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Out-of-Hospital Administration of Intravenous Glucose-Insulin-Potassium in Patients With Suspected Acute Coronary Syndromes

The IMMEDIATE Randomized Controlled Trial

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Context Laboratory studies suggest that in the setting of cardiac ischemia, immediate intravenous glucose-insulin-potassium (GIK) reduces ischemia-related arrhythmias and myocardial injury. Clinical trials have not consistently shown these benefits, possibly due to delayed administration.

Objective To test out-of hospital emergency medical service (EMS) administration of GIK in the first hours of suspected acute coronary syndromes (ACS).

Design, Setting, and Participants Randomized, placebo-controlled, double-blind effectiveness trial in 13 US cities (36 EMS agencies), from December 2006 through July 31, 2011, in which paramedics, aided by electrocardiograph (ECG)-based decision support, randomized 911 (871 enrolled) patients (mean age, 63.6 years; 71.0% men) with high probability of ACS.

Intervention Intravenous GIK solution (n=411) or identical-appearing 5% glucose placebo (n=460) administered by paramedics in the out-of-hospital setting and continued for 12 hours.

Main Outcome Measures The prespecified primary end point was progression of ACS to myocardial infarction (MI) within 24 hours, as assessed by biomarkers and ECG evidence. Prespecified secondary end points included survival at 30 days and a composite of prehospital or in-hospital cardiac arrest or in-hospital mortality, analyzed by intent-to-treat and by presentation with ST-segment elevation.

Results There was no significant difference in the rate of progression to MI among patients who received GIK (n=200; 48.7%) vs those who received placebo (n=242; 52.6%) (odds ratio [OR], 0.88; 95% CI, 0.66-1.13; *P*=.28). Thirty-day mortality was 4.4% with GIK vs 6.1% with placebo (hazard ratio [HR], 0.72; 95% CI, 0.40-1.29; *P*=.27). The composite of cardiac arrest or in-hospital mortality occurred in 4.4% with GIK vs 8.7% with placebo (OR, 0.48; 95% CI, 0.27-0.85; *P*=.01). Among patients with ST-segment elevation (163 with GIK and 194 with placebo), progression to MI was 85.3% with GIK vs 88.7% with placebo (OR, 0.74; 95% CI, 0.40-1.38; *P*=.34); 30-day mortality was 4.9% with GIK vs 7.7% with placebo (HR, 0.63; 95% CI, 0.27-1.49; *P*=.29). The composite outcome of cardiac arrest or in-hospital mortality was 6.1% with GIK vs 14.4% with placebo (OR, 0.39; 95% CI, 0.18-0.82; *P*=.01). Serious adverse events occurred in 6.8% (n=28) with GIK vs 8.9% (n=41) with placebo (*P*=.26).

Conclusions Among patients with suspected ACS, out-of-hospital administration of intravenous GIK, compared with glucose placebo, did not reduce progression to MI. Compared with placebo, GIK administration was not associated with improvement in 30-day survival but was associated with lower rates of the composite outcome of cardiac arrest or in-hospital mortality.

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EXPERIMENTAL AND CLINICAL studies have shown intravenous glucose-insulin-potassium (GIK) to have 2 types of benefits in cardiac ischemic syndromes. One is protecting against myocardial injury by providing metabolic support to ischemic myocardium, which should limit progression

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of unstable angina pectoris to myocardial infarction (MI), lessen infarct size, and thereby preserve left ventricular (LV) function.[1-8] The other is preventing arrhythmias and cardiac arrest associated with ischemia-related metabolic derangements thought to be promoted by the elevated free fatty acid (FFA) levels during acute coronary syndromes (ACS).[1,9] One or both mechanisms could be expected to reduce short- and long-term mortality.

The potential benefit of GIK is thought to be related to timeliness of administration after onset of cardiac ischemia, especially for prevention of cardiac arrest, for which risk is highest the first hour of ACS/acute MI.[10] To date, clinical trials of GIK may have missed the opportunity to detect this effect because enrollment and treatment have awaited hospital diagnosis of MI, most often ST-elevation myocardial infarction (STEMI), hours after ischemic symptom onset and initial coronary occlusion.[8,11-16] To achieve the potential benefits related to early treatment, GIK ideally should be administered on presentation of ACS in the out-of-hospital setting rather than awaiting diagnosis of MI or STEMI at the hospital.

This study, the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) Trial, tested the effect of out-of-hospital administration of GIK, given to patients on the earliest recognition of ACS, on progression to MI and on the secondary outcomes including cardiac arrest, mortality, and heart failure (HF).

METHODS

The study design of the IMMEDIATE Trial has been published.[17] This study was a double-blind, randomized controlled clinical effectiveness trial of intravenous GIK evaluating whether GIK will reduce progression of unstable angina pectoris to MI, mortality, cardiac arrest, development of HF, and infarct size in patients with suspected ACS.[17]

Prior to the start of enrollment, but after funding, the investigators and the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) Protocol Review Committee agreed rather than to enroll patients in both the emergency medical service (EMS) setting and the emergency department (ED) setting, as originally planned, to only enroll patients via EMS to ensure earliest possible administration of the study drug. The enrollment goal had been 15 450 participants to have statistical power to detect an effect on all-cause 30-day and 1-year mortality. Enrollment of participants in only out-of-hospital settings required more time and more extensive resources than available to the trial and reaching 15 450 study participants became highly unlikely within available resources.

This led to an NHLBI and the NHLBI-appointed data and safety monitoring board (DSMB) decision on June 20, 2008, to temporarily stop enrollment and allow for the reordering of the study hypotheses based on the adjusted target enrollment of 880 participants.[17] This provided sufficient statistical power to support progression to MI as the new primary end point, while preserving as secondary end points the original primary mortality outcomes and 2 previously designated major secondary end points (the composite of prehospital or in-hospital cardiac arrest or acute mortality and the composite of prehospital or in-hospital cardiac arrest, mortality, or hospitalization for HF within 1 year).[17] The IMMEDIATE Trial collected data on outcomes at 30 days and at 1 year. This report includes the 30-day outcome data; 1 year outcome data are still being collected.

GIK and Placebo Administration

The GIK solution was 30% glucose (300 g/L), 50 U/L of regular insulin, and 80 mEq of KCl/L administered intravenously using portable infusion pumps at 1.5 mL/kg/h (approximately 100 mL/h for a 70-kg patient)[17] for 12 hours. Placebo was administered as 5% glucose solution in identical-appearing packaging.

Study End Points

The prospectively specified primary end point was progression of suspected ACS (ie, unstable angina pectoris or MI) to MI within 24 hours as determined by biomarker and electrocardiogram (ECG) evidence of myocardial necrosis. The major secondary end points[17] included survival at 30 days and 1 year; the composite of prehospital or in-hospital cardiac arrest or in-hospital mortality; the composite of mortality or hospitalization for HF within 30 days and within 1 year; and the composite of cardiac arrest or mortality or hospitalization for HF within 1 year. Additional prespecified secondary end points were clinical, biochemical, and nuclear imaging data related to possible GIK preservation of myocardial function, prevention of HF, and prevention of arrhythmic complications of ACS.[17]

Enrollment and Intervention

In 13 US cities, from December 1, 2006, through July 31, 2011, paramedics in 36 participating EMS systems evaluated for enrollment all patients aged 30 years or older for whom an out-of-hospital 12-lead ECG was obtained to evaluate chest pain or other symptoms suggestive of ACS. Identification of ACS by paramedics was aided by the ECG-based Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) and Thrombolytic Predictive Instrument (TPI) decision support, using an ACI-TIPI threshold of 75% or higher predicted probability of having ACS, detection of suspected STEMI by the TPI, or both.[18] Previously tested[19,20] ACI-TIPI and TPI software for ambulance ECGs were provided by the manufacturers of EMS systems' extant equipment (Physio-Control, Philips Healthcare, and Zoll Medical). Additionally, any local STEMI criteria for notifying receiving hospitals of the need for immediate access to the catheterization laboratory were followed.[18] Patients with clinically significant HF (more than basilar rales), renal failure requiring dialysis, or who were unable to give informed consent were excluded. Random assignment

was 1:1 by the paramedic's initiation of the blinded identical-appearing GIK or placebo study drug infusion packets.

The trial used processes specified for emergency exception from informed consent in the Code of Federal Regulations (21CFR §50.24),[21] including community consultation, institutional review board approval, and paramedic reading of an information card prior to randomization to gain assent, with full written consent once the patient was stabilized at the hospital.[22] Separate written consent was obtained for the biological mechanism cohort for blood tests during the 12 hours of treatment and for 30-day assessments by LV imaging scan and blood testing. An NIH-appointed DSMB oversaw enrollment to ensure safe and ethical study conduct, an independent statistician generated reports for the DSMB, and there were no statistical interim efficacy analyses.

Data Collection

Study personnel collected demographic and presenting data on participants and, to assess the diversity of the sample, patients' self-reported race and ethnicity. Clinical data collected included detailed information on EMS, ED, and hospital care, including ECGs, myocardial necrosis biomarkers, cardiac catheterization, and other tests pertaining to ACS. Glucose and potassium levels were obtained on ED arrival, at 6 hours after the start of the study drug infusion, and once the infusion was stopped (including if prematurely). Biological mechanism cohort participants were tested for hemoglobin A_{1C}, insulin levels, FFA levels, and fractionation on hospital arrival, at 6 hours, and at 12 hours. Participants with ACS who received study drug for at least 8 hours and consented for biological mechanism testing returned at 30 days for technetium Tc 99m sestamibi imaging and blood tests.[17]

Determination of Diagnoses and End Points

Based on clinical presentation, for monitoring purposes during enrollment, site investigators assigned diagnoses of MI by Killip class, unstable angina pectoris by Canadian Cardiovascular Society class, non-ACS cardiac disease, and noncardiac disease based on out-of-hospital, ED, and 24-hour ECGs, biomarkers, and clinical data.[17,20] Independently, blinded to study group, glucose and potassium test results, and whether the study infusion was stopped early, the clinical events committee adjudicated final diagnoses and all clinical and hospitalization end points used for analyses, including progression to MI based on biomarkers and ECGs, presentation with ST-segment elevation, and whether a participant had an aborted MI. To identify the analytic cohort of those presenting with ST-segment elevation suggestive of STEMI, 3 cardiologists independently read the initial out-of-hospital ECG, blinded to study group, to determine whether the patient was sufficiently likely to have had a STEMI to meet criteria for referral for immediate cardiac catheterization and reperfusion.

Participants in the biological mechanism cohort returned for sestamibi perfusion and LV function imaging at 30 days. Standardized interpretation of imaging studies was performed at the SPECT Core Laboratory at Tufts Medical Center; FFA measurements were done by OmegaQuant; and brain-type natriuretic peptide, insulin levels, and other blood tests were performed at Tufts Clinical and Translational Science Institute.

Data and Statistical Analysis

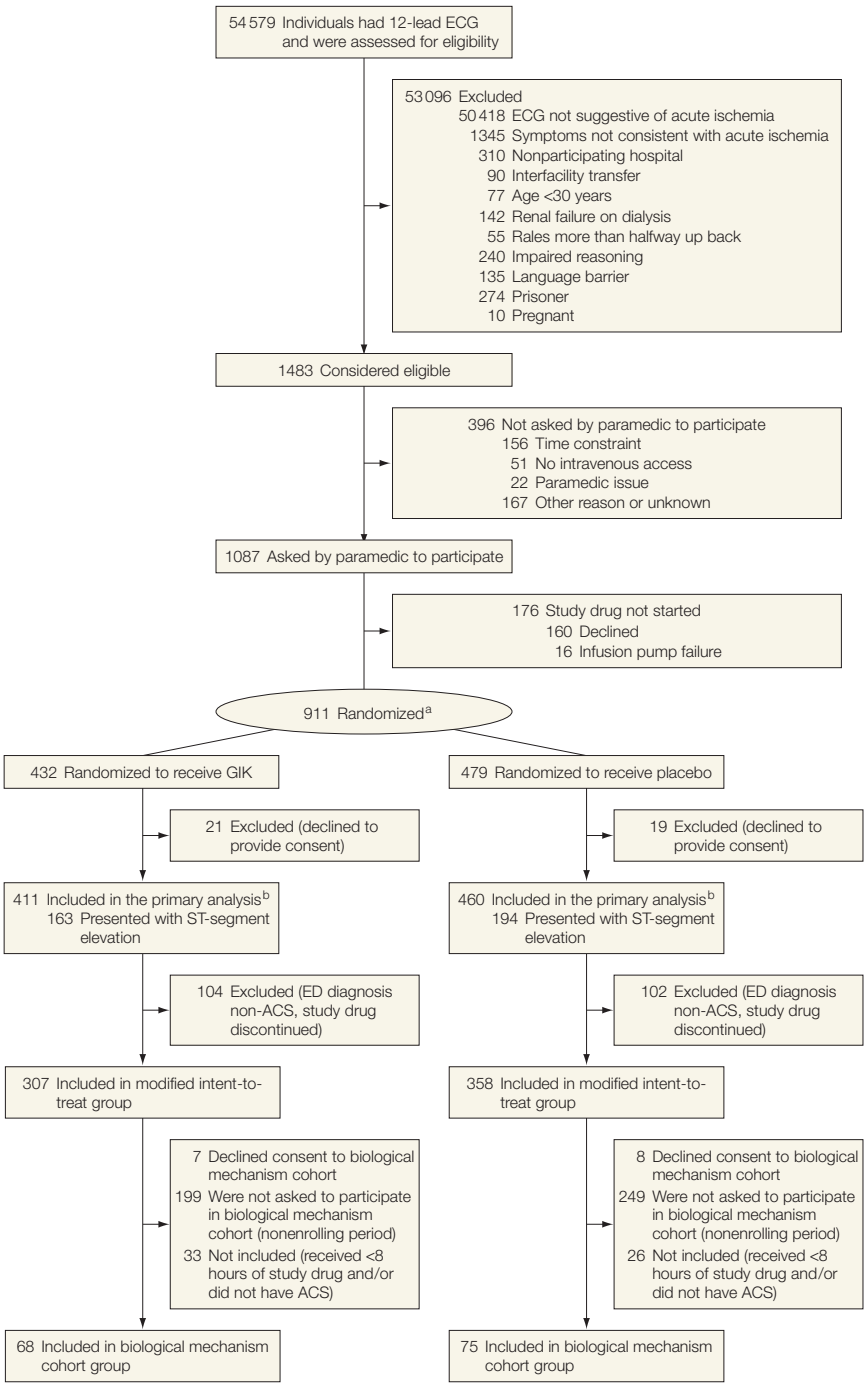
All analyses were conducted using the intent-to-treat (ITT) cohort, composed of all randomized participants who gave written informed consent, based on group at randomization. Forty randomized participants agreed to have the study drug started in the ambulance but later declined to provide written informed consent at the hospital and were excluded from the analysis. Additional analyses were conducted including participants presenting with ST-segment elevation using the cohort defined above. Analyses also were conducted on the modified ITT cohort, those among the ITT cohort considered by the receiving ED physicians to have ACS and who therefore continued receiving the study drug, corresponding to how GIK would be used in practice. Those who received treatment for at least 8 hours were eligible for enrollment into the biological mechanism cohort.

For the primary end point of progression to MI, a sample size of 800 evaluable study participants was selected to provide 90% power to detect a relative 20.5% reduction from 55.7% to 44.3% between the placebo and GIK groups.[17] To accommodate attrition, 880 study participants were planned for randomization. For the other major secondary end points and subgroups (eFigure, available at http://www.jama.com), logistic regression models were used for treatment comparisons of binary study end points, and analyses of time-to-event outcomes were assessed by Cox proportional hazards regressions. Generalized estimating equations (GEE) and robust variance estimators were used to account for potential clustering across multiple enrollments by individual participants. To adjust for potential imbalance of patient characteristics following randomization, treatment comparisons also were conducted using quintiles of a propensity score for treatment allocation, using a forced logistic regression model to predict treatment group (GIK or placebo). All statistical testing used a 2-sided .05 level of significance, without adjustment for prespecified multiple comparisons.

In the biological mechanism cohort, mean FFA levels were compared between treatments across time periods using general linear models with total FFA level as the dependent variable and treatment (GIK vs control), time from study drug infusion initiation, and time from symptom onset as independent variables. Robust GEE variance estimators were used to account for repeated measurements on participants. Thirty-day

mean infarct size and LV ejection fraction were compared between the GIK group and the control group using the Wilcoxon rank-sum test. Statistical analyses were conducted using SAS version 9.2.

Figure. Screening and Enrollment of Participants in the IMMEDIATE Randomized Controlled Trial



ACS indicates acute coronary syndromes; ECG, electrocardiogram; and ED, emergency department.
[a]Randomized group included 18 participants (8 in glucose-insulin-potassium [GIK] group, 10 in placebo group) who did not meet eligibility requirements.
[b]The 871 enrollments occurred in 850 individual patients.

RESULTS

A total of 911 participants were randomized, with 871 enrollments of 850 individual patients (FIGURE). Of those randomized, 40 (21 in the GIK group, 19 in the placebo group) did not give written consent on hospital arrival and were not enrolled. The median duration of study drug treatment for nonenrolled patients was 0.9 hours (interquartile range, 0.3-2.6 hours). Results are based on enrollments as the unit of analysis (ITT).

TABLE 1 shows demographic and clinical features by treatment with GIK (n=411) or placebo (n=460). Participants were typical of patients presenting with suspected ACS and MI: average age was 63 years, 71% were men, and 86% presented with a chief complaint of chest pain. They were randomized a median of 90 minutes after ischemic symptom onset. Forty-one percent presented with ST-segment elevation on the initial out-of-hospital ECG and 47% underwent percutaneous coronary intervention. There was balance in the characteristics of GIK and placebo participants. eTable 1 presents these details for the modified ITT cohort.

TABLE 2 shows the main end points. For the primary end point of progression to MI, there was no statistically significant difference between patients in the GIK group (48.7%) vs those in the placebo group (52.6%) (odds ratio [OR], 0.88; 95% CI, 0.66-1.13; $P=.28$). Among participants receiving GIK, 11.1% of initially presenting MIs were adjudicated as having been aborted, vs 8.0% with placebo (OR, 1.4; 95% CI, 0.8-2.7; $P=.23$). For the major secondary end points, 30-day mortality was 4.4% with GIK vs 6.1% with placebo (hazard ratio [HR], 0.72; 95% CI, 0.40-1.29; $P=.27$); the composite end point of cardiac arrest or in-hospital mortality occurred in 4.4% with GIK vs 8.7% with placebo (OR, 0.48; 95% CI, 0.27-0.85; $P=.01$).

Also in Table 2 are results among participants who presented with ST-segment elevation on their initial out-of-hospital ECG (163 who received GIK and 194 who received placebo). Pro-

gression to MI occurred in 85.3% of those in the GIK group vs 88.7% in the placebo group (OR, 0.74; 95% CI, 0.40-1.38; *P*=.34). Thirty-day mortality was 4.9% with GIK vs 7.7% with placebo (HR, 0.63; 95% CI, 0.27-1.49; *P*=.29); the composite of cardiac arrest or in-hospital mortality occurred in 6.1% with GIK vs 14.4% with placebo (OR, 0.39; 95% CI, 0.18-0.82; *P*=.01). Results for these outcomes in the ITT group using propensity adjustments (eTable 2) were consistent with the unadjusted results and consistent with the results in the modified ITT group (eTable 3).

The eFigure depicts effects for clinically important subgroups. For those treated within the first hour, there was no difference between the GIK and placebo groups in rates of progression to MI (OR, 0.67; 95% CI, 0.41-1.09; *P*=.11), although occurrence of the composite of cardiac arrest or in-hospital mortality was lower in the GIK group vs the placebo group (OR, 0.28; 95% CI, 0.10-0.79; *P*=.02). There was no association between GIK administration after 6 hours and any outcome. There were no differences in outcomes among those older vs younger than age 65, nor for those with diabetes vs without diabetes.

TABLE 3 shows results of the biological mechanism cohort. Median infarct size was 2% of LV mass among those receiving GIK (n=49 patients) vs 10% of LV mass with placebo (n=61 patients) (*P*=.01). Among those presenting with ST-segment elevation, infarct size was 3% of LV mass with GIK (n=35) vs 12% with placebo (n=40) (*P*=.05). Consistent with GIK lowering FFA during ACS, FFA levels were 367 µmol/L (95% CI, 269-465) with GIK vs 578 µmol/L with placebo (95% CI, 500-657) (*P*<.001).

Event rates were closely monitored and regularly reported to the DSMB. Serious adverse events occurred in 6.8% (n=28) in the GIK group and 8.9% (n=41) in the placebo group (*P*=.26). Serious cardiac events occurred in 4.6% (n=19) in the GIK group and 7.6% (n=35) in the placebo group (*P*=.07). Other serious adverse events included injection site reaction (n=1, placebo), hyperkalemia (n=1, placebo), and fluid overload (n=1, placebo; n=3, GIK). Nonserious adverse events occurred in 71.8% (n=295) in the GIK group and 46.5% (n=214) with placebo. The rates of nonserious cardiac events in the GIK

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants by Treatment Group (N = 871)[a]

Characteristics	No./Total (%) GIK (n = 411)	Placebo (n = 460)
Age, mean (SD), y	63.9 (13.9)	63.3 (14.1)
Sex		
Women	113/411 (27.5)	140/460 (30.4)
Men	298/411 (72.5)	320/460 (69.6)
Race[b]		
White	332/403 (82.4)	392/451 (86.9)
Black	52/403 (12.9)	42/451 (9.3)
Asian	6/403 (1.5)	3/451 (0.7)
American Indian or Alaskan Native	8/403 (2.0)	8/451 (1.8)
Native Hawaiian or other Pacific Islander	2/403 (0.5)	2/451 (0.4)
Other	4/403 (1.0)	4/451 (0.9)
Hispanic ethnicity	44/402 (10.9)	58/445 (13.0)
Chief complaint on presentation		
Chest pain	358/411 (87.1)	391/460 (85.0)
Shortness of breath	15/411 (3.6)	19/460 (4.1)
Initial out-of-hospital blood pressure, mean (SD), mm Hg		
Systolic	143.3 (32.0)	143.4 (34.9)
Diastolic	84.4 (23.6)	85.0 (25.1)
Initial out-of-hospital heart rate, mean (SD), beats/min	86.8 (24.7)	86.6 (25.6)
Initial out-of-hospital respiratory rate, mean (SD), breaths/min	19.3 (4.2)	19.5 (4.4)
Time from symptom onset to study drug, median (IQR), min	90.0 (50.0-159.3)	90.0 (52.0-159.3)
Time from symptom onset to study drug, min		
0 to 30	24/401 (6.0)	20/457 (4.4)
31 to 60	101/401 (25.2)	121/457 (26.5)
61 to 90	60/401 (15.0)	74/457 (16.2)
91 to 180	66/401 (16.5)	82/457 (17.9)
181 to 360	46/401 (11.5)	55/457 (12.0)
361 to 24 h	37/401 (9.2)	36/457 (7.9)
Within 24 h, unspecified	31/401 (7.7)	34/457 (7.4)
>24 h	36/401 (9.0)	35/457 (7.7)
ST-segment elevation on presenting out-of-hospital ECG	163/411 (39.7)	194/460 (42.2)
ACI-TIPI score, mean (SD), %[c]	74.6 (22.6)	76.9 (20.6)
TPI triggered	84/411 (20.4)	116/460 (25.2)
Medical conditions by history		
Diabetes	121/411 (29.4)	121/460 (26.3)
Heart failure	68/411 (16.5)	77/460 (16.7)
Myocardial infarction	152/411 (37.0)	159/460 (34.6)
Hospital acute reperfusion treatment		
Thrombolytic therapy	3/411 (0.7)	8/460 (1.7)
Percutaneous coronary intervention	198/411 (48.2)	208/460 (45.2)
Coronary artery bypass graft	12/411 (2.9)	13/460 (2.8)

Abbreviations: ACI-TIPI, Acute Cardiac Ischemia Time-Insensitive Predictive Instrument; ECG, electrocardiogram; TPI, Thrombolytic Predictive Instrument.
[a] No significant differences were noted between GIK and placebo groups.
[b] Race was self-reported.
[c] ACI-TIPI score ≥75% was part of the inclusion criteria.

group (24.3%, n=100) and the placebo group (25.4%, n=117) were similar. The frequencies of postinfusion potassium levels greater than 5.5 mEq/L and glucose levels greater than 160 mg/dL and greater than 300 mg/dL, including for patients with and without diabetes, are included in eTable 4.

Trial enrollment excluded patients presenting with Killip classes greater than II, but some participants developed sufficient HF during their index ACS hospitalization to be classified as Killip class III or IV by the clinical events committee. This occurred in 10 of 411 participants (2.4%, 95% CI, 1.2%-4.4%) receiving GIK and 15 of 460 (3.3%, 95% CI, 1.8%-5.3%) receiving placebo.

COMMENT

This placebo-controlled, double-blind, randomized clinical effectiveness trial of EMS administration of GIK for ACS was designed to translate the effects seen in laboratory research on metabolic modulation of ischemic injury into an approach that could be considered for widespread clinical practice. Accordingly, rather than awaiting a hospital-based definitive diagnosis of MI as done in previous trials, GIK was administered immediately by paramedics in the out-of-hospital setting based on their clinical impression of ACS, aided by computerized ECG-based decision support. In responding to 911 emergency calls, assisted by ACI-TIPI and TPI predictions of ACS and STEMI printed on the out-of-hospital ECGs, paramedics identified patients with a high probability of having ACS and initiated GIK at a median time from ischemic symptom onset of only 90 minutes, compared with 6 or more hours in previous GIK trials.[6,13,14] Thereby, the IMMEDIATE Trial was intended to test for 2 types of potential benefit seen in laboratory studies: reduction in myocardial damage and reduction in cardiac arrest and mortality.[1,11]

Relative to the hypothesized reduction in myocardial damage, administration of GIK did not significantly reduce the incidence of the primary outcome of progression of unstable angina pectoris to MI. This may be because some patients had already progressed to MI with biomarker evidence by the time of initial presentation, particularly those with ST-segment elevation, and thus could not demonstrate benefit by this definition. However, among the relatively small subgroup of patients who underwent imaging at 30 days, infarct size was reduced both for those in the entire ACS cohort (n=110) and for those presenting with ST-segment elevation (n=75). It is pos-

Table 2. Hospital and 30-Day Outcomes by Group (N = 871)

	No. of Events (%)		Risk Ratio for GIK vs Placebo (95% CI)	*P* Value
	GIK	Placebo		
Outcome for all participants	n = 411	n = 460		
Progression to MI	200 (48.7)	242 (52.6)	OR, 0.88 (0.66-1.13)	.28
30-d mortality	18 (4.4)	28 (6.1)	HR, 0.72 (0.40-1.29)	.27
Cardiac arrest[a] or in-hospital mortality	18 (4.4)	40 (8.7)	OR, 0.48 (0.27-0.85)	.01
Cardiac arrest[a]	15 (3.6)	29 (6.3)	OR, 0.56 (0.30-1.07)	.08
In-hospital mortality	13 (3.2)	23 (5.0)	OR, 0.62 (0.31-1.24)	.18
30-d mortality or heart failure[b]	23 (5.6)	35 (7.6)	HR, 0.73 (0.43-1.23)	.24
30-d heart failure[b]	6 (1.5)	10 (2.2)	HR, 0.67 (0.24-1.82)	.43
Outcome for participants presenting with ST-segment elevation[c]	n = 163	n = 194		
Progression to MI	139 (85.3)	172 (88.7)	OR, 0.74 (0.40-1.38)	.34
30-d mortality	8 (4.9)	15 (7.7)	HR, 0.63 (0.27-1.49)	.29
Cardiac arrest[a] or in-hospital mortality	10 (6.1)	28 (14.4)	OR, 0.39 (0.18-0.82)	.01
Cardiac arrest[a]	9 (5.5)	21 (10.8)	OR, 0.49 (0.23-1.03)	.06
In-hospital mortality	6 (3.7)	14 (7.2)	OR, 0.49 (0.18-1.31)	.16
30-d mortality or heart failure[b]	9 (5.5)	19 (9.8)	HR, 0.56 (0.25-1.23)	.15
30-d heart failure[b]	1 (0.6)	6 (3.1)	HR, 0.20 (0.02-1.61)	.13

Abbreviation: MI, myocardial infarction.
[a] Defined as prehospital or in-hospital cardiac arrest.
[b] Defined as hospitalization for heart failure within 30 d.
[c] Analysis done only on participants presenting with ST-segment elevation on out-of-hospital electrocardiogram.

Table 3. Biological Mechanism Cohort: 30-Day Infarct Size, LVEF, and FFA Levels

Outcome	GIK	Placebo	*P* Value	
30-d infarct size, % of LV mass, median (IQR)				
All participants	2 (0 to 11) [n = 49]	10 (0 to 27) [n = 61]		.01
Participants with ST-segment elevation[a]	3 (0 to 13) [n = 35]	12 (1 to 27) [n = 40]		.05
LVEF, median (IQR), %				
All participants	65 (55 to 71) [n = 43]	60 (54 to 67) [n = 57]		.13
Participants with ST-segment elevation[a]	64 (56 to 71) [n = 34]	61 (55 to 68) [n = 39]		.46
FFA, mean (95% CI), μmol/L			Difference[b] (95% CI)	
All participants	367 (269 to 465) [n = 151]	578 (500 to 657) [n = 160]	–211 (–295 to –129)	<.001
Participants with ST-segment elevation, mean (95% CI)[a]	354 (279 to 428) [n = 104][c]	591 (513 to 669) [n = 96][c]	–238 (–329 to –148)	<.001

Abbreviations: FFA, free fatty acid; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction.
[a] Participants presenting with ST-segment elevation on out-of-hospital electrocardiogram.
[b] Adjusted for time from symptom onset to treatment and time from treatment to FFA.
[c] Number of FFA samples.

sible that infarct size may better capture a myocardial preservation effect of GIK in this setting, consistent with the metabolic support model of infarct limitation seen in experimental studies. This concept could be tested in future trials because the infarct size results were based on only a small subgroup of patients in the present trial.

Relative to the hypothesized reduction in cardiac arrest and mortality, there was no effect of GIK administration on 30-day mortality in the entire cohort, among patients presenting with ST-segment elevation, in the modified ITT analysis, or in the propensity-adjusted analysis. However, the composite of cardiac arrest or in-hospital mortality was reduced for those treated with GIK, both among all those with ACS and among those presenting with ST-segment elevation. This is consistent with the clinical basis for the IMMEDIATE Trial early treatment model, that many cardiac arrests and deaths from ACS/acute MI occur early after symptom onset, largely due to ischemia-related ventricular fibrillation progressing to cardiac arrest.[1,9]

Cellular FFAs and their derivatives accumulate during ischemia and disrupt sarcolemmal and mitochondrial membranes and thereby increase intracellular calcium and promote arrhythmias.[1,9] Experimental studies[12] have shown that GIK decreases circulating FFA levels and myocardial FFA uptake, and thereby may potentially reduce susceptibility to ischemic arrhythmias and cardiac arrest. The finding of a reduction of FFA levels with GIK in the biological mechanism subgroup is consistent with this concept. Moreover, that the effect of GIK on cardiac arrest and in-hospital mortality was apparent when GIK was administered in the first hour after symptom onset is consistent with this period of very early highest risk for cardiac arrest.

As an effectiveness trial rather than an efficacy trial, patient selection and treatment in the IMMEDIATE Trial were performed as would occur in usual practice. We previously reported the effectiveness of ECG-based ACI-TIPI and TPI decision support for improving paramedic identification of ACS and ST-segment elevation in a wide variety of EMS systems.[18] Paramedic administration of intravenous GIK in the out-of-hospital setting using this approach appears feasible for patients with symptoms suggestive of ACS who call EMS. The absence of an unfavorable safety signal from this duration of GIK treatment suggests that EMS personnel initiating treatment of those who ultimately proved to not have an ACS—which will occur in conjunction with identifying and treating those who do have ACS—should not have unfavorable consequences. Thus this approach should enable consideration of adopting early out-of-hospital administration of this low-cost treatment in some EMS systems.

Because prior GIK trials focused on the treatment of STEMI,[8,11-14,16] we prespecified analyses of patients presenting with ST-segment elevation among all trial participants. A favorable effect on the primary end point, progression to MI, was not seen in this subgroup possibly because many such patients already manifested biomarker evidence of infarction on presentation. However, as with the entire cohort, patients presenting with ST-segment elevation had no improvement in 30-day survival but appeared to have signals of potential benefit among the major secondary end points (Table 2).

Most previous GIK trials have not found benefit, despite the consistently favorable effects in preclinical models. Among possible reasons that this trial suggested potential benefit on the secondary end point of cardiac arrest or in-hospital mortality for patients presenting with ST-segment elevation is that participants in the IMMEDIATE Trial were treated much earlier, following the use of GIK in preclinical models. For example, the median time from symptom onset to treatment initiation for the CREATE-ECLA Trial was approximately 6 hours[14] compared with 90 minutes in the IMMEDIATE Trial. Also, in prior trials, the temporal sequence of GIK administration and reperfusion was not consistent with the experimental model of benefit of GIK for STEMI, which is that treatment is required during ischemia prior to reperfusion. In the CREATE-ECLA GIK group, 68% of patients received GIK after reperfusion, thereby largely eliminating the proposed benefit of GIK in STEMI of extending the window for benefit from metabolic support before reperfusion.[15] Also, prior GIK trials[8,11-14,16] were not double-blind placebo-controlled trials, and as described in CREATE-ECLA, there were treatment differences between GIK and non-GIK groups that might have influenced use of other treatments based on the lack of blinding.[14]

Despite these differences, one area in which there was agreement between prior trials and the IMMEDIATE Trial is that GIK administration was found to be safe, even in this wide variety of EMS settings. Related to safety, given that high levels of glucose, insulin, and potassium in the GIK solution might be of concern in the treatment of patients with diabetes, we prespecified separate effectiveness and safety analyses for these patients. The results suggest that the adverse effects for patients with diabetes (121 in the GIK group and 121 in the placebo group) were not substantially greater than for patients without diabetes, and future trials or treatment strategies should not exclude such patients.

This trial excluded patients who presented with clinically obvious HF because of concern about the volume load from the study infusion, especially for those receiving placebo, for whom no benefit could be expected. This resulted in exclusion of approximately 5% of otherwise eligible patients with ACS who initially manifested significant pulmonary congestion (Killip classes III and IV). No increase in clinical HF was seen with administration of GIK among treated participants. For those who did progress to Killip class III or IV MI during the index hospitalization, there was a trend toward a reduction in the composite outcome of mortality or HF

within 30 days with GIK, although absolute numbers of such patients were small. This is supported by early clinical work using the same GIK formula for MI, but for 48 rather than 12 hours of treatment for MI, a 4-fold greater volume infusion, and yet pulmonary capillary wedge pressure decreased and cardiac output and ejection fraction increased, presumably reflecting improved systolic and diastolic function due to GIK myocardial metabolic support during ischemia and reperfusion.[4]

Several important limitations must be considered in evaluating these data. The primary end point was not significantly different between groups, and the observed favorable results of GIK were based on prespecified but secondary end points, although biologically plausible and consistent with preclinical studies. The study tested one primary hypothesis, 3 major secondary, and 6 other secondary hypotheses. All were prespecified and no adjustment for multiple comparisons among the secondary end points was made; thus, reported significance levels should be considered approximate. Accordingly, given the lack of complete consistency of the findings, and the modest *P* values for most of the statistically significant findings, it would be appropriate to describe the observed favorable effects on the secondary outcomes as generating clinically testable hypotheses for evaluation in larger cohorts. Also, the absolute numbers of end points were relatively small. The results on infarct size, while also consistent with experimental studies of early GIK therapy in the setting of ischemia, were based on the relatively small biological mechanism cohort subgroup of patients involved in the trial. Additionally, understanding of the long-term effects of GIK on HF and mortality will require longer follow-up, which is under way.

In conclusion, among patients with suspected ACS, out-of-hospital administration of intravenous GIK by paramedics, compared with administration of glucose placebo, did not reduce progression to MI. Compared with placebo, GIK administration was not associated with improvement in 30-day survival but was associated with lower rates of the composite outcome of cardiac arrest or in-hospital mortality. Further studies are needed to assess the out-of-hospital use of GIK as therapy for patients with ACS.

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