One-Year Outcomes of Out-of-Hospital Administration of Intravenous Glucose, Insulin, and Potassium (GIK) in Patients With Suspected Acute Coronary Syndromes (from the IMMEDIATE [Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care] Trial)

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The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care Trial of very early intravenous glucose-insulin-potassium (GIK) for acute coronary syndromes (ACS) in out-of-hospital emergency medical service (EMS) settings showed 80% reduction in infarct size at 30 days, suggesting potential longer-term benefits. Here we report 1-year outcomes. Prespecified 1-year end points of this randomized, placebo-controlled, double-blind, effectiveness trial included all-cause mortality and composites including cardiac arrest, mortality, or hospitalization for heart failure (HF). Of 871 participants randomized to GIK versus placebo, death occurred within 1 year in 11.6% versus 13.5%, respectively (unadjusted hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.57 to 1.23, p = 0.36). The composite of cardiac arrest or 1-year mortality was 12.8% versus 17.0% (HR 0.71, 95% CI 0.50 to 1.02, p = 0.06). The composite of hospitalization for HF or mortality within 1 year was 17.2% versus 17.2% (HR 0.98, 95% CI 0.70

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See page 1605 for disclosure information.

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to 1.37, p = 0.92). The composite of mortality, cardiac arrest, or HF hospitalization within 1 year was 18.1% versus 20.4% (HR 0.85, 95% CI 0.62 to 1.16, p = 0.30). In patients presenting with suspected ST elevation myocardial infarction, HRs for 1-year mortality and the 3 composites were, respectively, 0.65 (95% CI 0.33 to 1.27, p = 0.21), 0.52 (95% CI 0.30 to 0.92, p = 0.03), 0.63 (95% CI 0.35 to 1.16, p = 0.14), and 0.51 (95% CI 0.30 to 0.87, p = 0.01). In patients with suspected acute coronary syndromes, serious end points generally were lower with GIK than placebo, but the differences were not statistically significant. However, in those with ST elevation myocardial infarction, the composites of cardiac arrest or 1-year mortality, and of cardiac arrest, mortality, or HF hospitalization within 1 year, were significantly reduced. **(Am J Cardiol 2014;113:1599−1605)**

The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) Trial was a randomized, placebo-controlled, double-blind, clinical effectiveness trial of the administration of intravenous glucose-insulin-potassium (GIK) very early in the evolution of acute coronary syndromes (ACSs), by emergency medical service (EMS) paramedics, run in 13 cities across the United States.[1−3] Before the IMMEDIATE Trial, experimental and clinical studies had shown GIK to protect myocardium from ischemic injury and lessen infarct size and thereby to preserve left ventricular (LV) function, but clinical trials of the use of GIK for patients seen in hospitals for established acute myocardial infarction (AMI) had not generally shown these benefits.[4−13] In the IMMEDIATE Trial, rather than awaiting hospital diagnosis of AMI or ST elevation myocardial infarction (STEMI) to initiate GIK, as done in previous trials, GIK was delivered very early in the course of ACS, in the out-of-hospital setting. Paramedics, using electrocardiograph-based support by the acute cardiac ischemia time-insensitive predictive instrument (ACI-TIPI) and the thrombolytic predictive instrument (TPI), initiated GIK as soon as possible in the community, and the infusion was continued in the receiving hospital for 12 hours total.[2,14,15] At 30 days, although the reduction in the primary end point of progression to AMI was not statistically significant, there were significant reductions in the composite end point of cardiac arrest or mortality and an 80% reduction in infarct size, suggesting possible longer-term benefits.[1] One-year follow-up of trial participants for prespecified study end points, including mortality, heart failure (HF), and the composite of cardiac arrest, mortality, or HF, are reported here to address the degree to which such benefits might be sustained.

Methods

This study was a double-blind, randomized, controlled clinical effectiveness trial of intravenous GIK; its design[3] and 30-day results,[1] including the primary study end point, have been previously published. Here we report 1-year results on the prespecified clinical end points: all-cause mortality, the composite end point of mortality or hospitalization for HF within 1 year, and the composite end point of cardiac arrest, mortality, or HF hospitalization within 1 year.

Analyses were prespecified to be examined for the cohort defined by intent-to-treat for consenting participants with presumed ACS and for a subset of the cohort presenting with suspected STEMI.

From December 2006 through July 2011, paramedics in 36 EMS systems in 13 cities across the United States evaluated for study enrollment all patients aged ≥30 for whom a 12-lead electrocardiogram (ECG) was obtained for chest pain or other possible ACS symptoms. Paramedics were aided by electrocardiograph-based software that printed the ACI-TIPI patients' predicted probabilities of ACS and that determined whether the TPI detected a likely STEMI. Paramedics were instructed to enroll patients who had an ACI-TIPI predicted probability of having ACS of ≥75%, had STEMI identified by the TPI, and/or who would have been identified as having STEMI by the community's STEMI alert system. Excluded were patients with HF evidenced by more than basilar rales, those on dialysis for renal failure, or those unable to give assent. Assignment to study group was random by paramedic initiation of the blinded identical-appearing GIK or placebo study drug infusion packets.

As detailed elsewhere,[3] the trial used exception from informed consent requirements for emergency research processes as in the Code of Federal Regulations (21CFR 50.24).[16] This process included community consultation and notification, institutional review board approval, and having the paramedic read an information card to the patients before randomization and then asking for assent; full written consent was obtained once stabilized at the hospital.[3,17] Oversight was provided by a Data and Safety Monitoring Board appointed by the National Heart, Lung, and Blood Institute; there were no interim efficacy analyses. Funding was from the National Heart, Lung, and Blood Institute; insulin was donated by Eli Lilly and Company (Indianapolis, Indiana); ACI-TIPI or TPI defibrillator-electrocardiograph software was provided by the manufacturers of EMS systems' equipment, Philips Healthcare (Andover, Massachusetts), Physio-Control Inc. (Redmond, Washington), and Zoll Medical Corporation (Chelmsford, Massachusetts); no restrictions were imposed on study procedures or publication.

The study drug GIK solution had 30% glucose (300 g/L), 50 U/L of regular insulin, and 80 mEq of potassium chloride per liter, which had been shown to improve myocardial perfusion.[18] The placebo was a 5% glucose solution in identical packaging. Per the study protocol, the study solution was administered at 1.5 ml/kg/hour (approximately 100 ml/hour for a patient weighing 70 kg) for 12 hours intravenously by way of an infusion pump.

Collected were demographic (including race and ethnicity by self-report) and presenting data, including

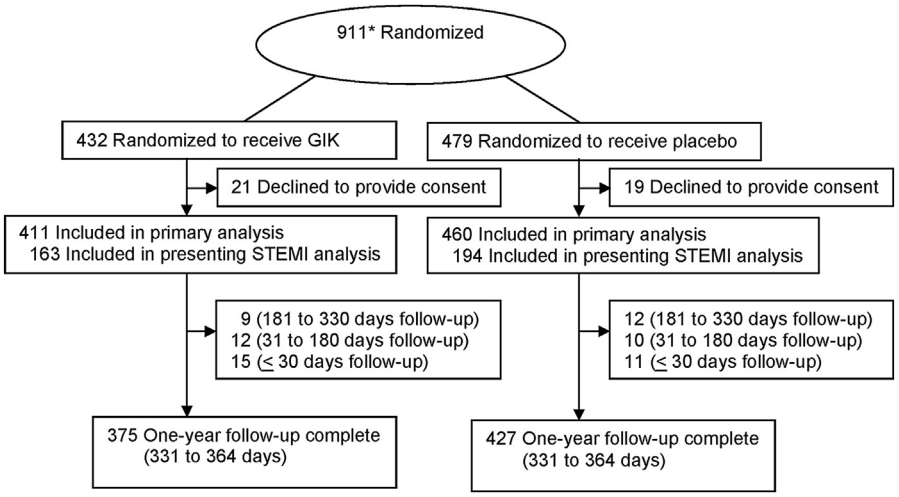

Figure 1. Study participant flow chart. *Includes 18 participants (8 GIK treated and 10 placebo treated) who did not meet eligibility criteria but were randomized.

detailed information on EMS, emergency department (ED), and hospital care (including ECGs, cardiac biomarkers, cardiac catheterization, and other tests pertaining to ACS). For safety purposes, as reported elsewhere,[3] glucose and potassium blood tests were performed on ED arrival, at 6 hours after the start of the study drug, and once the study infusion was stopped. Also reported elsewhere[1] are data collected on biological mechanism cohort participants.

A Clinical Events Committee adjudicated final diagnoses and the causes of all hospitalization end points used for analyses. The Committee members assigned diagnoses of AMI (including by Killip class), unstable angina pectoris (including by Canadian Cardiovascular Society Angina Classification), non-ACS cardiac disease, and noncardiac disease, based on out-of-hospital, ED, and 24-hour ECGs, biomarkers, and clinical data. In their review, they were blinded to study group, glucose and potassium tests, and whether the study infusion was stopped early. The analytical cohort of patients presenting with suspected STEMI was identified by having 3 cardiologists (blinded to study group) independently read the initial (out-of-hospital) ECG and determine whether the patient was sufficiently likely to have experienced an STEMI to deserve immediate referral for cardiac catheterization and reperfusion.

All analyses were done on the intent-to-treat cohort with treatment assignment as randomized. In addition, primary analyses were conducted for the subcohort of those patients presenting with STEMI, as defined previously. Analyses also were conducted on a modified intent-to-treat cohort, comprising those in the intent-to-treat cohort whom ED physicians confirmed as having ACS and therefore continued on the study drug, as GIK presumably would be used in clinical practice.

As described in the report of the 30-day outcomes,[1] the primary end point of the IMMEDIATE Trial was progression to myocardial infarction based on biomarkers and ECGs. It was calculated that a sample size of 800 evaluable study participants would provide 90% power to detect a relative 20.5% reduction from 55.7% to 44.3% between the placebo and GIK groups for this end point. To accommodate attrition, 880 study participants were planned for randomization.

Time-to-event outcomes were analyzed using Cox proportional hazards regressions and the assumption of proportional hazards checked using a Kolmogorov-type supremum test. Robust variance estimators were used to account for potential clustering across multiple enrollments by individual participant's time-to-event analyses. For composite events, the time to the first occurrence of any component of the composite was used. All statistical testing used 2-sided 0.05 level of significance and were done using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Of 911 patients randomized, there were 871 enrollments for 850 subjects, as shown in Figure 1. (Of those randomized, 40 subjects initially agreed to have the study drug started in the ambulance but later declined written informed consent at the hospital and were excluded: 21 GIK group participants and 19 placebo group participants.) Enrollments were used as the unit of analysis. Demographic and clinical features are listed in Table 1. The average age was 63 years, 71% were men, and 86% presented with a chief complaint of chest pain. Randomization into the trial occurred at a median of 90 minutes after ischemic symptom onset. STEMI was suspected in 41%; 47% of participants received percutaneous coronary intervention. Characteristics of GIK and placebo participants were similar.

The main results are listed in Table 2. In all participants, the 1-year mortality rates estimated from unadjusted Kaplan-Meier (K-M) curves were 11.6% with GIK versus 13.5% with placebo (unadjusted hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.57 to 1.23, $p = 0.36$); the K-M rates of the composite of cardiac arrest or 1-year mortality were 12.8% for GIK and 17.0% for placebo (HR 0.71, 95% CI 0.50 to 1.02, $p = 0.06$); the K-M rates for the composite of hospitalization for HF or mortality within 1 year were 17.2% for both GIK and placebo (HR 0.98, 95% CI 0.70 to 1.37, $p = 0.92$); and the K-M rates for the composite of cardiac arrest, 1-year mortality, or HF hospitalization within 1 year were 18.1% with GIK versus 20.4%

Table 1
Baseline demographic and clinical characteristics of study participants by treatment group (n = 871)

Characteristics	GIK (n = 411)	Placebo (n = 460)
Age (yrs)	63.9 ± 13.9	63.3 ± 14.1
Gender		
Women	113 (27.5)	140 (30.4)
Men	298 (72.5)	320 (69.6)
Race*		
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 ethnic group	44/402 (10.9)	58/445 (13.0)
Chief complaint on presentation		
Chest pain	358/411 (87.1)	391/460 (85.0)
Dyspnea	15/411 (3.6)	19/460 (4.1)
Initial out-of-hospital blood pressure (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 (beats/min)	86.8 ± 24.7	86.6 ± 25.6
Initial out-of-hospital respiratory rate (breaths/min)	19.3 ± 4.2	19.5 ± 4.4
Time from symptom onset to study drug (≤24 hours)		
Median	90.0	90.0
Interquartile range	50.0−159.3	52.0−159.3
Time from symptom onset to study drug		
0−30 minutes	24/401 (6.0)	20/457 (4.4)
31−60 minutes	101/401 (25.2)	121/457 (26.5)
61−90 minutes	60/401 (15.0)	74/457 (16.2)
91−180 minutes	66/401 (16.5)	82/457 (17.9)
181−360 minutes	46/401 (11.5)	55/457 (12.0)
361 minutes−24 h	37/401 (9.2)	36/457 (7.9)
Within 24 hours (unspecified)	31/401 (7.7)	34/457 (7.4)
>24 hours	36/401 (9.0)	35/457 (7.7)
STEMI on presenting out-of-hospital ECG (%)	163/411 (39.7)	194/460 (42.2)
ACI-TIPI score†	74.6 ± 22.6	76.9 ± 20.6
TPI triggered	84/411 (20.4)	116/460 (25.2)
Medical history		
Diabetes mellitus	121/411 (29.4)	121/460 (26.3)
HF	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)

Data are presented as mean ± SD, n (%), or n/total (%), unless otherwise specified.
Nineteen patients had 21 repeat visits.
No significant differences were noted between GIK and placebo.
* Race was self-reported.
† ACI-TIPI score ≥75% was part of the inclusion criteria.

with placebo (HR 0.85, 95% CI 0.62 to 1.16, p = 0.30). The causes of death are listed in Table 3.

In Table 4 are results in participants who presented with suspected STEMI, including 163 who received GIK and 194 who received placebo. One-year mortality rates estimated from unadjusted K-M curves were 8.3% with GIK versus 12.6% with placebo (HR 0.65, 95% CI 0.33 to 1.27, p = 0.21); the K-M rates of the composite of cardiac arrest or mortality within 1 year were 10.8% with GIK versus 19.3% with placebo (HR 0.52, 95% CI 0.30 to 0.92, p = 0.03); the composite of hospitalization for HF or mortality within 1 year was 10.2% with GIK versus 15.7% with placebo (HR 0.63, 95% CI 0.35 to 1.16, p = 0.14); and the composite outcome of cardiac arrest, 1-year mortality, or HF hospitalization within 1 year was 12.0% with GIK versus 21.9% with placebo (HR 0.51, 95% CI 0.30 to 0.87, p = 0.01).

Figure 2 shows the K-M plot for the end point of all-cause mortality for all participants and Figure 3 for the composite outcome of in-hospital cardiac arrest or HF or mortality for all participants. Figure 4 and Figure 5 present the K-M plots for participants presenting with ST-segment elevation for the outcomes of all-cause mortality and the

Table 2
IMMEDIATE Trial incidence of in-hospital cardiac arrest or 1-year mortality overall in all patients in the intent-to-treat cohort

Outcome	Treatment	Unadjusted Rate, n/ Total (%)	Unadjusted K-M Rate (%)	Unadjusted HR (GIK vs Placebo)	95% CI of Unadjusted HR	Unadjusted Cox Regression p Value
1-yr mortality	GIK	45/411 (10.9)	11.6	0.83	0.57−1.23	0.355
	Placebo	60/460 (13.0)	13.5			
Cardiac arrest or mortality	GIK	50/411 (12.2)	12.8	0.71	0.50−1.02	0.062
	Placebo	76/460 (16.5)	17.0			
In-hospital cardiac arrest	GIK	15/411 (3.6)		0.56	0.30−1.02	0.060
	Placebo	29/460 (6.3)				
1-yr HF or mortality	GIK	67/411 (16.3)	17.2	0.98	0.70−1.37	0.915
	Placebo	76/460 (16.5)	17.2			
1-yr HF	GIK	35/411 (8.5)	9.6	1.22	0.74−2.02	0.439
	Placebo	32/460 (7.0)	7.8			
Cardiac arrest, HF, or mortality	GIK	71/411 (17.3)	18.1	0.85	0.62−1.16	0.299
	Placebo	91/460 (19.8)	20.4			

Table 3
Adjudicated cause of death

Subgroup	No. of Deaths by Treatment	
	GIK	Placebo
All: total no. of deaths (1-yr analysis)	45	60
Death cardiac: arrhythmic	3	2
Death cardiac: HF	6	10
Death cardiac: ischemia	13	22
Death cardiac: not otherwise specified	12	9
Death non-cardiac	11	17

composite outcome of in-hospital cardiac arrest, HF, or mortality, respectively.

Discussion

This placebo-controlled, double-blind, randomized, clinical effectiveness trial of community-based EMS use of GIK for ACS was intended to translate the effects seen in experimental laboratory research into an approach that could work in widespread clinical practice. In previous trials, GIK was administered in hospitals once a diagnosis of AMI was established. In the IMMEDIATE trial, to better duplicate the experimental benefits, GIK was administered immediately after evaluation by paramedics in the community based on their clinical impression of ACS, supplemented by ACI-TIPI and TPI predictions printed on the out-of-hospital ECGs.[2,3] This approach allowed initiation of GIK at a median of 90 minutes after the onset of ischemic symptoms, rather than the typical 6 hours seen in previous GIK trials.[2] Thereby, benefits from GIK that the IMMEDIATE Trial sought to detect were reductions in myocardial damage, acute cardiac arrest, and acute mortality. The degree to which this 1-time 12-hour GIK treatment might be reflected a year later has not been previously reported.

In the previously reported 30-day results, the reduction of progression to biomarker-confirmed AMI was not significant, but the degree of LV protection, as evidenced by the mitigation of infarct size in the biological mechanism cohort, was significant at 30 days. These participants underwent single-photon emission computed tomography cardiac imaging at 30 days: among those presenting with ACS, infarct size was reduced from a median of 10% of LV mass to 2% of LV mass with GIK ($p = 0.01$), and among those presenting with STEMI, infarct size in the placebo-treated patients was 12% of LV mass compared with only 3% with GIK ($p = 0.05$). If sustained, this preservation of myocardium would be expected to lead to longer-term benefits of better survival and avoidance of HF. Indeed, some such effect could have been inferred from the 30-day results[1] that included a 40% reduction in the composite incidence of cardiac arrest, 30-day mortality, or HF hospitalization within 30 days ($p = 0.03$) and a 54% reduction in this composite in those presenting with STEMI ($p = 0.02$).

The 1-year outcomes (Table 2) generally demonstrate point estimates favoring GIK for individual events and for composites, but CIs overlap 1.0 in most analyses. However, this study was not specifically powered to detect a significant difference in these outcome measures. Nonetheless, selected biologically plausible outcomes did reach significance in favor of GIK, consistent with the 30-day results. For those treated with GIK, the composite of cardiac arrest and 1-year mortality was lower in all those with suspected ACS, 12.8% for GIK versus 17.0% for placebo (HR 0.71, 95% CI 0.50 to 1.02, $p = 0.06$) and in those presenting with ST elevation, 10.8% with GIK versus 19.3% with placebo (HR 0.52, 95% CI 0.30 to 0.92, $p = 0.03$). This also was the case for the 3-way composite of cardiac arrest, 1-year mortality, or HF hospitalization within 1 year for those presenting with STEMI (HR 0.51, 95% CI 0.30 to 0.87, $p = 0.01$). These results are supportive of the potential impact of GIK and that a larger trial should be designed to have power to detect such effects—both at 30 days and at 1 year.

In suggesting the need for another larger GIK trial, it should be noted that although the results presented here and in the 30-day IMMEDIATE Trial results[1] are consistent with experimental results,[5] they are distinct in some ways from previous GIK clinical trials, most dramatically, the >20,000-patient CREATE-ECLA-OASIS [Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation—Estudios Clinicos Latino America (CREATE-ECLA) and Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)] trials.[11,19] However, the IMMEDIATE Trial study design and execution is very different from other GIK clinical

Table 4
IMMEDIATE Trial incidence of in-hospital cardiac arrest or 1-year mortality overall in patients presenting with ST elevation on ECG

Outcome	Treatment	Unadjusted Rate, n/ Total (%)	Unadjusted K-M Rate (%)	Unadjusted HR (GIK vs Placebo)	95% CI of Unadjusted HR	Unadjusted Cox Regression p Value
1-yr mortality	GIK	13/163 (8.0)	8.3	0.65	0.33−1.27	0.208
	Placebo	24/194 (12.4)	12.6			
Cardiac arrest or mortality	GIK	17/163 (10.4)	10.8	0.52	0.30−0.92	0.025
	Placebo	37/194 (19.1)	19.3			
In-hospital cardiac arrest	GIK	9/163 (5.5)		0.49	0.23−1.03	0.061
	Placebo	21/194 (10.8)				
1-yr HF or mortality	GIK	16/163 (9.8)	10.2	0.63	0.35−1.16	0.139
	Placebo	30/194 (15.5)	15.7			
1-yr HF	GIK	6/163 (3.7)	4.2	0.65	0.24−1.74	0.389
	Placebo	11/194 (5.7)	6.1			
Cardiac arrest, HF, or mortality	GIK	19/163 (11.7)	12.0	0.51	0.30−0.87	0.014
	Placebo	42/194 (21.6)	21.9			

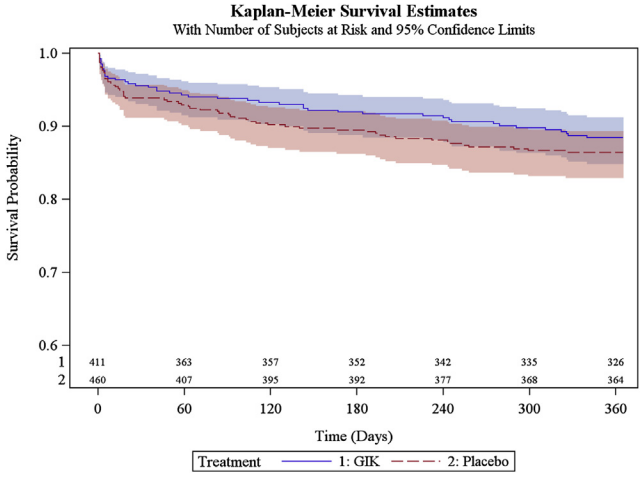

Figure 2. Cumulative incidence of freedom from death through 1 year (intent-to-treat participants).

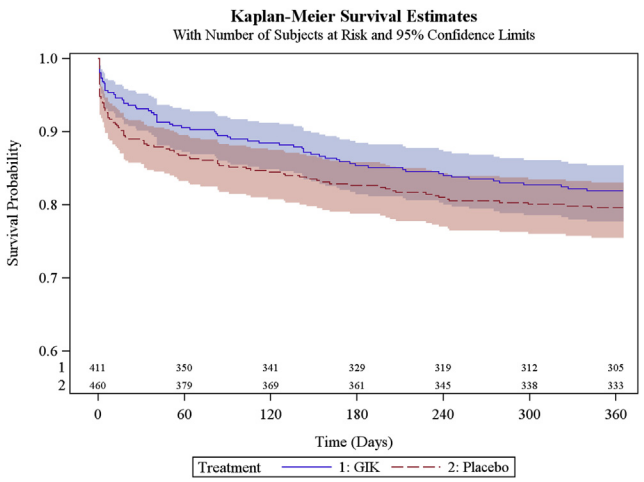

Figure 3. Cumulative incidence of freedom from in-hospital cardiac arrest, HF, or death through 1 year (intent-to-treat participants).

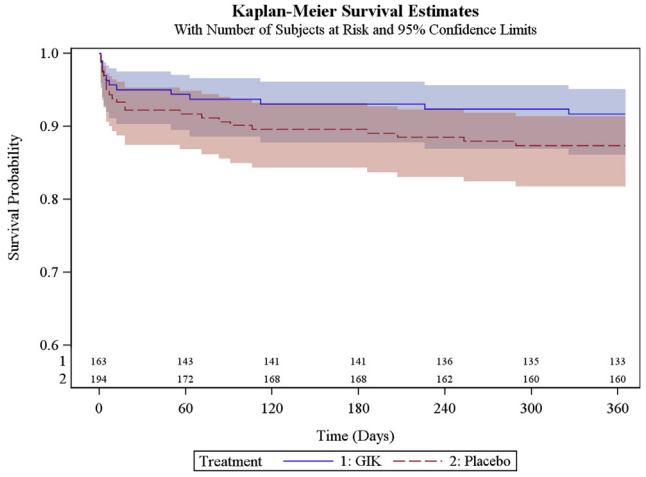

Figure 4. Cumulative incidence of freedom from death through 1 year (participants presenting with ST-segment elevation).

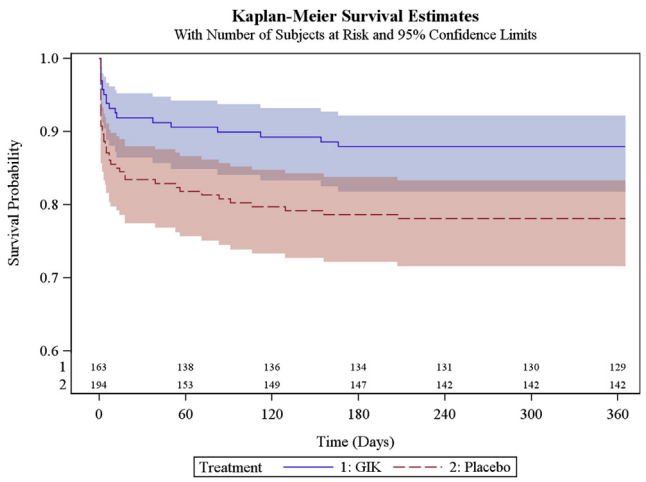

Figure 5. Cumulative incidence of freedom from in-hospital cardiac arrest, HF, or death through 1 year (participants presenting with ST-segment elevation).

trials, which likely explains the disparate outcomes. The other trials were not double-blind, placebo-controlled, randomized trials, as was the IMMEDIATE Trial. Most importantly, the IMMEDIATE Trial tested GIK administered to patients with ACS, *as early as possible,* emulating previous successful animal experiments. All previous

clinical trials gave GIK only after the patient had arrived at the hospital and had an AMI documented, typically 6 hours after symptom onset, compared with a median of 90 minutes in the IMMEDIATE Trial. This delayed administration is not consistent with the concept of GIK providing metabolic support during ischemia before reestablishment of coronary perfusion and, therefore, would not be expected to show significant results. In CREATE-ECLA, 17.4% patients did not get reperfusion and 68.3% were given GIK *after,* not before, coronary reperfusion—so for 85.7% there was no opportunity at all for the GIK to provide metabolic support that might have prolonged the window of benefit from reperfusion.[6,20] In contrast, in the IMMEDIATE Trial, the results of the biological mechanism cohort in which infarct size was 80% smaller with GIK is consistent with such metabolic support.

In summary, the 30-day results of the IMMEDIATE Trial previously reported and the 1-year results presented here demonstrate trends toward, and in some cases statistically significant, improved clinical outcomes. Such scientifically plausible findings warrant additional clinical trials to further evaluate this simple, inexpensive, and potentially very impactful treatment for ACS and particularly STEMI.

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Disclosures

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