Challenges in the conduct of large simple trials of important generic questions in resource-poor settings: The CREATE and ECLA trial program evaluating GIK (glucose, insulin and potassium) and low-molecular-weight heparin in acute myocardial infarction

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Background Approximately 15.5 million deaths from cardiovascular diseases occur every year. About half are due to acute myocardial infarction (AMI), and 80% occur in low- and middle-income countries. Therefore, low-cost therapies would be invaluable. Although glucose-insulin-potassium (GIK) infusion and low-molecular-weight heparin (LMWH) appear to be promising in AMI, the available trials are inconclusive and these treatments require rigorous evaluation.

Methods The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clínicos Latino America (CREATE-ECLA) study is a randomized controlled trial in ST-elevation AMI patients evaluating a 24-hour infusion of Glucose-Insulin-Potassium (GIK) intravenous vs usual care (control) on 30-day mortality in 20 000 patients from 21 countries. Patients from India and China (n = 15 000) are also randomized using a factorial design to receive low-molecular-weight heparin (Reviparin) or placebo injection twice daily for 7 days to assess the impact on the composite outcomes of death, reinfarction or stroke (first co-primary outcome) or the composite + refractory ischemia (second co-primary outcome).

Results Twenty thousand two hundred and one (20,201) GIK/control patients and 15,570 Reviparin/placebo patients have been included, with results expected in November 2004.

Conclusions The CREATE-ECLA trial will provide definitive answers to the role of 2 practical, promising and low-cost therapies, LMWH and GIK, in AMI patients. If effective, these therapies could be used in small medical centers in low- and middle- income countries. The experiences in this trial indicate that large trials of important questions can be successfully conducted in resource-poor settings, by academic groups without industry involvement. (Am Heart J 2004;148: 1068–78.)

See related Editorial on page 924.

Approximately 15.5 million deaths from cardiovascular diseases (CVD) occur every year.[1] Of these, about half are due to acute myocardial infarction (AMI), and over 80% of these occur in low- and middle-income countries (LIC and MIC), especially in the Indian subcontinent and China. Aspirin, thrombolytic therapy,

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Table I. Trials of subcutaneous or intravenous unfractionated heparin in patients with acute myocardial infarction treated with thrombolytic therapy

Trial	Treatment	N	Any death, n (%)	Reinfarction, n (%)	Any stroke, n (%)
SC heparin versus control					
ISIS-3[7]	SC Heparin + ASA	20656	2132 (10.3)	378 (1.9)	261 (1.3)
	ASA alone	20643	2189 (10.6)	414 (2.0)	240 (1.2)
GISSI-2[8]	SC Heparin + ASA	10361	968 (9.3)	218 (2.1)	115 (1.1)
	ASA alone	10407	983 (9.4)	239 (2.3)	119 (1.1)
IV heparin versus SC heparin					
GUSTO-1[6]	SK + IV Heparin	10410	763 (7.4)	438 (4.0)	144 (1.4)
	SK + SC Heparin	9841	712 (7.2)	343 (3.4)	117 (1.2)

SC, Subcutaneous, *IV,* intravenous; *ASA,* aspirin.

Table II A. Trials of low molecular weight heparin versus placebo in patients with acute myocardial infarction

Trial	Treatment	N	Setting	Duration	Death	Re-MI	Major Bleeds	Hemorrhagic Stroke
FRAMI 1997[9]	Dalteparin	338	Started 8 hrs after TT	Hospital period	23	6	11	3
	Placebo	338			23	8	1	0
Glick 1996[10]	Clexane	43	Started 5 days after TT	25 days	0	2	0	0
	Placebo	60			1	13	0	0
BIOMACS II 1999[11]	Dalteparin	54	Adjunct to SK	1 day	4	8	2	0
	Placebo	47			6	2	0	0
AMI-SK[12]	Enoxaparin	253	Adjunct to SK	3–8 days	17	6	12	0
	Placebo	243		3–8 days	17	18	6	1
Total	LMWH vs.	688	–	–	44 (6.4%)	22 (3.2%)	25 (3.6%)	3 (0.44%)
	Placebo	688	–	–	47 (6.8%)	41 (6.0%)	7 (1.0%)	1 (0.15%)
	OR (95% CI)*	–	–	–	0.75 (0.36–1.55)	0.54 (0.33–0.91)	3.00 (1.50–6.00)	2.01 (0.40–9.99)

Re-MI, Reinfarction; *TT,* thrombolytic therapy; *SK,* streptokinase.
*The odds ratio (OR) and 95% confidence intervals (CI) are calculated using the Yusuf-Peto modification of the Mantel-Haenszel method.[35]

β-blockers and angiotensin converting enzyme (ACE)-inhibitors improve prognosis in AMI,[2] and have been adopted widely. Recent trials suggest that primary percutaneous coronary angioplasty (PCI) offers some benefit over thrombolytic therapy,[3] but rapid access to primary PCI is limited in most parts of the world. Combinations of newer anti-platelet regimens[4] or direct thrombin inhibitors[5] have not yielded clear incremental benefit, but cause increased bleeding. Although heparin is commonly used after AMI, especially in patients receiving a fibrin-specific thrombolytic agent, and some trials of low-molecular-weight heparin (LMWH) appear promising, there is no convincing evidence that these agents reduce mortality in patients receiving thrombolytic therapy and aspirin (Tables I, II, *A* and II, *B*).[6–8,9–12,13–18] Although LMWH reduces reinfarction, there appears to be no impact on mortality. Furthermore, there are significant increases in major bleeds and a trend towards more hemorrhagic strokes with both agents (Tables II, *A* and II, *B*). Therefore, the net benefit-risk ratio is not clear. Further, some of the larger trials were not blinded, so one cannot exclude the potential for biases in the ascertainment of outcomes that involve judgement (eg, early reinfarction). The uncertainty about the net benefits and risks of LMWH is reflected in no clear recommendation for the use of thrombin inhibitors in AMI, especially in those receiving a thrombolytic agent that is not fibrin-specific. Although UFH is widely used after a fibrin-specific thrombolytic agent, this is based on improved coronary artery patency in 2 small trials, which did not have the power to reliably assess the impact on clinical outcomes such as death, reinfarction, bleeding, or strokes. Therefore, a large definitive trial of LMWH vs placebo, is urgently needed.

Metabolic modulation in AMI with glucose-insulin-potassium (GIK) infusions was proposed in the 1960s. GIK suppresses myocardial uptake of free fatty acids, thereby reducing myocardial oxygen requirements and improving ventricular contractility. It also increases intramyocellular potassium. These effects may reduce life-threatening arrhythmias, and improve ventricular

Table II B. Trials of low molecular weight heparin versus unfractionated heparin in acute myocardial infarction

Trial	Treatment	N	Setting	Duration	Death	Re-MI	Major bleeds	Hemorrhagic stroke
Baird 1998[13]	Enoxaparin	149	Adjunct to TT	4 days	9	22	NR	NR
	UFH	151			16	30		
HART II 2000[14]	Enoxaparin	200	Adjunct to tPA	3 days	9	NR	7	2
	UFH	200			10	NR	6	2
TETAMI[15]	Enoxaparin	604	AMI patients ineligible	2–8 days	42	15	9	4
	UFH	620	for reperfusion		41	18	8	4
ENTIRE TIMI 23[16]	Enoxaparin	324	Adjunct to TNK and Abx	Max. 8 days	10	6	17	4
	UFH	159		Min. 36 hours	5	13	6	1
ASSENT 3[17]	Enoxaparin	2040	Adjunct to TNK	Max. 7 days	109	54	62	18
	UFH	2038		48 hours	122	86	44	19
ASSENT 3 PLUS[18]	Enoxaparin	818	Prehospital adjunct to	Max 7 days	61	29	33	18
	UFH	821	TNK	48 hours	49	48	23	8
TOTAL	LMWH vs	4135	–	–	240/3971 (5.8%)	126/3935 (3.2%)	128/3986 (3.2%)	46/3986 (1.2%)
	UFH	3989	–	–	243/3989 (6.1%)	195/3789 (5.1%)	87/3838 (2.3%)	34/3838 (0.89%)
	OR (95% CI)*	–	–	–	0.97 (0.81–1.17)	0.61 (0.48–0.76)	1.38 (1.05–1.81)	1.30 (0.84–2.03)

Re-MI, Reinfarction; *NR,* not recorded; *TT,* thrombolytic therapy; *tPA,* tissue plasminogen Activator; *Abx,* abciximab; *TNK,* tenecteplase.
*The odds ratio (OR) and 95% confidence intervals (CI) are calculated using the Yusuf-Peto modification of the Mantel-Haenszel method.[35]

function, which could reduce mortality. A meta-analysis of 15 small trials[19–34] involving almost 5 000 patients indicates an 18% relative-risk reduction in mortality ($P = .03$), but with wide CIs (Table III and Figure 1)[35] However, trials which evaluated high doses of glucose and insulin reported a 30% relative-risk reduction (RRR) in mortality ($P = .03$) compared to a non-significant 11% RRR with low-dose GIK. Most of these trials antedate thrombolytic agents or aspirin, and some had incomplete follow-up or lack of information on the integrity of randomization. Although encouraging, a large definitive trial of GIK in the context of modern management of AMI is required. Despite the low costs of GIK and potential global applicability, a large trial of this question is yet to be done, perhaps because of a lack of commercial interest, and complex rules which hamper the conduct of large trials of academically-driven questions with little external funding.

Over the last 6 years, a group of us from several countries decided to perform 2 similar trials, the CREATE trial and the ECLA trial (Estudios Clínicos Latin America Study Group) aimed at reliably evaluating the role of high-dose GIK in 20 000 patients. In addition, in India and China (CREATE), we simultaneously evaluated a LMWH, Reviparin, in about 15 000 subjects. Although the 2 trials were designed and initiated separately, given the substantial similarity of the GIK components, an early decision was made to merge and standardize the 2 trials to more reliably evaluate GIK. Below, we describe the design of this study, the baseline characteristics, and discuss the challenges faced in establishing this trial.

The CREATE trial

The CREATE trial was initiated in 2000 by investigators from Canada, China, and India without external funding. It utilized "opportunistic" meetings and internal funds from the Population Health Research Institute (PHRI) at McMaster University and Hamilton Health Sciences. The study design was simple, data collection parsimonious and focused on major clinical outcomes. We emphasized data quality and adherence to the study regimen. This was facilitated by training investigators, data entry through the internet, central data review, central event adjudication of key outcomes, and judicious on-site monitoring.

Objectives of the trial

- For GIK, the primary outcome was a reduction in 30-day mortality compared to usual care.
- For Reviparin compared to placebo there were 2 co-primary outcomes: The first co-primary outcome was the composite of death, MI, or stroke at 7 days; the second co-primary outcome included the above + severe ischemia with ECG changes at 7 days.

Design and drug administration

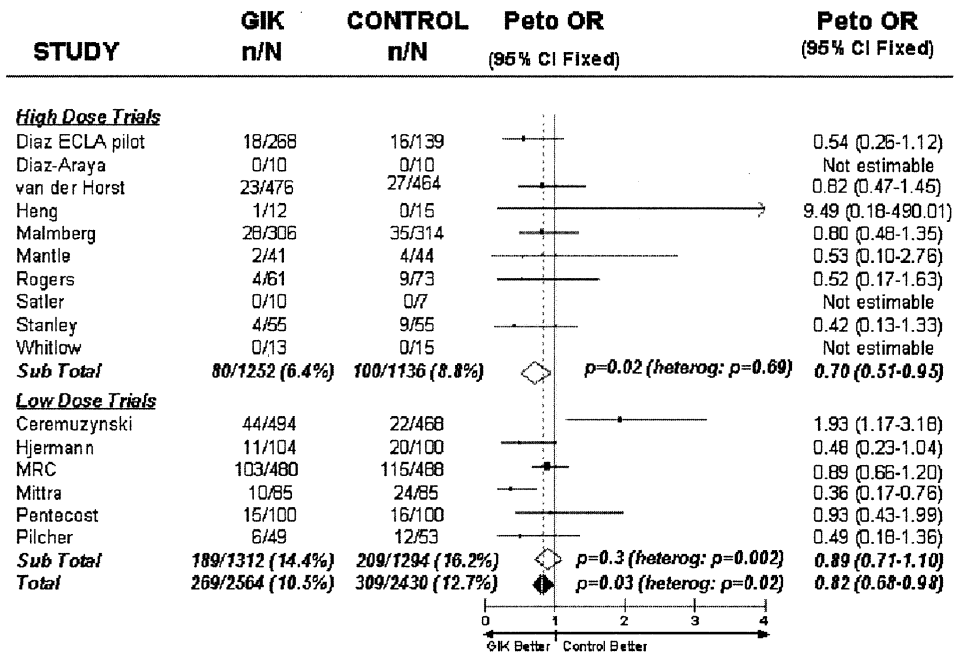
The CREATE trial utilizes a partial 2 × 2 factorial design comparing Reviparin (a low-molecular-weight heparin) to placebo given for 7 days or until discharge

Table III. Design of the Randomized trials of GIK vs. control in acute myocardial infarction, and GIK regimen used

STUDY	Year	2N	Duration of infusion	GIK regimen
Mittra[19]	1965	170	14 days	Low dose: Oral or I.V.: Oral: 240 g oral glucose O.D. + 10 U SC soluble insulin B.I.D. +52–78 mEq effervescent potassium O.D., or I.V.: 21/170 patients received 10% dextrose 500 cc + 10 U soluble insulin + 20 mEq KCl infused at 40–60 drops/minutes (1.5–2 L/day) for 3–4 days, then oral dose upto 14 days, versus usual care control
Pilcher[20]	1967	102	14 days	Low dose: Oral: using Mittra regimen above, versus oral placebo tablets
Pentecost[21]	1968	200	48 h	Low dose: I.V. 10% dextrose 1500 cc + 30 U soluble insulin + 30 mEq potassium for first 24 hours; 10% dextrose 1000 cc + 30 U soluble insulin + 20 mEq potassium for second 24 hours, versus usual care control
M.R.C.[22]	1968	968	14 days	Low dose: Oral or I.V.: Oral: 160 g glucose in water 1500 mL per day + 20 U SC soluble insulin per day + 52 mEq potassium per day, or I.V.: 40 mL of 50% glucose, then 10% glucose in water 1500 mL per 24 hours + 30 U soluble insulin per 24 hours + 45 mEq KCl per day, versus oral placebo (starch and lactose) control
Hjermann[23]	1971	204	10 days	Low dose: Oral: 200 g glucose per day + 16 U long acting insulin per day + 55 mEq potassium per day, versus placebo juice containing sodium cyclamate and placebo SC insulin control
Heng[24]	1977	27	6–12 h	High dose: I.V.: 50% glucose (5.5 mmol/kg) infused for 10 minutes at 2.0 mL/kg + 0.4 U/kg soluble insulin, then 50% glucose (4.2 mmol/kg/hr) + 0.3 U/kg soluble insulin + 0.15 mmol/kg KCl infused at 1.5 mL/kg/hr; or 50% glucose (5.55 mmol/kg) infused at 2.0 mL/kg for 10 minutes (4.2 mmol/kg/hr), then 50% glucose infused at 1.5 mL/kg/hr (4.2 mmol/kg/hr), versus control of normal saline solution infused for 10 minutes at 2 mL/kg, then at 1.5 mL/kg/hr (4.2 mmol/kg/hr)
Stanley[25]	1978	110	48 h	High dose: I.V.: 300 g glucose + 50 U regular insulin + 80 mEq KCl/L infused at 1.5 mL/kg/hr, versus control solution of half-normal saline
Rogers[26]	1979	134	48 h	High dose: I.V.: 300 g glucose + 50 U insulin + 80 mEq potassium/L infused at 1.5 mL/kg/hr, versus control solution of half-normal saline at a rate to keep catheter patent
Mantle[27]	1981	85	48 h	High dose: I.V.: 300 g glucose + 50 U insulin + 80 mEq KCl/L infused at 1.5 mL/kg/hr for 48 hrs, then 0.45% NaCl + 5000 U/L heparin at "keep open" rate of 20 mL/hr through CV and PA lumen for one day, versus control of same heparinized 0.45% NaCl solution through both lumens of catheter at "keep open" rate for whole study period (3 days)
Whitlow[28]	1982	28	48 h	High dose: I.V.: 300 g glucose + 50 U regular insulin + 80 mEqKCL/L infused at 1.5 mL/kg/hr for 48 hrs, then 0.45% NaCl for 2 days at 20 mL/hr, versus control of 0.45% NaCl at 20 mL/hr for 4 days
Salter[29]	1987	17	48 h	High dose: I.V.: 300 g glucose + 50 U regular insulin + 80 mEq potassium/L infused at 1.5 mL/kg/hr versus control of 5% dextrose in water at 1.5 mL/kg/hr
Malmberg[30]	1995	620	24 h	High dose: I.V.: 5% glucose 500 cc + 80 U soluble insulin (no potassium) infused at 30 mL/hr and rate adjusted to blood glucose nomogram, then s.c. soluble insulin 3 times daily and medium-long acting insulin once daily for 3 months with dosage for stable normoglycemia, versus usual care only (insulin if clinically indicated)
Diaz[31]	1998	407	24 h	Low or High dose: I.V.: Low dose: 10% glucose + 20 U insulin + 40 mmol KCL infused at 1.0 mL/kg/hr/hr High dose: 25% glucose + 50 U soluble insulin + 80 mmol KCL infused at 1.5 mL/kg/hr versus usual care control
Ceremuzynski[32]	1999	962	24 h	Low dose I.V.: 10% dextrose 1000 mL + 32 U rapid insulin + 20 U Humulin R insulin (mixed insulin for only 369/954 patients; due to hypoglycemia, remaining patients received only 20 U short-acting Humulin R in infusion) + 6.0 g potassium chlorate infused at 42 mL/hr, versus control of 0.9% NaCl 1000 mL at 42 mL/h for 24 hrs
Diaz-Araya[33]	2002	20	24 h	High dose: I.V.: 30% glucose + 50 U insulin + 40 mM KCl/L infused at 1.5 mL/kg/hr versus control of normal saline solution at 1.5 mL/kg/hr
van der Horst[34]	2003	940	8–12 h	High dose: I.V.: 20% glucose in 500 mL water + 80 mmol KCl infused at 3.0 mL/kg/hr, with infusion of 50 U short-acting insulin in 50 mL 0.9% NaCl with infusion rate adjusted to blood glucose nomogram versus control of no infusion

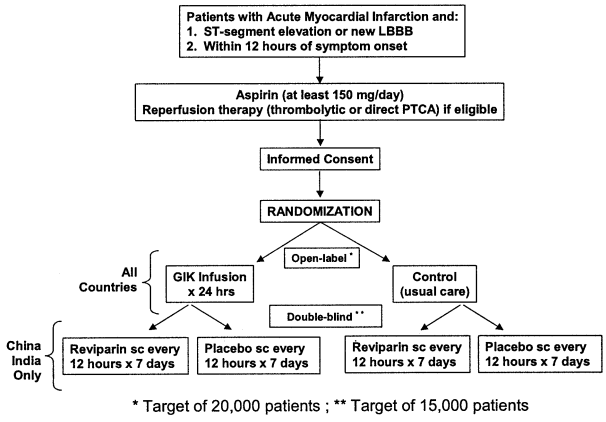
(if discharge is earlier than 7 days [double blind]), and GIK vs control (open) given for 24 hours. All patients in India and China were randomized to both parts of the trial (n = 15,570 patients), whereas those from Pakistan were only included in the GIK component (total of 20,201 patients). All patients presenting with suspected AMI and ST-segment elevation or new left bundle branch block within 12 hours of symptom onset, and who were without contraindications to heparin or GIK and who provided written consent or witnessed oral consent were randomized (Figure 2 -Study design flow chart). It was recommended that study

Figure 1



Overall results of trials of GIK vs control on all-cause in-hospital mortality.[36] The trial by Ceremuzynski measured outcomes at 35 days. Data from individual trials are combined utilizing a modified Mantel-Haenszel method.[35]

Figure 2



CREATE-ECLA partial factorial study design.

drugs be initiated within 15 minutes of thrombolytic therapy. The dose of Reviparin or placebo was weight-based. Patients < 50 kg received 3436 IU antiXa Ph Eur units* of Reviparin every 12 hours subcutaneously; those between 50–75 kg received 5153 IU antiXa Ph Eur units* every 12 hours; and those > 75 kg received 6871 IU antiXa Ph Eur units* every 12 hours. Drugs and placebo were provided by Abbott Laboratories. In patients undergoing primary PTCA, open-label unfractionated heparin could be used for up to 24 hours, with study medication being initiated thereafter, 1 hour after removal of the sheath. All other non-study thrombin inhibitors were not allowed, unless there was a clinical need, in which case blinded-study medication was discontinued.

Glucose-insulin-potassium was prepared by adding 25 IU of insulin (regular or human) and 40 mmol of KCl to a 500 mL bag of 25% glucose, and infused through a dedicated 14-gauge peripheral intravenous (IV) site at a rate of 1.5 mL/kg/h for 24 hours (regimen identical to ECLA pilot).[31] Patients randomized to the control group received usual care. Glucose, potassium and sodium levels were checked at baseline, 6 hours, and 24 hours. Adjustments to the rate of infusion of GIK were allowed based on blood glucose and potassium levels and on the Killip Class status of the patient. Fluid intake and output for the first 24 hours was recorded in all subjects.

All other aspects of patient management were at the discretion of the local treating physician. All centers

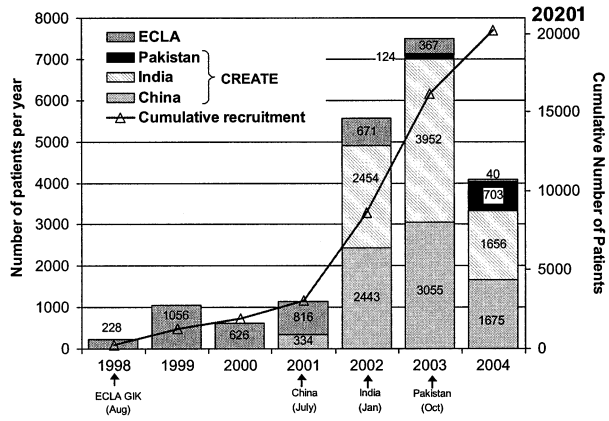
*European Pharmacopoeia; measured against Ph Eur LMWH-BRP standard, 1995.

obtained local Ethics Committee approval, and in addition, the Project Office obtained approval from the Institutional Review Board of the Hamilton Health Sciences and McMaster University, Hamilton, Canada.

The ECLA study

The ECLA group had independently completed a pilot trial in 1996, with promising results with high-dose GIK.[31] Utilizing the high-dose GIK regimen, the main ECLA trial was initiated in mid-1998 in Latin America, with later expansion to Kuwait, Europe, the USA, and Australasia; this component recruited 3804 patients. Given the identical nature of the GIK regimen in CREATE and ECLA, and primary outcomes (30-day mortality) and similarity in data-collection between the 2 trials, the 2 trials were merged in November 2002 for evaluation of GIK. This ensured that 20 000 patients would be randomized by mid-2004. Harmonization of key aspects (definitions, data collection, etc.) of the 2 studies occurred.

Figure 3



CREATE-ECLA Number of patients recruited per year between August 20, 1998 – July 9, 2004.

Study organization

The study involves 274 centers in China, 67 in India, 4 in Pakistan, 46 in Argentina, 22 in Brazil, 1 in Kuwait, 16 in Venezuela, 9 in North America, and 14 in Europe. Data from centers in China were sent by mail to the National Center (NC) in Beijing, from Indian Centers to the NC in Bangalore, from Pakistani centers to the NC in Karachi, and from all other centers to the ECLA office in Rosario, Argentina. These regional coordinating centers entered the data into a web-based Oracle database (other than in ECLA) that was connected online to the Population Health Research Institute (PHRI) in Hamilton, Canada. Extensive consistency and edit checks, and central-event adjudication ensured high data quality. Data from the ECLA trial were transferred to the PHRI at regular intervals, where additional data checks were conducted prior to statistical analyses and reports.

An independent Data and Safety Monitoring Board (DSMB) was formed by joining the Boards that had been set up for each of the 2 trials. One member of the ECLA DSMB (S. Yusuf) stepped down from the joint Board as soon as the studies were combined and remained blinded to the subsequent data. At that time, $<$ 1000 subjects had been reviewed by the ECLA DSMB. The newly constituted Board periodically reviewed the accumulating data on efficacy and safety. Three formal interim analyses occurred when 25%, 50% and 75% of the data were available. For the first 2 looks, the boundary for benefit was 4 SDs (χ^2 of 16; $P < .0001$) for 30-day mortality (GIK) or the first co-primary outcome for Reviparin. For the third look, the boundary was 3.5 (χ^2 of 12.25; $P < .00047$) deviations. The boundary had to remain crossed on 2 successive examinations of the data about 3 months apart, to ensure robustness and consistency of results.

Power

Anticipating a 12% rate at 7 days in the placebo group for the first co-primary outcome of death, MI, or stroke with 15 000 patients, there would be 93% power to detect a 15% relative-risk reduction with Reviparin. For the GIK comparison, with a 10% death rate at 30 days in the control group, with 20 000 subjects, there would be 95% power to detect a RRR of 15%, and 80% power to detect a RRR of 11.7%.

Patient Recruitment

Recruitment commenced in August 1998 in South America, July 2001 in China, January 2002 in India, and October 2003 in Pakistan (Figure 3). By July 9, 2004, the overall trial had recruited 20,201 patients, with 15,507 into the component evaluating Reviparin.

Baseline characteristics

Table IV summarizes key baseline characteristics. About two thirds of the patients were randomized in $<$ 6 hours of symptom onset. 84.6% of the patients were in Killip Class I, with 15.4% having some evidence of heart failure. The baseline glucose level is 9.0 mmol/L and potassium is 4.0 mEq/L. Thrombolytic therapy was used in 74.1%, and primary PCI in 9.1%. Rates of reperfusion therapy were higher in India (94.0%) compared to China (62.1%). Of the patients in India and China, pre-randomization heparin was given in 9.4% of patients, and non-study heparin after randomization was used in only 9.9% of patients. Reviparin or matching placebo was given in 98.7% of individ-

Table IV. Key characteristics of CREATE-ECLA trial patients

	CREATE				
Baseline characteristic	**India**	**China**	**Pakistan**	**ECLA**	**Overall**
Number of patients	8060	7510	827	3804	20,201
Number of case report forms	8060	7510	827	3798	20,195
Age (mean & SD)	55.5 (11.8)	62.7 (11.9)	55.4 (11.3)	57.9 (12.4)	58.6 (12.4)
% Males	82.2	70.7	80.9	80.9	77.6
Onset of symptoms to randomization (%)					
<6 Hours	65.1	57.6	53.1	78.1	64.3
6–12 Hours	34.9	42.1	46.9	20.9	35.4
Median time (hours)	4.5	5.2	5.7	3.7	4.7
Previous MI (%)	7.0	7.9	7.4	11.3	8.1
Diabetes (%)	22.8	11.2	23.9	18.6	17.7
Hypertension (%)	28.0	40.6	48.6	47.0	37.1
Weight (kg)	64.0 (10.6)	66.5 (11.8)	68.3 (9.8)	77.4 (14.4)	67.7 (12.8)
Blood pressure (mmHg)	129.21/ 84.1	126.0/ 78.9	127.1/ 80.5	134.6/ 81.5	129.0 81.5
Heart rate (beats/min)	84.2	77.5	80.6	78.0	79.0
Killip class >1 (%)	14.4	18.1	10.9	12.2	15.4
Mean glucose (mmol/L)	9.1 (4.9)	8.6 (4.3)	9.2 (5.3)	9.7 (4.7)	9.0 (4.7)
Medications in hospital (%)					
Thrombolytic therapy	91.9	52.5	89.7	75.3	74.1
Direct PCI	2.5	10.0	3.7	22.4	9.1
Aspirin	97.9	95.8	99.6	98.4	97.3
Ticlopidine/clopidogrel	80.2*	27.8	78.6*	16.0	48.6
IV Nitrates	59.4	91.8	60.6	70.2	73.5
β-Blocker	70.0	61.5	91.7	82.1	70.0
ACE inhibitor	73.6	71.7	85.5	68.2	72.4
Lipid lowering	62.3	71.3	88.0	NR	NR
Calcium antagonist	6.1	12.8	3.4	7.8	8.8

NR, Not recorded.
*The high rates of use of a thienopyride is due to the availability of a combination tablet of aspirin + clopidogrel.

uals and GIK was given in 98.0% of patients randomized to GIK. Aspirin was used in 97.3%, clopidogrel in 48.6%, β-blockers in 70.0%, ACE inhibitors in 72.4%, lipid-lowering medications in 67.7% (other than in ECLA, where this information was not collected), and calcium channel blockers in 8.8%. Thus, a high proportion of patients received proven pharmacologic therapies and there was excellent adherence to the allocated study treatments.

Challenges faced during the conduct of the trial

This study has been a formidable undertaking and has been successful in recruiting the overall target of 20 000 patients. The lack of external funding required that investigator meetings were generally attached to other meetings, although annual regional meetings were held in India and China. The centers in ECLA were not provided with any compensation and the centers in CREATE (India, China, and Pakistan) received modest compensation per patient to cover their visible costs. Despite this, over the last 2 years of the study, recruitment rates averaged 7000 patients per year. The National Coordinating Centers obtained national regulatory approvals and licences for drug imports. These processes were extremely bureaucratic and slow (9–18 months in each country), and were chiefly designed to be done by pharmaceutical companies or independent contract research organizations (CRO) at considerable expense. A quote from a CRO in India for obtaining approval and monitoring the trial exceeded the entire cost of running the study in India (note that, in most countries, there is no streamlined and efficient mechanism to obtain regulatory approvals for studies conducted independent of industry). Several of the participating centers did not have institutional review boards (IRBs) or ethics committees, so national and independent IRBs had to be used. There were considerable initial delays in receiving the packaged drugs (Reviparin/placebo) from the company, which was in the midst of a takeover, and the study was not considered to be of sufficiently high priority within the new organization. For most centers, the

CREATE study was the first trial in which they had participated, so considerable training (at small study meetings and by phone) was needed. Despite their enthusiasm and the relative simplicity of the study, some centers initially had problems with accurate completion of forms, complying with certain aspects of the study protocol, and maintaining careful documents. Therefore, we instituted a system of on-site monitoring and training which trained staff at sites in CREATE, and provided support. This improved protocol adherence and data quality considerably. For randomization in India, the study initially used sealed envelopes (due to lack of low-cost, reliable and accessible telephone lines 24 hours-a-day at all hospitals). Despite multiple safeguards, allocation errors occurred in a few patients. Therefore, despite higher costs, randomization was switched to a 24-hour central telephone system in Bangalore, India, which substantially reduced the allocation error rate. In China, 24-hour central randomization was used throughout, and so few errors occurred.

Given that the centers were compensated very modestly, the study was repeatedly threatened by the withdrawal of centers who wished to participate in "competing" trials, sponsored by pharmaceutical companies with higher rates of compensation. This substantially slowed recruitment into ECLA so that, instead of the original target of 10 000 patients over 3 years, only 4000 patients were randomized over 6 years. This was less of a problem in India and China, where only a few centers stopped randomizing by the end of 2003 to participate in other trials. Nevertheless, most centers had made important contributions to the trial. During 2003, the epidemic of Severe Acute Respiratory Syndrome (SARS) in China adversely affected recruitment and several participating hospitals were closed down, or stopped admitting AMI patients.

What lessons have we learned from the CREATE-ECLA experience and collaboration? First, if important generic questions are incorporated into a very simple protocol, sufficient numbers of physicians are still willing and able to collaborate at little or no reimbursement. Second, the "merger" of CREATE and ECLA was possible because of long-standing previous collaboration between the investigators from the 2 groups, and a mutual commitment to sharing credit. This led to ensuring a statistically robust, reliable result regarding GIK, rather than the potential for an inconclusive result from the ECLA study alone. Third, the bureaucratic hurdles for conducting this trial in India and China were formidable and took between 9–18 months to overcome, chiefly through the tenacity, determination and dedication of the National Coordinators in Beijing and Bangalore. Fourth, even in a very simple trial, some streamlined and sensible ("helpful and supportive" as opposed to "policing") monitoring could help in improving study quality, especially when centers had not previously participated in trials. Fifth, much of the increasing regulatory bureaucracy imposed by guidelines such as the "Good Clinical Practice" guidelines may not enhance the quality of the study or improve patient safety more than careful attention to a few key aspects of study design, conduct (such as proper randomization and complete and unbiased outcome ascertainment), and periodic review of the data by an independent DSMB. In fact, there is a danger that these well-intentioned guidelines could prevent the conduct of important low-cost academic trials of generic (non-pharmaceutical) questions by imposing burdensome and expensive processes which may be of little scientific, medical, or ethical value. Sixth, peer review and governmental organizations should develop mechanisms to support international trials and epidemiologic studies. Current funding mechanisms do not generally support such studies in multiple countries, especially if they are low- or middle-income countries.

In conclusion, the CREATE-ECLA trial will provide definitive answers regarding the value of 2 practical and promising therapies (LMWH and GIK) in AMI. These therapies, if proven to be effective, could be used even in small medical centers in low- and middle-income countries. The practical experiences in conducting this trial indicate how large trials of important questions can be successfully conducted in resource-poor settings, by academic groups without industry involvement. However, such studies are uncommon and, therefore, a large number of important questions remain unaddressed. This emphasizes the need to develop funding structures and regulations that will facilitate global low-cost trials of important public health questions.

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Appendix

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