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 Raya, Robin Ruthazer, Joni R. Beshansky, David M. Kent, Jayanta T. Mukherjee, Hadeel Alkofide, Harry P. Selker

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 of 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 present 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 6.8% 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 UL1TR000173.

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).

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).
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 revised in 1983. The final protocol 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.

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.
and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates.

Although univariate analyses did not demonstrate significant predictive value of QTc or duration of symptoms, a composite variable of QTc with duration of chest pain since onset was created as described in the literature [10]. This variable was tested in the multivariable model, and no improvement in model performance was found.

We used both heart rate and systolic blood pressure to account for the hemodynamic state of the patient, including a composite variable found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: age

and 85 years, and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: age

and 85 years, and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: age

and 85 years, and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: age

and 85 years, and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: age

and 85 years, and ages between 60 and 85 years demonstrated a smooth pattern and was treated as a continuous variable. This resulted in a small degree of further improvement in model performance.

Univariate analyses of systolic blood pressure suggested a non-linear relationship; systolic blood pressure less than 105 mm Hg was adverse-

No improvement was noted in the model as measured by C statistic. In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. However, blood tests were found significant for predicting mortality from ACS in another study [14]. No improvement was noted in the model as measured by C statistic.

In the out-of-hospital setting, systolic blood pressure was found to be a significant covariate and respiratory rate was of borderline significance. When vital signs recorded in the ED were analyzed, systolic and diastolic blood pressures, heart rate, and respiratory rate were significant covariates. However, blood tests were judged unattractive 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.

Based on all these considerations, stepwise multivariable logistic regression selection resulted in a final model with four variables: 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 treatment (dichotomized at 1 h), in Table 2.

Fig. 1 in the Appendix shows the ROC curve for the model’s predictions; good discrimination is reflected by the C statistic (ROC area) of 0.75, and calibration, in Table 3, shows good agreement of predicted to actual outcomes. The C statistic for the GIK group was 0.73 with a 95% confidence interval of 0.61–0.85. Fig. 2 in the Appendix shows the ROC curve for the treatment group while the adjoining Table 1 and Fig. 3 show the calibration.

Based on the final model, we calculated a predicted risk score as a continuous 0–100% variable. For potential clinical use, tertiles of risk categories were created and event rates calculated for each risk category. Among the placebo group participants, the event rate was 3.4% in the low risk category, 5.6% in the moderate risk category, and 17.6% in high-risk category (Table 4).

Finally, we applied the model to the entire IMMEDIATE Trial dataset (placebo and GIK arms) and examined the effect of GIK on the different risk categories by introducing an interaction term. A significant interaction was not found across all the risk categories. In the entire cohort, the odds of the composite outcome cardiac arrest or in-hospital mortality related to GIK was 0.45 (CI 0.24, 0.83, p = 0.01). Assuming a constant odds ratio across the spectrum of calculated risk, the predicted absolute risk reduction was much more pronounced for the high-risk group compared to the low-risk group (8.6% vs. 0.8%), with corresponding numbers needed to treat (NNT) of 12 and 125 respectively. A constant odds ratio was used as there was no interaction noted between GIK and the risk categories.

We studied the clinical profile of the patients in different risk groups among the IMMEDIATE Trial participants. Table 5 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 1 h of ischemic symptom onset, and twice as often had ST elevation on their initial ECG. The presence of these clinical characteristics in high-risk patients is consistent with our predictive model and with the objective of expediting treatment of the most at-risk patients.

3.1. Development of a risk scoring system and calculation of IMMEDIATE Score

For potentially easier use in the field by the first responder EMS we developed a simple scoring system based on the rounding to the integer scores of the coefficients of the four variables in our final model. In this scoring system, henceforth called IMMEDIATE Score, age below 60 years has been assigned a score of 0 and the age group above 60 and less than or equal to 65 years has been assigned a score of 1, with each 5-year increment increasing the score by 1 to a maximum of 6 for age ≥ 85 years. Presence of ST elevation in the presenting ECG gives a score of 5, low systolic blood pressure (<105 mm Hg) at the first assessment by the EMS gives a score of 3 and presentation within 1 h of symptom onset gives a score of 2. Absence of ST elevation, systolic blood pressure more than 105 mm Hg and presentation later than 1 h from the onset of symptoms each gives a score of zero in this scale. Thus the range of the scale may vary from 0 to 16. Table 2 in the Appendix illustrates the scale with the estimated probabilities of death or cardiac arrest for each possible score. The scale has excellent calibration (Fig. 4 in the Appendix) and reasonably maintains the power of discrimination demonstrated by the predictive model with a C statistic of 0.70 (95% CI: 0.63 to 0.77) compared to the C statistic of 0.75 in the final model. Although the C statistic and the corresponding area under the ROC curve (Fig. 5 in the Appendix) for the scoring system is found to be marginally less than that of the final full model, this difference was not statistically significant.

3.2. Reclassification of risk groups based on scoring system

For each model subjects were categorized into 3 risk groups using two methods, first into 3 groups of equal size and second into groups of equal risk ranges. We assessed the degree of reclassification using predictABLE package in R. No significant difference was noted between the two models by either approach as measured by categorical Net Reclassification Improvement (NRI) or Integrated Discrimination Improvement (IDI) (Table 3 in the Appendix) Apparent reclassification in favor of the lower risk categories (Table 4 and its effect on ARR and NNT (ARR 2.9% and NNT 35 in both moderate and high risk categories) while an equal number of patients are used to create risk tertiles is possibly explained by varying weights of different predictors and rounding to the nearest integer in the simple risk scoring model in addition to the small number of events in different risk groups. Although taking higher integers to represent the coefficients of the model may reduce this shift and maintain rigor in the predictive value of the variables, they may be difficult to use at the bedside. We encourage a computer based use of the predictive model to estimate the probability of cardiac arrest or death. Nevertheless, this simple and easy to use risk scoring system can be utilized by the EMS to identify patients at higher risk without any significant loss of discrimination power of the original model. This may expedite important treatment decisions and use of valuable resources, more so in areas where access to computer based risk stratification is not readily available.

4. Discussion

Based on patients with ACS not receiving GIK in the IMMEDIATE Trial, we developed a predictive model for the composite outcome of cardiac arrest or in-hospital mortality, based on four variables: age, systolic blood pressure, ST elevation on the presenting ECG, and time from

| Variable                  | Estimate | 95% CI    | OR       | 95% CI    | p value |
|---------------------------|----------|-----------|----------|-----------|---------|
| (Intercept)               | −6.95    | −9.78     | −4.24    |           |         |
| Age, truncated at 60 and 85<sup>a</sup> | 0.06     | 0.02      | 1.06     | 1.02      | 1.10    | 0.002  |
| ST elevation on out-of-hospital ECG | 1.44     | 0.71      | 2.22     | 4.22      | 2.04    | 9.24   | <0.001 |
| Pre-hosp systolic blood pressure <105 mm Hg | 0.99     | 0.14      | 1.78     | 2.68      | 1.15    | 5.96   | 0.02   |
| Time from symptom onset to start of treatment (<60 min) | 0.68     | −0.05     | 1.40     | 1.97      | 0.95    | 4.06   | 0.07   |

<sup>a</sup> N = 57 participants treated with placebo and with non-missing data (3 participants excluded because of missing blood pressure), C statistic 0.75.

<sup>b</sup> Age < 60 treated as 60 and age > 85 treated as 85 year.
onset of ischemic symptoms. Applied to its development set, its predictive accuracy was good, reflected by a C statistic of 0.75, as was its calibration, represented by agreement between the predicted and actual outcome rates.

When the model’s predictions were used to create three equal-sized risk groups, there were noticeable differences between risk tertiles. These categories showed potential for identifying those patients with the most to gain from early treatment with GIK. Whereas the overall odds ratio for GIK’s impact on the composite endpoint of cardiac arrest or mortality in the entire IMMEDIATE Trial cohort was 0.45 (p = 0.01), high-risk patients appear to have the most potential for benefit. Those in the high-risk group had an absolute risk reduction by GIK of 8.6%, with a NNT of 12, versus in the low-risk group having an absolute risk reduction of 0.8% and a NNT of 125. An apparent increase in the event rate in the intermediate risk category was possibly due to the statistical effect of the small number of events in this category.

Treatments of ACS has evolved substantially over the last three decades, resulting in significant reductions in morbidity and mortality, but early mortality remains high [16]. To help address this, there have been efforts to develop predictive models and risk stratification methods [7,17–21] to support evidence-based treatment that parallel advances in thrombolysis, antiplatelet therapy, and coronary interventions. To represent the underlying risk of patients with suspected ACS for the composite outcome of cardiac arrest or mortality, we used data from the untreated (placebo) group of the IMMEDIATE Trial. Compared to previous models, ours is simpler, having just four variables that are clinically straightforward and easily collected in EMS and ED settings. Once validated on other data, the model should be applicable to use in the field. In such use, our findings suggest that it could assist identification of the high-risk patients who would benefit most from administration of GIK by the EMS and thus could help focus treatment on them.

The overall effect of GIK in the IMMEDIATE Trial on our study outcome, and confirmed in our analyses, was an odds ratio of 0.45 (p = 0.01). This is independent of other patient-level variables and is very encouraging, but in clinical settings, it is understood that there is heterogeneity of treatment effect, and being able to select those most likely to benefit is important [22]. The utility of this is illustrated by the difference in potential benefit in the high versus the low risk groups: 8.6% compared to 0.8%, respectively. Thus avoiding cardiac arrest or mortality should be much more efficient in the high-risk group, for whom only 12 must be treated to prevent one outcome, versus 125 in the low-risk group. 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.

For ease of use in resource limited areas where computer based risk stratification is not easily available we developed a simple integer version of the scoring system, the IMMEDIATE Score. By using this 16 point scoring system, the EMS responders can estimate the risk of death or cardiac arrest for an individual patient in the appropriate clinical context and tailor clinical decisions accordingly.

The strengths of our study come from data used for the analysis, the IMMEDIATE Trial, a double-blinded placebo-controlled NIH-sponsored clinical effectiveness trial that used carefully adjudicated outcomes. Another strength is our model’s use of few and readily recognizable clinical predictors (age, SBP, duration from symptom onset, and ST elevation in ECG on presentation) and its very good predictive performance. Also, following further validation, it shows promise as being potentially attractive for identifying patients for treatment in varied EMS and ED settings.

### Table 4
Event rates by risk tertiles and treatment groups.

| Risk tertiles | Observed number of events and rates n (%) | Predicted |
|---------------|------------------------------------------|-----------|
|               | GIK (n = 408) | Placebo (n = 457) | OR | ARRI |
| Total | 17 (4.2) | 40 (8.8) | 0.45 (0.23, 0.83) | p-value = 0.01 |
| Low | 2 (1.4) | 5 (3.4) | - | 0.8% | 125 |
| Moderate | 8 (6.2) | 9 (5.6) | - | 3.3% | 30 |
| High | 7 (5.1) | 26 (17.6) | - | 8.6% | 12 |

OR = Odds ratio; ARRI = Absolute risk reduction; NNT = Number needed to treat. p value for interaction for test of homogeneity of odds ratio across risk tertiles = 0.12. There is no significant interaction between GIK and risk tertile for the outcome.

* ARRI based on a common odds ratio of 0.45 applied to each stratum.

### Table 5
Clinical characteristics of participants in different risk tertiles.

| Clinical characteristics | Overall | High risk | Moderate risk | Low risk |
|--------------------------|---------|-----------|---------------|---------|
| Age (years), mean        | 63.6    | 67.9      | 67.6          | 55.5    |
| Systolic blood pressure  | 143     | 132       | 144           | 153     |
| (mm Hg) mean             |         |           |               |         |
| Systolic blood pressure < 105 mm Hg (%) | 12% | 28% | 7% | 0% |
| Presentation ≤ 1 h (%)   | 37%     | 63%       | 16%           | 28%     |
| ST elevation on presenting ECG (%) | 41% | 82% | 41% | 0% |

4.1. Limitations

There are a number of limitations to this study. The overall IMMEDIATE Trial with 871 participants had a total of 58 of the composite events, and for our model, using only the placebo group, we had only 40 events. This is relatively few compared to the candidate number of variables explored. Also, data were not collected for a few 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 might be of interest to investigate laboratory parameters like CRP, initial glucose level, and potassium levels, but only the relatively small IMMEDIATE Trial Biological Mechanism Cohort had these data. Moreover, these tests are not uniformly and promptly available in the EMS setting and thus were considered unattractive for this predictive model ultimately aimed at immediate use in EMS and ED care.

Finally, for validation of our findings and prior to general clinical use, the predictive model we developed must be tested on other datasets. This also applies to the finding of the 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.
5. Conclusions

This IMMEDIATE Trial-based predictive model appears to accurately identify patients with suspected ACS who are at high risk of cardiac arrest or death and who could benefit most from GIK. That the model’s risk factors include earliness of treatment reinforces recent understanding that earlier treatment with GIK is more efficacious. Once the model has been validated in other datasets and in practice, it could be helpful in identifying patients most likely to deserve immediate attention and acute interventions for ACS, including very early out-of-the-hospital GIK.

Conflict of interest

None.

Acknowledgments

We thank Robert Goldberg, PhD, Jessica Paulus, ScD, and Norma Terrin, PhD for their review and editorial assistance of the article. We thank Cathy Griffin for the expert manuscript preparation. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcha.2015.07.001.

References

[1] L.H. Opie, K. Bruyneel, P. Owen, Effects of glucose, insulin and potassium infusion on tissue metabolic changes within first hour of myocardial infarction in the baboon, Circulation 52 (1975) 49–57.

[2] K. Malmberg, L. Ryden, S. Eftendic, J. Herlitz, P. Nicol, A. Waldenstrom, et al., 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. 26 (1995) 57–65.

[3] K. Malmberg, 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 314 (1997) 1512–1515.

[4] S. Yusuf, S.R. Mehta, R. Diaz, E. Paolasso, P. Pais, D. Xavier, 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, Ann. Heart J. 148 (2004) 1068–1078.

[5] S.R. Mehta, S. Yusuf, R. Diaz, J. Zhu, P. Pais, D. Xavier, 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 293 (2005) 437–446.

[6] H.P. Selker, J.R. Beshansky, P.R. Sheehan, J.M. Massaro, J.L. Griffith, R.B. D’Agostino, et al., Out-of-hospital administration of intravenous glucose–insulin–potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial, JAMA 307 (2012) 1925–1933.

[7] H.P. Selker, J.R. Beshansky, J.L. Griffith, T.P. Aulderheide, D.S. Ballin, S.A. Bernard, et al., Use of the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIP) 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. 129 (1998) 845–855.

[8] H.P. Selker, J.R. Beshansky, J.L. Griffith, R.B. D’Agostino, J.M. Massaro, J.E. Udelson, 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. 163 (2012) 315–322.

[9] H.P. Selker, J.L. Griffith, R.B. D’Agostino, A tool for judging coronary care unit admission appropriateness, valid for both real-time and retrospective use. A time-insensitive predictive instrument (TIP) for acute cardiac ischemia: a multicenter study, Med. Care 29 (1991) 610–627.

[10] H.P. Selker, J.L. Griffith, J.R. Beshansky, C.H. Schmid, R.M. Califf, R.B. D’Agostino, et al., Patient-specific predictions of outcomes in myocardial infarction for real-time emergency use: a thrombolytic predictive instrument, Ann. Intern. Med. 127 (1997) 538–556.

[11] C.H. Schmid, R.B. D’Agostino, J.L. Griffith, J.R. Beshansky, H.P. Selker, 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. Epidemiol. 50 (1997) 1219–1229.

[12] H.P. Selker, M.H. Raitt, C.H. Schmid, M.M. Laks, J.R. Beshansky, J.L. Griffith, et al., Time-dependent predictors of primary cardiac arrest in patients with acute myocardial infarction, Am. J. Cardiol. 91 (2003) 280–286.

[13] H.P. Selker, J.L. Griffith, R.B. D’Agostino, A time-insensitive predictive instrument for acute myocardial infarction mortality: a multicenter study, Med. Care 29 (1991) 1196–1211.

[14] O. Dovers, C. Ozdol, T. Sayin, D. Oral, QT interval dispersion: non-invasive marker of ischemic injury in patients with unstable angina pectoris? Jpn. Heart J. 41 (2000) 597–603.

[15] S.H. Hohnloser, Effect of coronary ischemia on QT dispersion, Prog. Cardiovasc. Dis. 42 (2000) 351–358.

[16] Organization, WH, in: center Wm (Ed.), Fact Sheet No. 317: Cardiovascular Diseases (CVDs), 2012.

[17] J.S. Forrester, C. Diamond, K. Chatterjee, H.J. Swan, Medical therapy of acute myocardial infarction: a multicenter, randomized, controlled, clinical effectiveness trial, Ann. Intern. Med. 129 (1998) 1356–1362.

[18] T. Killip III, J.T. Kimball, Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients, Am. J. Cardiol. 20 (1967) 457–464.

[19] H.P. Selker, R.B. D’Agostino, M.M. Laks, A predictive instrument for acute ischemic heart disease to improve coronary care unit admission practices: a potential online tool in a computerized electrocardiograph. J. Electrocardiol. 21 (1988) 511–517 (Suppl).

[20] H.P. Selker, 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. 137 (2002) 87–95.

[21] D.M. Kent, P.M. Rothwell, P.J. Ioannidis, D.G. Altman, R.A. Hayward, Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal, Trials (2010).