The “holy grail” in the field of cardioprotection is to develop pharmacological agents that can be administered as adjunctive treatment to reperfusion that will reduce myocardial infarct size and improve clinical outcomes. Numerous pharmacological agents and strategies have been studied over the years with variable results in both animal models and humans. Of drugs that have been studied, only a few have shown benefit in clinical trials. Aside from agents or devices than can restore and maintain reperfusion (thrombolytics, balloons, stents, aspirin, clopidogrel, IIb/IIIa inhibitors, low–molecular-weight heparin, and others), the only commonly used adjunctive agents shown to have cardioprotective effects when administered early after coronary occlusion and in addition to reperfusion are β-blockers. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are also used, but these can be given after infarction (as late as 1 week) and must be continued long-term to reduce left ventricular remodeling. Recently, adenosine and induced hypothermia have also shown promise as early adjunctive agents. For example, when intravenous adenosine was coupled with early reperfusion therapy, myocardial infarct size by single-photon emission computed tomography analysis and the composite end point of death and heart failure were reduced at 6 months. Hypothermia, induced by use of a heat-exchange cooling catheter, benefited a subgroup of patients who were successfully cooled to \( T \approx 35^\circ C \) before reperfusion. Superoxide dismutase, magnesium, inhibitors of neutrophil adhesion, complement inhibitors, fluosol, RheothRx, the K\(_{\text{ATP}}\) channel/nitrate nicorandil, and others failed to show a benefit as adjuncts to reperfusion. Clinical research evaluating many of these agents in acute myocardial infarction has halted.

One of the most controversial of these adjunctive agents still under investigation is GIK (glucose-insulin-potassium), a “cocktail” delivered at the time of infarction that has demonstrated variable results in both the prereperfusion and postreperfusion eras. GIK was one of the first agents to be studied for protection of the ischemic myocardium. Numerous reasons exist for the continued interest in GIK despite its variable track record in clinical trials: (1) Substantial laboratory evidence supports a cardioprotective effect in various models of ischemia/reperfusion; (2) some clinical trials have demonstrated positive results in specific patient subgroups; (3) the treatment is relatively “nontoxic” and free of major clinical side effects; and (4) recent evidence suggests that insulin itself, a component of GIK, administered as a strategy to restore normoglycemia, may be cardioprotective because it has antiinflammatory, antiapoptotic, and provasodilatory properties. In addition, the recognition that hyperglycemia is an important independent factor associated with a poor outcome in the setting of acute myocardial infarction and other critical illnesses has renewed interest in the use of insulin. A byproduct of GIK as a treatment strategy with a “metabolic” profile is the use of insulin with and without glucose or potassium when administered to restore normoglycemia at the time of acute myocardial infarction, intensive care unit hospitalization, or coronary artery bypass grafting.

The purpose of the present report is to review major clinical trials of GIK or its components for acute myocardial infarction since the publication of a large meta-analysis in Circulation in 1997. Review of these articles published over the last 10 years will focus on major outcomes of GIK and its effect on blood glucose, where these data were provided. The literature search (from PubMed) involved identification of major outcome studies performed over the last 10 years in which GIK or its components were administered as adjunctive treatment to patients with acute coronary syndromes.

**Mechanisms of GIK**

Various mechanisms have been proposed to explain how GIK may be cardioprotective. In the early 1960s, the electrocardiographer Sodi-Pallares pioneered the use of GIK as a “polarizing” solution to stabilize membranes and restore potassium to ischemic cardiomyocytes. Benefits of GIK focused primarily on normalization of ECG abnormalities. Opie suggested 2 major mechanisms by which GIK may be protective: a decrease in free fatty acid concentrations (via a reduction in lipolysis) and promotion of glycolysis. GIK can suppress plasma levels of free fatty acids that are elevated as a consequence of the release of counterregulatory hormones and cytokines at the time of acute cardiovascular stress.
Although free fatty acids are the dominant substrate for myocardial cells under aerobic conditions, under ischemic conditions, a shift occurs toward anaerobic glycolysis, and long-chain free fatty acids can have deleterious effects. As stated by Hendrickson et al., free fatty acids can result in accumulation of toxic intermediates of free fatty acid metabolism . . . , inhibition of glucose utilization, particularly glycolysis during ischemia/and or reperfusion, and uncoupling of oxidative metabolism from electron transfer. Because enhancement of glycolysis during ischemia has been shown to reduce ischemic damage, factors that inhibit glycolysis, such as free fatty acids, would be expected to have a deleterious effect during ischemia/reperfusion. Free fatty acid metabolism in this setting also results in higher production of lactate and hydrogen ions, which can reduce cardiac contractility, cause diastolic dysfunction, and reduce the heart’s threshold for arrhythmias. Rogers et al. reported a study of 70 patients with acute myocardial infarction in whom an infusion of GIK caused a dramatic fall in free fatty acid levels. Compared with a matched control group of patients, the mortality rate was reduced 4-fold in those receiving GIK.

Although an earlier theory held that GIK worked by both increasing the availability and facilitating the entry of glucose into the cardiomyocyte, this “oversupply” of glucose (depending on the GIK formulation used) can lead to acute elevation of glucose compared with the pretreatment level. Hyperglycemia is now recognized to be associated with a host of negative cardiovascular phenomena, including abnormal vascular responsiveness, thrombus formation, increased platelet aggregation, and inflammation, as well as having direct effects on cardiac systolic and diastolic function. As will be discussed later, any benefit due to GIK could be counterbalanced or neutralized by the hyperglycemia that often accompanies GIK administration, particularly when given in high-dose formulation. In contrast, insulin is thought to have an antiinflammatory, antioxidant effect, as well as a vasodilatory effect through the release of nitric oxide and increased expression of endothelial nitric oxide synthase. Insulin also inhibits platelet aggregation and has a profibrinolytic effect. The mechanisms by which insulin may have a cardioprotective effect are complex and are shown in further detail in Figure 1. A glucose and insulin infusion causes potassium to move intracellularly, so the addition of exogenous potassium helps prevent hypokalemia and helps to electrically stabilize the myocardial cell membrane to avoid arrhythmias.

Preclinical Studies Mainly Showed a Benefit of GIK

In the early 1970s, some of the first preclinical studies suggested that GIK infusion could limit myocardial necrosis. Preclinical studies of GIK are described in the online-only Data Supplement.

The 1997 Meta-Analysis

Fath-Ordoubadi et al. published a 1997 meta-analysis of GIK treatment for acute myocardial infarction that included 9 trials with 1932 patients published during the period from 1966 through 1996. They included studies that were placebo controlled and properly randomized, and they described documentation of in-hospital mortality. On the basis of this meta-analysis, 205 (21%) of 972 patients in the placebo group died in the hospital versus 154 (16.1%) of 956 in the GIK groups (P=0.004, OR 0.72, 95% confidence interval [CI] 0.57 to 0.90). This 28% reduction in mortality led the authors to conclude that “GIK therapy may have an important role in reducing the in-hospital mortality after acute myocardial infarction.” Of course, it is important to realize that these studies were largely done in the prereperfusion era, and the in-hospital mortality rate of 21% would be considered quite high by today’s standards. Still, the important conclusion drawn from this meta-analysis was that GIK could be a viable adjunctive treatment.

Clinical Trials of GIK Published After the 1997 Meta-Analysis

Key recent trials on GIK or glucose-insulin (in which the main ingredient is a continuous infusion of insulin with enough glucose to reduce the risk of hypoglycemia) in acute coronary syndromes published around the same time as and after the 1997 meta-analysis are shown in Table 1. Some of the major trials utilizing GIK are discussed in more detail below.

Estudios Cardiologicos Latinoamerica Pilot Study

A major GIK trial reported in 1998 was the ECLA (Estudios Cardiologicos Latinoamerica) pilot study. This study included 470 patients with suspected myocardial infarction admitted within 24 hours of chest pain who were randomized in a 2:1 ratio to high- or low-dose GIK versus control. High-dose GIK was defined as 25% glucose, 50 IU of regular insulin per liter, and 80 mmol of KCl per liter at an infusion rate of 1.5 mL · kg⁻¹ · h⁻¹ over 24 hours. Low-dose GIK was 10% glucose, 20 IU of regular insulin per liter, and 40 mmol of KCl per liter at an infusion rate of 1.0 mL · kg⁻¹ · h⁻¹ over 24 hours. A total of 61.9% of
<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Syndrome</th>
<th>No. of Patients</th>
<th>Treatment Regimen</th>
<th>Outcome</th>
<th>Effect of Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECLA Pilot (1998)</td>
<td>Acute MI</td>
<td>470</td>
<td>High- or low-dose GIK vs control</td>
<td>No significant difference in major and minor in-hospital events. Less electromechanical dissociation in GIK group. In reperfusion patients, lower mortality with GIK (5.2%) vs controls (15.2%; ( P=0.008 )). Mortality benefit persisted at 1 y</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Pol-GIK (1999)</td>
<td>Acute MI</td>
<td>954</td>
<td>Low-dose GIK vs control</td>
<td>No difference in number of patients who developed cardiac event, including cardiac death. Total mortality actually higher in GIK group</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Diaz-Araya et al (2002)</td>
<td>Acute MI</td>
<td>20</td>
<td>GIK vs normal saline</td>
<td>No difference in the increase in markers of oxidative stress between groups</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Van der Horst et al, GIPS I (2003)</td>
<td>Acute MI</td>
<td>940</td>
<td>GIK vs no infusion</td>
<td>No difference in mortality between groups. GIK reduced mortality in a cohort of patients without heart failure (1.2% vs 4.2%). It increased mortality in those with heart failure. Follow-up studies showed no benefit even in the group with no heart failure</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Castro et al (2003)</td>
<td>Acute MI</td>
<td>37</td>
<td>GIK vs placebo</td>
<td>No difference in myocardial salvage index ((^{99m})Tc sestamibi scintigraphy), ejection fraction, or 1-year survival between groups</td>
<td>Not reported</td>
</tr>
<tr>
<td>REVIVAL (2004)</td>
<td>Acute MI</td>
<td>312</td>
<td>GIK vs control</td>
<td>No difference in myocardial salvage index ((^{99m})Tc sestamibi scintigraphy) or mortality between groups. Increase in salvage index among diabetics who received GIK</td>
<td>Not reported</td>
</tr>
<tr>
<td>Krijanac et al (2005)</td>
<td>Acute MI</td>
<td>120</td>
<td>GIK vs control</td>
<td>Incidence of major adverse cardiac events (cardiac death, reinfarction, ventricular fibrillation, ventricular tachycardia, severe heart failure) at 1 mo was 10% with GIK vs 32.5% in control group (( P=0.0043 )). Benefit of GIK persisted at 1 y. GIK improved LVEF at 1 y</td>
<td>Not reported</td>
</tr>
<tr>
<td>Yazici et al (2005)</td>
<td>Non-ST-elevation acute coronary syndrome</td>
<td>52</td>
<td>GIK vs control</td>
<td>Increase in troponin I significantly lower at 12 and 24 h in GIK groups vs controls</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>Van der Horst et al (2005)</td>
<td>Acute MI</td>
<td>940</td>
<td>GIK vs control</td>
<td>No difference between groups in pattern or magnitude of CK-MB release. No difference in LVEF at 2.5–2.7 d. Lower frequency of LVEF ≤30% (12%) in GIK group vs controls (18%; ( P=0.01 ))</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van der Horst et al (2005)</td>
<td>Acute MI</td>
<td>612</td>
<td>GIK vs control</td>
<td>Complete plus partial resolution of ST-segment elevation occurred in 87% of GIK patients vs 78% of controls (( P=0.004 )). No difference in 1-y mortality between GIK and controls</td>
<td>Not reported</td>
</tr>
<tr>
<td>CREATE-ECLA (2005)</td>
<td>Acute MI</td>
<td>2021</td>
<td>GIK vs usual care</td>
<td>No difference in 30-d mortality between groups. No difference in rates of cardiac arrest, cardiogenic shock, reinfarction between groups. No difference in rates of heart failure. No benefit in subgroups such as diabetics</td>
<td>GIK increased blood glucose vs control. At 6 h: 187 mg/dL in GIK vs 148 mg/dL in control group. Blood glucose levels higher at 24 h in GIK group</td>
</tr>
<tr>
<td>GIPS II (2006)</td>
<td>Acute MI without heart failure</td>
<td>889</td>
<td>GIK vs control</td>
<td>30-Day mortality did not differ between groups. No difference in myocardial infarct size based on CK levels</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bucciarelli-Ducci et al (2006)</td>
<td>Acute MI</td>
<td>73</td>
<td>High-dose GIK vs saline</td>
<td>No difference in % who achieved TIMI flow grade 3 after PCI between groups. Final blush grade of 3 in 50% of GIK patients vs only 24% of controls (( P&lt;0.05 )). Improvement in LVEF at 6 mo in GIK vs control. LV remodeling by echocardiography occurred in 3% of GIK patients vs 24% of controls</td>
<td>GIK reduced blood glucose from 158±64 mg/dL on admission to 137±54 mg/dL at 24 h</td>
</tr>
</tbody>
</table>
the patients received reperfusion therapy, primarily with thrombolysis (95%); only 5% of these underwent primary angioplasty. Blood glucose levels tended to be lower at baseline in the GIK group (~147 mg%) than in the control group (~155 mg%) and increased with GIK infusion at 6 to 24 hours (~162 mg% at 6 hours in the GIK group versus ~147 mg% in controls), but at 48 hours, with completion of the infusion, blood glucose levels were slightly lower in the GIK group (~124 mg% versus ~130 mg% in the control group). A nonsignificant trend was present toward a decrease in major and minor in-hospital events in the GIK group. Combined high- and low-dose GIK groups demonstrated a nonsignificant trend toward lower in-hospital mortality (6.7%) than in control patients (11.5%; \( P=\text{NS} \)). Electromechanical dissociation was lower in the GIK group (1.5%) than in the control group (5.8%; \( P=0.016 \)). For patients receiving reperfusion, GIK was associated with a significant decrease in mortality (5.2% vs 15.2% in the control group; relative risk 0.34, 95% CI 0.15 to 0.78, \( P=0.008 \)) and electromechanical dissociation. Nonsignificant reductions were noted in severe heart failure and ventricular fibrillation with GIK that were most pronounced in patients who received reperfusion. At 1 year, patients receiving reperfusion therapy who had been randomized to high-dose GIK experienced higher survival; however, phlebitis occurred in 45 patients (16.8%) receiving GIK. The ECLA GIK pilot study was intriguing,

Table 1. Continued

<table>
<thead>
<tr>
<th>Study (Year of Publication)</th>
<th>Syndrome</th>
<th>No. of Patients</th>
<th>Treatment Regimen</th>
<th>Outcome</th>
<th>Effect of Blood Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI48 (1995)</td>
<td>Acute MI with diabetes</td>
<td>620</td>
<td>Insulin-glucose infusion + multidose subcutaneous insulin vs conventional therapy</td>
<td>At 1 y, mortality in infusion group was 18.6% vs 26.1% in control group (( P=0.0273 ))</td>
<td>Blood glucose levels had a decrease in serum glucose from 211 to 173 mg/dL.</td>
</tr>
<tr>
<td>DIGAMI49 (1997)</td>
<td>Acute MI diabetics</td>
<td>1253</td>
<td>1. Acute insulin-glucose infusion plus long-term insulin-based glucose control. 2. Insulin-glucose infusion plus standard glucose control. 3. Routine, usual practice</td>
<td>No difference in mortality among the 3 groups. No difference in nonfatal reinfarction or strokes among 3 groups. Follow-up ( \sim 2.1 ) y</td>
<td>Blood glucose levels were 12.5–12.9 mmol/L at baseline and decreased at 24 h in all groups; slightly greater reductions were seen in groups 1 and 2 (9.1 mmol/L, which received insulin-glucose, than in group 3 (10.0 mmol/L). A target fasting blood glucose of 5–7 mmol/L for group 1 was not achieved</td>
</tr>
<tr>
<td>DIGAMI II50 (2005)</td>
<td>Acute MI diabetics</td>
<td>240</td>
<td>Insulin-dextrose infusion vs standard therapy</td>
<td>No difference in in-hospital, 3-mo, or 6-mo mortality. Decrease in heart failure with infusion therapy (12.7%) vs standard therapy (22.8%; ( P=0.04 )). Decrease in reinfarction with infusion (2.4%) vs standard therapy (6.1%; ( P=0.05 ))</td>
<td>No difference between groups</td>
</tr>
<tr>
<td>HI-551 (2006)</td>
<td>Acute MI</td>
<td>32</td>
<td>GIK vs saline</td>
<td>Absolute increase in C-reactive protein less in GIK group vs control (1.9±0.5 vs 3.3±0.8 mg/L). GIK reduced serum amyloid A levels; it increased plasminogen activator inhibitor. CK-MB peaked earlier and lower in GIK group</td>
<td>Baseline control group had a plasma glucose of 146 mg/dL that fell to 131 mg/dL over 48 h. Baseline glucose was 132 mg/dL in the GIK group and fell to 124 mg/dL at 48 h</td>
</tr>
<tr>
<td>Chaudhuri et al52 (2004)</td>
<td>Acute MI</td>
<td>2748</td>
<td>High-dose GIK vs no infusion</td>
<td>Study terminated prematurely with announcement of CREATE-ECLA results. No difference in 30-d or 6-mo outcome of death, heart failure, or composite of death or heart failure between groups</td>
<td>As part of combined analysis with CREATE-ECLA, GIK increased levels of glucose and potassium and resulted in net fluid gain, which explained higher mortality and trend toward increased heart failure in GIK group from 0 to 3 d</td>
</tr>
</tbody>
</table>

**MI** indicates myocardial infarction; LVEF, left ventricular ejection fraction; LV, left ventricular; CK, creatine kinase; TIMI, Thrombolysis In Myocardial Infarction; and PCI, percutaneous coronary intervention.
and the authors concluded that the positive findings in reperfused patients warranted a larger-scale study.

**Polish Glucose-Insulin-Potassium Trial**

In 1999, the Polish Glucose-Insulin-Potassium (Pol-GIK) trial was published. A total of 954 patients with acute myocardial infarction were randomized within 24 hours of chest pain to low-dose GIK (n=494) or control (n=460). Low-dose GIK consisted of 1000 mL of 10% dextrose, 32 to 20 U of insulin, and 80 mEq of potassium by intravenous infusion over 24 hours at a rate of 42 mL/h. Baseline glucose levels were similar in the GIK (6.9 mmol/L) and control (7.0 mmol/L) groups. At 12 hours, glucose levels were 6.2 mmol/L in the GIK group and 6.3 mmol/L in the control group. At 24 hours, glucose levels were 5.9 mmol/L in the GIK group and 6.2 mmol/L in controls. At 35 days, no difference was noted in cardiac mortality events between the GIK group (6.5%) and the control group (4.6%; OR 1.45, 95% CI 0.79 to 2.68, P=0.20). Also, no difference was found in the number of patients who developed any cardiac event, including cardiac death, between the GIK group (n=214 [43.3%]) and the control group (n=192 [41.7%]; OR 1.07, 95% CI 0.82 to 1.38, P=0.62). Of concern was that total mortality, including noncardiac death, was actually higher in the GIK group (n=44 [8.9%]) than in the control group (n=22 [4.8%]; P=0.01). Some of the noncardiac deaths were due to stroke (5 patients; 1% in the GIK group versus 0 in the control group), gastrointestinal bleed (2 in the GIK group, 0 in the control group), and 3 cases of neoplastic disease (all 3 in the GIK group, 2 with pulmonary embolism, and 0 in the control group). The causes of increased mortality were deemed not attributable to the GIK but due to chance. Low-dose GIK did not increase survival or improve the clinical outcome for acute myocardial infarction. Apstein and Opie commented in an editorial that the absence of a benefit of GIK in the Pol-GIK trial compared with the ECLA pilot study of 1998 could be explained by the differences between the 2 trials, because the mortality risk in the patient populations differed, and higher doses of GIK were used in the ECLA pilot study.

**Glucose-Insulin-Potassium Study I**

Van der Horst and colleagues studied a larger cohort of patients with acute myocardial infarction treated with primary coronary angioplasty who were randomized to adjunctive therapy with GIK or conventional care with no infusion. GIK was given as an infusion of 80 mmol of KCl in 500 mL of 20% glucose at a rate of 3 mL per kilogram of body weight per hour over an 8- to 12-hour period and a continuous infusion of short-acting insulin (50 U of Actrapid HM, Novo Nordisk) in 50 mL of 0.9% sodium chloride. The insulin component of the GIK cocktail was adjusted to obtain blood glucose levels between 7.0 and 11.0 mmol/L. After initiation of the GIK infusion, patients underwent coronary angiography and angioplasty. The primary end point of the study was 30-day mortality. Median blood glucose level on admission was 8.5 mmol/L for both groups; at 16 hours after admission, levels were 7.7 mmol/L in the GIK group and 8.1 mmol/L in the control patients, and thus, no significant difference in blood glucose levels was found between groups. The primary end point occurred in 23 (4.8%) of 476 patients in the GIK group versus 27 (5.8%) of 464 patients in the control group (P=NS). Although GIK did not reduce mortality in the total patient population, it did reduce mortality in a cohort of patients (n=856) who presented without signs of heart failure. In this subgroup, 5 (1.2%) of 426 patients died at 30 days in the GIK group versus 18 (4.2%) of 430 in the control group (relative risk 0.28, 95% CI 0.1 to 0.75). However, among 84 patients with signs of congestive heart failure (Killip class ≥2), 18 (36%) of 50 patients died in the GIK group versus 9 (26.5%) of 34 in the control group (relative risk 1.44, 95% CI 0.65 to 3.22). An obvious explanation for the absence of benefit in the group with heart failure was the adverse effect of the volume load of GIK. The authors concluded that although GIK did not reduce mortality in all myocardial infarction patients, the risk for death at 30 days was reduced in the group without heart failure on presentation. However, follow-up studies from the same group showed that GIK failed to affect outcome (survival, reinfarction, or revascularization) in patients with myocardial infarction and no heart failure at 30 days or 1 year (see Glucose-Insulin-Potassium Study II).

**Castro et al; Reevaluation of the Intensified Venous Metabolic Support for Acute Infarct Size Limitation**

Although the benefits of GIK were initially described as a reduction of myocardial infarct size in animal models, there have been few reports that measured the effect of GIK on infarct size in humans. Neither a study by Castro et al nor the Reevaluation of the Intensified Venous Metabolic Support for Acute Infarct Size Limitation (REVIVAL) showed an overall benefit of GIK on infarct size assessed by 99mTc sestamibi. In the latter study, an increase was found in salvage index among diabetic patients who received GIK.

**Krljanac et al Study**

A study by Krljanac et al in 2005 showed benefits of GIK on major adverse cardiac events in patients with ST-segment elevation myocardial infarction who received thrombolytic therapy. In this randomized, prospective, open-label study, 120 patients were treated within 12 hours of symptom onset with high-dose GIK (25% glucose, 50 IU of soluble insulin per liter, and 80 mmol of potassium chloride per liter at an infusion rate of 1 mL·kg⁻¹·h⁻¹ over 24 hours) as adjunctive therapy to thrombolytic therapy or received thrombolytic therapy alone. The incidence of major adverse cardiac events (composite of cardiac death, reinfarction, ventricular fibrillation and/or tachycardia, and severe heart failure) at 1 month was 10% in the GIK group versus 32.5% in the control group (relative risk 0.24, 95% CI 0.09 to 0.63, P=0.0043). The rate of major adverse cardiac events was also lower at 1 year in the GIK group (13%) than in the control group (40%; relative risk 0.22, 95% CI 0.09 to 0.55, P=0.0012). At 1 year, the GIK group demonstrated a significant improvement in left ventricular ejection fraction (from 48% to 51%; P<0.01), whereas the control group did not (from 46% to 47%). The effect of therapy on glucose levels was not reported. Hence,
this study showed that high-dose GIK plus reperfusion reduced adverse clinical events at both 1 month and 1 year.

**Van der Horst et al 2005 Study**
Van der Horst et al\(^9\) assessed the effect of GIK on myocardial infarct size and left ventricular function in a randomized, controlled study in which patients with acute myocardial infarction underwent primary percutaneous coronary intervention. In the GIK treatment arm, patients received a continuous infusion of 80 mmol of KCl in 500 mL of 20% glucose at a rate of 3 mL · kg\(^{-1}\) · h\(^{-1}\) and short-acting insulin (50 U of Actrapid HM) in 50 mL of 0.9% sodium chloride. The dose of insulin in the GIK infusion was adjusted to obtain blood glucose levels between 7.0 and 11.0 mmol/L. GIK infusion was initiated as soon as possible after randomization for at least 8 hours and up to 12 hours; patients went to the catheterization laboratory after admission and randomization to treatment group. The control group did not receive an infusion. No difference between groups was found relative to the pattern or magnitude of creatine kinase–myocardial band isoenzyme (MB) release. Peak creatine kinase-MB (±SD) was 249±228 U/L in the GIK group versus 240±200 U/L in the no-infusion (control) group (\(P=NS\)). Left ventricular ejection fraction was measured by radionuclide ventriculography or echocardiography at \(\approx2.5\) to 2.7 days after admission and was 43.7±11.0% in the GIK group versus 42.4±11.7% in the control group (\(P=0.12\)). A lower frequency of left ventricular ejection fraction \(\leq30\%\) (12%) was noted in the GIK group compared with the control group (18%; \(P=0.01\)). Glucose levels during adjunctive treatment were not reported. In another analysis, the same investigator\(^40\) reported that GIK improved the resolution of ST-segment elevation in patients with acute myocardial infarction. In that 612-patient cohort, no difference was found in 1-year mortality between GIK patients (5.5%) and controls (4.3%; \(P=0.58\)).

**Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–ECLA Study**
The Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–ECLA study was the largest study to assess the effects of GIK on mortality in patients with acute ST-segment elevation myocardial infarction.\(^4\) The study included 20 201 patients with ST-segment elevation acute myocardial infarction presenting within 12 hours of symptoms. Patients were randomized to high-dose GIK for 24 hours plus usual care or usual care alone. GIK was given as 25% glucose, regular insulin 50 U/L, and potassium 80 mEq/L at an infusion rate of 1.5 mL · kg\(^{-1}\) · h\(^{-1}\) for 24 hours. It was recommended that the infusion be started before coronary intervention and be continued for 24 hours. A total of 976 control patients (9.7%) and 1004 GIK patients (10.0%) died at 30 days (\(P=NS\)). Rates of cardiac arrest were similar in the control (1.5%) and GIK (1.4%) groups, as were rates of cardiogenic shock (6.3% versus 6.6%, respectively) and reinfarction (2.4% versus 2.3%, respectively). No differences were observed in rates of heart failure at 7 days between groups. No benefit of GIK could be found in preselected subgroups, including the group with diabetes mellitus, those with and without heart failure, or those receiving or not receiving reperfusion (either percutaneous coronary intervention or thrombolysis).

At baseline, mean glucose levels were 162 mg/dL (9.0 mmol/L) in both groups. At 6 hours, glucose levels in the GIK group increased (187 mg/dL, or 10.4 mmol/L), whereas in the control group, the mean glucose level fell to 148 mg/dL (8.2 mmol/L). At 24 hours, the mean glucose level was higher in the GIK group (155 mg/dL [8.6 mmol/L]) than in the control group (135 mg/dL [7.5 mmol/L]). One theory as to why this large trial failed to show a benefit of GIK is that the insulin and glucose components of the infusion were not adjusted early in the hospitalization to prevent rises in glucose compared with the admission level. Higher baseline glucose levels in the control group were associated with higher mortality. The authors stated, “It may be worthy of further study to assess whether lowering serum glucose concentration with a modified regimen is associated with improved outcomes.” Some speculation exists that the “neutral” effect on mortality of GIK in CREATE-ECLA may actually represent a therapeutic benefit of insulin itself counterbalanced or negated by the increased mortality possibly related to the rise in glucose in the GIK group.

**Glucose-Insulin-Potassium Study II**
Another blow to the GIK concept came in 2005 with the reports of the Dutch Glucose-Insulin-Potassium Study II (GIIPS II).\(^41\) This trial was a follow-up to GIIPS I,\(^33\) which had shown a reduction in mortality in myocardial infarction in the subgroup of patients randomized to GIK who presented without heart failure. The interesting question raised by GIIPS I was whether GIK should be restricted to lower-risk patients because of its significant volume load. In GIIPS II, 889 patients who presented within 6 hours of an ST-segment elevation myocardial infarction and who were candidates for reperfusion therapy but did not have heart failure were randomized to GIK or control. GIK consisted of 20% glucose with 80 mmol potassium per liter, with short-acting insulin adjusted according to glucose levels. In this trial, 9% to 10% of patients had diabetes mellitus. The primary end point of 30-day mortality did not differ between the GIK group (2.9%) and the control group (1.8%). No difference was noted in myocardial infarct size based on creatine kinase levels. Predictors of 30-day mortality included hyperglycemia on admission, unsuccessful reperfusion, and anterior wall infarction. The effect of GIK on glucose levels in this study was not reported.

**Organization for the Assessment of Strategies for Ischemic Syndromes–6**
Recently, the results of the prematurely terminated Organization for the Assessment of Strategies for Ischemic Syndromes–6 (OASIS-6) trial evaluating GIK infusion versus no infusion were published along with a combined analysis with the CREATE-ECLA trial.\(^42\) OASIS-6 compared a solution of 25% glucose, regular insulin 50 U/L, and potassium 80 mEq/L to be administered as soon as possible after admission at an infusion rate of 1.5 mL · kg\(^{-1}\) · h\(^{-1}\) over 24
hours versus no solution; there also was a fondaparinux-versus-placebo arm of the study. When the negative CREATE-ECLA study results were announced, OASIS-6 was terminated after 2748 patients had been randomized (12,000 patients with acute myocardial infarction had been anticipated for the study). At 30 days and at 6 months, no differences were observed in the clinical outcomes of death, heart failure, or their composite between groups. A combined analysis of OASIS-6 and CREATE-ECLA showed a higher death rate in the GIK group (6.2%) than in controls (5.5%) at 3 days (hazard ratio 1.13, 95% CI 1.02 to 1.26, \( P=0.03 \)), which was attributed to increased levels of glucose and potassium and net fluid gain.

In summary, the preponderance of clinical trials of GIK since the 1997 Circulation meta-analysis have been negative. Specifically, most did not show a benefit of GIK on mortality. A mortality benefit was observed in patients reperfused in the ECLA study and in patients without heart failure in 1 study; however, the benefit of GIK in patients who did not present with heart failure was not reproduced in subsequent studies by the same group.34,41 One small thrombolytic study by Krljanac et al37 did show a decrease in major cardiovascular adverse events with high-dose GIK and showed a long-term benefit. Most studies that investigated myocardial infarct size did not show a benefit. However, in REVIVAL,36 a subgroup of patients with diabetes mellitus had an increase in myocardial salvage index, and in a 2005 study by Yazici et al,38 increases in troponin 1 levels were lower with GIK. However, these studies were the exception. Most studies that assessed myocardial infarct size by single-photon emission computed tomography analysis or creatine kinase-MB release failed to show a benefit of GIK.

### Glucose-Insulin and Insulin Infusions for Myocardial Infarction

The GIK trials mentioned above evaluated GIK as a fixed metabolic “cocktail” (albeit in different doses) that did not have a specific treatment target. It was given to patients such that the individual components of the formulation were not titrated to the hemodynamic status of the patient (volume) or the metabolic status (admission glucose level) in many of the trials. In addition, GIK was administered at variable intervals titrated to the hemodynamic status of the patient (volume) or the metabolic status (admission glucose level) in many of the trials. In addition, GIK was administered at variable intervals related to the time and manner of reperfusion and for varying durations after presentation. Many of these previous trials did not take into account the glucose level on admission or the directional change in glucose during the course of GIK infusion. Why is this important?

### Hyperglycemia Is Deleterious in the Setting of Acute Myocardial Infarction

Several studies suggest that hyperglycemia has negative effects in patients experiencing myocardial infarction. Strander et al observed that an increase of 18 mg/dL (1 mmol/L) in glucose increased mortality risk by 5% in those with diabetes mellitus and 4% in those without. Those patients with no history of diabetes mellitus but an admission glucose level of 200 mg/dL (11.1 mmol/L) or greater after infarction had mortality rates comparable to those of diabetic patients. Kosiborod et al studied a large sample of elderly patients (n = 141,680) who were hospitalized for myocardial infarction in the mid-1990s. Of note, 26% of hyperglycemic patients (glucose >240 mg/dL) did not have previous histories of diabetes mellitus. Higher glucose levels were associated with increased 30-day mortality, and this observation was most prominent among those without a history of diabetes mellitus. Goyal et al observed that in nondiabetic patients (n = 1219) who participated in a large trial of acute myocardial infarction, a higher baseline glucose level predicted lower survival. In a multivariable model, for every 0.6-mmol/L increase in glucose level, an increase in mortality occurred with a hazard ratio of 1.12 (95% CI 1.04 to 1.20). Also, a greater decline in glucose over 24 hours of hospitalization predicted a lower mortality; for every 0.6-mmol/L drop in the first 24 hours, a lower mortality at 30 days was observed (hazard ratio 0.91, 95% CI 0.86 to 0.96). Of note, in patients with known diabetes mellitus, neither baseline glucose level nor change in level over this time period predicted mortality in a multivariate model. Meier et al showed that plasma glucose at hospital admission and previous metabolic control were determinants of myocardial infarct size and survival both in patients with and in those without type 2 diabetes mellitus. Higher glucose levels were associated with lower survival and higher creatine kinase-MB levels. Table 2 outlines some of the theories on how acute hyperglycemia could adversely affect the outcome of acute myocardial infarction. What remains unclear is whether hyperglycemia is a mediator of adverse outcomes after myocardial infarction (as suggested in Table 2), a marker of adverse outcomes, or both. One could argue that any negative outcome of myocardial infarction, such as shock or heart failure, would stimulate a stress response with an increase in catecholamines and cortisol that could trigger hyperglycemia (as a marker).

Some trials have been published that have used glucose-insulin or insulin as infusions (rather than GIK) and have focused on attempting to maintain normoglycemia in either diabetic or nondiabetic patients; that is, they have taken more of a metabolic approach to therapy. These studies are discussed below.

| Table 2. Acute Effects of Hyperglycemia in Acute Myocardial Infarction |
|--------------------------|--------------------------|
|                          | Endothelial dysfunction  |
|                          | Platelet hyperreactivity  |
|                          | Increased cytokine activation |
| Increased lipolysis and free fatty acid levels | |
| Reduced glycolysis and glucose oxidation | |
| Osmotic diuresis; potentially reduced cardiac output | |
| Increased oxidative stress (? increased myocardial apoptosis) | |
| Impaired microcirculatory function (“no-reflow” phenomenon) | |
| Impaired ischemic preconditioning | |
| Impaired insulin secretion and insulin-stimulated glucose uptake | |

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The Diabetes Insulin-Glucose in Acute Myocardial Infarction Studies
An important study published before the 1997 meta-analysis but not included in it, because it involved only diabetic patients, was the Diabetes Insulin-Glucose in Acute Myocardial Infarction (DIGAMI) study. A total of 620 patients with diabetes (the majority with type 2 diabetes mellitus) with acute myocardial infarction were randomized to insulin-glucose infusion followed by multidose subcutaneous insulin administered long-term or to conventional therapy. Infusion was maximized to achieve normoglycemia. The group receiving insulin-glucose infusion had an early reduction in their serum glucose levels from 211 mg/dL at baseline to 173 mg/dL. At 1 year, mortality in the infusion group was 18.6% versus 26.1% (P=0.0273) in the control group.

Mortality was lower in patients who maintained a blood glucose level of 7 mmol/L (11%; P=0.05). Baseline blood glucose levels were 10.8±4.1 mmol/L in the insulin/dextrose infusion group and 11.1±3.5 mmol/L in the conventional therapy arm (P=NS); at 24 hours, blood glucose levels were 8.3±2.2 mmol/L in the insulin/dextrose group versus 9.0±2.8 mmol/L in the conventional therapy arm (P=NS). Mortality was lower in patients who maintained a blood glucose level ≤8 mmol/L during the first 24 hours (2%) than in patients with a blood glucose level >8 mmol/L (11%; P=0.02). Thus, although the investigators did not observe a significant reduction in overall mortality in patients receiving the insulin/dextrose infusion, they suggested that “it remains possible that tight glycemic control with insulin therapy after acute myocardial infarction improves outcomes.”

Antiinflammatory Effect
Chaudhuri et al showed that in patients with acute ST-segment elevation myocardial infarction treated with reteplase, GIK infusion reduced levels of C-reactive protein and serum amyloid A and attenuated an increase in plasminogen activator-I, which suggests that GIK has an antiinflammatory and profibrinolytic effect.

GIK, Insulin-Glucose in the Intensive Care Setting and With Cardiac Surgery
The focus of the present review has been the use of GIK in the setting of acute myocardial infarction. However, the reader should be aware that a vast body of literature also exists on the use of GIK, insulin-glucose, or insulin alone in critically ill patients (due to various causes) in the intensive care unit, as well as in the cardiac surgery patient. Although it is beyond the scope of the present article to review these studies
Lessons Learned and Suggestions for Future Studies

Over the past 10 years, the results of numerous clinical studies using GIK or glucose-insulin for the treatment of acute myocardial infarction have varied remarkably, more so than the numerous positive preclinical studies. At the present time, GIK cannot be recommended as standard adjunctive treatment with reperfusion. In retrospect, certain factors may explain the negative results of several of the trials and make it difficult to compare the results of the trials. GIK was typically used in many of the clinical trials as a fixed-dose cocktail without adjustments in the amount of intravenous volume or glucose administered.4,33,42 GIK in some patients could paradoxically increase mortality by raising glucose levels or causing volume overload early in the course of myocardial injury.4,33,42 In addition, either glucose levels before initiation of GIK or in response to GIK were not reported in many of the cited studies, which makes comparisons difficult. The metabolic status of the patient, including the presence or absence of insulin resistance syndrome or of type 1 or type 2 diabetes mellitus, could be a factor in the overall effect of GIK, because myocardial responsiveness to insulin and glucose may vary in these conditions.61 Not all studies separated patients with or without diabetes mellitus or took into account the type of diabetes. Finally, the time of delivery of any adjuvant treatment is an important factor in the setting of acute myocardial infarction. The time of delivery of GIK in relationship to the onset of myocardial infarction or the onset of reperfusion was highly variable among these studies.

Recommendation for Future Studies

In future studies, baseline glucose levels should be determined immediately, and GIK, insulin-glucose, or insulin infusions should be started as soon as possible. Administration should be initiated in the emergency ward or in the ambulance, that is, before reperfusion. Optimally, percutaneous coronary intervention (angioplasty with or without stenting) should be the preferred mode of reperfusion and should be successful >90% of the time. The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE), a trial sponsored by the National Institutes of Health, is evaluating the prehospital administration of GIK in the ambulance. The primary hypothesis is that early GIK will reduce 30-day and 1-year mortality.62

It is crucial that the GIK, insulin-glucose, or insulin therapy be administered in such a fashion to prevent the development or exacerbation of hyperglycemia (and hypoglycemia) throughout the acute phase of myocardial infarction. Therefore, blood glucose levels need to be monitored frequently and the dosage of insulin and the amount of glucose adjusted as needed to prevent hyperglycemia (and hypoglycemia). In 1 recent meta-analysis, the suggestion was made that high-dose GIK was more beneficial than low-dose GIK (Figure 2).63 Furthermore, a GIK study should avoid enrolling patients who present with fluid overload and particularly those with severely compromised left ventricular function. Finally, patients who continue to manifest glucose intolerance or who have a new diagnosis of diabetes mellitus after their infarct should be treated long-term with agents to control their blood glucose. Our hope is that by early targeting of the glucose level in acute myocardial infarction, GIK, glucose-insulin, or insulin will achieve the target goals of infarct-size reduction and beneficial clinical outcomes.64
Disclosures

Drs Klonen and Nesto are consultants to Sanofi-Aventis.

References


Key Words: diabetes mellitus • glucose • heart failure • myocardial infarction • pharmacology
Glucose-Insulin-Potassium for Acute Myocardial Infarction: Continuing Controversy
Over Cardioprotection
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_Circulation_. 2008;117:2523-2533
doi: 10.1161/CIRCULATIONAHA.107.697979
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
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PRE-CLINICAL STUDIES MAINLY SHOWED A BENEFIT OF GIK

Sodi-Pallares, Charles Rackley and others performed extensive preclinical and clinical studies in the 1960s and 1970s as reviewed by Surawicz. The work of Maroko, Braunwald and associates showed in a canine model of coronary occlusion that GIK preserved myocardial CK tissue levels and electron microscopic evidence of cardiac damage. In isolated heart models of ischemia/reperfusion GIK preserved ATP levels, creatine phosphate, energy charge, and improved postischemic recovery of contractile function. In one study of isolated hearts, insulin given at reperfusion significantly attenuated myocardial infarct size and this benefit was shown to be mediated through prosurvival signaling pathways. GIK has shown benefit in a host of in-vivo coronary artery occlusion - reperfusion preclinical studies. In anesthetized pigs undergoing 90 minutes of moderate regional ischemia and 90 minutes of reperfusion, GIK increased myocardial glucose uptake and improved recovery of both global and regional left ventricular function. In a canine study of 50 minutes of ischemia and four hours of reperfusion GIK reduced myocardial infarct size and apoptosis, improved cardiac function as well as coronary artery blood flow. Insulin alone also had a beneficial effect. However in this study glucose-insulin actually increased blood glucose levels which was associated with worsened ischemia/reperfusion injury. Many other in-vivo animal studies suggested that GIK reduced myocardial infarct size, reduced apoptosis, improved reperfusion and/or improved postischemic function. However, not all studies were positive. Heng studied dogs subjected to proximal coronary artery occlusion. GIK resulted in a modest increase in lactate in the veins draining the infarct but did not have
an effect on glucose uptake or on creatine kinase activity in the infarct. Bellows in our group investigated the effect of GIK in anesthetized rabbits subjected to 30 minutes of coronary artery occlusion and four hours of reperfusion. GIK had no effect on myocardial infarct size expressed as a percentage of the area at risk. However, in our study, GIK substantially increased serum glucose levels. In general, the preponderance of preclinical studies assessing GIK or insulin have shown benefits on aspects of ischemia/reperfusion injury; however, some studies, as ours, did not show a benefit particularly when GIK delivery resulted in hyperglycemia. The directional changes in glycemia when GIK is administered may be a crucial factor in the overall outcome of this treatment.
GIK, INSULIN-GLUCOSE IN THE INTENSIVE CARE SETTING AND WITH CARDIAC SURGERY

The focus of this review has been the use of GIK in the setting of acute myocardial infarction. However, the reader should be aware that there is also a vast literature on the use of GIK, or insulin-glucose, or insulin in critically ill patients (due to various causes) in the intensive care unit as well as in the cardiac surgery patient. While it is beyond the scope of the present paper to review these studies in depth, several highlights of this field are worthy of attention and are presented. In 2001, Van Den Berghe et al (53) published a prospective, randomized controlled study of 1548 adults admitted to the surgical intensive care unit who received either intensive insulin treatment by continuous infusion to achieve blood glucose levels between 80 - 110 mg/dL or conventional treatment (insulin only if blood glucose levels > 215 mg/dL and maintenance of levels between 180 - 200 mg/dL). At one year, mortality with intensive insulin was 4.6% versus 8.0% for conventional treatment (p < 0.04). Intensive insulin treatment was best at reducing mortality due to multiple organ failure with proven sepsis. There were a number of other benefits afforded by intensive insulin: reduction of in-hospital mortality by 34%; reductions in bloodstream infections, renal failure, transfusions, and polyneuropathy, and the need for and duration of mechanical ventilation. The authors concluded that intensive insulin treatment by continuous infusion targeted to a blood glucose at or below 110 mg/dL decreases morbidity and mortality in critically ill patients. In another paper, the lead author postulated on a number of protective mechanisms by which insulin aids the critically ill patient. (54)
Some of these mechanisms include prevention of glucotoxicity in critically ill patients as these patients have cellular glucose overload and more pronounced toxic side effects related to oxidative phosphorylation. The author also points out that insulin alters lipoproteins in a favorable way, has anabolic and anti-inflammatory effects, prevents endothelial dysfunction and hypercoagulation, and possesses anti-apoptotic effects.

There are two large ongoing prospective, randomized, control studies evaluating the issue of tight glucose control in the setting of the intensive care unit; Glucontrol Study: Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients and the NICE-SUGAR Study (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation). Final results of these studies are pending.

The use of insulin or GIK in cardiac surgery remains controversial\(^{(55)}\) and in general this treatment is not typically considered standard care.

**GIK in Cardiac Surgery**

Bothe et al\(^{(56)}\) reported a meta-analysis of the use of GIK in cardiac surgery (coronary artery bypass grafting or heart valve replacement) and as of 2004 found 11 studies (468 patients) with contractile function as a primary endpoint. Six of the studies described a significant improvement in postoperative cardiac recovery with GIK and GIK patients needed less inotropic support with catecholamines. Of note, atrial fibrillation occurred less frequently with GIK (23%) compared to patients that did not receive GIK (42%; \(p = 0.009\)). The authors of the meta-analysis concluded that GIK improves postoperative contractile function and reduces the incidence of atrial fibrillation. They called for a large, randomized multicenter trial. A review of the literature by Schipke and
coworkers\textsuperscript{(57)} stated that 74 of 91 studies showed evidence for benefits of GIK or insulin in cardiac surgery including improvement in the recovery of myocardial tissue. The authors also questioned why this type of therapy has not been incorporated into standard care of the cardiac surgical patient. In 2004, Lazar et al\textsuperscript{(58)} reported 141 diabetic patients who underwent coronary artery bypass grafting and were randomized to tight glycemic control (serum glucose 125 - 200 mg/dL) using GIK or standard therapy (serum glucose < 250 mg/dL) with intermittent subcutaneous insulin for 12 hours. GIK therapy with tighter glucose control reduced the incidence of atrial fibrillation (16.6\% with GIK versus 42\% with standard therapy; p = 0.0017) as well as resulted in a shorter postoperative hospital stay (6.5 ± 0.1 versus 9.2 ± 0.3 days; p = 0.003). Over two years following surgery GIK patients had greater survival, decreased episodes of recurrent ischemia and fewer wound infections. This study confirmed an earlier paper by the same group also showing that diabetic patients undergoing CABG had improved postoperative cardiac indices and less need for inotropic support with GIK treatment.\textsuperscript{(59)} However, as in the acute myocardial infarction literature there are also negative studies. Lell et al\textsuperscript{(60)} in 2002 failed to show a benefit of GIK on release of cardiac enzymes in patients undergoing elective off-pump coronary artery bypass surgery. However, in this study GIK induced hyperglycemia. Thus, there is a need for larger prospective, randomized, multicenter studies comparing tight glycemic control with GIK, glucose-insulin, or insulin in the cardiac surgical population. The outcome of a positive benefit on cardiac function, mortality, and/or arrhythmias could result in metabolic modulation becoming a standard of care for this group of patient.