

Perioperative care in adults

**[K] Evidence review for blood glucose control
management**

NICE guideline

Intervention evidence review

November 2019

Draft for Consultation

*This evidence review was developed by
the National Guideline Centre*

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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	<p>Critical outcomes:</p> <ul style="list-style-type: none">• 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 <p>Important outcomes:</p> <ul style="list-style-type: none">• 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 **1.4 Clinical evidence**

2 **1.4.1 Included studies**

3 Thirty randomised controlled trials were included in the review;^{1, 5, 9, 26, 27, 31, 32, 39-43, 52, 55, 59, 60, 74,}
4 ^{77, 78, 113, 114, 120, 137, 142, 143, 146, 153, 157, 159, 162, 166, 169, 170} these are summarised in Table 2 below.

5 Evidence from these studies is summarised in the clinical evidence summary below (Table
6 3).

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

9 **1.4.2 Excluded studies**

10 See the excluded studies list in appendix I.

1 **1.4.3 Summary of clinical studies included in the evidence review**

2 **Table 2: Summary of studies included in the evidence review**

Study	Intervention and comparison	Population	Outcomes	Comments
Abdelmalak 2013 ¹	<p>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</p> <p>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</p>	<p>Patients having major non-cardiac surgery.</p> <p>USA</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Pulmonary ○ Cardiac ○ Neurological • Infection • Hypoglycaemic events 	
Albacker 2007 ⁵	<p>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</p> <p>Standard care: Intraoperative titrated intravenous insulin infusion, titrated according to sliding scale starting at blood glucose level of 10 mmol/L.</p>	<p>Patients undergoing elective cardiopulmonary bypass graft (CABG).</p> <p>USA</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Pulmonary ○ Cardiac • Infection • Length of hospital stay • Length of ICU stay 	14/44 diabetics, type unclear.

Study	Intervention and comparison	Population	Outcomes	Comments
Azarfarin 2011 ⁹	<p>N=22</p> <p>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</p> <p>Standard care: No intervention was done unless the BG level exceeded 200 mg/dL (treated by bolus insulin). N=60</p>	<p>Nondiabetic patients of ASA status II or III who underwent elective cardiopulmonary bypass graft (CABG) surgery.</p> <p>Iran</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Pulmonary ○ Neuropsychological ○ Cardiac • Infections • Hypoglycaemic events 	
Butterworth 2005 ²⁶	<p>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</p>	<p>Nondiabetic patients scheduled to undergo CABG with cardiopulmonary bypass.</p> <p>USA</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Pulmonary ○ Neurological • Hypoglycaemic events • Length of hospital stay • Hospital readmission 	

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>at the direction of the study nurse. N=188</p> <p>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</p>			
Cao 2011 ²⁷	<p>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</p> <p>Standard care: Conventional group in which the postoperative blood glucose was maintained at a level below 11.0 mmol/l. N=123</p>	<p>Patients who were to undergo open elective gastrectomy for gastric cancer anticipated to require parenteral nutrition.</p> <p>China</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Total ○ Pulmonary • Hypoglycaemic events • Infections • Length of hospital stay 	Post-operative BG control
Chan 2009 ³¹	<p>Glucose control: Tight glycaemic control, with target glucose level of 80-130 mg/dl. N=55</p>	<p>Patients scheduled for open-heart surgery requiring cardiopulmonary bypass.</p> <p>Brazil</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ 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
	<p>Standard care: Standard glycaemic control, with target glucose level of 160-200 mg/dl N=54</p>		<ul style="list-style-type: none"> • Infections • Length of hospital stay • Length of ICU stay 	
Chaney 1999 ³²	<p>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</p> <p>Standard care: No glucose control group were not administered insulin to control intraoperative blood glucose levels. N=10</p>	<p>Nondiabetic patients scheduled for CABG surgery.</p> <p>USA</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Cardiac ○ Neuropsychological • Hypoglycaemic events • Length of hospital stay 	
Desai 2012 ³⁹ /Pezzella 2014 ¹²⁰	<p>Glucose control: Strict perioperative glycaemic control with a target glucose range of 90 to 120 mg/dL. N=98</p> <p>Standard care: Glucommander parameters for a target glucose range of 121 to 180 mg/dL. N=91</p>	<p>Patients undergoing coronary artery bypass grafting.</p> <p>USA</p>	<ul style="list-style-type: none"> • Mortality • Quality of life • Complications: <ul style="list-style-type: none"> ○ Cardiac ○ Pulmonary ○ Neurological • Infections • Hypoglycaemic events 	<p>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.</p>

Study	Intervention and comparison	Population	Outcomes	Comments
Duncan 2015 ⁴¹ /Duncan 2018 ⁴²	<p>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</p> <p>Standard care: Intraoperative glycaemic management with standard glycaemic management, low-dose insulin infusion targeting glucose >150 mg/dl⁻¹ N=730</p>	<p>Adults scheduled for elective coronary artery bypass grafting, valve repair or replacement, or a combination of these procedures with cardiopulmonary bypass.</p> <p>USA/Canada</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ 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	<p>Glucose control: Intensified glucose control, added insulin given when BG were between 5.5 and 8.3 mmol/L. N=7</p> <p>Standard care: Infusion of fast-acting insulin to glucose solution according to a standard sliding scale protocol. N=7</p>	<p>Patients with type II diabetes admitted for programmed surgical procedures under general anaesthetic.</p> <p>Spain</p>	<ul style="list-style-type: none"> • Hypoglycaemic event 	
Emam 2010 ⁴³	<p>Glucose control: Strict perioperative glycaemic control following the Braithwaite protocol, with a target glucose range of 100 to 150 mg/dL.</p>	<p>Patients with type II diabetes undergoing open heart procedures.</p> <p>Saudi Arabia</p>	<ul style="list-style-type: none"> • Infection • Hypoglycaemic event • Length of hospital stay • Length of ICU stay 	

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>N=80</p> <p>Standard care: BG control by a sliding scale to maintain BG <200 mg/dL. N=40</p>			
Gandhi 2007 ⁵²	<p>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</p> <p>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</p>	<p>Adults with and without diabetes who were undergoing on-pump cardiac surgery.</p> <p>USA</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ 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	<p>Glucose control: Therapy group with blood glucose target 120–160 mg/dl. N=105</p> <p>Standard care: Post-operative targeted blood glucose levels 161–200 mg/dl N=107</p>	<p>Cardiac surgery patients admitted to ICU post-operatively.</p> <p>Greece</p>	<ul style="list-style-type: none"> • Mortality • Infection • Hypoglycaemic event • Length of hospital stay • Length of ICU stay 	Post-operative BG control.
Grey 2004 ⁵⁹	<p>Glucose control: Intravenous insulin infusions were administered to maintain</p>	<p>Adult patients admitted to a 12-bed surgical ICU requiring treatment of</p>	<ul style="list-style-type: none"> • Mortality • Hypoglycaemic event • Infections 	Post-operative BG control.

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>serum glucose values in the range of 80 to 120 mg/dL. N=34</p> <p>Standard care: Intravenous insulin infusions were administered to maintain serum glucose values in the range of 180 to 220 mg/dL N=27</p>	<p>hyperglycemia (glucose values \geq140 mg/dL).</p> <p>USA</p>	<ul style="list-style-type: none"> Length of ICU stay 	
Groban 2002 ⁶⁰	<p>Glucose control: Intraoperative insulin infusion to maintain BG between 80-120 mg/dL, started if BG was >100mg/dL after induction. N=188</p> <p>Standard care: Received saline solution as placebo. BG levels were allowed to fluctuate without intervention. N=193</p>	<p>Nondiabetic patients scheduled for elective CABG surgery.</p> <p>USA</p>	<ul style="list-style-type: none"> Mortality Hypoglycaemic events Length of hospital stay 	
Hoedemaekers 2005 ⁷⁴	<p>Glucose control: Intensive postoperative insulin therapy to maintain blood glucose between 80 and 110 mg/dl N=10</p> <p>Standard care: Conventional postoperative insulin therapy to maintain</p>	<p>Non-diabetic patients undergoing elective coronary artery bypass grafting.</p> <p>The Netherlands</p>	<ul style="list-style-type: none"> 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	<p>Glucose control: Strict blood glucose control below 6.1 mmol/L (110 mg/dL) with intensive insulin therapy. N=477</p> <p>Standard care: Conventional postoperative insulin therapy to receive insulin therapy when blood glucose levels exceeded 12 mmol/L (220 mg/dL) N=493</p>	Cardiac surgery patients. Belgium	<ul style="list-style-type: none"> • Mortality • Quality of life • Hypoglycaemic events • Length of ICU stay 	Post-operative BG control
Ji 2014 ⁷⁸	<p>Glucose control: Tight glucose control. Continuous infusion of insulin during surgery to maintain BG of 80-110 mg/dL. N=37</p> <p>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</p>	Nondiabetic patients with aortic valve disease referred for isolated valve replacement. China	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Cardiac • Infections • Hypoglycaemic events • Length of hospital stay • Length of ICU stay 	

Study	Intervention and comparison	Population	Outcomes	Comments
Okabayashi 2009a ¹¹³	<p>Glucose control: Received programmed infusions of insulin determined by the control algorithm of the closed-loop system. N=44</p> <p>Standard care: Glucose levels were controlled using a manual injection of insulin according to the commonly used sliding scale. N=44</p>	<p>Patients undergoing hepatectomy.</p> <p>Japan</p>	<ul style="list-style-type: none"> • Mortality • Infections • Hypoglycaemic events • Length of hospital stay 	<p>Closed loop vs sliding scale</p>
Okabayashi 2009b ¹¹⁴	<p>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</p> <p>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</p>	<p>Patients having elective pancreatic resection for pancreatic disease.</p> <p>Japan</p>	<ul style="list-style-type: none"> • Mortality • Hypoglycaemic events 	

Study	Intervention and comparison	Population	Outcomes	Comments
	mg/dL. N=13			
Rujirojindakul 2014 ¹³⁷	<p>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</p> <p>Standard care: In the control group, insulin was administered bolus intravenously if blood glucose level was more than 13.8 mmol N=100</p>	<p>Patients scheduled for cardiac surgery with the cardiopulmonary bypass.</p> <p>Thailand</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Cardiac ○ Neuropsychological • Infections • Hypoglycaemic events • Length of hospital stay • Length of ICU stay 	
Sato 2011 ¹⁴²	<p>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</p>	<p>Patients undergoing elective CABG surgery.</p> <p>Canada</p>	<ul style="list-style-type: none"> • Hypoglycaemic events 	

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>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</p>			
Sato 2010 ¹⁴³	<p>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</p> <p>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</p>	<p>Patients scheduled for elective resection of primary or secondary hepatic malignancy.</p> <p>Japan</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Neurological • Hypoglycaemic events 	
Schricker 2014 ¹⁴⁶	<p>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</p>	<p>Patients scheduled for elective cardiac surgery.</p> <p>Canada</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Pulmonary • Infection • Length of ICU stay 	30% Diabetes mellitus (type not reported)

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>maintain the blood glucose within the target level of 3.5–6.1 mmol L⁻¹ N=16</p> <p>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</p>			
Smith 2002 ¹⁵³	<p>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</p> <p>Standard care: Received an equal volume of 5% dextrose in water as placebo. N=22</p>	<p>Patients scheduled for elective multivessel coronary artery surgery using either conventional CPB or OP-CAB techniques.</p> <p>UK</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Cadiac • Infection • Length of hospital stay 	<p>Off-pump and on-pump groups combined.</p> <p>Unclear if standard care group BP was controlled.</p>
Szabo 2001 ¹⁵⁷	<p>Glucose control: High dose post-operative GIK treatment. Insulin was infused</p>	<p>Patients with type II diabetes undergoing elective coronary surgery.</p>	<ul style="list-style-type: none"> • Mortality 	<p>Post-operative BG control</p>

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>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</p> <p>Standard care: Standard post-operative glucose control. Insulin infusion was given if BG exceeded 10mmol/L. N=10</p>			
Tohya 2018 ¹⁵⁹	<p>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</p> <p>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</p>	<p>Thirty patients aged ≥ 60 years undergoing a radical operation of oral malignant tumours with tissue reconstruction (≥ 8 h).</p> <p>Japan</p>	<ul style="list-style-type: none"> • Complications: <ul style="list-style-type: none"> ○ Pulmonary • Infection • Length of hospital stay 	

Study	Intervention and comparison	Population	Outcomes	Comments
Visser 2005 ¹⁶⁶	<p>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</p> <p>Standard care: Standard institutional perioperative care. N=11</p>	<p>Patients with normal left ventricular function scheduled for elective CABG.</p> <p>The Netherland</p>	<ul style="list-style-type: none"> • Hypoglycaemic events • Length of stay in ICU • Length of hospital stay 	<p>Unclear if control group received BG control</p>
Yuan 2015 ¹⁶⁹	<p>Glucose control: Intensive glycaemic management with continuous insulin infusion (target glucose 4.4–6.1 mmol/l (80–110 mg/dl)) N=106</p> <p>Standard care: Conventional glycaemic management with intermittent bolus insulin (target glucose <11.1 mmol/l (<200 mg/dl)) N=106</p>	<p>Patients with type II diabetes who underwent gastrectomy.</p> <p>China</p>	<ul style="list-style-type: none"> • Mortality • Complications: <ul style="list-style-type: none"> ○ Pulmonary • Infections • Hypoglycaemic events 	<p>Post-operative BG control</p>
Zheng 2010 ¹⁷⁰	<p>Glucose control: Insulin continuously infused adjusted to maintain BG levels between 70-110 mmol/dL during and after surgery. N=50</p>	<p>Nondiabetic patients undergoing valve replacement with cardiopulmonary bypass.</p> <p>China</p>	<ul style="list-style-type: none"> • 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	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)
		imprecision			
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	RD 0.02 (0 to	Moderate 5 per 1000	5 fewer per 1000

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)
		due to inconsistency	0.03)		(from 5 fewer to 5 fewer)
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)
<p>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 4 Downgraded by 1 increment if the the optimal information size to provide desired power is 80-90% or by 2 increments if <80%</p>					

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) NHP II: 0 (0-3)	Median Nottingham health profile (IQR): NHP I:15 (0-48) NHP II: 0 (0-2)	0.4
	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 ¹¹³ (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

1 **1.5 Economic evidence**

2 **1.5.1 Included studies**

3 No health economic studies were included.

4 **1.5.2 Excluded studies**

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

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

8 **1.6 Evidence statements**

9 **1.6.1 Clinical evidence statements**

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

11 **Glucose control versus standard care**

12 **Mortality**

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

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

17 **Adverse events**

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

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

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

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

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

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

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

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

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

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

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

14 **Infection**

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

17 **Hypoglycaemic events**

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

20 **Length of hospital stay**

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

23 **Length of ICU stay**

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

26 **Readmissions**

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

29 **Evidence not suitable for GRADE analysis**

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

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

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

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

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

5 **1.6.2 Health economic evidence statements**

- 6 • No relevant economic evaluations were identified.

7 **1.7 The committee's discussion of the evidence**

8 Please see recommendations 1.4.6 – 1.4.7 in the guideline.

9 **1.7.1 Interpreting the evidence**

10 **1.7.1.1 The outcomes that matter most**

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

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

20

21 **1.7.1.2 The quality of the evidence**

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

27 **1.7.1.3 Benefits and harms**

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

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

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

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

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

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

15

16 **1.7.2 Cost effectiveness and resource use**

17 No economic evaluations were identified for this question.

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

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

29 **1.7.3 Other factors the committee took into account**

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

32

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

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

43

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

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

References

1. Abdelmalak BB, Bonilla A, Mascha EJ, Maheshwari A, Tang WH, You J et al. Dexamethasone, light anaesthesia, and tight glucose control (DeLiT) randomized controlled trial. *British Journal of Anaesthesia*. 2013; 111(2):209-21
2. Abdelmalak BB, Duncan AE, Bonilla A, Yang D, Parra-Sanchez I, Fergany A et al. The intraoperative glycemic response to intravenous insulin during noncardiac surgery: a subanalysis of the DeLiT randomized trial. *Journal of Clinical Anesthesia*. 2016; 29:19-29
3. Albacker T, Carvalho G, Schricker T, Lachapelle K. High-dose insulin therapy attenuates systemic inflammatory response in coronary artery bypass grafting patients. *Annals of Thoracic Surgery*. 2008; 86(1):20-7
4. Albacker T, Lachapelle K. Insulin therapy for improving cardiac surgical outcomes. *Current Drug Targets*. 2009; 10(6):499-504
5. Albacker TB, Carvalho G, Schricker T, Lachapelle K. Myocardial protection during elective coronary artery bypass grafting using high-dose insulin therapy. *Annals of Thoracic Surgery*. 2007; 84(6):1920-7; discussion 1920-7
6. Anonymous. Intensive versus conventional glucose control in critically ill patients. The NICE-SUGAR Study Investigators. *New England Journal of Medicine*. 2009; 360(13):1283-1297
7. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Critical Care Medicine*. 2008; 36(12):3190-7
8. Azagury DE, Ris F, Pichard C, Volonte F, Karsegard L, Huber O. Does perioperative nutrition and oral carbohydrate load sustainably preserve muscle mass after bariatric surgery? A randomized control trial. *Surgery for Obesity and Related Diseases*. 2015; 11(4):920-6
9. Azarfarin R, Sheikhzadeh D, Mirinazhad M, Bilehjani E, Alizadehasl A. Do nondiabetic patients undergoing coronary artery bypass grafting surgery require intraoperative management of hyperglycemia? *Acta Anaesthesiologica Taiwanica*. 2011; 49(2):41-5
10. Barcellos Cda S, Wender OC, Azambuja PC. Clinical and hemodynamic outcome following coronary artery bypass surgery in diabetic patients using glucose-insulin-potassium (GIK) solution: a randomized clinical trial. *Revista Brasileira de Cirurgia Cardiovascular*. 2007; 22(3):275-84
11. Behrendt W, Raumanns J, Hanse J, Giani G. Glucose, fructose, and xylitol in postoperative hypocaloric parenteral nutrition. *Infusionstherapie*. 1988; 15(4):170-5
12. Berkers J, Gunst J, Vanhorebeek I, Van den Berghe G. Glycaemic control and perioperative organ protection. *Best Practice & Research Clinical Anaesthesiology*. 2008; 22(1):135-49
13. Bertrand OF, Poirier P, Rodés-Cabau J, Rinfret S, Title L, Dzavik V et al. A multicentre, randomized, double-blind placebo-controlled trial evaluating rosiglitazone for the prevention of atherosclerosis progression after coronary artery bypass graft surgery in patients with type 2 diabetes. Design and rationale of the Veln-Coronary

- 1 aTherOsclerosis and Rosiglitazone after bypass surgery (VICTORY) trial. Canadian
2 Journal of Cardiology. 2009; 25(9):509-515
- 3 14. Besch G, Perrotti A, Mauny F, Puyraveau M, Baltres M, Flicoteaux G et al. Clinical
4 effectiveness of intravenous exenatide infusion in perioperative glycemic control after
5 coronary artery bypass graft surgery: A phase II/III randomized trial. Anesthesiology.
6 2017; 127(5):775-787
- 7 15. Besogul Y, Tunerir B, Aslan R, Isiksoy S, Colak O, Kural T. Clinical, biochemical and
8 histochemical assessment of pretreatment with glucose-insulin-potassium for patients
9 undergoing mitral valve replacement in the third and fourth functional groups of the
10 New York Heart Association. Cardiovascular Surgery. 1999; 7(6):645-50
- 11 16. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL et al.
12 Superiority of moderate control of hyperglycemia to tight control in patients
13 undergoing coronary artery bypass grafting. Journal of Thoracic and Cardiovascular
14 Surgery. 2011; 141(2):543-51
- 15 17. Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive
16 insulin therapy in critical neurosurgical patients. Anesthesiology. 2009; 110(3):611-9
- 17 18. Blaha J, Mraz M, Kopecky P, Stritesky M, Lips M, Matias M et al. Perioperative tight
18 glucose control reduces postoperative adverse events in nondiabetic cardiac surgery
19 patients. Journal of Clinical Endocrinology and Metabolism. 2015; 100(8):3081-3089
- 20 19. Blixt C, Ahlstedt C, Ljungqvist O, Isaksson B, Kalman S, Rooyackers O. The effect of
21 perioperative glucose control on postoperative insulin resistance. Clinical Nutrition.
22 2012; 31(5):676-81
- 23 20. Bode BW, Braithwaite SS, Steed RD, Davidson PC. Intravenous insulin infusion
24 therapy: indications, methods, and transition to subcutaneous insulin therapy.
25 Endocrine Practice. 2004; 10(Suppl 2):71-80
- 26 21. Boldt J, Knothe C, Zickmann B, Dunnes S, Dapper F, Hempelmann G. Influence of
27 different glucose-insulin-potassium regimes on glucose homeostasis and hormonal
28 response in cardiac surgery patients. Anesthesia and Analgesia. 1993; 76(2):233-8
- 29 22. Bothe W, Olschewski M, Beyersdorf F, Doenst T. Glucose-insulin-potassium in
30 cardiac surgery: a meta-analysis. Annals of Thoracic Surgery. 2004; 78(5):1650-7
- 31 23. Brodin LA, Dahlgren G, Ekestrom S, Settergren G, Ohqvist G. Influence of glucose-
32 insulin-potassium on left ventricular function during coronary artery bypass grafting.
33 Scandinavian Journal of Thoracic and Cardiovascular Surgery. 1993; 27(1):27-34
- 34 24. Bruemmer-Smith S, Avidan MS, Harris B, Sudan S, Sherwood R, Desai JB et al.
35 Glucose, insulin and potassium for heart protection during cardiac surgery. British
36 Journal of Anaesthesia. 2002; 88(4):489-95
- 37 25. Buchleitner AM, Martínez-Alonso M, Hernández M, Solà I, Mauricio D. Perioperative
38 glycaemic control for diabetic patients undergoing surgery. Cochrane Database of
39 Systematic Reviews 2012, Issue 9. Art. No.: CD007315. DOI:
40 10.1002/14651858.CD007315.pub2.
- 41 26. Butterworth J, Wagenknecht LE, Legault C, Zaccaro DJ, Kon ND, Hammon JW, Jr. et
42 al. Attempted control of hyperglycemia during cardiopulmonary bypass fails to
43 improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus
44 undergoing coronary artery bypass grafting. Journal of Thoracic and Cardiovascular
45 Surgery. 2005; 130(5):1319

- 1 27. Cao S, Zhou Y, Chen D, Niu Z, Wang D, Lv L et al. Intensive versus conventional
2 insulin therapy in nondiabetic patients receiving parenteral nutrition after D2
3 gastrectomy for gastric cancer: a randomized controlled trial. *Journal of*
4 *Gastrointestinal Surgery*. 2011; 15(11):1961-1968
- 5 28. Cao SG, Zhou YB, Zhang CK, Chen D, Yu YY, Lu LF. Effect of intensive insulin
6 therapy on the clinical results of postoperative patients with gastric cancer. *Chinese*
7 *Journal of Surgery*. 2008; 46(12):918-920
- 8 29. Cardona S, Pasquel FJ, Fayfman M, Peng L, Jacobs S, Vellanki P et al.
9 Hospitalization costs and clinical outcomes in CABG patients treated with intensive
10 insulin therapy. *Journal of Diabetes and Its Complications*. 2017; 31(4):742-747
- 11 30. Celkan MA, Kazaz H, Daglar B, Celik A, Koruk S, Kocoglu H. Effects of glucose-
12 insulin-potassium solution on cardiac cytokines and enzymes. *Thoracic and*
13 *Cardiovascular Surgeon*. 2006; 54(8):532-6
- 14 31. Chan RP, Galas FR, Hajjar LA, Bello CN, Piccioni MA, Auler JO, Jr. Intensive
15 perioperative glucose control does not improve outcomes of patients submitted to
16 open-heart surgery: a randomized controlled trial. *Clinics*. 2009; 64(1):51-60
- 17 32. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain
18 normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative
19 hypoglycemia. *Anesthesia and Analgesia*. 1999; 89(5):1091-5
- 20 33. Chin KJ, Macachor J, Ong KC, Ong BC. A comparison of 5% dextrose in 0.9%
21 normal saline versus non-dextrose-containing crystalloids as the initial intravenous
22 replacement fluid in elective surgery. *Anaesthesia and Intensive Care*. 2006;
23 34(5):613-7
- 24 34. Chuah LL, Miras AD, Papamargaritis D, Jackson SN, Olbers T, le Roux CW. Impact
25 of perioperative management of glycemia in severely obese diabetic patients
26 undergoing gastric bypass surgery. *Surgery for Obesity and Related Diseases*. 2015;
27 11(3):578-84
- 28 35. Codere-Maruyama T, Schricker T, Shum-Tim D, Wykes L, Nitschmann E, Guichon C
29 et al. Hyperinsulinemic-normoglycemic clamp administered together with amino acids
30 induces anabolism after cardiac surgery. *American Journal of Physiology -*
31 *Regulatory Integrative & Comparative Physiology*. 2016; 311(6):R1085-R1092
- 32 36. Coleman GM, Gradinac S, Taegtmeier H, Sweeney M, Frazier OH. Efficacy of
33 metabolic support with glucose-insulin-potassium for left ventricular pump failure after
34 aortocoronary bypass surgery. *Circulation*. 1989; 80(3 Pt 1):191-6
- 35 37. D'Alessandro C, Leprince P, Golmard JL, Ouattara A, Aubert S, Pavie A et al. Strict
36 glycemic control reduces EuroSCORE expected mortality in diabetic patients
37 undergoing myocardial revascularization. *Journal of Thoracic and Cardiovascular*
38 *Surgery*. 2007; 134(1):29-37
- 39 38. De La Rosa GDC, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga
40 NE et al. Strict glycaemic control in patients hospitalised in a mixed medical and
41 surgical intensive care unit: a randomised clinical trial. *Critical Care*. 2008; 12:R120-
42 R120
- 43 39. Desai SP, Henry LL, Holmes SD, Hunt SL, Martin CT, Hebsur S et al. Strict versus
44 liberal target range for perioperative glucose in patients undergoing coronary artery
45 bypass grafting: a prospective randomized controlled trial. *Journal of Thoracic and*
46 *Cardiovascular Surgery*. 2012; 143(2):318-25

- 1 40. Diez JJ. Perioperative management of type 2 diabetes mellitus by two techniques of
2 insulin infusion. A randomized clinical study. *Endocrinologia*. 1991; 38:108-112
- 3 41. Duncan AE, Kateby Kashy B, Sarwar S, Singh A, Stenina-Adognravi O,
4 Christoffersen S et al. Hyperinsulinemic normoglycemia does not meaningfully
5 improve myocardial performance during cardiac surgery: A randomized trial.
6 *Anesthesiology*. 2015; 123(2):272-87
- 7 42. Duncan AE, Sessler DI, Sato H, Sato T, Nakazawa K, Carvalho G et al.
8 Hyperinsulinemic normoglycemia during cardiac surgery reduces a composite of 30-
9 day mortality and serious in-hospital complications: A randomized clinical trial.
10 *Anesthesiology*. 2018; 128(6):1125-1139
- 11 43. Emam IA, Allan A, Eskander K, Dhanraj K, Farag el S, El-Kadi Y et al. Our
12 experience of controlling diabetes in the peri-operative period of patients who
13 underwent cardiac surgery. *Diabetes Research and Clinical Practice*. 2010;
14 88(3):242-6
- 15 44. Everett E, Mathioudakis N. Inpatient glycemic management of non-cardiac CVD:
16 Focus on stroke and PVD. *Current Diabetes Reports*. 2018; 18:49
- 17 45. Fan Y, Zhang AM, Xiao YB, Weng YG, Hetzer R. Glucose-insulin-potassium therapy
18 in adult patients undergoing cardiac surgery: a meta-analysis. *European Journal of*
19 *Cardio-Thoracic Surgery*. 2011; 40(1):192-9
- 20 46. Fisette A, Hassanain M, Metrakos P, Doi SA, Salman A, Schricker T et al. High-dose
21 insulin therapy reduces postoperative liver dysfunction and complications in liver
22 resection patients through reduced apoptosis and altered inflammation. *Journal of*
23 *Clinical Endocrinology and Metabolism*. 2012; 97(1):217-226
- 24 47. Freitas PS, Romanzini AE, Ribeiro JC, Bellusse GC, Galvão CM. Blood glucose
25 control in the perioperative period: evidence for preventing surgical site infections.
26 *Revista Eletronica de Enfermagem*. 2013; 15(2):541-550
- 27 48. Fujino H, Itoda S, Esaki K, Tsukamoto M, Sako S, Matsuo K et al. Intra-operative
28 administration of low-dose IV glucose attenuates post-operative insulin resistance.
29 *Asia Pacific Journal of Clinical Nutrition*. 2014; 23(3):400-7
- 30 49. Fujita Y, Tokunaga C, Yamaguchi S, Nakamura K, Horiguchi Y, Kaneko M et al.
31 Effect of intraoperative amino acids with or without glucose infusion on body
32 temperature, insulin, and blood glucose levels in patients undergoing laparoscopic
33 colectomy: a preliminary report. *Acta Anaesthesiologica Taiwanica*. 2014; 52(3):101-6
- 34 50. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous
35 insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic
36 Project. *Endocrine Practice*. 2004; 10(Suppl 2):21-33
- 37 51. Gandhi GY, Murad MH, Flynn DN, Erwin PJ, Cavalcante AB, Bay Nielsen H et al.
38 Effect of perioperative insulin infusion on surgical morbidity and mortality: systematic
39 review and meta-analysis of randomized trials. *Mayo Clinic Proceedings*. 2008;
40 83(4):418-30
- 41 52. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC et al. Intensive
42 intraoperative insulin therapy versus conventional glucose management during
43 cardiac surgery: a randomized trial. *Annals of Internal Medicine*. 2007; 146(4):233-43
- 44 53. Gandhi H, Sarvaia A, Malhotra A, Acharya H, Shah K, Rajavat J. Effects of glargine
45 insulin on glycemic control in patients with diabetes mellitus type II undergoing off-
46 pump coronary artery bypass graft. *Annals of Cardiac Anaesthesia*. 2018; 21(2):167-
47 172

- 1 54. Ghods K, Davari H, Ebrahimian A. Evaluation of the effect of metformin and insulin in
2 hyperglycemia treatment after coronary artery bypass surgery in nondiabetic patients.
3 *Annals of Cardiac Anaesthesia*. 2017; 20(4):427-431
- 4 55. Giakoumidakis K, Eltheni R, Patelarou E, Theologou S, Patris V, Michopanou N et al.
5 Effects of intensive glycemetic control on outcomes of cardiac surgery. *Heart and Lung*.
6 2013; 42(2):146-51
- 7 56. Giannini F, Latib A, Jabbour RJ, Ruparella N, Aurelio A, Ancona MB et al. Impact of
8 post-procedural hyperglycemia on acute kidney injury after transcatheter aortic valve
9 implantation. *International Journal of Cardiology*. 2016; 221:892-7
- 10 57. Girard C, Quentin P, Bouvier H, Blanc P, Bastien O, Lehot JJ et al. Glucose and
11 insulin supply before cardiopulmonary bypass in cardiac surgery: a double-blind
12 study. *Annals of Thoracic Surgery*. 1992; 54(2):259-63
- 13 58. Gonzalez-Michaca L, Ahumada M, Ponce-de-Leon S. Insulin subcutaneous
14 application vs. continuous infusion for postoperative blood glucose control in patients
15 with non-insulin-dependent diabetes mellitus. *Archives of Medical Research*. 2002;
16 33(1):48-52
- 17 59. Grey NJ, Perdrizet GA. Reduction of nosocomial infections in the surgical intensive-
18 care unit by strict glycemetic control. *Endocrine Practice*. 2004; 10(Suppl 2):46-52
- 19 60. Groban L, Butterworth J, Legault C, Rogers AT, Kon ND, Hammon JW. Intraoperative
20 insulin therapy does not reduce the need for inotropic or antiarrhythmic therapy after
21 cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia*. 2002;
22 16(4):405-12
- 23 61. Gustafson PA, Zarro DL, Palanzo DA, Manley NJ, Montesano RM, Quinn M et al.
24 Conventional approach to glucose management for diabetic patients undergoing
25 coronary artery bypass surgery. *Perfusion*. 2002; 17(2):141-4
- 26 62. Haga KK, McClymont KL, Clarke S, Grounds RS, Ng KY, Glyde DW et al. The effect
27 of tight glycaemic control, during and after cardiac surgery, on patient mortality and
28 morbidity: A systematic review and meta-analysis. *Journal of Cardiothoracic Surgery*.
29 2011; 6:3
- 30 63. Haider W, Benzer H, Schutz W, Wolner E. Improvement of cardiac preservation by
31 preoperative high insulin supply. *Journal of Thoracic and Cardiovascular Surgery*.
32 1984; 88(2):294-300
- 33 64. Hallhagen S, Svedjeholm R, Ekroth R, Nilsson F, Svensson S, Vinnars E et al.
34 Effects of insulin on myocardial uptake of branched chain amino acids soon after
35 cardiac operations. *Journal of Thoracic and Cardiovascular Surgery*. 1992; 103(1):98-
36 107
- 37 65. Hasegawa A, Iwasaka H, Hagiwara S, Koga H, Hasegawa R, Kudo K et al. Anti-
38 inflammatory effects of perioperative intensive insulin therapy during cardiac surgery
39 with cardiopulmonary bypass. *Surgery Today*. 2011; 41(10):1385-90
- 40 66. Hassanain M, Metrakos P, Fisette A, Doi SA, Schricker T, Lattermann R et al.
41 Randomized clinical trial of the impact of insulin therapy on liver function in patients
42 undergoing major liver resection. *British Journal of Surgery*. 2013; 100(5):610-8
- 43 67. Hatzakorzian R, Carvalho G, Bui H, Sato T, Wykes L, Shum-Tim D et al. High-dose
44 insulin administration is associated with hypoaminoacidemia during cardiac surgery.
45 *Metabolism: Clinical and Experimental*. 2011; 60(10):1392-7

- 1 68. Hatzakorzian R, Shum-Tim D, Wykes L, Hulshoff A, Bui H, Nitschmann E et al.
2 Glucose and insulin administration while maintaining normoglycemia inhibits whole
3 body protein breakdown and synthesis after cardiac surgery. *Journal of Applied*
4 *Physiology*. 2014; 117(11):1380-7
- 5 69. Hawkins K, Donihi AC, Korytkowski MT. Glycemic management in medical and
6 surgical patients in the Non-ICU setting. *Current Diabetes Reports*. 2013; 13(1):96-
7 106
- 8 70. Hayakawa J, Motohashi H, Sairenji M, Kobayashi O, Takahashi M, Usuda Y. The
9 effects of intraoperative glucose infusion on portal blood insulin concentration and
10 hepatic mitochondrial redox state during surgery: comparison of short-term and
11 continuous infusions. *Surgery Today*. 2000; 30(3):228-34
- 12 71. He W, Zhang TY, Zhou H, Li T, Zhao JY, Zhao D et al. Impact of intensive insulin
13 therapy on surgical critically ill patients. *Chinese Journal of Surgery*. 2007;
14 45(15):1052-1054
- 15 72. Hecking M, Haidinger M, Doller D, Werzowa J, Tura A, Zhang J et al. Early basal
16 insulin therapy decreases new-onset diabetes after renal transplantation. *Journal of*
17 *the American Society of Nephrology*. 2012; 23(4):739-749
- 18 73. Higgs M, Fernandez R. The effect of insulin therapy algorithms on blood glucose
19 levels in patients following cardiac surgery: a systematic review. *JBIC Database Of*
20 *Systematic Reviews And Implementation Reports*. 2015; 13(5):205-43
- 21 74. Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M, Van der Hoeven JG.
22 Intensive insulin therapy does not alter the inflammatory response in patients
23 undergoing coronary artery bypass grafting: a randomized controlled trial
24 [ISRCTN95608630]. *Critical Care*. 2005; 9:R790-7
- 25 75. Hua J, Chen G, Li H, Fu S, Zhang LM, Scott M et al. Intensive intraoperative insulin
26 therapy versus conventional insulin therapy during cardiac surgery: a meta-analysis.
27 *Journal of Cardiothoracic and Vascular Anesthesia*. 2012; 26(5):829-34
- 28 76. Hynninen M, Borger MA, Rao V, Weisel RD, Christakis GT, Carroll JA et al. The
29 effect of insulin cardioplegia on atrial fibrillation after high-risk coronary bypass
30 surgery: a double-blinded, randomized, controlled trial. *Anesthesia and Analgesia*.
31 2001; 92(4):810-6
- 32 77. Ingels C, Debaveye Y, Milants I, Buelens E, Peeraer A, Devriendt Y et al. Strict blood
33 glucose control with insulin during intensive care after cardiac surgery: impact on 4-
34 years survival, dependency on medical care, and quality-of-life. *European Heart*
35 *Journal*. 2006; 27(22):2716-24
- 36 78. Ji Q, Ding W, Mei Y, Wang X, Feng J, Cai J. Protective effects of tight glucose control
37 during cardiopulmonary bypass on myocardium in adult nondiabetic patients
38 undergoing valve replacement. *Canadian Journal of Cardiology*. 2014; 30(11):1429-
39 35
- 40 79. Kalfon P, Giraudeau B, Ichai C, Guerrini A, Brechot N, Cinotti R et al. Tight
41 computerized versus conventional glucose control in the ICU: a randomized
42 controlled trial. *Intensive Care Medicine*. 2014; 40(2):171-81
- 43 80. Kang H, Ahn KJ, Choi JY, Park HJ, Park SJ, Lee SK. Efficacy of insulin glargine in
44 perioperative glucose control in type 2 diabetic patients. *European Journal of*
45 *Anaesthesiology*. 2009; 26(8):666-70

- 1 81. Kang ZQ, Huo JL, Zhai XJ. Effects of perioperative tight glycaemic control on
2 postoperative outcomes: a meta-analysis. *Endocrine Connections*. 2018; 7(12):R316-
3 R327
- 4 82. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in
5 hospitalized patients: a systematic review. *Annals of Internal Medicine*. 2011;
6 154(4):268-82
- 7 83. Kirdemir P, Yildirim V, Kiris I, Gulmen S, Kuralay E, Ibrism E et al. Does continuous
8 insulin therapy reduce postoperative supraventricular tachycardia incidence after
9 coronary artery bypass operations in diabetic patients? *Journal of Cardiothoracic and*
10 *Vascular Anesthesia*. 2008; 22(3):383-7
- 11 84. Kittelson K. Glycaemic control: a literature review with implications for perioperative
12 nursing practice. *AORN Journal*. 2009; 90(5):714-26; quiz 727-30
- 13 85. Kjellman UW, Bjork K, Dahlin A, Ekroth R, Kirno K, Svensson G et al. Insulin(GIK)
14 improves myocardial metabolism in patients during blood cardioplegia. *Scandinavian*
15 *Cardiovascular Journal*. 2000; 34(3):321-30
- 16 86. Korusic A, Hauptman A, Brundula A, Duzel V, Husedzinovic I, Horic M et al.
17 Perioperative management with glucose solution and insulin. *Collegium*
18 *Antropologicum*. 2009; 33(2):653-7
- 19 87. Koskenkari JK, Kaukoranta PK, Kiviluoma KT, Raatikainen MJ, Ohtonen PP, Ala-
20 Kokko TI. Metabolic and hemodynamic effects of high-dose insulin treatment in aortic
21 valve and coronary surgery. *Annals of Thoracic Surgery*. 2005; 80(2):511-7
- 22 88. Koskenkari JK, Kaukoranta PK, Rimpilainen J, Vainionpaa V, Ohtonen PP, Surcel
23 HM et al. Anti-inflammatory effect of high-dose insulin treatment after urgent coronary
24 revascularization surgery. *Acta Anaesthesiologica Scandinavica*. 2006; 50(8):962-9
- 25 89. Kuusisto A. Insulin treatment for diabetes on the day of surgery. *Duodecim*. 1990;
26 106(5):415-421
- 27 90. Langenberg CJ, Pietersen HG, Geskes G, Wagenmakers AJ, Lange SD, Schouten
28 HJ et al. The effect of glutamate infusion on cardiac performance is independent of
29 changes in metabolism in patients undergoing routine coronary artery bypass
30 surgery. *Clinical Science*. 2001; 101(6):573-80
- 31 91. Langlois J, Bouyer B, Larroque B, Dauzac C, Guigui P. Glycaemic instability of non-
32 diabetic patients after spine surgery: a prospective cohort study. *European Spine*
33 *Journal*. 2014; 23(11):2455-2461
- 34 92. Lazar HL, Chipkin S, Philippides G, Bao Y, Apstein C. Glucose-insulin-potassium
35 solutions improve outcomes in diabetics who have coronary artery operations. *Annals*
36 *of Thoracic Surgery*. 2000; 70(1):145-50
- 37 93. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycaemic
38 control in diabetic coronary artery bypass graft patients improves perioperative
39 outcomes and decreases recurrent ischemic events. *Circulation*. 2004; 109(12):1497-
40 1502
- 41 94. Lazar HL, Philippides G, Fitzgerald C, Lancaster D, Shemin RJ, Apstein C. Glucose-
42 insulin-potassium solutions enhance recovery after urgent coronary artery bypass
43 grafting. *Journal of Thoracic and Cardiovascular Surgery*. 1997; 113(2):354-60;
44 discussion 360-2
- 45 95. Lell WA, Nielsen VG, McGiffin DC, Schmidt FE, Jr., Kirklin JK, Stanley AW, Jr.
46 Glucose-insulin-potassium infusion for myocardial protection during off-pump

- 1 coronary artery surgery. *Annals of Thoracic Surgery*. 2002; 73(4):1246-51; discussion
2 1251-2
- 3 96. Li JY, Sun S, Wu SJ. Continuous insulin infusion improves postoperative glucose
4 control in patients with diabetes mellitus undergoing coronary artery bypass surgery.
5 *Texas Heart Institute Journal*. 2006; 33(4):445-51
- 6 97. Lindholm L, Bengtsson A, Hansdottir V, Westerlind A, Jeppsson A. Insulin (GIK)
7 improves central mixed and hepatic venous oxygenation in clinical cardiac surgery.
8 *Scandinavian Cardiovascular Journal*. 2001; 35(5):347-52
- 9 98. Lindholm L, Nilsson B, Kirno K, Sellgren J, Nilsson F, Jeppsson A. Is skeletal muscle
10 luxury perfusion the main hemodynamic effect of high-dose insulin in cardiac
11 surgery? *Scandinavian Cardiovascular Journal*. 2000; 34(4):396-402
- 12 99. Liu HC, Zhou YB, Chen D, Niu ZJ, Yu Y. Effect of intensive insulin therapy on resting
13 energy expenditure in postoperative patients underwent radical distal gastrectomy.
14 *Chinese Journal of Surgery*. 2011; 49(9):789-794
- 15 100. Ljungqvist O, Thorell A, Gutniak M, Haggmark T, Efendic S. Glucose infusion instead
16 of preoperative fasting reduces postoperative insulin resistance. *Journal of the
17 American College of Surgeons*. 1994; 178(4):329-336
- 18 101. Lolley DM, Myers WO, Ray JF, 3rd, Sautter RD, Tewksbury DA. Clinical experience
19 with preoperative myocardial nutrition management. *Journal of Cardiovascular
20 Surgery*. 1985; 26(3):236-43
- 21 102. Lolley DM, Ray JF, 3rd., Myers WO, Sheldon G, Sautter RD. Reduction of
22 intraoperative myocardial infarction by means of exogenous anaerobic substrate
23 enhancement: prospective randomized study. *Annals of Thoracic Surgery*. 1978;
24 26(6):515-24
- 25 103. Ma L, Wu K, An YY, Song T, Yu XY. [Effect of intensive glucose control during peri-
26 operative period on prognosis of patients undergoing cardiac surgery: a meta-
27 analysis]. *Chinese Critical Care Medicine*. 2012; 24(4):201-6
- 28 104. Marfella R, Di Filippo C, Portoghese M, Ferraraccio F, Rizzo MR, Siniscalchi M et al.
29 Tight glycemic control reduces heart inflammation and remodeling during acute
30 myocardial infarction in hyperglycemic patients. *Journal of the American College of
31 Cardiology*. 2009; 53(16):1425-1436
- 32 105. Marfella R, Rizzo MR, Siniscalchi M, Paolisso P, Barbieri M, Sardu C et al. Peri-
33 procedural tight glycemic control during early percutaneous coronary intervention up-
34 regulates endothelial progenitor cell level and differentiation during acute ST-
35 elevation myocardial infarction: effects on myocardial salvage. *International Journal of
36 Cardiology*. 2013; 168(4):3954-62
- 37 106. Marfella R, Sasso FC, Cacciapuoti F, Portoghese M, Rizzo MR, Siniscalchi M et al.
38 Tight glycemic control may increase regenerative potential of myocardium during
39 acute infarction. *Journal of Clinical Endocrinology and Metabolism*. 2012; 97(3):933-
40 942
- 41 107. Miriam A, Korula G. A simple glucose insulin regimen for perioperative blood glucose
42 control: the Vellore regimen. *Anesthesia and Analgesia*. 2004; 99(2):598-602
- 43 108. National Institute for Health and Care Excellence. Developing NICE guidelines: the
44 manual, updated 2018. London. National Institute for Health and Care Excellence,
45 2014. Available from: [https://www.nice.org.uk/process/pmg20/chapter/introduction-
46 and-overview](https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview)

- 1 109. Navaratnarajah M, Rea R, Evans R, Gibson F, Antoniadou C, Keiralla A et al. Effect
2 of glycaemic control on complications following cardiac surgery: literature review.
3 Journal of Cardiothoracic Surgery. 2018; 13(1):10
- 4 110. Nicolson SC, Jobes DR, Zucker HA, Steven JM, Schreiner MS, Betts EK. The effect
5 of administering or withholding dextrose in pre-bypass intravenous fluids on
6 intraoperative blood glucose concentrations in infants undergoing hypothermic
7 circulatory arrest. Journal of Cardiothoracic and Vascular Anesthesia. 1992; 6(3):316-
8 318
- 9 111. Nilsson FN, Berglin EE, Ekroth R, Holm G, Milocco I, Mjos OD et al. Effects of graded
10 insulin infusions on plasma levels of free fatty acids, adrenaline and noradrenaline
11 directly after open heart surgery. Thoracic and Cardiovascular Surgeon. 1987;
12 35(2):96-100
- 13 112. Okabayashi T, Maeda H, Sun ZL, Montgomery RA, Nishimori I, Hanazaki K.
14 Perioperative insulin therapy using a closed-loop artificial endocrine pancreas after
15 hepatic resection. World Journal of Gastroenterology. 2009; 15(33):4116-21
- 16 113. Okabayashi T, Nishimori I, Maeda H, Yamashita K, Yatabe T, Hanazaki K. Effect of
17 intensive insulin therapy using a closed-loop glycemic control system in hepatic
18 resection patients: a prospective randomized clinical trial. Diabetes Care. 2009;
19 32(8):1425-7
- 20 114. Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, Maeda H, Yatabe T et al.
21 Continuous postoperative blood glucose monitoring and control by artificial pancreas
22 in patients having pancreatic resection: a prospective randomized clinical trial.
23 Archives of Surgery. 2009; 144(10):933-7
- 24 115. Okabayashi T, Shima Y. Are closed-loop systems for intensive insulin therapy ready
25 for prime time in the ICU? Current Opinion in Clinical Nutrition and Metabolic Care.
26 2014; 17(2):190-9
- 27 116. Oldfield GS, Commerford PJ, Opie LH. Effects of preoperative glucose-insulin-
28 potassium on myocardial glycogen levels and on complications of mitral valve
29 replacement. Journal of Thoracic and Cardiovascular Surgery. 1986; 91(6):874-8
- 30 117. Ouattara A, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I et al. Poor
31 intraoperative blood glucose control is associated with a worsened hospital outcome
32 after cardiac surgery in diabetic patients. Anesthesiology. 2005; 103(4):687-94
- 33 118. Parekh J, Roll GR, Wisel S, Rushakoff RJ, Hirose R. Effect of moderately intense
34 perioperative glucose control on renal allograft function: a pilot randomized controlled
35 trial in renal transplantation. Clinical Transplantation. 2016; 30(10):1242-1249
- 36 119. Pearlstone DB, Wolf RF, Berman RS, Burt M, Brennan MF. Effect of systemic insulin
37 on protein kinetics in postoperative cancer patients. Annals of Surgical Oncology.
38 1994; 1(4):321-32
- 39 120. Pezzella AT, Holmes SD, Pritchard G, Speir AM, Ad N. Impact of perioperative
40 glycemic control strategy on patient survival after coronary bypass surgery. Annals of
41 Thoracic Surgery. 2014; 98(4):1281-5
- 42 121. Polderman JA, Ma XL, Eshuis WJ, Hollmann MW, DeVries JH, Preckel B et al.
43 Efficacy of continuous intravenous glucose monitoring in perioperative glycaemic
44 control: a randomized controlled study. British Journal of Anaesthesia. 2017;
45 118(2):264-266
- 46 122. Polderman JAW, van Steen SCJ, Thiel B, Godfried MB, Houweling PL, Hollmann MW
47 et al. Peri-operative management of patients with type-2 diabetes mellitus undergoing

- 1 non-cardiac surgery using liraglutide, glucose-insulin-potassium infusion or
2 intravenous insulin bolus regimens: a randomised controlled trial. *Anaesthesia*. 2018;
3 73(3):332-339
- 4 123. Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J et al. A
5 prospective randomised multi-centre controlled trial on tight glucose control by
6 intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive
7 Care Medicine*. 2009; 35(10):1738-48
- 8 124. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P, Clinical Guidelines
9 Committee of the American College of P. Use of intensive insulin therapy for the
10 management of glycemic control in hospitalized patients: a clinical practice guideline
11 from the American College of Physicians. *Annals of Internal Medicine*. 2011;
12 154(4):260-7
- 13 125. Quinn DW, Pagano D, Bonser RS, Rooney SJ, Graham TR, Wilson IC et al.
14 Improved myocardial protection during coronary artery surgery with glucose-insulin-
15 potassium: a randomized controlled trial. *Journal of Thoracic and Cardiovascular
16 Surgery*. 2006; 131(1):34-42
- 17 126. Rabi D, Clement F, McAlister F, Majumdar S, Sauve R, Johnson J et al. Effect of
18 perioperative glucose-insulin-potassium infusions on mortality and atrial fibrillation
19 after coronary artery bypass grafting: a systematic review and meta-analysis.
20 *Canadian Journal of Cardiology*. 2010; 26(6):178-84
- 21 127. Raghavan SR, Ballehaninna UK, Chamberlain RS. The impact of perioperative blood
22 glucose levels on pancreatic cancer prognosis and surgical outcomes: an evidence-
23 based review. *Pancreas*. 2013; 42(8):1210-7
- 24 128. Ranasinghe AM, Quinn DW, Pagano D, Edwards N, Faroqui M, Graham TR et al.
25 Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic
26 performance and are associated with reduced troponin I release after on-pump
27 coronary artery bypass grafting. *Circulation*. 2006; 114(1 Suppl):I245-50
- 28 129. Rao V, Borger MA, Weisel RD, Ivanov J, Christakis GT, Cohen G et al. Insulin
29 cardioplegia for elective coronary bypass surgery. *Journal of Thoracic and
30 Cardiovascular Surgery*. 2000; 119(6):1176-84
- 31 130. Rao V, Christakis GT, Weisel RD, Ivanov J, Borger MA, Cohen G. The insulin
32 cardioplegia trial: myocardial protection for urgent coronary artery bypass grafting.
33 *Journal of Thoracic and Cardiovascular Surgery*. 2002; 123(5):928-35
- 34 131. Rao V, Cohen G, Weisel RD, Merante F, Ikonomidis JS, Ivanov J et al. The use of
35 glucose and insulin during hypothermic and normothermic CABG. *Annals of the
36 New York Academy of Sciences*. 1996; 793(1):494-497
- 37 132. Rassias AJ, Marrin CA, Arruda J, Whalen PK, Beach M, Yeager MP. Insulin infusion
38 improves neutrophil function in diabetic cardiac surgery patients. *Anesthesia and
39 Analgesia*. 1999; 88(5):1011-6
- 40 133. Raucoles-Aime M, Labib Y, Levraut J, Gastaud P, Dolisi C, Grimaud D. Use of I.V.
41 insulin in well-controlled non-insulin-dependent diabetics undergoing major surgery.
42 *British Journal of Anaesthesia*. 1996; 76(2):198-202
- 43 134. Raucoles-Aime M, Lugin D, Boussofara M, Gastaud P, Dolisi C, Grimaud D.
44 Intraoperative glycaemic control in non-insulin-dependent and insulin-dependent
45 diabetes. *British Journal of Anaesthesia*. 1994; 73(4):443-9

- 1 135. Ray JF, 3rd., Tewksbury DA, Myers WO, Wenzel FJ, Sautter RD. Can the frequency
2 of myocardial infarction be reduced during coronary artery operations. *Annals of*
3 *Thoracic Surgery*. 1977; 23:14-9
- 4 136. Rucka Z, Koutna I, Tesarova L, Potesilova M, Stejskal S, Simara P et al. Intravenous
5 insulin therapy during lung resection does not affect lung function or surfactant
6 proteins. *BMC Pulmonary Medicine*. 2014; 14:155
- 7 137. Rujirojindakul P, Liabsuetrakul T, McNeil E, Chanchayanon T, Wasinwong W,
8 Oofuvong M et al. Safety and efficacy of intensive intraoperative glycaemic control in
9 cardiopulmonary bypass surgery: a randomised trial. *Acta Anaesthesiologica*
10 *Scandinavica*. 2014; 58(5):588-96
- 11 138. Salerno TA, Wasan SM, Charrette EJ. Glucose substrate in myocardial protection.
12 *Journal of Thoracic and Cardiovascular Surgery*. 1980; 79(1):59-62
- 13 139. Sanjay OP, Prashanth P, Tauro DI. Attempting to maintain normoglycemia during
14 cardiopulmonary bypass with insulin may initiate post-operative hypoglycemia. *Indian*
15 *Journal of Clinical Biochemistry*. 2003; 18(2):119-26
- 16 140. Sathya B, Davis R, Taveira T, Whitlatch H, Wu WC. Intensity of peri-operative
17 glycemic control and postoperative outcomes in patients with diabetes: a meta-
18 analysis. *Diabetes Research and Clinical Practice*. 2013; 102(1):8-15
- 19 141. Sato H, Carvalho G, Sato T, Lattermann R, Matsukawa T, Schricker T. The
20 association of preoperative glycemic control, intraoperative insulin sensitivity, and
21 outcomes after cardiac surgery. *Journal of Clinical Endocrinology and Metabolism*.
22 2010; 95(9):4338-4344
- 23 142. Sato H, Hatzakorzian R, Carvalho G, Sato T, Lattermann R, Matsukawa T et al. High-
24 dose insulin administration improves left ventricular function after coronary artery
25 bypass graft surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. 2011;
26 25(6):1086-91
- 27 143. Sato H, Lattermann R, Carvalho G, Sato T, Metrakos P, Hassanain M et al.
28 Perioperative glucose and insulin administration while maintaining normoglycemia
29 (GIN therapy) in patients undergoing major liver resection. *Anesthesia and Analgesia*.
30 2010; 110(6):1711-8
- 31 144. Savaşkan D, Yurtseven N, Tuygun AK, Aksoy P, Canik S. The effects of insulin given
32 prior to release of cross-clamp on coronary sinus lactate levels in coronary artery
33 surgery. *Anatolian Journal of Cardiology*. 2006; 6(3):248-252
- 34 145. Sawada A, Kamada Y, Hayashi H, Ichinose H, Sumita S, Yamakage M. Effect of
35 intraoperative glucose infusion on catabolism of adipose tissue and muscle protein in
36 patients anesthetized with remifentanyl in combination with sevoflurane during major
37 surgery: A randomized controlled multicenter trial. *Anesthesia and Analgesia*. 2016;
38 123(4):869-76
- 39 146. Schricker T, Sato H, Beaudry T, Codere T, Hatzakorzian R, Pruessner JC.
40 Intraoperative maintenance of normoglycemia with insulin and glucose preserves
41 verbal learning after cardiac surgery. *PloS One*. 2014; 9(6):e99661
- 42 147. Sebranek JJ, Lugli AK, Coursin DB. Glycaemic control in the perioperative period.
43 *British Journal of Anaesthesia*. 2013; 111(Suppl 1):i18-34
- 44 148. Shah B, Berger JS, Amoroso NS, Mai X, Lorin JD, Danoff A et al. Periprocedural
45 glycemic control in patients with diabetes mellitus undergoing coronary angiography
46 with possible percutaneous coronary intervention. *American Journal of Cardiology*.
47 2014; 113(9):1474-80

- 1 149. Shi Z, Ma L, Wang H, Yang Y, Li X, Schreiber A et al. Insulin and hypertonic glucose
2 in the management of aseptic fat liquefaction of post-surgical incision: a meta-
3 analysis and systematic review. *International Wound Journal*. 2013; 10(1):91-7
- 4 150. Shim YH, Kweon TD, Lee JH, Nam SB, Kwak YL. Intravenous glucose-insulin-
5 potassium during off-pump coronary artery bypass surgery does not reduce
6 myocardial injury. *Acta Anaesthesiologica Scandinavica*. 2006; 50(8):954-61
- 7 151. Sieber F, Smith DS, Kupferberg J, Crosby L, Uzzell B, Buzby G et al. Effects of
8 intraoperative glucose on protein catabolism and plasma glucose levels in patients
9 with supratentorial tumors. *Anesthesiology*. 1986; 64(4):453-9
- 10 152. Slas AJ, Craig RM, Vazquez RM. Hypocaloric amino acid infusion in postoperative
11 diabetics. *American Journal of Intravenous Therapy and Clinical Nutrition*. 1984;
12 11(1):22+30-31
- 13 153. Smith A, Grattan A, Harper M, Royston D, Riedel BJ. Coronary revascularization: a
14 procedure in transition from on-pump to off-pump? The role of glucose-insulin-
15 potassium revisited in a randomized, placebo-controlled study. *Journal of*
16 *Cardiothoracic and Vascular Anesthesia*. 2002; 16(4):413-20
- 17 154. Sokos GG, Bolukoglu H, German J, Hentosz T, Magovern GJ, Jr., Maher TD et al.
18 Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular
19 function in patients undergoing coronary artery bypass grafting. *American Journal of*
20 *Cardiology*. 2007; 100(5):824-9
- 21 155. Subramaniam B, Panzica PJ, Novack V, Mahmood F, Matyal R, Mitchell JD et al.
22 Continuous perioperative insulin infusion decreases major cardiovascular events in
23 patients undergoing vascular surgery: a prospective, randomized trial.
24 *Anesthesiology*. 2009; 110(5):970-7
- 25 156. Svensson S, Ekroth R, Nilsson F, Ponten J, William-Olsson G. Insulin as a
26 vasodilating agent in the first hour after cardiopulmonary bypass. *Scandinavian*
27 *Journal of Thoracic and Cardiovascular Surgery*. 1989; 23(2):139-43
- 28 157. Szabo Z, Arnqvist H, Hakanson E, Jorfeldt L, Svedjeholm R. Effects of high-dose
29 glucose-insulin-potassium on myocardial metabolism after coronary surgery in
30 patients with Type II diabetes. *Clinical Science*. 2001; 101(1):37-43
- 31 158. Thomas DJ, Platt HS, Alberti KG. Insulin-dependent diabetes during the peri-
32 operative period. An assessment of continuous glucose-insulin-potassium infusion,
33 and traditional treatment. *Anaesthesia*. 1984; 39(7):629-37
- 34 159. Tohya A, Kohjitani A, Ohno S, Yamashita K, Manabe Y, Sugimura M. Effects of
35 glucose-insulin infusion during major oral and maxillofacial surgery on postoperative
36 complications and outcomes. *JA Clinical Reports*. 2018; 4:9
- 37 160. Tsang MW, Davidoff R, Korach A, Apstein CS, Hesselvik JF, Nguyen H et al.
38 Diastolic dysfunction after coronary artery bypass grafting- the effect of glucose-
39 insulin-potassium infusion. *Journal of Cardiac Surgery*. 2007; 22(3):185-91
- 40 161. Umpierrez G, Cardona S, Pasquel F, Jacobs S, Peng L, Unigwe M et al. Randomized
41 controlled trial of intensive versus conservative glucose control in patients undergoing
42 coronary artery bypass graft surgery: GLUCO-CABG Trial. *Diabetes Care*. 2015;
43 38(9):1665-72
- 44 162. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P et al.
45 Randomized study of basal-bolus insulin therapy in the inpatient management of
46 patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery).
47 *Diabetes Care*. 2011; 34(2):256-61

- 1 163. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et
2 al. Intensive insulin therapy in critically ill patients. *New England Journal of Medicine*.
3 2001; 345(19):1359-67
- 4 164. van Kuijk JP, Schouten O, Flu WJ, den Uil CA, Bax JJ, Poldermans D. Perioperative
5 blood glucose monitoring and control in major vascular surgery patients. *European*
6 *Journal of Vascular and Endovascular Surgery*. 2009; 38(5):627-34
- 7 165. Vanhorebeek I, Ingels C, Van den Berghe G. Intensive insulin therapy in high-risk
8 cardiac surgery patients: evidence from the Leuven randomized study. *Seminars in*
9 *Thoracic and Cardiovascular Surgery*. 2006; 18(4):309-16
- 10 166. Visser L, Zuurbier CJ, Hoek FJ, Opmeer BC, de Jonge E, de Mol BA et al. Glucose,
11 insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic
12 clamp: effects on inflammatory response during coronary artery surgery. *British*
13 *Journal of Anaesthesia*. 2005; 95(4):448-57
- 14 167. Wahby EA, Abo Elnasr MM, Eissa MI, Mahmoud SM. Perioperative glycemic control
15 in diabetic patients undergoing coronary artery bypass graft surgery. *Journal of the*
16 *Egyptian Society of Cardio-Thoracic Surgery*. 2016; 24(2):143-149
- 17 168. Wallin M, Barr G, Owall A, Lindahl SG, Brismar K. The influence of glucose-insulin-
18 potassium (GIK) on the GH/IGF-1/IGFBP-1 axis during elective coronary artery
19 bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia*. 2003; 17(4):470-
20 7
- 21 169. Yuan J, Liu T, Zhang X, Si Y, Ye Y, Zhao C et al. Intensive Versus Conventional
22 Glycemic Control in Patients with Diabetes During Enteral Nutrition After
23 Gastrectomy. *Journal of Gastrointestinal Surgery*. 2015; 19(8):1553-8
- 24 170. Zheng R, Gu C, Wang Y, Yang Z, Dou K, Wang J et al. Impacts of intensive insulin
25 therapy in patients undergoing heart valve replacement. *Heart Surgery Forum*. 2010;
26 13(5):E292-8
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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	<ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies will be published in the final review.</p>
5.	Condition or domain being studied	Perioperative care
6.	Population	<p>Inclusion: Adults 18 years and over having surgery.</p> <p>Exclusion:</p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • glucose control (insulin therapy, intra to postoperative)
8.	Comparator/Reference standard/Confounding factors	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • non-English language studies • cross-over randomised controlled trials • studies published before 2000
11.	Context	n/a
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> • 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 <p>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.</p>
13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> • length of hospital stay • unplanned ICU admission • ICU length of stay (planned and unplanned) • hospital readmission <p>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.</p>
14.	Data extraction (selection and coding)	<p>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.</p> <p>Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <ul style="list-style-type: none"> • Systematic reviews: Risk of Bias in

		<p>Systematic Reviews (ROBIS)</p> <ul style="list-style-type: none"> • 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 <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> • 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 <p>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.</p>
16.	Strategy for data synthesis	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p> <p>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.</p> <p>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/</p> <ul style="list-style-type: none"> • 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.

		<ul style="list-style-type: none"> List any other software planned to be used. <p>Heterogeneity between the studies in effect measures will be assessed using the I² statistic and visually inspected. An I² 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.</p>		
17.	Analysis of sub-groups	Subgroups: <ul style="list-style-type: none"> 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 $\geq 30\text{kg/m}^2$ 		
18.	Type and method of review	<input checked="" type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	[To be added.]		
22.	Anticipated completion date	[To be added.]		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>

		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
24.	Named contact	<p>5a. Named contact National Guideline Centre</p> <p>5b Named contact e-mail perioperativecare@nice.org.uk</p> <p>5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre</p>		
25.	Review team members	<p>From the National Guideline Centre:</p> <p>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</p>		
26.	Funding sources/sponsor	<p>This systematic review is being completed by the National Guideline Centre which receives funding from NICE.</p>		
27.	Conflicts of interest	<p>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.</p>		
28.	Collaborators	<p>Development of this systematic review will be</p>		

		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	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> • 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	<input type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input type="checkbox"/>	Discontinued
35..	Additional information	<p>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.</p>	
36.	Details of final publication	www.nice.org.uk	

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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	<ul style="list-style-type: none"> • 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	<p>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.</p> <p>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</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • 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. <p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies.</p> <p><i>Setting:</i></p> <ul style="list-style-type: none"> • 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 glyated) 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)

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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

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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

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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*))
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2 B.2 Health Economics literature search strategy

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

9 **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

10

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

1

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

1

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

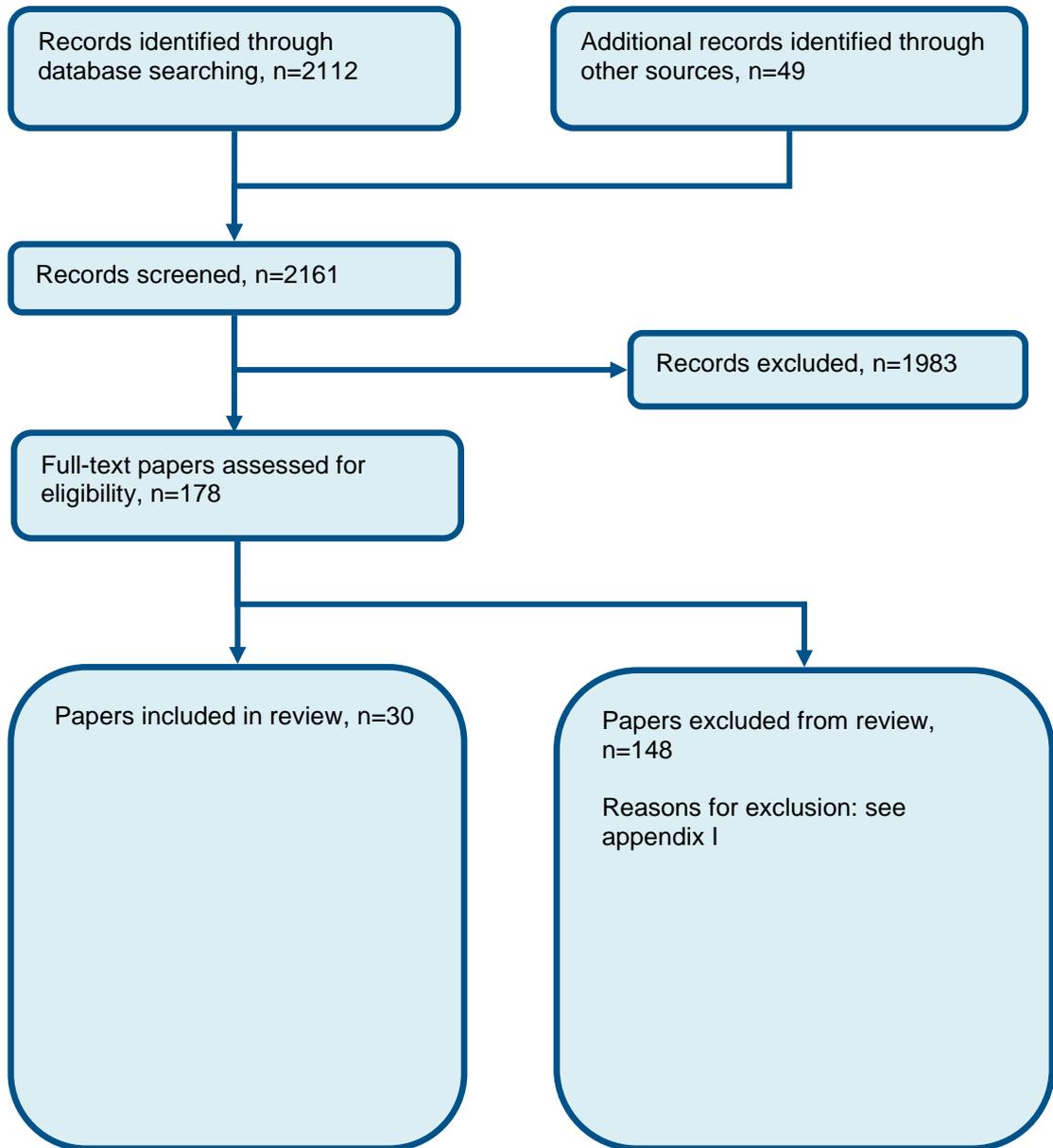
1

2

1

Appendix C: Clinical evidence selection

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



2

3

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/m ² : BMI <30kg/m ² 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 states '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.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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 ;</p> <p>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 ;</p>	
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 ≥ 30 kg/m ² : 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 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
	<p>infusion, titrated according to sliding scale starting at blood glucose level of 10 mmol/L.</p> <p>. Duration 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</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p> <p>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</p> <p>Protocol outcome 4: Length of stay in intensive care unit - Actual outcome: length of ICU stay at length of stay;</p>	

Study	Albacker 2007⁵
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 2011⁹
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 center 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 ≥ 30 kg/m ² : 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	<p>(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</p> <p>(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</p>
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 ≥ 30 kg/m ² : BMI < 30 kg/m ² 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	<p>(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</p> <p>(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</p>

Study	Butterworth 2005 ²⁶
	<p>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</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL</p> <p>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 ;</p> <p>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 ;</p> <p>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 ;</p> <p>Protocol outcome 4: Hospital readmission - Actual outcome: Rehospitalisation 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 ;</p>	
Protocol outcomes not reported by the	Quality of life ; Infection (including SSI) ; Length of hospital stay ; Unplanned ICU admission ; Length of

Study	Butterworth 2005²⁶
study	stay in intensive care unit

Study	Cao 2011²⁷
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 mellitus 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 \geq 30kg/m ² : BMI <30kg/m ² 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 2011²⁷
	<p>through the central or peripheral vein. This was terminated when the oral or enteral ingestion exceeded 50% of target energy requirements. . Indirectness: No indirectness</p> <p>(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.</p> <p>. 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</p>
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 track 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 2011²⁷
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 2009³¹
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. Zerbin 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
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>
	<p>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.</p>

Study	Chan 2009³¹
Protocol outcomes not reported by the study	Quality of life ; Length of stay in intensive care unit ; Hospital readmission

Study	Chaney 1999³²
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 \geq 30kg/m ² : 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, CABG+pvalve 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
	<p>- 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</p> <p>Protocol outcome 2: Adverse events and complications</p> <p>- 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</p> <p>- 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</p> <p>- 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</p> <p>Protocol outcome 3: Infection (including SSI)</p> <p>- 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</p> <p>Protocol outcome 4: Hypoglycaemia</p> <p>- 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</p>
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
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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 \geq 30kg/m ² : 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	<p>(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).</p> <p>. 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</p> <p>(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.</p>

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
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p>	
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 to 50% 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
	<p>• dl-1, respectively. Hypoglycemia was treated by administration of 20% dextrose (25 to 100 ml).. Indirectness: No indirectness</p> <p>(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</p>
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
	<p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>
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 $\geq 30\text{kg/m}^2$: 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	<p>(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.</p> <p>. 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</p> <p>(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 $<200\text{mg/dL}$.</p>

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
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>Protocol outcome 5: Length of stay in intensive care unit</p>	

Study	Emam 2010⁴³
	- 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 2007⁵²
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 \geq 30kg/m ² : 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
	<p>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.</p> <p>. Indirectness: No indirectness</p> <p>(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)</p> <p>. Indirectness: No indirectness</p>
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
<p>Protocol outcome 1: Mortality</p> <p>- 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.</p> <p>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</p>	<p>Protocol outcome 2: Adverse events and complications</p> <p>- 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.</p> <p>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</p> <p>- Actual outcome: neurological complications - stroke at up to 30 days after surgery; Group 1: 8/185, Group 2: 1/186</p> <p>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</p>
<p>Protocol outcome 3: Infection (including SSI)</p> <p>- Actual outcome: deep sternal infection at up to 30 days after surgery; Group 1: 6/185, Group 2: 7/186</p> <p>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</p>	<p>Protocol outcome 4: Length of hospital stay</p> <p>- 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</p> <p>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</p>

Study	Gandhi 2007⁵²
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 2013⁵⁵
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 hear 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	<p>(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</p> <p>(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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p> <p>Protocol outcome 3: Hypoglycaemia</p>	

Study	Giakoumidakis 2013 ⁵⁵
	<p>- 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</p> <p>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</p> <p>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</p>
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	<p>(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.</p> <p>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..</p> <p>Indirectness: No indirectness</p> <p>(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.</p> <p>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..</p> <p>Indirectness: No indirectness</p>
Funding	Funding not stated

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

Study	Grey 2004 ⁵⁹
CONTROL	
<p>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</p> <p>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</p> <p>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</p> <p>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</p>	
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 hepatic 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/m ² : 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	<p>(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</p> <p>(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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus NO GLUCOSE CONTROL</p> <p>Protocol outcome 1: Mortality - Actual outcome: In hospital mortality at length of hospital stay; Group 1: 3/188, Group 2: 0/193</p>	

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/m ² : 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	<p>(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</p> <p>. 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, CaCl₂ 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</p> <p>(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</p> <p>. Indirectness: No indirectness</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p>	

Study	Hoedemaekers 2005 ⁷⁴
	<p>- 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 \pm SD 114.4 \pm 15.1 versus 97.6 \pm 19.8 mg/dl; $p = 0.05$) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A</p> <p>Protocol outcome 2: Hypoglycaemia</p> <p>- Actual outcome: hypoglycaemia at 24 hours post ICU admission; Group 1: 0/10, Group 2: 0/10</p> <p>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 \pm SD 114.4 \pm 15.1 versus 97.6 \pm 19.8 mg/dl; $p = 0.05$) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A</p> <p>Protocol outcome 3: Length of stay in intensive care unit</p> <p>- 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</p> <p>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 \pm SD 114.4 \pm 15.1 versus 97.6 \pm 19.8 mg/dl; $p = 0.05$) ; Group 1 Number missing: 0, Reason: N/A; Group 2 Number missing: 0, Reason: N/A</p>
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 enrollment 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/m ² : 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	<p>(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.</p> <p>. 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.</p> <p>. Indirectness: No indirectness</p> <p>(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).</p> <p>. Duration length of ICU stay. Concurrent medication/care: When the patient was discharged from the</p>

Study	Ingels 2006 ⁷⁷
	<p>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.</p> <p>. Indirectness: No indirectness</p>
Funding	Equipment / drugs provided by industry (Novo Nordisk Denmark)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (POSTOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p> <p>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</p>	

Study	Ingels 2006 ⁷⁷
<p>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</p>	
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	<p>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.</p> <p>Ten patients were excluded (concomitant coronary heart disease undergoing coronary artery bypass grafting in 3 patients, concomitant hypothyroid in 2, concomitant infective endocarditis in 3, previous cardiac surgery in 1, and postoperative requirement of an intra-aortic balloon pump in 1)</p>
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 ≥ 30 kg/m ² : 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
	<p>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 ;</p> <p>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 ;</p> <p>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 ;</p> <p>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</p>

Study	Ji 2014 ⁷⁸
	<p>- Low; Indirectness of outcome: No indirectness ;</p> <p>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 ;</p> <p>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 ;</p>
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 \geq 30kg/m ² : 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
<p>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 ;</p> <p>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 ;</p> <p>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 ;</p> <p>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</p>	

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 \geq 30kg/m ² : 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 glycaemic control system using theSTG-22 unit as an artificial endocrine pancreas.

Study	Okabayashi 2009b ¹¹⁴
	<p>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.</p> <p>. Duration length of surgery and 18 hours in ICU. Concurrent medication/care: unclear. Indirectness: No indirectness</p> <p>(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.</p> <p>. Duration length of surgery and 18 hours ICU stay. Concurrent medication/care: unclear. Indirectness: No indirectness</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p>	
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 addition to CABG (eg, CABG+valve 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/m ² : 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
	<p>of 72 hours perioperatively.</p> <p>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</p> <p>(n=98) Intervention 2: Standard care - Liberal glucose control. Glucomander 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 Glucomander. 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.</p> <p>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</p>

Funding	Funding not stated
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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 \geq 30kg/m ² : 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 2014¹³⁷
Interventions	<p>(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</p> <p>(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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p>	

Study	Rujirojindakul 2014 ¹³⁷
	<p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>
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/m ² : 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 ⁻¹ min ⁻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 2010¹⁴³
	<p>subcutaneous insulin was administered using a sliding scale.. Indirectness: No indirectness</p> <p>(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 (≥ 110 mg/dL), an insulin infusion of 1 U/h ($63\text{--}110$ mg/dL) was started. This was then titrated according to the sliding scale shown in Table 1, aiming at a blood glucose between 3.5 and 6.1 mmol/L (7.9 mmol/L ($63\text{--}143$ mg/dL) 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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p>	
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 2011¹⁴²
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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 hemodialysis 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/m ² : 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	<p>(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 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</p> <p>(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.</p> <p>. Duration 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</p>

Study	Sato 2011¹⁴²
	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
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p>	
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 2014¹⁴⁶
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, aged 18–90 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/m ² : 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	<p>(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 duration of surgery. Concurrent medication/care: Postoperative glycemc control in both groups was performed using standard protocols aimed at a blood glucose concentration between 4 and 10 mmol L. . Indirectness: No indirectness</p> <p>(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 duration of surgery. Concurrent medication/care: Postoperative glycemc 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</p>
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	

Study	Schricker 2014 ¹⁴⁶
	<p>- Actual outcome: pulmonary complications at length of hospital stay; Group 1: 1/14, 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</p> <p>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</p> <p>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</p>
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 Brompton 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%).

Study	Smith 2002 ¹⁵³
Exclusion criteria	Pre-existing conduction abnormalities (eg, left bundle-branch block, AF), insulin-dependant diabetes, serum 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	<p>(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.</p> <p>. Duration 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.</p> <p>. Indirectness: No indirectness</p> <p>(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.</p> <p>. Duration 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.</p> <p>. Indirectness: No indirectness</p>
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	
<p>Protocol outcome 1: Adverse events and complications</p> <ul style="list-style-type: none"> - 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 <p>Protocol outcome 2: Infection (including SSI)</p> <ul style="list-style-type: none"> - 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 <p>Protocol outcome 3: Length of hospital stay</p> <ul style="list-style-type: none"> - 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

Study	Szabo 2001 ¹⁵⁷
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	patients with type 2 diabetes undergoing elective coronary surgery for stable angina pectdis.
Exclusion criteria	left ventricular ejection fraction of <0.40, age over 80 years, serious late complications of daibetes, liver dieisease, 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	<p>(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</p> <p>(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</p>
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

Study	Szabo 2001¹⁵⁷
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: 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 2018¹⁵⁹
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:

Study	Tohya 2018 ¹⁵⁹
Indirectness of population	No indirectness
Interventions	<p>(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.</p> <p>. Duration 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</p> <p>(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.</p> <p>. Duration 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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (INTRAOPERATIVE) versus LIBERAL GLUCOSE CONTROL</p> <p>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</p> <p>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</p>	

Study	Tohya 2018¹⁵⁹
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: 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 2005¹⁶⁶
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,

Study	Visser 2005¹⁶⁶
	<p>NovoNordisk, Copenhagen, Denmark) was infused continuously at a fixed rate of 0.1 IU·kg⁻¹·h⁻¹. A separate 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.</p> <p>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.</p> <p>. 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.</p> <p>. Indirectness: No indirectness</p> <p>(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.</p> <p>. Indirectness: Serious indirectness; Indirectness comment: unclear if control group received BG control</p>
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 withdrawal 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, diarrhea, 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 insulintin. BG was monitored every 2-4 hours when stable and adjusted

Study	Yuan 2015¹⁶⁹
	<p>according to the IV insulin algorithm.</p> <p>. 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</p> <p>(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</p>
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

Study	Yuan 2015¹⁶⁹
- Actual outcome: severe hypoglycaemia at length of hospital stay; Group 1: 8/106, 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 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 2010¹⁷⁰
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/m ² : 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 induced 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

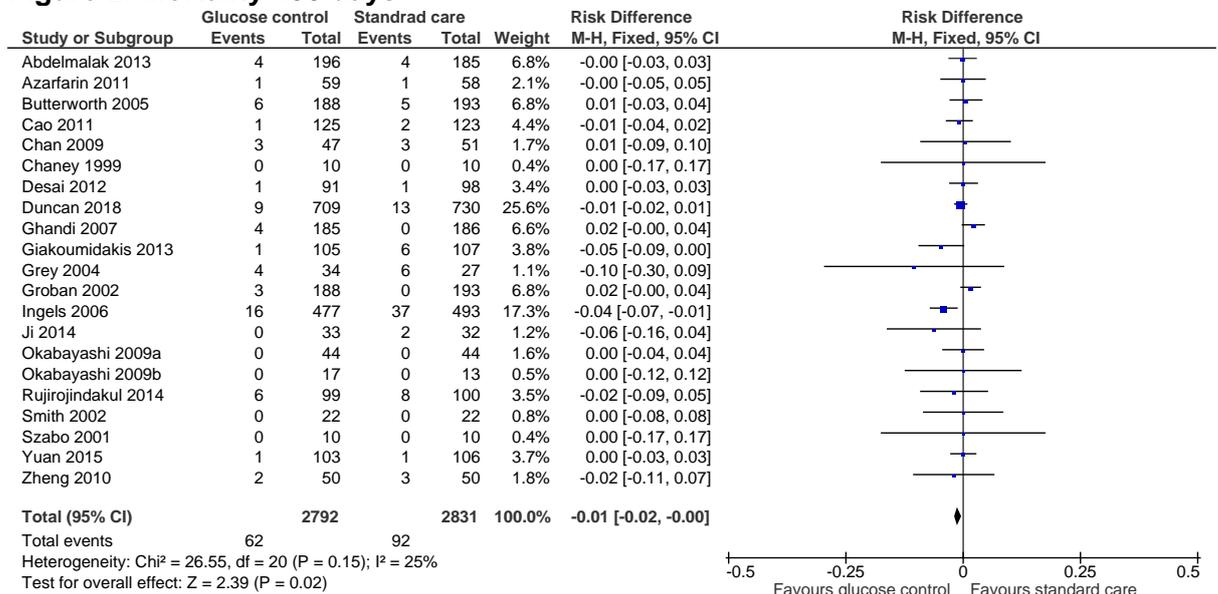
Study	Zheng 2010 ¹⁷⁰
	<p>ml of 20% glucose was administered intravenously instead. insulin administration was terminated when body temperature begun to recover. post operative blood glucose levels were measured every 60 minutes post operatively and insulin infusion started if BG exceeded 110 mg/dl. . Duration unclear. Concurrent medication/care: Blood samples and cardia index measurements were taken at 7 time points perioperatively.. Indirectness: No indirectness</p> <p>(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</p>
Funding	Academic or government funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INSULIN THERAPY (PERIOPERATIVE) versus NO GLUCOSE CONTROL</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>Protocol outcome 5: Length of stay in intensive care unit</p>	

Study	Zheng 2010¹⁷⁰
- 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 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

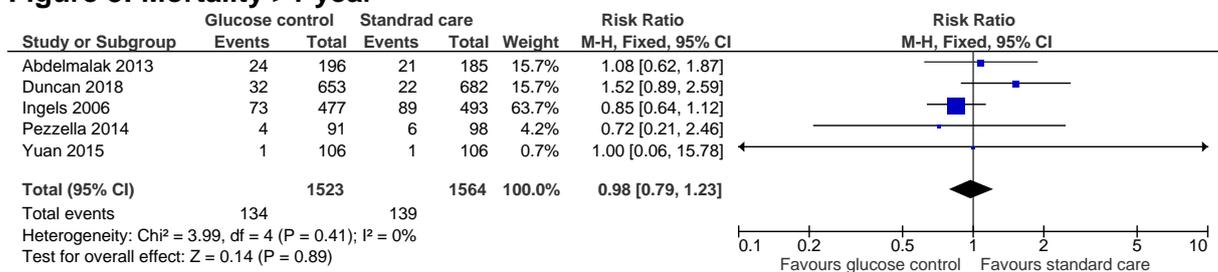
E.1 Glucose control versus standard care

Figure 2: Mortality <30 days



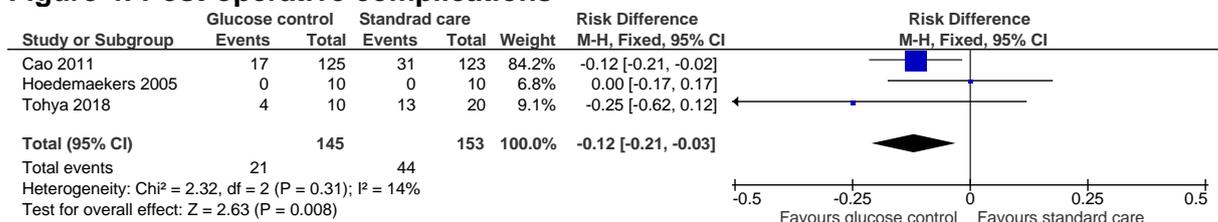
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Figure 3: Mortality >1 year



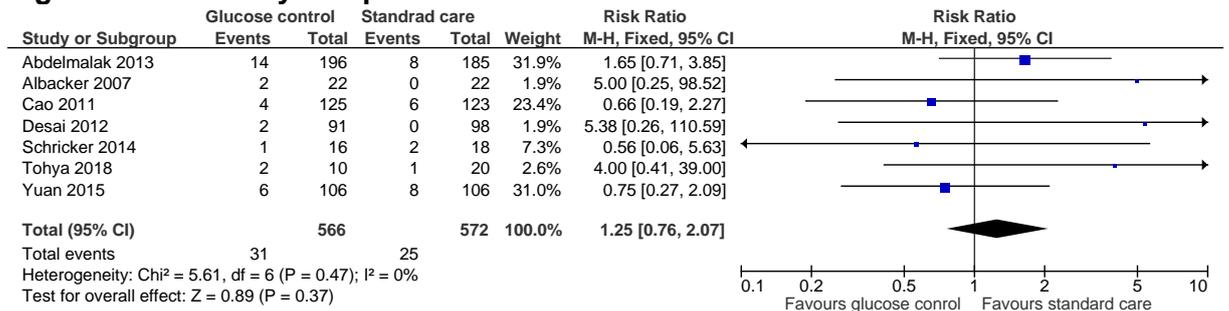
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Figure 4: Post-operative complications



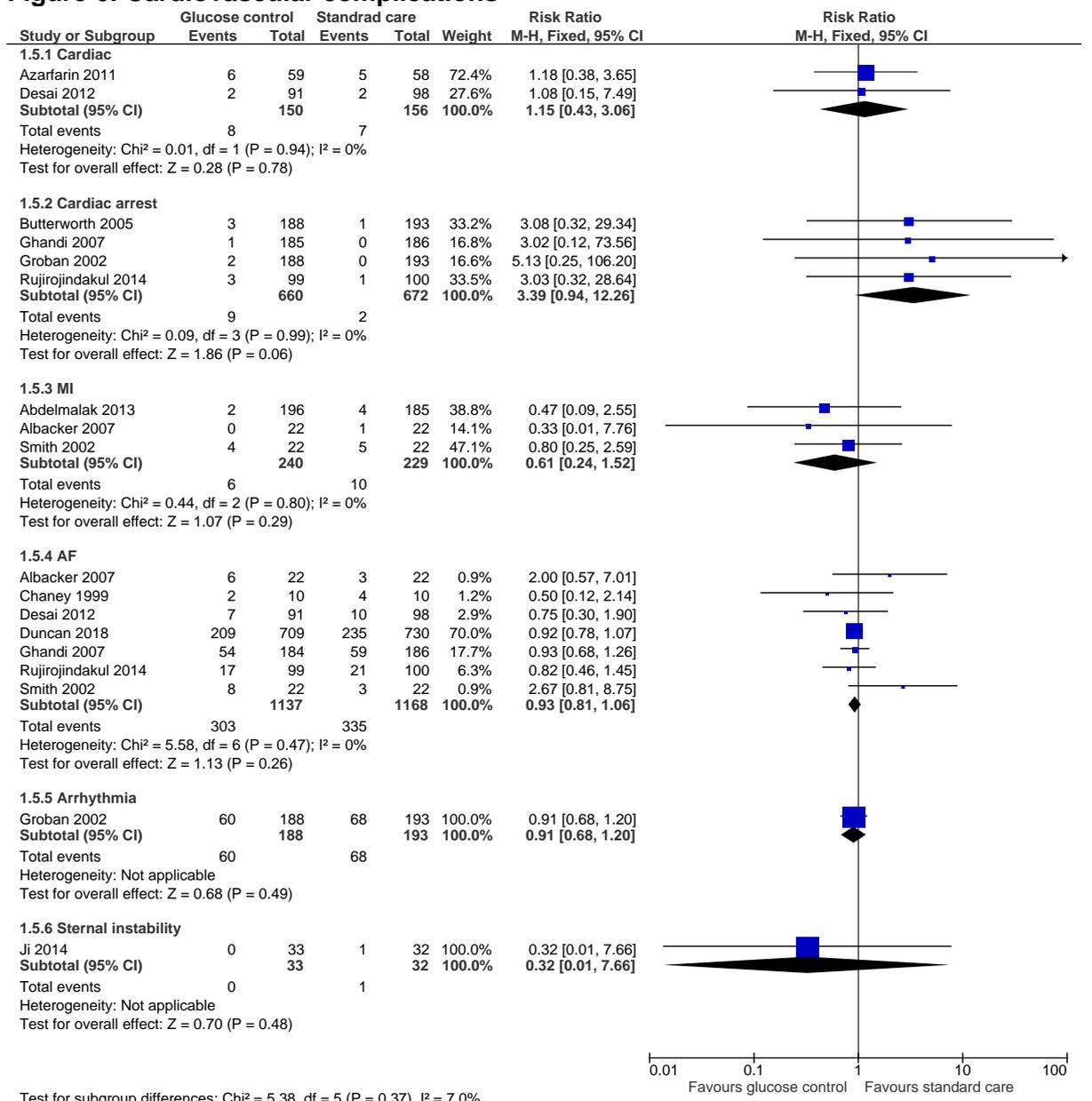
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Figure 5: Pulmonary complications



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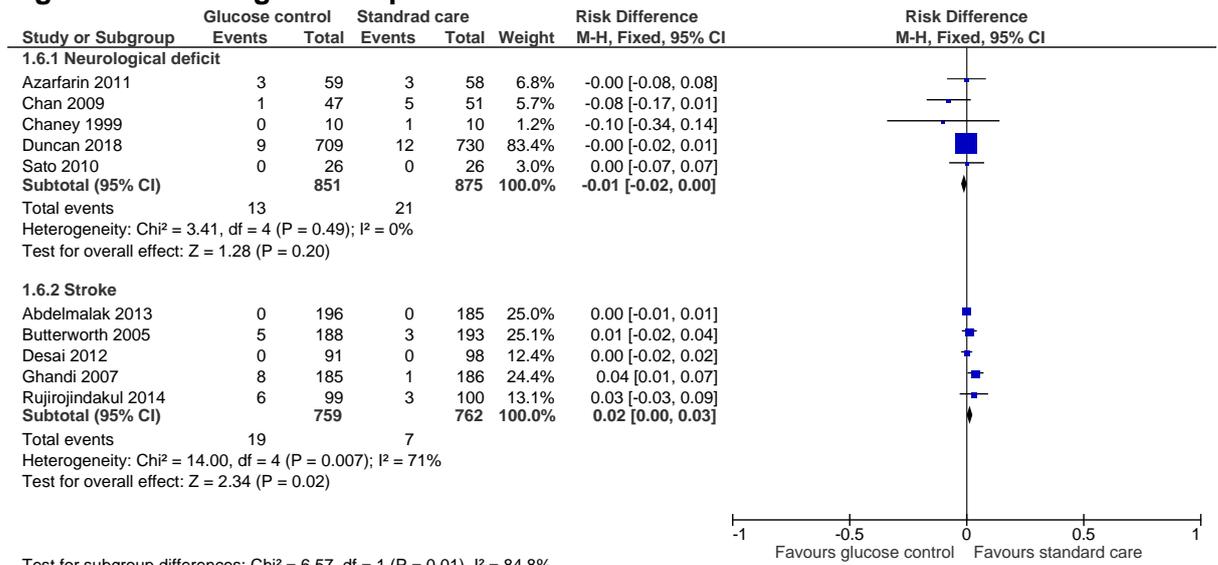
Figure 6: Cardiovascular complications



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

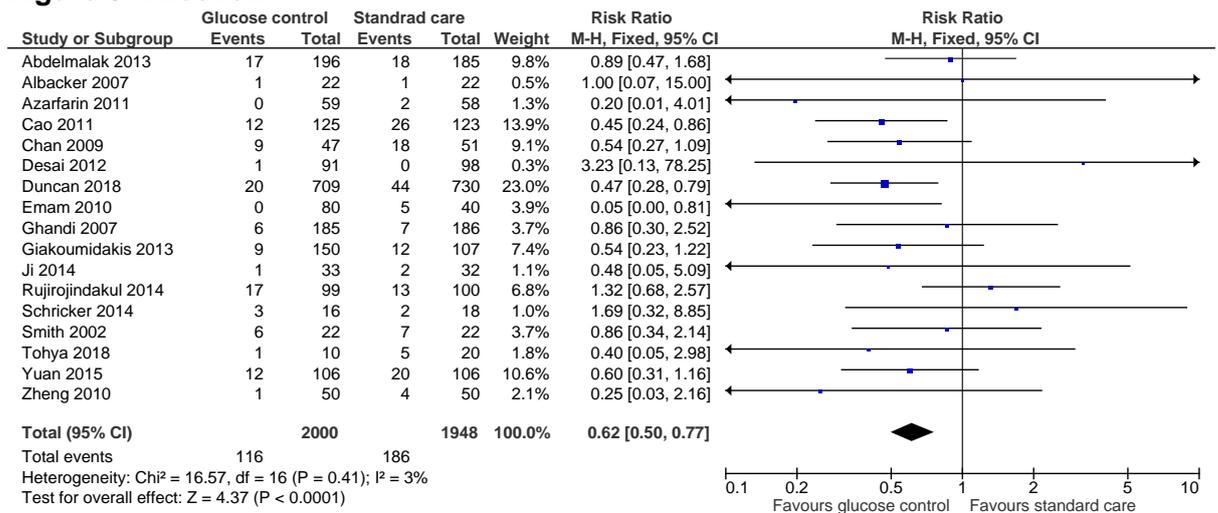
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Figure 7: Neurological complications



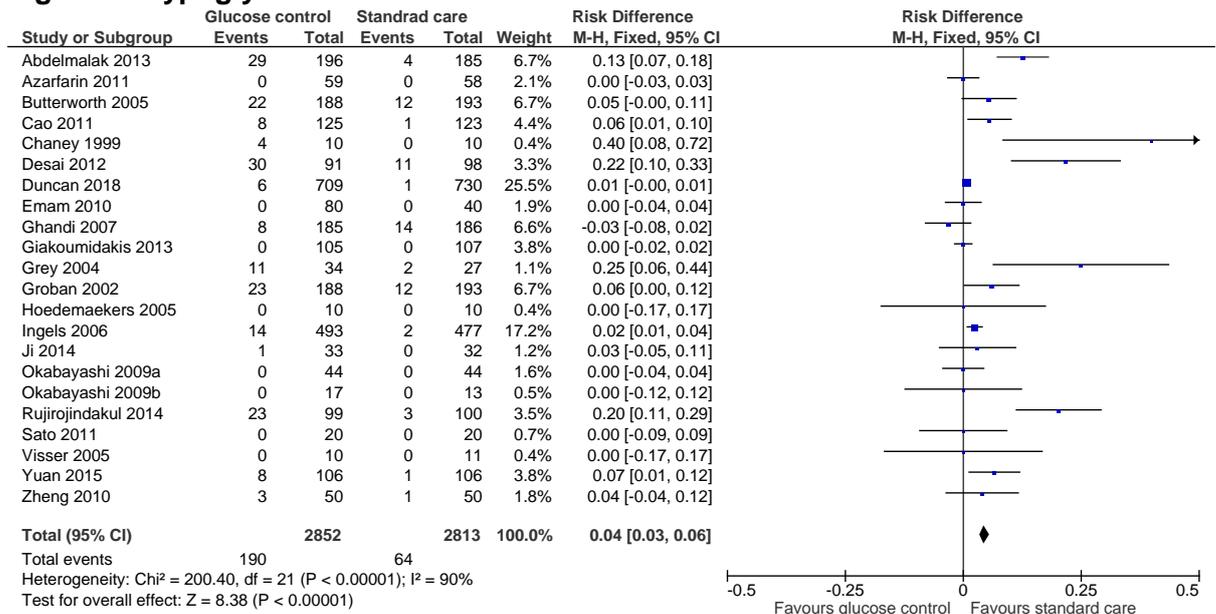
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Figure 8: Infection



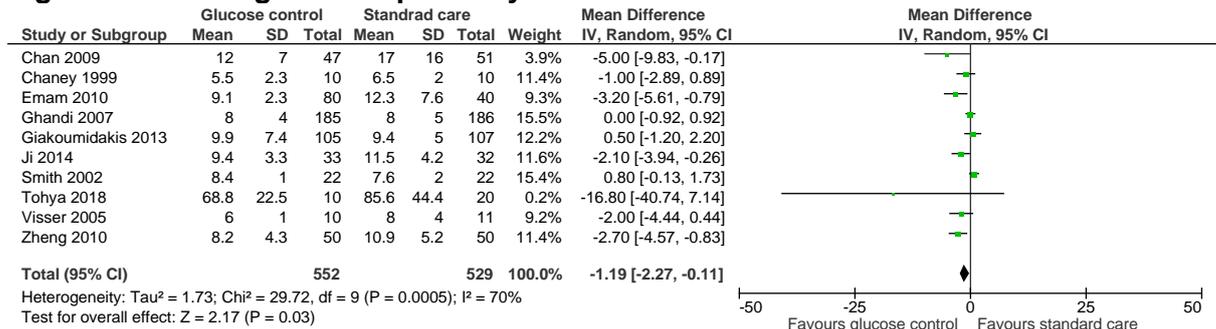
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Figure 9: Hypoglycaemic events



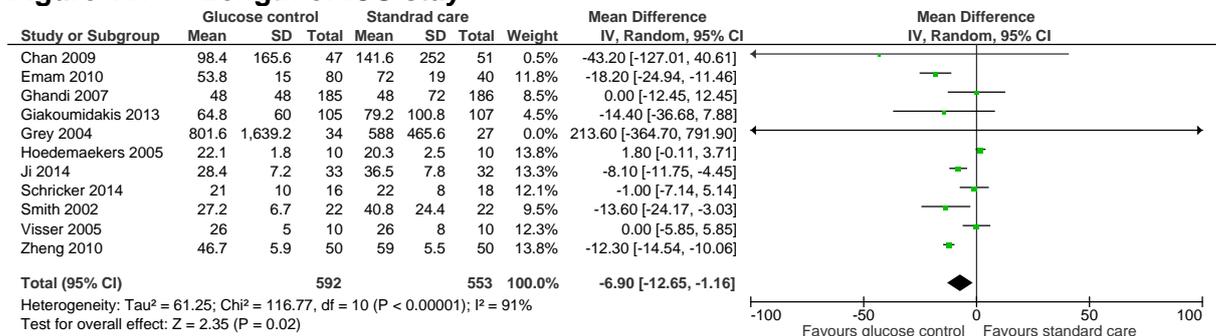
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Figure 10: Length of hospital stay



2

Figure 11: Length of ICU stay



3

Figure 12: Hospital readmissions



1

2

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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕⊕○ 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)	⊕⊕○○ 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)	⊕⊕○○ 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)	⊕⊕⊕⊕ 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)	⊕⊕⊕⊕ 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)	⊕⊕⊕⊕ 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)	⊕⊕⊕⊕ 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)	⊕⊕⊕⊕ 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)	⊕⊕⊕○ 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)	⊕⊕○○ 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)	⊕⊕⊕○ 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.

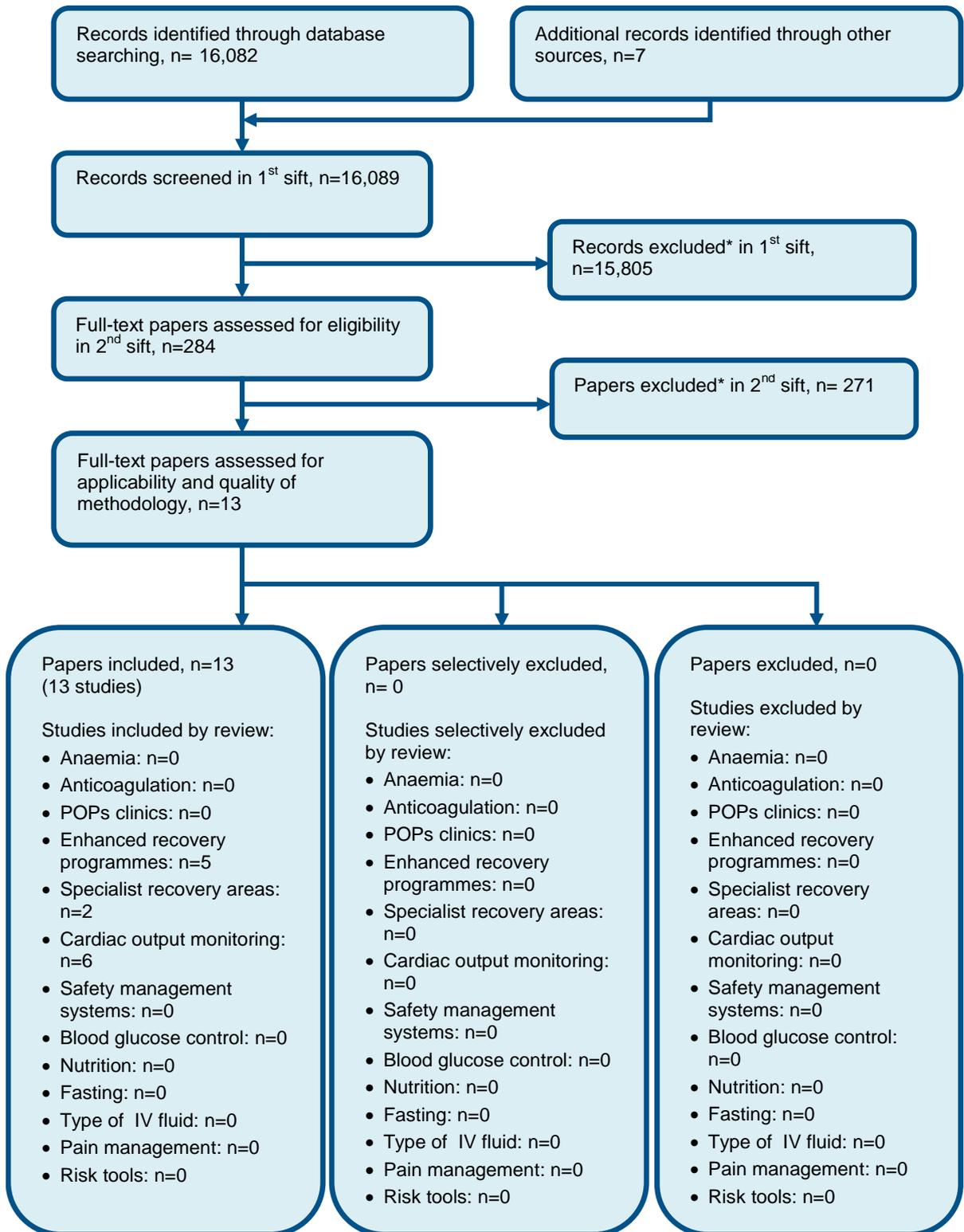
² Downgraded by 1 or 2 increments because of heterogeneity, I²>50%, p<0.04, unexplained by subgroup analysis

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

1
2

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.

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Appendix I: Excluded studies

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I.1 Excluded clinical studies

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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
Hatzakorjian 2011 ⁶⁷	Inappropriate outcome
Hatzakorjian 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

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2 I.2 Excluded health economic studies

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

7 **Table 11: Studies excluded from the health economic review**

Reference	Reason for exclusion
None	

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