National Institute for Health and Care Excellence

Final

Perioperative care in adults

[K] Evidence review for blood glucose control management

NICE guideline NG180

Evidence reviews underpinning recommendations 1.4.6 and 1.4.7 in the NICE guideline

August 2020

Final

This evidence review was developed by the National Guideline Centre

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ISBN: 978-1-4731-3827-8

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1 Blood glucose control management

1.1 Review question: What is the clinical and cost effectiveness of blood glucose control management in adults undergoing surgery?

1.2 Introduction

The prevalence of diabetes in the general UK population is thought to be about 6.5% but data from the 2017 National Diabetes Inpatient Audit (NaDIA) suggests that on average across the UK 18% of all inpatients have diabetes, and for people presenting for surgery this figure is probably higher. As well as having increased length of stay, as a result of complications, surgical patients with diabetes have increased mortality. Complications not only cause immediate patient harm, but patients who have suffered perioperative complications continue to experience increased morbidity for several years. It is therefore necessary to prevent perioperative complications. Non-diabetic patients are also a risk of complication from hyperglycemia.

NaDIA 2017 identified that harm to inpatients with diabetes has multiple causes including hypoglycaemia, hospital acquired diabetic ketoacidosis, medication errors and inappropriate use of insulin infusions. There has been much debate on whether the benefits of tight glycaemic control with insulin outweigh the risk of harm from hypoglycaemia caused by intensive insulin therapy with intravenous insulin infusions.

Current NICE recommendations suggest that adults with type1 diabetes should aim for a fasting plasma glucose level of 5-7mmol/litre in the community and 5-8mmol/ litre during surgery or acute illness. The purpose of this review is to determine whether these recommendations are applicable to people with type 2 diabetes and non-diabetic people.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults 18 years and over having surgery.
Interventions	Glucose control (insulin therapy, intra to postoperative)
Comparisons	Standard care (liberal/no glucose control)
Outcomes	Critical outcomes: • health-related quality of life • mortality • adverse events and complications (Clavien-Dindo, postoperative morbidity score (POMS), cardiovascular, respiratory and neurological complications) • infections (including surgical site) • hypoglycaemia Important outcomes: • length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • hospital readmission

Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs.

1.4 Clinical evidence

1.4.1 Included studies

Thirty randomised controlled trials were included in the review;[1, 5, 9, 26, 27, 31, 32, 39-43, 52, 55, 59, 60, 74, 77, 78, 113, 114, 120, 137, 142, 143, 146, 153, 157, 159, 162, 166, 169, 170] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments

Abdelmalak 2013[1]	**Glucose control:**
	Blood glucose concentrations were targeted to 4.4–6.1 mmol litre^{-1} (80–110 mg/dl^{-1}), beginning shortly after induction of anaesthesia.
	N=196
	
	Standard care:
	Blood glucose concentrations were targeted to 10–11.1 mmol litre^{-1} (180–200 mg dl^{-1}), beginning shortly after induction of anaesthesia..
	N=185
		Patients having major non-cardiac surgery.
		
		USA
			• Mortality
			• Complications:
			  ○ Pulmonary
			  ○ Cardiac
			  ○ Neurological
			• Infection
			• Hypoglycaemic events	

Albacker 2007[5]	**Glucose control:**
	Fixed high-dose systemic insulin infusion at 5 mU/kg/min. Dextrose 20% was infused in the same group at a rate adjusted to maintain a blood glucose of 4 to 6 mmol/L.
	N=22
	
	Standard care:
	Intraoperative titrated intravenous insulin infusion, titrated according to sliding scale starting at blood glucose level of 10 mmol/L.
		Patients undergoing elective cardiopulmonary bypass graft (CABG).
		
		USA
			• Complications:
			  ○ Pulmonary
			  ○ Cardiac
			• Infection
			• Length of hospital stay
			• Length of ICU stay
				14/44 diabetics, type unclear.

Study	Intervention and comparison	Population	Outcomes	Comments
	N=22			

Azarfarin 2011[9]	**Glucose control:**
	In the study group, insulin was infused to maintain blood glucose (BG) level between 110 mg/dL and 126 mg/dL. The measurement was performed every 30 minutes intraoperatively until the closure of the sternum and thereafter every 2 hours up to 48 hours postoperatively.
	N=60
	
	Standard care:
	No intervention was done unless the BG level exceeded 200 mg/dL (treated by bolus insulin).
	N=60
		Nondiabetic patients of ASA status II or III who underwent elective cardiopulmonary bypass graft (CABG) surgery.
		
		Iran
			• Mortality
			• Complications:
			  ○ Pulmonary
			  ○ Neuropsychological
			  ○ Cardiac
			• Infections
			• Hypoglycaemic events	

Butterworth 2005[26]	**Glucose control:**
	Arterial blood samples were obtained at 15-minute intervals during CABG to measure blood glucose concentrations with a handheld glucose meter. After induction of anaesthesia, insulin infusion at 2 U/h in a 70-kg patient was started when the blood glucose concentration exceeded 100 mg/dL. When blood glucose concentrations decreased to less than 70 mg/dL, 100 to 200 mL of dextrose 5% was administered
		Nondiabetic patients scheduled to undergo CABG with cardiopulmonary bypass.
		
		USA
			• Mortality
			• Complications:
			  ○ Pulmonary
			  ○ Neurological
			• Hypoglycaemic events
			• Length of hospital stay
			• Hospital readmission	

Study	Intervention and comparison	Population	Outcomes	Comments
	at the direction of the study nurse. N=188 **Standard care:** Arterial blood samples were obtained at 15-minute intervals during CABG to measure blood glucose concentrations with a handheld glucose meter. Blood glucose concentrations were measured and recorded for later analysis. A saline infusion was periodically adjusted to preserve blinding. N=193			

Cao 2011[27]	**Glucose control:**
	Intensive group in which the postoperative blood glucose was maintained at a level between 4.4 and 6.1 mmol/l.
	N=125
	
	Standard care:
	Conventional group in which the postoperative blood glucose was maintained at a level below 11.0 mmol/l.
	N=123
		Patients who were to undergo open elective gastrectomy for gastric cancer anticipated to require parenteral nutrition.
		
		China
			• Mortality
			• Complications:
			  ○ Total
			  ○ Pulmonary
			• Hypoglycaemic events
			• Infections
			• Length of hospital stay
				Post-operative BG control

Chan 2009[31]	**Glucose control:** Tight glycaemic control, with target glucose level of 80-130 mg/dl. N=55	Patients scheduled for open-heart surgery requiring cardiopulmonary bypass. Brazil	• Mortality • Complications: ○ Neurological • Hypoglycaemic events	Thirty-two patients were diagnosed with diabetes mellitus and sixty-six were diagnosed as non-diabetic. Type of diabetes not reported.

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard care: Standard glycaemic control, with target glucose level of 160-200 mg/dl N=54		• Infections • Length of hospital stay • Length of ICU stay	

Chaney 1999[32]	**Glucose control:**
	Tight glucose control group received an IV infusion initiated regular insulin 2 units/hr to control BG. Infusion initiated during induction of anaesthesia that was continued until sternal closure at the end of surgery.
	N=10
	
	Standard care:
	No glucose control group were not administered insulin to control intraoperative blood glucose levels.
	N=10
		Nondiabetic patients scheduled for CABG surgery.
		
		USA
			• Complications:
			  ○ Cardiac
			  ○ Neuropsychological
			• Hypoglycaemic events
			• Length of hospital stay	

Desai 2012[39] /Pezzella 2014[120]	**Glucose control:**
	Strict perioperative glycaemic control with a target glucose range of 90 to 120 mg/dL.
	N=98
	
	Standard care:
	Glucommander parameters for a target glucose range of 121 to 180 mg/dL.
	N=91
		Patients undergoing coronary artery bypass grafting.
		
		USA
			• Mortality
			• Quality of life
			• Complications:
			  ○ Cardiac
			  ○ Pulmonary
			  ○ Neurological
			• Infections
			• Hypoglycaemic events
				Intraoperative glucose measures and interventions were under the purview of the anaesthesiologist, whose goal was to maintain a BG level between 100 and 180 mg/dL. Maintenance of BG levels according to their randomized arm was started in the ICU using the programmed Glucommander.

Study	Intervention and comparison	Population	Outcomes	Comments

Duncan 2015[41]/Duncan 2018[42]	**Glucose control:**
	Intraoperative glycaemic management with a fixed high-dose insulin and concomitant variable glucose infusion titrated to glucose concentrations of 80 to 110 mg/dl^{-1}
	N=709
	
	Standard care:
	Intraoperative glycaemic management with standard glycaemic management, low-dose insulin infusion targeting glucose >150 mg/dl^{-1}
	N=730
		Adults scheduled for elective coronary artery bypass grafting, valve repair or replacement, or a combination of these procedures with cardiopulmonary bypass.
		
		USA/Canada
			• Mortality
			• Complications:
			  ○ Cardiac
			  ○ Neurological
			• Infection
			• Hypoglycaemic event
			• Length of hospital stay
			• Length of ICU stay
			• Hospital readmission
				Unclear but presumed that data from earlier trial included in latter trial. Studies merged for shared outcomes.

Diez 1991[40]	**Glucose control:** Intensified glucose control, added insulin given when BG were between 5.5 and 8.3 mmol/L. N=7 **Standard care:** Infusion of fast-acting insulin to glucose solution according to a standard sliding scale protocol. N=7	Patients with type II diabetes admitted for programmed surgical procedures under general anaesthetic. Spain	• Hypoglycaemic event	
Emam 2010[43]	**Glucose control:** Strict perioperative glycaemic control following the Braithwaite protocol, with a target glucose range of 100 to 150 mg/dL.	Patients with type II diabetes undergoing open heart procedures. Saudi Arabia	• Infection • Hypoglycaemic event • Length of hospital stay • Length of ICU stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	N=80 **Standard care:** BG control by a sliding scale to maintain BG <200 mg/dL. N=40			

Gandhi 2007[52]	**Glucose control:**
	Continuous insulin infusion to maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL)
	N=199
	
	Standard care:
	Patients in the conventional treatment group were not given insulin during surgery unless glucose levels were greater than 11.1 mmol/L (>200 mg/dL).
	N=201
		Adults with and without diabetes who were undergoing on-pump cardiac surgery.
		
		USA
			• Mortality
			• Complications:
			  ○ Cardiac
			  ○ Neurological
			• Infection
			• Hypoglycaemic event
			• Length of hospital stay
			• Length of ICU stay
				Both groups were treated with insulin infusion to maintain normoglycaemia after surgery.

Giakoumidakis 2013[55]	**Glucose control:** Therapy group with blood glucose target 120–160 mg/dl. N=105 **Standard care:** Post-operative targeted blood glucose levels 161–200 mg/dl N=107	Cardiac surgery patients admitted to ICU post-operatively. Greece	• Mortality • Infection • Hypoglycaemic event • Length of hospital stay • Length of ICU stay	Post-operative BG control.
Grey 2004[59]	**Glucose control:** Intravenous insulin infusions were administered to maintain	Adult patients admitted to a 12-bed surgical ICU requiring treatment of	• Mortality • Hypoglycaemic event • Infections	Post-operative BG control.

Study	Intervention and comparison	Population	Outcomes	Comments
	serum glucose values in the range of 80 to 120 mg/dL. N=34 **Standard care:** Intravenous insulin infusions were administered to maintain serum glucose values in the range of 180 to 220 mg/dL N=27	hyperglycemia (glucose values ≥140 mg/dL). USA	• Length of ICU stay	
Groban 2002[60]	**Glucose control:** Intraoperative insulin infusion to maintain BG between 80-120 mg/dL, started if BG was >100mg/dL after induction. N=188 **Standard care:** Received saline solution as placebo. BG levels were allowed to fluctuate without intervention. N=193	Nondiabetic patients scheduled for elective CABG surgery. USA	• Mortality • Hypoglycaemic events • Length of hospital stay	
Hoedemaekers 2005[74]	**Glucose control:** Intensive postoperative insulin therapy to maintain blood glucose between 80 and 110 mg/dl N=10 **Standard care:** Conventional postoperative insulin therapy to maintain	Non-diabetic patients undergoing elective coronary artery bypass grafting. The Netherlands	• Complications • Hypoglycaemic event • Length of ICU stay	Post-operative BG control

Study	Intervention and comparison	Population	Outcomes	Comments
	blood glucose less than 200 mg/dl N=10			
Ingels 2006[77]	**Glucose control:** Strict blood glucose control below 6.1 mmol/L (110 mg/dL) with intensive insulin therapy. N=477 **Standard care:** Conventional postoperative insulin therapy to receive insulin therapy when blood glucose levels exceeded 12 mmol/L (220 mg/dL) N=493	Cardiac surgery patients. Belgium	• Mortality • Quality of life • Hypoglycaemic events • Length of ICU stay	Post-operative BG control
Ji 2014[78]	**Glucose control:** Tight glucose control. Continuous infusion of insulin during surgery to maintain BG of 80-110 mg/dL. N=37 **Standard care:** Control group had BG measured every 20 minutes throughout surgery. If BG exceeded 200 mg/dL participants received a bolus of 4 units of insulin every hour until BG returned to <200 mg/dL. N=38	Nondiabetic patients with aortic valve disease referred for isolated valve replacement. China	• Mortality • Complications: ○ Cardiac • Infections • Hypoglycaemic events • Length of hospital stay • Length of ICU stay	

Study	Intervention and comparison	Population	Outcomes	Comments
Okabayashi 2009a[113]	**Glucose control:** Received programmed infusions of insulin determined by the control algorithm of the closed-loop system. N=44 **Standard care:** Glucose levels were controlled using a manual injection of insulin according to the commonly used sliding scale. N=44	Patients undergoing hepatectomy. Japan	• Mortality • Infections • Hypoglycaemic events • Length of hospital stay	Closed loop vs sliding scare
Okabayashi 2009b[114]	**Glucose control:** Closed-loop glycemic control system maintained stable blood glucose concentrations by the automatic infusion of regular insulin or glucose into the circulation. N=17 **Standard care:** Continuous monitoring of blood glucose by the artificial pancreas and routine checking by nursing staff every 2 hours. In this group, blood glucose levels were controlled by the subcutaneous injection of regular human insulin; the dose was determined by the sliding scale, and the target blood glucose level to avoid hypoglycemia was 150 to 200	Patients having elective pancreatic resection for pancreatic disease. Japan	• Mortality • Hypoglycaemic events	

Study	Intervention and comparison	Population	Outcomes	Comments
	mg/dL. N=13			

Rujirojindakul 2014[137]	**Glucose control:**
	A hyperinsulinemic normoglycaemic clamp with GIK solution was used to maintain blood glucose levels between 4.4 and 8.3 mmol/l, and the solution was infused via central venous catheter after catheter insertion until sternal closure.
	N=100
	
	Standard care:
	In the control group, insulin was administered bolus intravenously if blood glucose level was more than 13.8 mmol
	N=100
		Patients scheduled for cardiac surgery with the cardiopulmonary bypass.
		
		Thailand
			• Mortality
			• Complications:
			  ○ Cardiac
			  ○ Neuropsychological
			• Infections
			• Hypoglycaemic events
			• Length of hospital stay
			• Length of ICU stay	

Sato 2011[142]	**Glucose control:** Applying the principles of the hyperinsulinemic-normoglycemic clamp technique in the GIN group, insulin was administered at 5mU/kg/min during surgery. Glucose 20% was infused at a rate adjusted to maintain blood glucose 4.0-6.0 mmol/L. BG was measured every 15 minutes. N=20	Patients undergoing elective CABG surgery. Canada	• Hypoglycaemic events	

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard care: Control group received insulin if BG was > 10.0mmol/L based on a sliding scale, also aiming at normoglycemia. BG was measured every 30 minutes. N=20			
Sato 2010[143]	**Glucose control:** GIN therapy group, insulin was administered at 2 mU/kg^{-1}/min^{-1} during surgery. At the end of surgery, the insulin infusion was decreased to 1 mU/kg^{-1}/min^{-1} and continued for 24 hours. Dextrose 20% was infused at a rate adjusted to maintain blood glucose within the target range of 3.5 to 6.1 mmol/L^{-1}. N=26 **Standard care:** Conventional insulin sliding scale during and after surgery. If the blood glucose was >6.1 mmol/ L^{-1}/mg/ dL^{-1} an insulin infusion of 1 U /h^{-1}. N=26	Patients scheduled for elective resection of primary or secondary hepatic malignancy. Japan	• Complications: ○ Neurological • Hypoglycaemic events	
Schricker 2014[146]	**Glucose control:** GIN group: In the operating theatre, blood glucose levels were measured every 5–15 minutes and appropriate adjustments of the dextrose infusion rate were made to	Patients scheduled for elective cardiac surgery. Canada	• Complications: ○ Pulmonary • Infection • Length of ICU stay	30% Diabetes mellitus (type not reported)

Study	Intervention and comparison	Population	Outcomes	Comments
	maintain the blood glucose within the target level of 3.5–6.1 mmol L^{-1} N=16 **Standard care:** In the control group, arterial blood glucose measurements were performed every 30 to 60 minutes while in the operating room. At any of these measurements, if the blood glucose was greater than 10.0 mmol L^{-1}, an insulin bolus of 2 U was given followed by an infusion of 2 U h^{-1} N=18			
Smith 2002[153]	**Glucose control:** GIK infusion, with BG levels measured at 0.5 hour intervals from start to 2 hours after cessation of the GIK infusion. BG levels were maintained at 5 to 10 mmol/L N=22 **Standard care:** Received an equal volume of 5% dextrose in water as placebo. N=22	Patients scheduled for elective multivessel coronary artery surgery using either conventional CPB or OP-CAB techniques. UK	• Complications: ○ Cadiac • Infection • Length of hospital stay	Off-pump and on-pump groups combined. Unclear if standard care group BP was controlled.
Szabo 2001[157]	**Glucose control:** High dose post-operative GIK treatment. Insulin was infused	Patients with type II diabetes undergoing elective coronary surgery.	• Mortality	Post-operative BG control

Study	Intervention and comparison	Population	Outcomes	Comments
	at a rate of 1 IU/h/kg for 6 hours. A bolus of 25 IU injected after 5 minutes. A 30% glucose solution was infused to keep BG between 7 and 10 mmol/L N=10 **Standard care:** Standard post-operative glucose control. Insulin infusion was given if BG exceeded 10mmol/L. N=10			
Tohya 2018[159]	**Glucose control:** Regular insulin was continuously applied with glucose-added acetate Ringer's solution (5–10 g glucose per 500 mL). Blood glucose was adjusted within the target concentration of 80–120 mg/dL. N=10 **Standard care:** Combination of acetate Ringer's solution which contains 1% (W/V) glucose and lactate Ringer's solution, which contains no glucose, was infused. Regular insulin was subcutaneously applied each time when a blood glucose concentration of ≥ 180 mg/dL occurred. N=20	Thirty patients aged ≥ 60 years undergoing a radical operation of oral malignant tumours with tissue reconstruction (≥8 h). Japan	• Complications: ○ Pulmonary • Infection • Length of hospital stay	

Study	Intervention and comparison	Population	Outcomes	Comments
Visser 2005[166]	**Glucose control:** Standard institutional perioperative care with additional infusions of insulin and glucose (GIK) adjusted to maintain blood glucose levels within a target range of 4.0–5.5 mmol/L^{-1}. N=10 **Standard care:** Standard institutional perioperative care. N=11	Patients with normal left ventricular function scheduled for elective CABG. The Netherland	• Hypoglycaemic events • Length of stay in ICU • Length of hospital stay	Unclear if control group received BG control
Yuan 2015[169]	**Glucose control:** Intensive glycaemic management with continuous insulin infusion (target glucose 4.4–6.1 mmol/l (80–110 mg/dl)) N=106 **Standard care:** Conventional glycaemic management with intermittent bolus insulin (target glucose <11.1 mmol/l (<200 mg/dl)) N=106	Patients with type II diabetes who underwent gastrectomy. China	• Mortality • Complications: ○ Pulmonary • Infections • Hypoglycaemic events	Post-operative BG control
Zheng 2010[170]	**Glucose control:** Insulin continuously infused adjusted to maintain BG levels between 70-110 mmol/dL during and after surgery. N=50	Nondiabetic patients undergoing valve replacement with cardiopulmonary bypass. China	• Mortality • Infections • Hypoglycaemic events • Length of hospital stay • Length of ICU stay	

Study	Intervention and comparison	Population	Outcomes	Comments
	Standard care: Received standard institutional operative and post-operative care, but no control for blood glucose. N=50			

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Glucose control versus standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with Glucose control (95% CI)
Mortality	5623 (21 studies) <30 days	⨁⨁⨁⨀ MODERATE4 due to imprecision	RD -0.01 (-0.02 to 0.00)	Moderate	
				32 per 1000	10 fewer per 1000 (from 0 fewer to 20 fewer)
Mortality	3087 (5 studies) >1 years	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.98 (0.79 to 1.23)	Moderate	
				61 per 1000	1 fewer per 1000 (from 13 fewer to 14 more)
Post-operative complication	298 (3 studies)	⨁⨁⨁⨀ MODERATE1 due to imprecision	RD 0 (0 to -0.03)	Moderate	
				252 per 1000	111 fewer per 1000 (from 30 fewer to 165 fewer)
Complications: pulmonary	1138 (7 studies)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.25 (0.76 to 2.07)	Moderate	
				49 per 1000	12 more per 1000 (from 12 fewer to 52 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with Glucose control (95% CI)
Complications: cardiovascular - Cardiac	306 (2 studies)	⨁⨁◯◯ LOW1 due to imprecision	RR 1.15 (0.46 to 3.06)	Moderate	
				53 per 1000	8 more per 1000 (from 0 fewer to 34 more)
Complications: cardiovascular - Cardiac arrest	1332 (4 studies)	⨁⨁⨁◯ MODERATE1 due to imprecision	RR 3.39 (0.94 to 12.26)	Moderate	
				3 per 1000	7 more per 1000 (from 0 fewer to 34 more)
Complications: cardiovascular - MI	469 (3 studies)	⨁⨁◯◯ LOW1 due to imprecision	RR 0.61 (0.24 to 1.52)	Moderate	
				46 per 1000	18 fewer per 1000 (from 35 fewer to 24 more)
Complications: cardiovascular - AF	2305 (7 studies)	⨁⨁⨁⨁ HIGH	RR 0.93 (0.81 to 1.06)	Moderate	
				210 per 1000	15 fewer per 1000 (from 40 fewer to 13 more)
Complications: cardiovascular - Arrhythmia	381 (1 study)	⨁⨁◯◯ LOW1,3 due to imprecision, risk of bias	RR 0.91 (0.68 to 1.2)	Moderate	
				352 per 1000	32 fewer per 1000 (from 113 fewer to 70 more)
Complications: cardiovascular - Sternal instability	65 (1 study)	⨁⨁◯◯ LOW1 due to imprecision	RR 0.32 (0.01 to 7.66)	Moderate	
				31 per 1000	21 fewer per 1000 (from 31 fewer to 208 more)
Complications: neurological - Neurological deficit	1726 (5 studies)	⨁⨁⨁⨁ HIGH	RD 0 (-0.02 to 0)	Moderate	
				52 per 1000	52 fewer per 1000 (from 52 fewer to 53 fewer)
Complications: neurological - Stroke	1521 (5 studies)	⨁⨁◯◯ LOW2 due to inconsistency	RD 0.02 (0 to 0.03)	Moderate	
				5 per 1000	5 fewer per 1000 (from 5 fewer to 5 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard care	Risk difference with Glucose control (95% CI)
Infections	3948 (17 studies)	⨁⨁⨁⨁ HIGH	RR 0.62 (0.5 to 0.77)	Moderate	
				111 per 1000	42 fewer per 1000 (from 26 fewer to 56 fewer)
Hypoglycaemic events	5665 (22 studies)	⨁⨁⨁⨁ HIGH	RD 0.04 (0.03 to 0.05)	Moderate	
				22 per 1000	44 more per 1000 (from 33 more to 55 more)
Length of hospital stay (days)	1081 (10 studies)	⨁⨁⨁⨀ MODERATE2 due to inconsistency		The mean length of hospital stay in the control groups was 12.89 days	The mean length of hospital stay in the intervention groups was 1.19 lower (2.27 to 0.11 lower)
Length of ICU stay (hours)	1145 (11 studies)	⨁⨁⨀⨀ LOW2 due to inconsistency		The mean length of ICU stay in the control groups was 89.3 hours	The mean length of ICU stay in the intervention groups was 6.90 lower (12.65 to 0.16 lower)
Hospital readmission	478 (2 studies)	⨁⨁⨁⨀ MODERATE1 due to imprecision	RR 0.71 (0.41 to 1.21)	Moderate	
				83 per 1000	24 fewer per 1000 (from 49 fewer to 17 more)

(a) Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
(b) Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis.
(c) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
(d) Downgraded by 1 increment if the optimal information size to provide desired power is 80-90% or by 2 increments if <80%.

Table 4: Evidence not suitable for GRADE analysis: Glucose control versus standard care

Outcome	Study (no. of participants)	Risk of bias	Standard care results	Glucose control results	*P* value
Quality of life	Ingels 2006[77] (603)	High	Median Nottingham health profile (IQR): NHP I:13 (0-45)	Median Nottingham health profile (IQR): NHP I:15 (0-48)	0.4

Outcome	Study (no. of participants)	Risk of bias	Standard care results	Glucose control results	*P* value
			NHP II: 0 (0-3)	NHP II: 0 (0-2)	
	Pezzella 2014[120] (41)	High	SF-12: There was no difference between the glucose control groups in HRQL improvement at 6 months post-operation.		0.7
Length of hospital stay (days)	Albacker 2007[5] (44)	Low	Median: 6	Median: 5.5	0.48
	Butterworth 2005[26] (381)	Low	Median (range): 6 (3-85)	Median (range): 7 (3-51)	n/a
	Cao 2011[27] (248)	Low	Median (range): 10 (7-28)	Median (range): 8 (6-26)	<0.001
	Duncan 2018[42] (1399)	Low	Median (95% CI): 8 (6-12)	Median (95% CI): 8 (6-12)	0.35
	Groban 2002[60] (381)	High	Median (range): 6 (3-85)	Median (range): 7 (3-51)	0.62
	Okabayashi 2009[a113] (88)	Very high	Patients in the artificial pancreas group required a significantly shorter hospitalisation than patients in the sliding scale group.		0.049
	Rujirojindakul 2014[137] (199)	Low	Median (IQR): 13 (10-17)	Median (IQR): 13 (10-17.5)	0.48
Length of ICU stay (hours)	Albacker 2007[5] (44)	High	The groups had a similar length of stay in the ICU at 24 hours.		0.94

Outcome	Study (no. of participants)	Risk of bias	Standard care results	Glucose control results	*P* value
	Duncan 2018[42] (1320)	Low	Median (95% CI): 27 (25.2-27.3)	Median (95% CI): 25 (24.9-26.3)	0.025
	Ingels 2006[77] (960)	High	Median (IQR): 48 (48-96)	Median (IQR): 48 (48-72)	0.4
	Rujirojindakul 2014[137] (199)	Low	Median (IQR): 43.8 (24.6-82.5)	Median (IQR): 34.5 (21.6-85.4)	0.32
	Szabo 2001[157] (20)	High	Median: 24	Median: 24	n/a
Hypoglycaemia	Chan 2009[31] (98)	High	Hypoglycaemic episodes per number of glucose measurements		0.67
			2.1%	2.9%	
	Diez 1991[40] (14)	High	1 episode per 28 patient days	1 episode per 9.33 patient days	n/a
	Sato 2010[143] (52)	Very high	Mild hypoglycaemia occurred more frequently after surgery in the GIN therapy group than the standard therapy group.		<0.001
Infection	Grey 2004[59] (61)	High	Bloodstream infections, IVDI or IVDI-related bloodstream infections, and surgical site infections developed in a significantly higher percentage of patients in the standard glucose control group than the tight glucose control group.		<0.05
	Okabayashi 2009a[113] (88)	Very high	The incidence of SSI in the artificial pancreas group was significantly lower than that in the sliding scale group.		0.030

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No health economic studies were included.

1.5.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.6 Evidence statements

1.6.1 Clinical evidence statements

No evidence was identified for health-related quality of life or unplanned ICU admission.

Glucose control versus standard care

Mortality

Twenty one studies demonstrated a clinically important benefit of glucose control in 30-day mortality compared to and standard care (21 studies, n=5623, moderate quality evidence).

Five studies showed no clinically important difference in mortality after 1 year between glucose control and standard care (5 studies, n=3087, moderate quality evidence).

Adverse events

Three studies found a clinically important benefit of glucose control for the number of post-operative complications compared to standard care (3 studies, n=298, moderate quality evidence).

Seven studies showed no clinically important difference in pulmonary complications between glucose control and standard care (7 studies, n=1138, low quality evidence).

Twelve studies showed no clinically important difference in cardiovascular complications between glucose control and standard care (12 studies, n=3868, high quality evidence).

Two studies showed no clinically important difference in cardiovascular complications (cardiac complications) between glucose control and standard care (2 studies, n=306, low quality evidence).

Four studies showed no clinically important difference in cardiovascular complications (cardiac arrest) between glucose control and standard care (4 studies, n=1332, moderate quality evidence).

Two studies showed no clinically important difference in cardiovascular complications (myocardial infarction) between glucose control and standard care (2 studies, n=469, low quality evidence).

Seven studies showed no clinically important difference in cardiovascular complications (atrial fibrillation) between glucose control and standard care (7 studies, n=2305, high quality evidence).

One study showed no clinically important difference in cardiovascular complications (arrhythmia) between glucose control and standard care (1 study, n=381, low quality evidence).

One study showed no clinically important difference in cardiovascular complications (sternal instability) between glucose control and standard care (1 study, n=75, low quality evidence).

Five studies showed no clinically important difference in neurological complications (neurological deficit) between glucose control and standard care (5 studies, n=1726, high quality evidence).

Five studies showed no clinically important difference in neurological complications (stroke) between glucose control and standard care (5 studies, n=1521, low quality evidence).

Infection

Seventeen studies showed no clinically important difference for infections between glucose control and standard care (17 studies, n=3948, high quality evidence).

Hypoglycaemic events

Twenty two studies showed no clinically important difference for hypoglycaemic events between glucose control and standard care (21 studies, n=5665, high quality evidence).

Length of hospital stay

Ten studies showed no clinically important difference in length of hospital stay between glucose control and standard care (10 studies, n=1081, moderate quality evidence).

Length of ICU stay

Eleven studies showed no clinically important difference in length of ICU stay between glucose control and standard care (11 studies, n=1145, low quality evidence).

Readmissions

Two studies showed no clinically important difference in hospital readmissions between glucose control and standard care (2 studies, n=478, moderate quality evidence).

Evidence not suitable for GRADE analysis

Two studies found no statistically significant difference in quality of life between glucose control and standard care (2 studies, n=644, high risk of bias).

Seven studies showed no statistically significant difference in length of hospital stay between glucose control and standard care (7 studies, n=2865, low risk of bias).

Five studies showed no statistically significant difference in length of ICU stay between glucose control and standard care (5 studies, n=2668, high risk of bias).

Three studies showed a trend to harm with glucose control for hypoglycaemic events compared to standard care.

Two studies showed a statistically significant benefit with tight glucose control for risk of infection compared to standard care (2 studies, n=149, very high risk of bias).

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

Please see recommendations 1.4.6 – 1.4.7 in the guideline.

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee highlighted that inadequate glucose control is associated with risk of increased length of stay as a result of complications and even increased mortality. There has also been debate as to whether the benefits of tight glycaemic control with insulin outweighs the risk of harm from hypoglycaemia caused by intensive insulin therapy with intravenous insulin infusions. As such, the committee considered critical outcomes for decision making to be health-related quality of life, mortality, adverse events and complications, infections and hypoglycaemia, and important outcomes to be length of hospital stay, unplanned ICU admission, ICU length of stay and hospital readmission

No evidence was identified for health-related quality of life or unplanned ICU admission.

1.7.1.2 The quality of the evidence

The quality of evidence that was suitable for GRADE analysis ranged from low to high. The majority of the evidence was graded at moderate quality. This was mostly due to imprecision of data, reducing the certainty with which the committee could make conclusions from the evidence. The committee felt that the evidence presented was of sufficient quality and quantity to support the recommendations made.

1.7.1.3 Benefits and harms

The committee reviewed the body of evidence comparing tight glucose control to standard care.

Across most of the outcomes there was little evidence of clinically important difference between the two glucose control methods.

There was a visible trend of more hypoglycaemic events with tight glucose control, although this difference did not meet the threshold of clinically important difference. The committee felt that this was still a significant observation, given the significance of hypoglycaemic events and the efforts that should be made to avoid such outcomes.

Evidence showed a slight increase in risk in mortality at 30 days, although this difference was not seen at 1 year post-operatively. The committee considered that across all of the evidence from mortality, there was little to suggest a significant impact from glucose control.

Evidence from three studies showed a lower risk of post-operative complications with tight glucose control. However, evidence from seven studies showed no difference in pulmonary complications, evidence from 13 studies showed no difference in cardiovascular complications, and evidence from 10 studies showed no difference in neurological complications. There was also no evidence of difference in rate of infections, length of hospital stay, length of ICU stay or hospital readmissions.

The committee agreed that people undergoing surgery may require some blood glucose control to reduce the risk of infections, but also that healthcare professionals should endeavour to avoid the adverse events such as hypoglycaemic events from lowering a patient's blood sugar too much in an attempt to achieve a tight blood glucose control due to the serious health implications. The committee added that a more liberal blood glucose control may allow planned surgery to go ahead even if the person undergoing surgery's blood sugar is outside of the optimum range, where this surgery may have otherwise been unnecessarily cancelled.

1.7.2 Cost effectiveness and resource use

No economic evaluations were identified for this question.

The clinical review showed that there was little evidence of an important difference between the two blood glucose control methods. The committee highlighted that both forms of blood glucose control would require monitoring the patient during surgery, which requires nurse time. The amount of insulin required to maintain the adequate blood glucose level varies between people, but with tight glucose control it may require more insulin and additional staff time as the patients are being monitored more strictly. Conclusions could not be made regarding the cost effectiveness of tight blood glucose control during surgery due to the clinical evidence not showing a benefit, and that it may lead to an increase in resource use.

The committee acknowledged that the recommendation would not lead to a substantial resource impact as current practice across most centres is to not routinely aim for tight blood glucose control.

1.7.3 Other factors the committee took into account

The committee recognised the importance of consulting with an inpatient specialist diabetes team before decisions around blood glucose monitoring and diabetes management are made during perioperative surgery.

The committee discussed that the range for blood glucose could be 6-10 mmol/L was desirable but this was not the focus of the evidence review.

The committee noted that patients who undergo surgery often develop a hypermetabolic stress response, which is characterised by hyperglycaemia and insulin resistance. The committee suggested that hyperglycaemia can often be an index of the stress the patient is undergoing perioperatively. The aim of intensive or tight glucose control is to achieve normoglycemia, although the evidence showed no overall clinical benefit to this strategy.

The committee were aware of a large body of research conducted in ICU medical patients reviewing the efficacy of tight glucose control. The committee noted that this evidence suggested an increased risk of hypoglycaemic events with tight glucose control. The committee considered this evidence when making a recommendation for patients undergoing surgery.

The recommendation will prevent surgical cancellations if a patient does not have optimised glucose control.

The committee were aware of the recommendations on target blood glucose in the NICE guideline of type 2 diabetes (NG28)

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: Blood glucose control management

ID	Field	Content
0.	PROSPERO registration number	Not registered on PROSPERO
1.	Review title	What is the clinical and cost effectiveness of blood glucose control management in adults undergoing surgery?
2.	Review question	What is the clinical and cost effectiveness of blood glucose control management in adults undergoing surgery?
3.	Objective	To determine the clinical and cost effectiveness of blood glucose control management in adults during surgery.
4.	Searches	• Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Perioperative care
6.	Population	Inclusion: Adults 18 years and over having surgery. Exclusion: • children and young people aged 17 years and younger • surgery for burns, traumatic brain injury or neurosurgery • people with type 1 diabetes
7.	Intervention/Exposure/Test	• glucose control (insulin therapy, intra to postoperative)
8.	Comparator/Reference standard/Confounding factors	• standard care (no glucose control)

9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. Observational studies if no RCT evidence is identified.
10.	Other exclusion criteria	Exclusions: • non-English language studies • cross-over randomised controlled trials • studies published before 2000
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	• health-related quality of life • mortality • adverse events and complications (Clavien-Dindo, postoperative morbidity score (POMS), cardiovascular, respiratory and neurological complications) • infections (including surgical site) • hypoglycaemia The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
13.	Secondary outcomes (important outcomes)	• length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • hospital readmission The committee did not agree to on any established minimal clinically important differences, therefore the default MIDs will be used and any difference in mortality will be considered clinically important.
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in

		Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I • Case control study: CASP case control checklist • Controlled before-and-after study or Interrupted time series: Effective Practice and Organisation of Care (EPOC) RoB Tool • Cross sectional study: JBI checklist for cross sectional study • Case series: Institute of Health Economics (IHE) checklist for case series 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • CERQual will be used to synthesise data from qualitative studies. • WinBUGS will be used for network meta-analysis, if possible given the data identified.

<table>
<tr><td></td><td></td><td colspan="3">• List any other software planned to be used.

Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects.</td></tr>
<tr><td>17.</td><td>Analysis of sub-groups</td><td colspan="3">Subgroups:
• older adults (over 60)
• surgery grade based on NICE preoperative tests for elective surgery guideline categorisation
• American Society of Anesthesiologists (ASA) Physical Status grade
• cardiac surgery
• people with type 2 diabetes
• BMI ≥30kg/m^2</td></tr>
<tr><td rowspan="8">18.</td><td rowspan="8">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
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<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">[To be added.]</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">[To be added.]</td></tr>
<tr><td rowspan="7">23.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
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<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
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		Data analysis	☐	☐
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail perioperativecare@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Ms Kate Ashmore Ms Kate Kelley Ms Sharon Swain Mr Ben Mayer Ms Maria Smyth Mr Vimal Bedia Mr Audrius Stonkus Ms Madelaine Zucker Ms Margaret Constanti Ms Annabelle Davis Ms Lina Gulhane		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be		

		overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website.	
29.	Other registration details	n/a	
30.	Reference/URL for published protocol	n/a	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Perioperative care, glucose, blood sugar	
33.	Details of existing review of same topic by same authors	n/a	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	Commissioning information: Update MTG3 Cardiac monitoring devices as part of this new guideline. The guidance review found that significant changes in the care pathway involving CardioQ-ODM meant there was a case for updating the guidance from both clinical and economic perspectives. Since MTG3 was published, system-wide initiatives to improve perioperative care, such as the Enhanced Recovery Programmes, may have resulted in interventions, (including intraoperative fluid management (IOFM) using technologies such as CardioQ-ODM), becoming widely adopted for major surgery.	
36.	Details of final publication	www.nice.org.uk	

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[108] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. For example, economic evaluations based on observational studies will be excluded, when the clinical review is only looking for RCTs,

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018.[108]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 30 May 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
Epistemonikos (Epistemonikos Foundation)	Inception - 10 May 2019	Systematic review studies

Medline (Ovid) search terms

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or complicat*)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	*Postoperative Complications/
7.	or/1-6
8.	limit 7 to English language
9.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
10.	8 not 9

11.	letter/
12.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
13.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
14.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
15.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or complicat*)).ti,ab.
16.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
17.	*Postoperative Complications/
18.	or/1-6
19.	limit 7 to English language
20.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
21.	8 not 9
22.	letter/
23.	editorial/
24.	news/
25.	exp historical article/
26.	Anecdotes as Topic/
27.	comment/
28.	case report/
29.	(letter or comment*).ti.
30.	or/11-18
31.	randomized controlled trial/ or random*.ti,ab.
32.	19 not 20
33.	animals/ not humans/
34.	exp Animals, Laboratory/
35.	exp Animal Experimentation/
36.	exp Models, Animal/
37.	exp Rodentia/
38.	(rat or rats or mouse or mice).ti.
39.	or/21-27
40.	10 not 28
41.	Blood Glucose/
42.	(glucose adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
43.	(blood sugar* adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
44.	((glycaemic or glycemic or glycaemia or glycemia or hyperglycemia or hyperglycaemia or dysglycaemia or dysglycemia or hypoglycaemia or hypoglycemia) adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
45.	(insulin adj2 (therap* or infusion* or intravenous* or IV)).ti,ab.
46.	exp Diabetes Mellitus/
47.	(diabet* adj2 (mellitus or type 1 or type1 or type I or type one)).ti,ab.
48.	(diabet* adj2 (type 2 or type2 or type II or type two)).ti,ab.

49.	Hemoglobin A, Glycosylated/
50.	((glycosylated or glycated) adj2 (hemoglobin or haemoglobin)).ti,ab.
51.	(Hb A1* or HbA1*).ti,ab.
52.	(glycohemoglobin A or glycohaemoglobin A).ti,ab.
53.	or/30-41
54.	29 and 42
55.	randomized controlled trial.pt.
56.	controlled clinical trial.pt.
57.	randomi#ed.ab.
58.	placebo.ab.
59.	randomly.ab.
60.	clinical trials as topic.sh.
61.	trial.ti.
62.	or/44-50
63.	Meta-Analysis/
64.	Meta-Analysis as Topic/
65.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
66.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
67.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
68.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
69.	(search* adj4 literature).ab.
70.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
71.	cochrane.jw.
72.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
73.	or/52-61
74.	43 and (51 or 62)

Embase (Ovid) search terms

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or complicat*)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	*Postoperative complication/
7.	or/1-6
8.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
9.	7 not 8
10.	limit 9 to English language
11.	letter.pt. or letter/

12.	note.pt.
13.	editorial.pt.
14.	case report/ or case study/
15.	(letter or comment*).ti.
16.	or/11-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental Animal/
23.	animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	10 not 26
28.	Glucose blood level/
29.	(glucose adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
30.	(blood sugar* adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
31.	((glycaemic or glycemic or glycaemia or glycemia or hyperglycemia or hyperglycaemia or dysglycaemia or dysglycemia or hypoglycaemia or hypoglycemia) adj2 (monitor* or measur* or control* or level* or regulat* or manag*)).ti,ab.
32.	(insulin adj2 (therap* or infusion* or intravenous* or IV)).ti,ab.
33.	exp Diabetes Mellitus/
34.	(diabet* adj2 (mellitus or type 1 or type1 or type I or type one)).ti,ab.
35.	(diabet* adj2 (type 2 or type2 or type II or type two)).ti,ab.
36.	Hemoglobin A, Glycosylated/
37.	((glycosylated or glycated) adj2 (hemoglobin or haemoglobin)).ti,ab.
38.	(Hb A1* or HbA1*).ti,ab.
39.	(glycohemoglobin A or glycohaemoglobin A).ti,ab.
40.	or/28-39
41.	27 and 40
42.	random*.ti,ab.
43.	factorial*.ti,ab.
44.	(crossover* or cross over*).ti,ab.
45.	((doubl* or singl*) adj blind*).ti,ab.
46.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
47.	crossover procedure/
48.	single blind procedure/
49.	randomized controlled trial/
50.	double blind procedure/
51.	or/42-50
52.	systematic review/
53.	Meta-Analysis/
54.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.

55.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
56.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
57.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
58.	(search* adj4 literature).ab.
59.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
60.	cochrane.jw.
61.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
62.	or/52-61
63.	51 or 62
64.	41 and 63

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Preoperative Care] explode all trees
#2.	MeSH descriptor: [Perioperative Care] explode all trees
#3.	MeSH descriptor: [Perioperative Period] explode all trees
#4.	MeSH descriptor: [Perioperative Nursing] explode all trees
#5.	(or #1-#4)
#6.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)):ti,ab
#7.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)):ti,ab
#8.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) near/3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine or complicat*)):ti,ab
#9.	((care* or caring or treat* or nurs* or recover* or monitor*) near/3 (before or prior or advance or during or after) near/3 (surg* or operat* or anaesthes* or anesthes*)):ti,ab
#10.	MeSH descriptor: [Postoperative Complications] this term only
#11.	(or #5-#10)
#12.	MeSH descriptor: [Blood Glucose] explode all trees
#13.	(glucose near/2 (monitor* or measur* or control* or level* or regulat* or manag*)):ti,ab
#14.	(blood sugar* near/2 (monitor* or measur* or control* or level* or regulat* or manag*)):ti,ab
#15.	((glycaemic or glycemic or glycaemia or glycemia or hyperglycemia or hyperglycaemia or dysglycaemia or dysglycemia or hypoglycaemia or hypoglycemia) near/2 (monitor* or measur* or control* or level* or regulat* or manag*)):ti,ab
#16.	(insulin near/2 (therap* or infusion* or intravenous* or IV)):ti,ab
#17.	MeSH descriptor: [Diabetes Mellitus] explode all trees
#18.	(diabet* near/2 (mellitus or type 1 or type1 or type I or type one)):ti,ab
#19.	(diabet* near/2 (type 2 or type2 or type II or type two)):ti,ab
#20.	MeSH descriptor: [Glycated Hemoglobin A] explode all trees
#21.	((glycosylated or glycated) near/2 (hemoglobin or haemoglobin)):ti,ab
#22.	(Hb A1* or HbA1*):ti,ab
#23.	(glycohemoglobin A or glycohaemoglobin A):ti,ab
#24.	(or #12-#23)
#25.	#11 and #24

Epistemonikos (Epistemonikos Foundation) search terms

1.	(title:(pre-operative* OR preoperative* OR preop* OR pre-op* OR pre-surg* OR presurg* OR perioperative* OR peri-operative* OR intraoperative* OR intra-operative* OR intrasurg* OR intra-surg* OR peroperat* OR per-operat* OR postoperative* OR postop* OR post-op* OR post-surg* OR postsurg*) OR abstract:(pre-operative* OR preoperative* OR preop* OR pre-op* OR pre-surg* OR presurg* OR perioperative* OR peri-operative* OR intraoperative* OR intra-operative* OR intrasurg* OR intra-surg* OR peroperat* OR per-operat* OR postoperative* OR postop* OR post-op* OR post-surg* OR postsurg*)) AND (title:(glucose OR sugar OR diabet*) OR abstract:(glucose OR sugar OR diabet*))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the perioperative care population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 30 May 2019	Exclusions Health economics studies
Embase	2014 – 30 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 02 May 2019 NHSEED - Inception to 02 May 2019	None

Medline (Ovid) search terms

1.	exp Preoperative Care/ or exp Perioperative Care/ or exp Perioperative Period/ or exp Perioperative Nursing/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
5.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
6.	1 or 2 or 3 or 4 or 5
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	7 or 8
10.	postoperative care/ or exp Postoperative Period/ or exp Perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.

12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp Preoperative Care/ or Preoperative Period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	6 or 9 or 14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
41.	39 not 40
42.	economics/
43.	value of life/
44.	exp "costs and cost analysis"/
45.	exp Economics, Hospital/
46.	exp Economics, medical/
47.	Economics, nursing/
48.	economics, pharmaceutical/
49.	exp "Fees and Charges"/
50.	exp budgets/
51.	budget*.ti,ab.
52.	cost*.ti.
53.	(economic* or pharmaco?economic*).ti.
54.	(price* or pricing*).ti,ab.
55.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

56.	(financ* or fee or fees).ti,ab.
57.	(value adj2 (money or monetary)).ti,ab.
58.	or/42-57
59.	41 and 58

Embase (Ovid) search terms

1.	*preoperative period/ or *intraoperative period/ or *postoperative period/ or *perioperative nursing/ or *surgical patient/
2.	((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
3.	((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)).ti,ab.
4.	((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
5.	1 or 2 or 3 or 4
6.	peroperative care/ or exp peroperative care/ or exp perioperative nursing/
7.	(intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*).ti,ab.
8.	((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
9.	6 or 7 or 8
10.	postoperative care/ or exp postoperative period/ or perioperative nursing/
11.	(postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*).ti,ab.
12.	(after adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
13.	(post adj3 (operat* or anaesthes* or anesthes*)).ti,ab.
14.	10 or 11 or 12 or 13
15.	exp preoperative care/ or preoperative period/
16.	(pre-operat* or preoperat* or pre-surg* or presurg*).ti,ab.
17.	((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)).ti,ab.
18.	15 or 16 or 17
19.	5 or 9 or 14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/

33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	limit 36 to English language
38.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
39.	37 not 38
40.	health economics/
41.	exp economic evaluation/
42.	exp health care cost/
43.	exp fee/
44.	budget/
45.	funding/
46.	budget*.ti,ab.
47.	cost*.ti.
48.	(economic* or pharmaco?economic*).ti.
49.	(price* or pricing*).ti,ab.
50.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
51.	(financ* or fee or fees).ti,ab.
52.	(value adj2 (money or monetary)).ti,ab.
53.	or/40-52
54.	39 and 53

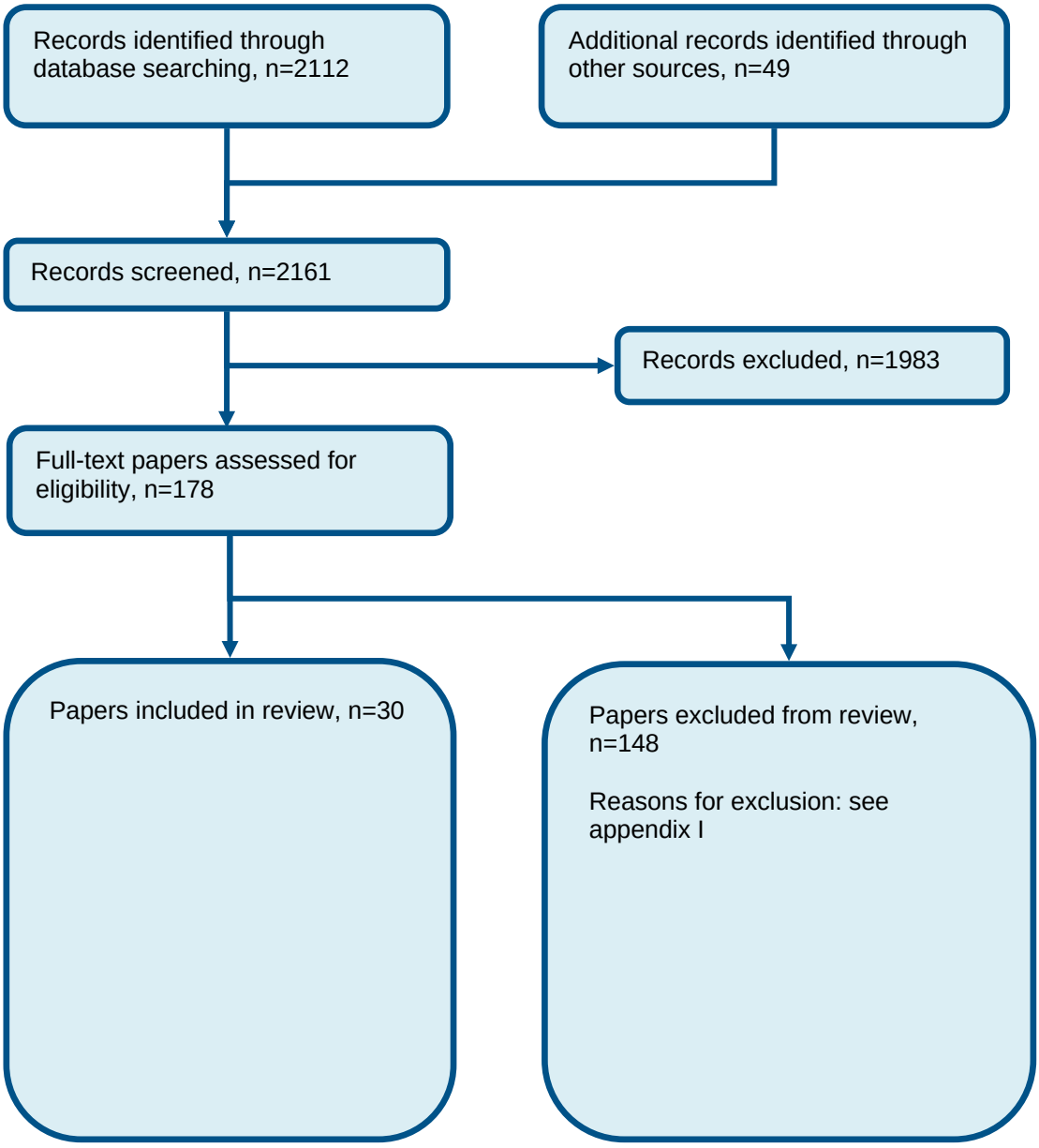
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Preoperative Care EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Perioperative Care EXPLODE ALL TREES
#3.	MeSH DESCRIPTOR Perioperative Period EXPLODE ALL TREES
#4.	MeSH DESCRIPTOR Perioperative Nursing EXPLODE ALL TREES
#5.	(((perioperative* or peri-operative* or intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#6.	(((care* or caring or treat* or nurs* or recover* or monitor*) adj3 (before or prior or advance or during or after) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#7.	(((pre-operative* or preoperative* or preop* or pre-op* or pre-surg* or presurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#8.	(((postoperative* or postop* or post-op* or post-surg* or postsurg*) adj3 (care* or caring or treat* or nurs* or monitor* or recover* or medicine)))
#9.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10.	(* IN HTA)
#11.	(* IN NHSEED)
#12.	#9 AND #10
#13.	#9 AND #11
#14.	MeSH DESCRIPTOR Intraoperative Care EXPLODE ALL TREES
#15.	#1 OR #2 OR #3 OR #4 OR #14

#16.	((intraoperative* or intra-operative* or intrasurg* or intra-surg* or peroperat* or per-operat* or perioperat* or peri-operat*))
#17.	(((during or duration) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#18.	((postop* or post-op* or post-surg* or postsurg* or perioperat* or peri-operat*))
#19.	((after adj3 (surg* or operat* or anaesthes* or anesthes*)))
#20.	((post adj3 (operat* or anaesthes* or anesthes*)))
#21.	((pre-operat* or preoperat* or pre-surg* or presurg*))
#22.	(((before or prior or advance or pre or prepar*) adj3 (surg* or operat* or anaesthes* or anesthes*)))
#23.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#24.	#10 AND #23
#25.	#11 AND #23
#26.	#12 OR #13 OR #24 OR #25

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of blood glucose control management



Appendix D: Clinical evidence tables

Study	Abdelmalak 2013[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=381)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	≥40 yr old having open major vascular surgery
Exclusion criteria	Patients who received i.v. or oral steroid therapy within 30 days, had any contraindications to the proposed interventions, had an ASA Physical Status (ASA PS)>IV, or were not fluent in English.
Age, gender and ethnicity	Age - Mean (SD): 64 (11). Gender (M:F): percentage male: Glucose group 64, standard care 70. Ethnicity: Not stated
Further population details	1. Age: Systematic review: mixed (equal to or over 40 years). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Systematic review: mixed (I to IV). 3. BMI ≥30kg/m2: BMI <30kg/m2 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear 6. Type 2 diabetes: Not stated / Unclear (Just sates 'diabetes', which was 28% and 26% for the glucose and standard care group respectively.).
Indirectness of population	No indirectness
Interventions	(n=196) Intervention 1: Glucose control - Insulin therapy (intraoperative). Blood glucose concentrations were targeted to 4.4–6.1 mmol litre-1 (80–110 mg/dl-1), beginning shortly after induction of anaesthesia. . Duration 1 year. Concurrent medication/care: Not stated. Indirectness: No indirectness (n=185) Intervention 2: Standard care - Liberal glucose control. Blood glucose concentrations were targeted to 10–11.1 mmol litre-1 (180–200 mg dl-1), beginning shortly after induction of anaesthesia

Study	Abdelmalak 2013[1]
	Duration 1 year. Concurrent medication/care: Not stated. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Financial support for the submitted work from Aspec Medical (now Covidien), Cleveland Clinic Research Project Committee, Anesthesiology Institute (departmental funds), Abbott Laboratories Inc. (limited support; supplied reagents for CRP analysis), W.H.W.T received grant support (money to the institution) in support of other studies from Abbott Laboratories. This is an investigator-initiated trial independent of the study sponsors.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL Protocol outcome 1: Mortality - Actual outcome: Mortality at <30 days; Group 1: 4/196, Group 2: 4/185 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: Mortality at 1 year; Group 1: 24/196, Group 2: 21/185 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Adverse events and complications - Actual outcome: Pulmonary complications at Unclear; Group 1: 14/196, Group 2: 8/185 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: Myocardial infarction at Unclear; Group 1: 2/196, Group 2: 4/185 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: Stroke at Unclear; Group 1: 0/196, Group 2: 0/185 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Quality of life ; Infection (including SSI) ; Hypoglycaemia ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Albacker 2007[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Canada; Setting: Mcgill university health centre
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients referred to a single surgeon for CABG surgery.
Exclusion criteria	emergency CABG, redo CABG, combined CABG, any other cardiac procedure and any deviation from protocol.
Age, gender and ethnicity	Age - Mean (SD): 62 (4). Gender (M:F): 36/8. Ethnicity: unclear
Further population details	1. Age: Systematic review: mixed 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. BMI ≥30kg/m2: Not stated / Unclear 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear 6. Type 2 diabetes: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Glucose control - Insulin therapy (intraoperative). Fixed high-dose systemic insulin infusion at 5 mU/kg/min. Dextrose 20% was infused in the same group at a rate adjusted to maintain a blood glucose of 4 to 6 mmol/L. . Duration of surgery. Concurrent medication/care: in diabetic patients taking oral hypoglycemics, administration of these were discontinued 24 hours before the operation and administration of subcutaneous insulin was administered on a sliding scale. for diabetic patients taking insulin their daily dose was held then ending before surgery and an intravenous insulin infusion was titrated to maintain blood glucose below the level of 10 mmol/l.. Indirectness: No indirectness (n=22) Intervention 2: Standard care - Liberal glucose control. Intraoperative titrated intravenous insulin

Study	Albacker 2007[5]
	infusion, titrated according to sliding scale starting at blood glucose level of 10 mmol/L. . Duration of surgery. Concurrent medication/care: in diabetic patients taking oral hypoglycemics, administration of these were discontinued 24 hours before the operation and administration of subcutaneous insulin was administered on a sliding scale. for diabetic patients taking insulin their daily dose was held then ending before surgery and an intravenous insulin infusion was titrated to maintain blood glucose below the level of 10 mmol/l.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Adverse events and complications
- Actual outcome: pulmonary complications at length of stay; Group 1: 2/22, Group 2: 0/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: MI at length of stay; Group 1: 0/22, Group 2: 1/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: AF at length of stay; Group 1: 6/22, Group 2: 3/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Infection (including SSI)
- Actual outcome: superficial wound infection at length of stay; Group 1: 1/22, Group 2: 1/22
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Length of hospital stay
- Actual outcome: length of hospital stay at length of stay;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Length of stay in intensive care unit
- Actual outcome: length of ICU stay at length of stay;

Study	Albacker 2007[5]
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hypoglycaemia ; Unplanned ICU admission ; Hospital readmission

Study	Azarfarin 2011[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Iran; Setting: single referral teaching centre
Line of therapy	Not applicable
Duration of study	Intervention time: The measurement was performed every 30 minutes intraoperatively until the closure of the sternum and thereafter every 2 hours up to 48 hours postoperatively
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: elective CABG surgery
Stratum	Overall: not applicable
Subgroup analysis within study	Not applicable: not applicable
Inclusion criteria	One hundred twenty nondiabetic patients of American Society of Anesthesiologists status Class II or III who underwent elective CABG surgery from December 2008 to October 2009 in Madani Heart Hospital, a referral teaching centre in northwest of Iran
Exclusion criteria	Patients with American Society of Anesthesiologists status Class IV, those who received insulin or oral hypoglycemic agents before surgery and those in whom inotropic drugs or intra-aortic balloon pump (IABP) were used, were excluded from the study. Also, patients with considerable intraoperative blood loss, hyperkalemia that required insulin and glucose infusion for treatment, and who had seen cardiac arrest before were excluded from the study.
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (SD): study group - 57.0 (10.3) control group 56.3 (9.3). Gender (M:F): 96/23. Ethnicity: not

	reported
Further population details	1. Age: Not stated / Unclear (unclear how many patients over 60). 2. American Society of Anesthesiologists (ASA) Physical Status grade: ASA 4 3. BMI ≥30kg/m2: Not stated / Unclear (unclear how many patients over 30 BMI). 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes: Non-diabetic
Indirectness of population	No indirectness: not applicable
Interventions	(n=60) Intervention 1: Glucose control - Insulin therapy (intraoperative). In the study group, insulin was infused to maintain BG level between 110 mg/dL and 126 mg/dL (a modified insulin therapy protocol). Because of concerns about hypoglycemia occurrence, target BG level was changed from tight control (80-110 mg/dL) to semitight control (110-126 mg/dL). The measurement was performed every 30 minutes intraoperatively until the closure of the sternum and thereafter every 2 hours up to 48 hours postoperatively. . Duration intraoperatively. Concurrent medication/care: Anesthesia was induced with benzodiazepine (midazolam, 0.05-0.1 mg/kg); opioid (fentanyl, 25-40 mg/kg, or sufentanil, 2.5-4 mg/kg); and muscle relaxant (cisatracurium, 0.2 mg/kg). Anesthesia was maintained with midazolam (1-2 mg/kg/min), fentanyl (1e2 mg/kg/h), and cisatracurium (1-3 mg/kg/min). In this study, the patients underwent “CABG with cardiopulmonary bypass (on-pump)” or “without cardiopulmonary bypass (off-pump),” During the postoperative period, insulin bolus was administered if BG level exceeded 200 mg/dL [as a part of the intensive care unit (ICU) management in both groups not related to the study protocol] . Indirectness: No indirectness; Indirectness comment: not applicable (n=60) Intervention 2: Standard care - No glucose control. no intervention was done unless the BG level exceeded 200 mg/dL (treated by bolus insulin).. Duration intraoperatively. Concurrent medication/care: Anesthesia was induced with benzodiazepine (midazolam, 0.05-0.1 mg/kg); opioid (fentanyl, 25-40 mg/kg, or sufentanil, 2.5-4 mg/kg); and muscle relaxant (cisatracurium, 0.2 mg/kg). Anesthesia was maintained with midazolam (1-2 mg/kg/min), fentanyl (1-2 mg/kg/h), and cisatracurium (1-3 mg/kg/min). In this study, the patients underwent “CABG with cardiopulmonary bypass (on-pump)” or “without cardiopulmonary bypass (off-pump),”. Indirectness: No indirectness; Indirectness comment: not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: mortality at during hospital stay; Group 1: 1/59, Group 2: 1/58; Comments: One patient in each

group died during postoperative ICU stay because of cardiogenic

shock.

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: not applicable; Group 1 Number missing: 1, Reason: excessive intraoperative blood loss; Group 2 Number missing: 2, Reason: severe hemodynamic instability

Protocol outcome 2: Adverse events and complications
- Actual outcome: cardiac complications at during hospital stay; Group 1: 6/59, Group 2: 5/58; Comments: In the study group, six patients

experienced cardiac complications (new-onset atrial fibrillation in five patients and myocardial infarction in one). In control group, five patients experienced cardiac complications (new-onset atrial fibrillation in four patients and myocardial infarction in one),

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: not applicable; Group 1 Number missing: 1, Reason: excessive intraoperative blood loss; Group 2 Number missing: 2, Reason: severe hemodynamic instability
- Actual outcome: pulmonary complications at during hospital stay;
Risk of bias: All domain - ; Indirectness of outcome: No indirectness, Comments: not applicable
- Actual outcome: neuropsychosocial complications at during hospital stay;
Risk of bias: All domain - ; Indirectness of outcome: No indirectness, Comments: not applicable

Protocol outcome 3: Hypoglycaemia
- Actual outcome: hypoglycemic events at during hospital stay;
Risk of bias: All domain - ; Indirectness of outcome: No indirectness, Comments: not applicable

Protocol outcomes not reported by the study	Quality of life ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	**Butterworth 2005[26]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=381)
Countries and setting	Conducted in USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months

Study	Butterworth 2005[26]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	English-speaking adults between the ages of 35 and 80 years scheduled to undergo coronary artery bypass grafting with cardiopulmonary bypass.
Exclusion criteria	People with a history of diabetes mellitus treated by diet, oral hypoglycemic agents, or insulin were excluded. People with a history of a neurodegenerative disease (eg, Alzheimer or Parkinson disease), major depressive disorder, or psychosis in the past 5 years were also excluded.
Age, gender and ethnicity	Age - Other: 50 years: 17%, 51-60 years: 29%, 61-70 years: 35%, >70years: 19%. Gender (M:F): 308/73. Ethnicity: 95% white, 5% black population
Further population details	1. Age: Systematic review: mixed (>50 years). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. BMI ≥30kg/m2: BMI <30kg/m2 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear 6. Type 2 diabetes: Non-diabetic (People with a history of diabetes mellitus treated by diet, oral hypoglycemic agents, or insulin were excluded).
Indirectness of population	No indirectness
Interventions	(n=188) Intervention 1: Glucose control - Insulin therapy (intraoperative). Arterial blood samples were obtained at 15-minute intervals during CABG to measure blood glucose concentrations with a handheld glucose meter. After induction of anaesthesia, insulin infusion at 2 U/h in a 70-kg patient was started when the blood glucose concentration exceeded 100 mg/dL. When blood glucose concentrations decreased to less than 70 mg/dL, 100 to 200 mL of dextrose 5% was administered at the direction of the study nurse.. Duration Intraoperative treatment. Concurrent medication/care: All subjects were premedicated with morphine, 0.1 mg·kg-1 administered intramuscularly, and, in most cases, oral lorazepam, 50 ug·kg-1. Anesthesia consisted of intravenous fentanyl, 25 to 50 ug·kg-1, and midazolam, 0.1 to 0.3 mg·kg-1. After neuro-muscular blockade (in most cases intravenous pancuronium, 0.1-0.15 mg·kg-1), intubated subjects were ventilated with oxygen-enriched air. Enflurane at inhaled concentrations of 1% or less was sometimes used to supplement general anesthesia. Dextrose was present in cardioplegic solutions. Indirectness: No indirectness (n=193) Intervention 2: Standard care - No glucose control. Arterial blood samples were obtained at 15-minute intervals during CABG to measure blood glucose concentrations with a handheld glucose meter. Blood glucose concentrations were measured and recorded for later analysis. A saline infusion was periodically adjusted to preserve blinding. Duration Intraoperative treatment . Concurrent medication/care: All

Study	Butterworth 2005[26]
	subjects were premedicated with morphine, 0.1 mg·kg-1 administered intramuscularly, and, in most cases, oral lorazepam, 50 ug·kg-1. Anesthesia consisted of intravenous fentanyl, 25 to 50 ug·kg-1, and midazolam, 0.1 to 0.3 mg·kg-1. After neuro-muscular blockade (in most cases intravenous pancuronium, 0.1-0.15 mg·kg-1), intubated subjects were ventilated with oxygen-enriched air. Enflurane at inhaled concentrations of 1% or less was sometimes used to supplement general anesthesia. Dextrose was present in cardioplegic solutions.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL Protocol outcome 1: Mortality - Actual outcome: Mortality at 24 hours; Group 1: 6/188, Group 2: 5/193 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Adverse events and complications - Actual outcome: Cardiac arrest at 24 hours; Group 1: 3/188, Group 2: 1/193 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: Stroke at 24 hours; Group 1: 5/188, Group 2: 3/193 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Hypoglycaemia - Actual outcome: Hypoglycaemia (blood glucose of <70 mg/dL) at 24 hours; Group 1: 22/188, Group 2: 12/193 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Hospital readmission - Actual outcome: Rehospitilisation at 24 hours; Group 1: 19/188, Group 2: 28/193 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the	Quality of life ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of

Study	Butterworth 2005[26]
study	stay in intensive care unit

Study	Cao 2011[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=260)
Countries and setting	Conducted in China; Setting:
Line of therapy	Unclear
Duration of study	Intervention + follow up: 28 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged between 18 and 80 years undergoing open elective gastrectomy for gastric cancer and required at least 5 days of parenteral nutrition
Exclusion criteria	Diabetes mellitis or impaired glucose tolerance, contraindications for parenteral nutrition or unnecessary to receive parenteral nutrition postoperatively assessed by clinical nutritionist, palliative surgery, taking corticosteroids, steroids, growth hormone, or immunosuppressive drugs within 2 weeks prior to the study, patients received neoadjuvant radiochemotherapy and patient was diagnosed with gastric stump cancer or recurrent gastric cancer.
Age, gender and ethnicity	Age - Mean (SD): Glucose group: 58.5 (8.1); standard care group: 59.9 (7.6). Gender (M:F): Glucose group: 83/42; standard care group: 79/44. Ethnicity: Not stated
Further population details	1. Age: Systematic review: mixed (18-80 years). 2. American Society of Anesthesiologists (ASA) Physical Status grade: Systematic review: mixed (ASA I, II and III). 3. BMI ≥30kg/m2: BMI <30kg/m2 4. Cardiac surgery: Non-cardiac surgery (Gastrectomy for gastric cancer). 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear 6. Type 2 diabetes: Non-diabetic
Indirectness of population	No indirectness
Interventions	(n=132) Intervention 1: Glucose control - Insulin therapy (postoperative). Intensive group in which the postoperative blood glucose was maintained at a level between 4.4 and 6.1 mmol/l. . Duration Unclear. Concurrent medication/care: Parenteral nutrition given for at least 5 days after surgery

Study	Cao 2011[27]
	through the central or peripheral vein. This was terminated when the oral or enteral ingestion exceeded 50% of target energy requirements. . Indirectness: No indirectness (n=128) Intervention 2: Standard care - Liberal glucose control. Conventional group in which the postoperative blood glucose was maintained at a level below 11.0 mmol/l. . Duration Unclear. Concurrent medication/care: Parenteral nutrition given for at least 5 days after surgery through the central or peripheral vein. This was terminated when the oral or enteral ingestion exceeded 50% of target energy requirements. . Indirectness: No indirectness
Funding	Academic or government funding (This study was supported by the Health Science and Technology Development Project of Shandong (2005HZ024).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: Postoperative hospital mortality at Post-operative/time frame unclear; Group 1: 1/125, Group 2: 2/123
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing

Protocol outcome 2: Adverse events and complications
- Actual outcome: Postoperative overall complications at Post-operative/time frame unclear; Group 1: 17/125, Group 2: 31/123
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing
- Actual outcome: Pneumonia at Post-operative/time frame unclear; Group 1: 4/125, Group 2: 6/123
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing

Protocol outcome 3: Infection (including SSI)
- Actual outcome: Wound, intra-abdominal and urinary tract infections at Post-operative/time frame unclear; Group 1: 12/125, Group 2: 26/123
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing

Protocol outcome 4: Hypoglycaemia
- Actual outcome: Severe hypoglycaemia at Post-operative/time frame unclear; Group 1: 8/125, Group 2: 1/123

Study	Cao 2011[27]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing Protocol outcome 5: Length of hospital stay - Actual outcome: Postoperative hospital stay (days) at Post-operative/time frame unclear; Median (range): glucose control group 8 (6-26), standard care group 10 (7-28); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: 5% missing; Group 2 Number missing: , Reason: 4% missing	
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Chan 2009[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=109)
Countries and setting	Conducted in Brazil
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	The study group included adults from both genders who were older than 21 years of age and who were undergoing open-heart cardiac surgery with cardiopulmonary bypass.
Exclusion criteria	The exclusion criteria included: (1) renal failure (creatinine>1.5 g/dl), (2) neurological dysfunction (diagnosis from medical records), (3) chronic pulmonary obstructive disease (CPOD), (4) current use of any type of antibiotic, (5) current use of inotropic support, (6) emergency and urgent surgeries and (7) reoperation's.
Age, gender and ethnicity	Age - Mean (SD): Control group 58 (12), treated group 57 (12). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: Systematic review: mixed 2. American Society of Anesthesiologists (ASA) Physical Status grade: (ASA P4 (%) control group 86.3, treated group 70.2). 3. BMI ≥30kg/m2: BMI <30kg/m2 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline

Study	Chan 2009[31]
	categorisation: Not stated / Unclear 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: Glucose control - Insulin therapy (perioperative). Tight glycaemic control, with target glucose level of 80-130 mg/dl.. Perioperative and 36 hours post-surgery. Concurrent medication/care: Continuous intravenous regular insulin was used to control glucose levels (regular insulin, U100, Biobrás, Montes Claros, Brazil) when protocol criteria were met, using an infusion device.. Indirectness: No indirectness (n=54) Intervention 2: Standard care - Liberal glucose control. Standard glycaemic control, with target glucose level of 160-200 mg/dl. Infusion of insulin was initiated only if blood glucose levels exceeded 200 mg/dl.. Perioperative and 36 hours post-surgery. Concurrent medication/care: Continuous intravenous regular insulin was used to control glucose levels (regular insulin, U100, Biobrás, Montes Claros, Brazil) when protocol criteria were met, using an infusion device. Indirectness: No indirectness
Funding	Other (E.J. Zerbini Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: Death at 30 days post surgery; Group 1: 3/47, Group 2: 3/51
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.

Protocol outcome 2: Adverse events and complications
- Actual outcome: neurological dysfunction at post-surgical; Group 1: 1/47, Group 2: 5/51
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.

Study	Chan 2009[31]
Protocol outcome 3: Infection (including SSI) - Actual outcome: Infections at post-surgical; Group 1: 9/47, Group 2: 18/51 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock. Protocol outcome 4: Hypoglycaemia - Actual outcome: Hypoglycaemia at post-surgical; Group 1: 4/51, Group 2: 6/47; Comments: hypoglycemic episodes per number of glucose measurements = insulin group 2.9%, control group 2.1%. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock. Protocol outcome 5: Length of hospital stay - Actual outcome: Hospital length (days) [mean (SD)] at post-surgical; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock. Protocol outcome 6: Unplanned ICU admission - Actual outcome: ICU length (days) [mean (SD)] at post-surgical; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: study group had significantly lower BMI; Group 1 Number missing: 7, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.; Group 2 Number missing: 4, Reason: Unclear which group but patients withdrawn due to requiring a second operation due to bleeding, hemodynamic instability that required an aortic balloon, and serious ventricular tachycardia that required electric shock.	

Study	Chan 2009[31]
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

Study	Chaney 1999[32]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	USA
Line of therapy	Not applicable
Duration of study	Duration of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Nondiabetic patients scheduled for CABG surgery.
Exclusion criteria	People receiving preoperative insulin and / or oral hypoglycaemics
Age, gender and ethnicity	Age: TC 65 (13) NC 73 (7). Gender (16:4): Ethnicity: Not reported
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Glucose control: Tight glucose control group received an IV infusion initiated regular insulin 2 units/hr to control BG. Infusion initiated during induction of anaesthesia that was continued until sternal closure at the end of surgery. (n=10) Intervention 2: Standard care: No glucose control group were not administered insulin to control intraoperative blood glucose levels.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL	

Study	Chaney 1999[32]
Protocol outcome 1: Complications - Actual outcome: Cardiac complications; Group 1: 2/10, Group 2: 4/10 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; - Actual outcome: Neuropsychological complications; Group 1: 0/10, Group 2: 1/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness Protocol outcome 2: Hypoglycaemic events - Actual outcome: Hypoglycaemic events; Group 1: 4/10, Group 2: 0/10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness Protocol outcome 3: Length of hospital stay - Actual outcome: length of hospital stay; Group 1: mean 5.5 days (SD 2.3); n=10, Group 2: mean 6.5 days (SD 2); n=10 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Infection (including SSI) ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Desai 2012[39]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=189)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Unclear
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All diabetic patients who underwent first-time, isolated, nonemergency CABG. Nondiabetic patients who underwent first-time, isolated, non emergency CABG who were found to have had 3 consecutive BG

Study	Desai 2012[39]
	readings greater than 150 mg/dL or any 1 BG reading greater than 200 mg/dL perioperatively, which is aligned with the current STS guidelines. Patients who were started on an insulin infusion while in the operating room.
Exclusion criteria	Patients who underwent open surgery other than isolated CABG. Patients who were found not to require an insulin infusion post-CABG. Patients who underwent a concomitant procedure in addition to CABG (eg, CABGþvalve repair).
Age, gender and ethnicity	Age - Mean (SD): 62.7 ± 9.8. Gender (M:F): 159/30.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=91) Intervention 1: Glucose control - Insulin therapy (perioperative). Strict perioperative glycaemic control with a target glucose range of 90 to 120 mg/dL. Duration length of hospital stay. Concurrent medication/care: Intraoperative glucose measures and interventions were under the purview of the anaesthesiologist, whose goal was to maintain a BG level between 100 and 180 mg/dL. Maintenance of BG levels according to their randomized arm was started in the ICU using the programmed Glucommander. BG levels less than 40 mg/dL or greater than 500 mg/dL were sent to the laboratory for further analysis; however, treatment was initiated for low BG if indicated. Patients were maintained on the electronic-based protocol of intravenous insulin for a minimum of 72 hours perioperatively.. Indirectness: No indirectness (n=98) Intervention 2: Standard care - Liberal glucose control. Glucommander parameters for a target glucose range of 121 to 180 mg/dL.. Duration length of hospital stay. Concurrent medication/care: Intraoperative glucose measures and interventions were under the purview of the anaesthesiologist, whose goal was to maintain a BG level between 100 and 180 mg/dL. Maintenance of BG levels according to their randomized arm was started in the ICU using the programmed Glucommander. BG levels less than 40 mg/dL or greater than 500 mg/dL were sent to the laboratory for further analysis; however, treatment was initiated for low BG if indicated. Patients were maintained on the electronic-based protocol of intravenous insulin for a minimum of 72 hours perioperatively.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality

Study	Desai 2012[39]
- Actual outcome: mortality at within 30 days post operatively; Group 1: 1/91, Group 2: 1/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group Protocol outcome 2: Adverse events and complications - Actual outcome: pulmonary complications - pneumonia at within 30 days post operatively; Group 1: 2/91, Group 2: 0/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group - Actual outcome: cardiovascular complications - AF at within 30 days post operatively; Group 1: 7/91, Group 2: 10/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group - Actual outcome: neurological complications - stroke at within 30 days post operatively; Group 1: 0/91, Group 2: 0/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group Protocol outcome 3: Infection (including SSI) - Actual outcome: wound infection at within 30 days post operatively; Group 1: 1/91, Group 2: 0/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group Protocol outcome 4: Hypoglycaemia - Actual outcome: hypoglycaemic events at within 30 days post operatively; Group 1: 30/91, Group 2: 11/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 pts switched to liberal group; Group 2 Number missing: 0, Reason: 27 pts switched to strict insulin group	
Protocol outcomes not reported by the study	Quality of life ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Diez 1991[40]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=14)
Countries and setting	Conducted in Spain; Setting: not stated
Line of therapy	Unclear
Duration of study	Other:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 2 diabetes admitted to hospital for programmed surgical operations under general anesthetic at the urology, gynecology and ORL units were studied.
Exclusion criteria	not stated
Age, gender and ethnicity	Age - Mean (SD): exp group - 62.6.8 (5.6) control - 67.8 (11.0). Gender (M:F): 5/9. Ethnicity: not stated
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=7) Intervention 1: Glucose control - Insulin therapy (perioperative). Intensified glucose control perioperatively with IV insulin solution containing 0.1 U/ml. insulin was controlled according to a sliding scale and added insulin was given when BG were between 5.5 and 8.3 mmol/L at a rate of 15 ml/h. for each glucose concentration elevation of 2.8 mmol/l above these values, insulin infusion rate was increased by 5 mol/h up to a max of 60 ml/h. BG was measured hourly during the first 4 hours, every 2 hours during the following 6 and then every 3-4 hours (at least 12 daily measurements). . Duration 3 days pre op to 4 days post op. Concurrent medication/care: during pre op days insulin was administered by 2 daily injections and were adjusted accordingly to glycemic profiles. BG measures were taken at least 4 x per day. on the day of surgery subcutaneous insulin was omitted. during the post op days the previous therapeutic schedules were maintained until adequate feeding was obtained. . Indirectness: No indirectness (n=7) Intervention 2: Standard care - Liberal glucose control. Infusion of fast-acting IV insulin to glucose solution according to a standard sliding scale protocol when BG were above 4.4 mmol/l. BG measurements were taken 6 x per day.

Study	Diez 1991[40]
	. Duration 3 days pre op and 4 days post op. Concurrent medication/care: during pre op days insulin was administered by 2 daily injections and were adjusted accordingly to glycemic profiles. BG measures were taken at least 4 x per day. on the day of surgery subcutaneous insulin was omitted. during the post op days the previous therapeutic schedules were maintained until adequate feeding was obtained. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL Protocol outcome 1: Hypoglycaemia - Actual outcome: hypoglycemic event at 4 days post op; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Duncan 2018[42]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1439)
Countries and setting	Conducted in Canada, USA
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults between 18 and 90 yr old scheduled for elective coronary artery bypass grafting, valve repair or

Study	Duncan 2018[42]
	replacement, or a combination of these procedures with cardiopulmonary bypass between August 2007 and April 2015 were screened for inclusion by research personnel.
Exclusion criteria	exclusion criteria included - off-pump cardiac surgery, anticipated hypothermic circulatory arrest, elevated baseline cardiac troponin I (greater than 0.5 ng.l–1, Montreal) or troponin T (greater than 0.1 ng · ml–1, Cleveland), kidney disease requiring renal replacement therapy, or active infection requiring ongoing antibiotic therapy.
Age, gender and ethnicity	Age - Mean (SD): 66 ± 11. Gender (M:F): 1063/376. Ethnicity: unclear
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=709) Intervention 1: Glucose control - Insulin therapy (intraoperative). Intraoperative glucose management with hyperinsulinemic normoglycemia involved a fixed-dose insulin infusion of 5 mU/kg–1/min–1 with a concomitant variable glucose (dextrose 20%) infusion supplemented with potassium (40 mEq/l–1) and phosphate (30 mmol /l–1) as previously described. 24 The glucose infusion was initiated at approximately 40 to 60 ml /hr–1 when serum glucose concentration was approximately 110 mg/dl–1 or less, and manually titrated to target glucose concentrations of 80 to 110 mg/dl–1 every 10 to 15 min throughout surgery. Additional boluses of insulin were given for blood glucose greater than 110 mg · dl–1. At sternal closure, the insulin infusion was reduced to 1 m/ kg–1/ min–1 and converted to a standard low-dose insulin infusion upon intensive care unit admission. After intensive care unit arrival, the glucose infusion was decreased by 25 to50% every 20 min when the blood glucose was greater than 110 mg · dl–1. When the infusion was at 20 ml · h–1 or less and blood glucose was greater than 110 mg · dl–1, the infusion was discontinued. Blood glucose concentrations were followed for 45 to 60 min after discontinuation of the dextrose infusion to ensure that hypoglycemia was avoided.. Duration length of surgery. Concurrent medication/care: Upon intensive care unit admission, both groups transitioned to the same standardized postoperative insulin treatment protocol in the intensive care unit. This involved measurement of blood glucose by arterial blood gas analysis approximately every 2 h with adjustment of insulin infusion to maintain serum glucose less than 150 mg · dl– on postoperative day one and less than 120 mg · dl–1 on day two and later. In 2009, after publication of the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, 9 the postoperative glucose target increased to less than 180 mg · dl–1. Severe and moderate hypoglycemia was defined as blood glucose less than 40 and 60 mg

Study	Duncan 2018[42]
	・ dl–1, respectively. Hypoglycemia was treated by administration of 20% dextrose (25 to 100 ml).. Indirectness: No indirectness (n=730) Intervention 2: Standard care - Liberal glucose control. Standard glucose management involved a conventional low-dose insulin infusion titrated to blood glucose concentrations measured by arterial blood gas analysis every 30 to 90 min throughout surgery. This low-dose insulin infusion was initiated for blood glucose concentration greater than 120 mg・dl–1 before initiation of cardiopulmonary bypass or greater than 150 mg・ dl–1 during or after cardiopulmonary bypass, at a rate based on patient weight and current glucose concentration. Subsequent adjustments were based on a sliding scale of current blood glucose concentration and the change from the previous measurement. Supplemental boluses of insulin were given with acute increases (greater than 30 mg・ dl–1) in blood glucose. . Duration length of surgery. Concurrent medication/care: Upon intensive care unit admission, both groups transitioned to the same standardized postoperative insulin treatment protocol in the intensive care unit. This involved measurement of blood glucose by arterial blood gas analysis approximately every 2 h with adjustment of insulin infusion to maintain serum glucose less than 150 mg・ dl–1 on postoperative day one and less than 120 mg・ dl–1 on day two and later. In 2009, after publication of the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, 9 the postoperative glucose target increased to less than 180 mg・ dl–1. Severe and moderate hypoglycemia was defined as blood glucose less than 40 and 60 mg ・ dl–1, respectively. Hypoglycemia was treated by administration of 20% dextrose (25 to 100 ml).. Indirectness: No indirectness
Funding	Principal author funded by industry (Dr Duncan receives funding from Fresenius Kabi for research unrelated to this investigation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: mortality within 30 days of surgery at within 30 days of surgery; Group 1: 9/709, Group 2: 13/730
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: mortality at 1 year post op at 1 year post op; Group 1: 32/653, Group 2: 22/682
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 56, Reason: study drop outs - no reason stated; Group 2 Number missing: 48, Reason: study drop outs - no reason stated

Study	Duncan 2018[42]
	Protocol outcome 2: Adverse events and complications - Actual outcome: AF at duration of hospitalisation; Group 1: 209/709, Group 2: 235/730 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: neurological deficit at duration of hospitalisation; Group 1: 9/709, Group 2: 12/730 Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Infection (including SSI) - Actual outcome: serious infection at duration of hospitalisation; Group 1: 20/709, Group 2: 44/730 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Hypoglycaemia - Actual outcome: hypoglycaemic events at duration of hospitalisation; Group 1: 6/709, Group 2: 1/730 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Length of hospital stay - Actual outcome: length of hospital stay at length of stay; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: study drop outs - no reason stated; Group 2 Number missing: 17, Reason: study drop outs - no reason stated Protocol outcome 6: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of stay; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 60, Reason: study drop outs - no reason stated; Group 2 Number missing: 59, Reason: study drop outs - no reason stated
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Hospital readmission

Study	Emam 2010[43]
Study type	RCT (Patient randomised; Parallel)

Study	Emam 2010[43]
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Saudi Arabia; Setting: King Fahd Military complex
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 2 diabetes undergoing open cardiac surgery
Exclusion criteria	none reported
Recruitment/selection of patients	patients with type 2 diabetes undergoing open cardiac surgery from 2005 to 2008
Age, gender and ethnicity	Age - Mean (SD): Insulin group = 58, control group = 56. Gender (M:F): 96/24. Ethnicity: not stated
Further population details	1. Age: Not stated / Unclear 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: Not stated / Unclear 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes: Type 2 diabetes
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: Glucose control - Insulin therapy (perioperative). Strict perioperative glycaemic control following the Braithwaite protocol, commencing the evening before surgery, intraoperatively until the third day post surgery. IV insulin infusion was administered to maintain a target glucose range of 100 to 150 mg/dL. BG levels were checked very 1h until patients had achieved stability then checked every 2h. . Duration 24 hours pre operatively until 3 days post-operatively. Concurrent medication/care: All patients were admitted at least 24 hours prior to surgery and baseline investigations were obtained. patients continued on IV insulin infusions post operatively and BG estimations were carried out hourly in the operating room and initially post operatively. patients were converted to subcutaneous insulin on the third day post operatively. . Indirectness: No indirectness (n=40) Intervention 2: Standard care - Liberal glucose control. patients discontinued their hypoglycemic regimen on the day of surgery and started SC insulin by a sliding scale. BG levels were checked every 4 h. During surgery patients followed a simple IV insulin protocol to maintain BG <200mg/dL.

Study	Emam 2010[43]
	. Duration 24 hours pre operatively until post operatively . Concurrent medication/care: All patients were admitted at least 24 hours prior to surgery and baseline investigations were obtained. patients continued on IV insulin infusions post operatively and BG estimations were carried out hourly in the operating room and initially post operatively. patients were converted to subcutaneous insulin on the third day post operatively. . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: in hospital deaths at in hospital stay; Group 1: 0/80, Group 2: 0/40
Risk of bias: All domain - High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: reported difference in the number of patients with moderate uncontrolled diabetes which was higher in the study group; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Infection (including SSI)
- Actual outcome: wound infection at in hospital stay; Group 1: 0/80, Group 2: 5/40
Risk of bias: All domain - High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: reported difference in the number of patients with moderate uncontrolled diabetes which was higher in the study group; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Hypoglycaemia
- Actual outcome: hypoglycemic events at in hospital stay; Group 1: 0/80, Group 2: 0/40
Risk of bias: All domain - High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: reported difference in the number of patients with moderate uncontrolled diabetes which was higher in the study group; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Length of hospital stay
- Actual outcome: length of hospital stay at in hospital stay; Group 1: mean 9.1 days (SD 2.3); n=80, Group 2: mean 12.3 days (SD 7.6); n=40
Risk of bias: All domain - High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: reported difference in the number of patients with moderate uncontrolled diabetes which was higher in the study group; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Length of stay in intensive care unit

Study	Emam 2010[43]
- Actual outcome: length of ICU stay at in hospital stay; Group 1: mean 2.25 days (SD 0.63); n=80, Group 2: mean 3 days (SD 0.79); n=40 Risk of bias: All domain - High, Selection – High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: reported difference in the number of patients with moderate uncontrolled diabetes which was higher in the study group; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Unplanned ICU admission ; Hospital readmission

Study	Gandhi 2007[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=400)
Countries and setting	Conducted in USA; Setting: St. Marys Hospital, Rochester, Minnesota, which is a tertiary care teaching hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days post surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: surgeon, surgical procedure (with/without CABG), diabetes
Subgroup analysis within study	Stratified then randomised:
Inclusion criteria	Adults undergoing elective cardiac surgery
Exclusion criteria	pts who had off-pump cardiopulmonary bypass procedures
Age, gender and ethnicity	Age - Mean (SD): 62 (15) and 63 (16). Gender (M:F): 273/127.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=199) Intervention 1: Glucose control - Insulin therapy (intraoperative). intravenous insulin infusion, 250 units of NovoLin R (Novo Nordisk, Princeton, New Jersey) in 250mL of 0.45% sodium chloride infusion to

Study	Gandhi 2007[52]
	maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL) . Duration length of surgery. Concurrent medication/care: both study groups, we measured arterial plasma glucose concentration every 30 minutes, starting just before anesthetic induction by using hexokinase method on a Double P Modular System (Roche Diagnostics, Indianapolis, Indiana). Intraoperative procedures, including cardiopulmonary bypass, monitoring, laboratory testing, and treatment, were left to the discretion of anesthesiologists and cardiac surgeons. Post operatively - Intravenous insulin infusion was started in patients in the conventional treatment group on their arrival in the ICU. Thereafter, both study groups were treated identically, with the intravenous insulin infusion rates adjusted by a nursing staff that was not involved with the study according to a standard protocol. The target blood glucose range was 4.4 (80 mg/dL) to 5.6 mmol/L (100 mg/dL). Arterial blood glucose levels were measured every 1 to 2 hours by using the Accu-Check Inform blood glucose monitoring system (glucometer) (Roche Diagnostics). During the first 24 hours after surgery, patients were given only clear liquids by mouth; we did not administer subcutaneous insulin or oral diabetic medications during this time. Thereafter, the hospital diabetes consulting service saw all patients and provided individualized recommendations for ongoing care. . Indirectness: No indirectness (n=201) Intervention 2: Standard care - Liberal glucose control. Patients in the conventional treatment group did not receive insulin during surgery unless their glucose levels exceeded 11.1 mmol/L (200 mg/dL). If glucose concentration was between 11.1 (200 mg/dL) and 13.9 mmol/L (250 mg/dL), patients received an intravenous bolus of 4 units insulin every hour until the glucose concentration was less than 11.1 mmol/L (<200 mg/dL). If the intraoperative glucose concentration was greater than 13.9 mmol/L (250 mg/dL), patients received an intravenous infusion of insulin that was continued until the glucose level was less than 8.3 mmol/L (150 mg/dL) . Duration length of surgery. Concurrent medication/care: Patients in the conventional treatment group did not receive insulin during surgery unless their glucose levels exceeded 11.1 mmol/L (>200 mg/dL). If glucose concentration was between 11.1 (200 mg/dL) and 13.9 mmol/L (250 mg/dL), patients received an intravenous bolus of 4 units insulin every hour until the glucose concentration was less than 11.1 mmol/L (<200 mg/dL). If the intraoperative glucose concentration was greater than 13.9 mmol/L (250 mg/dL), patients received an intravenous infusion of insulin that was continued until the glucose level was less than 8.3 mmol/L (<150 mg/dL) . Indirectness: No indirectness
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL	

Study	Gandhi 2007[52]
Protocol outcome 1: Mortality - Actual outcome: mortality at up to 30 days after surgery; Group 1: 4/185, Group 2: 0/186; Comments: 15 randomly assigned patients were excluded (8 in the intensive treatment group and 7 in the conventional treatment group) from the final intention-to-treat analyses because their glucose levels were less than 5.6 mmol/L (<100 mg/dL) during surgery. Among the patients who received study interventions, 3 of 188 patients in the intensive treatment group and 5 of 191 patients in the conventional treatment group were lost to follow-up after being discharged from the hospital. Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up Protocol outcome 2: Adverse events and complications - Actual outcome: cardiac complications including; heart block requiring pacemaker, new-onset AF, cardiac arrest at up to 30 days after surgery; Group 1: 60/185, Group 2: 60/186; Comments: 1 cardiac arrest in the insulin controlled group versus 0 in conventional treatment. 5 heart block in the insulin group versus 1 in the conventional treatment group. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up - Actual outcome: neurological complications - stroke at up to 30 days after surgery; Group 1: 8/185, Group 2: 1/186 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up Protocol outcome 3: Infection (including SSI) - Actual outcome: deep sternal infection at up to 30 days after surgery; Group 1: 6/185, Group 2: 7/186 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up Protocol outcome 4: Length of hospital stay - Actual outcome: length of hospital stay at up to 30 days after surgery; Group 1: mean 8 days (SD 4); n=185, Group 2: mean 8 days (SD 5); n=186 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as	

Study	Gandhi 2007[52]
blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up Protocol outcome 5: Length of stay in intensive care unit - Actual outcome: length of ICU stay at up to 30 days after surgery; Group 1: mean 2 days (SD 2); n=185, Group 2: mean 2 days (SD 3); n=186 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 14, Reason: 3 withdrew as surgery cancelled. 8 excluded as blood glucose level was less than 5.6 mmol/l 3 lost to follow up; Group 2 Number missing: 15, Reason: 3 withdrew as surgery cancelled. 7 excluded as blood glucose level was less than 5.6 mmol/l. 5 lost to follow up	
Protocol outcomes not reported by the study	Quality of life ; Hypoglycaemia ; Unplanned ICU admission ; Hospital readmission

Study	Giakoumidakis 2013[55]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=212)
Countries and setting	Conducted in Greece; Setting: 8 bed cardiac surgery ICU in a general tertiary hospital in Athens, Greece
Line of therapy	Unclear
Duration of study	Intervention + follow up: duration of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	open heart surgery, surgery requiring CPB, patients ages 18 or above and patients informed consent.
Exclusion criteria	renal dysfunction or failure, neurological or mental disorder, COPD, pre-operative use of any antibiotics, emergency and urgent surgeries, history of previous cardiac surgery, ICU length of stay <24 hours, mediastinal re-exploration for bleeding, hemodynamic support with intra-aortic balloon pump intraoperatively and/or during the first 24 hours post op and the use of cardioversion for severe ventricular arrhythmias within the first 24h of ICU hospitalisation.
Age, gender and ethnicity	Age - Mean (SD): glucose control - 64.9 (11.5) control group - 66.9 (11.1). Gender (M:F): 142/70.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4.

Study	Giakoumidakis 2013[55]
	Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=105) Intervention 1: Glucose control - Insulin therapy (postoperative). blood glucose levels measured on ICU admission and every 2h during the first 24h ICU stay. Patients received IV infusion of fast-acting insulin solution (100IU of Actrapid HM in 100ml of 0.9% NaCl) when blood glucose levels exceeded 160 mg/dl. the protocol aimed to maintain blood glucose levels between 120 mg/dl and 160 mg/dl. insulin infusion was stopped when blood glucose levels were 160mg/dl or lower.. Duration 24 hours post operatively. Concurrent medication/care: Blood glucose levels measured on ICU admission and every 2h during the first 24h ICU stay. blood glucose levels were controlled for 24 hours post op in all patients. insulin was given by continuous intravenous infusion through a central venous catheter.. Indirectness: No indirectness (n=107) Intervention 2: Standard care - Liberal glucose control. Patients received insulin when blood glucose levels exceeded 200 mg/dl. the protocol aimed to maintain blood glucose levels between 160 mg/dl and 200 mg/dl. insulin infusion was stopped when blood glucose levels were 200 mg/dl or lower. . Duration 24 hours post operatively. Concurrent medication/care: Blood glucose levels measured on ICU admission and every 2h during the first 24h ICU stay. blood glucose levels were controlled for 24 hours post op in all patients. insulin was given by continuous intravenous infusion through a central venous catheter.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: 30 day mortality at 30 days post operatively ; Group 1: 1/105, Group 2: 6/107
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Infection (including SSI)
- Actual outcome: postoperative infection at length of hospital stay; Group 1: 9/105, Group 2: 12/107
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Hypoglycaemia

Study	Giakoumidakis 2013[55]
- Actual outcome: severe hypoglycaemic event at length of hospital stay; Group 1: 0/105, Group 2: 0/107 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: severe hypoglycaemia blood glucose less than or equal to 50 mg/dl; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Length of hospital stay - Actual outcome: length of hospital stay at length of hospital stay; Group 1: mean 9.9 days (SD 7.4); n=105, Group 2: mean 9.4 days (SD 5); n=107 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of hospital stay; Group 1: mean 2.7 days (SD 2.5); n=105, Group 2: mean 3.3 days (SD 4.2); n=107 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Unplanned ICU admission ; Hospital readmission

Study	Grey 2004[59]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=61)
Countries and setting	Conducted in USA; Setting: Hartford Hospital (Hartford, Connecticut), a large tertiary care facility. Patients admitted to a 12-bed general surgical ICU
Line of therapy	Unclear
Duration of study	Intervention + follow up: FU length of ICU stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adult patients admitted to a 12-bed general surgical ICU who required treatment for hyperglycemia
Exclusion criteria	Patients expected to have a brief stay or not

Study	Grey 2004[59]
	expected to survive beyond 48 hours were excluded from the study, as were those with active infections, with disseminated cancer, or receiving chemotherapy, irradiation, or corticosteroids
Age, gender and ethnicity	Age - Mean (SD): 55 ± 22 and 56 ±22. Gender (M:F): 43/18.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	General surgical ICU patients .
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Glucose control - Insulin therapy (postoperative). Intravenous insulin infusions were administered to maintain serum glucose values in the range of 80 to 120 mg/dL.. Duration length of ICU stay. Concurrent medication/care: All patients received care and intervention considered standard practice, as directed by the patient's physician in consultation with a board-certified surgical intensivist. all infections were treated by culture directed antimicrobial therapy. Insulin infusions were managed by surgical ICU nurses and adjusted according to an algorithm designed for this study. Investigators made rounds to see these patients twice daily and were available for telephone consultation 24 hours a day. The frequency of blood glucose measurement was based on insulin algorithms and supplemented by clinical judgment, as determined by the nurse at the bedside. Nutritional support was managed for all patients by a critical care nutritional support team, with use of standard guidelines.. Indirectness: No indirectness (n=27) Intervention 2: Standard care - Liberal glucose control. Intravenous insulin infusions were administered to maintain serum glucose values in the range of 180 to 220 mg/dL.. Duration length of ICU stay. Concurrent medication/care: All patients received care and intervention considered standard practice, as directed by the patient's physician in consultation with a board-certified surgical intensivist. all infections were treated by culture directed antimicrobial therapy. Insulin infusions were managed by surgical ICU nurses and adjusted according to an algorithm designed for this study. Investigators made rounds to see these patients twice daily and were available for telephone consultation 24 hours a day. The frequency of blood glucose measurement was based on insulin algorithms and supplemented by clinical judgment, as determined by the nurse at the bedside. Nutritional support was managed for all patients by a critical care nutritional support team, with use of standard guidelines.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE

Study	Grey 2004[59]
CONTROL Protocol outcome 1: Mortality - Actual outcome: mortality at length of ICU stay; Group 1: 4/34, Group 2: 6/27 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 34 ; Group 2 Number missing: 0, Reason: 27 Protocol outcome 2: Infection (including SSI) - Actual outcome: nosocomial infection rates - IVDI (intravascular device infection) or IVDI related blood stream infections, blood stream infections and surgical site infections at length of ICU stay; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 34 ; Group 2 Number missing: 0, Reason: 27 Protocol outcome 3: Hypoglycaemia - Actual outcome: Hypoglycaemic episodes at length of ICU stay; Group 1: 11/34, Group 2: 2/27 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 34 ; Group 2 Number missing: 0, Reason: 27 Protocol outcome 4: Length of hospital stay - Actual outcome: length of ICU stay at length of hospital stay; Group 1: mean 33.4 days in ICU (SD 68.3); n=34, Group 2: mean 24.5 days in ICU (SD 19.4); n=27 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 34 ; Group 2 Number missing: 0, Reason: 27	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Groban 2002[60]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=381)
Countries and setting	Conducted in USA; Setting: wake forest university school of medicine
Line of therapy	Unclear
Duration of study	Intervention + follow up:

Study	Groban 2002[60]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients scheduled for elective CABG surgery in 1991 -1996.
Exclusion criteria	<35 years, pregnant, MI within 30 days, valvular heart disease requiring concomitant surgery, alcohol or drug abuse, renal or heptic impairment, patients receiving insulin, oral hypoglycemic agents, intravenous inotropic or antiarrhythmic drugs, or intra-aortic balloon pump support.
Age, gender and ethnicity	Age - Other: patients over 35 years. Gender (M:F): 308/73.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=188) Intervention 1: Glucose control - Insulin therapy (intraoperative). Intraoperative insulin infusion (Humulin R regular insulin; Eli Lilly & Co, Indianapolis, IN) to maintain BG between 80-120 mg/dL, started if BG was >100mg/dL after induction. If blood glucose was <100mg/dL the insulin infusion was discontinued. 100-200ml dextrose 5% was given if blood glucose levels decreased to <70mg/dL.. Duration length of surgery. Concurrent medication/care: Study infusions initiated after induction anesthesia and continued until surgery was completed and patient transferred to ICU. patients were given study drug infusions at comparable rates (i.e. 2U of insulin/h or 2 mL of saline/h).. Indirectness: No indirectness (n=193) Intervention 2: Standard care - No glucose control. Patients received saline solution as placebo at a rate of 2mL/h. BG levels were allowed to fluctuate without intervention.. Duration length of surgery. Concurrent medication/care: Study infusions initiated after induction anesthesia and continued until surgery was completed and patient transferred to ICU. patients were given study drug infusions at comparable rates (i.e. 2U of insulin/h or 2 mL of saline/h).. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: In hospital mortality at length of hospital stay; Group 1: 3/188, Group 2: 0/193

Study	Groban 2002[60]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Hypoglycaemia - Actual outcome: hypoglycaemic events at length of hospital stay; Group 1: 23/188, Group 2: 12/193 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: length of hospital stay at length of hospital stay; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Infection (including SSI) ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Hoedemaekers 2005[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Netherlands; Setting: unclear - ICU
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 24 hours post ICU admission
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients aged 18 years or older scheduled for elective CABG were eligible for the study
Exclusion criteria	excluded if they had a history of diabetes, fasting blood glucose levels above 100 mg/dl on the day before surgery, myocardial infarction within 4 weeks before surgery, cardiogenic shock or renal failure (serum creatinine level above 1.7 mg/dl). Patients were also excluded if they had used any medication within 4 weeks before surgery known to modulate the inflammatory response (for example non-steroidal anti-

Study	Hoedemaekers 2005[74]
	inflammatory drugs or steroids) or when there were clinical signs of infection or inflammatory disease. Patients undergoing off pump cardiac surgery were excluded.
Age, gender and ethnicity	Age - Mean (SD): 63.2 ± 6.6, 65.2 ± 8.7. Gender (M:F): 18/2.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Glucose control - Insulin therapy (postoperative). patients received insulin (Actrapid HM; Novo Nordisk, Copenhagen, Denmark) intravenously to maintain blood glucose levels between 80 and 110 mg/dl . Duration 24 hours after admission to ICU. Concurrent medication/care: During surgery no blood glucose concentrations were measured, and none of the patients received insulin before admission to the ICU. Cardiopulmonary bypass was performed with a priming solution containing gelatin (Gelofusine®), mannitol, albumin, NaHCO3, CaCl 2 and heparin. After weaning from cardiopulmonary bypass, patients were given protamine to neutralize the heparin. Heparin antagonization was identical in both groups. On admission, all patients were infused continuously with 3.75 g of intravenous glucose per hour. . Indirectness: No indirectness (n=10) Intervention 2: Standard care - Liberal glucose control. patients received insulin (Actrapid HM; Novo Nordisk, Copenhagen, Denmark) intravenously when bloody glucose levels exceeded 200 mg/dl . Duration 24 hours post ICU admission. Concurrent medication/care: On admission, all patients were infused continuously with 3.75 g of intravenous glucose . Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Adverse events and complications
- Actual outcome: major complications at 24 hours post ICU admission; Group 1: 0/10, Group 2: 0/10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Hoedemaekers 2005[74]
- Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blood glucose levels on admission were slightly higher in the intensive treatment group than in the conventional treatment group (mean ± SD 114.4 ± 15.1 versus 97.6 ± 19.8 mg/dl; p = 0.05) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 2: Hypoglycaemia - Actual outcome: hypoglycaemia at 24 hours post ICU admission; Group 1: 0/10, Group 2: 0/10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blood glucose levels on admission were slightly higher in the intensive treatment group than in the conventional treatment group (mean ± SD 114.4 ± 15.1 versus 97.6 ± 19.8 mg/dl; p = 0.05) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: time in ICU at 24 hours post ICU admission; Group 1: mean 22.1 hours (SD 1.8); n=10, Group 2: mean 20.3 hours (SD 2.5); n=10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Blood glucose levels on admission were slightly higher in the intensive treatment group than in the conventional treatment group (mean ± SD 114.4 ± 15.1 versus 97.6 ± 19.8 mg/dl; p = 0.05) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Hospital readmission

Study	Ingels 2006[77]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	follow up study to RCT (n=970)
Countries and setting	Conducted in Belgium; Setting: Department of Intensive Care Medicine, University Hospital Gasthuisberg
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 4 year follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: reason for ICU admission
Subgroup analysis within study	Stratified then randomised: Pts in ICU for ≥3 days

Study	Ingels 2006[77]
Inclusion criteria	the original RCT included all adults receiving mechanical ventilation who were admitted to intensive care unit between February 2, 2000, and January 18, 2001, were eligible for enrolment in the study. This study reports the data from the subgroup of 970 patients admitted after cardiac surgery, either electively or after secondary complications. As previous observational studies have indicated that insulin therapy requires at least 3 days in order to exert potential benefit in this patient population, 6 we planned to also assess this subgroup of long stay patients.
Exclusion criteria	Only 14 patients were excluded: 5 who were participating in other trials, and 9 who were moribund or for whom there were do-not-resuscitate orders.
Age, gender and ethnicity	Age - Mean (SD): 66.5 ± 11. Gender (M:F): 853/117.
Further population details	1. Age: Not stated / Unclear 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not stated / Unclear 3. BMI ≥30kg/m2: Not stated / Unclear 4. Cardiac surgery: Cardiac surgery 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not stated / Unclear 6. Type 2 diabetes: Not stated / Unclear
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=477) Intervention 1: Glucose control - Insulin therapy (postoperative). An insulin infusion was started if the blood glucose level exceeded 110 mg per deciliter, and the infusion was adjusted to maintain normoglycemia (80 to 110 mg per deciliter [4.4 to 6.1 mmol per liter]). The maximal dose of insulin was arbitrarily set at 50 IU per hour. . Duration length of ICU stay. Concurrent medication/care: When the patient was discharged from the intensive care unit, a conventional approach was adopted (maintenance of blood glucose at a level between 180 and 200 mg per deciliter). Adjustments of the insulin dose were based on measurements of whole-blood glucose in undiluted arterial blood, performed at one to four-hour intervals with the use of a glucose analyzer. . Indirectness: No indirectness (n=493) Intervention 2: Standard care - Liberal glucose control. A continuous infusion of insulin (50 IU of Actrapid HM [Novo Nordisk, Copenhagen, Denmark] in 50 ml of 0.9 percent sodium chloride), with the use of a pump (Perfusor-FM, B. Braun, Melsungen, Germany), was started only if the blood glucose level exceeded 215 mg per deciliter, and the infusion was adjusted to maintain the level at a value between 180 and 200 mg per deciliter (10.0 and 11.1 mmol per liter). . Duration length of ICU stay. Concurrent medication/care: When the patient was discharged from the

Study	Ingels 2006[77]
	intensive care unit, a conventional approach was adopted (maintenance of blood glucose at a level between 180 and 200 mg per deciliter). Adjustments of the insulin dose were based on measurements of whole-blood glucose in undiluted arterial blood, performed at one to four-hour intervals with the use of a glucose analyzer. . Indirectness: No indirectness
Funding	Equipment / drugs provided by industry (Novo Nordisk Denmark)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Quality of life
- Actual outcome: Nottingham health profile I at 4 years post ICU admission;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 177, Reason: study drop outs no reason given ; Group 2 Number missing: 190, Reason: study drop outs no reason given
- Actual outcome: Nottingham health profile II at 4 years post ICU admission;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 272, Reason: study drop outs no reason given ; Group 2 Number missing: 296, Reason: study drop outs no reason given

Protocol outcome 2: Mortality
- Actual outcome: mortality < 30 days at < 30 days ; Group 1: 16/477, Group 2: 37/493
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: mortality > 1 year at > 1 year (2 years, 3 years and 4 years post ICU admission); Group 1: 73/477, Group 2: 89/493
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Infection (including SSI)
- Actual outcome: episodes of Hypoglycaemia at length of ICU stay; Group 1: 14/477, Group 2: 2/493
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: blood stream infection at length of ICU stay; Group 1: 9/477, Group 2: 12/493
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Study	Ingels 2006[77]
Protocol outcome 4: Length of stay in intensive care unit - Actual outcome: duration of ICU stay at length of hospital stay; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Adverse events and complications ; Hypoglycaemia ; Length of hospital stay ; Unplanned ICU admission ; Hospital readmission

Study	Ji 2014[78]
Study type	RCT
Number of studies (number of participants)	(n=75)
Countries and setting	Conducted in China; Setting: unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Isolated aortic valve replacement, New York Heart Association class I-III, left ventricular ejection fraction >35%, normal liver and kidney function without history of liver or kidney disease, no inflammatory or immunological diseases, and age>18 years.
Exclusion criteria	Any concomitant diseases including coronary heart disease, cardiomyopathy, diabetes mellitus, thyroid disease, infective endocarditis, malignant tumour, and hematological disorders; second cardiac surgery; unstable preoperative hemodynamics; impairment of blood glucose control; and postoperative requirement of intra-aortic balloon pump or left ventricular assist device. Ten patients were excluded(concomitant coronary heart disease undergoing coronaryartery bypass grafting in 3 patients, concomitant hypothyroid in 2, concomitant infective endocarditis in 3, previous cardiacsurgery in 1, and postoperative requirement of an intra-aortic balloon pump in 1)
Recruitment/selection of patients	Nondiabetic patients with aortic valve disease referred for isolated aortic valve replacement were

Study	Ji 2014[78]
	prospectively included.
Age, gender and ethnicity	Age: 44 (10). Gender (M:F): 29/36. Ethnicity: Not reported
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: Not reported. BMI ≥30kg/m2: Mean BMI 34 4. Cardiac surgery: Not reported 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: Not reported 6. Type 2 diabetes: Not reported
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Glucose control - Insulin therapy (perioperative). Tight glucose control. Continuous infusion of insulin during surgery to maintain BG of 80-110 mg/dL.. Duration unclear. Concurrent medication/care: no details provided . Indirectness: No indirectness (n=38) Intervention 2: Standard care - Liberal glucose control. Control group had BG measured every 20 minutes throughout surgery. If BG exceeded 200 mg/dL participants received a bolus of 4 units of insulin every hour until BG returned to <200 mg/dL. Duration unclear. Concurrent medication/care: no details given. Indirectness: No indirectness
Funding	Not reported
Protocol outcome 1: Mortality - Actual outcome: Mortality ; Group 1: 0/33, Group 2: 2/32 Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 2: Cardiac complications - Actual outcome: Sternal instability; Group 1: 0/33, Group 2: 1/32 Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Hypoglycaemia - Actual outcome: hypoglycaemic events; Group 1: 0/33, Group 2: 1/32 Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 3: Infections - Actual outcome: Infections at duration of ICU stay; 1/33, Group 2: 2/32. Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover	

Study	Ji 2014[78]
- Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Length of stay in hospital - Actual outcome: duration of hospital stay (days); Group 1: 9.4 (3.3), n=33, Group 2: 11.5 (4.2), n=32. Insulin group had shorter post-operative length of hospital stay. P=0.03. Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Protocol outcome 4: Length of stay in ICU - Actual outcome: duration of hospital stay (hours); Group 1: 28.4 (7.2), n=33, Group 2: 14.8 (3.5), n=32. Insulin group had shorter length of ICU stay. P<0.0001 Risk of bias: All domain – Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Unplanned ICU admission ; Hospital readmission

Study	Okabayashi 2009a[113]
Study type	RCT
Number of studies (number of participants)	(n=88)
Countries and setting	Conducted in Japan; Setting: unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hepatectomized patients
Exclusion criteria	Not reported

Study	Okabayashi 2009a[113]
Recruitment/selection of patients	unclear
Age, gender and ethnicity	Age - Not reported: not given. Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=44) Intervention 1: Glucose control - Insulin therapy (perioperative). Patients received programmed infusions of insulin determined by the control algorithm of the closed-loop system. . Duration unclear. Concurrent medication/care: no details provided . Indirectness: No indirectness (n=44) Intervention 2: Standard care - Liberal glucose control. Glucose levels were controlled using a manual injection of insulin according to the commonly used sliding scale.. Duration unclear. Concurrent medication/care: no details given. Indirectness: No indirectness
Funding	Academic or government funding

Protocol outcome 1: Mortality
- Actual outcome: mortality at 30 days post op at 30 days post op; Group 1: 0/44, Group 2: 0/44
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 2: Hypoglycaemia
- Actual outcome: hypoglycaemic events at duration of ICU stay; Group 1: 0/44, Group 2: 0/44
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 3: Infections
- Actual outcome: Infections at duration of ICU stay; The incidence of SSI in the artificial pancreas group was significantly lower than that in the sliding scale group.
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;

Protocol outcome 4: Length of stay in hospital
- Actual outcome: duration of hospital stay; Patients in the artificial pancreas group required a significantly shorter hospitalisation than patients in the

Study	Okabayashi 2009a[113]
sliding scale group. Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ;	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Okabayashi 2009b[114]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Japan; Setting: Kochi Medical School
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having elective pancreatic resection for pancreatic disease.
Exclusion criteria	Weight loss greater than 10% during the previous 6 months, signs of distant metastasis, and respiratory, renal, or heart disease.
Age, gender and ethnicity	Age - Mean (SD): insulin- 61.9 (13.6) control - 63.2)7.5). Gender (M:F): 18/12.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Glucose control - Insulin therapy (perioperative). This involved a closed-loop glycemic control system using theSTG-22 unit as an artificial endocrine pancreas.

Study	Okabayashi 2009b[114]
	Stable blood glucose concentrations were maintained by the automatic infusion of regular insulin or glucose into the circulation and monitored for 18 hours post op in ICU. . Duration length of surgery and 18 hours in ICU. Concurrent medication/care: unclear. Indirectness: No indirectness (n=15) Intervention 2: Standard care - Liberal glucose control. Continuous monitoring of blood glucose by the artificial pancreas and routine checking by nursing staff every 2 hours. In this group, blood glucose levels were controlled by the subcutaneous injection of regular human insulin; the dose was determined by the sliding scale, and the target blood glucose level to avoid hypoglycemia was 150 to 200 mg/dL. . Duration length of surgery and 18 hours ICU stay. Concurrent medication/care: unclear. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL Protocol outcome 1: Mortality - Actual outcome: mortality at 30 days post op at 30 days post op; Group 1: 0/17, Group 2: 0/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 2 patients with pancreatic carcinoma with peritoneal dissemination were excluded Protocol outcome 2: Hypoglycaemia - Actual outcome: hypoglycaemic events at duration of ICU stay; Group 1: 0/17, Group 2: 0/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 2, Reason: 2 patients with pancreatic carcinoma with peritoneal dissemination were excluded	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Pezzella 2014[120]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=189)
Countries and setting	Conducted in USA; Setting:
Line of therapy	Unclear
Duration of study	Follow up (post intervention): 40 +- 4.4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	All diabetic patients who underwent first-time, isolated, non emergency CABG. Nondiabetic patients who underwent first-time, isolated, non emergency CABG who were found to have had 3 consecutive BG readings greater than 150 mg/dL or any 1 BG reading greater than 200 mg/dL perioperatively, which is aligned with the current STS guidelines. Patients who were started on an insulin infusion while in the operating room.
Exclusion criteria	Patients who underwent open surgery other than isolated CABG. Patients who were found not to require an insulin infusion post-CABG. Patients who underwent a concomitant procedure in ad- dition to CABG (eg, CABGþvalve repair).
Age, gender and ethnicity	Age - Mean (SD): 62.7 ±9.8. Gender (M:F): 159/30.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=91) Intervention 1: Glucose control - Insulin therapy (perioperative). Strict perioperative glycaemic control with a target glucose range of 90 to 120 mg/dL. Strict perioperative glycaemic control with a target glucose range of 90 to 120 mg/dL.. Duration 48 months post op FU. Concurrent medication/care: Intraoperative glucose measures and interventions were under the purview of the anaesthesiologist, whose goal was to maintain a BG level between 100 and 180 mg/dL. Maintenance of BG levels according to their randomized arm was started in the ICU using the programmed Glucommander. BG levels less than 40 mg/dL or greater than 500 mg/dL were sent to the laboratory for further analysis; however, treatment was initiated for low BG if indicated. Patients were maintained on the electronic-based protocol of intravenous insulin for a minimum

Study	Pezzella 2014[120]
	of 72 hours perioperatively. All patients were given standard discharge instructions according to their diabetic status. Patients with a history of diabetes were returned to their presurgery diabetic control method before discharge. Patients with previously undiagnosed diabetes were referred to their primary care physician or endocrinologist for further assessment and treatment. Patients without a history of diabetes were instructed to maintain a controlled diet. After discharge there was no further study intervention for glucose management.. Indirectness: No indirectness (n=98) Intervention 2: Standard care - Liberal glucose control. Glucommander parameters for a target glucose range of 121 to 180 mg/dL.. Duration 48 months post op FU. Concurrent medication/care: Intraoperative glucose measures and interventions were under the purview of the anaesthesiologist, whose goal was to maintain a BG level between 100 and 180 mg/dL. Maintenance of BG levels according to their randomized arm was started in the ICU using the programmed Glucommander. BG levels less than 40 mg/dL or greater than 500 mg/dL were sent to the laboratory for further analysis; however, treatment was initiated for low BG if indicated. Patients were maintained on the electronic-based protocol of intravenous insulin for a minimum of 72 hours perioperatively. All patients were given standard discharge instructions according to their diabetic status. Patients with a history of diabetes were returned to their presurgery diabetic control method before discharge. Patients with previously undiagnosed diabetes were referred to their primary care physician or endocrinologist for further assessment and treatment. Patients without a history of diabetes were instructed to maintain a controlled diet. After discharge there was no further study intervention for glucose management.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Quality of life
- Actual outcome: SF-12 at before surgery and 6 months post op;
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 switched to liberal care; Group 2 Number missing: 0, Reason: 27 switched to strict glucose control care

Study	Pezzella 2014[120]
Protocol outcome 2: Mortality - Actual outcome: mortality by 48 months post op at 48 months post op; Group 1: 4/91, Group 2: 6/98 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 11 switched to liberal care; Group 2 Number missing: 0, Reason: 27 switched to strict glucose control care	
Protocol outcomes not reported by the study	Adverse events and complications ; Infection (including SSI) ; Hypoglycaemia ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Rujirojindakul 2014[137]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=200)
Countries and setting	Conducted in Thailand; Setting: The study was conducted in Songklanagarind Hospital, Southern Thailand, a tertiary-care university hospital with 853 beds
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients over 15 years old who were scheduled for cardiac surgery with the cardiopulmonary bypass were enrolled.
Exclusion criteria	patients who had active infections or history of insulin allergy and off pump cardiopulmonary bypass procedures were excluded.
Age, gender and ethnicity	Age - Median (range): 54. Gender (M:F): Define.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	patients over 15 years old were included .
Indirectness of population	No indirectness

Study	Rujirojindakul 2014[137]
Interventions	(n=100) Intervention 1: Glucose control - Insulin therapy (intraoperative). A hyperinsulinemic normo-glycaemic clamp with modified GIK solution was used to maintain blood glucose levels between 4.4 and 8.3 mmol/l, and the solution was infused via central venous catheter after catheter insertion until sternal closure. Insulin was infused continuously at a fixed rate of 0.3 U/kg/h, with a maximal rate of 20 U/h. A separate mixture of 25% glucose 50 ml, potassium chloride 20 mEq and magnesium sulfate 2 g was infused at 0.75 ml/kg/h and was adjusted to maintain targeted blood glucose levels by an attending anaesthesiologist. This solution was prepared by an attending nurse anaesthetist. Before CPB, insulin was administered bolus if blood glucose level remained > 6.0 mmol/l according to the following: insulin 2 U, 4 U, 6 U, 8 U and 10 U were given when blood glucose levels were 6.0–7.9 mmol/l, 8.0– 9.9 mmol/l, 10.0–11.9 mmol/l, 12.0–13.9 mmol/l and > 14.0 mmol/l, respectively. Duration length of surgery. Concurrent medication/care: Safety features were built into our protocol to minimise hypoglycaemia by giving 50% glucose 25 ml when blood glucose level was < 4.1 mmol/l. If blood glucose level was < 3.3 mmol/l, blood sample was sent to a central laboratory to confirm hypoglycaemia. By design, both groups had 12-h post-operative blood glucose controlled levels at less than 11.1 mmol/l to make sure that any observed differences in outcome would be due to the effects of intraoperative glycaemic control.. Indirectness: No indirectness (n=100) Intervention 2: Standard care - Liberal glucose control. insulin was administered bolus intravenously if blood glucose level was more than 13.8 mmol/l according to the institutional protocol. Insulin 5 U, 10 U and 15 U were given when blood glucose levels were between 13.9 and 16.6 mmol/l, 16.7 and 19.4 mmol/l, and more than 19.4 mmol/l, respectively.. Duration length of surgery. Concurrent medication/care: Safety features were built into our protocol to minimise hypoglycaemia by giving 50% glucose 25 ml when blood glucose level was < 4.1 mmol/l. If blood glucose level was < 3.3 mmol/l, blood sample was sent to a central laboratory to confirm hypoglycaemia. By design, both groups had 12-h post-operative blood glucose controlled levels at less than 11.1 mmol/l to make sure that any observed differences in outcome would be due to the effects of intraoperative glycaemic control. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: mortality at 30 days post op; Group 1: 6/99, Group 2: 8/100
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A

Study	Rujirojindakul 2014[137]
	Protocol outcome 2: Adverse events and complications - Actual outcome: cardiac - new AF, cardiac arrest, heart block requiring pace maker at 30 days post op; Group 1: 21/99, Group 2: 23/100 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A - Actual outcome: neurological - stroke at 30 days post op; Group 1: 6/99, Group 2: 3/100 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A Protocol outcome 3: Infection (including SSI) - Actual outcome: infection at 30 days post op; Group 1: 17/99, Group 2: 13/100 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A Protocol outcome 4: Hypoglycaemia - Actual outcome: hypoglycaemic events at 30 days post op; Group 1: 23/99, Group 2: 3/100 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A Protocol outcome 5: Length of hospital stay - Actual outcome: length of hospital stay at 30 days post op; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A Protocol outcome 6: Length of stay in intensive care unit - Actual outcome: length of ICU stay at 30 days post op; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: did not receive intervention - change in operation; Group 2 Number missing: 0, Reason: N/A
Protocol outcomes not reported by the study	Quality of life ; Unplanned ICU admission ; Hospital readmission

Study	Sato 2010[143]
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	(n=56)
Countries and setting	Conducted in Canada, Japan; Setting: McGill university health center
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 hours post op
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis: DM and non DM patients
Inclusion criteria	Patients scheduled for elective resection of primary or secondary hepatic malignancy (2 segments) between July 2007 and June 2008
Exclusion criteria	Inability to give written informed consent, severe anemia (hemoglobin 10 g dL 1), hemodialysis, or conditions that contraindicated the use of epidural anesthesia.
Age, gender and ethnicity	Age - Mean (SD): GIN = 58.7± 12.5 control = 56.6 ± 13.7. Gender (M:F): 28/24.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes: Type 2 diabetes
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Glucose control - Insulin therapy (intraoperative). 2U of insulin was administered IV followed by an infusion of 2mU kg-1 .min-1 (110 mg dl-1)Ten minutes after starting the insulin infusion, and when the blood glucose was <6.1 mmol dl-1. Dextrose 20% supplemented with phosphate (30 mmol . L-1) was administered. In the operating room, blood glucose levels were measured every 15 minutes, and the dextrose infusion rate was adjusted to maintain arterial glycemia between 3.5 and 6.1 mmol □dL-1 (63–110 mg.dL-1min-1). At the end of the surgery, the insulin infusion was decreased to 1 mU. kg-1. The blood glucose was measured hourly for 24 hours in the ICU, and the dextrose infusion rate was modified by the attending nurse according to the protocol.. Duration 24 hours post op in ICU. Concurrent medication/care: In diabetic patients, the administration of oral hypoglycemic drugs was discontinued 24 hours before surgery. If patients received insulin, the daily dose was held the evening before surgery, and

Study	Sato 2010[143]
	subcutaneous insulin was administered using a sliding scale.. Indirectness: No indirectness (n=28) Intervention 2: Standard care - Liberal glucose control. Blood glucose measurements were performed before the induction of anesthesia, every 30 minutes during surgery, and hourly in the ICU for 24 hours. If the blood glucose was □6.1 mmol □ L□1 mg □ dL□1 (110), an insulin infusion of 1 U □ h□1(63–110 mg □ dL□1 was started. This was then titrated according to the sliding scale shown in Table 1, aiming at a blood glucose between 3.5 and 6.1mmol □ L□1 7.9 mmol □ L□1 (63–143 mg □ dL□1) during surgery and 3.5 and) after surgery.. Duration 24 hours post op. Concurrent medication/care: In diabetic patients, the administration of oral hypoglycemic drugs was discontinued 24 hours before surgery. If patients received insulin, the daily dose was held the evening before surgery, and subcutaneous insulin was administered using a sliding scale.. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL Protocol outcome 1: Adverse events and complications - Actual outcome: incidence of neurological sequelae at 24 hours post op; Group 1: 0/26, Group 2: 0/26 Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Blinding details: During surgery, blood glucose sampling was more frequent in the GIN therapy group. ; Group 1 Number missing: 2; Group 2 Number missing: 2 Protocol outcome 2: Hypoglycaemia - Actual outcome: hypoglycaemic events at 24 hours post op; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Blinding details: During surgery, blood glucose sampling was more frequent in the GIN therapy group. ; Group 1 Number missing: 2; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Sato 2011[142]

Study	Sato 2011[142]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Canada; Setting: a university hospital in Canada
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients scheduled for elective CABG requiring cardiopulmonary bypass
Exclusion criteria	Patients showing elevated troponin I (>0.5 ng/L) levels or an ejection fraction <40%, as well as patients requiring hemodialyisis or an intra-aortic balloon pump were excluded.
Age, gender and ethnicity	Age - Mean (SD): GIN group - 64 ± 8, control - 65 ± 11. Gender (M:F): 29/11.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Glucose control - Insulin therapy (intraoperative). Applying the principles of the hyperinsulinemic-normoglycemic clamp technique in the GIN group, insulin was administered at 5mU/kg/min during surgery. Glucose 20% was infused at a rate adjusted to maintain blood glucose 4.0-6.0 mmol/L. BG was measured every 15 minutes. Duration of surgery. Concurrent medication/care: BG measurements were taken before induction of anesthesia and measured throughout surgery using the accu-chek glucose monitor. Insulin - (Humulin R regular insulin; Eli Lilly and Co, indianapolis, Ni) was given intravenously to both groups depending on the protocol. . Indirectness: No indirectness (n=20) Intervention 2: Standard care - Liberal glucose control. The control group received insulin if BG was > 10.0mmol/L based on a sliding scale, also aiming at normoglycemia. BG was measured every 30 minutes. . Duration of surgery. Concurrent medication/care: BG measurements were taken before induction of anesthesia and measured throughout surgery using the accu-chek glucose monitor. Insulin - (Humulin R

Study	Sato 2011[142]
	regular insulin; Eli Lilly and Co, indianapolis, Ni) was given intravenously to both groups depending on the protocol. . Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL Protocol outcome 1: Hypoglycaemia - Actual outcome: hypoglycaemic events at unclear; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Schricker 2014[146]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=34)
Countries and setting	Conducted in Canada; Setting:
Line of therapy	Unclear
Duration of study	Duration of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for elective cardiac surgery, aged18–90 years and able to give written informed consent.
Exclusion criteria	Patients scheduled for off-pump coronary artery bypass grafting, with anticipated deep hypothermic circulatory arrest, elevated baseline troponin I levels (.0.5 ngL-1) or requiring hemodialysis were excluded.

Study	Schricker 2014[146]
Age, gender and ethnicity	Age - Mean (SD): GIN group = 66±11 control = 60 ±13. Gender (M:F): 19/7.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Extra comments	.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Glucose control - Insulin therapy (intraoperative). GIN group: a priming bolus of 2 U insulin was followed by an infusion of insulin at 5 mU Kg-1 min (Humulin R regular insulin 100 U 100 mL -1 0.9% normal saline). Approximately 10 minutes after starting the insulin infusion, and when the blood glucose was,6.1 mmol L-1, dextrose 20% was administered intravenously . In the operating theatre, blood glucose levels were measured every 5–15 minutes and appropriate adjustments of the dextrose infusion rate were made to maintain the blood glucose within the target level of 3.5–6.1 mmol L-1 A priming bolus of 2 U insulin was followed. Duration of surgery. Concurrent medication/care: Postoperative glycemic control in both groups was performed using standard protocols aimed at a blood glucose concentration between 4 and 10 mmol L. . Indirectness: No indirectness (n=18) Intervention 2: Standard care - Liberal glucose control. Arterial blood glucose measurements were performed every 30 to 60 minutes while in the operating room. At any of these measurements, if the blood glucose was greater than 10.0 mmol L-1, an insulin bolus of 2 U was given followed by an infusion of 2 U h1 (Humulin R regular insulin 100 U 100 mL-1 0.9% normal saline). The insulin rate was adjusted according to the following sliding scale, to a maximum of 20 Uh-1. . Duration of surgery. Concurrent medication/care: Postoperative glycemic control in both groups was performed using standard protocols aimed at a blood glucose concentration between 4 and 10 mmol L-1. . Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Adverse events and complications
- Actual outcome: pulmonary complications at length of hospital stay; Group 1: 1/14, Group 2: 2/12

Study	Schricker 2014[146]
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: the type of cardiac surgery was not balanced between the two groups; Group 1 Number missing: 2, Reason: no reason stated; Group 2 Number missing: 6, Reason: no reason stated Protocol outcome 2: Infection (including SSI) - Actual outcome: UTI and superficial wound infection at length of hospital stay; Group 1: 3/14, Group 2: 2/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: the type of cardiac surgery was not balanced between the two groups; Group 1 Number missing: 2, Reason: no reason stated; Group 2 Number missing: 6, Reason: no reason stated Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: Length of ICU stay at length of hospital stay; Group 1: mean 21 hours (SD 10); n=14, Group 2: mean 22 hours (SD 8); n=12 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: the type of cardiac surgery was not balanced between the two groups; Group 1 Number missing: 2, Reason: no reason stated; Group 2 Number missing: 6, Reason: no reason stated	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hypoglycaemia ; Length of hospital stay ; Unplanned ICU admission ; Hospital readmission

Study	Smith 2002[153]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in United Kingdom; Setting: The Royal Bromptom and Harefield hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for elective CABG surgery with significant stenosis of at least 2 coronary arteries and moderate or preserved ventricular function (left ventricular ejection fraction >30%).
Exclusion criteria	Pre-existing conduction abnormalities (eg, left bundle-branch block, AF), insulin-dependant diabetes, serum

Study	Smith 2002[153]
	creatine >200mmol/L, emergent cardia surgery and reoperation or combined surgical procedures (eg. CABG and carotid endarterectomy/vulvular surgery).
Age, gender and ethnicity	Age - Mean (SD): 59.8±4.1 67.5 ±2. Gender (M:F): 37/7.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Glucose control - Insulin therapy (intraoperative). GIK infusion consisting of 0.5 IU/kg insulin (Human Actrapid, Novo, Nordisk, Copenhagen, Denmark), 2.5ml of 50% D/W per IU of insulin, 0.25 mmol of potassium chloride per mL of 50% D/W and 0.04 g of magnesium sulfate per mL of 50% D/W. GIK solution started via venus catheter immediately after induction of anesthesia and maintained for 6 hours after re perfusion. BG levels measured at 0.5 hour intervals from start to 2 hours after cessation of the GIK infusion. BG levels were maintained at 5 to 10 mmol/L. . Duration of surgery and 6 hours after reperfusion. Concurrent medication/care: GIK infusion or placebo started via venus catheter immediately after induction of anesthesia and maintained for 6 hours after re perfusion. blood glucose, potassium and base deficit were measured at regular intervals during the perioperative period and at 0.5-hour intervals for the first 8 hours after reperfusion using a blood gas analyser. . Indirectness: No indirectness (n=22) Intervention 2: Standard care - No glucose control. Patients received an equal volume of 5% dextrose in water as placebo without the magnesium supplementation. Placebo solution started via venus catheter immediately after induction of anesthesia and maintained for 6 hours after re perfusion. . Duration of surgery and 6 hours after reperfusion. Concurrent medication/care: GIK infusion or placebo started via venus catheter immediately after induction of anesthesia and maintained for 6 hours after re perfusion. blood glucose, potassium and base deficit were measured at regular intervals during the perioperative period and at 0.5-hour intervals for the first 8 hours after reperfusion using a blood gas analyser. . Indirectness: No indirectness
Funding	Academic or government funding

Study	Smith 2002[153]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL Protocol outcome 1: Adverse events and complications - Actual outcome: incidence of perioperative myocardial infarction at incidence within 5 days post op; Group 1: 4/22, Group 2: 5/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: postoperative AF at within 5 days post op; Group 1: 8/22, Group 2: 3/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Infection (including SSI) - Actual outcome: postoperative wound or respiratory infection at 5 days post; Group 1: 6/22, Group 2: 7/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: length of hospital stay at length of hospital stay; Group 1: mean 8.4 days (SD 1); n=22, Group 2: mean 7.6 days (SD 2); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hypoglycaemia ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Szabo 2001[157]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=20)
Countries and setting	Conducted in Sweden; Setting: Linkoping university hospital heart centre, Sweden
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Study	Szabo 2001[157]
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 2 diabetes undergoing elective coronary surgery for stable angina pectdris.
Exclusion criteria	left ventricular ejection fraction of <0.40, age over 80 years, serious late complications of diabetes, liver disease, poorly controlled diabetes or metabolic disturbance other than diabetes.
Age, gender and ethnicity	Age - Mean (SD): GIK group -58±2, control group - 56 ±3. Gender (M:F): 6/4.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Glucose control - Insulin therapy (postoperative). High dose GIK postoperatively - fast acting insulin (Actrapid Novo) was infused at a rate of 1 i.u .h-1kg, BW for 6 hours. A bolus of 25 i.u was also injected after 5 min. A 30% glucose solution also supplemented with 10mmol/l magnesium and 40mmol/l phosphate was also infused with the aim of keeping blood glucose between 7 and 10 mmol/l. After stopping insulin infusion the glucose infusion was decreased gradually. . Duration postoperatively for 6 hours. Concurrent medication/care: all patients were operated on before midday. beta blockers and calcium antagonists were administered orally but ACE inhibitors, oral diabetic treatment and insulin were withheld. the patients were premedicated intramuscularly with 8-10 mg of oxycodone and 0.4-0.5mg of scopolamine.. Indirectness: No indirectness (n=10) Intervention 2: Standard care - Liberal glucose control. Standard post-operative care including insulin infusion if necessary to keep blood glucose below 10 mmol/l. . Duration postoperatively for 6 hours. Concurrent medication/care: All patients were operated on before midday. beta blockers and calcium antagonists were administered orally but ACE inhibitors, oral diabetic treatment and insulin were withheld. the patients were premedicated intramuscularly with 8-10 mg of oxycodone and 0.4-0.5mg of scopolamine.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Length of hospital stay
- Actual outcome: mortality at unclear; Group 1: 0/10, Group 2: 0/10
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Szabo 2001[157]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of ICU stay; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Infection (including SSI) ; Hypoglycaemia ; Unplanned ICU admission ; Hospital readmission

Study	Tohya 2018[159]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=30)
Countries and setting	Conducted in Japan; Setting: School of medical and dental sciences Kagoshima University Japan
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients 60 years or older diagnosed with oral malignant tumors and scheduled for radical operation with tissue reconstruction (scheduled time required equal to or more than 8 hours). Patients were category 1 (normal healthy patients, no organic, physiological or psychiatric disturbances) or 2 (patients with mild systemic disease, no functional limitations) of ASA physical status classification.
Exclusion criteria	Patients who had DM, who were not able to continue GI infusion due to hypoglycaemia or whose actual operation time was less than 8 hours were excluded from analysis.
Age, gender and ethnicity	Age - Mean (SD): 74.13 ± 8.6. Gender (M:F): 19/11. Ethnicity: Not reported
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness

Study	Tohya 2018[159]
Interventions	(n=10) Intervention 1: Glucose control - Insulin therapy (intraoperative). Regular insulin was continuously applied with glucose added acetate Ringer's solution (5–10 g glucose per 500 mL). Blood glucose was adjusted within the target concentration of 80–120 mg/dL. . Duration of surgery. Concurrent medication/care: routine patient monitoring included non - invasive blood pressure, invasive blood pressure through the radial artery, electrocardiogram, pulse oximetry, and inspired/expired anesthetic gas and carbon dioxide which were included in the patient monitor.. Indirectness: No indirectness (n=20) Intervention 2: Standard care - Liberal glucose control. A combination of acetate Ringer's solution which contains 1% (W/V) glucose and lactate Ringer's solution, which contains no glucose, was infused. Regular insulin was subcutaneously applied each time when a blood glucose concentration of ≥ 180 mg/dL occurred. . Duration of surgery. Concurrent medication/care: routine patient monitoring included non - invasive blood pressure, invasive blood pressure through the radial artery, electrocardiogram, pulse oximetry, and inspired/expired anesthetic gas and carbon dioxide which were included in the patient monitor.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Adverse events and complications
- Actual outcome: pulmonary complications - pneumonia at length of stay in hospital ; Group 1: 2/10, Group 2: 1/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: post operative complications at length of stay in hospital ; Group 1: 4/10, Group 2: 13/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Infection (including SSI)
- Actual outcome: surgical site infection at length of stay in hospital ; Group 1: 1/10, Group 2: 5/20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Tohya 2018[159]
- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Length of hospital stay - Actual outcome: days until discharge at length of stay in hospital ; Group 1: mean 68.8 days (SD 22.5); n=10, Group 2: mean 85.6 days (SD 44.4); n=20 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Hypoglycaemia ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Visser 2005[166]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=21)
Countries and setting	Conducted in Netherlands; Setting: academic medical centre, university of Amsterdam
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with normal left ventricular function scheduled for elective CABG.
Exclusion criteria	Patients with DM, ejection fraction <45%, unstable angina pectoris, or atrioventricular conduction defects, patients taking corticosteroids or non-steroidal anti-inflammatory drugs or undergoing additional surgical procedure.
Age, gender and ethnicity	Age - Mean (range): 62.5 (54-70). Gender (M:F): 18/3.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Glucose control - Insulin therapy (perioperative). Soluble insulin (Actrapid, NovoNordisk, Copenhagen, Denmark) was infused continuously at a fixed rate of 0.1 IU·kg1·h 1. A separate

Study	Visser 2005[166]
	mixture of glucose 30% (Baxter-Clintec Benelux SA, Brussels, Belgium), potassium chloride 80 mmol litre 1 and phosphate 60 mmol litre 1 was infused at a variable rate adjusted to maintain blood glucose levels within a target range of 4.0–5.5 mmol litre 1. The infusion of glucose was started at a rate of 0.5 ml·kg 1·h 1. In all patients the first glucose samples were taken 15 and 30 min after the start of the glucose and insulin infusions. Adjustments to the glucose 30% infusion rate were made depending on the BG levels and additional infusions of insulin and glucose were administered as required. . Duration length of surgery and 24 hours post operatively. Concurrent medication/care: standard institutional perioperative care. Post operatively all patients were admitted to ICU and throughout the ICU stay, a continuous infusion of glucose 5% was given at a rate of 30 ml h 1 (1.5 g h 1) to all patients through a central venous line. . Indirectness: No indirectness (n=11) Intervention 2: Standard care - No glucose control. Patients received standard institutional perioperative care.. Duration length of surgery and 24 hours post operatively. Concurrent medication/care: standard institutional perioperative care. Post operatively all patients were admitted to ICU and throughout the ICU stay, a continuous infusion of glucose 5% was given at a rate of 30 ml h 1 (1.5 g h 1) to all patients through a central venous line. . Indirectness: Serious indirectness; Indirectness comment: unclear if control group received BG control
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus NO GLUCOSE CONTROL

Protocol outcome 1: Hypoglycaemia
- Actual outcome: hypoglycaemic events at length of hospital stay; Group 1: 0/10, Group 2: 0/11
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 2: Length of hospital stay
- Actual outcome: length of hospital stay at length of hospital stay; Group 1: mean 6 days (SD 1); n=10, Group 2: mean 8 days (SD 4); n=11
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Study	Visser 2005[166]
Protocol outcome 3: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of ICU stay; Group 1: mean 26 hours (SD 5); n=10, Group 2: mean 26 hours (SD 8); n=11 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Quality of life ; Mortality ; Adverse events and complications ; Infection (including SSI) ; Unplanned ICU admission ; Hospital readmission

Study	Yuan 2015[169]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=212)
Countries and setting	Conducted in China; Setting: The First affiliated hospital of Zhenhzhou university
Line of therapy	Unclear
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	adult patients with type 2 DM undergoing gastrectomy for gastric tumors.
Exclusion criteria	patients excluded if a withdrawl request was made by the patients or surrogate, the patient underwent laparotomy or palliative surgery, the patient was unable to tolerate enteral nutrition, as shown by vomiting, diarrhoea, or abdominal distention, or the naso-jejunal tube became occluded or was pulled out.
Age, gender and ethnicity	Age - Mean (SD): 60.8 ± 13.4. Gender (M:F): 87/125.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: Glucose control - Insulin therapy (postoperative). Intensive glycaemic management with continuous insulin infusion (target glucose 4.4–6.1 mmol/l (80–110 mg/dl). patients were started on an intravenous infusion of 0.5-1 u/h insultin. BG was monitored every 2-4 hours when stable and adjusted according to the IV insulin algorithm.

Study	Yuan 2015[169]
	. Duration unclear. Concurrent medication/care: patients were infused with 250ml of normal saline starting within 12h after surgery. patients received feedings of 20l/h SP or TPH through a naso-jejunal tube beginning on the first post operative day, with the rate increasing 10 ml/h as tolerated every 12-14 h.. Indirectness: No indirectness (n=106) Intervention 2: Standard care - Liberal glucose control. Conventional glycaemic management with intermittent bolus insulin (target glucose <11.1 mmol/l (<200 mg/dl). patients were administered insulin subcutaneously every 4-6 h based on the results of the bedside glucose monitoring with extra injections administered if necessary.. Duration unclear. Concurrent medication/care: patients were infused with 250ml of normal saline starting within 12h after surgery. patients received feedings of 20l/h SP or TPH through a naso-jejunal tube beginning on the first post operative day, with the rate increasing 10 ml/h as tolerated every 12-14 h.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: mortality at length of hospital stay; Group 1: 1/106, Group 2: 1/106
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events and complications
- Actual outcome: pulmonary complication - pneumonia at length of hospital stay; Group 1: 6/106, Group 2: 8/106
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Infection (including SSI)
- Actual outcome: surgical site infection and UTI at length of hospital stay; Group 1: 12/106, Group 2: 20/106
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Hypoglycaemia
- Actual outcome: severe hypoglycaemia at length of hospital stay; Group 1: 8/106, Group 2: 1/106

Study	Yuan 2015[169]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Length of hospital stay ; Unplanned ICU admission ; Length of stay in intensive care unit ; Hospital readmission

Study	Zheng 2010[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in China; Setting: unclear
Line of therapy	Unclear
Duration of study	Intervention + follow up: length of hospital stay
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing heart valve replacement with CBP.
Exclusion criteria	preoperative kidney or liver disease or dysfunction, preoperative coagulation disorder, palliative operation or a second operation.
Age, gender and ethnicity	Age - Mean (SD): Insulin group - 43.3± 11.7, control group - 44.0 ±11.5. Gender (M:F): 89/11.
Further population details	1. Age: 2. American Society of Anesthesiologists (ASA) Physical Status grade: 3. BMI ≥30kg/m2: 4. Cardiac surgery: 5. Surgery grade based on NICE preoperative tests for elective surgery guideline categorisation: 6. Type 2 diabetes:
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Glucose control - Insulin therapy (perioperative). Insulin continuously infused adjusted to maintain BG levels between 70-110 mmol/dL during and after surgery. 0.3 to 0.4 U/kg insulin per hour was continuously infused intravenously after anesthesia was inducted according to the Portland Protocol with modifications. The insulin dosage was changed to 10 U/h when the thoracic cavity was open, the insulin dosage was further adjusted to 1 to 1.5 U/kg per hour when CPB commenced. blood glucose was tested every 15 minutes. there was no insulin input at blood concentrations less than or equal to 50 mg/dL, but 50 ml of 20% glucose was administered intravenously instead. insulin administration was terminated when body

Study	Zheng 2010[170]
	temperature begun to recover. post operative blood glucose levels were measured every 60 minutes post operatively and insulin infusion started if BG exceeded 110 mg/dl. . Duration unclear. Concurrent medication/care: Blood samples and cardia index measurements were taken at 7 time points perioperatively.. Indirectness: No indirectness (n=50) Intervention 2: Standard care - No glucose control. Received standard institutional operative and post-operative care, but no control for blood glucose.. Duration unclear. Concurrent medication/care: blood samples and cardia index measurements were taken at 7 time points perioperatively.. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus NO GLUCOSE CONTROL

Protocol outcome 1: Mortality
- Actual outcome: in hospital mortality at hospital stay; Group 1: 2/50, Group 2: 3/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Infection (including SSI)
- Actual outcome: Nosocomial wound infection at length of hospital stay; Group 1: 1/50, Group 2: 4/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Hypoglycaemia
- Actual outcome: hypoglycaemic events at length of hospital stay; Group 1: 3/50, Group 2: 1/50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Length of hospital stay
- Actual outcome: length of hospital stay at length of hospital stay; Group 1: mean 8.2 days (SD 4.3); n=50, Group 2: mean 10.9 days (SD 5.2); n=50
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Length of stay in intensive care unit
- Actual outcome: length of ICU stay at length of hospital stay; Group 1: mean 46.7 hours (SD 5.9); n=50, Group 2: mean 59 hours (SD 5.5); n=50

Study	Zheng 2010[170]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life ; Adverse events and complications ; Unplanned ICU admission ; Hospital readmission

Appendix E: Forest plots

E.1 Glucose control versus standard care

Figure 2: Mortality <30 days

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Abdelmalak 2013	4	196	4	185	6.8%	-0.00 [-0.03, 0.03]
Azarfarin 2011	1	59	1	58	2.1%	-0.00 [-0.05, 0.05]
Butterworth 2005	6	188	5	193	6.8%	0.01 [-0.03, 0.04]
Cao 2011	1	125	2	123	4.4%	-0.01 [-0.04, 0.02]
Chan 2009	3	47	3	51	1.7%	0.01 [-0.09, 0.10]
Chaney 1999	0	10	0	10	0.4%	0.00 [-0.17, 0.17]
Desai 2012	1	91	1	98	3.4%	0.00 [-0.03, 0.03]
Duncan 2018	9	709	13	730	25.6%	-0.01 [-0.02, 0.01]
Ghandi 2007	4	185	0	186	6.6%	0.02 [-0.00, 0.04]
Giakoumidakis 2013	1	105	6	107	3.8%	-0.05 [-0.09, 0.00]
Grey 2004	4	34	6	27	1.1%	-0.10 [-0.30, 0.09]
Groban 2002	3	188	0	193	6.8%	0.02 [-0.00, 0.04]
Ingels 2006	16	477	37	493	17.3%	-0.04 [-0.07, -0.01]
Ji 2014	0	33	2	32	1.2%	-0.06 [-0.16, 0.04]
Okabayashi 2009a	0	44	0	44	1.6%	0.00 [-0.04, 0.04]
Okabayashi 2009b	0	17	0	13	0.5%	0.00 [-0.12, 0.12]
Rujirojindakul 2014	6	99	8	100	3.5%	-0.02 [-0.09, 0.05]
Smith 2002	0	22	0	22	0.8%	0.00 [-0.08, 0.08]
Szabo 2001	0	10	0	10	0.4%	0.00 [-0.17, 0.17]
Yuan 2015	1	103	1	106	3.7%	0.00 [-0.03, 0.03]
Zheng 2010	2	50	3	50	1.8%	-0.02 [-0.11, 0.07]
Total (95% CI)		**2792**		**2831**	**100.0%**	**-0.01 [-0.02, -0.00]**
Total events	62		92			

Heterogeneity: Chi² = 26.55, df = 20 (P = 0.15); I² = 25%
Test for overall effect: Z = 2.39 (P = 0.02)

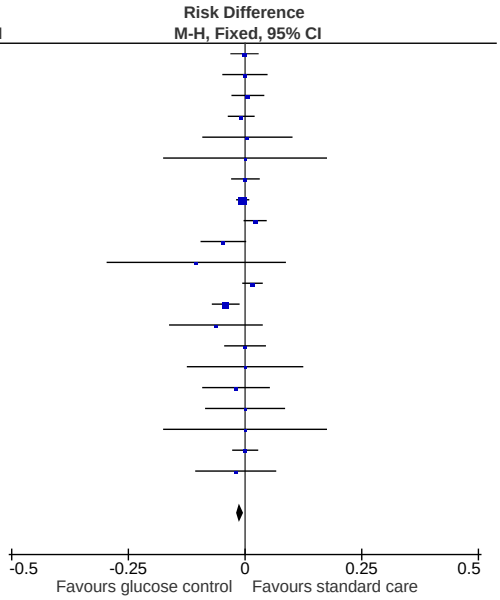


Figure 3: Mortality >1 year

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmalak 2013	24	196	21	185	15.7%	1.08 [0.62, 1.87]
Duncan 2018	32	653	22	682	15.7%	1.52 [0.89, 2.59]
Ingels 2006	73	477	89	493	63.7%	0.85 [0.64, 1.12]
Pezzella 2014	4	91	6	98	4.2%	0.72 [0.21, 2.46]
Yuan 2015	1	106	1	106	0.7%	1.00 [0.06, 15.78]
Total (95% CI)		**1523**		**1564**	**100.0%**	**0.98 [0.79, 1.23]**
Total events	134		139			

Heterogeneity: Chi² = 3.99, df = 4 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

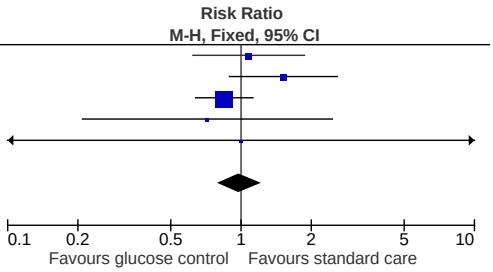


Figure 4: Post-operative complications

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cao 2011	17	125	31	123	84.2%	-0.12 [-0.21, -0.02]
Hoedemaekers 2005	0	10	0	10	6.8%	0.00 [-0.17, 0.17]
Tohya 2018	4	10	13	20	9.1%	-0.25 [-0.62, 0.12]
Total (95% CI)		**145**		**153**	**100.0%**	**-0.12 [-0.21, -0.03]**
Total events	21		44			

Heterogeneity: Chi² = 2.32, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 2.63 (P = 0.008)

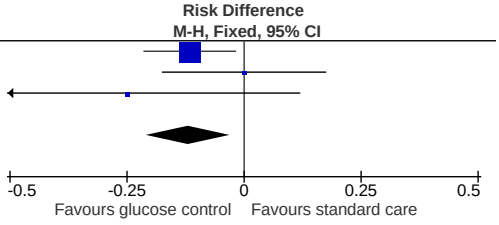


Figure 5: Pulmonary complications

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmalak 2013	14	196	8	185	31.9%	1.65 [0.71, 3.85]
Albacker 2007	2	22	0	22	1.9%	5.00 [0.25, 98.52]
Cao 2011	4	125	6	123	23.4%	0.66 [0.19, 2.27]
Desai 2012	2	91	0	98	1.9%	5.38 [0.26, 110.59]
Schricker 2014	1	16	2	18	7.3%	0.56 [0.06, 5.63]
Tohya 2018	2	10	1	20	2.6%	4.00 [0.41, 39.00]
Yuan 2015	6	106	8	106	31.0%	0.75 [0.27, 2.09]
Total (95% CI)		**566**		**572**	**100.0%**	**1.25 [0.76, 2.07]**
Total events	31		25			

Heterogeneity: Chi² = 5.61, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.89 (P = 0.37)

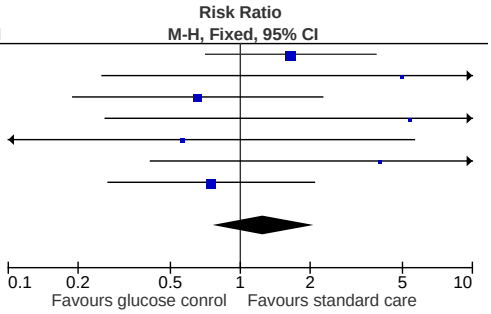


Figure 6: Cardiovascular complications

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Cardiac						
Azarfarin 2011	6	59	5	58	72.4%	1.18 [0.38, 3.65]
Desai 2012	2	91	2	98	27.6%	1.08 [0.15, 7.49]
Subtotal (95% CI)		**150**		**156**	**100.0%**	**1.15 [0.43, 3.06]**
Total events	8		7			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)

1.5.2 Cardiac arrest						
Butterworth 2005	3	188	1	193	33.2%	3.08 [0.32, 29.34]
Ghandi 2007	1	185	0	186	16.8%	3.02 [0.12, 73.56]
Groban 2002	2	188	0	193	16.6%	5.13 [0.25, 106.20]
Rujirojindakul 2014	3	99	1	100	33.5%	3.03 [0.32, 28.64]
Subtotal (95% CI)		**660**		**672**	**100.0%**	**3.39 [0.94, 12.26]**
Total events	9		2			

Heterogeneity: Chi² = 0.09, df = 3 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.86 (P = 0.06)

1.5.3 MI						
Abdelmalak 2013	2	196	4	185	38.8%	0.47 [0.09, 2.55]
Albacker 2007	0	22	1	22	14.1%	0.33 [0.01, 7.76]
Smith 2002	4	22	5	22	47.1%	0.80 [0.25, 2.59]
Subtotal (95% CI)		**240**		**229**	**100.0%**	**0.61 [0.24, 1.52]**
Total events	6		10			

Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)

1.5.4 AF						
Albacker 2007	6	22	3	22	0.9%	2.00 [0.57, 7.01]
Chaney 1999	2	10	4	10	1.2%	0.50 [0.12, 2.14]
Desai 2012	7	91	10	98	2.9%	0.75 [0.30, 1.90]
Duncan 2018	209	709	235	730	70.0%	0.92 [0.78, 1.07]
Ghandi 2007	54	184	59	186	17.7%	0.93 [0.68, 1.26]
Rujirojindakul 2014	17	99	21	100	6.3%	0.82 [0.46, 1.45]
Smith 2002	8	22	3	22	0.9%	2.67 [0.81, 8.75]
Subtotal (95% CI)		**1137**		**1168**	**100.0%**	**0.93 [0.81, 1.06]**
Total events	303		335			

Heterogeneity: Chi² = 5.58, df = 6 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.13 (P = 0.26)

1.5.5 Arrhythmia						
Groban 2002	60	188	68	193	100.0%	0.91 [0.68, 1.20]
Subtotal (95% CI)		**188**		**193**	**100.0%**	**0.91 [0.68, 1.20]**
Total events	60		68			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)

1.5.6 Sternal instability						
Ji 2014	0	33	1	32	100.0%	0.32 [0.01, 7.66]
Subtotal (95% CI)		**33**		**32**	**100.0%**	**0.32 [0.01, 7.66]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Chi² = 5.38, df = 5 (P = 0.37), I² = 7.0%

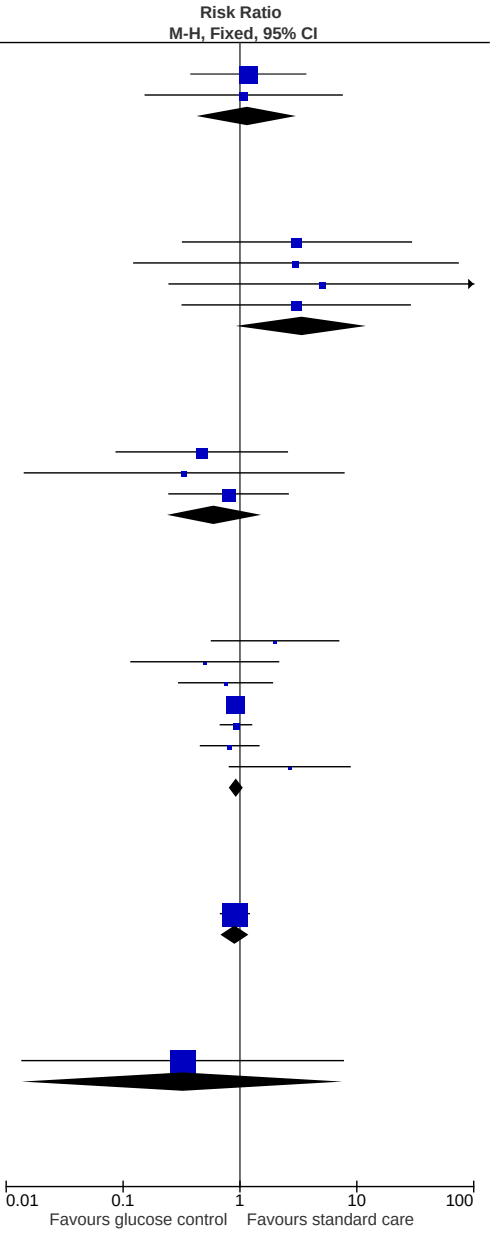


Figure 7: Neurological complications

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
1.6.1 Neurological deficit						
Azarfarin 2011	3	59	3	58	6.8%	-0.00 [-0.08, 0.08]
Chan 2009	1	47	5	51	5.7%	-0.08 [-0.17, 0.01]
Chaney 1999	0	10	1	10	1.2%	-0.10 [-0.34, 0.14]
Duncan 2018	9	709	12	730	83.4%	-0.00 [-0.02, 0.01]
Sato 2010	0	26	0	26	3.0%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**851**		**875**	**100.0%**	**-0.01 [-0.02, 0.00]**
Total events	13		21			
Heterogeneity: Chi² = 3.41, df = 4 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
1.6.2 Stroke						
Abdelmalak 2013	0	196	0	185	25.0%	0.00 [-0.01, 0.01]
Butterworth 2005	5	188	3	193	25.1%	0.01 [-0.02, 0.04]
Desai 2012	0	91	0	98	12.4%	0.00 [-0.02, 0.02]
Ghandi 2007	8	185	1	186	24.4%	0.04 [0.01, 0.07]
Rujirojindakul 2014	6	99	3	100	13.1%	0.03 [-0.03, 0.09]
Subtotal (95% CI)		**759**		**762**	**100.0%**	**0.02 [0.00, 0.03]**
Total events	19		7			
Heterogeneity: Chi² = 14.00, df = 4 (P = 0.007); I² = 71%						
Test for overall effect: Z = 2.34 (P = 0.02)						
Test for subgroup differences: Chi² = 6.57, df = 1 (P = 0.01), I² = 84.8%						

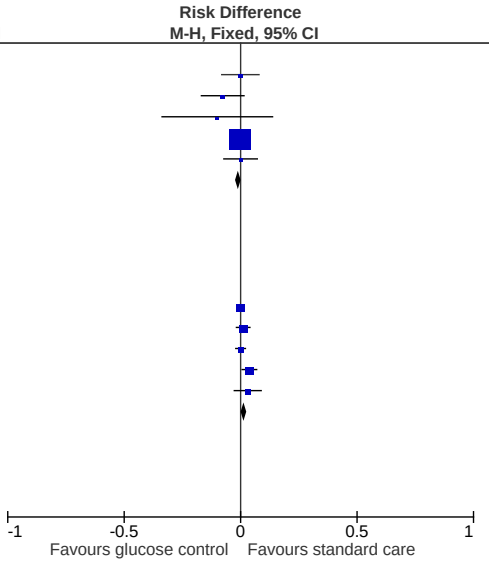


Figure 8: Infection

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Abdelmalak 2013	17	196	18	185	9.8%	0.89 [0.47, 1.68]
Albacker 2007	1	22	1	22	0.5%	1.00 [0.07, 15.00]
Azarfarin 2011	0	59	2	58	1.3%	0.20 [0.01, 4.01]
Cao 2011	12	125	26	123	13.9%	0.45 [0.24, 0.86]
Chan 2009	9	47	18	51	9.1%	0.54 [0.27, 1.09]
Desai 2012	1	91	0	98	0.3%	3.23 [0.13, 78.25]
Duncan 2018	20	709	44	730	23.0%	0.47 [0.28, 0.79]
Emam 2010	0	80	5	40	3.9%	0.05 [0.00, 0.81]
Ghandi 2007	6	185	7	186	3.7%	0.86 [0.30, 2.52]
Giakoumidakis 2013	9	150	12	107	7.4%	0.54 [0.23, 1.22]
Ji 2014	1	33	2	32	1.1%	0.48 [0.05, 5.09]
Rujirojindakul 2014	17	99	13	100	6.8%	1.32 [0.68, 2.57]
Schricker 2014	3	16	2	18	1.0%	1.69 [0.32, 8.85]
Smith 2002	6	22	7	22	3.7%	0.86 [0.34, 2.14]
Tohya 2018	1	10	5	20	1.8%	0.40 [0.05, 2.98]
Yuan 2015	12	106	20	106	10.6%	0.60 [0.31, 1.16]
Zheng 2010	1	50	4	50	2.1%	0.25 [0.03, 2.16]
Total (95% CI)		**2000**		**1948**	**100.0%**	**0.62 [0.50, 0.77]**
Total events	116		186			
Heterogeneity: Chi² = 16.57, df = 16 (P = 0.41); I² = 3%						
Test for overall effect: Z = 4.37 (P < 0.0001)						

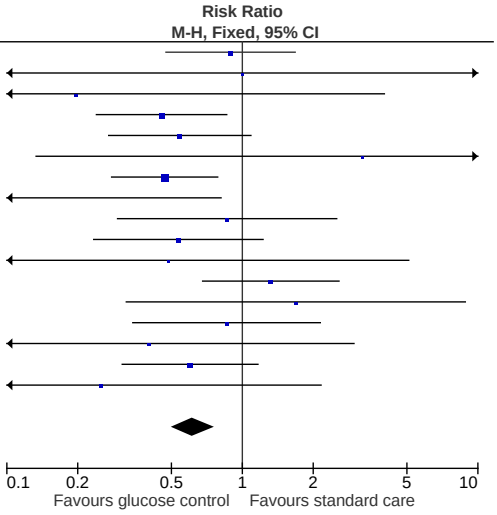


Figure 9: Hypoglycaemic events

Study or Subgroup	Glucose control Events	Total	Standrad care Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Abdelmalak 2013	29	196	4	185	6.7%	0.13 [0.07, 0.18]
Azarfarin 2011	0	59	0	58	2.1%	0.00 [-0.03, 0.03]
Butterworth 2005	22	188	12	193	6.7%	0.05 [-0.00, 0.11]
Cao 2011	8	125	1	123	4.4%	0.06 [0.01, 0.10]
Chaney 1999	4	10	0	10	0.4%	0.40 [0.08, 0.72]
Desai 2012	30	91	11	98	3.3%	0.22 [0.10, 0.33]
Duncan 2018	6	709	1	730	25.5%	0.01 [-0.00, 0.01]
Emam 2010	0	80	0	40	1.9%	0.00 [-0.04, 0.04]
Ghandi 2007	8	185	14	186	6.6%	-0.03 [-0.08, 0.02]
Giakoumidakis 2013	0	105	0	107	3.8%	0.00 [-0.02, 0.02]
Grey 2004	11	34	2	27	1.1%	0.25 [0.06, 0.44]
Groban 2002	23	188	12	193	6.7%	0.06 [0.00, 0.12]
Hoedemaekers 2005	0	10	0	10	0.4%	0.00 [-0.17, 0.17]
Ingels 2006	14	493	2	477	17.2%	0.02 [0.01, 0.04]
Ji 2014	1	33	0	32	1.2%	0.03 [-0.05, 0.11]
Okabayashi 2009a	0	44	0	44	1.6%	0.00 [-0.04, 0.04]
Okabayashi 2009b	0	17	0	13	0.5%	0.00 [-0.12, 0.12]
Rujirojindakul 2014	23	99	3	100	3.5%	0.20 [0.11, 0.29]
Sato 2011	0	20	0	20	0.7%	0.00 [-0.09, 0.09]
Visser 2005	0	10	0	11	0.4%	0.00 [-0.17, 0.17]
Yuan 2015	8	106	1	106	3.8%	0.07 [0.01, 0.12]
Zheng 2010	3	50	1	50	1.8%	0.04 [-0.04, 0.12]
Total (95% CI)		**2852**		**2813**	**100.0%**	**0.04 [0.03, 0.06]**
Total events	190		64			

Heterogeneity: Chi² = 200.40, df = 21 (P < 0.00001); I² = 90%
Test for overall effect: Z = 8.38 (P < 0.00001)

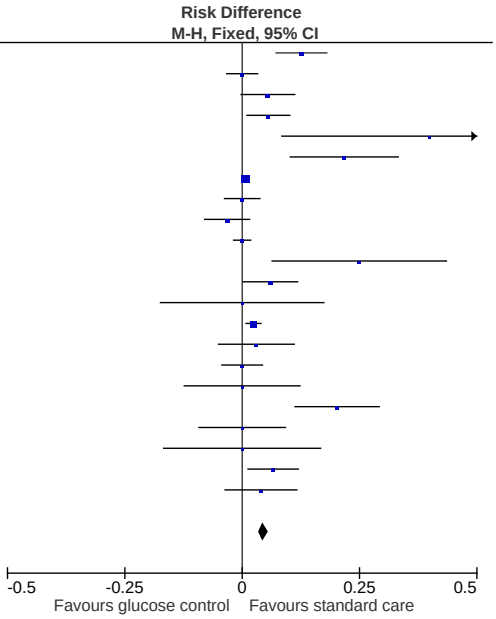


Figure 10: Length of hospital stay

Study or Subgroup	Glucose control Mean	SD	Total	Standrad care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chan 2009	12	7	47	17	16	51	3.9%	-5.00 [-9.83, -0.17]
Chaney 1999	5.5	2.3	10	6.5	2	10	11.4%	-1.00 [-2.89, 0.89]
Emam 2010	9.1	2.3	80	12.3	7.6	40	9.3%	-3.20 [-5.61, -0.79]
Ghandi 2007	8	4	185	8	5	186	15.5%	0.00 [-0.92, 0.92]
Giakoumidakis 2013	9.9	7.4	105	9.4	5	107	12.2%	0.50 [-1.20, 2.20]
Ji 2014	9.4	3.3	33	11.5	4.2	32	11.6%	-2.10 [-3.94, -0.26]
Smith 2002	8.4	1	22	7.6	2	22	15.4%	0.80 [-0.13, 1.73]
Tohya 2018	68.8	22.5	10	85.6	44.4	20	0.2%	-16.80 [-40.74, 7.14]
Visser 2005	6	1	10	8	4	11	9.2%	-2.00 [-4.44, 0.44]
Zheng 2010	8.2	4.3	50	10.9	5.2	50	11.4%	-2.70 [-4.57, -0.83]
Total (95% CI)			**552**			**529**	**100.0%**	**-1.19 [-2.27, -0.11]**

Heterogeneity: Tau² = 1.73; Chi² = 29.72, df = 9 (P = 0.0005); I² = 70%
Test for overall effect: Z = 2.17 (P = 0.03)

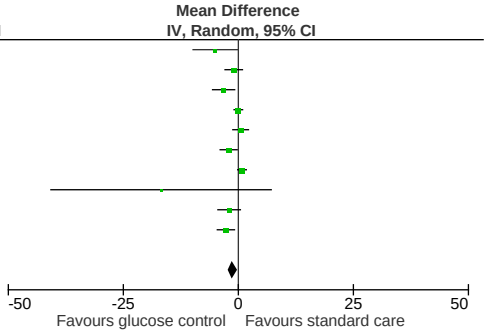


Figure 11: Length of ICU stay

Study or Subgroup	Glucose control Mean	SD	Total	Standrad care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chan 2009	98.4	165.6	47	141.6	252	51	0.5%	-43.20 [-127.01, 40.61]
Emam 2010	53.8	15	80	72	19	40	11.8%	-18.20 [-24.94, -11.46]
Ghandi 2007	48	48	185	48	72	186	8.5%	0.00 [-12.45, 12.45]
Giakoumidakis 2013	64.8	60	105	79.2	100.8	107	4.5%	-14.40 [-36.68, 7.88]
Grey 2004	801.6	1,639.2	34	588	465.6	27	0.0%	213.60 [-364.70, 791.90]
Hoedemaekers 2005	22.1	1.8	10	20.3	2.5	10	13.8%	1.80 [-0.11, 3.71]
Ji 2014	28.4	7.2	33	36.5	7.8	32	13.3%	-8.10 [-11.75, -4.45]
Schricker 2014	21	10	16	22	8	18	12.1%	-1.00 [-7.14, 5.14]
Smith 2002	27.2	6.7	22	40.8	24.4	22	9.5%	-13.60 [-24.17, -3.03]
Visser 2005	26	5	10	26	8	10	12.3%	0.00 [-5.85, 5.85]
Zheng 2010	46.7	5.9	50	59	5.5	50	13.8%	-12.30 [-14.54, -10.06]
Total (95% CI)			**592**			**553**	**100.0%**	**-6.90 [-12.65, -1.16]**

Heterogeneity: Tau² = 61.25; Chi² = 116.77, df = 10 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.35 (P = 0.02)

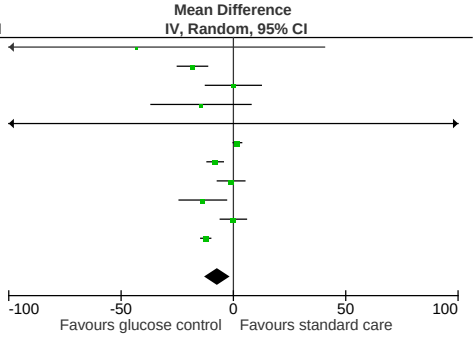
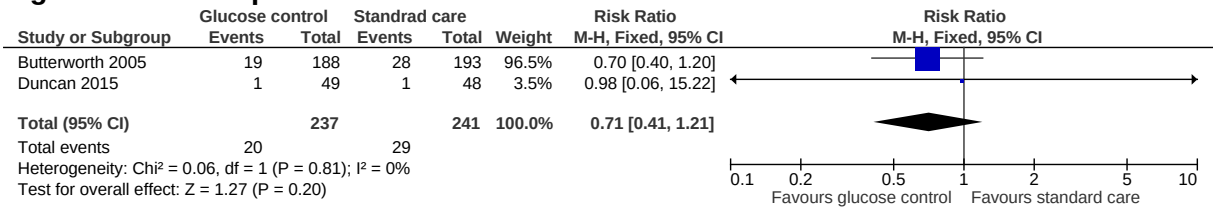


Figure 12: Hospital readmissions



Appendix F: GRADE tables

Table 9: Clinical evidence profile: Glucose control versus standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucose control	Control	Relative (95% CI)	Absolute		
Mortality (follow-up <30 days)												
21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	62/2792 (2.2%)	3.2%	RD -0.01 (-0.02 to 0.00)	10 fewer per 1000 (from 0 fewer to 20 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (follow-up >1 years)												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	134/1523 (8.8%)	6.1%	RR 0.98 (0.79 to 1.23)	1 fewer per 1000 (from 13 fewer to 14 more)	⊕⊕⊕O MODERATE	CRITICAL
Post-operative complication												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	21/145 (14.5%)	25.2%	RD -0.12 (-0.21 to -0.03)	111 fewer per 1000 (from 30 fewer to 164 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications: pulmonary												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	31/566 (5.5%)	4.9%	RR 1.25 (0.76 to 2.07)	12 more per 1000 (from 12 fewer to 52 more)	⊕⊕OO LOW	CRITICAL
Complications: cardiovascular - Cardiac												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/150 (5.3%)	5.3%	RR 1.15 (0.43 to 3.06)	8 more per 1000 (from 30 fewer to 109 more)	⊕⊕OO LOW	CRITICAL
Complications: cardiovascular - Cardiac arrest												

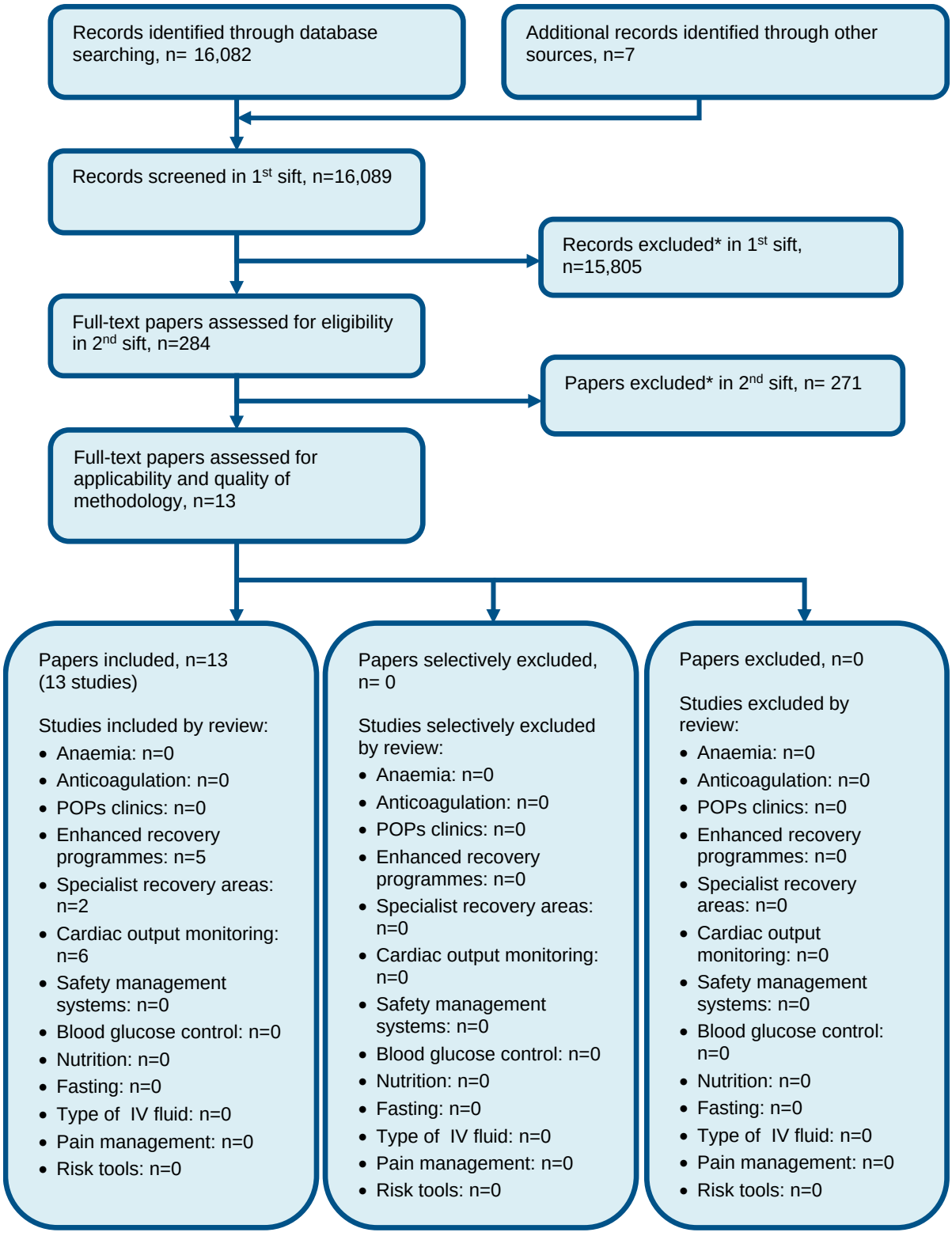
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/660 (1.4%)	0.3%	RR 3.39 (0.94 to 12.26)	7 more per 1000 (from 0 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications: cardiovascular - MI												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/240 (2.5%)	4.6%	RR 0.61 (0.24 to 1.52)	18 fewer per 1000 (from 35 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Complications: cardiovascular - AF												
7	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	303/1137 (26.6%)	21%	RR 0.93 (0.81 to 1.06)	15 fewer per 1000 (from 40 fewer to 13 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complications: cardiovascular - Arrhythmia												
1	randomised trials	serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	60/188 (31.9%)	35.2%	RR 0.91 (0.68 to 1.2)	32 fewer per 1000 (from 113 fewer to 70 more)	⊕⊕OO LOW	CRITICAL
Complications: cardiovascular - Sternal instability												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/33 (0%)	3.12%	RR 0.32 (0.01 to 7.66)	21 fewer per 1000 (from 31 fewer to 208 more)	⊕⊕OO LOW	CRITICAL
Complications: neurological - Neurological deficit												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/851 (1.5%)	5.2%	RD 0 (-0.02 to 0)	52 fewer per 1000 (from 52 fewer to 53 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Complications: neurological - Stroke												
5	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	19/759 (2.5%)	0.5%	RD 0.02 (0 to 0.03)	5 fewer per 1000 (from 5 fewer to 5 fewer)	⊕⊕OO LOW	CRITICAL
Infections												
17	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	116/2000 (5.8%)	9.5%	RR 0.62 (0.5 to 0.77)	42 fewer per 1000 (from 26 fewer to 56 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Hypoglycaemic events												
22	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	190/2854 (6.7%)	2.3%	RD 0.04 (0.03 to 0.05)	44 more per 1000 (from 33 more to 55 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Length of hospital stay (Better indicated by lower values)												
10	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	552	529	-	MD 1.19 lower (2.27 to 0.11 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Length of ICU stay (Better indicated by lower values)												
11	randomised trials	no serious risk of bias	very serious[2]	no serious indirectness	no serious imprecision	none	592	553	-	MD 6.90 lower (12.65 to 0.16 lower)	⊕⊕OO LOW	IMPORTANT
Hospital readmission												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/237 (8.4%)	8.3%	RR 0.71 (0.41 to 1.21)	24 fewer per 1000 (from 49 fewer to 17 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.
[2] Downgraded by 1 or 2 increments because of heterogeneity, I2>50%, p<0.04, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Appendix G: Health economic evidence selection

Figure 13: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Reference	Reason for exclusion
Abdelmalak 2016[2]	Inappropriate study design
Albacker 2008[3]	Inappropriate comparison
Albacker 2009[4]	Inappropriate study design
Anonymous 2009[6]	Inappropriate population
Arabi 2008[7]	Inappropriate population
Azagury 2015[8]	Inappropriate intervention
Barcellos Cda 2007[10]	Inappropriate intervention
Behrendt 1988[11]	Inappropriate intervention
Berkers 2008[12]	Inappropriate study design
Bertrand 2009[13]	Inappropriate study design
Besch 2017[14]	Inappropriate comparison
Besogul 1999[15]	Inappropriate intervention
Bhamidipati 2011[16]	Inappropriate study design
Bilotta 2009[17]	Inappropriate population
Blaha 2015[18]	Inappropriate comparison
Blixt 2012[19]	Inappropriate outcome
Bode 2004[20]	Inappropriate study design
Boldt 1993[21]	Inappropriate intervention
Bothe 2004[22]	Systematic review: references screened
Brodin 1993[23]	Inappropriate intervention
Bruemmer-Smith 2002[24]	Inappropriate intervention
Buchleitner 2012[25]	Systematic review: references screened
Cao 2008[28]	Not in English
Cardona 2017[29]	Inappropriate population
Celkan 2006[30]	Inappropriate intervention
Chin 2006[33]	Inappropriate outcome
Chuah 2015[34]	Inappropriate intervention
Codere-Maruyama 2016[35]	Inappropriate comparison
Coleman 1989[36]	Inappropriate intervention
D'Alessandro 2007[37]	Inappropriate study design
De La Rosa 2008[38]	Inappropriate population
Everett 2018[44]	Inappropriate study design
Fan 2011[45]	Systematic review: references screened

Fisette 2012[46]	Inappropriate intervention
Freitas 2013[47]	Not in English
Fujino 2014[48]	Inappropriate outcome
Fujita 2014[49]	Inappropriate intervention
Furnary 2004[50]	Inappropriate study design
Gandhi 2008[51]	Systematic review: studies included in review
Gandhi 2018[53]	Inappropriate comparison
Ghods 2017[54]	Inappropriate comparison
Giannini 2016[56]	Inappropriate study design
Girard 1992[57]	Inappropriate intervention
Gonzalez-Michaca 2002[58]	Inappropriate comparison
Gustafson 2002[61]	Inappropriate outcome
Haga 2011[62]	Systematic review: studies included in review
Haider 1984[63]	Inappropriate intervention
Hallhagen 1992[64]	Inappropriate outcome
Hasegawa 2011[65]	Inappropriate outcome
Hassanain 2013[66]	Inappropriate intervention
Hatzakorzian 2011[67]	Inappropriate outcome
Hatzakorzian 2014[68]	Inappropriate outcome
Hawkins 2013[69]	Inappropriate study design
Hayakawa 2000[70]	Inappropriate comparison
He 2007[71]	Not in English
Hecking 2012[72]	Inappropriate intervention
Higgs 2015[73]	Systematic review: not review PICO
Hua 2012[75]	Systematic review: references screened
Hynninen 2001[76]	Inappropriate intervention
Kalfon 2014[79]	Inappropriate population
Kang 2009[80]	Inappropriate comparison
Kang 2018[81]	Systematic review: references screened
Kansagara 2011[82]	Systematic review: references screened
Kirdemir 2008[83]	Inappropriate population
Kittelson 2009[84]	Inappropriate study design
Kjellman 2000[85]	Inappropriate intervention
Korusic 2009[86]	Inappropriate outcome
Koskenkari 2006[88]	Inappropriate comparison
Koskenkari 2005[87]	Inappropriate comparison
Kuusisto 1990[89]	Not in English
Langenberg 2001[90]	Inappropriate outcome
Langlois 2014[91]	Inappropriate study design
Lazar 2000[92]	Inappropriate comparison
Lazar 2004[93]	Inappropriate population

Lazar 1997[94]	Inappropriate comparison
Lell 2002[95]	Inappropriate intervention
Li 2006[96]	Inappropriate population
Lindholm 2001[97]	Inappropriate intervention
Lindholm 2000[98]	Inappropriate intervention
Liu 2011[99]	Not in English
Ljungqvist 1994[100]	Inappropriate intervention
Lolley 1978[102]	Inappropriate intervention
Lolley 1985[101]	Inappropriate intervention
Ma 2012[103]	Not in English
Marfella 2009[104]	Inappropriate intervention
Marfella 2013[105]	Inappropriate outcome
Marfella 2012[106]	Inappropriate intervention
Miriam 2004[107]	Inappropriate outcome
Navaratnarajah 2018[109]	Inappropriate study design
Nicolson 1992[110]	Inappropriate population
Nilsson 1987[111]	Inappropriate intervention
Okabayashi 2009[112]	Inappropriate study design
Okabayashi 2014[115]	Inappropriate study design
Oldfield 1986[116]	Inappropriate intervention
Ouattara 2005[117]	Inappropriate population
Parekh 2016[118]	Inappropriate population
Pearlstone 1994[119]	Inappropriate study design
Polderman 2017[121]	Inappropriate intervention
Polderman 2018[122]	Inappropriate comparison
Preiser 2009[123]	Inappropriate population
Qaseem 2011[124]	Inappropriate study design
Quinn 2006[125]	Inappropriate comparison
Rabi 2010[126]	Systematic review: studies included in review
Raghavan 2013[127]	Systematic review: not review PICO
Ranasinghe 2006[128]	Inappropriate comparison
Rao 1996[131]	Inappropriate comparison
Rao 2000[129]	Inappropriate intervention
Rao 2002[130]	Inappropriate intervention
Rassias 1999[132]	Inappropriate population
Raucoules-Aime 1996[133]	Inappropriate outcome
Raucoules-Aime 1994[134]	Inappropriate comparison
Ray 1977[135]	Inappropriate comparison
Rucka 2014[136]	Inappropriate outcome
Salerno 1980[138]	Inappropriate intervention
Sanjay 2003[139]	Inappropriate study design

Sathya 2013[140]	Systematic review: references screened
Sato 2010[141]	Inappropriate study design
Savaşkan 2006[144]	Not in English
Sawada 2016[145]	Inappropriate outcome
Sebranek 2013[147]	Inappropriate study design
Shah 2014[148]	Inappropriate intervention
Shi 2013[149]	Systematic review: not review PICO
Shim 2006[150]	Inappropriate intervention
Sieber 1986[151]	Inappropriate population
Slas 1984[152]	Inappropriate population
Sokos 2007[154]	Inappropriate intervention
Subramaniam 2009[155]	Inappropriate population
Svensson 1989[156]	Inappropriate outcome
Thomas 1984[158]	Inappropriate population
Tsang 2007[160]	Inappropriate intervention
Umpierrez 2015[161]	Inappropriate population
van den Berghe 2001[163]	Inappropriate population
van Kuijk 2009[164]	Inappropriate study design
Vanhorebeek 2006[165]	Inappropriate study design
Wahby 2016[167]	Inappropriate population
Wallin 2003[168]	Inappropriate outcome

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 11: Studies excluded from the health economic review

Reference	Reason for exclusion
None	