Cardioprotective Effects of Glucose-Insulin-Potassium Infusion in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis

Andres Hagerman, MD,* Raoul Schorer, MD,* Alessandro Putzu, MD,* Gleicy Keli-Barcelos, MD, PhD,* and Marc Licker, MD†

The infusion of glucose-insulin-potassium (GIK) has yielded conflicting results in terms of cardioprotective effects. We conducted a meta-analysis to examine the impact of perioperative GIK infusion in early outcome after cardiac surgery. Randomized controlled trials (RCTs) were eligible if they examined the efficacy of GIK infusion in adults undergoing cardiac surgery. The main study endpoint was postoperative myocardial infarction (MI) and secondary outcomes were hemodynamics, any complications and hospital resources utilization. Subgroup analyses explored the impact of the type of surgery, GIK composition and timing of administration. Odds ratio (OR) or mean difference (MD) with 95% confidence interval (CI) were calculated with a random-effects model. Fifty-three studies (n=6129) met the inclusion criteria. Perioperative GIK infusion was effective in reducing MI (k=32 OR 0.66[0.48, 0.89] P=0.0069), acute kidney injury (k=7 OR 0.57[0.4, 0.82] P=0.0023) and hospital length of stay (k=19 MD -0.89[-1.63, -0.16] days P=0.0175). Postoperatively, the GIK-treated group presented higher cardiac index (k=14 MD 0.43[0.29, 0.57] L/min P<0.0001) and lesser hyperglycemia (k=20 MD -30[-47, -13] mg/dL P=0.0005) than in the usual care group. The GIK-associated protection for MI was effective when insulin infusion rate exceeded 2 mU/kg/min and after coronary artery bypass surgery. Certainty of evidence was low given imprecision of the effect estimate, heterogeneity in outcome definition and risk of bias. Perioperative GIK infusion is associated with improved early outcome and reduced hospital resource utilization after cardiac surgery. Supporting evidence is heterogenous and further research is needed to standardize the optimal timing and composition of GIK solutions.

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Keywords: Glucose, Insulin, Potassium, Cardiac surgery, Myocardial injury, Mortality, Complications, CABG, Valve

Abbreviations: 95%CI, ninety-five percent confidence interval; AF, atrial fibrillation; AKI, acute kidney injury; AXC, aortic cross-clamping; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GIK, glucose-insulin-potassium; ICU, intensive care unit; IQR, interquartile range 25%-75%; k, model sample count; MD, mean difference; MI, myocardial infarction (postoperative); n, count (events or participants); OR, odds ratio; RCT, randomized controlled trial

*Dept. of Acute Medicine, Geneva University Hospitals, Geneva, Switzerland
†University of Geneva, Faculty of Medicine, Geneva, Switzerland

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Address reprint requests to Marc Licker, Dept. of Acute Medicine, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland. E-mail: marc-joseph.licker@hcuge.ch

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INTRODUCTION

Each year, cardiac surgery is performed worldwide in ~1.5 million individuals with ischemic, congenital and valvular disorders.1 Over time, outcomes after cardiac surgery have improved along with better preoperative patient preparation, progress in surgical and anesthetic management as well as cardioprotective protocols.2-5 Perioperative ischemia-reperfusion injuries and the release of free radicals and inflammatory mediators are incriminated in causing ventricular dysfunction that either resolves spontaneously or requires cardiovascular drug support and occasionally circulatory assistance.6-8 Importantly, cardiac complications such as postoperative myocardial infarction (MI) and heart failure are known predictors of increasing medical costs, poor survival and decreased quality of life.9,10 Among various cardioprotective protocols, the infusion of glucose-insulin-potassium (GIK) has been studied extensively. In animal models, GIK has been shown effective in reducing the extent of MI and the occurrence of ventricular arrhythmias while preserving ventricular function.11 These cardioprotective effects are mediated by pleiotropic glucose-dependent and -independent mechanisms of insulin involving preferential high-energy substrate production from glucose metabolism as well as upregulation of the reperfusion injury salvage kinase pathway.12 Since its introduction in 1962,13 GIK has failed to show conclusive clinical cardioprotective effects following percutaneous coronary intervention whereas favorable results have been reported after cardiac surgery.12,14 In previous systematic reviews,15-18 the interactions between GIK therapy and confounding factors (e.g., diabetes mellitus, type of surgery, glycaemia or timing and composition of GIK infusion) have not been examined. Hence, our meta-analysis addresses these issues and provides an up-to-date review of the impact of GIK on early postoperative outcome.

SEARCH STRATEGY

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the Cochrane methodology as well as in agreement with a preregistered protocol (PROSPERO CRD 42022120746).19,20 Ethical review board approval was waived due to the absence of new data collection. Minor deviations from the protocol are reported in a Supplemental file (S1). Three investigators (R.S., A.H. and A.P.) independently searched MEDLINE, EMBASE and the Cochrane Central Register of Clinical Trials from inception to September 19th, 2022. The search strategy aimed to select RCTs with the following terms: glucose-insulin-potassium, GIK, cardiac surgery, cardiopulmonary bypass, CPB, coronary artery bypass surgery, CABG, valve (S2). Additional articles were identified by manual review of the references of included studies.

STUDY SELECTION

Search results were examined at the abstract level and the full-text version was retrieved if relevant. Eligibility criteria were defined following the PICOS approach: (P) adult patients scheduled for elective or emergent cardiac surgery with or without cardio-pulmonary bypass (CPB); (I) use of GIK in the perioperative period; (C) usual care or placebo; (O) MI and (S) RCT. Exclusion criteria were inclusion of pediatric cases, studies with overlapping population or irrelevant study endpoints. Four authors (A.H, R.S, A.P., and G.K-B.) independently made the final assessment for inclusion into the analysis and disagreements were resolved through consensus or by third party adjudication (M.L.). If documents did not contain MI data or were unavailable as full-texts, the corresponding authors were contacted for further information. No language restriction was imposed.

DATA ABSTRACTION

The relevant information was extracted from each selected study by a single author (R.S.) and checked by 2 others (A.P. and G.K-B.). Disagreements were resolved by consensus or by third party adjudication (M.L.). Sources of clinical heterogeneity were also extracted according to the same process (ie, study design, clinical setting, inclusion/exclusion criteria. Study characteristics were collected regarding demographic data, the type of surgery, the duration of surgery as well as GIK composition (dose of insulin and glucose) and timing of administration (before, during or after CPB). The primary outcome was postoperative MI and secondary outcomes were in-hospital mortality, the postoperative occurrence of stroke, acute kidney injury (AKI), atrial fibrillation (AF), ventricular fibrillation (VF), any infections, postoperative glycaemia, cardiac index, the need for pharmacological or mechanical circulatory support as well as the duration of mechanical ventilation, intensive care unit (ICU) and hospital stay.

QUALITY ASSESSMENT

Two authors (R.S. and A.P.) independently assessed the internal validity of included trials according to the Cochrane Collaboration methodology (risk of bias 1 tool), namely: risk of bias associated to the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting and other biases.20 Studies were rated as low, unclear, or high risk of bias. Included trials were rated as low risk of bias when 5 or more evaluation domains were judged as low risk of bias.21 Studies that did not detail allocation concealment, blinding of participants and personnel or random sequence generation were graded as unclear.

The certainty of evidence was assessed using GRADE: the grading of recommendations assessment, development, and evaluation framework.22

STATISTICAL ANALYSIS

Odds ratio (OR) or mean difference (MD) with 95% confidence intervals (95%CI) were reported. Random effects models

MATERIAL AND METHODS

Search Strategy

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were used in all cases. Between-study variance for binary analyses was assessed using the Paule-Mandel estimator since the DerSimonian-Laird estimator is known to be unreliable with sparse data.23 Continuous models used the DerSimonian-Laird estimator. Prediction intervals were computed for all models. Heterogeneity was assessed using Cochrane’s Q and the I² value. All models used a continuity correction of 0.5 at each step, except for Peto models. The analysis was performed using R 4.0.4 with package “meta”.24,25 Analysis of the primary outcome was stratified by GIK timing, composition, insulin infusion rate (cutoff 2 mU/I/kg/min),11,26,27 presence of diabetes mellitus and type of surgical procedure (coronary artery bypass, valve or combined surgery). Sensitivity assessments were performed using both fixed and random effects models.

Figure 1. PRISMA workflow chart.
for continuous meta-analyses, while Peto models were used for binary meta-analyses. Small-study effect for the primary outcome was investigated by the trim-and-fill method.\textsuperscript{25}

**RESULTS**

After removing 3659 duplicates and adding 7 studies through manual search 2,647 citations were identified, of which 2,576 abstracts and 11 full-text articles were considered ineligible (S3).\textsuperscript{26} A total of 53 RCTs involving 6129 participants were included in the meta-analysis (Figure 1). Additional information was obtained from corresponding authors regarding 8 RCTs.\textsuperscript{30-40}

As reported in Table 1, studies were published between 1977 and 2021, were conducted in 21 countries and included CABG surgery: (39 RCTs),\textsuperscript{41-81} valve surgery (4 RCTs)\textsuperscript{82-85} and combined procedures (10 RCTs).\textsuperscript{39-42,86-91} The median of the mean times of CPB and aortic cross-clamping (AXC) were respectively 99 min (ranging from 47 to 167 min) and 59 min (ranging from 38 to 101 minutes). Patients with diabetes mellitus were enrolled in 31 RCTs. At the evaluation of risk of bias, 8 studies were rated at low risk,\textsuperscript{31,42,57,58,68,86-89} 5 with unclear risk\textsuperscript{45,62,66,69,70} and 40 trials at high risk of bias.\textsuperscript{30,40,43,44,46-56,59,61,63-65,67,71-87,91} The risks of bias assessment are summarized in Figure 2 and detailed in a supplementary file (S4).

The proportion of participants with a MI was 5.3% and 8.2% in the GIK and control groups, respectively. As illustrated in Figure 3, the GIK infusion was associated with a decrease in MI (k=32 OR 0.66[0.48, 0.89] \(P=0.0069\) \(I^2=0\%\)).\textsuperscript{41,42,45,47,49,51,54-58,61,63,65,67-71,73-81} The funnel plot for the primary analysis did not reveal a significant publication bias. A sensitivity cumulative meta-analysis with Peto OR yielded unchanged results (k=32 OR 0.58[0.42, 0.79] \(P=0.0007\) \(I^2=11\%\)). Adjustment for small-study effect left results unchanged (k=32 OR 0.66[0.48, 0.89] \(P=0.0069\) \(I^2=0\%\)) and subgroup analysis of low-risk of bias RCTs also supported the efficacy of GIK treatment (k=7 OR 0.67[0.45, 0.98] \(P=0.0396\) \(I^2=14\%\)).\textsuperscript{41,42,57,58,68,80,90}

A sub-analysis by stratifying all RCTs into 2 time periods ascertained the effectiveness of GIK to reduce the incidence of MI in the early period (from 1977 to 2005; k=19 OR 0.45 [0.22, 0.86]) and in the last period (from 2006 to 2021; k=13 OR 0.67 [0.49, 0.91]).

The GIK infusion was associated with fewer MIs after CABG (k=24 OR 0.47[0.32, 0.68]),\textsuperscript{5,47,49,51,54-58,61,63,65,67-71,73-81} with no difference between on-pump\textsuperscript{41,42,47,49,51,54-56,58,61,63,65,67-71,73-81} and off-pump subgroups (Q=0.23 \(P=0.6343\)).\textsuperscript{73,75} After combined surgery, there was a trend to support the cardioprotective efficacy of GIK (k=5 OR 0.84[0.48, 1.17]),\textsuperscript{31,42,88,80,91} whereas a single RCT including valve surgery, - although with favorable results-, did not allow further analysis. Importantly, stratification on the rate of insulin infusion indicated that an insulin infusion rate higher than 2 mU/kg/min was protective against MI (k=17 OR 0.42[0.28, 0.62]);\textsuperscript{11,47,49,51,54-58,61,63,65,67-71,73-81} whereas an insulin infusion rate lower than 2 mU/kg/min failed to provide beneficial effects (k=12 OR 0.79[0.48, 1.3]);\textsuperscript{42,45,56,58,61,65,68-71,78,83,90} (Q=3.9 \(P=0.0482\)). The occurrence of postoperative MI was decreased regardless of the timing of GIK infusion either started before CPB (k=22 OR 0.69[0.47, 0.9])\textsuperscript{41,42,45,49,51,54-58,61,63,65,68-71,75,78,81,83,90} or during/after CPB (k=10 OR 0.38 [0.17, 0.85]);\textsuperscript{77,76,77,79,88,91} \(Q=1.43\) \(P=0.2319\). No subgroup effects were found in trials including only non-diabetic patients (k=17 OR 0.55[0.36, 0.84]),\textsuperscript{49,54,56,57,61,63,67,68,70,73,75,80,88,90,91} only diabetic patients (k=2 OR 0.35[0.05, 2.64])\textsuperscript{38,65} or a mixed population (k=13 OR 0.55[0.3, 1.03]);\textsuperscript{41,42,45,47,51,55,69,71,76,77,79,81,83} (non-diabetics vs diabetics: Q=0.19 \(P=0.9113\); diabetes vs mixed: Q=0.19 \(P=0.9113\)). A summary of the heterogeneity of GIK composition is reported in a supplemental file (S5).

Meta-analyses of secondary endpoints are summarized in Table 2. Perioperative GIK infusion was associated with a reduction in postoperative AF (19.8% vs 24.8% in control groups) and in AKI (3.3% vs 5.7% in control groups), along with higher CI (3.16 vs 2.77 L/min/m² in control groups), faster ventilatory weaning as well as shorter ICU and hospital length of stay. There was no evidence of an association between GIK and in-hospital mortality, cardiovascular drug support, ventricular arrhythmias, infection or stroke.

Postoperative glycemia was higher in control than in GIK-treated patients (mean[SD] 185[49] mg/dL vs 155[42] mg/dL, respectively; MD[95%CI] -30[-46.63 to -13.06] mg/dL, \(P=0.0004\)).\textsuperscript{44,45,50,52,59,70,78,90,91} In both diabetic and non-diabetic subsets, GIK treatment was associated with lower postoperative glycemia: MD[95%CI] -73.3 [-87 to -59.5] mg/dL, \(I^2=75\%\); \(P=0.0396\)).\textsuperscript{41,42,57,58,60,64,65,70,73,77,79,82,90,91} Among diabetics, GIK had a higher impact on lowering postoperative glycemia compared to other populations (diabetics vs non-diabetics: Q=11.04 \(P=0.004\); non-diabetics vs mixed: Q=0.78 \(P=0.3775\)).

A summary of the GRADE assessment is reported in supplement S6. The certainty of evidence was graded as low for MI and secondary outcomes due to imprecision of the effect estimate and indirectness related to heterogeneity in outcome definition or GIK regimen.

A video summarizes the key features of this systematic review and is available on the journal website.

**DISCUSSION**

The previous systematic reviews had focused more on CABG surgery and had examined a restricted time frame\textsuperscript{15-18} whereas this updated meta-analysis of 53 RCTs (N=6129) included the last well-powered trials and covers the full spectrum of cardiac surgical procedures over more than 4 decades (Supplemental file S7).

In this meta-analysis, we found that, compared with usual care, perioperative GIK infusion was associated with fewer MI, AF and AKI, increased cardiac index, better postoperative glycemic control as well as earlier weaning from the ventilator, shorter length of stay in ICU and faster discharge from the
| Authors               | Country       | Age [y]         | M/F       | Diabetes        | LVEF [%]   | AXC [min] | Surgery | GIK Formula | GIK Timing |
|-----------------------|---------------|-----------------|-----------|-----------------|------------|-----------|---------|-------------|------------|
| Ahmad et al. 2017     | Pakistan      | 55(8)/54(10)    | (69/11)/(72/8) | No              | 53(9)/52(10) | 64(17)/62(18) | CABGS   | 0.5 mU/kg/min insulin, 5% dextrose, K 70 mEq/L | preop      |
| Albacker et al. 2007  | Canada        | 59(3)/65(2)     | (20/2)/(16/6) | Mixed           | 49(3)/47(3) | 65(5)/71(5) | CABGS   | 5 mU/kg/min insulin, 20% dextrose, K NA | preop, cpb, postop |
| Andel et al. 1990     | Czechoslovakia| 56(NA)/51(NA)   | NA        | No              | NA         | 57(NA)/54 (NA) | CABGS   | 1.5 mU/kg/min rapid insulin, 40% glucose, K 60 mEq/L | preop      |
| Barcellos et al. 2007 | Brazil        | 60(9)/59(6)     | (7/5)/(8/4) | Yes             | 60(14)/54(16) | 89(29)/87(22) | CABGS   | 1.2 mU/kg/min regular insulin, 5% glucose, K 80 mEq/L | preop, postop |
| Besogul et al. 1999   | Turkey        | 38(NA)/35(NA)   | (4/11)/(3/12) | Mixed           | 55(NA)/52 (NA) | 76(NA)/73 (NA) | Valve   | 0.2 mU/kg/min insulin, 20% glucose, K 45 mEq/L | preop      |
| Boldt et al. 1993     | Germany       | 62(7)/63(7)     | NA        | No              | 63(9)/64(7) | 45(8)/44(11) | CABGS   | 35.7 mU/kg/min regular insulin, glucose, K 70 mEq/L | preop      |
| Boldt et al. 1993     | Germany       | 61(6)/63(7)     | NA        | No              | 66(6)/64(7) | 48(8)/44(11) | CABGS   | 17.9 mU/kg/min regular insulin, glucose, K 70 mEq/L | preop      |
| Brodin et al. 1993    | Sweden        | 60(NA)/57(NA)   | (7/0)/(4/3) | Mixed           | NA         | 81(40)/55(21) | CABGS   | 22.5 mU/kg/min insulin, 30% glucose, K 2000 mEq/L | preop      |
| Bruemmer et al. 2002  | UK            | 64(10)/66(10)   | (19/0)/(15/5) | No              | NA         | 51(14)/45(12) | CABGS   | 2.5 mU/kg/min insulin, 50% glucose, K 160 mEq/L | preop, cpb, postop |
| Celkan et al. 2006    | Turkey        | 58(11)/56(11)   | NA        | No              | NA         | 70(15)/64(22) | CABGS   | 3.3 mU/kg/min insulin, 30% dextrose, K 160 mEq/L | preop, postop |
| Duncan et al. 2015    | USA           | 70(9)/70(11)    | (36/13)/(31/17) | mixed           | 59(15)/64(9) | NA         | Combined | 5 mU/kg/min insulin, 20% dextrose, K 40 mEq/L, PO 120 mEq/L | preop, cpb, postop |
| Duncan et al. 2018    | USA           | 66(11)/66(11)   | (520/189)/(546/184) | mixed           | NA         | 80(33)/81(31) | Combined | 5 mU/kg/min insulin, 20% dextrose, K 40 mEq/L | NA         |
| Ellenberger et al. 2018 | Switzerland | 71(11)/72(11)   | (73/80)/(37/32) | mixed           | 43(10)/47(9) | 79(36)/76(33) | Combined | 4.8 mU/kg/min rapid insulin, 40% glucose, K 10 mEq/L | preop      |
| Foroughi et al. 2012  | Iran          | 61(1)/59(1)     | (21/15)/(17/13) | No              | NA         | 62(19)/65(14) | CABGS   | 1.3 mU/kg/min regular insulin, 10% dextrose, K 80 mEq/L | preop, cpb |
| Girard et al. 1992    | France        | 58(9)/56(10)    | (27/13)/(29/11) | mixed           | NA         | 48(16)/45(16) | CABGS   | 16.7 mU/kg/min rapid insulin, 33% glucose, K 70 mEq/L | preop      |
| Haider et al. 1984    | Austria       | 58(NA)/52(NA)   | NA        | mixed           | NA         | 35(NA)/39(NA) | Valve   | 16.7 mU/kg/min rapid insulin, 33% glucose, K 70 mEq/L | preop      |

(continued on next page)
| Authors            | Country  | Age [y] | M/F       | Diabetes mellitus | LVEF [%] | AXC [min] | Surgery | GIK Formula | GIK Timing |
|--------------------|----------|---------|-----------|-------------------|----------|-----------|---------|-------------|------------|
| Hallhagen et al. 1992 | Sweden   | 57(3)/56(4) | NA        | No                | NA       | 61(6)/66(8) | CABG    | 22.7 mUI/kg/min rapid insulin, 40% glucose, K 100 mEq/L | postop     |
| Howell et al. 2011  | UK       | 70(10)/70(7) | (67/43)/ (77/30) | No | mixed  | NA | 44(NA)/39(NA) | Combined | NA | postop, preop |
| Jovic et al. 2009   | Serbia   | NA      | NA        | mixed             | NA       | 47(NA)/39(NA) | CABG    | 0.3 mUI/kg/min insulin, 10% glucose, K 80 mEq/L | preop, postop |
| Kjellman et al. 2000 | Sweden   | 64(3)/63(2) | (14/0)/(14/0) | No                | 47(4)/ 42(6) | 64(3)/64(3) | CABG | 66.7 mUI/kg/min insulin, 30% glucose, K 40 mEq/L | cpb        |
| Koskenkari et al. 2006 | Finland | 67(8)/67(8) | (13/6)/(15/5) | No                | NA       | 93(22)/84(13) | CABG | 16.7 mUI/kg/min rapid insulin, 30% glucose, K 20 mEq/L | cpb, postop |
| Laiq et al. 2015    | Pakistan | NA     | NA        | Yes               | NA       | 48(2)/45(1) | CABG | 1.5 mUI/kg/min regular insulin, 5% dextrose, K 80 mEq/L | preop, cpb, postop |
| Lazar et al. 1997   | USA      | 60(NA)/65(NA) | (11/4)/(10/5) | No                | 44(3)/41(2) | CABG | regular insulin, 30% dextrose, K 80 mEq/L | preop, postop |
| Lazar et al. 2000   | USA      | 65(9)/65(11) | (10/10)/(11/9) | Yes               | 41(10)/ 40(10) | 47(12)/42(11) | CABG | 1.1 mUI/kg/min regular insulin, 5% dextrose, K 80 mEq/L | preop, postop |
| Lazar et al. 2004   | USA      | 64(1)/64(2) | (42/46)/(30/23) | Yes               | 42(1)/ 41(2) | 48(2)/44(1) | CABG | 1.1 mUI/kg/min regular insulin, 5% dextrose, K 80 mEq/L | preop, postop |
| Leli et al. 2002    | USA      | 62(9)/57(10) | (11/10)/(13/7) | mixed             | 50(12)/ 41(16) | 34(13)/31(14) | CABG | regular insulin, 25% glucose, K 80 mEq/L | preop, cpb, postop |
| Lindholm et al. 2001 | Sweden   | 72(8)/74(7) | (8/8)/(5/9) | mixed             | 57(12)/ 57(15) | 84(32)/114(45) | Combined | 285.7 mUI/kg/min rapid insulin, 30% glucose, no K | postop     |
| Lolley et al. 1978  | USA      | 56(NA)/54(NA) | (84/30)/(126/31) | mixed             | NA       | 48(16)/44(15) | CABG | 5.7 mUI/kg/min regular insulin, 5% dextrose, K 22.5 mEq/L | cpb        |
| Lolley et al. 1985  | USA      | 56(1)/54(1) | (40/13)/(40/9) | mixed             | 62(2)/ 64(2) | 47(2)/42(2) | CABG | 4.8 mUI/kg/min regular insulin, 5% glucose, K 20 mEq/L | cpb        |
| Nilsson et al. 1987 | Sweden   | 52(NA)/64(NA) | (5/1)/(5/3)  | No                | NA       | 68(10)/78(7) | Combined | 2.5 mUI/kg/min rapid insulin, 40% glucose, K 100 mEq/L, PO 120 mEq/L | postop     |
| Nilsson et al. 1987 | Sweden   | 56(NA)/64(NA) | (4/2)/(5/3)  | No                | NA       | 87(7)/78(7) | Combined | 5 mUI/kg/min rapid insulin, 40% glucose, K 100 mEq/L, PO 120 mEq/L | postop     |
| Authors               | Country     | Age [y] | M/F | Diabetes mellitus | LVEF [%] | AXC [min] | Surgery       | GIK Formula | GIK Timing |
|----------------------|-------------|---------|-----|-------------------|----------|-----------|---------------|-------------|------------|
| Nilsson et al. 1987  | Sweden      | 60(NA)/64(NA) | (8/0)/(5/3) | No | NA | 80(7)/78(7) | Combined | 16.7 mU/kg/min rapid insulin, 40% glucose, K 100 mEq/L, PO 120 mEq/L | postop |
| Oldfield et al. 1986 | South Africa | 38(27)/41(19) | (6/14)/(8/15) | mixed | NA | 67(8)/63(6) | Valve | 0.2 mU/kg/min insulin, 20% glucose, K 45 mEq/L | preop |
| Quinn et al. 2006    | UK          | 64(9)/64(9) | NA | No | NA | 49(16)/48(18) | CABGS | 2.1 mU/kg/min rapid insulin, 40% dextrose, K 80 mEq/L | preop, cpb, postop |
| Ranasinghe et al. 2006 | UK       | 64(9)/64(9) | (137/20)/(132/28) | No | NA | 49(15)/47(18) | CABGS | 0.9 mU/kg/min rapid insulin, 40% dextrose, K 80 mEq/L | preop, cpb, postop |
| Ray et al. 1977      | USA         | NA      | NA | mixed | NA | NA | CABGS | 700 mU/kg/min insulin, 10% glucose, K 120 mEq/L | cpb |
| Roh et al. 2015      | Korea       | 61(11)/64(11) | (27/26)/(24/29) | mixed | 62(10)/62(11) | 96(41)/95(35) | Combined | 1.7 mU/kg/min insulin, 30% glucose, K 80 mEq/L | preop |
| Ruijrojindakul et al. 2014 | Thailand | 52(19)/55(15) | (55/44)/(57/43) | mixed | NA | 62(24)/60(23) | Combined | 5 mU/kg/min insulin, 25% glucose, K 400 mEq/L | preop, cpb, postop |
| Salerno et al. 1980  | Canada      | NA      | NA | No | NA | 48(NA)/45(NA) | CABGS | 0.3 mU/kg/min insulin, 10% dextrose, K 40 mEq/L | preop |
| Sato et al. 2011     | Canada      | 64(8)/65(11) | (14/6)/(15/5) | mixed | 54(8)/55(8) | 84(29)/82(30) | CABGS | 5 mU/kg/min insulin, 20% glucose, K NA, PO 120 mEq/L | NA |
| Seied et al. 2010    | Iran        | 58(10)/61(8) | (9/16)/(14/6) | Yes | 51(8)/50(12) | 60(15)/61(17) | CABGS | 1.1 mU/kg/min regular insulin, 5% dextrose, K 80 mEq/L | preop, cpb, postop |
| Shim et al. 2006     | Korea       | 64(9)/59(10) | (12/31)/(11/28) | Mixed | 59(13)/62(12) | NA | CABGS | 3.1 mU/kg/min regular insulin, 50% dextrose, K 160 mEq/L | preop, cpb, postop |
| Shim et al. 2013     | Korea       | 63(NA)/55(NA) | (20/13)/(23/10) | Mixed | 35(11)/39(9) | NA | CABGSOff-pump | 3.3 mU/kg/min regular insulin, 50% glucose, K 160 mEq/L | preop, cpb, postop |
| Smith et al. 2002    | UK          | 64(8)/68(8) | (9/2)/(10/2) | Mixed | NA | 45(14)/40(16) | CABGSOff-pump | 0.8 mU/kg/min rapid insulin, 50% dextrose, K 250 mEq/L | preop, cpb, postop |
| Straus et al. 2013   | Bosnia      | 62(8)/61(7) | (35/15)/(29/21) | Yes | Mixed | 50(NA)/45(NA) | 42(NA)/39(NA) | CABGS | 251.7 mU/kg/min rapid insulin, 40% glucose, K 100 mEq/L, PO 120 mEq/L | cpb |
| Svensson et al. 1989 | Sweden      | 61(4)/59(2) | NA | Mixed | 50(7)/59(4) | 65(7)/57(8) | CABGS | NA | cpb |

(continued on next page)
| Authors            | Country     | Age [y]       | M/F         | Diabetes mellitus | LVEF [%] | AXC [min] | Surgery     | GIK Formula | GIK Timing |          |
|--------------------|-------------|---------------|-------------|-------------------|----------|-----------|-------------|-------------|------------|-----------|
| Szabo et al. 2001  | Sweden      | 58(6)/56(9)   | (9/1)/(7/3) | Yes               | NA       | 45(22)/46(16) | CABGS       | 16.7 mUI/kg/min rapid insulin, 30% glucose, no K, PO 160 mEq/L | postop     |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Tsang et al. 2007  | USA         | 64(9)/67(7)   | (12/2)/(15/2) | Mixed             | 61(11)/58(14) | 43(8)/42(9) | CABGS       | 0.8 mUI/kg/min regular insulin, 30% dextrose, K 80 mEq/L | preop, postop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Tunerir et al. 1998| Turkey      | 38(NA)/35(NA) | (4/11)/(3/12) | Mixed            | 55(NA)/52(NA) | 76(NA)/73(NA) | Valve | 0.2 mUI/kg/min insulin, 20% glucose, K 45 mEq/L | preop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Turkoz et al. 2000 | Turkey      | 64(2)/60(2)   | (10/5)/(13/3) | No                | 40(3)/41(1) | 63(5)/63(6) | CABGS       | 2.3 mUI/kg/min insulin, 30% dextrose, K 160 mEq/L | preop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Visser et al. 2005 | Netherlands | 63(NA)/62(NA) | (8/2)/(10/1)  | No                | NA       | 57(34)/57(17) | CABGS       | 1.7 mUI/kg/min rapid insulin, 30% glucose, K 80 mEq/L, PO 240 mEq/L | preop, cpb, postop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Wallin et al. 2003 | Sweden      | 66(9)/63(9)   | (8/1)/(7/2)  | No                | NA       | 87(24)/87(24) | Combined | 9.2 mUI/kg/min insulin, glucose, K 140 mEq/L | preop, cpb, postop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Wistbacka et al. 1992 | Finland  | 56(7)/55(8)   | (13/3)/(14/2) | No             | 56(5)/59(7) | 104(31)/93(27) | CABGS | 2 mUI/kg/min rapid insulin, 17% glucose, K 16.8 mEq/L | preop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Wistbacka et al. 1994 | Finland  | 55(10)/57(9)  | (16/4)/(16/4) | No             | 58(13)/57(11) | 100(36)/102(23) | CABGS | 1.2 mUI/kg/min rapid insulin, 20% glucose, K 147 mEq/L, PO 94 mEq/L | preop, cpb, postop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Zhao et al. 2020   | China       | 42(14)/42(14) | (199/266)/(206/25) | No | NA       | 51(30)/52(31) | Combined + Congenital | 1.1 mUI/kg/min regular insulin, 20% glucose, K 80 mEq/L | preop, cpb, postop |
|                    |             |               |             |                   |          |           |             |             |            |           |
| Zuurbier et al. 2008 | Netherlands | 63(NA)/64(NA) | (18/5)/(18/3) | No | NA       | 62(29)/56(17) | CABGS | 1.7 mUI/kg/min rapid insulin, 30% glucose, K 80 mEq/L, PO 240 mEq/L | preop, cpb, postop |

AXC, aortic cross clamping; CABGS, coronary artery bypass graft surgery; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; M/F, male/female
hospital. GIK-induced cardioprotection effects was effective in both diabetic and non-diabetic patients, regardless of the perioperative timing of administration and at insulin dosages higher than 2 mU/kg/min.

Over the 4 decades spanned by this review, perioperative care and the study population risk profile have considerably evolved. Indeed, the infusion of blood or buffered crystalloid solutions directly into the aortic root or selectively into coronary arteries to minimize myocardial injuries became standard since the late 90s. Furthermore, myocardial preconditioning with inhaled anesthetics has been introduced that could also contribute to improve clinical outcomes. Meanwhile, the recent trials have included older participants and new criteria have been adopted to diagnose MI after cardiac surgery. The stable proportion of MI over the review period likely resulted from the (opposite) effects of improved cardioprotective strategies and higher risk profiles of cardiac surgical patients with more sensitive criteria for MI. Altogether, despite improvements in surgical techniques and the higher risk profile of surgical patients, we found similar GIK-induced cardioprotective effects in the early and most recent periods (1977-2005 vs 2006-2021).

Interestingly, we found that perioperative reduction in myocardial injuries was associated with insulin given at rates higher than 2 mU/kg/min. In the context of fasting and surgical stress, this insulin dose regimen causes a shift in ATP production from free fatty acid to glucose oxidation and the increased myocardial ATP store has been associated with improved left ventricular function after experimental ischemia-reperfusion and in patients with heart failure. In this meta-analysis, the usual care group more frequently exhibited hyperglycemia that has been incriminated in blunting anesthetic preconditioning and increasing cardiomyocyte apoptosis. Likewise, the presence of hyperglycemia after major trauma or myocardial infarct has been associated with a higher risk of cardiovascular complications and mortality. In line with our findings, the negative results reported in GIK trials involving patients with acute coronary syndrome could be attributed to insufficient insulin dosages (1 to 1.25 mU/kg/min) and the consequent prolonged period of hyperglycemia.

In most RCTs (39 out of 53), GIK infusion was started before CPB, continued over a median duration of 6 hours and was associated with higher cardiac index (+15%). In contrast with the “oxygen-wasting” effects of adrenergic inotropes owing to fatty acid oxidation, GIK infusion has been shown to provide more efficient cardiac mechanical work by promoting the “oxygen-sparing” pathway of glucose oxidation. In cardiac surgical patients, better preservation of the left ventricular function has been reported following CPB in GIK-treated patients compared with controls. Recent case reports confirm that GIK administration may enhance cardioprotection in non-cardiac surgery and facilitate weaning from mechanical circulatory support in patients with acute cardiogenic shock. In this meta-analysis, faster extubation time, lesser AKI as well as shorter ICU and hospital stay could all be attributed to the improved hemodynamic conditions and in turn, enhanced oxygen transport to the respiratory muscles and the kidneys in GIK treated patients.

Limitations

Our findings are to be interpreted cautiously due to several limitations. Firstly, definitions and reporting of the primary outcome (MI) varied over time and across the different trials with MI criteria being specifically validated in the context of CABG (type V MI) but not for other cardiac procedures according to the Fourth Universal Definition of Myocardial Infarction. However, the various treatments and diagnostic criteria for MI (also AKI) reported in this meta-analysis were equally distributed in the 2 treatment arms and therefore equally influenced the occurrence of MI and other adverse events. Secondly, our study population mainly included middle-aged patients with moderately reduced or preserved left ventricular function undergoing on-pump elective cardiac procedures with AXC < 120 min. Ischemic and anesthetic conditioning are less effective in the senescent heart and in patients treated with beta-blockers. Our data did not allow to discriminate the effects of GIK among elderly patients, those undergoing

Figure 2. risk of bias per-criterion summary.
Figure 3. Forest plot and funnel plot for the main outcome (postoperative myocardial infarction).
complex surgical procedures, as well as the interactions with cardiovascular treatments. Nevertheless, blunting of the postoperative hyperglycemic in GIK-treated patients could contribute to mitigate the perioperative myocardial injuries in addition to the direct insulin mediated anti-apoptotic and metabolic effects on the cardiomyocytes. Thirdly, since all RCTs investigated early outcomes, we ignore whether short-term functional and clinical improvements could translate into better quality of life and prolonged survival. Fourthly, many RCTs included small populations while some large, recent RCTs held little weight in the analysis. Moreover, the analysis of the impact of diabetes mellitus, combined surgery or valve replacement, emergency procedures and off-pump CABG yielded small subgroups of trials, precluding clinical interpretation. Finally, a majority of RCTs were graded as unclear or high risk of bias and the GRADE certainty of evidence was fairly low, indicating a potential for modification or even reversal of effect estimates in future studies.

**CONCLUSION**

Perioperative GIK infusion is associated with improved early outcome and reduced hospital resource utilization after cardiac surgery.

| Table 2. Meta-Analyses of Secondary Endpoints |
|-----------------------------------------------|
| N RCTs (N participants) | Controls | GIK | TE (95%CI) | I² (P-value) |
|--------------------------|----------|-----|-----------|-------------|
| **In-hospital mortality** | 38 (4,599) | 58/2,338 | 36/2,261 | OR=0.71 (0.49-1.04) | 0% (0.08) |
| **AKI** | 7 (2,939) | 85/1,481 | 49/1,458 | OR=0.57 (0.4-0.82) | 0% (0.002) |
| **Atrial fibrillation** | 27 (4,664) | 587/2,366 | 455/2,298 | OR=0.68 (0.5-0.92) | 52% (0.013) |
| **Cardiac index [L/min]** | 14 (707) | 2.6(0.9) | 3.1(0.9) | MD=0.43 (0.29-0.57) | 79% (<0.001) |
| **Glycemia [mg]** | 20 (2,024) | 182.4(66.5) | 152.5(46.8) | MD=29.84 (-46.63 to -13.06) | 99% (<0.001) |
| **Hospital LOS [d]** | 19 (1,852) | 9(3.3) | 8.1(3.2) | MD=-0.89 (-1.63 to -0.16) | 93% (0.018) |
| **ICU LOS [h]** | 20 (4,023) | 29.8(24.3) | 24.6(24.4) | MD=-5.17 (-7.35 to -2.99) | 99% (<0.001) |
| **Infection** | 11 (3,201) | 139/1,613 | 112/1,588 | OR=0.78 (0.5-1.23) | 41% (0.283) |
| **Mechanical ventilation** | 16 (2,247) | 13.6(6.3) | 11.9(4.8) | MD=-1.68 (-2.87 to -0.5) | 97% (0.005) |
| **Stroke** | 8 (1,743) | 18/875 | 17/868 | OR=0.96 (0.48-1.92) | 0% (0.916) |
| **Ventricular Fibrillation** | 11 (1,758) | 210/903 | 159/855 | OR=0.87 (0.56-1.35) | 0% (0.527) |

RCT, randomized control trial; N, participants count; GIK, insulin-glucose-potassium; TE, treatment effect (odds ratio [OR] or mean difference [MD]); 95%CI, 95% confidence interval; AKI, acute kidney injury; AF, atrial fibrillation; CI, cardiac index; LOS, length of stay; ICU, intensive care unit; MVT, mechanical ventilation time; VF, ventricular fibrillation.
surgery (Figure 4, Video abstract). Current supporting evidence is heterogeneous and further research should examine the dose-response and timing of GIK regimens to protect the heart also in higher risk patients such as those with failing heart or ongoing myocardial ischemia.

SUPPLEMENTARY MATERIAL

Scanning this QR code will take you to the article title page to access supplementary material.

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