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Safety and efficacy of glucose–insulin–potassium treatment in coronary artery bypass graft surgery and percutaneous coronary intervention

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Summary

The purpose of this meta-analysis was to evaluate protective effects of glucose–insulin–potassium (GIK) on outcomes after coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). We systematically searched Medline/Pubmed, Elsevier, Embase, Web of Knowledge and Google Scholar. A total of 1206 studies were retrieved during the extensive literature search of all major databases; however, 38 trials reporting the end-point of interest were selected. We performed a pooled analysis of outcomes following PCI: incidence of cardiac arrest [odds ratio (OR) of 0.91; 95% confidence interval (CI): 0.76–1.09; $P = 0.3$], stroke (OR of 1.71; 95% CI: 0.37–1.37; $P = 0.3$), cardiogenic shock (OR of 1.02; 95% CI: 0.92–1.14; $P = 0.6$), reinfarction (OR of 0.95; 95% CI: 0.81–1.14; $P = 0.5$) and mortality (OR of 1.04; 95% CI: 0.96–1.13; $P = 0.3$); and following CABG: incidence of atrial fibrillation (OR of 0.86; 95% CI: 0.70–1.05; $P = 0.1$), incidence of ventricular fibrillation (OR of 0.83; 95% CI: 0.62–1.13; $P = 0.2$), reinfarction (OR of 0.97; 95% CI: 0.74–1.27; $P = 0.8$), infection (OR of 1.04; 95% CI: 0.67–1.62; $P = 0.8$), length of intensive care unit stay (LIS) [standard mean differences (SMD) of −0.27; 95% CI: −0.40 to −0.14; $P = 0.000$], length of hospital stay (LHS) (SMD of −0.035; 95% CI: −0.12 to −0.05; $P = 0.4$) and mortality (OR of 0.72; 95% CI: 0.41–1.26; $P = 0.2$). Our results showed that GIK did not have considerable cardioprotective effects. However, patients undergoing CABG seem to be better responders to GIK therapy compared with patients undergoing PCI. Furthermore, in contrast to CABG, GIK therapy in patients undergoing PCI might be associated with more complications rather than protective effects.

Keywords: Glucose–insulin–potassium • Coronary artery bypass graft • Percutaneous coronary intervention • Myocardial infarction • Clinical outcome • Atrial fibrillation

INTRODUCTION

Ischaemic heart disease is usually caused by thrombotic occlusion of major epicardial coronary arteries in the absence of sufficient collateral blood supply [1, 2]. Infarct size, morbidity and mortality after myocardial infarction (MI) are considerably reduced by reperfusion therapy, such as thrombolysis or primary percutaneous coronary intervention (PCI) [1, 2]. Coronary artery bypass graft (CABG) surgery is another type of reperfusion therapy that is often associated with significant changes of metabolic reactions and inflammatory response [3]. An improvement in clinical outcomes after PCI and CABG may be achieved by therapy strategies influencing cardiac metabolism [4–6]. Myocardial ischaemia evokes, within minutes, excessive release of catecholamines and produces metabolic and hormonal reactions, such as significant decrease in secretion of insulin, and increase in free fatty acids (FFAs) [4–6]. Glucose–insulin–potassium (GIK) has several potential mechanisms for improving clinical outcomes after MI. GIK therapy is associated with reduced amount of circulating FFAs and promotes the use of glucose as the primary energy substrate for myocardial tissue [7, 8]. Glucose is less oxygen consuming when compared with FFAs and has beneficial effects on myocardial function and membrane stability [9, 10]. Furthermore, insulin activates intracellular signalling pathways that promote cell survival and inhibit events related to apoptosis [11]. Intracellular levels of potassium are depleted during ischaemia, whereas provision of potassium increases its levels within myocytes, thereby raising the threshold for ventricular arrhythmias [12, 13]. Animal and clinical studies have shown that GIK therapy has two types of benefits in cardiac ischaemic syndrome. The first mechanism protects against the progress from unstable angina pectoris to MI, preserving left ventricular function; the second one prevents arrhythmias and cardiac arrest associated with ischaemia-related metabolic derangements [3–10]. This meta-analysis sought to determine the strength of evidence for the efficacy and safety of GIK therapy on clinical outcomes after PCI and CABG.

MATERIALS AND METHODS

We systematically searched Medline/Pubmed, Elsevier, Embase, Web of Knowledge and Google Scholar till 25 July 2014, selecting clinical trials of interest. The medical subject headings search string for this literature search was 'glucose–insulin–potassium', 'GIK', 'GIP', 'PGI', and 'myocardial infarction', 'MI', 'percutaneous coronary intervention', 'PCI', 'coronary artery bypass grafting', 'CABG', 'CAB'. Inclusion criteria were as follows: (i) randomized controlled trial (RCT); (ii) comparison of GIK with a control group and (iii) reporting data on the incidence of post-procedural complications according to the checklist.

Two researchers (Sadegh Ali-Hassan-Sayegh and Ali Mohammad Dehghan) independently and separately extracted the data from each trial. Data extracted from each RCT related to PCI included author's name, sample size, mean age, gender, details of therapeutic regimens, type of administration, dose of glucose, dose and type of insulin, dose of potassium and Jadad score; and also the amount of left ventricular ejection fraction, and incidence of stroke, cardiac arrest, cardiogenic shock, MI, heart failure (HF), hypoglycaemia, hyperglycaemia, hyperkalaemia, phlebitis, glucose and potassium level as well as mortality. Data extracted from each RCT related to CABG included author's name, sample size, mean age, gender, details of therapeutic regimens, type of administration, type of CABG (on-pump or off-pump), dose of glucose, dose and type of insulin, dose of potassium and Jadad score; and also the incidence of atrial fibrillation, stroke, ventricular fibrillation, infections, renal disease, MI, length of ventilation time, ICU and hospital stay, hypoglycaemia, hyperglycaemia, hyperkalaemia, phlebitis, glucose and potassium level as well as mortality. Subgroup analysis was performed for exploration of heterogeneity between studies according to: (i) dose of GIK (high or low), (ii) type of infusion (IV or cardioplegia) and (iii) type of surgery (on- or off-pump).

All data were analysed by STATA version 11.0 utilizing METAN. A value of $P < 0.1$ for the Q test or $I^2 > 50\%$ indicated significant heterogeneity among the studies. Where there was no heterogeneity, fixed-effect models were preferentially reported. Quality assessment of RCTs was assessed using the Jadad scale; an overall study quality score (ranging from 0 to 5) was assigned by each reviewer. Publication bias was assessed by using funnel plots and Begg's test. Begg's test was based on the rank correlation between the observed effect sizes and observed standard errors, whereas in Egger's regression intercept, which is similar to Begg's test, actual values were used instead of ranks. For Begg's and Egger's test statistics, two-sided P-values were reported.

RESULTS

A total of 1206 studies were retrieved during the extensive literature search of all major databases; however, 844 (69.9%) were excluded after initial review. Of 362 studies included during the initial steps, 324 were excluded owing to insufficient representation of endpoints analysed. Finally, 38 RCTs met the criteria of inclusion and were used for our meta-analysis. Baseline and demographic characteristics of enrolled studies are presented in Tables 1 and 2.

Study characteristics, effect measures and outcomes after percutaneous coronary intervention

Cardiac arrest: Twenty-four thousand eight hundred and forty-six patients were analysed from six RCTs that reported data on cardiac arrest (Table 3). After removing two RCTs with two zero-columns, a total of 24 768 patients from four studies were enrolled into the analysis. Baseline and demographic characteristics are presented in Table 1. From all patients, 12 367 cases were allocated to GIK and 12 401 cases to the control group. The overall incidence rate of cardiac arrest was 1.9% (range: 1.4–5%) accounting for 1.9% in the GIK group and 2% in the control group. GIK therapy failed to reduce the incidence of cardiac arrest with an odds ratio (OR) of 0.91 [95% confidence interval (CI): 0.76–1.09; $P = 0.3$] in the fixed model. No significant heterogeneity was seen among the RCTs ($\chi^2 = 4.26$, $I^2 = 29.6$, $P = 0.2$). Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, $P = 1.0$; Egger's test, $P = 1.0$).

Stroke: Four thousand four hundred and twenty-one patients were analysed from four RCTs that provided data on stroke (Table 3). From all patients, 2291 cases were allocated to the GIK group and 2130 to the control group. The overall incidence rate of stroke was 0.8% (range: 0.5–1.4%) with 0.6% in the GIK group and 0.9% in the control group. GIK therapy failed in reducing the incidence of stroke after PCI with an OR of 1.71 (95% CI: 0.37–1.37; $P = 0.3$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 5.02$, $I^2 = 40.2\%$, $P = 0.3$).

Cardiogenic shock: Twenty-four thousand three hundred and eighty-two patients were analysed from six RCTs with data on the incidence of cardiogenic shock (Table 3). Several RCTs with missing events in both groups were excluded, resulting in 24 304 patients from four studies (Table 3)—12 224 receiving GIK therapy and 12 080 controls. The overall incidence rate of cardiogenic shock was 6.04% (range: 2.4–6.4%), accounting for 6.1% in the GIK group and 5.9% in the control group. Incidence of cardiogenic shock was not significantly different between both groups with an OR of 1.02 (95% CI: 0.92–1.14; $P = 0.6$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 1.0$, $I^2 = 0.0\%$, $P = 0.8$). Begg's and Egger's tests showed no potential publication bias among the included RCTs (Begg's test, $P = 0.497$; Egger's test, $P = 0.497$).

Re-myocardial infarction: Twenty-five thousand six hundred and sixty-three patients from eight RCTs presented data on re-myocardial infarction (re-MI). Following exclusion of a single RCT with 2 zero-columns, 25 637 patients from 11 studies remained for the final analysis (Table 3), with 12 909 cases in the GIK group and 12 728 in the control group. The overall incidence rate of re-MI was 2.4% (range: 1.1–3.7%), accounting for 2.3% in the GIK group and 2.5% in the control group. GIK therapy was not associated with reduced incidence of re-MI after PCI with an OR of 0.95 (95% CI: 0.81–1.14; $P = 0.5$) in the fixed model (Fig. 1). No significant heterogeneity was observed among the RCTs ($\chi^2 = 4.46$, $I^2 = 0.0\%$, $P = 0.6$). Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, $P = 0.652$; Egger's test, $P = 0.652$).

Heart failure: Four RCTs provided outcomes in terms of HF. The overall incidence rate of progression of HF was 9.1%: 8.3% in the GIK group and 9.9% in the control group (Table 3). GIK therapy succeeded in reducing the incidence of progression of HF with an OR of 0.8 (95% CI: 0.64–0.99; $P = 0.04$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 4.17$, $I^2 = 28.1\%$, $P = 0.2$).

Mortality: Ten RCTs reported data on death. Mortality occurred in 8.9% of cases in the GIK group and 8.6% in the control group. In fact, 1 out of 10 comparisons did not present any postoperative death in 2 comparative arms; therefore, the remaining 9 RCTs (27 397 patients) were used to perform the meta-analysis

Table 1: Demographic characteristics of randomized controlled trials on PCI

Jadad	Potassium dose (mEq/l)	Insulin type and dose	Glucose given (%)	Male (%)		Mean age (years)		*n*			Infusion method	Regimen	Author or study name
				C	GIK	C	GIK	Total	C	GIK			
3	80	50 IU/l, regular	25	71.6	73.1	62.1	61.5	2478	1374	1374	IV	1.5 ml/kg/h	OASIS-6 [14]
2	60	300 IU/l	30	78.9	78.5	58.9	61.4	47	19	28	IV	1.5 ml/kg/h	Demircan [15]
4	80	32/20 IU/l	10	67.2	70	60	62	954	460	494	IV	42 ml/h	POL GIK trial [16]
3	160	100 IU/l actrapid	30	78.8	85	57	60	73	33	40	IV	1.5 ml/kg/h	Ducci [17]
3	60	300 IU/l	30	76	70.4	59	60	52	25	27	IV	1.5 ml/kg/h	Yazici [18]
3	160	Variable	20	80.1	74.2	61	59	612	302	310	IV	3 m/kg/h	GIPS-I [19]
2	80	Variable actrapid	20	73.9	73.4	61.2	61.8	889	445	444	IV	2 ml/kg/h	GIPS-II [20]
2	80	50 IU/l	30	85.2	81.5	60	56	81	27	54	IV	Variable	Türel [21]
4	80	50 IU/l, regular	25	77.6	77.6	58.6	58.6	20195	10 107	10 088	IV	1.5 ml/kg/h	ECLA trial [22]
5	80	50 IU/l	30	69.6	72.5	63.3	63.9	871	460	411	IV	1.5 ml/kg/h	Selker [23]
3	64	40 IU/l	20	72.6	71.6	64.1	60.8	312	157	155	IV	1.8 ml/kg/h	Pache [24]
2	80	50 IU/l	25	58.3	64.3	63.2	67	26	12	14	IV	1.5 ml/kg/h	Li [25]
3	80	50 IU/l	25	68.3	77	60.5	58.2	274	139	135	IV	1.5 ml/kg/h	ECLA pilot trial High dose [26]
3	40	20 IU/l	10	68.3	75.9	60.5	58	272	139	133	IV	1 ml/kg/h	ECLA pilot trial Low dose [26]

C: control group; GIK: glucose–insulin–potassium; IV: intravenously.

(Table 3). GIK therapy had a trend towards increasing the incidence of mortality with an OR of 1.04 (95% CI: 0.96–1.13; $P = 0.3$) in the fixed model (Fig. 2). No significant heterogeneity was observed among the RCTs ($\chi^2 = 12.6$, $I^2 = 36.8\%$, $P = 0.1$).

Hypoglycaemia: The overall incidence rate of hypoglycaemia was 0.4%: 0.7% in the GIK group and 0.1% in the control group (Supplementary material, Table S3). GIK therapy was associated with a significantly higher incidence of hypoglycaemia with an OR of 4.0 (95% CI: 2.42–6.64; $P = 0.00$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 1.73$, $I^2 = 0.0\%$, $P = 0.6$).

Hyperglycaemia: The overall incidence rate of hyperglycaemia from three RCTs included was 13.8%, with 18.5% in the GIK group and 9.2% in the control group (Supplementary material, Table S3). GIK therapy was associated with an increased incidence of hyperglycaemia, with an OR of 2.3 (95% CI: 1.6–3.5; $P = 0.00$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 0.28$, $I^2 = 0.0\%$, $P = 0.8$).

Hyperkalaemia: The overall incidence rate of hyperkalaemia was 4.2% in the GIK group and 1.6% in the control group (Supplementary material, Table S3). GIK therapy significantly increased the incidence of hyperkalaemia with an OR of 2.71 (95% CI: 2.26–3.24; $P = 0.000$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 0.71$, $I^2 = 0.0\%$, $P = 0.3$).

Phlebitis: The overall incidence rate of phlebitis from three trials included was 3.4% in the GIK group and 0.16% in the control group (Supplementary material, Table S3). GIK therapy significantly increased the incidence of phlebitis with an OR of 20.15 (95% CI: 12.6–32; $P = 0.000$) in the random model. Significant heterogeneity was observed among the RCTs ($\chi^2 = 6.5$, $I^2 = 69.2\%$, $P = 0.03$).

Mean changes of blood level of glucose and potassium: From 125 patients, 69 cases were allocated to the GIK group and 56 to the control group (Supplementary material, Table S3). The GIK group had a trend towards an increased mean level of glucose with an standard mean differences (SMD) of 10.09 (95% CI: −4.70 to 24.89; $P = 0.1$) in the fixed model. A total of 73 patients from 3 RCTs were analysed in terms of the mean level of serum potassium. Pooled analysis indicated that GIK had a trend towards an increased mean level of serum potassium with an SMD of 0.2 (95% CI: −0.05 to −0.47; $P = 0.1$).

Study characteristics, effect measures and clinical outcomes after coronary artery bypass grafting

Atrial fibrillation: One thousand seven hundred and ninety-nine patients were analysed from 14 RCTs representing outcomes regarding atrial fibrillation (Supplementary material, Table S1), with 934 patients in the GIK group and 865 patients in the control group. The overall incidence rate of atrial fibrillation was 31.1% (range: 7.5–51%), accounting for 29.6% in the GIK group and 32.8% in the control group. GIK therapy had a trend towards decreased perioperative atrial fibrillation with an OR of 0.86 (95% CI: 0.70–1.05; $P = 0.1$) in the random model (Fig. 3). Significant heterogeneity was observed among the RCTs ($\chi^2 = 30.03$, $I^2 = 56.7\%$, $P = 0.005$). A subgroup analysis is presented in Supplementary material, Table S4. Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, $P = 0.412$; Egger's test, $P = 0.412$).

Ventricular fibrillation: One thousand two hundred and four patients were analysed from four RCTs that represented outcomes regarding ventricular fibrillation (Supplementary material, Table S1), with 631 patients in the GIK group and 573 patients in the control group. GIK therapy had a trend towards decreased perioperative ventricular fibrillation with an OR of 0.83 (95% CI: 0.62–1.13; $P = 0.2$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 2.67$, $I^2 = 0.0\%$, $P = 0.4$).

Stroke: One thousand two hundred and thirty-two patients were analysed from three RCTs regarding the incidence of stroke. Only one RCT did not present any events in both groups and was excluded, whereas 1166 patients remained for the final analysis (Supplementary material, Table S1). GIK therapy could not reduce

Table 2: Demographic characteristics of randomized controlled trials on CABG

Jadad	Potassium dose	Insulin type and dose	Glucose given	Type of CABG	Male (%)		Mean age (years)		*n*			Infusion method	Regimen	Author
					C	GIK	C	GIK	Total	C	GIK			
4	N.D.	10 IU/l	N.D.	On-pump	70.9	74.9	64	64	501	258	243	Cardioplegia	N.D.	Hynninen [27]
2	80 mEq/l	0.1 IU/kg/h actrapid	30%	On-pump	85.7	78.3	64	63	44	21	23	IV	N.D.	Zuurbier [28]
1	0.15 mmol/kg/h	0.12 IU/kg/h actrapid	0.2 g/kg/h	On-pump	80	80	56.8	55.1	40	20	20	IV	N.D.	Wistbacka [29]
1	0.12 mmol/kg/h	0.12 IU/kg/h Rapid acting	0.6 g/kg/h	On-pump	87.5	81.3	54.9	55.9	32	16	16	IV	N.D.	Wistbacka [30]
2	N.D.	N.D.	N.D.	On-pump	58	70	61.08	62.5	100	50	50	IV	N.D.	Straus [31]
2	0.25 mmol of KCL per ml of 50% D/W	0.5 IU/kg actrapid	2.5 ml of 50% D/w per IU of insulin	On- and off-pump	91.6	77.2	63.5	63.5	44	22	22	IV	N.D.	Smith [32]
4	160 mEq/l	650 IU/l regular	50%	OPCAB	69.7	60.6	67	64	66	33	33	IV	0.3 ml/kg/h	Shim [33]
4	80 mEq/l	160 IU/l regular	5%	On-pump	70	36	61.2	57.7	50	25	25	IV	30 ml/h	Seied-hosseini [34]
2	N.D.	1 IU/kg/h	30%	On-pump	70	90	56	58	20	10	10	N.D.	N.D.	Szabo [35]
4	N.D.	10 IU/l	N.D.	On-pump	74	73.9	63	64	1127	570	557	Cardioplegia	N.D.	Rao [36]
1	N.D.	10 IU/l	N.D.	On-pump	N.D.	N.D.	N.D.	N.D.	24	11	13	Cardioplegia	N.D.	Rao [37]
5	N.D.	10 IU/l regular	42 mmol/l and 84 mmol/l	On-pump	100	100	60	62	56	27	29	Cardioplegia	N.D.	Rav [38]
4	80 mEq/l	70 IU/l actrapid	40%	On-pump	81	86.2	63.6	64.4	280	142	138	IV	0.75 ml/kg/h	Quinn [39]
2	1.7 mEq/kg and 20 mEq/l	2.1 IU/kg regular and 20 IU/l regular	1.6 g/kg and 5%	On-pump	80.3	78.1	54.4	56.3	391	157	234	N.D.	N.D.	Lolley [40]
1	Variable	Actrapid	Variable	On-pump	35.7	50	74	72	30	14	16	N.D.	N.D.	Lindholm [41]
2	10 mEq/h	100 IU as a bolus with a flow of 250 IU/h actrapid	30%	On-pump	100	100	63	67	22	11	11	IV	N.D.	Lindholm [42]
3	80 mEq/l	50 IU/l	25%	OPCAB	65	52.4	57.2	61.6	41	20	21	Pulmonary artery catheter	1.5 ml/kg/h	Lell [43]
2	80 mEq/l	50 IU/l regular	30%	On-pump	66.7	73.4	65	60	30	15	15	IV	1 ml/kg/h	Lazar [44]
1	80 mEq/l	160 IU/l regular	5%	On-pump	66.7	58.3	63.5	63.7	141	69	72	IV	30 ml/h	Lazar [45]
1	Variable rate	1 IU/kg/h actrapid	30% variable rate	On-pump	75	68.4	67.4	66.8	39	20	19	IV	N.D.	Koskenkari [46]
4	80 mEq/l	80 IU/l regular	10%	On-pump	56.7	58.3	59	61	66	30	36	N.D.	1 ml/kg/h	Foroughi [47]
2	0.25 mmol/k/h	1.35 IU/kg/h actrapid	0.5 g/kg/h	On-pump	57.1	100	57	60	14	7	7	N.D.	N.D.	Brodin [48]
2	100 mEq/l	8o IU/l	50%	N.D.	N.D.	N.D.	N.D.	N.D.	22	11	11	N.D.	1 ml/kg/h	Coleman [49]
2	N.D.	N.D.	50%	On-pump	N.D.	N.D.	N.D.	N.D.	60	30	30	IV	N.D.	Salerno [50]
2	N.D.	N.D.	N.D.	On-pump	100	100	N.D.	N.D.	30	15	13	Cardioplegia	N.D.	Kjellman [51]

N.D.: no data; C: control group; GIK: glucose–insulin–potassium; IV: intravenously; OPCAB: off-pump coronary artery bypass; CABG: coronary artery bypass grafting.

Table 3: Reports of clinical outcomes of randomized controlled trials for PCI studies

30-day mortality		Re-MI		HF		Cardiogenic shock		Cardiac arrest		Stroke		LVEF		Total number	Author
C	GIK	C	GIK	C	GIK	C	GIK	C	GIK	C	GIK	C	GIK		
92	104	43	47	165	144	63	55	65	60	15	6	No data		2478	OASIS-6 [14]
22	44	12	7	No data		11	12	13	21	0	5	No data		954	POL GIK trial [16]
No data		No data		No data		No data		No data		No data		45 ± 6	46 ± 9	73	Ducci [17]
No data		No data		No data		0	0	0	0	No data		No data		52	Yazici [18]
27	23	7	4	No data		No data		No data		No data		42.4 ± 11.7	43.7 ± 11	612	GIPS-I [19]
8	13	No data		No data		No data		No data		No data		No data		889	GIPS-II [20]
1	1	2	1	8	5	No data		No data		No data		No data		27	Türel [21]
976	1004	246	236	No data		640	667	151	139	No data		No data		10 107	ECLA trial [22]
28	18	No data		10	6	No data		29	15	No data		No data		460	Selker [23]
5	7	4	6	No data		No data		No data		2	2	No data		312	Pache [24]
No data		0	0	No data		0	0	0	0	No data		No data		26	Li [25]
16	10	5	4	15	13	8	9	No data		3	2	No data		274	ECLA pilot trial
															High dose [26]
16	8	5	4	15	8	8	5	No data		3	1	No data		272	ECLA pilot trial
															Low dose [26]

C: control group; GIK: glucose–insulin–potassium; HF: heart failure; Re-MI: re-myocardial infarction; LVEF: left ventricular ejection fraction.

the incidence of stroke after CABG with an OR of 1.09 (95% CI: 0.54–2.20; $P = 0.8$) in the fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 0.48$, $I^2 = 0.0\%$, $P = 0.4$).

Renal disease: There were no significant differences between both groups regarding the incidence of renal disease, with an OR of 0.62 (95% CI: 0.15–2.51; $P = 0.5$) in the fixed model with 105 patients included from 2 RCTs (Supplementary material, Table S1).

Re-myocardial infarction: One thousand six hundred and eighty-five patients from six RCTs were included into the analysis on re-MI (Supplementary material, Table S1). The overall incidence rate of re-MI was 15.6% (range: 5.1–19.9%) with 15.1% in the GIK group and 16.2% in the control group. GIK therapy did not have ability to reduce the incidence of re-MI after CABG with an OR of 0.97 (95% CI: 0.74–1.27; $P = 0.8$) using a fixed model. No significant heterogeneity was observed among the RCTs ($\chi^2 = 8.65$, $I^2 = 42.2\%$, $P = 0.1$). Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, $P = 0.851$; Egger's test, $P = 0.851$).

Infection: Five hundred and seventy-two patients from six RCTs represented outcomes in terms of infection (Supplementary material, Table S1) with an overall incidence rate of 18% (range: 4.5–29.5%): 18.1% in the GIK group and 17.8% in the control group. The incidence of postoperative infection was not significantly different between the two groups, with an OR of 1.04 (95% CI: 0.67–1.62; $P = 0.8$) in the fixed model (Fig. 4). No significant heterogeneity was observed among the RCTs ($\chi^2 = 6.84$, $I^2 = 41.5\%$, $P = 0.1$). Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, $P = 0.142$; Egger's test, $P = 0.142$).

Postoperative duration of ventilation: The mean duration for all trials was 11.2 ± 7 h, with 10.8 ± 9.7 for the GIK and 11.5 ± 4.4 for the control group (Supplementary material, Table S2). Applying a random-effect model, pooled analysis revealed that GIK therapy failed in reducing the duration of ventilation with an SMD of −0.053 (95% CI: −0.14 to 0.37; $P = 0.2$). There was significant heterogeneity among the studies ($\chi^2 = 362.53$, $I^2 = 97.8\%$, $P = 0.000$). A subgroup analysis is presented in Supplementary material, Table S4.

Postoperative length of ICU stay: The mean LIS from 11 trials (1044 patients) included was 46.4 ± 26.6 h, with 42.5 ± 23.2 for the GIK group and 50.2 ± 29.9 for the control group (Supplementary material, Table S2). GIK therapy significantly reduced the LIS with an SMD of −0.27 (95% CI: −0.40 to −0.14; $P = 0.000$) in the random-effect model. Significant heterogeneity was observed among the RCTs ($\chi^2 = 300.3$, $I^2 = 96.7\%$, $P = 0.000$). A subgroup analysis is presented in Supplementary material, Table S4.

Postoperative length of hospital stay: The mean LHS from 12 trials (2161 patients) included in the analysis was 8 ± 3.9 days with 7.9 ± 4.6 for the GIK group and 8.2 ± 3.2 for the control group (Supplementary material, Table S2). In terms of the LHS, there were no significant differences between the two groups, with an SMD of −0.035 (95% CI: −0.12 to −0.05; $P = 0.4$) in the random-effect model. Significant heterogeneity was observed among the RCTs ($\chi^2 = 320.3$, $I^2 = 96.6\%$, $P = 0.000$). A subgroup analysis is presented in Supplementary material, Table S4.

Mortality: Two thousand five hundred and seven patients from 19 RCTs presented outcomes regarding mortality. Following the exclusion of 10 RCTs with missing events in both groups, 2046 patients were analysed (Supplementary material, Table S2) with 1057 patients in the GIK group and 989 patients in the control group. The mortality incidence rate was 1.8% in the GIK group and 2.7% in the control group; GIK therapy had a trend towards

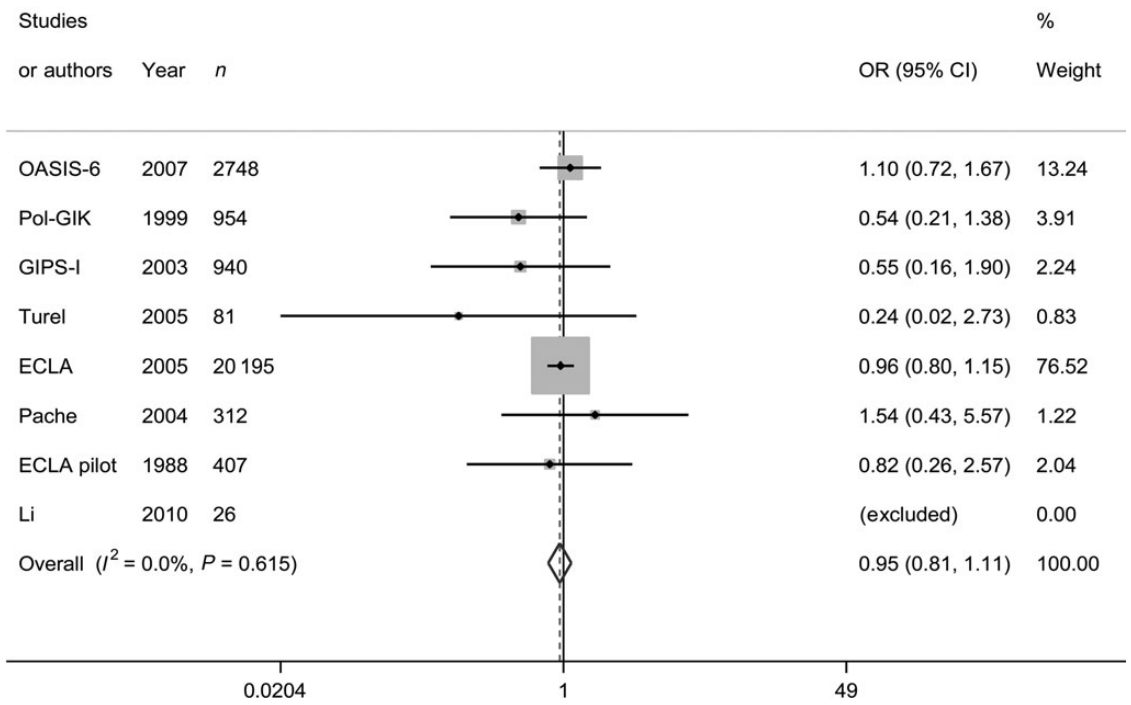

Figure 1: Forest plot of OR for GIK therapy on the incidence of reinfarction following PCI (OR <1 favoured GIK and OR >1 favoured control). OR: odds ratio; GIK: glucose–insulin–potassium; PCI: percutaneous coronary intervention; CI: confidence interval.

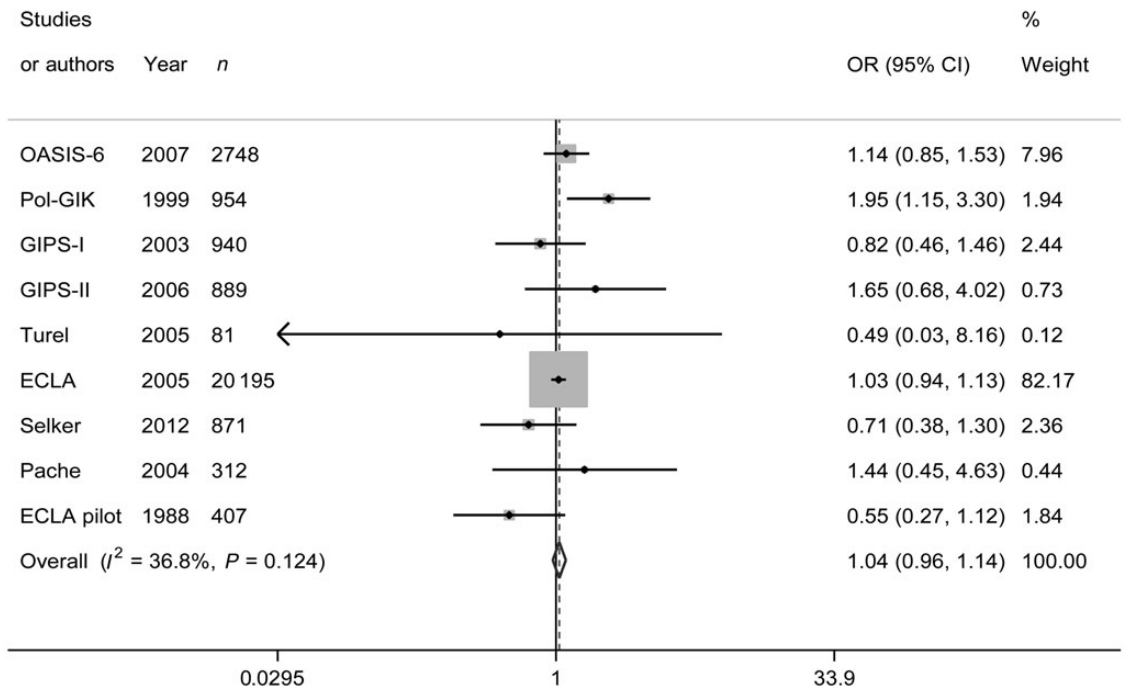

Figure 2: Forest plot of OR for GIK therapy on the incidence of mortality following PCI (OR <1 favoured GIK and OR >1 favoured control). OR: odds ratio; GIK: glucose–insulin–potassium; PCI: percutaneous coronary intervention; CI: confidence interval.

decreased incidence of mortality with an OR of 0.72 (95% CI: 0.41–1.26; P = 0.2) in the fixed model. No significant heterogeneity was observed among the RCTs (χ^2 = 6.41, I^2 = 0.0%, P = 0.6). Begg's and Egger's tests showed that there was no potential publication bias among the included RCTs (Begg's test, P = 0.310; Egger's test, P = 0.310).

Hypoglycaemia and hyperglycaemia: The overall incidence rate of hypoglycaemia was 4.1%, accounting for 5.5% in the GIK group and 2.8% in the control group. GIK therapy was associated with an increased incidence of hypoglycaemia of with an OR of 1.9 (95% CI: 1.15–3.36; P = 0.01) in the fixed model. No significant heterogeneity was observed among the RCTs (χ^2 = 1.69, I^2 = 0.0%, P = 0.4).

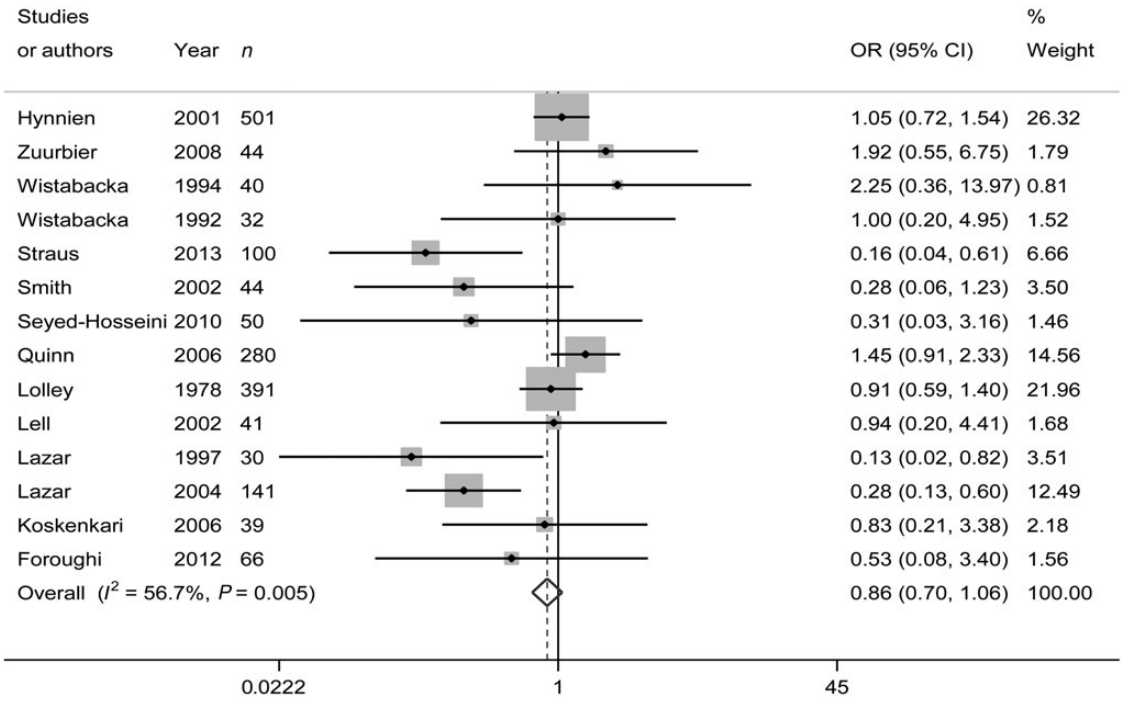

Figure 3: Forest plot of OR for GIK therapy on the incidence of atrial fibrillation following CABG (OR <1 favoured GIK and OR >1 favoured control). OR: odds ratio; GIK: glucose–insulin–potassium; CABG: coronary artery bypass grafting; CI: confidence interval.

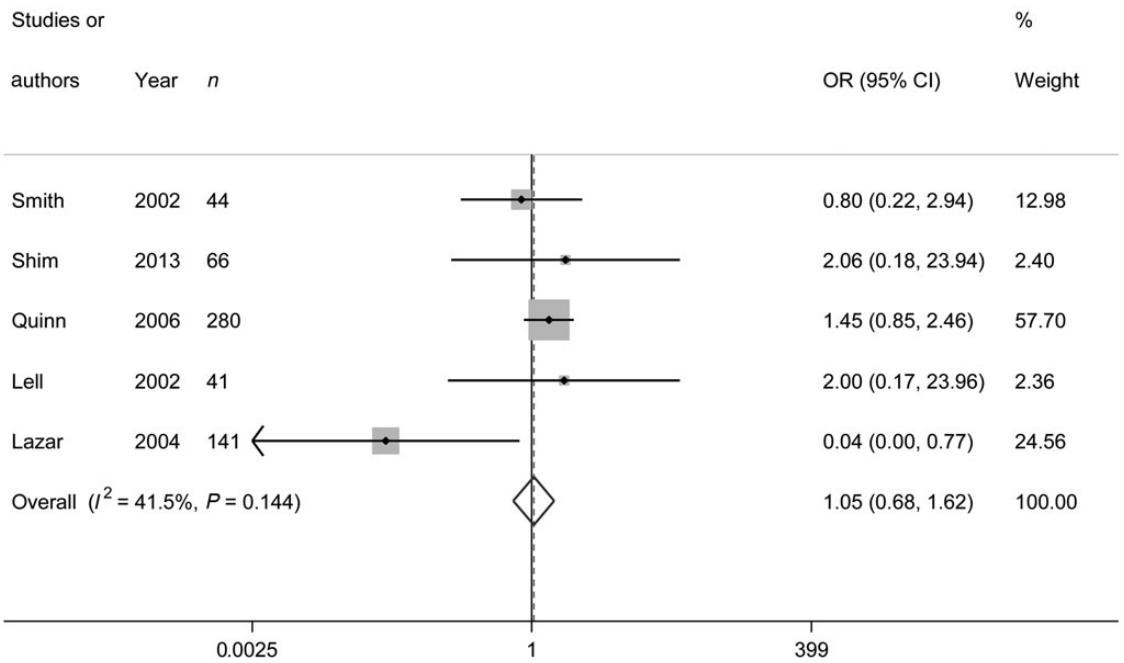

Figure 4: Forest plot of OR for GIK therapy on the incidence of infection following CABG (OR <1 favoured GIK and OR >1 favoured control). OR: odds ratio; GIK: glucose–insulin–potassium; CABG: coronary artery bypass grafting; CI: confidence interval.

In terms of hyperglycaemia, two RCTs were analysed, having revealed that GIK therapy can significantly decrease the incidence of hyperglycaemia with an OR of 0.34 (95% CI: 0.25–0.45; P = 0.00).

DISCUSSION

Owing to the permanently increasing incidence of ischaemic heart disease around the world, with increasing incidence rates of morbidity and mortality and considerably reduced quality of life, the necessity of finding effective treatment modalities with cardioprotective characteristics is felt more profoundly than ever [1, 2]. During episodes of cardiac ischaemia, the myocardium converts from ascorbic carbohydrate metabolism to anaerobic fatty acid metabolism, which results in the production of metabolites and free radicals that are toxic to the myocardium and are associated with arrhythmia and decreased myocardial contractility [5–11]. Insulin as a regulating factor of blood sugar was shown to be

associated with vasodilatory effects; additionally, when it is administered in euglycaemic individuals, it shows anti-inflammatory and anti-thrombotic effects. The simultaneous administration of insulin and glucose is known to be a metabolic treatment leading to the protection of the myocardium against metabolic changes [7–11]. Several experimental studies reported that administration of GIK therapy may preserve myocardial perfusion and left ventricular function, as determined by haemodynamic parameters [52, 53]. The OASIS trial, a large-scale multicentred randomized trial, revealed that the administration of GIK is not only ineffective in patients undergoing PCI compared with the control group, but also results in increased mortality [14]. Our findings demonstrate that GIK administration in patients undergoing PCI cannot decrease the incidence of re-MI, cardiac arrest and carcinogenic shock compared with the control group. However, it has a significant decreasing effect on the progression of HF from mild to severe. These findings suggest that GIK might not improve the remaining tissue damage; however, it might prohibit the exacerbation of tissue injury. Hence, patients who seek GIK administration less frequently are exposed to higher risks of HF aggravation. Furthermore, our results indicate that the number of patients with complications such as hypoglycaemia, hyperglycaemia, hyperkalaemia and phlebitis following GIK administration is higher compared with the control group. GIK is inclined to increase the mean blood glucose and potassium levels; hence, its administration may be crucial for high-risk patients with metabolic disturbances, history of uncontrolled diabetes and history of cardiac arrhythmia, leading to detrimental clinical sequels. The present study, moreover, reports that GIK is associated with a slight trend towards increased mortality. Indeed, it is well recognized that a patient's glucose level at admission is a stronger predictor of mortality in the setting of acute MI [54, 55]. Probably, increased mortality risk following administration of GIK may be related to the manifestation of complications related to drug administration, specifically in high-risk patients. The study by Mamas *et al.* [56] argues that many trials do not show beneficial effects of a low-dose GIK solution on reducing morbidity and mortality rates because the doses of glucose and insulin used are not sufficient to suppress FFA levels. For this reason, we separately analysed the high-dose and low-dose studies in order to investigate the effects of GIK therapy more accurately. Our subgroup analysis demonstrates that the administration of low-dose GIK therapy cannot significantly reduce re-MI, stroke, cardiogenic shock and cardiac arrest. However, high-dose GIK therapy can cause a significant decrease in HF and stroke, yet it has no significant effect on re-MI, cardiogenic shock and cardiac arrest. Thus, it can be speculated that the administration of high-dose GIK can hinder the exacerbation and aggravation of myocardial tissue damage showing cardioprotective properties. However, our findings also indicate that GIK therapy might slightly increase mortality at both low and high doses. It is consistent with results from the pilot ECLA trial study, where no significant differences in terms of mortality were observed between low-dose and high-dose GIK treatment [26]. In summary, cardioprotective effects of GIK might only manifest after high-dose treatment, whereas low doses might be ineffective.

Finally, based on our findings, it can be summarized that although GIK therapy is not able to decrease re-MI, cardiogenic shock and cardiac arrest in patients undergoing PCI, it can prevent the exacerbation of HF. On the other hand, the cardioprotective effects of GIK first appear with higher doses. Furthermore, the incidence of complications, such as hypoglycaemia, hyperglycaemia, hyperkalaemia and phlebitis might increase with an increase in the dose of GIK.

In terms of surgical revascularization, surgical stress results in metabolic changes related to increased neuroendocrine activity, leading to increased lipolysis, elevated blood glucose levels, impaired glucose tolerance and peripheral insulin resistance. During ischaemia, there is a shift from oxidative lipolysis to anaerobic glycolysis [57–60]. Following such unfavourable conditions, the parameters of cardiac functioning and postischaemic clinical consequences are affected negatively. In this study, we were able to show that, in patients undergoing GABG, GIK tends to decrease AF, VF and mortality. It can also significantly decrease the LIS, though it is ineffective in terms of reducing stroke, infections and renal disorders, and not having beneficial influence on the length of ventilation time and LHS. Therefore, patients undergoing CABG seem to be better responders to GIK therapy compared with patients undergoing PCI, whereas GIK therapy in patients undergoing PCI might be associated with more complications rather than protective effects.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

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