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The CREATE-ECLA Trial Group Investigators*

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Effect of Glucose-Insulin-Potassium Infusion on Mortality in Patients With Acute ST-Segment Elevation Myocardial Infarction

The CREATE-ECLA Randomized Controlled Trial

The CREATE-ECLA Trial Group
Investigators*

THE CONCEPT OF METABOLIC modulation of acute myocardial infarction (AMI) with glucose-insulin-potassium (GIK) infusion was originally proposed in the 1960s.¹ This infusion is a simple, low-cost, and widely practicable therapy. If effective, it has the potential to widely affect mortality due to AMI in all regions of the world, including those of both lower and higher income.

Glucose-insulin-potassium infusion may reduce mortality through several different mechanisms.² Exogenous insulin suppresses circulating levels and myocardial uptake of free fatty acids, which are toxic to the ischemic myocardium.³⁻⁵ Provision of high-dose glucose can improve the efficiency of myocardial energy production during acute ischemia by becoming the preferred fuel for the heart.^{2,6} Because intracellular levels of potassium are depleted during ischemia, provision of exogenous potassium increases levels within the myocyte, thereby raising the threshold for ventricular arrhythmias.^{7,8}

A meta-analysis of 16 trials of GIK infusion vs control involving almost 5000 patients indicated a reduction in mortality risk with GIK infusion therapy of 18%, with wide confidence intervals

See also pp 427 and 489.

Context Glucose-insulin-potassium (GIK) infusion is a widely applicable, low-cost therapy that has been postulated to improve mortality in patients with acute ST-segment elevation myocardial infarction (STEMI). Given the potential global importance of GIK infusion, a large, adequately powered randomized trial is required to determine the effect of GIK on mortality in patients with STEMI.

Objective To determine the effect of high-dose GIK infusion on mortality in patients with STEMI.

Design, Setting, and Participants Randomized controlled trial conducted in 470 centers worldwide among 20201 patients with STEMI who presented within 12 hours of symptom onset. The mean age of patients was 58.6 years, and evidence-based therapies were commonly used.

Intervention Patients were randomly assigned to receive GIK intravenous infusion for 24 hours plus usual care (n=10091) or to receive usual care alone (controls; n=10110).

Main Outcome Measures Mortality, cardiac arrest, cardiogenic shock, and reinfarction at 30 days after randomization.

Results At 30 days, 976 control patients (9.7%) and 1004 GIK infusion patients (10.0%) died (hazard ratio [HR], 1.03; 95% confidence interval [CI], 0.95-1.13; *P* = .45). There were no significant differences in the rates of cardiac arrest (1.5% [151/10107] in control and 1.4% [139/10088] in GIK infusion; HR, 0.93; 95% CI, 0.74-1.17; *P* = .51), cardiogenic shock (6.3% [640/10107] vs 6.6% [667/10088]; HR, 1.05; 95% CI, 0.94-1.17; *P* = .38), or reinfarction (2.4% [246/10107] vs 2.3% [236/10088]; HR, 0.98; 95% CI, 0.82-1.17; *P* = .81). The rates of heart failure at 7 days after randomization were also similar between the groups (16.9% [1711/10107] vs 17.1% [1721/10088]; HR, 1.01; 95% CI, 0.95-1.08; *P* = .72). The lack of benefit of GIK infusion on mortality was consistent in prespecified subgroups, including in those with and without diabetes, in those presenting with and without heart failure, in those presenting early and later after symptom onset, and in those receiving and not receiving reperfusion therapy (thrombolysis or primary percutaneous coronary intervention).

Conclusion In this large, international randomized trial, high-dose GIK infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock in patients with acute STEMI.

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(CIs) (hazard ratio [HR], 0.82; 95% CI, 0.68-0.98; *P* = .03).⁹ The benefit appeared to be larger in trials that tested a high-dose GIK infusion regimen (HR, 0.70; 95% CI, 0.51-0.95; *P* = .02).⁹

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Although these data are promising, given the variability and limitations in the design of the various trials included and the wide CIs of the estimates of benefit, a large and well-designed randomized trial is needed to reliably assess the effects of high-dose GIK infusion on mortality in patients with AMI. The CREATE-ECLA program was born from the common goal of several international investigators interested in answering the question of whether this promising, low-cost, and widely applicable therapy is beneficial in patients presenting with AMI.

METHODS

Design

CREATE-ECLA was a randomized trial with a partial 2×2 factorial design evaluating the effects of a 24-hour infusion of high-dose GIK and 7 days of treatment with the low-molecular-weight heparin reviparin in patients with acute ST-segment elevation MI (STEMI). Details of the trial design have been published previously.⁹ The results of the comparison of reviparin with placebo are reported separately.¹⁰ All 470 centers worldwide obtained local ethics committee approval; in addition, the Population Health Research Institute Project Office obtained approval from the shared institutional review board of McMaster University and Hamilton Health Sciences, Hamilton, Ontario.

Following written or witnessed oral informed consent, patients presenting with AMI with ST-segment elevation or new left bundle-branch block within 12 hours of symptom onset were randomly assigned to receive, in addition to usual care, either GIK infusion for 24 hours or usual care alone (control). Individuals with contraindications for GIK infusion, including type 1 diabetics and those with known renal impairment (creatinine >2 mg/dL [>176.8 $\mu\text{mol/L}$]) or known hyperkalemia at randomization were excluded. To meet the reviparin/placebo eligibility criteria, patients in India and China were further excluded if they had active bleeding or were at high risk of

bleeding or had recent major surgery or trauma within 2 weeks, systolic blood pressure of 180 mm Hg or more, severe anemia, hemorrhagic stroke within 12 months, oral anticoagulant therapy, heparin-induced thrombocytopenia, pregnancy, or other conditions limiting life expectancy to less than 1 month. Patients with anticipated poor compliance with randomized treatments and any factor that jeopardized 30-day follow-up (eg, no fixed address, long distance to hospital) were excluded.

Study Protocol

The study infusion was prepared locally and consisted of 25% glucose, 50 U/L of regular insulin, and 80 mEq/L of potassium to be infused at a rate of 1.5 mL/kg per hour for 24 hours. The GIK infusion was initiated immediately after randomization. For patients undergoing primary percutaneous coronary intervention (PCI), it was recommended that the infusion be started before the procedure and continued for 24 hours. For patients receiving thrombolytic therapy, the infusion was started as soon as possible after randomization. Serum glucose, potassium, and sodium levels were measured at baseline and 6 and 24 hours after randomization. Adjustments to GIK infusion rate for Killip class and blood potassium level were made according to a standard nomogram similar to that used in the ECLA pilot trial.¹¹ The fluid balance during the 24 hours of treatment was carefully monitored in all patients.

Study Organization

The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) began enrollment in July 2001 as a 2×2 factorial randomized trial of reviparin vs placebo and GIK infusion vs control in China and India. A separate trial of GIK infusion vs control (Estudios Cardiologicas Latin America Study Group [ECLA] 2 GIK Full Scale Trial) using an identical GIK regimen in patients similar to that in CREATE had begun enrolling pa-

tients in August 1998. Both studies were formally merged into 1 trial, called the CREATE-ECLA International GIK Study, on November 14, 2002, with a single steering and operations committee and a single data and safety monitoring board. The rationale for combining the 2 studies into 1 large trial was to optimize study power to reliably detect or exclude even a moderate benefit of treatment. The study was extended to include Pakistan in October 2003. The design of the overall CREATE-ECLA program therefore used a partial 2×2 factorial design, with one randomization to GIK infusion or control (all patients) and a second randomization to double-blind therapy with reviparin or matching placebo (in India and China).

The Population Health Research Institute (PHRI), McMaster University and Hamilton Health Sciences, coordinated the overall trial. Regional coordination occurred through national coordinating offices. Data for ECLA were coordinated at the ECLA coordinating center in Rosario, Argentina; for China at the Beijing Hypertension League Institute, Beijing; for India at St John's National Academy of Health Sciences, Bangalore; and for Pakistan at Aga Khan University Hospital, Karachi. An international steering committee, consisting of national coordinators and members of the PHRI, oversaw the conduct of the study. An independent data and safety monitoring board periodically reviewed safety and efficacy data. An event adjudication committee performed adjudication of reinfarction, stroke, life-threatening/major bleeding, and recurrent ischemia with electrocardiographic changes in all regions except for ECLA countries. The national coordinating offices in India, China, and Pakistan established a streamlined monitoring program regionally, with each site having at least 1 monitoring visit to check key source data, informed consent, and protocol adherence. The regional coordinating centers entered the data into an Internet-based database that was connected online to the PHRI, McMaster

University and Hamilton Health Sciences. Extensive consistency and edit checks at the national coordinating offices as well as at the PHRI ensured high data quality.

Patients returned to the hospital at 30 days or shortly thereafter for a pre-arranged follow-up clinic appointment with study personnel. A list of patients with overdue 30-day follow-up forms was regularly compiled and mailed to centers using the Internet database. Patients, close family relatives, neighbors, or the patients' physicians were contacted by telephone or mail in the event of a missed follow-up appointment, inability to attend clinic, or death.

Randomization to GIK infusion or control was grouped in blocks, with the block size kept confidential and the randomization list stratified by center. All patients in ECLA countries, China, and Pakistan were randomized by telephone to the national coordinating offices in Rosario, Argentina; Beijing, China; or Karachi, Pakistan. In India, patients were initially randomized using sealed opaque envelopes ($n=5127$), but subsequent patients ($n=2933$) had central telephone randomization. Despite extensive precautions, randomization errors occurred in 173 of 15 570 patients (1.1%). These patients were included in their originally intended allocations for analyses.

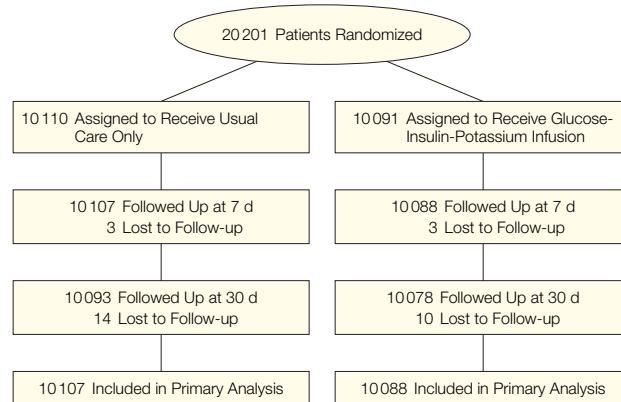
Outcomes

The primary outcome measure was mortality from any cause at 30 days after randomization. Secondary outcome measures included the composite of death or nonfatal cardiac arrest, death or cardiogenic shock, death or reinfarction, and each of these individually. Definitions of primary outcome measures have been reported previously.⁹

Statistical Analysis

With a mortality rate of 10% in the control group at 30 days, the study had 99% power to detect a 20% relative risk reduction with GIK infusion, and 95% power to detect a 15% relative risk reduction.

Figure 1. Flow of Participants Through the CREATE-ECLA Trial



All analyses were performed using the intention-to-treat approach. Time to death up to 30 days between the GIK infusion and control groups was compared using the log-rank statistic. After confirming the proportional hazards assumption, the point estimate of the relative risk and its associated 95% CI were derived from the Cox proportional hazards model. The primary comparisons between GIK infusion and control were adjusted for randomization to reviparin or placebo. Statistical significance was claimed at a computed (2-sided) $P \leq .05$.

Predefined subgroup analyses included time from symptom onset to treatment (<4 , 4 to <8 , and ≥ 8 hours), baseline reperfusion therapy (thrombolysis or primary PCI) vs no reperfusion therapy, heart failure at presentation vs no heart failure at presentation, and diabetes vs no diabetes. Tests for interaction between GIK infusion and reviparin were not significant ($P = .99$ for mortality and $P = .85$ for death, MI, or stroke). All statistical analyses were carried out with SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Overall, 20 201 patients were randomized; 8060 from India, 7510 from China, 3804 from ECLA centers, and 827 from Pakistan. Follow-up was 99.97% complete at 7 days and 99.85% complete at 30 days (FIGURE 1). Only 30 (0.15%) of

20 201 patients randomized were lost to follow-up. Six of these 30 patients (3 infusion and 3 control) had no in-hospital or follow-up data collected, yielding a total data set of 20 195 patients for analysis. The median time from symptom onset to randomization was 4.7 hours, with 8361 (41.4%) of patients randomized within 4 hours, 7661 (37.9%) between 4 and 8 hours, and 4073 (20.2%) between 8 and 12 hours.

Of patients allocated to GIK infusion in China, India, and Pakistan, 8020 (97.9%) received therapy. Nonstudy GIK was used in 152 (1.9%) control patients randomized (ECLA did not collect these data). Study infusion was started within 1 hour of randomization in more than 90% of patients (8882/9835). The full 24-hour infusion was completed in 84.2% (8280/9835), with 92.2% (9069/9835) receiving at least 10 hours of therapy.

Reperfusion therapy was given in 16 711 patients (82.7%); 14 957 (74.1%) patients received thrombolytic therapy and 1831 (9.1%) received primary PCI (77 patients received both). Among patients receiving reperfusion therapy, the median time from symptom onset to reperfusion (thrombolysis or primary PCI) was 3.9 hours in the GIK infusion group and 3.8 hours in the control group.

Baseline Characteristics

Baseline patient characteristics were similar in the 2 groups (TABLE 1). The

Table 1. Baseline Patient Characteristics*

Characteristics	Usual Care Only (n = 10 107)	Glucose-Insulin-Potassium Infusion (n = 10 088)
Age, mean (SD), y	58.6 (12.5)	58.6 (12.2)
Aged >75 y	822 (8.1)	767 (7.6)
Female sex	2267 (22.4)	2255 (22.4)
Type 2 diabetes	1802 (17.8)	1780 (17.6)
Known hypertension	3755 (37.2)	3739 (37.1)
Congestive heart failure†	137 (1.7)	135 (1.6)
Stroke†	453 (5.5)	426 (5.2)
Weight, mean (SD), kg	67.8 (12.8)	67.5 (12.8)
Blood pressure, mean (SD), mm Hg		
Systolic	128.8 (26.4)	129.1 (26.6)
Diastolic	81.5 (16.2)	81.6 (16.1)
Heart rate, mean (SD), beats/min	79.7 (18.5)	79.5 (18.4)
Electrocardiographic changes		
ST elevation	10 035 (99.3)	10 015 (99.3)
Anterior	5174 (51.2)	5185 (51.4)
Inferior	4612 (45.6)	4604 (45.6)
Lateral	249 (2.5)	226 (2.2)
New left bundle-branch block	69 (0.7)	68 (0.7)
Symptom onset to randomization, h		
Median (interquartile range)	4.6 (2.8-7.3)	4.7 (2.8-7.3)
<4	4218 (41.7)	4124 (40.9)
4-<8	3775 (37.4)	3886 (38.5)
≥8	2114 (20.9)	2078 (20.6)
Killip class at randomization		
I	8606 (85.1)	8490 (84.2)
II/III	1339 (13.2)	1435 (14.2)
IV	160 (1.6)	157 (1.6)

*Data are expressed as No. (%) unless otherwise noted.

†These variables were reported in India, China, and Pakistan only (usual care only, n = 8206; glucose-insulin-potassium infusion, n = 8191).

Table 2. Concurrent Medications and Reperfusion Strategy*

Therapy	Usual Care Only (n = 10 107)	Glucose-Insulin-Potassium Infusion (n = 10 088)
Aspirin	9818 (97.1)	9826 (97.4)
Clopidogrel/ticlopidine	4920 (48.7)	4891 (48.5)
β-Blocker	7074 (70.0)	7063 (70.0)
Angiotensin-converting enzyme inhibitor	7235 (72.5)	7287 (72.2)
Lipid-lowering drug†	5646 (68.8)	5456 (66.6)
Intravenous nitroglycerine	7482 (74.0)	7365 (73.0)
Glycoprotein IIb/IIIa inhibitor	279 (2.8)	277 (2.7)
Diuretic		
Any	2343 (23.2)	2411 (23.9)
Oral†	602 (7.3)	537 (6.6)
Intravenous†	1296 (15.8)	1458 (17.8)
Thrombolytic therapy	7503 (74.2)	7454 (73.9)
Streptokinase	5185 (51.3)	5211 (51.7)
Urokinase	1832 (18.1)	1762 (17.5)
Alteplase	371 (3.7)	371 (3.7)
Primary percutaneous coronary intervention	906 (9.0)	925 (9.2)
Any reperfusion therapy	8368 (82.8)	8343 (82.7)

*Data are expressed as No. (%).

†These variables were reported in India, China, and Pakistan only (usual care only, n = 8206; glucose-insulin-potassium infusion, n = 8191).

mean age was 58.6 years, with 1589 (7.9%) older than 75 years. A total of 3582 patients (17.7%) had diabetes and 7494 (37.1%) had a known history of hypertension. Mean systolic blood pressure was 129.0 mm Hg and mean diastolic blood pressure was 81.5 mm Hg. The majority of patients (n=17 096; 84.7%) presented as Killip class I and 3091 (15.4%) presented as Killip class II, III, or IV.

Medications in the hospital were similar between the groups (TABLE 2). A total of 19 644 (97.3%) were treated with aspirin, 9811 (48.6%) received clopidogrel or ticlopidine, 14 137 (70%) received β-blockers, and 14 522 (72.4%) received angiotensin-converting enzyme inhibitors. A total of 11 102 (67.7%) received lipid-lowering therapy in CREATE (data not recorded in ECLA). In CREATE, 766 (53.3%) of 1438 with type 2 diabetes in the control group and 720 (53.3%) of 1436 with type 2 diabetes in the GIK infusion group received supplemental nonstudy insulin (data not recorded in ECLA). Overall, in CREATE, any nonstudy insulin was used in 1325 control patients (16.1%) and any supplemental nonstudy insulin was used in 1479 GIK infusion patients (18.1%).

Efficacy Outcomes

At 30 days, a total of 976 control patients (9.7%) and 1004 GIK infusion patients (10.0%) died within 30 days of randomization (HR, 1.03; 95% CI, 0.95-1.13; $P = .45$) (TABLE 3 and FIGURE 2A). Cardiac arrest occurred in 151 control patients (1.5%) and in 139 GIK infusion patients (1.4%) (HR, 0.93; 95% CI, 0.74-1.17; $P = .51$). Cardiogenic shock developed in 640 control patients (6.3%) and 667 GIK infusion patients (6.6%) (HR, 1.05; 95% CI, 0.94-1.17; $P = .38$). There were no significant differences in the number of patients with the composite of death or nonfatal cardiac arrest (Table 3 and Figure 2B). Similarly, there were no significant differences in the composites of death or cardiogenic shock and death or reinfarction. There were no significant differences between the groups in any of these outcomes at 7 days (Table 3).

After the first day, 1.9% of control patients had recurrent ischemia (with or without electrocardiographic changes) compared with 1.5% in the GIK infusion group (absolute risk reduction, 0.4%; HR, 0.80; 95% CI, 0.65-1.00; $P=.047$). At 7 days, the absolute risk reduction in recurrent ischemia widened (660 [6.5%] in the control group vs 560 [5.6%] in the GIK infusion group; absolute risk reduction, 0.9%; HR, 0.85; 95% CI, 0.76-0.95; $P=.004$) and was maintained at 30 days (784 [7.8%] in the control group vs 703

[7.0%] in the GIK infusion group; absolute risk reduction, 0.8%; HR, 0.90; 95% CI, 0.81-0.99; $P=.04$).

There were no significant differences between the groups in the occurrence of ventricular fibrillation/tachycardia (21.4% [2166/10107] in the control group vs 21.0% [2122/10088] in the GIK infusion group; HR, 0.98; 95% CI, 0.92-1.04; $P=.53$), advanced second- or third-degree heart block (19.8% [2002/10107] vs 19.9% [2010/10088]; HR, 1.01; 95% CI, 0.95-1.07; $P=.71$) or in electromechanical dissociation (0.5%

[46/10107] vs 0.4% [44/10088]; HR, 0.96; 95% CI, 0.64-1.46; $P=.86$).

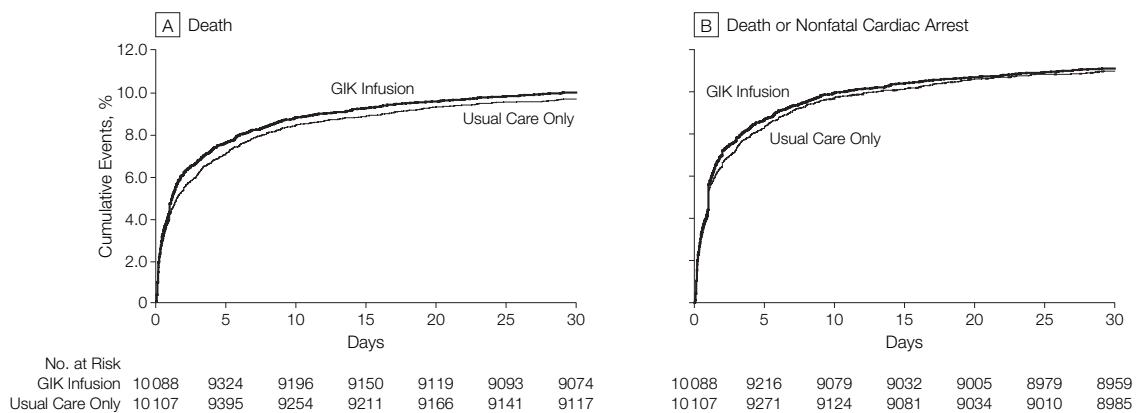
Safety Outcomes

There was no difference between the groups in outcomes related to fluid volume overload. A new episode of heart failure at 7 days after randomization occurred in 1711 patients (16.9%) in the control group and 1721 (17.1%) in the GIK infusion group (HR, 1.01; 95% CI, 0.95-1.08; $P=.72$) (TABLE 4). At 30 days, the rates of heart failure were 17.4% (1761/10107) and 17.4% (1758/

Table 3. Primary and Secondary Outcomes

Outcome	No. (%)		Hazard Ratio (95% Confidence Interval)	P Value
	Usual Care Only (n = 10 107)	Glucose-Insulin-Potassium Infusion (n = 10 088)		
30 Days				
Death	976 (9.7)	1004 (10.0)	1.03 (0.95-1.13)	.45
Nonfatal cardiac arrest	151 (1.5)	139 (1.4)	0.93 (0.74-1.17)	.51
Cardiogenic shock	640 (6.3)	667 (6.6)	1.05 (0.94-1.17)	.38
Reinfarction	246 (2.4)	236 (2.3)	0.98 (0.82-1.17)	.81
Death or cardiac arrest	1108 (11.0)	1119 (11.1)	1.01 (0.93-1.10)	.73
Death or cardiogenic shock	1182 (11.7)	1212 (12.0)	1.03 (0.95-1.12)	.45
Death or reinfarction	1154 (11.4)	1179 (11.7)	1.03 (0.95-1.12)	.49
7 Days				
Death	771 (7.6)	816 (8.1)	1.06 (0.96-1.17)	.22
Nonfatal cardiac arrest	139 (1.4)	126 (1.2)	0.91 (0.72-1.16)	.45
Cardiogenic shock	608 (6.0)	628 (6.2)	1.04 (0.93-1.16)	.49
Reinfarction	202 (2.0)	190 (1.9)	0.96 (0.79-1.17)	.70
Death or cardiac arrest	900 (8.9)	926 (9.2)	1.03 (0.94-1.13)	.48
Death or cardiogenic shock	1012 (10.0)	1056 (10.5)	1.06 (0.97-1.16)	.18
Death or reinfarction	920 (9.1)	965 (9.6)	1.06 (0.97-1.16)	.23

Figure 2. Cumulative Hazard Rates of Death and Death/Nonfatal Cardiac Arrest Within 30 Days



For death, hazard ratio (HR), 1.03 (95% confidence interval [CI], 0.95-1.13); $P=.45$. For death or nonfatal cardiac arrest, HR, 1.01 (95% CI, 0.93-1.10); $P=.73$. GIK indicates glucose-insulin-potassium.

Table 4. Glucose-Insulin-Potassium Infusion Safety Outcomes at 7 Days*

Outcome	Usual Care Only (n = 10 107)	Glucose-Insulin-Potassium Infusion (n = 10 088)	Hazard Ratio (95% Confidence Interval)	P Value
Heart failure	1711 (16.9)	1721 (17.1)	1.01 (0.95-1.08)	.72
Hyperkalemia (>5.5 mEq/L)	161 (1.6)	431 (4.3)	2.76 (2.30-3.31)	<.001
Significant phlebitis	17 (0.2)	339 (3.4)	20.64 (12.07-33.62)	<.001
Symptomatic hypoglycemia†	11 (0.1)	34 (0.4)	3.11 (1.57-6.13)	<.001

*Data are expressed as No. (%) unless otherwise noted.

†This variable was reported in India, China, and Pakistan only (usual care only, n = 8206; glucose-insulin-potassium infusion, n = 8191).

10088) in each group (HR, 1.00; 95% CI, 0.94-1.07; $P = .88$). Symptomatic hypoglycemia was uncommon in CREATE but was more frequent in the GIK infusion group (0.1% [11/8206] in the control group and 0.4% [34/8191] in the GIK infusion group) (Table 4). Hyperkalemia (>5.5 mEq/L) was also more frequent in the GIK infusion group than in the control group (4.3% [431/10088] in the GIK infusion group vs 1.6% [161/10107] in the control group; HR, 2.76; 95% CI, 2.30-3.31) (Table 4). Further analysis of the subgroup with hyperkalemia indicated more deaths at 30 days in the control group (38/161; 23.6%) compared with the GIK infusion group (62/431; 14.4%), suggesting that the hyperkalemia associated with GIK use was not deleterious. Significant phlebitis (at the site of infusion) was more frequent in the GIK infusion group (339/10088; 3.4%) compared with the control group (17/10107; 0.2%; $P < .001$).

Subgroups

The neutral effect of GIK on mortality was not significantly heterogeneous in any of the prespecified subgroup analyses (FIGURE 3). Consistent results were observed in those defined by baseline glucose levels, Killip class, and time from symptom onset to randomization (<4, 4 to <8, and ≥ 8 hours). Among patients presenting very early, there was also no evidence of benefit with GIK infusion: within 1 hour, 21 of 288 controls vs 27 of 275 GIK infusion patients (HR, 1.36; 95% CI, 0.77-2.40); between 1 and 2 hours, 78 of 1022 vs 82 of 954, respectively (HR, 1.14; 95% CI, 0.83-1.55); and between 2 and 4 hours, 251 of 2908 vs 257 of 2895, respectively (HR, 1.03;

95% CI, 0.87-1.23). Similarly, there was consistency of the neutrality of GIK infusion in those receiving and not receiving baseline reperfusion therapy (Figure 3). Although the point estimate for mortality was lower in those who received primary PCI (57/906 in the control group vs 44/925 in the infusion group; HR, 0.75; 95% CI, 0.51-1.11) compared with those who did not (919/9201 vs 960/9163, respectively; HR, 1.05; 95% CI, 0.96-1.15; $P = .26$), there was no significant interaction with the overall result in this group of patients (Figure 3).

In patients in whom GIK infusion was started before initiation of reperfusion therapy, mortality was 12.2% (175/1437), and in patients in whom GIK infusion was started after initiation of reperfusion therapy, mortality was 8.2% (569/6900). Mortality in control patients who received reperfusion therapy was 8.7% (729/8368).

We noted no heterogeneity of treatment effect by region.

Serum Glucose and Electrolytes

Mean glucose levels were 162 mg/dL (9.0 mmol/L) in the GIK infusion and control groups at baseline. At 6 hours after randomization, the mean glucose level in the GIK infusion group increased to 187 mg/dL (10.4 mmol/L); in the control group it decreased to 148 mg/dL (8.2 mmol/L). By 24 hours after randomization, the mean glucose level was 155 mg/dL (8.6 mmol/L) in the GIK infusion group and 135 mg/dL (7.5 mmol/L) in the control group. When baseline glucose levels in the control group were divided into tertiles, higher baseline glucose levels were associated with higher mortality at 30 days (6.6% in the lowest tertile, 8.5%

in the middle tertile, and 14.0% in the highest tertile).

Mean serum potassium concentration was 4.0 mEq/L in both groups at baseline. At 6 and 24 hours after randomization, potassium concentration was higher in the GIK infusion group (4.2 mEq/L and 4.4 mEq/L, respectively) compared with the control group (4.1 mEq/L and 4.0 mEq/L, respectively). Serum sodium levels were similar in the 2 groups.

In the GIK infusion group, a mean of 2941 mL of fluid was administered and the urine output was 1923 mL, for a net fluid gain of 1018 mL. In the control group, a mean of 1843 mL of fluid was administered and the urine output was 1397 mL, for a net fluid gain of 446 mL. Therefore, the net difference in fluid gain between the GIK infusion and control groups was 572 mL.

COMMENT

The CREATE-ECLA trial demonstrated that high-dose GIK solution given for 24 hours in patients presenting with acute STEMI has a neutral effect on mortality, cardiac arrest, and cardiogenic shock. The goal of our study was to reliably assess the effects of high-dose GIK in preventing mortality and major cardiovascular events in patients with STEMI. Given that there were more than 1900 deaths in the study, it was well powered to detect even a moderate effect on mortality. The lack of benefit on the secondary outcomes and the narrow 95% CIs excluded even a 5% relative risk benefit of the infusion. The very high adherence to the protocol and the excellent 30-day follow-up (99.85%) provide confidence in the validity of our findings and suggest that it is very un-

likely that the current regimen of high-dose GIK is of any material benefit in reducing mortality in patients with STEMI.

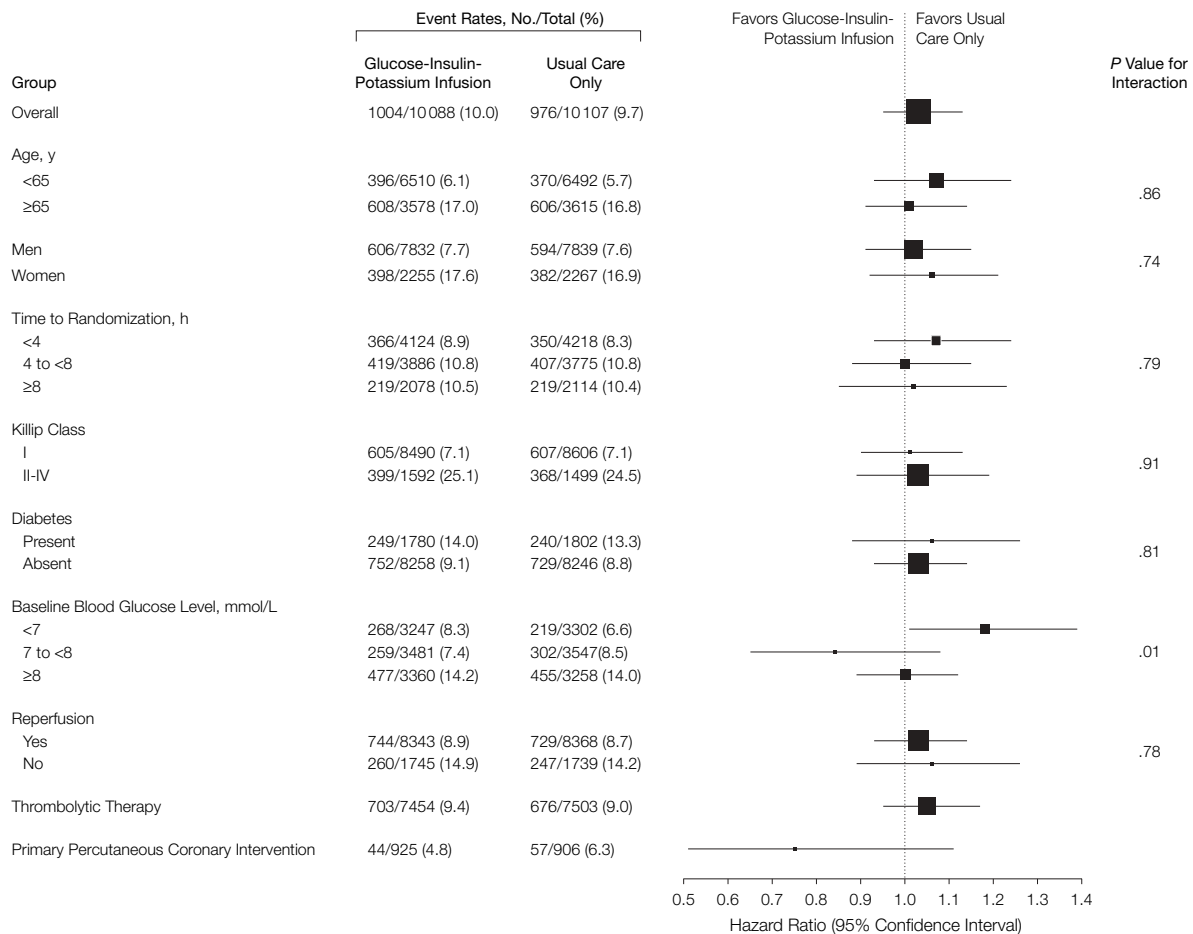
The lack of benefit with high-dose GIK in this trial involving more than 20000 patients differs from the meta-analyses of the much smaller trials of GIK in AMI.^{9,12} The phenomenon in which favorable results in small trials (or phase 2 studies) or their meta-analyses are not confirmed when a definitive trial is performed has been observed before.¹³⁻¹⁸ The apparent discrepancy between meta-analysis of small trials and a definitive large trial may relate to publication bias involving smaller trials, for which neutral studies are less likely to be published compared with similar studies with fa-

vorable results. Furthermore, the integrity of any meta-analysis is dependent on the quality of the studies on which it is based. Many of the smaller trials of GIK in AMI had methodological flaws, such as postrandomization exclusion of patients, improper randomization methods, inadequate concealment of randomization allocation, and incomplete follow-up, which may have affected the internal validity of these studies.⁹

Another problem with interpretation of previous trials is that overemphasis of subgroups in studies with a small sample size is potentially misleading.¹⁹ Of the 3 most recent trials, performed within the last decade, none was associated with a significant result in the primary outcome measure based on an

analysis of all randomized patients. The ECLA pilot trial found a favorable trend with GIK therapy on mortality, but a significant benefit was observed only in the subgroup receiving reperfusion therapy.¹¹ The Polish trial was the largest previous trial of GIK in AMI and found no benefit of a low-dose GIK regimen on cardiovascular death.²⁰ The Dutch Glucose-Insulin-Potassium Study (GIPS) found no significant benefit of GIK therapy in AMI patients undergoing primary PCI²¹ but observed an apparent benefit in the subgroup presenting as Killip class I. The first DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) trial found a nonsignificant favorable trend toward early reduction in mortality in patients with diabetes given glu-

Figure 3. Death at 30 Days by Predefined Subgroups



The solid black squares indicating hazard ratios are sized proportionally to the number of patients in each group.

cose-insulin infusion during the initial hospitalization.²² Only with longer-term aggressive glucose lowering was there a significant reduction in mortality at 1 year.

The results of the CREATE-ECLA trial raise some important questions. First, we found that higher baseline glucose concentrations were associated with higher mortality, a finding observed previously.²³ Although patients with higher baseline glucose levels may differ from those with normal glucose levels, the higher glucose concentration itself has been shown in other studies to be associated independently with a poorer prognosis.^{23,24} In our study, we observed an increase in serum glucose concentration in the GIK infusion group compared with the control group at 6 and 24 hours after treatment, raising the possibility that the higher serum glucose level in the GIK infusion group may have blunted the potential benefits of insulin. It may be worthy of further study to assess whether lowering serum glucose concentration with a modified regimen is associated with improved outcomes, especially in those with elevated glucose at baseline, as in the first DIGAMI study.

Second, would greater use of GIK in conjunction with reperfusion regimens, such as primary PCI or fibrin-specific thrombolytic agents that achieve higher early patency of the infarction-related artery, be associated with greater benefit with GIK? We found no evidence of heterogeneity in the lack of benefit of GIK infusion in the group of patients receiving thrombolytic therapy, nor in the more than 1800 patients receiving primary PCI. Similarly, there was a consistent lack of benefit of GIK in patients presenting very early (<1, 1-2, or >2-4 hours) after symptom onset. In addition, mortality was not lower in patients in whom GIK infusion was started before initiation of reperfusion therapy compared with those in whom it was started after initiation of reperfusion therapy. Thus, it seems unlikely from our data that initiation of GIK infusion very early after symptom onset, prior rather than

shortly after initiation of reperfusion therapy, or in conjunction with strategies that provide greater infarction-related artery patency would provide any material benefit.

Third, was the higher serum potassium concentration in the GIK infusion group harmful? There was no excess of bradycardia- or tachycardia-related deaths in the GIK infusion group. In fact, in the post hoc analysis of patients with hyperkalemia (>5.5 mEq/L), mortality was lower in the GIK infusion group compared with the control group. Prior studies²⁵⁻²⁷ have documented a clear relationship between ventricular arrhythmias and potassium concentrations less than 5.0 mEq/L in the setting of AMI, making it unlikely that the higher potassium concentration observed in the GIK infusion group was harmful.

The reduction in recurrent ischemia with GIK infusion was unexpected, especially since the apparent anti-ischemic benefit, although detectable at 24 hours, emerged largely after 24 hours, when the GIK infusion was stopped. It is possible that this outcome was subject to investigator reporting bias, especially since the trial was open label and this outcome was somewhat open to investigator interpretation. An alternative mechanistic explanation may have been that the GIK had an anti-ischemic effect by reducing free fatty acid uptake by the myocardium while providing glucose and insulin to promote glycolysis, thereby improving the efficiency of energy production and theoretically reducing ischemia in the process.^{3,4}

Overall, the GIK solution was well tolerated. Initially, there were concerns that the higher fluid volume associated with GIK would cause heart failure. However, despite a differential in net volume between the groups of 572 mL, there was no excess in heart failure in the GIK infusion group, regardless of baseline Killip class. It is possible that the higher concentrations of glucose in the GIK solution had an osmotic diuretic effect, thus facilitating a greater diuresis. The incidence of severe phlebitis was more frequent in the GIK in-

fusion group compared with the control group, a problem that was overcome in the trial by using larger veins (such as the antecubital vein) for infusion.

Our study was conducted mainly in low- and middle-income regions; therefore, our experiences have implications for trial design and conduct in these settings. First, the use of therapies of proven value (including reperfusion therapies, aspirin, β -blockers, angiotensin-converting enzyme inhibitors, and statins) was high, suggesting that these regions are fully capable of treating STEMI patients equally well as in higher-income regions. Second, the data quality and follow-up were excellent, allaying concerns that clinical trials conducted in these settings are less reliable. Third, CREATE-ECLA is an example of a trial that was conducted without the financial backing of any pharmaceutical company. Therefore, it serves as an example that investigators are willing to invest the time into reliably answering generic questions of high scientific merit, independent of industry, as long as protocols are kept very simple. Mechanisms to fund and facilitate such low-cost trials will allow evaluation of other simple and inexpensive therapies. Fourth, trials of affordable therapies that have the potential to make a large impact on the management of common diseases need to be performed worldwide. This need is particularly great in lower- and middle-income regions of the world, where the burden of cardiovascular diseases is highest.

In conclusion, the CREATE-ECLA randomized trial has reliably established that high-dose GIK infusion in patients with STEMI has no impact on mortality, cardiac arrest, or cardiogenic shock and is unlikely to be of any material value in patients with STEMI.

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It is the function of art to renew our perception. What we are familiar with we cease to see. The writer shakes up the familiar scene, and, as if by magic, we see a new meaning in it.

—Anais Nin (1903-1977)