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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☆,☆☆,☆☆☆,☆☆☆☆

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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].

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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

Table 1
Baseline characteristics of participants treated with placebo stratified 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

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 adversely related to the outcome. Therefore the systolic blood pressure variable was dichotomized at 105 mm Hg.

Time from onset of chest pain to presentation as a continuous linear variable was not predictive of the outcome. Based on clinical considerations and numbers of participants, the duration of symptoms was divided into two categories: early (within 1 h), and late (beyond 1 h). The odds of the outcome were four times higher in those treated (with placebo) within an hour of symptom onset compared to those presenting late, consistent with other analyses of cardiac arrest in acute infarction having a sharp drop-off after 1 h [13]. As many of the interventional trials used two or 3 h as the duration of symptoms at presentation, a sensitivity analysis was performed to look for any difference. However, no significant difference was found in its predictive value when two or 3 h were used as the cutoff points in place of 1 h.

Previous investigators [10] have suggested a predictive role of QTc as a function of time since onset of symptoms suggestive of ACS, reflects myocardial injury and prolongation of QTc (and QT dispersion) [14,15], potentially promoting ventricular arrhythmias and cardiac arrest. 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 significantly related to the outcome. 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 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.

Table 3
Calibration in the developmental data (placebo group of the IMMEDIATE Trial).

Risk tertile	Total	Mean predicted risk	Predicted number of events[a]	Observed number of events
Low	153	2.3%	3.6	5
Moderate	152	6.2%	9.4	8
High	152	17.8%	27.0	27

[a] Event = cardiac arrest or in-hospital death.

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

Table 2
Final model (developed on participants treated with placebo).[a]

Variable	Estimate	95% CI		OR	95% CI		p value
(Intercept)	−6.95	−9.78	−4.24				
Age, truncated at 60 and 85[b]	0.06	0.02	0.10	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

[a] N = 57 participants treated with placebo and with non-missing data (3 participants excluded because of missing blood pressure), C statistic 0.75.
[b] Age < 60 treated as 60 and age > 85 treated as 85 year.

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	ARR[a]	NNT
Total N = 865, missing = 6	17 (4.2)	40 (8.8)	0.45 (0.23, 0.83) p-value = 0.01		
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

OR = Odds ratio; *ARR = 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.

[a] ARR based on a common odds ratio of 0.45 applied to each stratum.

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.

Treatment 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 straight-forward 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.

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.

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 (mm Hg) mean	143	132	144	153
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%

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.

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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.

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