IJC Heart & Vasculature 9 (2015) 37–42

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

# A predictive model to identify patients with suspected acute coronary syndromes at high risk of cardiac arrest or in-hospital mortality: An IMMEDIATE Trial sub-study☆,☆☆,☆☆☆,☆☆☆☆

Madhab Ray [a,c,e], Robin Ruthazer [b], Joni R. Beshansky [b,f], David M. Kent [c,d,e], Jayanta T. Mukherjee [c,e], Hadeel Alkofide [c,e], Harry P. Selker [b,c,*]

[a] Lahey Hospital and Medical Center, Burlington, MA, United States
[b] Center for Cardiovascular Health Services Research, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, United States
[c] Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, United States
[d] Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, United States
[e] Sackler School of Graduate Biomedical Sciences, Tufts University, Boston, MA, United States
[f] Regis College, Regulatory and Clinical Research Management, Weston, MA, United States

ARTICLE INFO

*Article history:*
Received 28 May 2015
Accepted 14 July 2015
Available online 27 August 2015

*Keywords:*
Acute coronary syndrome
Glucose–insulin–potassium (GIK)
Predictive model
Cardiac arrest
Mortality
Emergency medical service

ABSTRACT

*Background:* The IMMEDIATE Trial of emergency medical service use of intravenous glucose–insulin–potassium (GIK) very early in acute coronary syndromes (ACS) showed benefit for the composite outcome of cardiac arrest or in-hospital mortality.
*Objectives:* This analysis of IMMEDIATE Trial data sought to develop a predictive model to help clinicians identify patients at highest risk for this outcome and most likely to benefit from GIK.
*Methods:* Multivariable logistic regression was used to develop a predictive model for the composite endpoint cardiac arrest or in-hospital mortality using the 460 participants in the placebo arm of the IMMEDIATE Trial.
*Results:* The final model had four variables: advanced age, low systolic blood pressure, ST elevation in the presenting electrocardiogram, and duration of time since ischemic symptom onset. Predictive performance was good, with a C statistic of 0.75, as was its calibration. Stratifying patients into three risk categories based on the model's predictions, there was an absolute risk reduction of 8.6% with GIK in the high-risk tertile, corresponding to 12 patients needed to treat to prevent one bad outcome. The corresponding values for the low-risk tertile were 0.8% and 125, respectively.
*Conclusions:* The multivariable predictive model developed identified patients with very early ACS at high risk of cardiac arrest or death. Using this model could assist treating those with greatest potential benefit from GIK.


## 1. Introduction

Studies in animals suggest that intravenous glucose–insulin–potassium (GIK), when administered very 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] which have been postulated to be due to the variable delay in the administration of GIK after the onset of ischemia. Supporting the importance of very early identification of suitable patients and treatment, the IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care) Trial, which studied very early administration of GIK to patients with an acute coronary syndrome (ACS) by emergency medical service (EMS), showed reduction in the composite endpoint of cardiac arrest or in-hospital mortality in the study group, thereby supporting the importance of prompt identification of these patients [6].

☆ *Acknowledgments of grant support*: 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 the National Heart, Lung and Blood Institute (U01HL077821, U01HL077823, and U01HL077826). The IMMEDIATE Trial is registered at www.ClinicalTrials.gov (NCT00091507).
☆☆☆ David Kent, MD, MSc is supported by a NIH grant 1UL1 TR001064.
☆☆☆☆ Each author takes the responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
* Corresponding author at: Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, 800 Washington St, #63, Boston, MA 02111, United States. Tel.: +1 617 636 5009; fax: +1 617 636 8023.
*E-mail address:* hselker@tuftsmedicalcenter.org (H.P. Selker).

http://dx.doi.org/10.1016/j.ijcha.2015.07.001

As treatment of ACS has evolved, including early primary percutaneous coronary intervention (PCI), there have been significant reductions in mortality. To maximize this impact, there is a need to identify patients with suspected ACS who are at high risk for cardiac arrest or death very early in their clinical course, such as during initial evaluation by EMS. This identification remains challenging, however. Among patients presenting with chest pain or other symptoms suggesting ACS, only about a quarter truly have ACS, and among those with ACS, rapid identification of those at high risk is crucial in order to provide prompt treatment and allocation of valuable attention and resources [7].

To address this need, using data from the IMMEDIATE Trial, we used logistic regression to develop a predictive model to stratify the risk of cardiac arrest or death among patients presenting with suspected ACS. We then examined the degree of GIK's treatment effect across risk groups defined by the predictive model.

## 2. Methods

### 2.1. Dataset

This study used data from the IMMEDIATE Trial. Details of the study protocol and inclusion and exclusion criteria have been published elsewhere [6,8].It was a randomized, placebo-controlled, double-blind, multicenter clinical effectiveness trial conducted across the United States that assessed the effect of intravenous GIK infusion initiated by EMS in the out-of-hospital setting for patients with suspected ACS. Of its 871 randomized participants; for the development of the predictive model, we used only data from the control (placebo) group, to represent the clinical course of ACS uninfluenced by GIK.

### 2.2. The 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) done for symptoms suggestive of ACS. To be included, a patient's out-of-hospital ECG had to meet at least one of the following criteria: a 75% or higher prediction of ACS by the acute ischemia time insensitive predictive instrument (ACI-TIPI) [7], the generation by the thrombolytic predictive instrument (TPI) of a statement recognizing ST elevation myocardial infarction (STEMI) [7], or a judgment by the paramedic that the ECG showed definite STEMI using local standards. Excluded were patients who had a language barrier, impaired reasoning, were prisoners, pregnant, or had rales suggesting heart failure. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

### 2.3. Presenting clinical variables

For analyses, 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 ischemic symptoms, vital signs (pulse, and systolic and diastolic blood pressures) obtained out-of-hospital and in the emergency department (ED), medical history 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 the axes of the P, T, and QRS waves. We also used the probability of ACS computed by the ACI-TIPI [7,9] and for the QTc variable, categories previously developed in a cardiac arrest model [10], and for heart rate and blood pressure, variables previously used in predictive models of cardiac arrest and in-hospital mortality [11–13].

### 2.4. Clinical outcome to be predicted

The outcome of interest was the composite of cardiac arrest or in-hospital mortality, as adjudicated for the IMMEDIATE Trial [6,8].

### 2.5. Development of predictive model

Using data from the IMMEDIATE Trial control participants, we compared baseline characteristics of those with and without the cardiac arrest or mortality composite outcome. Between group differences were assessed by logistic regression based on demographic, clinical, and ECG data. Variables that were significant at $p < 0.01$ were included in the multivariable model building process to identify patients at highest risk for the composite outcome (who thereby might benefit most by early administration of GIK). Collinearity was tested by examining the variance inflation factor (vif); if its square root was more than two, collinearity was suspected and the variable with lowest p value was used in further analyses.

Stepwise multivariable logistic regression analysis was performed using the most promising variables from the univariate analyses. Clinical meaningfulness and the Akaike Information Criteria (AIC) were used in variable selection, resulting in the model with four variables described below.

The final model was tested for predictive discrimination by C statistic (the equivalent of the area under the receiver-operating characteristic [ROC] curve). Predicted values from the final model were calculated for all patients (GIK and placebo treated), which were used to stratify patients into tertiles of risk. The observed 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, we evaluated the clinical characteristics of patients in the highest risk group for consideration for early GIK therapy.

## 3. Results

Table 1 shows the baseline characteristics of the study sample and rates of cardiac arrest or in-hospital mortality.

Of the 871 trial participants (411 given GIK and 460 given placebo), 58 had an out- or in-hospital cardiac arrest or died during the index hospitalization. Forty occurred in the control group (29 cardiac arrests, 23 with in-hospital mortality, and 12 with both), and 18 in the GIK group (15 cardiac arrests, 13 with in-hospital mortality, and 10 with both). To construct the risk predictive model of baseline risk, we used the data from the placebo group ($n = 460$). As in Table 1, when compared to the participants without any events, those with one of these events were slightly older and more likely women, presented later (but not significantly), had systolic blood pressures that were about 10 mm Hg lower and pulse rates about 10 beats per minute higher, had more frequent histories of previous coronary artery disease, more often had ST elevation on their presenting ECG, and had higher ACI-TIPI probabilities of having ACS. These differences are consistent with those who have cardiac arrest, are of more advanced age, have lower systolic blood pressure, tachycardia, history of coronary artery disease, ST elevation on presentation, and higher ACI-TIPI score, These were considered appropriate variables for the predictive model.

Among 34 candidate variables, 11 were statistically significant and one borderline significant. Among demographic variables, age was significant and gender was not. Neither traditional cardiovascular risk factors, nor history of coronary artery disease, heart failure, stroke, use of aspirin, or beta blocker were significantly related to the outcome. Further characterization of age using restricted cubic spline demonstrated a nonlinear relationship of age with the outcome of interest. 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, based on the data the age variable was truncated at 60