

# A meta-analysis of glucose-insulin-potassium therapy for treatment of acute myocardial infarction

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**BACKGROUND:** Glucose-insulin-potassium (GIK) therapy has been proposed to provide metabolic support to ischemic myocardium. A meta-analysis that included 1932 patients performed 10 years previously demonstrated that GIK therapy may have an important role in reducing mortality after acute myocardial infarction (AMI). Since then, many larger randomized trials investigating the role of GIK in the setting of AMI have been published; hence, the present study repeats the previous meta-analysis performed by the current authors to include these trials.

**METHOD AND RESULTS:** A systematic MEDLINE search for all randomized, placebo-controlled studies of GIK therapy in the setting of AMI was conducted and a meta-analysis of the mortality data was performed.

The concept of metabolic modulation in acute myocardial infarction (AMI) with glucose-insulin-potassium (GIK) infusion was initially proposed in the 1960s as a means of producing electrical stability in the myocardium during episodes of ischemia (1). Subsequently, it was proposed that GIK therapy provided metabolic support to ischemic myocardium. During episodes of cardiac ischemia, the myocardium converts from aerobic carbohydrate metabolism to anaerobic free fatty acid metabolism, which results in the production of metabolites and free radicals that are toxic to the myocardium, and are associated with ventricular arrhythmias (2) and decreased myocardial contractility (3). It was hypothesized that insulin and glucose infused as part of GIK therapy resulted in a shift from potentially harmful free fatty acid metabolism to glucose metabolism in the ischemic myocardium. Furthermore, suppression of plasma free fatty acid levels by insulin would further facilitate this effect (4). It is now more than 10 years since we published our meta-analysis evaluating the role GIK therapy on mortality after AMI (5), in which a total of 1932 patients from nine trials were evaluated. We demonstrated that the number of deaths was significantly lower in patients who received GIK (16.1%) than in patients who received placebo (21%). Based on the results of this meta-analysis, we concluded that GIK therapy most likely had a role in reducing in-hospital mortality following AMI. In our original meta-analysis, we argued that there was a need for a larger randomized trial to investigate the role of GIK as an adjunct to thrombolysis or primary percutaneous coronary intervention following AMI on mortality. Since then, many larger randomized trials investigating the role of GIK in the setting of AMI have been published. The Glucose-Insulin-Potassium Study-I (GIPS-I) (6) showed clinical benefit of GIK in ST segment elevation myocardial infarction (STEMI) patients without signs of heart failure;

A total of 16 randomized trials from 1966 to 2008 were identified, with 28,374 patients included in the current meta-analysis. There was a total of 1367 deaths (9.6%) in the GIK group, with 1351 deaths (9.6%) in the control group. Meta-analysis did not reveal any benefit from GIK treatment (OR 1.0; 95% CI 0.9 to 1.1; P=0.9). Subgroup analysis of patients given high-dose GIK and in patients in whom reperfusion was not obtained did not demonstrate a benefit from GIK therapy.

**CONCLUSION:** A meta-analysis of 16 randomized trials that spanned 40 years and involved more than 28,000 patients did not reveal any mortality benefit for ST segment elevation AMI using GIK therapy when data from the modern thrombolysis/primary percutaneous coronary intervention era were included.

**Key Words:** *Insulin; Meta-analysis; Myocardial infarction*

however, GIPS-II (7) could not confirm this finding. Two other recent large sample trials – the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment (CREATE)-Estudios Cardiológicos Latinoamerica (ECLA)-II (8), which included more than 20,000 patients, and the Polish-Glucose-Insulin-Potassium trial (Pol-GIK) (9) trial comprising close to 1000 patients – showed no beneficial effects from GIK therapy. Although The Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS-6) trial (10), a large, multicentre, randomized trial, was stopped prematurely after the enrollment of 2748 patients following publication of CREATE-ECLA II, it did not show any benefit from GIK therapy. We have therefore updated our meta-analysis to include these more recent trial data.

## METHODS

A MEDLINE search (1996 to February 2008) was performed using the search term “myocardial infarction” or “AMI” and a set of terms for GIK including “glucose”, “insulin”, “glucose-insulin”, “GIK”, “GIP”, “PGI”, “glucose-insulin-potassium” and “metabolic support”. Furthermore, references and review articles obtained in this manner were scrutinized to ensure that all relevant studies were identified. Only controlled studies that documented 30-day mortality rates and were properly randomized were selected. Studies that were published before 1996 were the subject of the previous meta-analysis (5), and these studies were also included in the current meta-analysis. Studies were excluded if they used inadequate means of randomization, such as allocations based on date of birth, alternate numbers, admission to a particular unit or date of presentation. Trials that used retrospective group or historic cases as a control group, and those that limited the study to a particular subgroup were also excluded. Only trial-level data were used for the present meta-analysis.

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**TABLE 1**  
**Design of the randomized placebo-controlled trials of glucose-insulin-potassium (GIK) therapy in acute myocardial infarction (AMI)**

Study (ref)	Year	Design (n)	Delay between onset of AMI and treatment	Exclusion criteria	GIK regimen	Treatment duration
ECLA pilot (16)	1998	Randomized, controlled, open (407)	<24 h	Severe renal impairment, hyperkalemia	High and low dose	24 h
Pol-GIK (9)	1999	Prospective, randomized placebo-controlled, open (954)	<24 h	Pulmonary congestion, renal failure, diabetes requiring insulin	Low dose	24 h
GIPS-I (6)	2003	Randomized, open (940)	<24 h	Thrombolysis, poor life expectancy	High dose	12 h
Pache et al (15)	2004	Randomized, open (312)	<48 h	NA	High dose	24 h
ECLA (8)	2005	Randomized, controlled, open (20,201)	<12 h	Type 1 diabetes mellitus, renal impairment, hyperkalemia	High dose	24 h
GIPS-II (7)	2006	Randomized, controlled (889)	<24 h	Pulmonary congestion	High dose	12 h
OASIS-6 (10)	2007	Randomized, controlled (2748)	<24 h but decreased to <12 h after 4300 patients recruited	Oral anticoagulants, moderate renal impairment	High dose	NA

ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; NA Not available; OASIS The Organization for the Assessment of Strategies for Ischemic Syndromes trial; Pol-GIK Polish Glucose-Insulin-Potassium study

### Statistical analysis

For individual trials, the  $\chi^2$  heterogeneity test (11) was used to calculate the significance, ORs and 95% CIs for the differences in mortality between the GIK and placebo group, except for trials in which the expected number of deaths was less than five. For trials in which the number of deaths was less than five, the Fisher's exact test was used (12). Statistical analysis was performed using Arcus Quickstat (Research Solutions, United Kingdom).

## RESULTS

Since the original meta-analysis (5), a total of nine trials (6-10,13-16) were identified, of which seven (6-10,15,16) were included in the current analysis (Table 1). Two trials (13,14) were excluded because only diabetic patients were enrolled in the Diabetes Mellitus, Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI-2) trial (13) and only patients who were diabetic or presented with hyperglycemia were included in the other study (14). Similar exclusion criteria were applied in the original meta-analysis (5) in which the DIGAMI-1 trial was excluded for the same reason. Studies that were conducted between 1998 and 2005, and those included in the present meta-analysis were open design. Delays between the onset of chest pain and treatment varied from less than 12 h to less than 48 h, with treatment duration of between 12 h and 24 h in all studies. All trials reported 30-day mortality. A total of 26,442 patients were included in the current meta-analysis, with 13,293 patients in the GIK treatment group and 13,149 patients in the control group. Mortality rates for the control group and GIK treatment group for the individual trials are presented in Table 2. Pooled data demonstrate that the total number of deaths was 1213 (9.1%) in the GIK group and 1146 (8.7%) in the control group. GIK treatment did not significantly influence 30-day mortality post-AMI (OR 1.05; 95% CI 0.97 to 1.14;  $P=0.34$ ) (Figure 1). Summation of these new data to the original meta-analysis data performed by Fath-Ourdoubadi and Beatt (5) on nine randomized trials (17-25) resulted in a total of 16 trials and 28,374 patients, with a total mortality of 1367 (9.6%) in the GIK group and 1351 (9.6%) in the control group. A repeat meta-analysis of these 16 randomized trials did not significantly alter the outcome (OR 1.0; 95% CI 0.9 to 1.1;  $P=0.9$ ) (Figure 2).

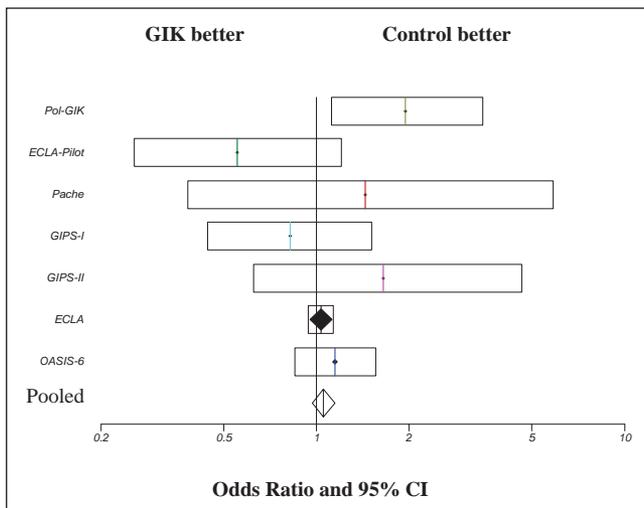
**TABLE 2**  
**Thirty-day mortality in randomized trials of glucose-insulin-potassium (GIK) therapy in acute myocardial infarction**

Study (reference), year	Patients, n		Deaths (at 30 days), n (%)		P
	GIK	Control	GIK	Control	
ECLA pilot (16), 1998	268	139	18 (6.7)	16 (11.5)	0.1
Pol-GIK (9), 1999	494	460	44 (8.9)	22 (4.8)	0.01
GIPS-I (6), 2003	476	464	23 (4.8)	27 (5.8)	0.5
Pache et al (15), 2004	155	157	7 (4.5)	5 (3.2)	0.85
ECLA (8), 2005	10,088	10,107	1004 (10)	976 (9.7)	0.45
GIPS-II (7), 2006	444	445	13 (2.9)	8 (1.8)	0.26
OASIS-6 (10), 2007	1368	1377	104 (7.6)	92 (6.7)	0.76

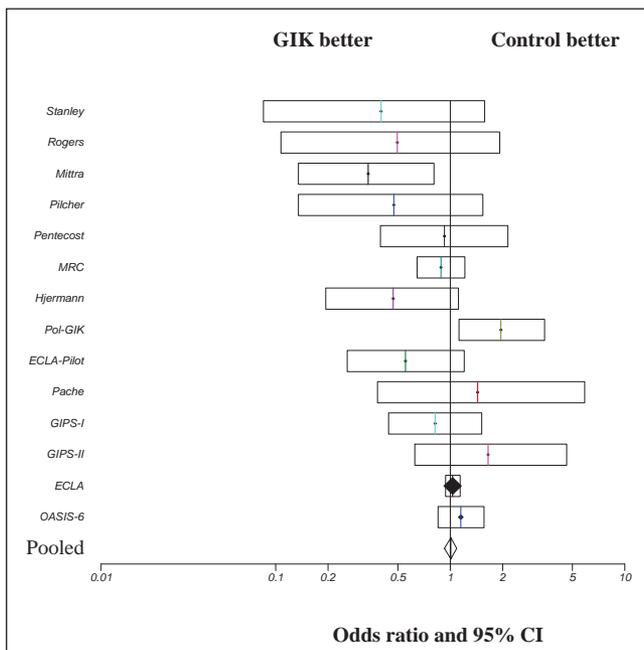
ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; OASIS The Organization for the Assessment of Strategies for Ischemic Syndromes trial; Pol-GIK Polish Glucose-Insulin-Potassium study

Most of the trial data analyzed in the Fath-Ourdoubadi and Beatt (5) meta-analysis were from an era when thrombolysis or primary percutaneous coronary intervention was not performed; therefore, the patients included in the present meta-analysis would represent AMI in which no reperfusion was achieved (with the exception of the study by Satler et al [25]). Consequently, the data from 1966 to 2007 were re-analyzed in the patient cohort in which reperfusion was not achieved to determine whether this influenced outcome. Studies in which reperfusion strategies were not used (16-23) and current studies (6,8,16) in which mortality data was presented in the nonreperfusion subgroup, were pooled. Analysis was performed on a total of 5716 patients, with 437 (15%) deaths in the GIK treatment group and 467 (16.4%) deaths in the control group. Figure 3 illustrates that no significant benefit was observed with GIK treatment in this subgroup (OR 0.92; 95% CI 0.80 to 1.06;  $P=0.27$ ).

Finally, data were pooled from the trials in which high-dose GIK solution was used (6-8,15,22-25). A total of 25,369 patients were included in the meta-analysis (Figure 4). A mortality of 9.1% was observed in the high-dose GIK group and 9.1% in



**Figure 1)** Comparison of 30-day mortality outcome in patients treated with glucose-insulin-potassium (GIK) therapy. ORs and 95% CIs are presented for individual studies and pooled data. ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; OASIS Organization for the Assessment of Strategies for Ischemic Syndromes trial; Pol-GIK Polish GIK trial

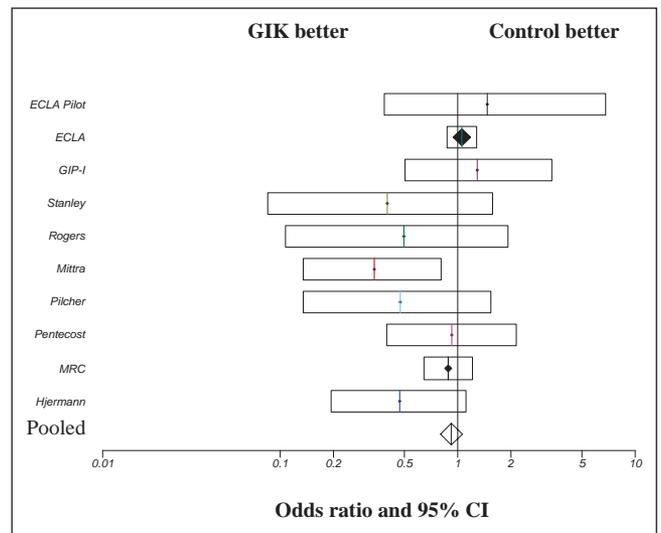


**Figure 2)** Comparison of 30-day mortality outcome in patients treated with glucose-insulin-potassium (GIK) therapy. ORs and 95% CIs are presented for individual studies and pooled data. ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; MRC Medical Research Council; OASIS Organization for the Assessment of Strategies for Ischemic Syndromes trial; Pol-GIK Polish GIK trial

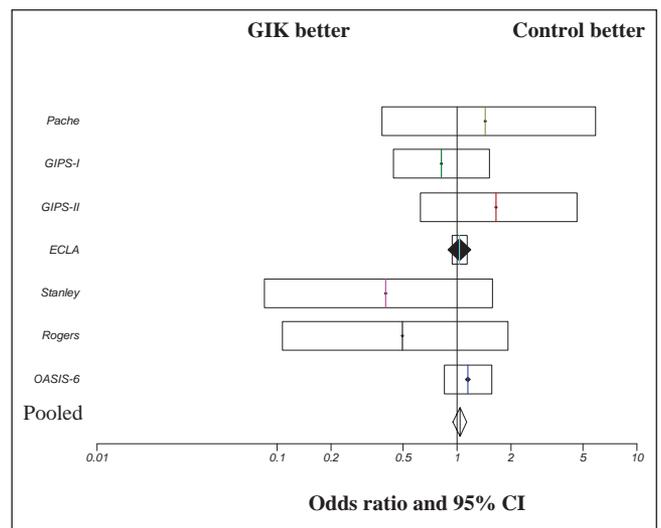
control group, with no observed benefit of high-dose GIK infusion on mortality observed (OR 1.04; 95% CI 0.95 to 1.13; P=0.43).

**DISCUSSION**

It is now 10 years since our most recent meta-analysis (5) that included 1932 patients, in which a 28% reduction in mortality post-AMI was demonstrated following treatment with GIK



**Figure 3)** Comparison of 30-day mortality outcome in patients treated with glucose-insulin-potassium (GIK) therapy in whom reperfusion was not attained. ORs and 95% CIs are presented for individual studies and pooled data. ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; MRC Medical Research Council; OASIS Organization for the Assessment of Strategies for Ischemic Syndromes trial



**Figure 4)** Comparison of 30-day mortality outcome in patients treated with high-dose glucose-insulin-potassium (GIK) therapy. ORs and 95% CIs are presented for individual studies and pooled data. ECLA Estudios Cardiológicos Latinoamerica; GIPS Glucose-Insulin-Potassium Study; OASIS Organization for the Assessment of Strategies for Ischemic Syndromes trial

(P=0.004). Since publication of this meta-analysis, many larger randomized controlled trials investigating the effects of GIK on patients with AMI have been conducted. GIPS-I (6) showed clinical benefit of GIK in STEMI patients without signs of heart failure; however, GIPS-II (7) could not confirm this finding. The ECLA GIK pilot trial (16) involving 407 patients demonstrated a nonsignificant decrease in mortality following GIK therapy (6.7%) when compared with placebo (11.5%). Similarly, in the more recent CREATE-ECLA (8), a trial

evaluating the effects of high-dose GIK on mortality in 20,000 patients with STEMI, showed no significant difference in mortality. The OASIS-6 trial (10), a large, multicentre, randomized trial, was stopped prematurely after having enrolled 2748 patients following publication of CREATE-ECLA; the OASIS-6 trial showed no benefit from GIK treatment. Our current meta-analysis of these more recent trials involving 26,442 patients demonstrates no significant difference between mortality in the GIK treatment group and the control group, even if the meta-analysis is repeated to include our original data.

In contrast, a recent analysis of the OASIS-6 and CREATE-ECLA trials combined trial populations and actually demonstrated an increased mortality associated with GIK treatment in the first three days. Although in agreement with our current data, this difference disappeared at 30 days (10). Interestingly, at 6 h and 24 h postrandomization, serum glucose levels were significantly greater in the GIK cohort than in the control group and, on average, the net fluid balance in the GIK cohort was 600 mL greater after 24 h.

Indeed, it is well recognized that admission glucose level is a stronger predictor of mortality in the setting of AMI (26,27). Analysis by Díaz et al (10) revealed that glucose and fluid balance were independent predictors of mortality at three days. Once these variables were accounted for, no excess mortality was observed at this time point in the GIK group. Clearly, this is a major limitation of all GIK studies performed to date in that any potential benefit incurred from metabolic modulation within the myocardium from GIK infusion may be offset by the detrimental effects of hyperglycemia and increased net fluid balance in the GIK arm of these trials.

Our original meta-analysis showing a benefit from GIK therapy was performed on studies conducted in an era when revascularization and thrombolysis were not routinely used in the treatment of AMI. Therefore, it is possible that GIK therapy benefits patients in whom revascularization is not achieved. Experimental evidence suggests a beneficial effect of GIK by shifting myocardial free fatty acid metabolism toward glucose metabolism. This consumes less oxygen and produces less toxic byproducts (28). Furthermore, reperfusion injury may be reduced by limiting apoptosis of postischemic myocardial cells. However, once adequate reperfusion has been established, GIK may be of only limited value because maximal myocardial salvage has already occurred. This potential benefit of treatment with GIK in patients in whom reperfusion is not achieved is not supported by our meta-analysis – there was no improvement in 30-day mortality rates post-treatment with GIK. It has also been argued that many trials do not show a beneficial effect of low-dose GIK solution on reducing mortality because the doses of glucose and insulin used are not sufficient to suppress free fatty acid levels (29). However, in the pilot ECLA study (16), no significant difference in mortality was observed between ‘low-dose’ and ‘high-dose’ GIK treatment. Indeed, our meta-analysis of trials that used only high-dose GIK infusion did not demonstrate any benefits on mortality rates.

The discrepancy in the outcome between the meta-analysis of nine smaller trials performed 10 years previously and the current meta-analysis involving six significantly larger trials is difficult to explain. It may relate to a publication bias of smaller trials for which neutral studies are less likely to be published

compared with similar studies with positive results. Furthermore, our meta-analysis is heavily weighted toward the CREATE-ECLA trial, which contributed 71.2% of the patients to the current analysis. Even when patients from the CREATE-ECLA trial are excluded, repeat meta-analysis of the dataset does not show any benefit of GIK in the setting of AMI (data not shown).

Our original meta-analysis was performed on studies in which beta-blockade and antiplatelet therapy was not routinely used, resulting in an increased ischemic burden in those patients and a greater metabolic insult to the myocardium. Under these conditions, it is possible that GIK therapy has more of a myocardial protective role. Indeed, beta-blockade itself may shift metabolism from free fatty acid oxidation to glucose oxidation (30); therefore, its routine use in the management of AMI in the current era may reduce the benefit from therapies such as GIK. There is good experimental evidence from animal models that GIK should be given early post-AMI, so as to reach the ischemic myocardium before reperfusion. In several animal species including rat (31), baboon (32) and rabbit (33), GIK was protective when started only a few minutes after coronary ligation. It is believed that early administration of GIK post-AMI can slow the rate of myocardial injury during ischemia and, consequently, substantially increase the extent of myocardial salvage when effective reperfusion occurs. However, in these animal models of ischemia, antiplatelet therapy, beta-blockade and revascularization therapy are not used in the context of AMI; therefore, relevance to clinical practice remains uncertain. In the CREATE-ECLA trial (8), which was by far the largest overall contributor to patient numbers in the current meta-analysis, 83% of patients had reperfusion therapy at a median time of 3.85 h after symptom onset, and randomization to GIK or control groups occurred almost 1 h later (median 4.7 h postsymptom onset) after which GIK was started mostly ‘within the next hour’ (ie, up to 2 h post reperfusion) (29). Importantly, these data would suggest that a key component of the CREATE-ECLA trial was commonly violated because the trial explicitly prescribed initiation of GIK infusion before reperfusion. Clearly, such a delayed and often postreperfusion administration of GIK minimized its potential to reduce mortality. Of note, however, in a subgroup analysis of OASIS-6 and CREATE ECLA, it appeared that time between symptom onset and randomization to a treatment arm did not significantly influence outcome, even when symptom onset occurred at less than 2 h (10). In contrast, GIK infusion was started within 15 min to 20 min after admission in the GIPS-1 study (6), which was approximately 30 min earlier than the average door to balloon time (and hence reperfusion) of 45 min. Interestingly, in this study, a benefit of GIK was demonstrated in the subgroup without signs of heart failure (Killip class 1), although this observation was not reproduced in the later GIPS-II study (7). Clearly, the timing of GIK in relation to reperfusion may have an important role in its potential for benefit. The ongoing National Institutes of Health-sponsored Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) study of prehospital initiation of GIK therapy for acute coronary syndrome patients aims to address this issue ([www.immediatetrial.com/](http://www.immediatetrial.com/)). It is anticipated that 15,540 patients will be included in this study and the

primary end point will be 30-day and one-year mortality. Secondary end points will include in-hospital cardiac arrest, progression of unstable angina pectoris to AMI, infarct size and heart failure. In contrast to other GIK trials, this trial will test the efficacy of GIK in all acute coronary syndromes rather than STEMI alone.

All GIK trials to date have investigated the role of GIK in STEMI. However, there are very little trial data investigating whether GIK plays a role in the treatment of other acute coronary syndromes. Yazici et al (34) studied the effects of high-dose GIK in a randomized study of 52 consecutive patients presenting with non-STEMI who underwent percutaneous coronary intervention. They demonstrated that GIK infusion initiated 24 h before coronary stenting for non-STEMI resulted in less myocardial damage as determined by postprocedure troponin I levels. Clearly, the role of GIK in non-STEMI warrants further investigation and it is hoped that the ongoing IMMEDIATE trial will provide further information regarding this issue.

### CONCLUSIONS

Our meta-analysis performed on 16 randomized trials that spanned more than 40 years and included more than 28,000 patients does not demonstrate any benefits from GIK on mortality post-ST segment elevation and does not support its use as a treatment strategy in AMI. Ongoing trials may clarify whether earlier initiation of GIK therapy is associated with benefit in acute coronary syndromes.

**CONFLICTS OF INTEREST:** The authors have no conflicts of interest to declare.

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