Effect of perioperative glucose-insulin-potassium infusions on mortality and atrial fibrillation after coronary artery bypass grafting: A systematic review and meta-analysis

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BACKGROUND: Glucose-insulin infusions (with potassium [GIK] or without [GI]) have been advocated in the setting of coronary artery bypass graft (CABG) surgery to optimize myocardial glucose use and to minimize ischemic injury.

OBJECTIVE: To conduct a meta-analysis assessing whether the use of GIK/GI infusions perioperatively reduce in-hospital mortality or atrial fibrillation (AF) after CABG surgery.

METHODS: Electronic databases (Medline, EMBASE and Cochrane Central Register of Controlled Trials [CENTRAL]) and references of retrieved articles were searched for randomized controlled trials that evaluated the effects of GIK or GI infusions, before or during CABG surgery, on in-hospital mortality and/or postoperative AF. Pooled ORs and 95% CIs were calculated for each outcome.

RESULTS: Twenty trials were identified and eligible for review. The summary OR for in-hospital mortality was 0.88 (95% CI 0.56 to 1.40), based on 44 deaths among 2326 patients. While postoperative AF was a more frequent outcome (occurring in 519 of 1540 patients in the 10 trials reporting this outcome), the overall pooled estimate of effect was nonsignificant (OR 0.79, 95% CI 0.54 to 1.15). This latter finding needs to be interpreted cautiously because it is accompanied by significant heterogeneity across trials.

CONCLUSIONS: Perioperative use of GIK/GI does not significantly reduce mortality or atrial fibrillation in patients undergoing CABG surgery. Unless future trial data in support of GIK/GI infusions become available, the routine use of these treatments in patients undergoing CABG surgery should be discouraged because the safety of these infusions has not been systematically examined.

Key Words: Coronary artery bypass graft surgery; GIK; Insulin; Meta-analysis

There has been interest in the role of insulin as a potential treatment for patients with ischemic heart disease. Insulin is a known vasodilator and, when administered to maintain euglycemia, it may have anti-inflammatory and antithrombotic effects (1,2). Insulin may also be used in combination with glucose as a metabolic therapy. In this setting, achieving euglycemia is not the therapeutic goal; rather, the intent is to provide the myocardium with the substrates for glucose metabolism (3). While free fatty acids are the preferred energy source for myocytes under

L'effet d'infusions périopératoires de glucose-insuline-potassium sur la mortalité et la fibrillation auriculaire après un pontage aortocoronarien : Une analyse bibliographique et une méta-analyse

HISTORIQUE : Les infusions de glucose-insuline (associées [GIK] ou non [GI] à du potassium) sont préconisées en cas de pontage aortocoronarien (PAC) pour optimiser l'utilisation de glucose myocardique et réduire au minimum les lésions ischémiques.

OBJECTIF : Effectuer une méta-analyse évaluant si le recours à des infusions périopératoires de GIK ou de GI réduit la mortalité ou la fibrillation auriculaire (FA) en milieu hospitalier après un PAC.

MÉTHODOLOGIE : Les chercheurs ont fouillé des bases de données électroniques (Medline, EMBASE et *Cochrane Central Register of Controlled Trials* [CENTRAL]) et les références des articles obtenus pour trouver les essais aléatoires et contrôlés sur les effets de GIK ou de GI avant ou pendant un PAC sur la mortalité hospitalière ou la FA postopératoire. Ils ont calculé les RRR groupés et les 95 % d'IC pour chaque issue.

RÉSULTATS : Les chercheurs ont repéré 20 essais admissibles à l'analyse. Le RRR résumé de mortalité hospitalière correspondait à 0,88 (95 % IC 0,56 à 1,40), d'après 44 décès chez 2 326 patients. Tandis que la FA postopératoire était une issue plus fréquente (observée chez 519 de 1 540 patients dans les dix essais faisant état de cette issue), l'évaluation groupée globale de l'effet n'était pas significative (RRR 0,79, 95 % IC 0,54 à 1,15). Cette dernière interprétation doit être interprétée avec prudence, car elle s'accompagne d'une importante hétérogénéité d'un essai à l'autre.

CONCLUSIONS : Le recours périopératoire au GIK ou au GI ne réduit pas la mortalité ou la FA de manière significative chez les patients qui subissent un PAC. À moins que de futures données tirées d'essais cliniques en appui aux infusions de GIK ou de GI ne soient publiées, il faudrait décourager l'utilisation systématique de ces traitements chez les patients subissant un PAC, car leur innocuité n'a pas fait l'objet d'un examen systématique.

nonischemic conditions, free fatty acid oxidation is inefficient and produces harmful metabolites under low oxygen conditions (4,5). It has been postulated that supplying glucose and insulin (with or without potassium) to the ischemic myocardium enhances oxygen-efficient glucose metabolism, which ultimately reduces ischemic injury.

The role of metabolic modulation in ischemic myocardium has been an area of active debate for 40 years. Glucose-insulin-potassium (GIK) infusions have been widely studied in the setting of acute myocardial

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ischemia. Although early trials in the setting of acute myocardial infarction (AMI) suggested a benefit from GIK therapy (6), more recent large, randomized, placebo-controlled trials (7,8) have failed to show any survival benefit and, in fact, revealed increased morbidity (particularly phlebitis, hyperkalemia and congestive heart failure).

The role of GIK as metabolic therapy for patients with ischemic heart disease undergoing revascularization remains unclear. Several small clinical trials have suggested that GIK provides benefit to patients undergoing coronary artery bypass graft (CABG) surgery. In reviewing this literature, Bothe et al (9) demonstrated that the use of GIK is associated with improved left ventricular recovery and favourable hemodynamics, and may even be associated with a reduction in atrial fibrillation (AF). No studies, however, have been large enough to evaluate the efficacy of GIK infusion in reducing more clinically relevant end points such as postoperative mortality, or to provide a definitive answer about postoperative AF. The GIK study (10) (in which GIK was used as an adjunct to percutaneous transluminal angioplasty following AMI) suggested that there was a significant reduction in early mortality associated with the use of GIK in patients without heart failure. A number of studies have assessed GIK and/or glucose-insulin (GI) infusions in the context of CABG surgery, but these have not, to date, been systematically and comprehensively reviewed.

Thus, we undertook a systematic review and meta-analysis of randomized trials examining the use of perioperative GIK or GI infusions in patients undergoing CABG surgery. Our objectives were to examine whether GIK or GI infusions during CABG surgery has an impact on postoperative rates of mortality or postoperative AF.

METHODS

Search strategy

The Medline database (1966 to June 2007), EMBASE (1980 to June 2007) and the Cochrane Central Register of Controlled Trials (CENTRAL, 1996 to June 2007) were searched for randomized, placebo-controlled trials that examined the perioperative use of GIK or GI infusions in the setting of CABG surgery using the Cochrane randomized controlled trial filter and the following MeSH headings/text words: coronary artery bypass, aortocoronary bypass, heart surgery, coronary artery bypass graft, CABG, glucose-insulin-potassium, insulin and GIK (full details of search terms and results are available from the corresponding author on request). Electronic searches were supplemented with a review of the reference lists of retrieved articles and by contacting experts in the field. The electronic search was up to date as of June 2009 and no language restrictions were applied.

Study selection criteria

Two individuals (DMR and FMC) independently evaluated the results of the electronic search and selected full-text articles for eligibility on the basis of four inclusion criteria: study design (a randomized, controlled trial); target population (individuals undergoing CABG surgery); intervention (perioperative GI or GIK versus placebo); and outcome (in-hospital mortality or postoperative AF). Non-English articles were translated using translation services available at www.translatorsbase.com.

Data extraction

Two individuals (DMR and FMC) independently extracted data from eligible articles. Data extracted included GI/GIK protocol (dose and infusion method), demographic data, trial characteristics, outcome data (in-hospital mortality and postoperative AF) and GIK/GI-related adverse events (hypoglycemia, hyperkalemia, hyperglycemia and phlebitis). Discrepancies were resolved by consensus.

Assessment of methodological quality

Two individuals (DMR and FMC) independently evaluated all included trials on the basis of methodological quality. Using the Jadad scale (11), an overall study quality score (ranging from 0 to 5) was assigned by each reviewer. The components of the Jadad score

Figure 1 Identification of eligible studies. Afib Atrial fibrillation; CENTRAL Cochrane Central Register of Controlled Trials; GI Glucose-insulin infusion; GIK Glucose-insulin-potassium infusion

consider the reporting and quality of randomization, the reporting and execution of double blinding, and the adequacy of follow-up. The reviewers also evaluated the studies regarding whether concealment of allocation was described and adequate.

Statistical analysis

Data from all selected trials were combined to calculate pooled ORs and 95% CIs. Heterogeneity was assessed using a Q test. The meta-analysis was performed using the DerSimonian-Laird random effects model (12). The meta-analyses were stratified by method of delivery of GIK or GI (cardioplegia solution or intravenous). Meta-regression was performed to assess the influence of methodological or clinical factors on the pooled estimate of effect. Two sensitivity analyses were performed: one excluded trials with no events in either arm, and the other excluded studies in which the clinical outcomes of interest (death and/or AF) were secondary or tertiary end points and the primary end point was a physiological measure. Assessment of publication bias was performed using funnel plots and Begg's test (13). All analyses were completed using STATA, version 8.0 (StataCorp LP, USA).

RESULTS

Identification of eligible studies

The search identified 117 citations from Medline, 122 citations from EMBASE and 44 citations from CENTRAL. Of these citations, 17 trials met the inclusion criteria and manual searches of their reference lists yielded another three relevant trials, for a total of 20 trials in our analysis (see Figure 1 for the Quality of Reporting of Meta-analyses [QUOROM] flow diagram [14]). One trial (15) examined the efficacy of GIK during both on- and off-pump procedures relative to intra-group controls. This trial was stratified by procedure in this analysis.

Characteristics of eligible studies

While five trials had Jadad scores of 3 to 5 (16-20), the remaining 15 trials had scores of 1 or 2, indicating generally low methodological quality and/or poor reporting. In addition, allocation was adequately concealed in only four trials. The studies used different perioperative GI/GIK protocols. Study protocols and participant characteristics are presented in Table 1.

In-hospital mortality

In-hospital mortality data were reported in 16 studies (2943 patients) (Table 2) (17-32). Mortality was not a primary outcome measure in any of the studies identified and none reported a statistically significant effect on this outcome. Pooling the data from all 16 trials generated an OR of 0.88 (95% CI 0.56 to 1.40) (Figure 2). Although there was no heterogeneity of results across trials (Q test = 5.6, P=0.99), the

TABLE 1
Characteristics of studies

Reference, year	GIK/GI	Infusion method	Control group				Treatment group				Jadad score	Glucose given	Insulin given	Potassium given
			Total, n	Men, n	Diabetes, n	Mean age*	Total, n	Men, n	Diabetes, n	Mean age*				
Brodin et al (21), 1993	GIK	Intravenous	7	4	0	57	7	7	1	60	2	0.5 g	1.35 U	0.25 mmol
Coleman et al (22), 1989	GIK	Intravenous	11	6	NA	64	11	9	NA	60	2	500 g	80 U	100 mEq/L
Hynninen et al (16), 2001	GI	Cardioplegia	258	183	70	64	243	182	75	65	4	NA	10 U	–
Kjellman et al (23), 2000	GIK	Intravenous	15	15	0	63	13	13	0	64	2	30%	4 U	40 mEq
Koskenkari et al (24), 2006	GIK	Intravenous	20	15	NA	67.4	19	13	NA	66.8	1	30%	5 U	20 KCl
Lazar et al (25), 1997	GIK	Intravenous	15	10	0	65	16	11	0	60	2	30%	50 U	80 mEq
Lazar et al (26), 2004	GIK	Intravenous	69	46	69	63.5	72	42	72	63.7	1	500 mL	80 U	40 mEq
Lell et al (17), 2002	GIK	Intravenous	20	13	9	57.2	21	11	6	61.6	3	25%	50 U	80 mEq
Lindholm et al (27), 2000	GIK	Intravenous	11	11	NA	63	11	11	NA	67	2	18 g	NA	NA
Lindholm et al (28), 2001	GI	Intravenous	14	5	NA	74	16	8	NA	72	1	NA	600 U	–
Lolley et al (29), 1978	GIK	Cardioplegia	157	126	NA	54.5	234	183	NA	56.3	2	1.6 g	2.1 U	1.7 mEq
Quinn et al (18), 2006	GIK	Intravenous	142	NA	0	63.6	138	NA	0	63.6	4	40%	70 U	80 mmol
Rao et al (30), 1998	GI	Cardioplegia	11	NA	NA	NA	13	NA	NA	NA	1	NA	10 U	
Rao et al (19), 2000	GI	Cardioplegia	27	27	0	NA	29	29	0	NA	5	42 mmol	NA	
Rao et al (20), 2002	GI	Cardioplegia	570	148	154	63	557	145	162	64	4	NA	10 U	
Salerno et al (31), 1980	GIK	Intravenous	30	NA	NA	NA	30	NA	NA	NA	2	10%	10 U	40 mEq
Smith et al (15), 2002														
Off pump	GIK	Intravenous	10	10	0	59.8	11	8	2	62.6	1	2.5 M	0.5 U	0.25 mmol
On pump	GIK	Intravenous	12	10	4	67.5	11	9	0	64.4	1	2.5 M	0.5 U	0.25 mmol
Szabo et al (32), 2001	GIK	Intravenous	10	7	10	56	10	9	10	58	2	30%	NA	NA
Wistabacka et al (33), 1992	GIK	Intravenous	16	14	NA	54.9	16	13	NA	55.9	1	0.6 g	0.12 U	0.12 mmol
Wistabacka et al (34), 1994	GIK	Intravenous	20	16	0	56.8	20	16	0	55.1	1	0.2 g	0.12 U	0.15 mmol

*Age presented in years. GI Glucose-insulin infusion; GIK Glucose-insulin-potassium infusion; NA Not available

TABLE 2
Summary of outcomes

Reference, year	Death				Atrial fibrillation			
	Control		Treatment		Control		Treatment	
	n	Events, n	n	Events, n	n	Events, n	n	Events, n
Brodin et al (21), 1993	7	0	7	2	7	NA	7	NA
Coleman et al (22), 1989	11	4	11	1	11	NA	11	NA
Hynninen et al (16), 2001	258	NA	243	NA	258	78	243	76
Kjellman et al (23), 2000	15	0	13	0	15	NA	13	NA
Koskenkari et al (24), 2006	20	0	19	0	20	6	19	5
Lazar et al (25), 1997	15	0	16	0	15	8	16	2
Lazar et al (26), 2004	69	0	72	0	69	29	72	12
Lell et al (17), 2002	20	0	21	0	20	4	21	4
Lindholm et al (27), 2000	11	0	11	0	11	NA	11	NA
Lindholm et al (28), 2001	14	2	16	0	14	NA	16	NA
Lolley et al (29), 1978	157	3	234	2	157	53	234	74
Quinn et al (18), 2006	142	2	138	3	142	66	138	77
Rao et al (30), 1998	11	0	13	0	11	NA	13	NA
Rao et al (19), 2000	27	0	29	0	27	NA	29	NA
Rao et al (20), 2002	570	13	557	12	570	NA	557	NA
Salerno et al (31), 1980	30	0	30	0	30	NA	30	NA
Smith et al (15), 2002								
Off pump	10	NA	11	NA	10	4	11	2
On pump	12	NA	11	NA	12	4	11	1
Szabo et al (32), 2001	10	0	10	0	10	NA	10	NA
Wistabacka et al (33), 1992	16	NA	16	NA	16	4	16	4
Wistabacka et al (34), 1994	20	NA	20	NA	20	2	20	4

NA Not available

event rate in this analysis was extremely low – only 24 deaths occurred in the 1303 (1.8%) patients randomly assigned to placebo compared with 20 deaths in the 1360 (1.5%) patients randomly assigned to GIK/GI. Twelve of the studies reporting mortality used GIK infusions and the other four used GI infusions; the pooled effect estimates for mortality did not differ by type of infusion (OR 0.85 [95% CI 0.43 to 1.67] for GI infusions compared with OR 0.92 [95% CI 0.49 to 1.72] for GIK infusions). Similarly, the pooled effect estimates did not differ with respect to route of administration (OR 0.87 [95% CI 0.47 to 1.62] for cardioplegic administration and OR 0.90 [95% CI 0.44 to 1.80] for intravenous administration).

Postoperative AF

Postoperative AF data were reported in 10 studies (1540 patients) (Table 2) (15-18,24-26,29,33,34), and AF was the primary end point in two studies (19,27). Details of AF outcome assessment are included in Table 3. Among patients randomly assigned to placebo, 258 of 739 patients (35%) developed postoperative AF compared with 261 of 801 (33%) in the GIK/GI group. The resulting pooled OR from the random effects model was 0.79 (95% CI 0.54 to 1.15) (Figure 3), with substantial heterogeneity across trials (Q test = 23.67, $P=0.014$).

Meta-regression and sensitivity analyses

Given the heterogeneity noted across the trials examining postoperative AF as an outcome, meta-regression was used to assess the possible influence of specific methodological and clinical characteristics of the included studies on the AF outcome (Table 4). This analysis showed that heterogeneity could not be explained by route of administration (coefficient = 0.35, $P=0.40$) or surgical procedure (on-pump versus off-pump, coefficient = 0.44, $P=0.58$). However, trial quality, as measured by the Jadad score, did explain some of the noted heterogeneity (coefficient = 0.26, $P=0.02$). A stratified analysis based on the Jadad score revealed that the studies with the lowest Jadad scores showed the greatest benefit with respect to AF reduction (OR 0.64 [95% CI 0.87 to 1.19]). As the scores increased, the benefit associated with GI/GIK infusions diminished, such that the highest quality study revealed no benefit and suggested that there was more AF among the patients who received GI/GIK (OR 1.23 [95% CI 0.84 to 1.62]).

Two sensitivity analyses were completed. Neither the exclusion of studies with no events in either arm, nor the exclusion of studies that had physiological outcomes as the primary outcome, significantly changed the pooled estimates of effect on in-hospital mortality or postoperative AF.

TABLE 3
Atrial fibrillation outcome definition and assessment

Reference	Method of rhythm assessment	Definition of atrial fibrillation
Lolley et al (29)	Telemetry	None: Only scattered atrial contractions Mild: Short periods (<1 day) of atrial fibrillation/flutter/tachycardia that resolved spontaneously or with minimal medical manipulation Severe: Longer periods (>1 day) of atrial rhythm disturbance that required multiple or high-dose anti-arrhythmic medications, cardioversion or had not resolved at time of discharge
Quinn et al (18)	ECGs performed on post op days 1 and 4	Atrial dysrhythmias requiring medical intervention or cardioversion
Lazar et al (25)	ECGs performed immediately post op and on days 1, 2, 5 and 7	Not reported
Lazar et al (26)	Telemetry and ECGs performed immediately post op and on days 1, 2, 5 and 7	Not reported
Lell et al (17)	Not reported	Not reported
Kosenkari et al (24)	Not reported	Not reported
Hynninen et al (16)	Telemetry and ECGs performed on post op days 1, 3 and 5	Any irregular rhythm with no evidence of organized atrial activity persisting longer than 30 s
Smith et al (15)	Not reported	Not reported
Wistbacka et al (33)	Continuous ECG while in intensive care unit	Not reported
Wistbacka et al (34)	Not reported	Not reported

ECG Electrocardiogram; Post op Postoperation

Figure 2) Forest plot for in-hospital mortality

GIK/GI-related adverse events

The reporting of adverse events related to the GIK/GI infusions is summarized in Table 5. Fifteen of the 20 eligible studies reported data on hypo- and/or hyperglycemia. However, the data could not be pooled because some studies reported mean glucose levels and other studies reported the frequency of clinically significant or protocol-defined glycemic abnormalities. Of the studies that reported glycemic abnormalities, six reported frequencies of hypoglycemia requiring treatment (18-21,26,34), and in five of these studies, hypoglycemia was more frequent among the GIK/GI-treated patients (18-21,34). Twelve studies reported data on hyperglycemia or mean glucose levels. Only three studies reported the frequency of hyperglycemia requiring treatment (17,18,20). Two of these studies (18,20) reported that hyperglycemia was more common among the control groups; conversely, Lell et al (17) documented more hyperglycemia in GIK/GI-treated arms. The remaining studies only reported mean glucose levels in the intervention and control arms (16,21,22,26,29,31-34). Three studies reported significant differences in mean glucose levels. Lazar et al (26) showed that GIK treatment was associated with a significantly lower mean glucose level compared with the control group.

Figure 3) Forest plot for postoperative atrial fibrillation

However, Brodin et al (21) and Lolley et al (29) found that GIK was associated with higher mean glucose levels in the postoperative period. Potassium abnormalities were less frequently reported and, due to inconsistencies in the outcome measurement, pooling of these data was not possible. Only six of the eligible 20 studies reported data on serum potassium levels (16,17,19,26,29,33). The study by Rao et al (19) was the only one to report the frequency of hyperkalemia requiring treatment, and in this study, there were five patients requiring treatment in the control arm and only one in the GI-treated arm. The remaining five studies reported mean serum potassium levels intra- and/or postoperatively, and of these, four showed no significant differences between groups with respect to potassium levels (16,17,26,33). Lolley et al (29) were the only group who demonstrated a higher intra-operative potassium level within the GI-treated group. There were no data on phlebitis in any of the studies included in the present review.

Assessment for possible publication bias

Begg's tests were conducted and funnel plots were constructed for each primary end point. These tests revealed no evidence of significant publication bias.

DISCUSSION

Our meta-analysis of 20 trials assessing the perioperative use of GIK/GI infusions in patients undergoing CABG surgery reveals no benefit with these therapies in either survival or the prevention of postoperative AF. Indeed, given the event rates in the trials conducted thus far, a definitive randomized trial to detect an effect size similar to what has been reported to date (pooled, 1.8% versus 1.5%, or a 0.3% absolute difference in mortality) would require more than 12,000 patients. The opportunity costs of such a trial must be weighed carefully given the evidence base demonstrating a lack of benefit for GIK/GI in AMI and our findings reported herein. While our analysis does suggest a trend toward benefit in the reduction of postoperative AF when GIK/GI was administered intravenously during CABG surgery, it is important to

TABLE 4
Stratified analyses and meta-regression (for the outcome of atrial fibrillation)

	OR (95% CI)	Meta-regression coefficient (P value)	Studies, n
Route of administration			
Cardioplegia	0.97 (0.71–1.31)	0.35 (0.40)	2
Intravenous	0.63 (0.32–1.26)		10
Procedure (on pump or off pump)			
On pump	0.98 (0.73–1.27)	0.44 (0.58)	10
Off pump	0.72 (0.28–2.01)		2
Jadad score			
1	0.64 (0.87–1.19)	0.26 (0.02)	6
2	0.88 (0.44–1.33)		3
3	0.94 (0.19–2.48)		1
4	1.23 (0.84–1.62)		2

note that this reflects a small absolute reduction (35% among controls versus 33% with GIK/GI infusion) in the rate of postoperative AF. Consideration must also be given to the methodological quality of the constituent trials. Our stratified analysis revealed that the benefit seen with GIK/GI was largest among the trials with the lowest quality scores, and the apparent benefit decreased as the trials increased in methodological rigour.

A recent trial by Gandhi et al (35) raised further questions regarding the value of perioperative insulin. In this study, 400 individuals about to undergo CABG surgery were randomly assigned to intensive treatment with insulin versus standard care. This trial was not eligible for inclusion in our meta-analysis because insulin was not always administered with either glucose or potassium. However, Ghandi et al documented that intensive insulin treatment was associated with a similar nonsignificant 3% reduction in new-onset AF following CABG surgery, but also raised considerable safety questions because those randomly assigned to intensive insulin treatment had a significantly higher incidence of stroke.

As one interprets the findings of our systematic review, a distinction should be made between the use of GIK/GI and tight glycemic control. The studies reviewed in the present meta-analysis examined the benefit of GIK/GI when administered as metabolic support. That is, these solutions were administered at a set concentration and rate to enhance glucose uptake and utilization within ischemic myocardium, in patients with and without diabetes. With the exception of one study (26), these solutions were not titrated to achieve a specific plasma glucose concentration. It has been postulated that studies that use GIK as a metabolic 'cocktail' – such as the Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation (CREATE) (8) – were negative because of this lack of attention to glycemic control. In the CREATE trial, the GIK group was relatively hyperglycemic compared with the control group. It has been established that hyperglycemia at the time of myocardial ischemia is associated with increased mortality in both diabetic and nondiabetic individuals (36). There is also evidence that acute hyperglycemia is associated with increased platelet and leukocyte activation (37,38). It has been speculated that in the CREATE trial, the potential benefits

TABLE 5
Frequency of adverse events

Adverse event	Studies reporting data on outcome, n (%)	Studies reporting event frequency*, n (%)	Studies reporting more events in GIK/GI, n (%)	Studies reporting more events in control, n (%)	Studies reporting no difference in events, n (%)
Hypoglycemia	6 (30)	6 (30)	5 (25)	0	1 (0.5)
Hyperglycemia	12 (60)	3 (15)	1 (0.5)	2 (1.0)	0
Hyperkalemia	6 (30)	1 (0.5)	0	1 (0.5)	0
Phlebitis	0	0	0	0	0

*Study actually reported on frequency of events requiring intervention. GI Glucose-insulin infusion; GIK Glucose-insulin-potassium infusion

of GIK were abrogated by the negative effects of the relative hyperglycemia. Conversely, trials that have examined the benefits associated with achieving glycemic control, such as the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) (6) trial, demonstrated benefit because it administered insulin and glucose to achieve strict glycemic targets. However, a recent meta-analysis of trials that examined the efficacy of intensive glycemic control in the critically ill (39) showed that this strategy was not effective in improving survival and significantly increased the risk of hypoglycemia.

Limitations

The present review and meta-analysis highlights several shortcomings in the perioperative GIK/GI literature. Many studies examining the use of GIK/GI infusions in CABG surgery are not adequately powered to examine hard clinical end points such as AF or mortality. Indeed, AF and mortality were not the primary outcomes in many of the studies analyzed in the present review. These trials were, in large part, studies that examined the physiological and metabolic consequences of the administration of GIK/GI during CABG surgery. Mortality and AF were the only clinically significant end points consistently reported. As highlighted in the review by Bothe et al (9), many studies also reported some measure of left ventricular recovery. However, these measures and the timing of left ventricular assessment differed greatly from study to study such that this end point did not lend itself well to statistical meta-analysis. Other clinically meaningful end points, such as postoperative myocardial infarction, congestive heart failure, length of stay or incidence of infection, were rarely, if ever, reported. Deficiencies in blinding and concealment of allocation also challenge the validity of these studies; while it may be argued that this is less of an issue for mortality, it is certainly germane with respect to the independent ascertainment of 'postoperative AF'. Indeed, a meta-regression analysis assessing the effect of the Jadad score revealed that trial quality may be one of the factors contributing to the heterogeneity noted among the trials included in the present meta-analysis.

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Our findings demonstrate that the use of GIK/GI does not lower the odds of in-hospital mortality. Furthermore, while there may be some 'positive signal' with respect to the effect of these infusions on postoperative AF, an analysis stratified by trial quality revealed that higher-quality trials showed no benefit at all. Safety considerations must also be taken into account with respect to the use of GIK/GI, with several trials and a recent meta-analysis raising numerous safety concerns regarding the widespread use of insulin-containing infusions in cardiac patients and in the critically ill (8,35,39). The present review also suggests an increased incidence of hypoglycemia related to the use of these interventions. Any decision to routinely use or further study GIK/GI to prevent AF must take into account the perhaps more compelling body of evidence supporting the use of amiodarone to prevent AF (40,41). Unless new evidence emerges, the use of GIK/GI infusions should be considered to be an unproven adjuvant medical treatment for patients undergoing CABG surgery and its use should be restricted to investigational protocols.

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