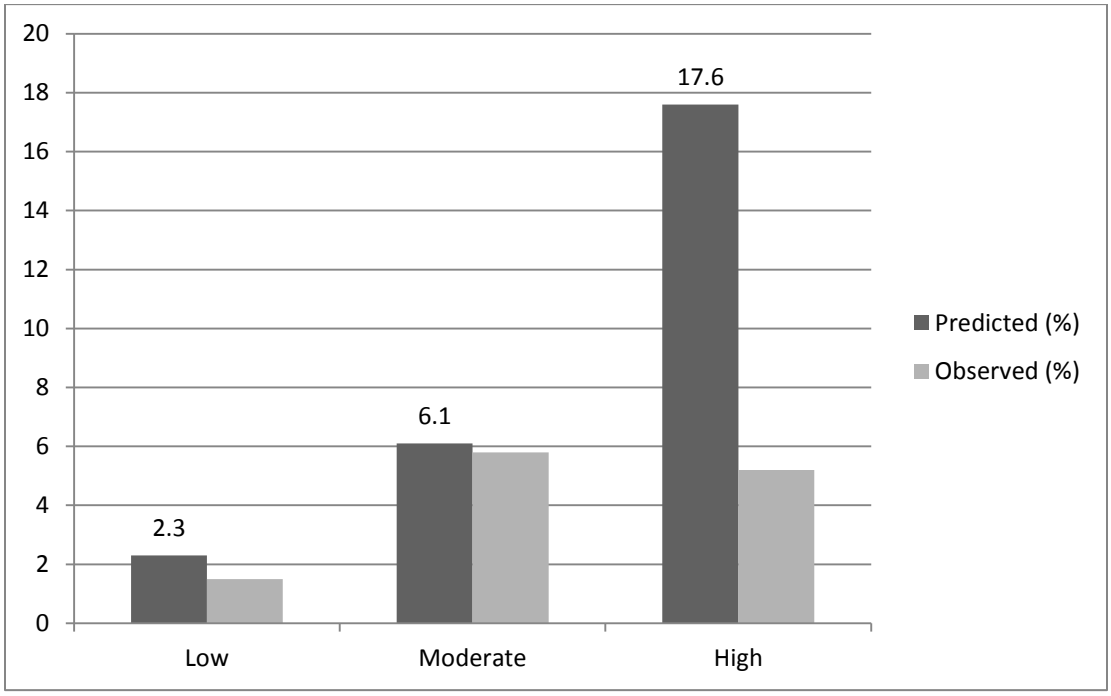


Figure 2 Effect of GIK in the Treatment Group



REFERENCES

1. Opie LH, Bruyneel K, Owen P. Effects of glucose, insulin and potassium infusion on tissue metabolic changes within first hour of myocardial infarction in the baboon. *Circulation*. 1975;52:49-57
2. Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, Wedel H, Welin L. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (digami study): Effects on mortality at 1 year. *J Am Coll Cardiol*. 1995;26:57-65
3. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. Digami (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) study group. *BMJ*. 1997;314:1512-1515
4. Yusuf S, Mehta SR, Diaz R, et al. Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The create and ecla trial program evaluating gik (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction. *Am Heart J*. 2004;148:1068-1078
5. Mehta SR, Yusuf S, Diaz R, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute st-segment elevation myocardial infarction: The create-ecla randomized controlled trial. *JAMA.* 2005;293:437-446
6. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: The immediate randomized controlled trial. *JAMA.* 2012;307:1925-1933
7. Selker HP, Beshansky JR, Griffith JL, et al. Study design for the immediate myocardial metabolic enhancement during initial assessment and treatment in emergency care (immediate) trial: A double-blind randomized controlled trial of intravenous glucose,

insulin, and potassium for acute coronary syndromes in emergency medical services. *Am Heart J*. 2012;163:315-322

8. Selker HP, Griffith JL, D'Agostino RB. A time-insensitive predictive instrument (tipi) for acute cardiac ischemia: A multicenter study. *Med Care*. 1991;29:610-627
9. Selker HP, Beshansky JR, Griffith JL, et al. Use of the acute cardiac ischemia time-insensitive predictive instrument (aci-tipi) to assist with triage of patients with chest pain or other symptoms suggestive of acute cardiac ischemia. A multicenter, controlled clinical trial. *Ann Intern Med*. 1998;129:845-855
10. Selker HP, Griffith JL, Beshansky JR, et al. Patient-specific predictions of outcomes in myocardial infarction for real-time emergency use: A thrombolytic predictive instrument. *Ann Intern Med*. 1997;127:538-556
11. Schmid CH, D'Agostino RB, Griffith JL, Beshansky JR, Selker HP. A logistic regression model when some events precede treatment: The effect of thrombolytic therapy for acute myocardial infarction on the risk of cardiac arrest. *J Clin Epi*. 1997;50:1219-1229
12. Selker HP, Raitt MH, Schmid CH, et al. Time-dependent predictors of primary cardiac arrest in patients with acute myocardial infarction. *Am J Cardiol*. 2003;91:280-286
13. Selker HP, Griffith JL, D'Agostino RB. A time-insensitive predictive instrument for acute myocardial infarction mortality: A multicenter study. *Med Care*. 1991;29:1196-1211
14. Oliver MF, Opie LH. Effects of glucose and fatty acids on myocardial ischaemia and arrhythmias. *Lancet*. 1994;343:155-158
15. Kurien VA, Yates PA, Oliver MF. Free fatty acids, heparin, and arrhythmias during experimental myocardial infarction. *Lancet*. 1969;2:185-187
16. Doven O, Ozdol C, Sayin T, Oral D. Qt interval dispersion: Non-invasive marker of ischemic injury in patients with unstable angina pectoris? *Jpn Heart J*. 2000;41:597-603
17. Hohnloser SH. Effect of coronary ischemia on qt dispersion. *Prog Cardiovasc Dis*. 2000;42:351-358

18. Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (first of two parts). *N Engl J Med*. 1976;295:1356-1362

19. Organization. WH. Fact sheet no. 317: Cardiovasc diseases . 2012;September 2012

20. Killip T, 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol*. 1967;20:457-464

21. Selker HP, D'Agostino RB, Laks MM. A predictive instrument for acute ischemic heart disease to improve coronary care unit admission practices: A potential on-line tool in a computerized electrocardiograph. *J Electrocardiol*. 1988;21 Suppl:S11-17

22. Selker HP. Coronary care unit triage decision aids: How do we know when they work? *Am J Med*. 1989;87:491-493

23. Selker HP, Beshansky JR, Griffith JL. Use of the electrocardiograph-based thrombolytic predictive instrument to assist thrombolytic and reperfusion therapy for acute myocardial infarction. A multicenter, randomized, controlled, clinical effectiveness trial. *Ann Intern Med*. 2002;137:87-95

24. Pozen MW, D'Agostino RB, Selker HP, Sytkowski PA, Hood WB. A predictive instrument to improve coronary-care-unit admission practices in acute ischemic heart disease. *N Engl Med*. 1984;310:1273-1278