Effectiveness of tight glycaemic control on mortality and morbidity in patients undergoing cardiac surgery in hospital: a systematic review

Submitted by

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Thesis submitted in fulfilment of the requirements for the degree of

Masters in Clinical Science

The Joanna Briggs Institute, Faculty of Health Sciences,

The University of Adelaide

February 2016

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Declaration

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Ali Azam Mohammad Morshed

5 February 2016

Acknowledgement

I would like to thank the following people who helped and inspired me during my Masters of Philosophy degree study. First and foremost, my utmost gratitude goes to my primary supervisor, Dr. Zachary Munn, who has provided me with relentless support throughout my thesis through his patience, knowledge and excellent positive attitude whilst allowing me room to work in my own way; without his supervision this thesis would not have been written or completed. I would also like to thank my supervisor, Associate Professor Craig Lockwood, for his professional guidance, advice and input at different stages of my study. Last but not least, I would like to acknowledge the invaluable support from the University of Adelaide and Joanna Briggs Institute staff.

Abstract

Background

Hyperglycaemia is a well-documented and common response to critical illness and metabolic stress during the perioperative period of cardiac surgery; however, there remains considerable controversy regarding the role of tight glycaemic control during and/or after cardiac surgery. The objective of this review was to identify the effectiveness of tight glycaemic control compared to conventional glycaemic control on the mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery.

Methods

A three-step search strategy was employed that aimed to locate both published and unpublished studies in the English language between 1990 until March 2014. An initial search in PubMed and CINAHL was followed by a second search using all identified keywords and index terms across multiple databases and grey literature sites. Critical appraisal was undertaken by two independent reviewers using the standard critical appraisal instrument from the Joanna Briggs Institute Meta-Analysis of Statistical Assessment and Review Instrument (JBI-MAStARI). Results from randomized controlled trials were pooled in statistical meta-analysis using RevMan V 5.3 software where appropriate. Effect sizes were calculated using a fixed effects model. Where the findings could not be pooled using meta-analysis, results are presented in a narrative form.

Results

Twelve studies including 2713 participants were identified that met the inclusion criteria and were considered to be of adequate methodological quality. The included randomised controlled trials were generally of good quality with a clear description of study design and statistical analysis methods employed. Meta-analysis was conducted on comparisons between very tight glycaemic control (80-150mg/dl), tight glycaemic control (100-200mg/dl) and conventional glycaemic control (160-250mg/dl).

For all patients (both diabetic and/or nondiabetic) undergoing cardiac surgery, very tight glycaemic control as compared to conventional glycaemic control significantly reduced all-cause mortality (odds ratio [OR] 0.59, 95% confidence interval [CI] of 0.37 to 0.96), length of stay in hospital (mean difference [MD] -0.21,95% CI of -0.28 to -0.14); and tight glycaemic control compared to conventional glycaemic control significantly reduced all-cause mortality (OR 0.25, 95% CI of 0.09 to 0.68), length of stay in intensive care units (MD -0.65, 95% CI of -0.68 to -0.62), length of stay in hospital (MD -2.70, 95% CI of -2.77 to 2.63), atrial fibrillation (OR 0.42, 95% CI 0.26 to 0.66) and renal failure (OR 0.09, 95% CI 0.02 to 0.51). In diabetic patients undergoing cardiac surgery, very tight glycaemic control in comparison with conventional glycaemic control showed significant reduction in length of stay in hospital (MD -0.21, 95% CI -0.28 to -0.14), and tight glycaemic control compared to conventional

glycaemic control showed significant reduction in length of stay in hospital (MD -2.71, 95% CI -2.78 to -2.63), length of stay in ICU (MD -0.65, 95% CI -0.68 to -0.62) and atrial fibrillation (OR 0.36, 95% CI 0.22 to 0.59).

Conclusions

The findings of this review indicate that very tight and/or tight glycaemic control compared to conventional glycaemic control during the periopertive period in patients undergoing cardiac surgery may have some positive effects in reducing mortality and morbidity following surgery.

Keywords

Tight glycaemic control, strict glycaemic control, aggressive glycaemic control, cardiac surgery, cardiovascular surgery, insulin therapy, intensive insulin therapy, mortality, morbidity, deep sternal infection, atrial fibrillation, mechanical ventilation, epicardial pacing.

Table 1: Summary of findings

Very tight glycaemic control versus conventional glycaemic control in all patients (diabetic and/or nondiabetic patients) undergoing cardiac surgery

Patient or population: All patients (Diabetic and/or nondiabetic patients) undergoing cardiac surgery
Settings: Inpatient
Intervention: Very tight glycaemic control(80-150mg/dl)
Comparison: Conventional glycaemic control(160-250mg/dl)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Conventional glycaemic control**	Corresponding risk **Very tight glycaemic control**				
All-cause mortality	**52 per 1000**	**32 per 1000** (20 to 50)	**OR 0.59** (0.37 to 0.96)	1729 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	
Length of stay in hospital(in days)	The mean length of stay in hospital (in days) in the control groups ranged from **3-17 days**	The mean length of stay in hospital (in days) in the intervention groups was **0.21 days lower** (0.28 to 0.14 lower)		861 (5 studies)	⊕⊕⊖⊖ **low**[3,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as I2 is 38% and heterogeneity is present.
[2] Downgraded as confidence intervals are imprecise and sample size is not large enough.
[3] Downgraded as wide variance of point estimate.
[4] Downgraded as small sample size.

Tight glycaemic control versus conventional glycaemic control in all patients (diabetic and/or nondiabetic patients) undergoing cardiac surgery

Patient or population: All patients (diabetic and/or nondiabetic patients) undergoing cardiac surgery
Settings: Inpatient
Intervention: Tight glycaemic control (100-200mg/dl)
Comparison: Conventional glycaemic control (160-250mg/dl)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Conventional glycaemic control**	Corresponding risk **Tight glycaemic control**				
All cause mortality	**72 per 1000**	**19 per 1000** (7 to 50)	**OR 0.25** (0.09 to 0.68)	529 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
Length of stay in hospital(in days)	The mean length of stay in hospital (in days) in the control groups ranged from **9-10 days**	The mean length of stay in hospital (in days) in the intervention groups was **2.7days lower** (2.77 to 2.63 lower)		553 (3 studies)	⊕⊕⊖⊖ **low**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as wide confidence intervals and small sample size
[2] Downgraded two levels as I2 is 87% indicates substantial to considerable heterogeneity

Very tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

Patient or population: Diabetic patients undergoing cardiac surgery
Settings: Inpatient
Intervention: Very tight glycaemic control(80-150mg/dl)
Comparison: Conventional glycaemic control(160-250mg/dl)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional glycaemic control	**Very tight glycaemic control**				
Length of stay in hospital (in days)	The mean length of stay in hospital (in days) in the control groups ranged from **3-11 days**	The mean length of stay in hospital (in days) in the intervention groups was **0.21 days lower** (0.28 to 0.14 lower)		182 (2 studies)	⊕⊕⊖⊖ **low**[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded as small sample size.

Tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

Patient or population: Diabetic patients undergoing cardiac surgery
Settings: Inpatients
Intervention: Tight glycaemic control (100-200mg/dl)
Comparison: Conventional glycaemic control (160-250mg/dl)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Conventional glycaemic control**	Corresponding risk **Tight glycaemic control**				
All-cause mortality	See comment[1]	See comment[1]	Not estimable	341 (2 studies)	See comment	
Length of stay in hospital (in days)	The mean length of stay in hospital (in days) in the control groups ranged from **9-10 days**	The mean length of stay in hospital (in days) in the intervention groups was **2.71 days lower** (2.78 to 2.63 lower)		341 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One study reported no event whereas another study was statistically significant.
[2] Small sample size.

Chapter 1: Introduction

1.1 Context of the review

Historically, diabetes mellitus (DM) has been associated with poor clinical outcomes after cardiac surgery, including a high incidence of morbidity (wound infections, ischemic events, cardiac arrhythmias, cardiac pacing, length of stay in the intensive care unit [ICU], neurological and renal complications) and mortality.[1-5] Over the last decade, the incidence of DM has increased markedly in developed countries. Knowledge of the patient's diabetic status preoperatively has led to advances in perioperative clinical management, including active and continuous blood glucose control (BGC) resulting in improved clinical outcomes.[6]

Nevertheless, imbalances in glucose metabolism after surgery are not specific to patients with DM.[7,8] It has been reported that up to 90% of patients without DM also have problems with their blood glucose homeostasis as a result of various surgical stresses.[7,8] In such patients, the disturbances in blood glucose homeostasis have been attributed to insulin resistance and/or a failure of pancreatic-cell function caused by systemic inflammatory response syndrome after cardiopulmonary bypass (CPB) and its effects on systemic temperature.[9-11]

1.1.1 Pathophysiology of hyperglycaemia

Hyperglycaemia is a well-documented and common response to critical illness and metabolic stress after cardiac surgery.[12,13] Stress-induced release of counter regulatory hormones such as cortisol, glucagon, epinephrine and growth hormone leads to upregulation in hepatic gluconeogenesis and glycogenolysis despite hyperinsulinaemia and compromised insulin-regulated peripheral glucose uptake.[14-17] Interestingly, total body glucose uptake is increased but occurs primarily in insulin-independent tissues such as brain cells and red blood cells.[17] Glucose uptake and glycogen synthesis in skeletal muscle are decreased, primarily due to a defect in the glucose transporter-4 (GLUT4).[18] Historically, hyperglycaemia in critical illness is considered a beneficial adaptation intended to supply energy to vital organs. However, evidence refutes this notion, proving that hyperglycaemia is an independent risk factor for morbidity and mortality in the perioperative period.[1,19] Although the adaptive rationale for the hyperglycaemic response is not well understood, acute hyperglycaemia has many deleterious effects, including decreased vasodilatation, impaired reactive endothelial nitric oxide generation, decreased complement function, increased expression of leukocyte and endothelial adhesion molecules, increased cytokine levels, and impaired neutrophil chemotaxis and phagocytosis, leading to increased inflammation, vulnerability to infection, and multiorgan system dysfunction.[32] Intensive insulin therapy (IIT) ameliorates some of the injurious effects of hyperglycaemia through the reduction of endothelial activation via decreasing circulating levels of

intercellular adhesion molecule (ICAM-1) and E-selectin,[21] protecting hepatocyte mitochondrial ultrastructure,[22] stimulating peripheral glucose uptake by increasing transcription of GLUT-4 and hexokinase,[23] normalizing C-peptide and circulating adiponectin levels,[24] and improving the serum lipid profile by increasing low-density lipoprotein and high-density lipoprotein levels while decreasing serum triglycerides.[23]

Patients with hyperglycaemia also have high circulating levels of proinflammatory cytokines, which in turn can lead to organ injury. Most prominent among these cytokines is tumour necrosis factor-α, which is well documented to cause both lung and renal injury.[25] Esposito et al. demonstrated increased tumour necrosis factor-α, interleukin-1β and interleukin-8 plasma levels during acute hyperglycaemia, with a reduction in these inflammatory cytokines after insulin administration.[26] The relationship between inflammatory cytokines and glucose metabolisms complex, in fact, hyperglycaemia itself, could be caused by cytokines via induction of peripheral insulin resistance. This association is witnessed clinically as patients with severe sepsis often requiring high doses of intravenous insulin to maintain normoglycemia.[27]

1.1.2 Perioperative effects of hyperglycaemia

Hyperglycaemia has been identified as a risk factor for perioperative morbidity and mortality. In 2001, Van den Berghe et al. published the first Leuven study, a randomized controlled trial (RCT) of more than 1500 surgical ICU patients in which IIT (target blood glucose [BG], 80–110 mg/dL) reduced in-hospital mortality by 34% when compared to standard therapy (target BG, 180–200 mg/dL) and significantly decreased morbidity, including bloodstream infections, acute renal failure, red-cell transfusions and critical-illness polyneuropathy.[28] Other studies have shown that tight glycaemic control during cardiac surgery is associated with decreased infection rates and improved survival,[29,30] that postoperative glycaemic control in cadaveric renal transplantation decreases allograft rejection,[31] and that intensive insulin improves outcomes in cases of acute neurologic injury[32,33]and acute myocardial infarction.[34]

However, more recently, there has been considerable controversy over the safety and efficacy of IIT. The second Leuven study showed that medical ICU patients may not benefit from IIT in the same way as their surgical counterparts,[35] and two studies were terminated by data safety monitoring boards due to the high incidence of severe hypoglycaemic events (BG ≤ 40 mg/dL) and other serious adverse events.[36,37] Intraoperative IIT during cardiac surgery may increase the incidence of death and stroke.[38] Furthermore, the use of insulin, in general, is not without its risks; along with anticoagulants, opiates, potassium chloride, and hypertonic saline, insulin is considered a “high-alert medication”, one that has the highest risk of causing injury when misused.[39]

1.1.3 Perioperative effects of hypoglycaemia

Hypoglycaemia can also be detrimental because the brain is an obligate glucose metaboliser. Severe hypoglycaemia causes neuronal necrosis via increased concentrations of excitatory amino acids, with a predilection for the neurons of the superficial layers of the cortex and the dentate gyrus of the hippocampus; however, the cerebellum and brainstem are spared injury.[40] Low blood glucose (BG) levels also lead to increased secretion of glucagon, epinephrine, growth hormones and cortisol. In diabetic patients, hypoglycaemia is associated with neurogenic and neuroglycopenic symptoms including seizure, coma or even death.[42] A nested case-control study identified seizures and comas after severe, prolonged hypoglycaemia in ICU patients; however, little is known about the effects of short-term accidental hypoglycaemia in this population.[42]

Observational studies have documented that hyperglycaemia after cardiothoracic surgical procedures is associated with higher rates (approximately two fold) of wound infection.[43,44] Interventions to reduce hyperglycaemia in this setting by IV insulin therapy have been shown to decrease infection rates[2,5,45] and cardiac-related mortality,[46] in comparison with historical control subjects.

Intensive insulin therapy targeting arterial glucose levels of 80–110 mg/dl (4.4–6.1 mmol/l) in a surgical ICU patient population resulted in significant decrease in morbidity and mortality.[28] However, implementation of the identical protocol in1200 medical ICU patients by the same investigators in the same institution diminished morbidity but failed to reduce mortality. A sixfold increase in severe hypoglycaemic events (BG < 40 mg/dl [2.2 mmol/l]) was observed in the intensively treated group (18.7 vs. 3.1%), and hypoglycaemia was identified as an independent risk factor for mortality.[35]

One of the largest studies to date, Normoglycemia in Intensive Care Evaluation – —Survival Using Glucose Algorithm Regulation (NICE-SUGAR), a multicentre, multinational RCT, tested the effects of tight glycaemic control on outcomes among 6104 critically ill participants, the majority of whom (>95%) required mechanical ventilation.[47] The 90-day mortality was significantly higher in the intensively treated versus the conventionally treated group (78 more deaths; 27.5 vs. 24.9%; P=0.02) in both surgical and medical patients. Mortality from cardiovascular causes was more common in the intensively treated group (76 more deaths; 41.6 vs. 35.8%; P=0.02). Severe hypoglycaemia was also more common in the intensively treated group (6.8 vs. 0.5%; P<0.001).[48]

A recent meta-analysis of RCTs reported comparisons between IIT with glycaemic targets of 72–126 mg/dl (4.0–7.0 mmol/l) (commonly, 80 to 110 mg/dl [4.4–6.1 mmol/l]) and less intensive therapy with targets of <150 to 220 mg/dl (<8.3–12.2 mmol/l) (commonly, 180 to 200 mg/dl [10.0–11.1 mmol/l]). Among the 8432 critically ill patients, there was no significant difference in mortality between intensive therapy and control groups (21.6 vs. 23.3%, respectively).[49] A decrease in septicaemia and a fivefold increase in hypoglycaemia (13.7 vs. 2.5%) were observed. In a second meta-analysis[48] including 13,567 critically ill patients, a favourable effect of intensive therapy on mortality was noted only in surgical ICU patients (relative risk, 0.63; CI, 0.44 to 0.91). There was a sixfold increase in the rate of occurrence of hypoglycaemia with use of intensive therapy in all ICU patients.[50]

1.1.4 Definition of glucose abnormalities and glucose monitoring strategies

Hyperglycaemia is defined as any BG value >140 mg/dl (>7.8 mmol/l). Levels that are significantly and persistently above this may necessitate treatment in hospitalised patients. In patients without a previous diagnosis of diabetes, elevated BG concentrations may be due to stress hyperglycaemia, a condition that can be established by a review of prior medical records or measurement of A1C. A1C values of >6.5–7.0% suggest that diabetes preceded hospitalisation.[51]

Hypoglycaemia is defined as any BG level <70 mg/dl (<3.9 mmol/l).[52] This is the standard definition in outpatients and correlates with the initial threshold for the release of counter regulatory hormones.[53] Severe hypoglycaemia in hospitalised patients has been defined by many clinicians as <40 mg/dl (<2.2 mmol/l), although this value is lower than the approximate 50 mg/dl (2.8 mmol/l) level at which cognitive impairment begins in normal individuals.[54] As with usual hyperglycaemia, hypoglycaemia among inpatients is also associated with adverse short-term and long-term outcomes. Early recognition and treatment of mild to moderate hypoglycaemia (40 and 69 mg/dl [2.2 and 3.8 mmol/l], respectively) can prevent deterioration to a more severe episode with potential adverse sequelae.[55,56]

For most inpatients who are eating usual meals, bedside BG monitoring with use of point-of-care (POC) glucose metres is performed before meals and at bedtime. It is important to avoid routine use of correction insulin at bedtime as it can increase the risk of hypoglycaemia during sleep. For inpatients who are receiving continuous enteral or parenteral nutrition, glucose monitoring is optimally performed every four to six hours. For patients who are receiving cycled enteral nutrition or parenteral nutrition, the schedule for glucose monitoring can be individualised but should be frequent enough to detect hyperglycaemia during feedings and the risk of hypoglycaemia when feedings are interrupted.[57,58] More frequent BG testing, ranging from every 30 min to every two hours, is required for patients receiving intravenous (IV) insulin infusions.[59] A variety of measurement techniques are currently in use for measuring blood glucose during the perioperative period, and it is not clear if they are equivalent to each other. For instance, the Leuven studies measured BG using whole undiluted blood and a blood gas analyzer,[35] whereas most ICUs rely on POC glucometres that use capillary blood.[93] Recently, Desachy et al. examined the accuracy of POC glucose strip assays for capillary and whole blood, as compared to laboratory results.[94] Point of care values were considered significantly different from the laboratory value when they disagreed by more than 20%; significant differences were found in 15% of capillary blood samples and 7% of whole blood samples. In a systematic review, Higgs et al. discussed different insulin therapy administration algorithms on glycaemic control in adult patients admitted to critical care environments following cardiac surgery. The methods of glycaemic control investigated were as follows: bolus administration of subcutaneous insulin, personnel directed continuous insulin infusion (CII), specifically nurse directed and endocrinologist directed CII algorithm, paper nomogram directed CII algorithm and computer calculator directed CII algorithm. The evidence obtained from this systematic review demonstrated

that computer calculator directed CII was an effective method for achieving and maintaining glycaemic control in the adult postoperative cardiac surgery population. However, given the limited availability of the computer calculator based algorithm, the implementation of a paper nomogram directed CII algorithm would be justified.[95]

1.1.5 Why a systematic review is needed

A search was done in the JBI Database of Systematic Reviews and Implementation Reports and the Cochrane database as well as PubMed to determine if there were any recent systematic reviews that had been conducted on this topic. A systematic review and meta-analysis was performed by Haga et al. in 2011, evaluating the effects of tight glycaemic control during and after cardiac surgery on patient mortality and morbidity. The meta-analysis searched only for published literature; there was no critical appraisal and there were no subgroup analyses for diabetic patients. Important outcomes also were not included (such as acute renal failure, stroke, deep sternal infection and re-infarction). As such, an update of this Haga et al. review is due.[60] We therefore believed that it was timely to conduct a systematic review following the guidance from JBI on this topic. The aim of this systematic review was to synthesize the best available evidence to determine whether tight glycaemic control is effective in patients undergoing cardiac surgery to improve their intraoperative and postoperative outcomes (mortality and morbidity). This review is based on an *a priori* protocol which has been published.[75]

1.2 Methodological basis of this review

1.2.1 Evidence-based healthcare and emergence of systematic reviews

The value of basing health policy and health care practices on the best available international evidence ("evidence-based health care") and on translating knowledge or evidence into action ("translation science" or "translational research") is a priority in all health sectors in most countries.[99] Evidence-based healthcare is a process that identifies policy or clinical questions and addresses these questions through the generation of knowledge and evidence in order to effectively and appropriately deliver healthcare in ways that are effective, feasible and meaningful to specific populations, cultures and settings.[99]

Evidence-based practice can be demonstrated as clinical decision making that considers the best available evidence, the context in which the care is delivered, client preference, and the professional judgment of the health professional. The JBI model of evidence-based healthcare incorporates the four major components of the evidence-based healthcare process:[99]

i. Healthcare evidence generation

ii. Evidence synthesis
iii. Evidence/knowledge transfer
iv. Evidence utilization.

Evidence-based healthcare is described as a cyclical process that identifies questions, concerns or issues based on global healthcare needs of clinicians or patients/consumers, and addresses these questions by generating knowledge and evidence in order that these needs are effectively and appropriately met in ways that are feasible, and meaningful to specific populations, cultures, and settings. This evidence is then appraised, synthesised and transferred to service delivery settings and health professionals who then utilise the evidence and evaluate its impact on health outcomes, health systems and professional practice.

The term “evidence” is used in the model to mean substantiation or confirmation that is needed in order to believe that something is true.[100] Health professionals seek evidence to substantiate the value and effectiveness of a very wide range of interventions, conditions and issues, therefore the type of evidence needed depends on the nature of the activity and its purpose. This unique approach is encompassed in the JBI Model of Evidence-based Health Care which provides a framework for the cyclical process to generate, synthesize and transfer the best available evidence and for the utilisation of resources for health professionals to improve global health.

1.2.2 Difference between systematic review and literature review

In evidence-based practice, systematic reviews are considered one of the highest levels of information available. Systematic reviews encompass a high level overview of primary research on a focused question that identifies, selects, synthesises and appraises all high quality research evidence relevant to that question. In comparison, non-systematic literature reviews qualitatively summarise evidence on a topic using informal or subjective methods to collect and interpret studies. Systematic reviews answer a focused clinical question eliminating bias whereas literature reviews provide a summary or overview of a topic. In a systematic review, there is a clearly defined and answerable clinical question whereas literature reviews can be of a general topic or a specific question. The components of systematic reviews are: pre-specified eligibility criteria, systematic search strategy, assessment of the validity of findings, interpretation and presentation of results and a reference list. It takes months to years for a systematic review to be completed but a literature review may be completed within weeks. Thorough knowledge of the topic, conducting searches of all relevant databases and statistical resource analyses (for meta-analyses) are required to perform a systematic review. Literature reviews only require an understanding of the topic and do not normally encompass a systematic search. Systematic reviews connect practising clinicians to high quality evidence and

support evidence-based practice whereas literature reviews provide a potentially biased summary of literature on a topic.[101]

1.2.3 The systematic review process and steps

The steps for conducting a systematic review are as follows:

Review question and inclusion criteria: Systematic reviews seeks to generate answers to specific questions, rather than present general summaries of the literature on a topic of interest.[102,103] Rather than creating new knowledge, a systematic review appraises, synthesises and transfers existing knowledge, and therefore relevant research must already exist on the topic.[102,104,105]

A review protocol is developed and published prior to the commencement of the systematic review. It details the eligibility of studies to be included in the review (based on the PICO [population, intervention, comparison and outcome] elements of the review question) and the methods to be used to conduct the review. The eligibility criteria outlined in the review protocol ensure that studies considered for inclusion are selected based on their research method, as well as on the PICO elements of the study, and not solely on the studies' findings.[104,105]

Searching for studies: Searching can be a complex task. The aim is to identify as many studies on the topic of interest as is feasible, and for this to be undertaken, a comprehensive search strategy must be developed and presented to readers.[104,105,107] A search strategy that escalates in complexity is common, starting with an initial search of major databases, such as MEDLINE (accessed through PubMed) and the Cumulative Index to Nursing and Allied Health (CINAHL), using keywords derived from the review question. This preliminary search helps to identify optimal search terms, including further keywords and subject headings or indexing terms, which are then used when searching all relevant databases. Finally, a manual search is conducted of the reference lists of all retrieved papers to identify any studies missed during the database searches. The search should also target unpublished studies to help minimise the risk of publication bias. [102,104,105]

Study selection and critical appraisal: The PICO elements defined in the inclusion criteria for the basis for the selection of studies for the systematic review. The inclusion criteria place the review question in a practical context and act as a clear guide for the review team as they determine which studies should be included.[104,105] This step is referred to as study selection.[103,104] Once it is determined which studies should be included, their methodological quality must be assessed during the critical appraisal step. To aid the transparency and reproducibility of this process in the systematic review, standardised instruments (checklists, scales) are commonly asked by the reviewers about the research they are appraising.

Data extraction and synthesis: As soon as the research quality has been established, relevant data aligned to the predetermined outcomes of the review must be extracted for the all-important synthesis of the findings. Data synthesised by systematic reviews are the results extracted from the individual research studies; as with critical appraisal, data extraction is often facilitated by the use of a tool or instrument that ensures that the most relevant and accurate data are collected and recorded.[104,105] Generic extraction tools for both quantitative and qualitative data are readily available.[107]

A meta-analysis *(*a method to statistically combine data extracted from the studies) may be included in a systematic review as a practical way of evaluating many studies. Meta-analysis should ideally be undertaken only when studies are similar enough; studies should sample from similar populations, have similar objectives and aims, administer the intervention of interest in a similar fashion, and (most important) measure the same outcomes.[104,105]

Interpretation of findings and recommendations for practice: The conclusions of the systematic review, along with recommendations for clinical practice and implications for future research, should be based on its findings. When considering the recommendations of a systematic review, the following need to make sure: clear and accurate summary of findings has been provided; specific directives for further research have been proposed, and the recommendations, both for practice and future research, need to be supported by the data presented.[104]

Reviewers must consider the quality of the studies when arriving at recommendations based on the results of those studies. For example, if the best available evidence was of low quality or only observational studies were available to answer the question of effectiveness, results based on this evidence must be interpreted with caution.[104]

1.3 Review questions/objectives

Broadly, the overall objective of this review was to identify the effectiveness of tight glycaemic control on mortality and morbidity in patients undergoing cardiac surgery.

Specific objectives were to identify:

- The effectiveness of tight glycaemic control on mortality and morbidity in adult (adult and aged) patients during the intraoperative and postoperative period after cardiac surgery in hospital.
- The effectiveness of tight glycaemic control on mortality and morbidity in diabetic patients during the intraoperative and postoperative period after cardiac surgery in hospital.

1.4 Inclusion criteria

1.4.1 Types of participants

This review considered studies that included adult patients over the age of 18 years, who had undergone any type of cardiac surgery with glycaemic control during and/or after the surgery (up to 30 days or their full length of stay in hospital following surgery). Both diabetic (type 1 and type 2 regardless of past glucose control treatment modality) and non-diabetic patients were considered for inclusion. Studies employing the glucose insulin potassium (GIK) protocol (originally not designed to achieve tight glycaemic control) were included if they satisfied the inclusion criteria. Patients undergoing surgeries other than cardiac surgeries were not included in this review.

1.4.2 Types of interventions

This review considered studies that evaluated the effectiveness of tight glycaemic control (as per study definition) on patients receiving glucose control in intraoperative and/or postoperative following cardiac surgery.

1.4.3 Types of comparators

This review considered comparators such as the effectiveness of usual care, normal or moderate glycaemic control on patients receiving glucose control in the intraoperative and/or postoperative period of cardiac surgery.

1.4.4 Types of studies

This review considered any randomized and pseudo-randomized controlled trial for inclusion.

1.4.5 Types of outcomes

This review considered studies that included the following outcome measures: (1) Mortality (within the first 30 days after surgery or mortality in intensive care unit/coronary care unit (ICU/CCU), (2) Length of stay in ICU, (3) Time on mechanical ventilation, (4) Atrial fibrillation (AF), (5) Need for epicardial pacing, (6) Deep sternal infection, (7) Stroke, (8) Acute renal failure (9) Re-infarction, and (10) Length of stay in hospital.

The final outcome (length of stay in hospital) was added in following study selection, as many studies had reported this outcome and it was viewed as important. This is a deviation from the original protocol.[75]

Chapter 2: Review methods

2.1 Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was utilised in this review. An initial limited search of PubMed and CINAHL was undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles were searched for additional studies. The search was limited to English publications. Studies published from 1990 until March 2014 only were considered for inclusion in this review as recent advancements in cardiac surgical techniques were only introduced from 1990.

The databases searched included:
CINAHL

Cochrane Library including Central

Embase

Clinical Trials.gov

ProQuest

PubMed

Science Direct

Web of Science

The search for unpublished studies included:

Google Scholar

ProQuest Dissertations and Theses

Initial keywords used:
Tight glycaemic control, strict glycaemic control, aggressive glycaemic control, cardiac surgery, cardiovascular surgery, insulin therapy, intensive insulin therapy, mortality, morbidity, deep sternal infection, atrial fibrillation, mechanical ventilation, epicardial pacing.
Informed by the findings from the initial exploratory searches in the range of databases to be covered, further key words were identified and a detailed search strategy developed and implemented for each database. The search strategies used to search leading databases is listed in Appendix I.

Using the search strategy, records were identified from the above mentioned databases. The results

obtained from each database search were electronically imported into a citation manager (EndNote), where the results from all the databases were pooled into a single library.

2.2 Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using the standardised critical appraisal instrument from JBI-MAStARI (Appendix ll). Any disagreements that arose between the reviewers were resolved through discussion, and a third reviewer was not required.

2.3 Data collection

Data was extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix lll). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Where data was missing or unclear, authors were contacted. The primary authors of two studies[63,64] included in this review were contacted for further information and clarification from one of the authors[64] was received.

2.4 Data synthesis

An analysis was conducted on all main outcomes where possible. The available data from RCTs and one pseudo-RCTs study was pooled in statistical meta-analysis using RevMan V 5.3 software (Cochrane).[76] A subgroup analysis was conducted where appropriate and included groups of both diabetic and non-diabetic patients, only diabetic patients, those on very tight glycaemic control and those on tight glycaemic control. Heterogeneity was assessed statistically using Cochrane's Q, I^2 and through visual inspection of the meta-analysis output on a forest plot. Decisions regarding the model and approach to meta-analysis were based on guidance from Tufanaru et al.[77] For dichotomous data, effect sizes were expressed as odd ratios (ORs) and their respective 95% confidence interval (CI) was calculated using the Mantel-Haenszel method, as the OR was the preferred effect size for the computation phase of meta-analysis of binary data regardless of the study design of the studies.[77] For continuous data, effect sizes were expressed as mean differences with their 95% CI. Where statistical pooling was not possible the findings were presented in a narrative form.

2.5 Findings of the review

The meta-analysis was conducted to identify the variation in outcomes within different studies which were looking at the same outcomes using similar interventions among similar population group. There was no inherent variation found between the included studies.

Based on the intervention (glycaemic control), we categorised the population into "very tight glycaemic control group" and "tight glycaemic control group". We measured outcomes in "both diabetic and/or nondiabetic" patients in one group and only "diabetic" patients in another group. Meta-analysis was performed where data could be pulled out. Meta-analysis could not be conducted where there was no event recorded in a study or there was only one study that measured the outcome or where different studies measured outcomes in different ways.

2.6 Methods of analysis

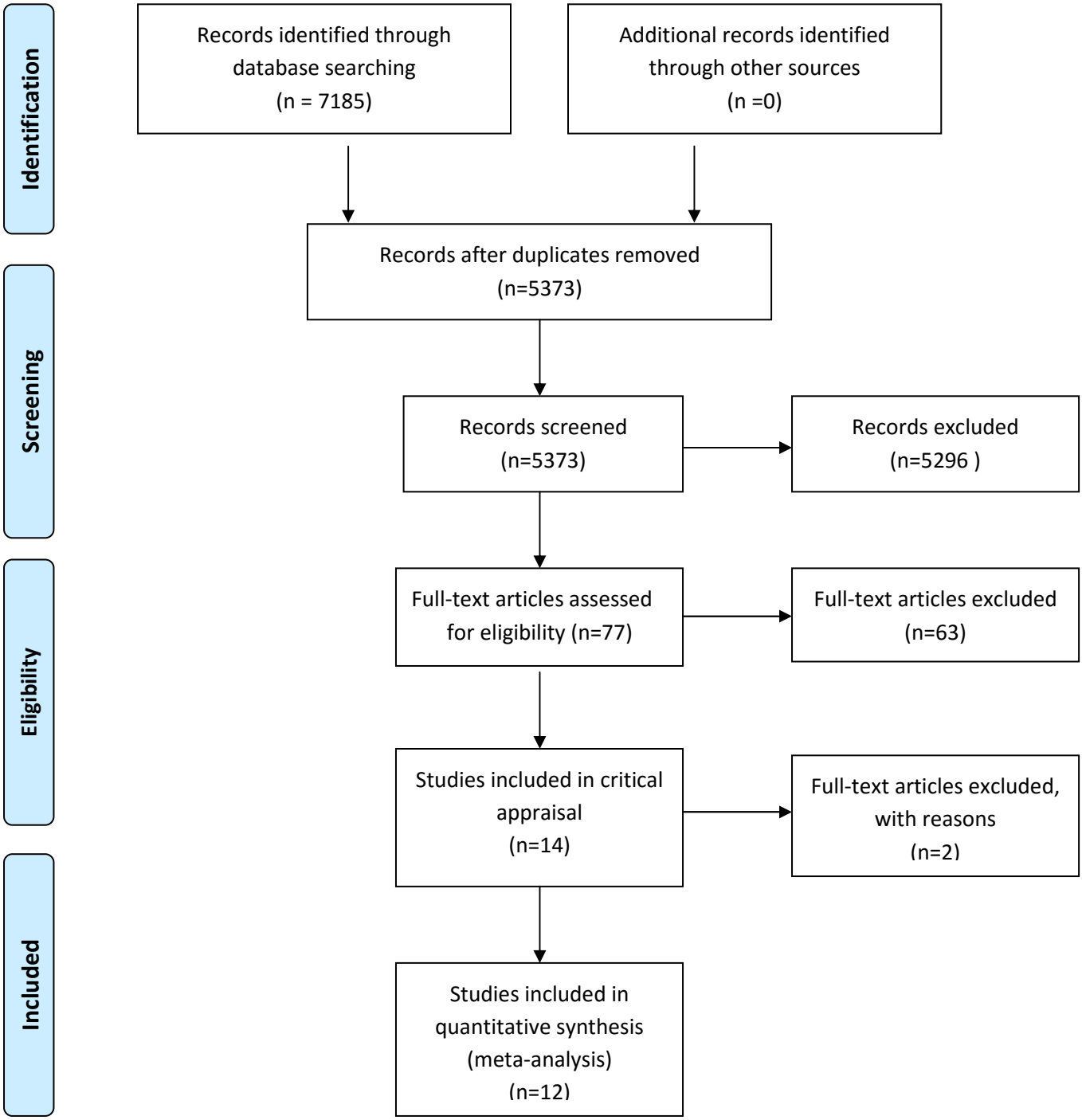
Meta-analysis decisions were informed by the work of Tufanaru et al..[77] As such, effect sizes were reported as ORs for dichotomous data and as weighted mean differences for continuous data. A fixed-effects model was preferred for all analyses as there were five studies or less in all the meta-analyses. For dichotomous data, the Mantel-Haenszel method was chosen as this model has been shown to have superior statistical properties where there are few events, as was the case in these analyses.[92] A fixed-effects inverse-variance method available in RevMan V5.3 was used for continuous data.

Chapter 3: Results

3.1 Description of the search and selection process

A total of 7185 potentially relevant citations were identified using the search strategies developed for each database (Appendix I). After removal of 1812 duplicates, 5373 articles remained for title and abstract screening.

The screening process involved viewing each article title and/or abstract against the review inclusion criteria and excluding those records that clearly did not meet the inclusion criteria. A total of 5296 records were excluded on screening, leaving 77 for full text review. After full text examination, 14 of these were included in critical appraisal. Of these, two studies were excluded with reasons. One of these[73] was excluded as it was a retrospective study. Another one[74] focussed on a different population group (explained in Appendix IV). Finally, following critical appraisal, 12 RCTs[61-72] with data on the outcome of interest were included in the systematic review. Figure 1 outlines an overview of the search and study inclusion process.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 1: Flow diagram of study selection process

3.2 Description of included studies

The included studies were conducted in different parts of the world and published in between 2006 and 2014. Five studies[62-65,70,71] were conducted in USA, one in Brazil,[63] one in Greece,[66] one in the Netherlands,[67] one in Turkey,[69] one in Egypt,[61] one in Iran[62] and one in Thailand.[72]

Among the 12 studies, four[61,69,70,71] of them included diabetic patients, two[62,67] non-diabetic patients and six[63-66,68,72] both diabetic and nondiabetic patients or only nondiabetic patients. One[65] of the studies reported individual data for diabetic and non-diabetic patients.

The studies described their comparisons as very strict/very tight glycaemic control or tight/moderate/ semi tight glycaemic control compared with conventional/liberal/less tight glycaemic control. Eight studies[61,63-65,67,68,71,72] compared very tight glycaemic control with liberal glycaemic control among cardiac surgical patients. All of those measured both diabetic and/or nondiabetic patients. However, three of those[61,65,71] measured only diabetic patients. Four other studies[62,66,69,70] compared tight glycaemic control with liberal glycaemic control in patients undergoing cardiac surgery. All of those measured both diabetic and/or nondiabetic patients. Two of those[69,70] measured only diabetic patients.

It was noted that the studies included in this review measured and defined tight glycaemic control in a wide range of 80-200 mg/dl across the studies. As such, this review is further categorised into "very tight glycaemic control" and "tight glycaemic control." The studies included in the "very tight glycaemic control" group aimed to control their blood glucose level at 80-150 mg/dl and in the "tight glycaemic control" group aimed to control their blood glucose level at 100-200 mg/dl. There is an overlap of glycaemic range in between these two groups which is due to variation of the upper and lower limit of blood glucose measurement range in different studies. The conventional glucose control ranged from 160 to 250 mg/dl in all included studies.

Asida et al.[61] conducted their study among 100 diabetic patients undergoing cardiac surgery in a teaching university hospital in Qena, Egypt. Patients were divided equally into group I (control group) where there was no tight glycaemic control and group II (study group) in which tight glycaemic control was done. Patients in the study group received intraoperatively an infusion of rapidly acting insulin according to a modified protocol to keep blood glucose levels between 80 and 110 mg/dl which continued in the ICU until complete recovery from anaesthesia. Patients in the control group followed the same protocol of insulin infusion only if their perioperative blood glucose level exceeded 180 mg/dl. The objective of the study was to estimate the association between blood glucose control and perioperative outcomes in these patients.

Azarfarin et al.[62] performed their study among nondiabetic patients who underwent elective coronary artery bypass grafting (CABG) surgery. The study was conducted to determine whether control of hyperglycaemia was needed during heart surgery in a teaching hospital in Iran. The patients were randomly divided equally into study and control groups. In the study group, insulin was infused to maintain BG level between 110 mg/dL and 126 mg/dL using a modified insulin therapy protocol, and in the control group the patients were only monitored every 30 minutes. Insulin therapy was limited to the intraoperative period. Of the 120 patients who enrolled in the randomised study, three were lost from the study: one patient in the study group because of excessive intraoperative blood loss, and two patients in the control group because of severe hemodynamic instability, usage of high dose inotropes and intra-aortic balloon pump (IABP). The objective was to study the effect of blood glucose (BG) control with insulin in preventing hyperglycaemia during and after CABG surgery in nondiabetic patients. Blood glucose levels during and up to 48 hours after surgery and early postoperative complications were compared between the study and control groups.

The study by Chan et al.[63] was conducted in a university hospital in Brazil where 109 consecutive diabetic and nondiabetic patients were enrolled during a six-month period. All patients were scheduled for open-heart surgery requiring cardiopulmonary bypass. Thirty-two patients were diagnosed with diabetes mellitus and 66 were diagnosed as nondiabetic. Patients were randomly allocated into two groups. One group consisted of 55 patients and had a target glucose level of 80-130 mg/dl, while the other comprised 54 patients and had a target glucose level of 160-200 mg/dl. These parameters were controlled during surgery and for 36 hours after surgery in the ICU. The objective of this study was to investigate the association between different target levels of glucose and the clinical outcomes of patients undergoing cardiac surgery with cardiopulmonary bypass. Primary outcomes were clinical outcomes, including time of mechanical ventilation, length of stay in the ICU, infection, hypoglycaemia, renal or neurological dysfunction, blood transfusion and length of stay in the hospital. The secondary outcome was a combined end-point (mortality at 30 days, infection or length of stay in the ICU of more than three days).

The study by Desai et al.[64] was conducted in Inova Heart and Vascular Institute, Virginia, USA, and included 189 diabetic and nondiabetic patients who underwent CABG, and compared two glucose control strategies on patient perioperative outcomes. The purpose of this study was to test the hypothesis that a liberal blood glucose strategy (121–180 mg/dL) is not inferior to a strict blood glucose strategy (90–120 mg/dL) for outcomes in patients after first-time isolated coronary artery bypass grafting and is superior for glucose control and target blood glucose management. Outcomes included time to target glucose range, amount of insulin given, number of readings in target range, number of patients with hypoglycaemic events (BG<60 mg/dL and BG<40 mg/dL), perioperative renal failure, deep sternal wound infection, pneumonia, length of stay, atrial fibrillation and operative mortality (death within 30 days).

Among them, 73 patients were diagnosed diabetic. Patients were randomly assigned to receive CII to maintain intraoperative glucose levels between 4.4 (80 mg/dL) and 5.6 mmol/L (100 mg/dL) (n=185) or conventional treatment (n=186). 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). Both groups were treated with CII to maintain normoglycaemia after surgery. The primary outcome variable was a composite of death, sternal wound infections, prolonged pulmonary ventilation, cardiac arrhythmias (new-onset atrial fibrillation, heart block requiring permanent pacemaker or cardiac arrest), stroke and acute renal failure within 30 days after surgery. Secondary outcome measures were length of stay in the ICU and hospital.

Giakoumidakis et al.[66] performed their study on 212 adult cardiac surgery patients (18 years and over) allocated by quasi-experimental design from September 2011 to January 2012 in a tertiary hospital in Athens, Greece. A control group (n = 107) with targeted blood glucose levels 161-200 mg/dl and a therapy group (n = 105) with blood glucose target 120-160 mg/dl were compared. The objective of the study was to investigate the effects of postoperative intensive glycaemic control on patient outcomes. The two groups were compared on their mortality, length of stay, duration of intubation, incidence of severe hypoglycaemia and frequency of postoperative infections.

The study by Hoedemaekers et al.[67] included 20 nondiabetic patients (18 years and older) undergoing elective coronary artery bypass grafting at a teaching hospital in the Netherlands. Patients undergoing off-pump cardiac surgery were excluded. After surgery, patients were randomly assigned to intensive insulin therapy (blood glucose between 80 and 110 mg/dl) or conventional insulin therapy (blood glucose less than 200 mg/dl). The objective of the study was to measure the effect of strict glycaemic control on the local and systemic pro-inflammatory and anti-inflammatory balance in nondiabetic patients undergoing elective CABG with cardiopulmonary bypass. Postoperative time on the ventilator and time in ICU were also measured.

Ingels et al.[68] performed their study as a pre-planned sub-analysis (n = 970) and follow-up of adult cardiac surgery patients who had been included in a large (n = 1548)[28], prospective, randomized controlled trial on the effects of intensive insulin therapy on the outcome of critical illness. The study was conducted in a tertiary hospital in Belgium and included both diabetic and nondiabetic patients. In the original study, all mechanically ventilated, adult patients admitted to their surgical ICU had been eligible for inclusion. After stratification based on the reason of ICU admission, patients were randomised to either strict blood glucose control below 6.1 mmol/L (110 mg/dL) with intensive insulin therapy, or to the conventional approach which only recommended insulin therapy when blood glucose levels exceeded 12 mmol/L (220 mg/dL). In this study the data was reported from the subgroup of 970 patients admitted after cardiac surgery, either electively or after secondary complications. Primary endpoint for the current study was four-year-all-cause mortality and the number of post-hospital discharge deaths. Secondary endpoints were two and three years survival,

hospital re-admission during the four years following ICU admission, level of activity and medical care requirements assessed by the Karnofsky Performance Status Scale at four years survival and the perceived quality of life assessed by a validated Dutch translation of the Nottingham Health Profile (NHP) at four years. In-hospital mortality and time on mechanical ventilation were also outcome measures.

The study by Kirdemir et al.[69] was performed in two different tertiary centres in Turkey between April 2005 and February 2007. Two hundred diabetic patients were included in this prospective randomised study. Patients were divided into two groups according to their insulin therapy in two different centres. Group 1 included 100 DM patients, and CIIs were administered. These patients received a CII titrated per protocol in the perioperative period (Portland protocol). The protocol prescribes insulin initiation, infusion and titration rates, and glucose testing frequency requirements to safely maintain a patient's blood glucose between desired target levels. Blood glucose was lowered to 100 to 150 mg/dL. Group 2 also included 100 DM patients, and subcutaneous insulin was injected every four hours in a directed attempt to maintain blood glucose levels below 200 mg/dL. Sliding scale dosage of insulin was titrated to each patient's glycaemic response during the prior four hours. The objective was to compare CII and intermittent subcutaneous insulin therapy for preventing supraventricular tachycardia. Other outcomes were mortality, length of stay in ICU, length of stay in hospital, time on mechanical ventilation, renal failure, stroke, transient ischemic attack (TIA), sternal wound infection, atrial fibrillation, atrial flutter, sinus tachycardia, multifocal atrial tachycardia, cardiopulmonary bypass time, cross-clamp time, distal anastomosis, low cardiac output, Intraaortic balloon pumping, positive ionotropic drug requirement, reoperative surgery, cardiac temponade, bleeding, sternal dehiscence mediastinitis, internal mammary artery, redial artery, sephanous vein anastomosis and postoperative glucose level.

Lazar et al. (2004)[70] conducted their trial among 141 adult diabetic patients undergoing CABG in a tertiary medical centre in Boston, USA. Seventy-two patients were in the study group (GIK) and 69 patients were in the control (no-GIK) group. Patients were randomly assigned to tight glycaemic control (serum glucose, 125 to 200 mg/dL) with GIK) solution or standard therapy (serum glucose <250 mg/dL) using intermittent subcutaneous insulin beginning before anaesthesia and continuing for 12 hours after surgery. The objective was to determine whether tight glycaemic control with a modified GIK solution in diabetic CABG patients would improve perioperative outcomes. Among the perioperative outcomes, 30-day mortality, myocardial infarction, pacing, atrial fibrillation, infections (pneumonia and wound), time on ventilators (hours), maximum weight gain, inotropic score, ICU stay (hours) and postoperative hospital stay (day) were measured.

The study by Lazar et al. *(*2011)[71] included 82 adult diabetic patients undergoing CABG on cardiopulmonary bypass, performed in the same centre as the study above. Eighty-two diabetic patients undergoing CABG were prospectively randomised to aggressive glycaemic control (90-120

mg/dL) or moderate glycaemic control (120-180 mg/dL) using continuous intravenous insulin solutions (100 units regular insulin in 100 mL normal saline) beginning at the induction of anaesthesia and continuing for 18 hours after CABG. Patients were randomly assigned to either a moderate group (42) or an aggressive group (40). This study sought to determine whether aggressive glycaemic control (90-120 mg/dL) would result in more optimal clinical outcomes and less morbidity than moderate glycaemic control (120-180 mg/dL) in diabetic patients undergoing CABG surgery. Primary end points were the incidence of major adverse events (major adverse events: 30 day mortality, myocardial infarction, neurologic events, deep sternal infections and atrial fibrillation), the level of serum glucose, and the incidence of hypoglycaemic events.

Rujirojindakul et al.[72] conducted their study among 199 adult diabetic and nondiabetic patients undergoing CPB in a university hospital in Thailand. A total of 199 adult patients (out of a planned 400) were randomly allocated to intensive or conventional treatment with target glucose levels of 4.4–8.3 mmol/l and < 13.8 mmol/l, respectively. This study aimed to determine the safety and efficacy of intraoperative intensive glycaemic treatment with modified GIK solution by hyperinsulinemic normoglycaemic clamp in cardiopulmonary bypass surgery patients. The primary outcome measure was a clinical infection rate within 30 days postoperatively and cytokine levels, including interleukin (IL)-6 and IL-10. The secondary outcome measures were hypoglycaemia, neurological or renal dysfunction, new atrial fibrillation, heart block requiring pacemaker, duration of mechanical ventilation, length of stay in the ICU and hospital, and mortality. The attending surgeons recorded all outcome measures occurring within 30 days postoperatively. The study was terminated early because of safety concerns (hypoglycaemia).

3.3 Methodological quality

From the search process, 14 studies were critically appraised by two independent reviewers to assess their methodological quality prior to inclusion in this review. No disagreements regarding the critical appraisal process occurred, and both reviewers agreed that two of these studies were not of satisfactory methodological quality and were therefore excluded. One of them was excluded because it focussed on a different population[74] and the other had a study design that did not meet the inclusion criteria[73] (Appendix V). Of the 12 studies[61-72] that reported on mortality and morbidity in patients undergoing cardiac surgery, ten studies[61-65,67,69-72] were randomised controlled trials, one study was[66] was a randomised quasi-experimental trial, and another[68] was a pre-planned sub-analysis and follow-up study of a randomised controlled trial.

The results of the quality assessment using the JBI-MAStARI appraisal tool for randomised and quasi-randomised controlled trials are presented in Table 2.

The included RCTs were generally of good quality with a clear description of study design and

statistical analysis methods employed. All RCTs scored a minimum of five against the ten appraisal questions (Appendix II). However, many of the studies scored “unclear” on questions 2,3 and 5 which assess allocation blinding, allocation concealment and outcomes of withdrawals from the study. For the main outcome of our review (mortality) inadequate blinding of outcome assessors and subjects is not a concern, however it may be a concern for other outcomes.

The scores for critical appraisal of these studies ranged from five to ten (Table 2).

Table 2: Critical appraisal scores of included randomised controlled trials/pseudo-randomised controlled trials

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total
Azarfarin et al. 2011[62]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Asida et al. 2013[61]	Y	U	U	N/A	U	Y	Y	Y	Y	Y	6/9
Chan et al. 2009[63]	Y	U	U	Y	U	Y	Y	Y	Y	Y	7/10
Hoedemaekers et al. 2005[67]	Y	U	Y	N/A	U	Y	Y	Y	Y	Y	7/9
Kirdemir et al. 2008[69]	Y	U	U	N/A	U	Y	Y	Y	Y	Y	6/9
Rujirojindakul et al. 2014[72]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/10
Desai et al. 2012[64]	Y	N	N	Y	N	Y	Y	Y	Y	Y	7/10
Gandhi et al. 2007[65]	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	9/10
Giakoumidakis	N	U	N	N/A	U	Y	Y	Y	Y	Y	5/9

et al. 2013[66]											
Ingels et al. 2006[68]	Y	Y	U	Y	U	Y	Y	Y	Y	Y	8/10
Lazar et al. 2004[70]	Y	U	U	Y	U	Y	Y	Y	Y	Y	7/10
Lazar et al. 2011[71]	Y	U	U	N/A	U	Y	Y	Y	Y	Y	6/9
%	91.66	33.33	33.33	85.71	25.00	100.00	100.00	100.00	100.00	100.00	

Y=Yes; N=No; U=Unclear; N/A=Not applicable

3.4 Meta-analysis of outcomes

3.4.1 Very tight glycaemic control versus conventional glycaemic control in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Eight studies[61,63,64,65,67,68,71,72] compared very tight glycaemic control with liberal glycaemic control. In these studies, measurement of very tight glycaemic control in varied significantly. Upper and lower limit of blood sugar level from all studies included in this group ranged from 80 to 150 mg/dl. The conventional glucose control ranged from 160 to 250 mg/dl in all included studies.

3.4.1.1 All-cause mortality

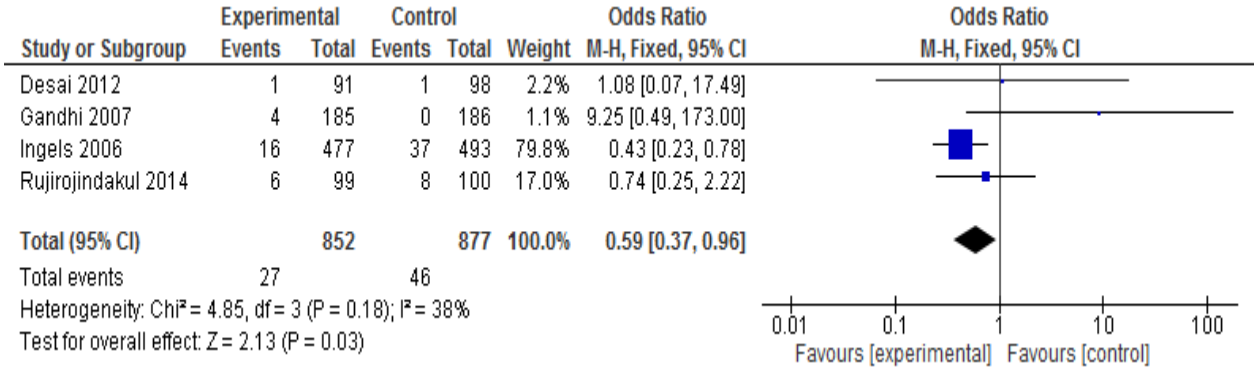


Figure 2: Meta-analysis of all-cause mortality in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery (fixed effect)

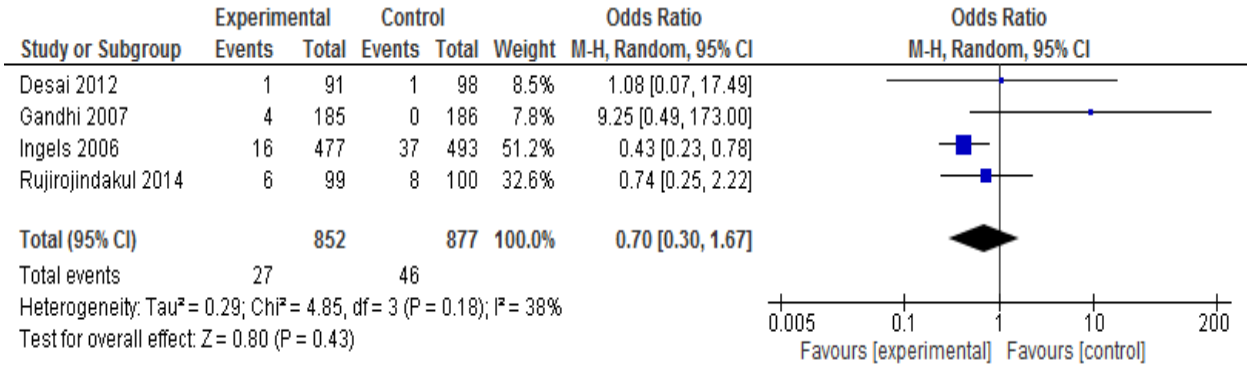


Figure 3: Meta-analysis of all-cause mortality in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery (random effect)

Mortality was evaluated in six trials[63-,65,68,71,72] that included 1916 participants, four of which were included in the meta-analysis. Outcomes that occurred during hospitalisation or within 30 days of surgery (perioperative period) were included.[65] Overall, the meta-analysis was statistically significant and showed that very tight glycaemic control increased perioperative mortality in patients undergoing cardiac surgery compared with liberal glycaemic control, as evidenced by an OR of 0.59 with a 95% CI of 0.37 to 0.96, (P value 0.03). There was no statistically significant heterogeneity (P value 0.18) and I^2 value of 38% indicates that the between-study variation is not important or moderately important (I^2=38%).[92]

Sensitivity analysis:

A sensitivity analysis was conducted to determine whether the model of meta-analysis (fixed) had an impact on the overall summary estimate. Analysis with a random effects model showed that the effect estimate changed from statistically significant to non-significant with this model (OR 0.70, 95% CI 0.30 to 1.67, P value 0.43). As such, the significant result achieved with the fixed effects model should be interpreted with some caution.

<u>Studies not included in meta-analysis:</u>

Lazar et al. (2011)[71] could not be included as there no event was reported in the experimental group (40 participants) nor in the control group (42 participants). Chan 2009[63] reported 6.4% mortality rate in the treated group compared with 5.9% in the control group (P value 1.0). We wrote to the authors that the presented data was percentage fraction and asked if they could provide their data as true frequencies. Unfortunately, this data were not available.

3.4.1.2 Length of stay in hospital

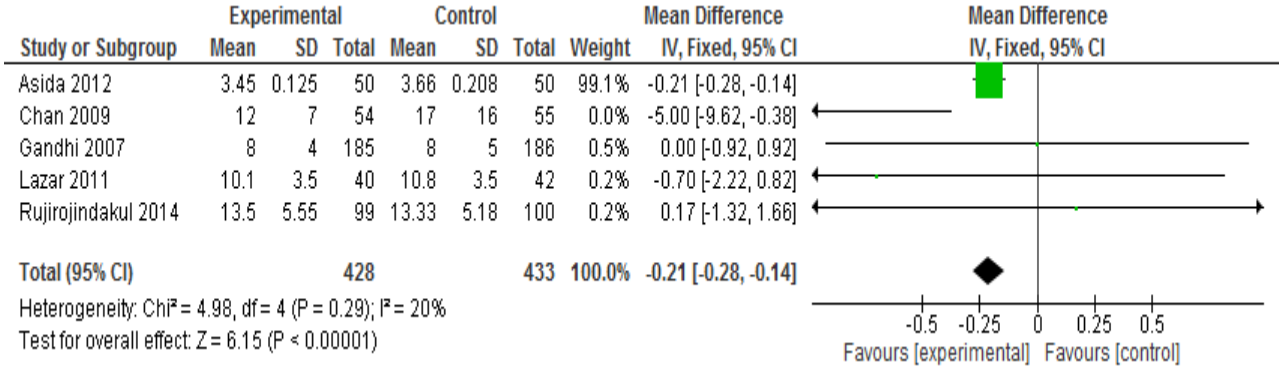


Figure 4: Meta-analysis of length of hospital stay in hospital in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Six studies including 1049 participants evaluated length of stay in hospital after cardiac surgery, five of which were included in the meta-analysis. Time was measured in days in these studies. Overall, the meta-analysis showed that very strict glycaemic control reduced the length of stay in hospital after cardiac surgery by 0.21 days compared with liberal glycaemic control with a 95% CI of -0.28 to -0.14 (P value <0.00001) which was statistically significant. There was no statistically significant heterogeneity (P=0.29) observed, and the I^2 value of 20% indicates that the between-study variation can be considered not important (I^2=20%).[92] Rujirojindakul 2014[72] reported results as median value and estimation of the sample mean and standard deviation was done using the tool provided by Wan et al.[78]

Studies not included in meta-analysis:

Desai 2012[64] could not be included due to non standard reporting of results. The study showed that three patients out of 91 with very strict glycaemic control stayed more than 10 days in hospital compared with two patients out of 98 with liberal glycaemic control who stayed more than 10 days in hospital.

3.4.1.3 Length of stay in ICU

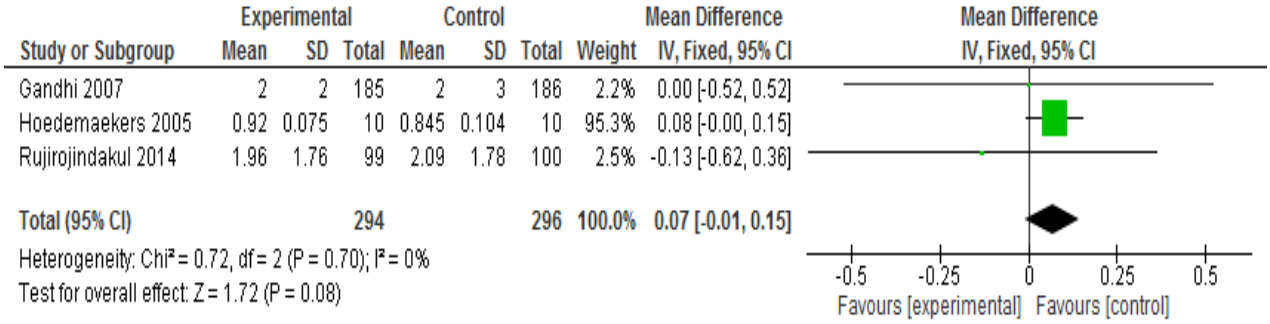


Figure 5: Meta-analysis of length of stay in ICU in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Three studies evaluated length of stay in ICU after cardiac surgery which included 590 participants. Time was measured in days. Overall, there was no statistically significant difference found in this meta-analysis that very tight glycaemic control reduced length of stay in ICU compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery. In fact, there was a trend towards shorter times in the control group as evidenced by a fixed effect mean difference 0.07 with a 95% CI of -0.01 to 0.15 (P value 0.07). There was no statistically significant heterogeneity (P=0.70), and the I^2 value of 0% indicates that between study- variation is not important (I^2=0%).[92] Rujirojindakul 2014[72] reported results as median value and estimation of the sample mean and standard deviation was done using the tool provided by Wan et al.[78]

3.4.1.4 Time on mechanical ventilation

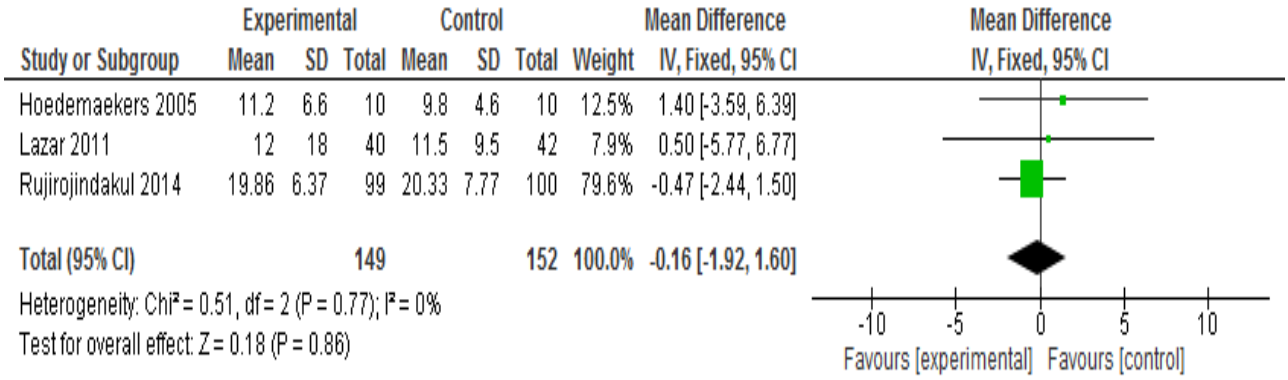


Figure 6: Meta-analysis of time on mechanical ventilation in very tight glycaemic control group compared to conventional glycaemic control group in (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Time on mechanical ventilation was evaluated in six studies which included 1751 participants, three of which were included in the meta-analysis. Time was measured in hours in this meta-analysis. Overall, time in ventilation was reduced by 0.16 hours in the very tight glycaemic control group compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery as evidenced by a fixed effect mean difference of -0.16 with a 95% CI of -1.92 to 1.60 (P value 0.86) which was statistically insignificant. There was no statistically significant heterogeneity (P=0.77), and the I^2 value of 0% indicates that between-study variation is not important (I^2=0%).[92] Rujirojindakul 2014[72] reported results as median value, and estimation of the sample mean and standard deviation was done using the tool provided by Wan et al.[78]

Studies not included in meta-analysis:

Three of the studies[63,65,68] could not be included in the meta-analysis as they reported the figures in different way. Ingels 2006[68] reported on 395 out of 477 patients with very tight glycaemic control extubated within 48 hours after surgery compared with 380 out of 493 patients with conventional glycaemic control (P value 0.026). Chan 2009[63] reported on median duration of intubation which was 10h 55min in the treatment group in comparison with 10h 15min in the control group (P value 0.831). In Gandhi 2007[65], it was reported that 36 participants out of 185 had been on prolonged intubation (>24 h) in the intensive glycaemic control group compared to 38 participants out of 186 in the conventional glycaemic control group (P value 0.82).

3.4.1.5 Stroke

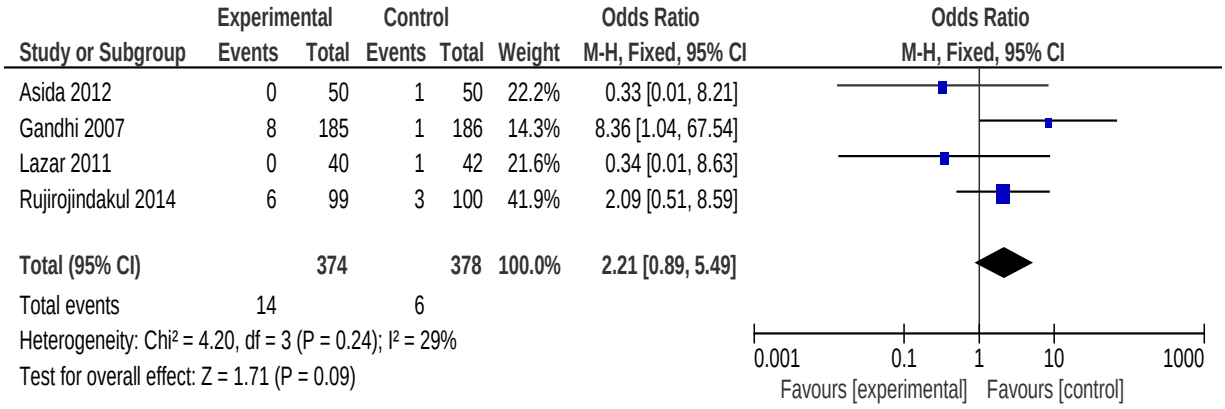


Figure 7: Meta-analysis of stroke in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Five studies which included 861 participants investigated stroke in cardiac surgery with glycaemic control as defined by study authors, four of which were included in the meta-analysis. Overall, there was no statistical significance found in the meta-analysis that very tight glycaemic control reduced the number of stroke patients compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery. In fact, there was a trend towards stroke occurring more frequently in the intervention group, as evidenced by an OR of 2.21 with a 95% CI of 0.89 to 5.49 (P value 0.09). There was no statistically significant heterogeneity (P=0.24), and the I^2 value of 29% indicates that the between-study variation is not important (I^2=29%).[92]

Studies not included in meta-analysis:

Chan 2009[63] could not be included in the meta-analysis as the authors reported in percentages where 9.8% participants in the control group (55 participants) suffered from neurological dysfunction compared with 2.1% in treated group (54 participants) (P value 0.207).

3.4.1.6 Atrial fibrillation

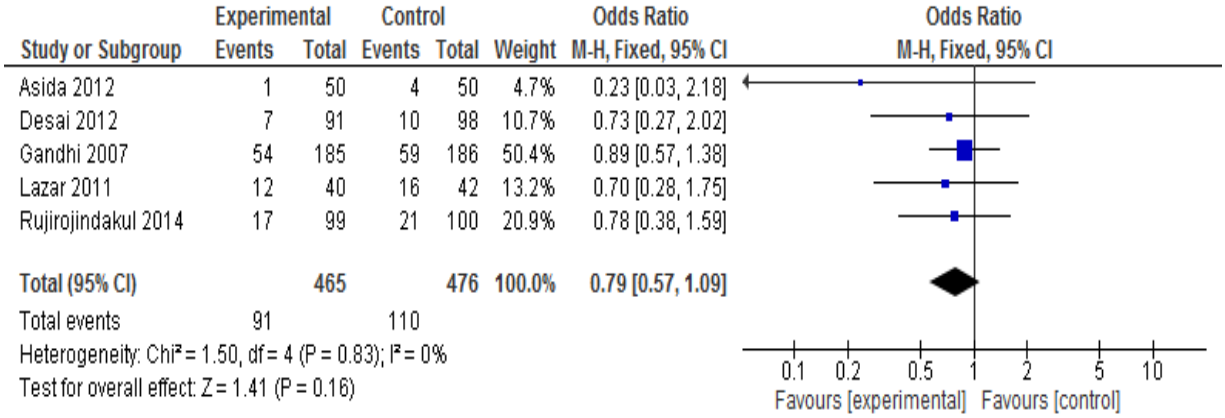


Figure 8: Meta-analysis of atrial fibrillation in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Atrial fibrillation was evaluated in five studies which included 941 participants. There was no statistically significant difference found between the very tight glycaemic control group in reducing atrial fibrillation compared to the liberal glycaemic control group in perioperative patients undergoing cardiac surgery as evidenced by an OR of 0.79 with a 95% CI of 0.57 to 1.09 (P value 0.16). There was no statistically significant heterogeneity (P=0.83), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.1.7 Renal failure

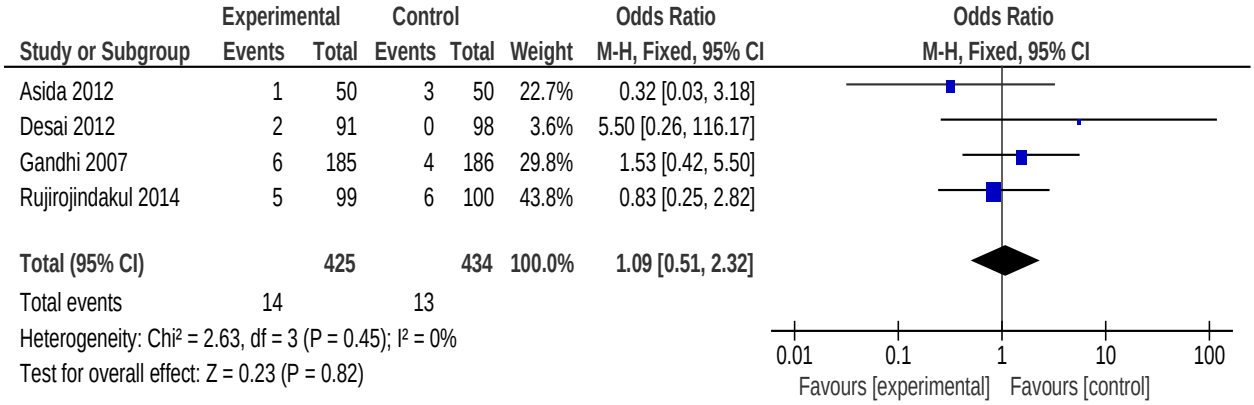


Figure 9: Meta-analysis of renal failure in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Five studies evaluated the occurrence of renal failure involving 968 participants, four of which were included in the meta-analysis. Overall, there was no statistical significance found in the meta-analysis that very tight glycaemic control reduced the incidence of renal failure compared with liberal glycaemic control in perioperative patients undergoing cardiac surgery as evidenced by an OR of 1.09 with a 95% CI of 0.51 to 2.32 (P value 0.82). There was no statistically significant heterogeneity (P=0.45), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

Studies not included in meta-analysis:

Chan 2009[63] could not be included in the meta-analysis as data was presented in percentages. Chan reported that 9.8% participants in the control group (55 participants) developed renal failure compared with 6.4% in the treated group (54 participants).

3.4.1.8 Deep sternal infection

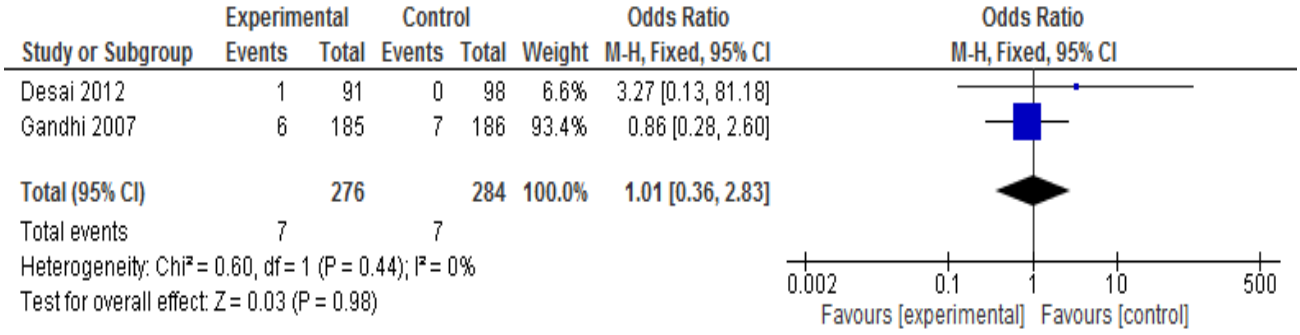


Figure 10: Meta-analysis of deep sternal infection in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Deep sternal infection was evaluated in three studies including 642 participants, two of which were included in the meta-analysis. Very tight glycaemic control did not reduce the number of deep sternal infections compared with conventional glycaemic control as evidenced by an OR of 1.01 with a 95% CI of 0.36 to 2.83 (P value 0.98). There was no statistically significant heterogeneity (P=0.44), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

Studies not included in meta-analysis:

Lazar et al. (2011)[71] could not be included as no event was reported in the experimental group (40 participants) nor in the control group (42 participants).

3.4.1.9 Need for cardiac pacing

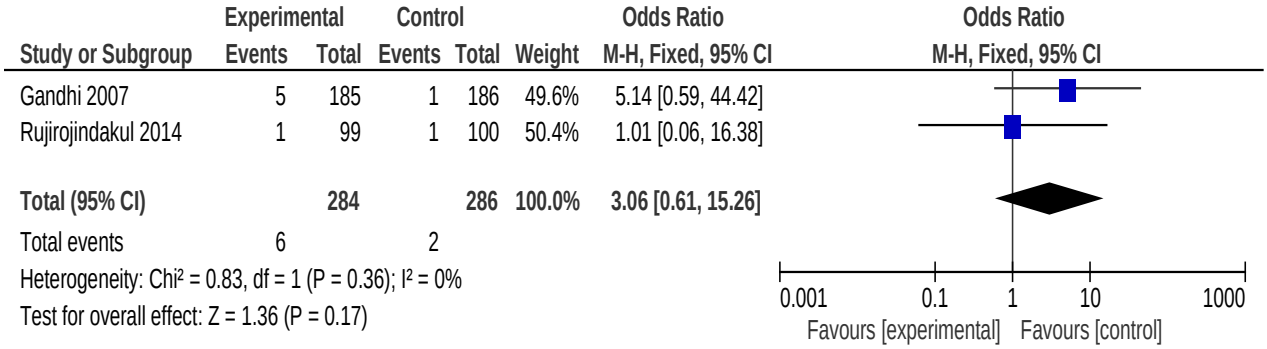


Figure 11: Meta-analysis of need for cardiac pacing in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Two studies evaluated heart block requiring cardiac pacing which included 570 participants. The meta-analysis showed no statistical significance that very tight glycaemic control reduced the incidence of cardiac pacing compared with conventional glycaemic control in both diabetic and/or nondiabetic patients undergoing cardiac surgery. In fact, there was a trend towards pacing being required more frequently in the intervention group as evidenced by an OR of 3.06 with a 95% CI of 0.61 to 15.26 (P value 0.17). There was no statistically significant heterogeneity (P=0.36), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.1.10 Re-infarction

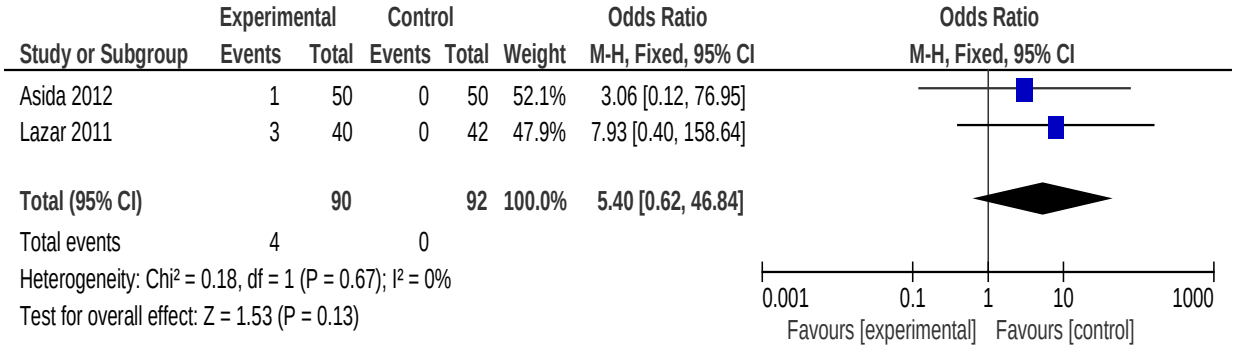


Figure 12: Meta-analysis of re-infarction in very tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Two studies investigated re-infarction after cardiac surgery which included 182 participants. The meta-analysis ws statistically non-significant and showed no reduction in the number of re-infarction with very strict glycaemic control compared with conventional glycaemic control in perioperative patients undergoing cardiac surgery. In fact, there was a trend towards re-infarction occurring more frequently in the experimental group as evidenced by an OR of 5.40 with a 95% CI of 0.62 to 46.84 (P value 0.13). There was no statistically significant heterogeneity (P=0.67), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.2 Tight glycaemic control versus conventional glycaemic control in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Four studies[62,66,69.70] compared tight glycaemic control with liberal glycaemic control and the results of these studies are described below. In these studies, measurement ranges varied significantly, and for this comparison "'tight" glycaemic control was defined as 100 to 200 mg/dl. In all included studies the conventional glucose control ranged from 160 to 250 mg/dl.

3.4.2.1 All-cause mortality

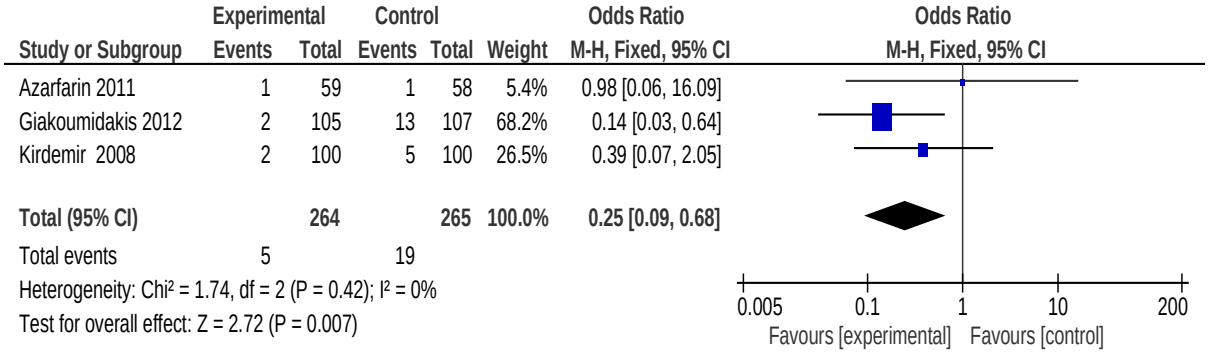


Figure 13: Meta-analysis of all-cause mortality in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Four studies evaluated mortality with tight glycaemic control in patients undergoing cardiac surgery which included 670 participants, with three studies being included in the meta-analysis. Overall, the meta-analysis showed a statistically significant difference that tight glycaemic control reduced the number of mortality compared with conventional glycaemic control in patients undergoing cardiac surgery as evidenced by an OR of 0.25 with 95% CI of 0.09 to 0.68 (P value 0.007). There was no statistically significant heterogeneity (P=0.42), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

Studies not included in meta-analysis:

Lazar et al. (2004)[70] could not be included as no event was reported neither in the experimental group (72 participants) nor in the control group (69 participants).

3.4.2.2 Length of stay in hospital

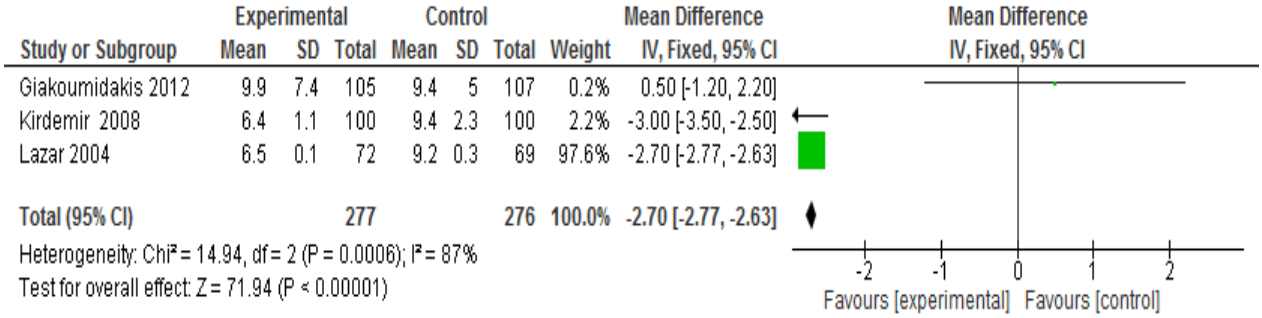


Figure 14: Meta-analysis of length of stay in hospital in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Length of stay in hospital in tight glycaemic control compared with liberal glycaemic control was reported in three studies including 553 participants. The meta-analysis shows that strict glycaemic control reduced length of stay in hospital compared with liberal glycaemic control by 2.7 days as evidenced by a mean difference of -2.70 with a 95% CI of -2.77 to -2.63, which was statistically significant (P value <0.00001). There was statistically significant heterogeneity (P=0.0006), and the I^2 value of 87% indicates that the between study variation is considerable (I^2=87%).[92]

3.4.2.3 Length of stay in ICU

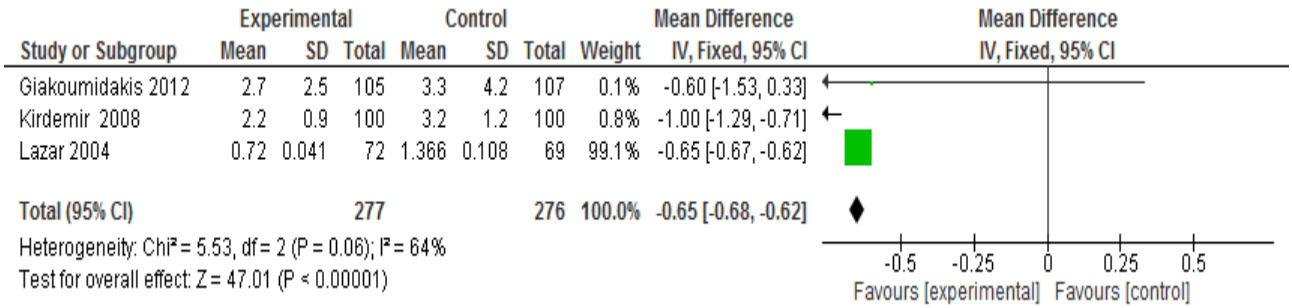


Figure 15: Meta-analysis of length of stay in ICU in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Three studies investigated length of stay in ICU after cardiac surgery which included 553 patients. The meta-analysis shows statistical significance (P value <0.00001) that strict glycaemic control reduced length of stay in ICU after cardiac surgery compared with liberal glycaemic control by 0.65 days as evidenced by a fixed-effect mean difference of -0.65 with a 95% CI of -0.68 to -0.62. There was no statistically significant heterogeneity (P=0.06), and the I^2 value of 64% indicates that the between-study variation is moderate to substantial (I^2=64%).[92]

3.4.2.4 Time on mechanical ventilation

Three studies evaluated time on mechanical ventilation which included 458 participants. Meta-analysis could not be performed due to non-standard reporting of the results, as the following narrative description shows. Kirdemir 2008[69] reported that three patients were on artificial ventilation for longer than 48 hours in the strict glycaemic control group (100 patients) in comparison with the liberal glycaemic control group (100 patients) where four patients were on artificial ventilation for longer than 48 hours (P value1.00). Lazar et al. (2004)[70] reported less time on mechanical ventilation (6.9±0.3 hours) in the strict glycaemic control group (72 patients) compared with liberal glycaemic control (69 patients) where time on mechanical ventilation was 10.7±0.6 hours (P value 0.63). Azarfarin 2011[62] reported on three patients being in prolonged (>18 hours) mechanical ventilation in the tight glycaemic control group (59 patients) compared with no case of prolonged mechanical ventilation in the liberal glycaemic control group (58 patients).

3.4.2.5 Stroke

Kirdemir 2008[69] evaluated the occurrence of stroke in patients undergoing cardiac surgery and included 200 participants. The study reported no significant difference between the tight glycaemic control group and the liberal glycaemic control group in reducing the occurrence of stroke (one patient in each group suffered from stroke) (P value = 1.00).

3.4.2.6 Atrial fibrillation

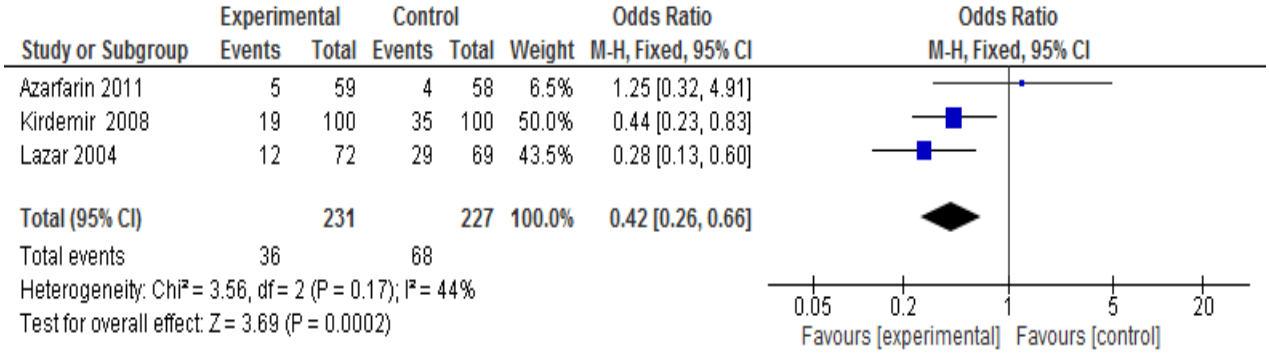


Figure 16: Meta-analysis of atrial fibrillation in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Three studies reported the occurrence of atrial fibrillation including 458 participants. The meta-analysis showed that tight glycaemic control decreased the number of atrial fibrillations compared with conventional glycaemic control as evidenced by an OR 0.42 with 95% CI 0.26 to 0.66 which is statistically significant (P value <0.0002). There was no statistically significant heterogeneity (P=0.38), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.2.7 Renal failure

Occurrence of renal failure in tight glycaemic control compared with moderate glycaemic control in patients undergoing cardiac surgery was reported in Kirdemir[69] which included 200 participants. The study reported no statistically significant difference (P value 1.00) between the tight glycaemic control group and the liberal glycaemic control group in reducing the occurrence of renal failure (two patients in each group suffered from renal failure).

3.4.2.8 Deep sternal infection

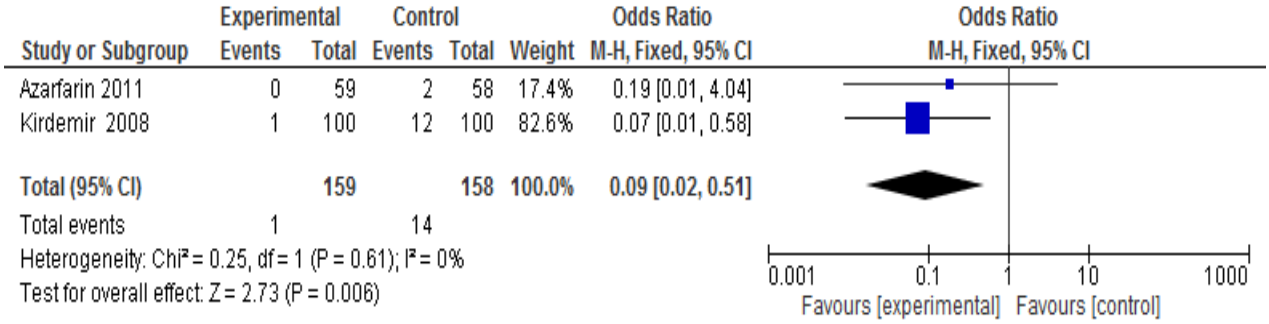


Figure 17: Meta-analysis of deep sternal infection in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

The incidence of deep sternal infection after cardiac surgery was evaluated in two studies which included 317 patients. The meta-analysis showed a statistically significant difference in that tight glycaemic control reduced the number of deep sternal infections compared with conventional glycaemic control in patients undergoing cardiac surgery as evidenced by an OR of 0.09 with a 95% CI of 0.02 to 0.51 (P value 0.006). There was no statistically significant heterogeneity (P=0.61), and the I^2 value of 0% indicates that the between-study variation may not be important (I^2=0%).[92]

3.4.2.9 Need for cardiac pacing

Need for cardiac pacing after cardiac surgery was evaluated in Lazar et al. (2004)[70] which included 141 participants. The study reported a statistically significant difference (P value 0.001) between the tight glycaemic control group and the liberal glycaemic control group in reducing the need for cardiac pacing. It was reported that 10 out of the 72 patients in tight glycaemic control group had to undergo cardiac pacing compared with 27 out of the 69 patients in the liberal glycaemic control group.

3.4.2.10 Re-infarction

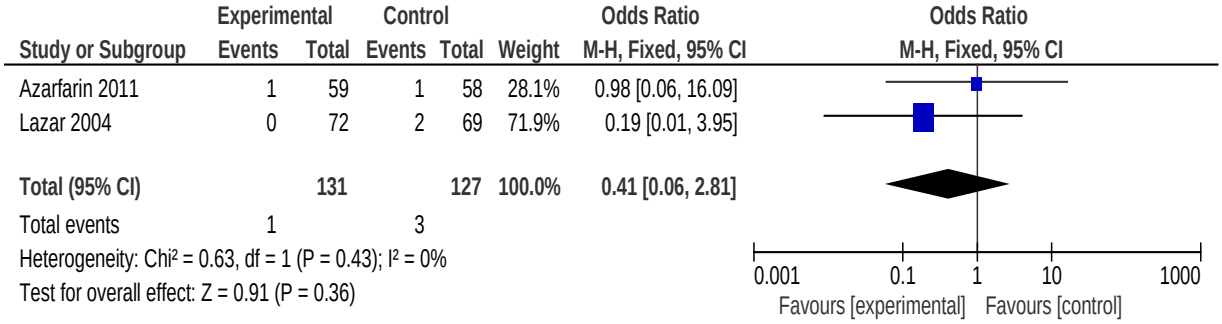


Figure 18: Meta-analysis of re-infarction in tight glycaemic control group compared to conventional glycaemic control group in all (both diabetic and/or nondiabetic) patients undergoing cardiac surgery

Re-infarction after cardiac surgery was evaluated in two studies including 258 patients. The meta-analysis showed no statistically significant difference between the tight glycaemic control group and the liberal glycaemic control group in reducing the number of re-infarction as evidenced by an OR of 0.41 with a 95% CI of 0.06 to 2.81 (P value 0.36). There was no statistically significant heterogeneity (P=0.43), and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.3 Very tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

Three studies[61,65,71] compared very tight glycaemic control with liberal glycaemic control included in this subgroup. In these studies, measurement ranges of very tight glycaemic control varied significantly, and for the purposes of this analysis was defined as the range 80 to 150 mg/dl. The conventional glucose control ranged from 160 to 250 mg/dl in all included studies.

3.4.3.1 All-cause mortality

Two studies evaluated mortality with very tight glycaemic control in diabetic patients undergoing cardiac surgery which included 155 participants. Among them, Lazar et al. (2011)[71] reported no event neither in experimental group(40 participants) nor in control group (42 participants).Gandhi 2007[65]

reported no statistical significant difference (P value 0.49) between very tight glycaemic control group and liberal glycaemic control group in reducing the number of perioperative mortality where they reported two cases of mortality in the very tight glycaemic control group (37 patients) compared with no case of mortality in liberal glycaemic control group (36 patients).

3.4.3.2 Length of stay in hospital

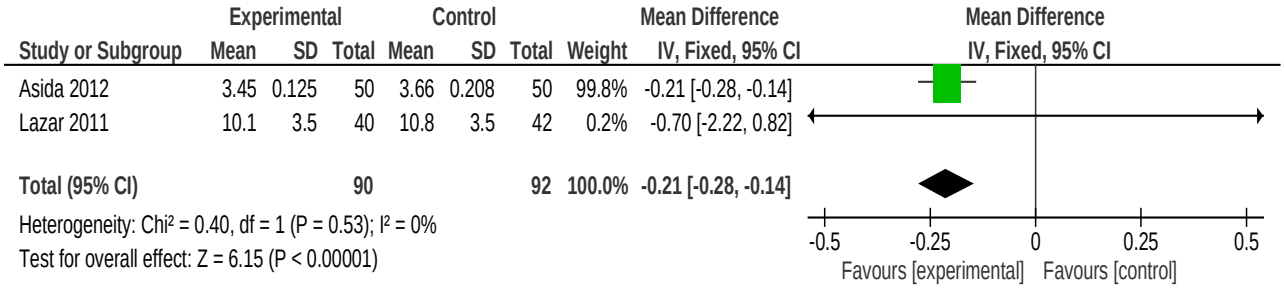


Figure 19: Meta-analysis of length of stay in hospital in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Two studies evaluated length of stay in hospital with very tight glycaemic control in diabetic patients after cardiac surgery including 182 participants. The meta-analysis shows that very strict glycaemic control reduced length of stay in hospital compared with liberal glycaemic control by 0.21 days as evidenced by a mean difference of -0.21 with a 95% CI of -0.28 to -0.14, which was statistically significant (P value <0.00001). There was no statistically significant heterogeneity (P=0.53) observed, and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.3.3 Length of stay in ICU

Gandhi 2007[65] investigated length of stay in ICU with very tight glycaemic control in diabetic patients undergoing cardiac surgery which included 73 participants. The study showed no significant changes (P value 0.63) between the experimental and control groups (mean length of stay in both groups was two days).

3.4.3.4 Time on mechanical ventilation

Lazar et al. (2011)[71] evaluated time on mechanical ventilation with very tight glycaemic control in diabetic patients undergoing cardiac surgery which included 82 participants. The study reported increased time on ventilation with the aggressive glycaemic control group (12.0 ± 18 hours) compared with the moderate glycaemic control group (11.5 ± 9.5 hours) which was statistically non-significant (P value 0.63).

3.4.3.5 Stroke

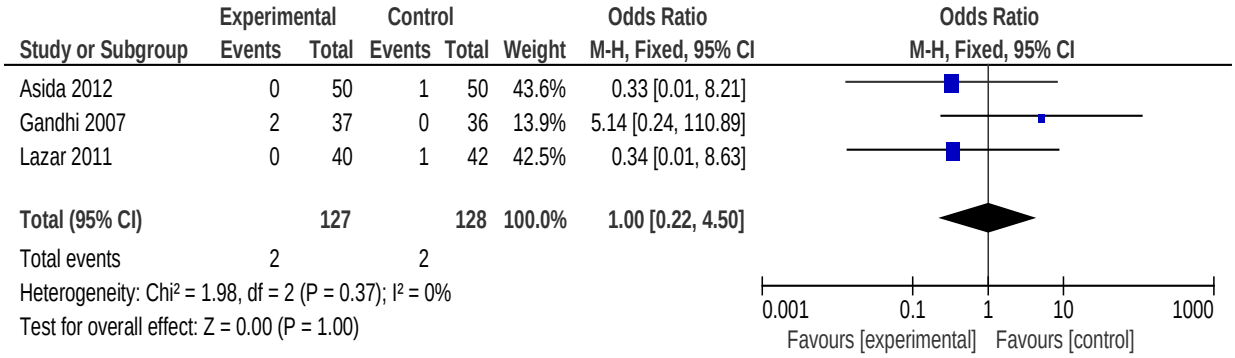


Figure 20: Meta-analysis of stroke in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Three studies evaluated stroke in diabetic patients with very tight glycaemic control during the perioperative period of cardiac surgery which included 255 participants. The meta-analysis was not statistically significant which showed that very tight glycaemic control did not reduce the number of strokes in diabetic patients compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery as evidenced by an OR of 1.00 with a 95% CI of 0.22 to 4.50 (P value 1.00). There was no statistically significant heterogeneity (P=0.37) observed, and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.3.6 Atrial fibrillation

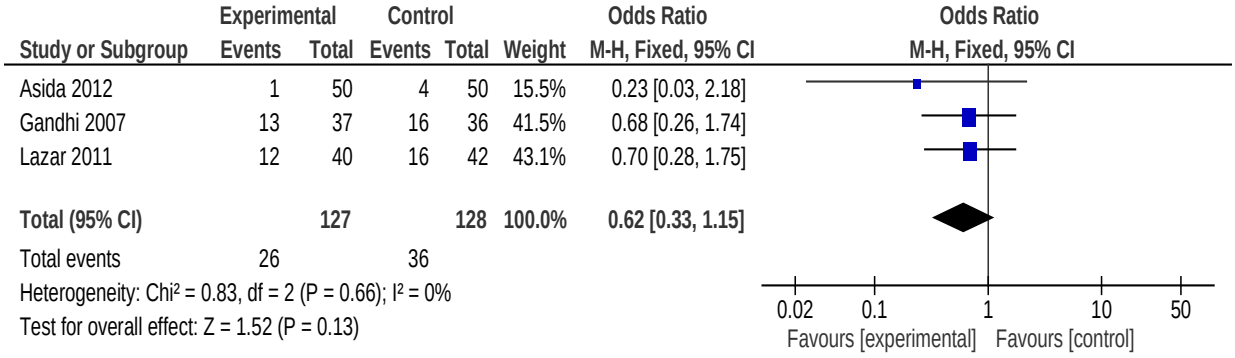


Figure 21: Meta-analysis of atrial fibrillation in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Three studies investigating atrial fibrillation with very tight glycaemic control in diabetic patients undergoing cardiac surgery which included 255 participants. There was no statistically significant difference found between very tight glycaemic control in reducing the number of atrial fibrillation in diabetic patients compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery as evidenced by an OR of 0.62 with a 95% CI of 0.33 to 1.15 (P value 0.13). There was no statistically significant heterogeneity (P=0.66) observed, and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.3.7 Renal failure

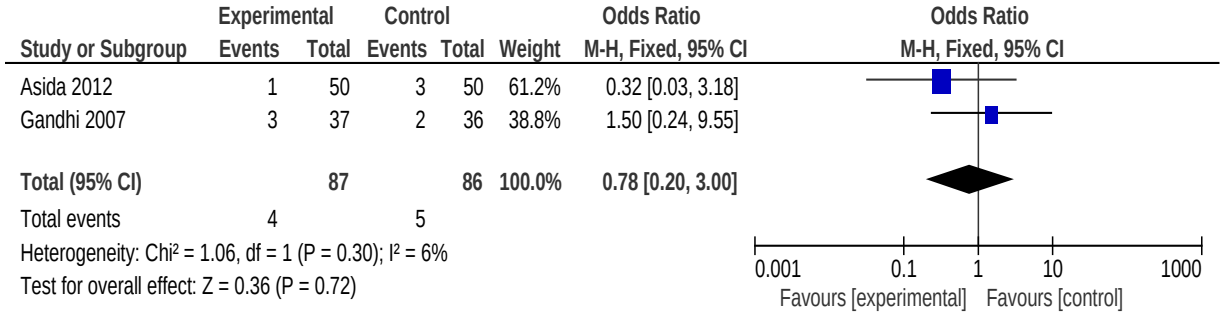


Figure 22: Meta-analysis of renal failure in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Renal failure with very tight glycaemic control in diabetic patients undergoing cardiac surgery was investigated in two studies which included 173 participants. There was no statistical significance found in the meta-analysis that very tight glycaemic control in diabetic patients reduced the incidence of renal failure compared with liberal glycaemic control in perioperative patients undergoing cardiac surgery as evidenced by an OR of 0.78 with a 95% CI of 0.20 to 3.00 (P value 0.72). There was no statistically significant heterogeneity (P=0.30) observed, and the I^2 value of 6% indicates that the between-study variation is not important (I^2=6%).[92]

3.4.3.8 Deep sternal infection

Incidence of deep sternal infection was evaluated in two studies with very tight glycaemic control in diabetic patients undergoing cardiac surgery and which included 155 patients. Lazar et al. (2011)[71] reported no event in the experimental group (40 participants) as well as in the control group (42 participants).Gandhi 2007[65] reported no statistically significant difference (P value 0.61) between the very tight glycaemic control group and the liberal glycaemic control group in reducing the number of deep sternal infection where there were 3 cases in the very tight glycaemic control group (37 patients) compared with 1 case in the liberal glycaemic control group (36 patients).

3.4.3.9 Need for cardiac pacing

Gandhi[65] evaluated the need for cardiac pacing in diabetic patients undergoing cardiac surgery and the study included 73 participants. The study reported a better outcome with liberal glycaemic control in comparison with very tight glycaemic control whereby two out of the 37 patients in the very tight glycaemic control group had to undergo cardiac pacing compared with no case of cardiac pacing among the 36 patients in the liberal glycaemic control group. However, it was not statistically significant.

3.4.3.10 Re-infarction

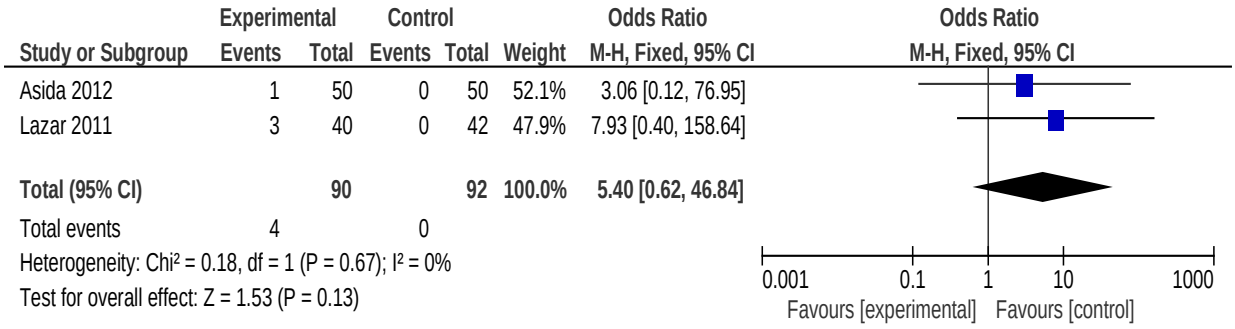


Figure 23: Meta-analysis of re-infarction in very tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Two studies investigated re-infarction after cardiac surgery involving 182 participants. The meta-analysis was not statistically significant (P value 0.13) which showed no reduction in the number of re-infarction with very strict glycaemic control compared with conventional glycaemic control in perioperative patients undergoing cardiac surgery. In fact, there was trend for re-infarction to occur more frequently in the intervention group as evidenced by an OR of 5.40 with a 95% CI of 0.62 to 46.84. There was no statistically significant heterogeneity (P=0.67) observed, and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.4 Tight glycaemic control versus conventional glycaemic control in diabetic patients undergoing cardiac surgery

Two studies[69,70] compared tight glycaemic control with liberal glycaemic control in diabetic patients and are included in this subgroup. In these studies, measurement ranges of very tight glycaemic control varied significantly. For this analysis, upper and lower limit of blood sugar level for tight glycaemic control is defined as 100 to 200 mg/dl. The conventional glucose control ranged from 160 to 250 mg/dl in all included studies.

3.4.4.1 All-cause mortality

Two studies evaluated mortality with tight glycaemic control in diabetic patients undergoing cardiac surgery involving 341 participants. Among them, Lazar et al. (2004)[70] reported no event in the experimental group (40 participants) as well as the control group (42 participants). Kirdemir[69] reported a statistically significant difference (P value 0.044) between the tight glycaemic control group and the liberal glycaemic control group in the reduction of the number of perioperative mortality where there were two cases of mortality in the tight glycaemic control group (100 patients) compared with five cases of mortality in the liberal glycaemic control group (100 patients).

3.4.4.2 Length of stay in hospital

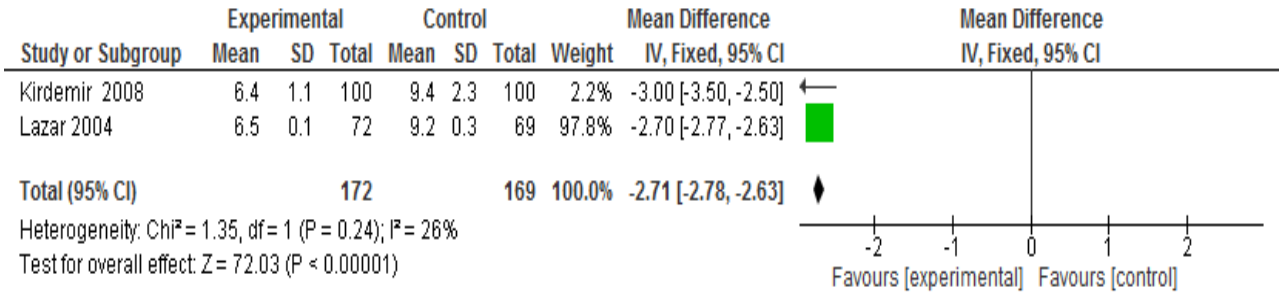


Figure 24: Meta-analysis of length of stay in hospital in tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Two studies evaluated length of stay in hospital with tight glycaemic control in diabetic patients undergoing cardiac surgery involving 341 participants. The meta-analysis shows that tight glycaemic control reduced length of stay in hospital compared with liberal glycaemic control by 2.71 days as

evidenced by a fixed-effect mean difference of -2.71 with a 95% CI of -2.71 to -2.63, which was statistically significant (P value <0.00001). There was no statistically significant heterogeneity (P=0.24) observed, and the I^2 value of 26% indicates that the between-study variation may not be important (I^2=26%).[92]

3.4.4.3 Length of stay in ICU

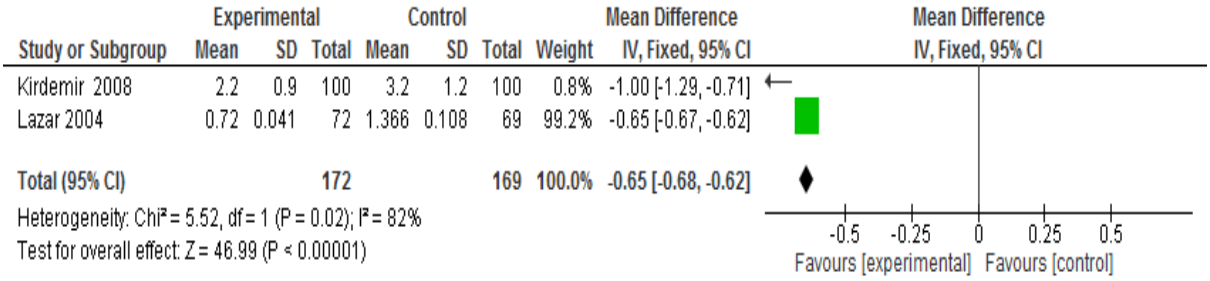


Figure 25: Meta-analysis of length of stay in ICU in tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Two studies investigated length of stay in ICU after cardiac surgery of diabetic patients which included 341 patients. The result of the meta-analysis was statistically significant (P value <0.00001). Tight glycaemic control reduced length of stay in ICU of diabetic patients after cardiac surgery compared with liberal glycaemic control by 0.65 days as evidenced by a mean difference of -0.65 with a 95% CI of -0.68 to -0.62. There was statistically significant heterogeneity (P=0.02), and the I^2 value of 82% indicates that the between-study variation is considerable (I^2=82%).[92]

3.4.4.4 Time on mechanical ventilation

Two studies evaluated time on mechanical ventilation and included 341 participants. Among them, Kirdemir 2008[69] reported that three patients were on artificial ventilation for longer than 48 hours in the strict glycaemic control group (100 patients) in comparison with the conventional glycaemic control group (100 patients) where 4 patients were on artificial ventilation for longer than 48 hours (P value 1.00). Lazar et al (2004)[70] reported less time on mechanical ventilation (6.9 ± 0.3 hours) in the strict glycaemic control group (72 patients) compared with liberal glycaemic control (69 patients) where time on mechanical ventilation was 10.7 ± 0.6 hours (P value 0.0002) which is statistically

significant. Overall, it is shown that strict glycaemic control is effective in reducing time on mechanical ventilation in diabetic patients during the perioperative period after cardiac surgery.

3.4.4.5 Stroke

Kirdemir 2008[69] evaluated stroke in diabetic patients with strict glycaemic control during cardiac surgery involving 200 participants. The study showed there was no significant difference between tight glycaemic control group compared with liberal glycaemic control group in reducing the number of stroke cases as one patient in each group suffered of stroke (P value 1.00).

3.4.4.6 Atrial fibrillation

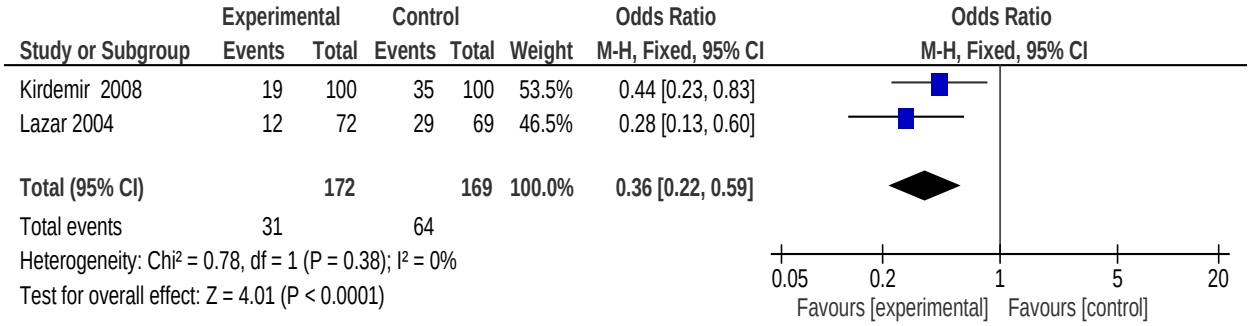


Figure 26: Meta-analysis of atrial fibrillation in tight glycaemic control group compared to conventional glycaemic control group in diabetic patients undergoing cardiac surgery

Two studies reported the occurrence of atrial fibrillation which included 341 participants. The meta-analysis showed that tight glycaemic control reduced the number of cases of atrial fibrillation compared with liberal glycaemic control in diabetic patients as evidenced by an OR of 0.36 with a 95% CI of0.22 to 0.59 which was statistically significant (P value<0.00001). There was no statistically significant heterogeneity (P=0.38) observed, and the I^2 value of 0% indicates that the between-study variation is not important (I^2=0%).[92]

3.4.4.7 Renal failure

Kirdemir2008[69] evaluated renal failure in diabetic patients with strict glycaemic control undergoing cardiac surgery including 200 participants. The study showed there was no significant difference between the tight glycaemic control group compared with the liberal glycaemic control group in

reducing the number of renal failure cases as 2 patients in each group suffered of renal failure (P value 1.00).

3.4.4.8 Deep sternal infection

Kirdemir[69] investigated sternal wound infection in diabetic patients with tight glycaemic control undergoing cardiac surgery involving 200 participants. The study showed there was a significant difference between the tight glycaemic control group compared with the liberal glycaemic control group in reducing incidence of sternal wound infection (P value 0.003). Two patients in the tight glycaemic control group suffered from renal failure compared with 12 patients in the less tight glycaemic control group.

3.4.4.9 Need for cardiac pacing

Need for cardiac pacing in diabetic patients after cardiac surgery was evaluated in the Lazar et al. (2004)[70] study which included 141 participants. The study reported a statistically significant difference (P value 0.001) between the tight glycaemic control group and the liberal glycaemic control group in reducing the need for cardiac pacing where it was reported that 10 out of the 72 patients in the tight glycaemic control group had to undergo cardiac pacing compared with 27 out of the 69 patients in the liberal glycaemic control group.

3.4.4.10 Re-infarction

Re-infarction in diabetic patients after cardiac surgery was evaluated in the Lazar et al. (2004)[70] study including 141 participants. The study reported no statistically significant difference (P value 0.46) between tight glycaemic control group and liberal glycaemic control group in reducing re-infarction whereby Lazar et al. (2004) reported no case of re-infarction in the tight glycaemic control group (72 patients) compared with the two cases of re-infarction in the liberal glycaemic control group (69 patients).

Chapter 4: Discussion

This review sought to synthesise the best available evidence regarding the effects of various levels (very tight, tight and conventional) of glycaemic control on mortality and morbidity in patients undergoing cardiac surgery. Both diabetic and nondiabetic patients were included in this review. During the search and retrieval process, 12 studies were identified that met the inclusion criteria and were considered to be of suitable methodological quality. Among the 12 studies[61-72] that reported on mortality and morbidity in patients undergoing cardiac surgery, ten studies[61-65,67,69-72] were randomised controlled trials, one was[66] a randomised quasi-experimental trial, and one[68] was a pre-planned sub-analysis and follow-up study of a randomised controlled trial.

The methodological quality of the included studies was generally high with a clear description of the study design and statistical analysis methods used. Of the final 12 studies, 10 were randomised while one was quasi-experimental and one was a sub-analysis of a randomised controlled trial. All studies included study and control groups. As randomised controlled trials are the ideal design for determining effectiveness, the high number of trials included in this review was deemed a good result. Although only two of the studies scored 10 out 10 in critical appraisal, this was to be expected due to the difficulty in blinding patients or assessors to the interventions. At times, due to lack of reporting, it was unclear if the studies met the critical appraisal criteria. Hence, it was ticked off unclear in those circumstances in critical appraisal. The sample size of included studies ranged from 20 to 970 with minimum variation. The included studies were conducted on populations in different geographical locations. Five studies[62,64,65,70,71] were conducted in USA, one in Brazil,[63] one in Greece,[66]one in Netherland,[67] one in Turkey,[69] one in Egypt,[61] one in Iran[62] and one in Thailand.[72]
Among the 12 studies, four[61,69,70,71] included diabetic patients, two[62,67] included nondiabetic patients and six[63-66,68,72]included both diabetic and nondiabetic patients. One[65] of the studies reported individual data for diabetic and nondiabetic patients. The outcomes are analysed in two subgroups: "both diabetic and/or nondiabetic patients" and "diabetic patients".

The studies either compared very strict/very tight glycaemic control or tight/moderate/semi tight glycaemic control with conventional/liberal/less tight glycaemic control. Eight studies[61,63-65,67,68,71,72] compared very tight glycaemic control with liberal glycaemic control among cardiac surgical patients. All of these measured both diabetic and/or nondiabetic patients, with three[61,65,71] measuring only diabetic patients. Four other studies[62,66,69.70] compared tight glycaemic control with liberal glycaemic control in patients undergoing cardiac surgery. All of these measured both diabetic and/or nondiabetic patients, with two of these[69,70] measuring only diabetic patients. Based on the range of BGC levels, this review includes a further categorised of "very tight glycaemic control" and "tight glycaemic control" groups as it was noted that the studies included in this review defined tight glycaemic control in a wider range of 80-200 mg/dl. To ensure consistency in comparisons across the studies, interventions were analysed for the three groups. Those included in the "very tight glycaemic control" group

measured their blood glucose level as 80-150 mg/dl and the "tight glycaemic control" group measured their blood glucose level as 100-200 mg/dl. For these two groups, there is an overlap of glycaemic range due to the variation in the upper and lower limits of blood glucose measurement in the studies. The conventional/liberal/normal glucose control ranges from 160 to 250 mg/dl in all included studies.

To the best of our knowledge, this review can be considered the most comprehensive of its type in this topic area, due to the inclusion of subgroups by population and intervention (i.e. "both diabetic and/or nondiabetic patients" and "diabetic patients", and "very tight glycaemic control" and "tight glycaemic control") and the inclusion of many outcomes. Although another systematic review has been published in this field,[60] there was no subgroup analysis on diabetic patients and more outcomes could have been included (e.g. acute renal failure, stroke, deep sternal infection and re-infarction). Additionally, that review, undertaken in 2011, is already out of date as. Whilst searching, a few literature reviews[60,83,84] were identified, but these did not follow a systematic process and the information is quite dated as the latest one was published in 2012 in Chinese. Systematic reviews are more appropriate than standard literature reviews for making recommendations for clinical practice, as they provide a comprehensive and unbiased summary of literature in one area, and include critical appraisal and methods that synthesise data from individual studies.[85]

4.1 Outcomes

4.1.1 All-cause mortality

Six randomised controlled trials[63-65,68,71,72] evaluated all-cause mortality in very tight glycaemic control (80-150mg/dl) groups compared to conventional glycaemic control (160-250 mg/dl) groups in both diabetic and/or nondiabetic patients undergoing cardiac surgery which in total involved 1916 participants which suggested that there may be a significant reduction in perioperative mortality in the very tight glycaemic control group. The data was heavily weighted by Ingels et al. [68] (79.8%), while the other studies reported a lower number of participants and less events. Desai et al.[64] reported no improvement with very tight glycaemic control where as Gandhi et al.[65] reported a higher number of deaths with very tight glycaemic control compared with conventional glycaemic control. Chan et al.[63] (not included in the meta-analysis) reported a higher percentage of mortality in the intervention group compared with control group. Lazar et al.[71] (2011) (not included in meta-analysis) reported no events in the experimental group or in control group. Moreover, a sensitivity analysis was conducted to determine whether the model of meta-analysis (fixed) had an impact on the overall summary estimate. Analysis with a random effects model showed that the effect estimate changed from statistically significant to non-significant with this model. As such, the significant result achieved with the fixed effects model should be interpreted with some caution. Nonetheless, , the 41% difference in

the odds of all-cause mortality in favour of the intervention group compared to the control group can be considered potentially clinically significant, although due to the limitations above it must be interpreted with caution.

Four studies[62,66,69,70] evaluated all cause mortality in tight glycaemic control (100-200 mg/dl) group compared to conventional glycaemic control (160-250 mg/dl) group in both diabetic and/or non diabetic patients undergoing cardiac surgery and showed a significant reduction in perioperative mortality in the tight glycaemic control group. The data was heavily weighted by Giakoumidakis[66] et al (68.2%) where it reported a higher number of deaths in the control group compared with the experimental group. Lazar et al. (2004)[70] reported no event neither in experimental nor in control group. This reduction in the intervention group odds of mortality by 75% of that in the control group can be considered a clinically significant difference.

Two studies[65,71] evaluated all cause mortality in the very tight glycaemic control (80-150 mg/dl) group compared to conventional glycaemic control (160-250 mg/dl) group in diabetic patients undergoing cardiac surgery. Among them, Lazar et al. (2011)[71] reported no event in either group. Although Gandhi[65]*et al* reported a reduction in mortality in control group, it was statistically nonsignificant.

Interestingly, all cause mortality in tight glycaemic control (100-200 mg/dl) group compared to conventional glycaemic control (160-250 mg/dl) group in diabetic patients undergoing cardiac surgery reported a different result. While Lazar et al.[70] (2004) reported no event in either group, Kirdemir[69] *et al* reported statistically significant reduction in number of death in tight glycaemic control group compared with the conventional glycaemic control group.

4.1.2 Length of stay in hospital

The meta-analysis which included six trials[61,63,64,65,71,72] that very strict glycaemic control reduced the length of stay in hospital after cardiac surgery by 0.21 days or 5.04 hours compared with liberal glycaemic control which is statistically significant. However, this small reduction in time may not be clinically significant. The meta-analysis data was heavily weighted by Asida et al. [61] (99.1%).

Length of stay in hospital in tight glycaemic control compared with liberal glycaemic control was reported in three studies[66,69,70] which shows that strict glycaemic control reduced length of stay in hospital compared with liberal glycaemic control by 2.7 days which is statistically significant. This large reduction in time can be considered clinically significant. There was statistically significant heterogeneity and study variation was substantial to considerable. Another study[86] assessing effects of tight blood glucose control (120 to 200 mg/dL), using CII in diabetic patients after cardiac surgery reported decreases in length of stay and deep surgical wound infections; however, the differences were nonsignificant.

Very tight glycaemic control in diabetic patients undergoing cardiac surgery showed that very strict glycaemic control (80-150mg/dl) reduced the length of stay in hospital after cardiac surgery by 0.21 days or 5.04 hours compared with liberal glycaemic control which is statistically significant. The meta-analysis showed that tight glycaemic control (100-200mg/dl) reduced length of stay in hospital compared with liberal glycaemic control by 2.71 days in diabetic patients, which was also statistically significant.

4.2.3 Length of stay in ICU

Length of stay in ICU in the very tight glycaemic control group found no statistical significant difference compared with conventional glycaemic control group in diabetic and/or nondiabetic patients. However, the meta-analysis was heavily weighted by Hoedemaekers[67] *et al* (95.3%) which included only 20 participants. The mean difference is 0.07, which means that on an average, patients in the control group (conventional glycaemic control) stay longer in ICU (by 0.07 of a day or 1.68 hours) which is unlikely to be clinically important.

Interestingly, the length of stay in the ICU in tight glycaemic control group in comparison with conventional glycaemic control group showed statistical significant difference that strict glycaemic control reduced length of stay in ICU after cardiac surgery compared with liberal glycaemic control by 0.65 days or 15.6 hours. This reduction in the length of time can be viewed as a clinically significant finding. However, the result should be interpreted with caution as there is statistically significant heterogeneity and the study variation is substantial to considerable.

Gandhi[65] *et al* is the only study that investigated the effect of very tight glycaemic control in length of stay in ICU among diabetic patients and showed no significant changes between the experimental and control group. On the other hand, meta-analysis showed that tight glycaemic control reduced the length of stay in ICU in diabetic patients after cardiac surgery compared with liberal glycaemic control by 0.65 days or 15.6 hours which was statistically significant. This can also be considered clinically significant.

4.2.4 Time on mechanical ventilation

Three out of six studies[63.65-68,71,72] included in the meta-analysis showed a slight reduction (0.16 hours) in ventilation time in the very tight glycaemic control group compared to liberal glycaemic control in perioperative patients undergoing cardiac surgery, which is statistically nonsignificant in diabetic and/or nondiabetic patients. Ingels et al.[68] and Gandhi et al.[65] also reported less time in mechanical ventilation in the very strict glycaemic control group compared to the conventional glycaemic control

group. However, Chan et al.[63] reported more time in mechanical ventilation in the very tight glycaemic control group.

Two studies[69,70] reported better outcomes in the tight glycaemic control group compared to the liberal glycaemic control group in diabetic and/or nondiabetic patients. However, one study[62] reported more patients in prolonged ventilation in the tight glycaemic control group in comparison with the liberal glycaemic control group.

Lazar et al. (2011)[71] reported increased time on ventilation with the very tight glycaemic control group compared with the moderate glycaemic control group in diabetic patients which is statistically nonsignificant. On the contrary, two other studies[69.70] showed that tight glycaemic control was effective in reducing time on mechanical ventilation in diabetic patients during the perioperative period after cardiac surgery.

4.2.5 Stroke

Four[61,65,71,72] out of five studies[61,63,65,71,72] included in the meta-analysis showed there was no statistical significance for very tight glycaemic control in reducing the number of stroke patients compared to liberal glycaemic control in diabetic and/or nondiabetic perioperative patients undergoing cardiac surgery. As the odds ratio was 2.21, the odds of having a stroke in the experimental group were 2.21 times the odds of having a stroke in the control group. This effect size is large enough to become clinically significant. However, this is not statistically significant.

Meta-analysis conducted in diabetic patients also revealed very tight glycaemic control did not have superiority over liberal glycaemic control in reducing the number of strokes in perioperative patients undergoing cardiac surgery. The OR of 1.00 indicates that there were equal odds of having stroke in both the experimental and control group which has no clinical significance.

Kirdemir et al.[69] evaluated stroke in diabetic patients which showed there was no significant difference between tight glycaemic control group compared with liberal glycaemic control group in reducing the number of stroke cases.

4.2.6 Atrial fibrillation

Atrial fibrillation is a common complication of cardiac surgery. Postoperative atrial fibrillation results in many complications and increased usage of healthcare resources. The reported prevalence and incidence of atrial fibrillation after cardiac surgery varied among the different studies, depending on population profile, type of surgery, arrhythmia definition and detection methods, and design of

study.[87] Meta-analysis in this review included five studies[61,64,65,71,72] and found no statistically significant difference between very tight glycaemic control and liberal glycaemic control in reducing atrial fibrillation in diabetic and/or nondiabetic patients undergoing cardiac surgery. Nonetheless, the 21% difference in the odds of atrial fibrillation in favour of the intervention group compared to the control group, although not statistically significant, can be considered clinically significant.

Three studies[62,69,70] included in the meta-analysis showed that tight glycaemic control decreased the number of atrial fibrillations compared with conventional glycaemic control group in diabetic and/or nondiabetic patients which is statistically significant. Nonetheless, the 68% difference in the odds in favour of the intervention group compared to the control group, although not statistically significant, can be considered clinically significant.

The meta-analysis showed no statistical significant difference between very tight glycaemic control and liberal glycaemic control group in reducing the cases of atrial fibrillation in diabetic patients undergoing cardiac surgery. Nevertheless, the 38% difference in the odds of atrial fibrillation in favour of the intervention group compared to the control group, although not statistically significant, can be considered clinically significant.

A meta-analysis which included two studies[69,70] showed that tight glycaemic control reduced the cases of atrial fibrillation in diabetic patients compared with liberal glycaemic control which is statistically significant and the 64% difference in the odds in favour of the intervention group compared to the control group can be considered clinically significant.

4.2.7 Renal failure

Four out of five studies[61,63,64,65,72] included in meta-analysis which found no statistical significance that very tight glycaemic control reduced the incidence of renal failure compared with liberal glycaemic control in perioperative diabetic and/or nondiabetic patients undergoing cardiac surgery. As the odds ratio was 1.09, the odds of having a renal failure in the experimental group were 1.09 times the odds of having a renal failure in the control group, which may not be clinically significant.

Renal failure with very tight glycaemic control in diabetic patients undergoing cardiac surgery was investigated in two studies,[61,65] with no statistically significant finding that very tight glycaemic control reduced the incidence of renal failure compared with liberal glycaemic control in perioperative patients. However, the 22% difference in the odds of renal failure in favour of the intervention group compared to the control group can be considered potentially clinically significant.

Kirdemir et al.[69] evaluated renal failure in diabetic patients which showed there was no significant difference between the tight glycaemic control group compared with the liberal glycaemic control group in the reduction of the number of renal failure cases.

4.2.8 Deep sternal infection

Infection of the sternotomy wound is a serious complication of open heart surgery. It is a potentially devastating and occasionally fatal complication.[89] Two out of three studies[64,65,71] included in a meta-analysis found no statistical significance that very tight glycaemic control (80-150mg/dl) reduced the number of deep sternal infection compared with conventional glycaemic control in diabetic and/or nondiabetic patients undergoing cardiac surgery. As the odds ratio was 1.01, the odds of having deep sternal infection in the experimental group were 1.01 times the odds of having deep sternal infection in the control group which may not be clinically significant. Lazar et al. (2011)[71] reported no event in either group.

Interestingly, the meta-analysis among both diabetic and/or nondiabetic patients included two studies[62,69] showed statistically significant difference that tight glycaemic control (100-200mg/dl) reduced the number of deep sternal infection compared with conventional glycaemic control in patients undergoing cardiac surgery. Moreover, the 91% difference in the odds of deep sternal infection in favour of the intervention group compared to the control group can be considered clinically significant.

The incidence of deep sternal infection was evaluated in two studies with very tight glycaemic control in diabetic patients undergoing cardiac surgery. Among them, Lazar et al. (2011)[71] reported no event in the experimental group nor in the control group. Gandhi et al.[65] reported no statistically significant difference between the very tight glycaemic control group and the liberal glycaemic control group in reducing the number of deep sternal infections.

On the other hand, Kirdemir et al.[69] investigated sternal wound infection in diabetic patients with tight glycaemic control undergoing cardiac surgery. The study showed there was a significant difference between the tight glycaemic control group compared with liberal glycaemic control group in the reduction of the incidence of sternal wound infections.

4.2.9 Need for cardiac pacing

Temporary epicardial pacing has a potential role of in the prevention of atrial fibrillation, which is extremely common in the period immediately following cardiac surgery (40% in some series).[3] The

meta-analysis which included two studies[65,72] showed no statistical significance that very tight glycaemic control reduced the number of instances of cardiac pacing compared with conventional glycaemic control in both diabetic and/or nondiabetic patients undergoing cardiac surgery. As the odds ratio was 3.06, the odds of having deep sternal infection in the experimental group were 3.06 times the odds of the need for cardiac pacing in the control group, which can be considered clinically significant.

Gandhi et al.[65] evaluated the need for cardiac pacing in diabetic patients undergoing cardiac surgery. Although statistically nonsignificant, the study reported a reduced number of instances of cardiac pacing with liberal glycaemic control in comparison with very tight glycaemic control.

The need for cardiac pacing in diabetic patients after cardiac surgery was evaluated in Lazar et al. (2004)[70] involving 141 participants. The study reported a statistically significant difference between the tight glycaemic control group and the liberal glycaemic control group in the reduction of the need for cardiac pacing. The 59% difference in the odds of cardiac pacing in favour of the intervention group compared to the control group can be considered clinically significant.

4.2.10 Re-infarction

Re-infarction is an important predictor of morbidity in patients undergoing cardiac surgery. The meta-analysis which included two studies[62,70] was statistically nonsignificant in relation to reduction of cases of re-infarction between the tight glycaemic control group compared with the conventional glycaemic control group among diabetic and/or nondiabetic patients undergoing cardiac surgery. However, the 59% difference in the odds of re-infarction in favour of the intervention group compared to the control group can be considered potentially clinically significant.

Two studies[61,71] included in meta-analysis showed no statistically significant difference between very tight glycaemic control compared with conventional glycaemic control in reducing the number of re-infarctions in diabetic patients who had undergone cardiac surgery. As the odds ratio is 5.40, the odds of having re-infarction in the experimental group are 5.40 times the odds of having re-infarction in the control group which can be clinically significant.

Lazar et al. (2004)[70] reported no statistically significant difference between tight glycaemic control group and liberal glycaemic control group in reducing cases of re-infarction in diabetic patients. However, it is reported no case of re-infarction in tight glycaemic control group compared with two cases of re-infarction in the liberal glycaemic control group.

4.3 Summary of Findings

The quality of seven findings out of 40 using the Gradepro GDT software[80] were assessed and included in a summary of findings table as the GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group suggested that a maximum of seven findings be selected.[90] According to the GRADE working group, the quality of evidence should be assessed for each important outcome and expressed using four (high, moderate, low, very low) categories.[90] The rating is not done for each study as a single unit but for each outcome, therefore it can vary from one outcome to another within a single study.[90] Outcomes assessed were all-cause mortality and length of stay in hospital in all four groups except the very tight glycaemic control group versus the conventional glycaemic control group of diabetic patients undergoing cardiac surgery where only length of stay in hospital was assessed. In very tight glycaemic control versus conventional glycaemic control among diabetic and/or nondiabetic patients undergoing cardiac surgery subgroup, a few studies had small sample sizes and the meta-analysis showed wide variance of point of estimate. In tight glycaemic control versus conventional glycaemic control among diabetic and/or nondiabetic patients undergoing cardiac surgery subgroup, where some studies had small sample sizes, meta-analysis showed wide variance in point of estimate and substantial to considerable study variation. Among diabetic patients, a few studies had small sample sizes and meta-analysis showed wide confidence interval in one subgroup and small sample size in another subgroup. In tight glycaemic control versus conventional glycaemic control, meta-analysis could not be performed as, among two studies that reported mortality, one study reported no event in either group whereas another study was statistically significant. Hence, grading could not be done for this outcome. Overall, all the findings assessed using the Gradepro GDT software[80] were graded low quality evidence except two which were graded moderate.

4.4 Current recommendations in clinical guidelines

The recommendations on glucose targets vary from one guideline to another. This could be due to differences in study population and patient management at various centres. The recommendation of the Society of Critical Care Medicine's practical guideline[96] is to maintain blood sugar level at less than 150 mg/dl in cardiac surgical patients which has proven to be effective in reducing the risk of deep sternal wound infection and death.[2,5,28,68,97] On the other hand, the Society of Thoracic Surgeons[98] has suggested a more relaxed blood glucose target of less than 180 mg/dl for cardiac surgical patients during their perioperative period except for those who have devices in place (blood glucose target less than 150 mg/dl).

4.5 Discussion on other related reviews and studies

The largest trial to date, Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR),[48] found that intensive glucose control (81–108 mg/dL) actually increased 90-day mortality compared with a more liberal glucose target (<180 mg/dL) among 6104 critically ill patients in ICU (medical, surgical and mixed ICU), whereas this review has found evidence that very tight glycaemic control in all patients(both diabetic and/or nondiabetic) and tight glycaemic control in all patients and diabetic patients reduced the incidence of all-cause mortality in cardiac surgical patients. This could be because the NICE-SUGAR study looked at both medical and surgical patients in ICU rather than solely patients undergoing cardiac surgery, as well as post-operative glucose control rather than perioperative glycaemic control and it aimed at a more strict glucose range (81–108 mg/dL), whereas in this review the level of very strict glycaemic control was of wider range (80-150 mg/dl) because of the study variation.

Griesdale et al.[50] conducted a review that included data from the NICE-SUGAR study around the same time latter was being conducted which showed interesting results that showed that patients in surgical ICU appeared to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44–0.91), whereas patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78–1.28; mixed ICU: RR 0.99, 95% CI 0.86–1.12). Fourteen trials out of 26 reported hypoglycaemia, and the pooled RR with intensive insulin therapy was 6.0 (95% CI 4.5–8.0).

Van den Berghe et al.[15] looked at intensive glucose control (80-110 mg/dl) in both diabetic and nondiabetic critically ill patients. The majority of those who underwent cardiac surgery reported a decrease in the incidence of septicaemia, number of blood transfusions, length of stay in ICU, incidence of renal failure, number of bloodstream infections and other morbidities. This trial showed the largest positive impact on mortality and led to further trials evaluating various blood glucose goals in cardiac surgery patients; however, none were able to recreate such a widely noticeable impact on patient outcomes. Although reduction in mortality and length of stay in ICU replicates the results of our review, there was no significant difference in the incidence of renal failure between the tight glycaemic control and conventional glycaemic control groups in our review.

A study by LeComte et al.[88] evaluated incidence of renal failure in patients with intensive blood glucose control utilising an insulin infusion (80–110 mg/dL) versus patients without intensive blood glucose control. To maintain blood glucose, all patients were initiated intraoperatively on fluids that contained dextrose. A significant decrease in the incidence of postoperative renal injury and renal failure was found, but only in nondiabetic patients.

Zerr et al.[5] found that elevated mean blood glucose levels within the first 48 hours after surgery were found to be associated with deep sternal wound infections and were an independent risk factor for deep sternal wound development. A study by Car et al.,[7] which included both diabetic and nondiabetic

patients and evaluated the effect of lower blood glucose goals (<130 mg/dL) demonstrated a significant benefit with intensive blood glucose control in patient morbidity outcomes; patient glucose levels were considered well controlled if they were <130 mg/dL for more than 50% of the time. A reduction in the incidence of sternal wound infections was observed when blood glucose levels were kept lowered during the second and final phase of the study.

Wiener et al.[49] performed another review on critically ill patients in ICU (medical, surgical and mixed ICU patients) and found no significant difference in hospital mortality or renal failure needing dialysis in tight glucose control versus usual care. Although tight glucose control was associated with a significant reduction in septicaemia overall, subgroup analysis suggested this benefit was limited to surgical ICU patients and there was a significant risk of hypoglycaemia in the tight glycaemic control group. Although the zero difference in the number of cases of renal failure is consistent with the results of our review, mortality showed opposite results to our review. Again, this may be because the review looked at both medical and surgical patients in ICU rather than solely focussing on patients undergoing cardiac surgery.

Ng et al.[84] performed another review on the efficacy and safety of tight glycaemic control during heart surgery which showed that tight blood glucose control reduced the incidence of atrial fibrillation and the need for epicardial pacing, as well as the duration of mechanical ventilation hours and stay in the ICU in days. Heterogeneity was high for the incidences of atrial fibrillation and epicardial pacing, and extremely high for the duration of mechanical ventilation and ICU stay. Only one of nine studies found "tight" blood glucose control to be associated with significantly more episodes of hypoglycaemia. Our review showed that number of cases of atrial fibrillation was reduced in the tight glycaemic control group in all patient and diabetic patients. Although tight glycaemic control showed reduction in need for cardiac pacing in the diabetic group, there was no significant reduction in time on mechanical ventilation observed in any group. Tight glycaemic control showed reduction in time spent in ICU in all patient groups.

Ma et al.,[83] in another review, looked at the effects of intensive glucose control during the perioperative period on the prognosis of patients undergoing cardiac surgery. The results showed that intensive glycaemic control could reduce the incidence of infection, duration of mechanical ventilation and length of stay in ICU, and could also slightly reduce the incidence of post-surgical atrial fibrillation. However, intensive glycaemic control could not reduce the need for epicardial pacing. In our review, it was found that the number of atrial fibrillation cases was reduced in the tight glycaemic control group in all patient and diabetic patients. Significant reduction in the incidence of sternal infection was found only in the diabetic group with tight glycaemic control. Although tight glycaemic control showed reduction in the need for cardiac pacing in the diabetic group, there was no significant reduction in time on mechanical ventilation observed in any group. Tight glycaemic control showed reduction in time spent in ICU in all patient groups.

Haga et al.[60] conducted a recent review which showed that tight compared to normal glycaemic control during and after cardiac surgery may provide some benefit to patients following cardiac surgery, including a reduction in early mortality and incidences of postoperative atrial fibrillation and the need for epicardial pacing. There was some evidence that tight glycaemic control may of the number of deaths in very tight and tight glycaemic control in all patient and diabetic patient groups which is consistent with Haga et al., whereas cases of atrial fibrillation were reduced in the tight glycaemic control group in all patient and diabetic patients. Tight glycaemic control showed reduction in the need for cardiac pacing in the diabetic group. There was no significant reduction in time on mechanical ventilation observed in any group. Tight glycaemic control showed reduction in time spent in ICU in all patient groups.

Another review conducted by Ooi et al.[91] on the effects of tight glycaemic control in reducing infection and improving neurological outcomes in critically ill neurosurgical and neurological patients found that tight glycaemic control lowered infection rates, improved neurological outcomes but that mortality was not affected. Five studies of that review were restricted to neurosurgical patients. Four others included neurological patients. The results in neurosurgical patients were different from those in cardiac surgical patients. In this review, there was no significant difference that tight glycaemic control lowered infection rates (deep sternal infection) or the number of cases of stroke although there was statistical significant difference found in the reduction of mortality in the very tight glycaemic control group.

4.6 Limitations of the review

There were some potential limitations with this review. Although a thorough systematic search was conducted across multiple databases targeting both published and unpublished literature, it is possible that some articles may have been missed. Also, studies may have been conducted after the search and have therefore not been included. This may mean that as further studies are published in this area, an update of this review will be required. A further limitation is that only articles published in English were included. Moreover, there were differences between included studies in defining different types of ("very tight", "tight" and "conventional") glycaemic control, and the ranges we defined may not be the same as others would. Furthermore, some data could not to be reported on as although we contacted authors for raw data for their studies, this was not always supplied.

Chapter 5: Conclusion

This review identified 12 studies that assessed the effectiveness of very tight and tight glycaemic control in reducing mortality and morbidity (length of stay in hospital, length of stay in ICU, time on mechanical ventilation, stroke, renal failure, deep sternal infection, atrial fibrillation, need for cardiac pacing and re-infarction) in both “diabetic and/or nondiabetic" and only "diabetic" patients undergoing cardiac surgery. There is some evidence that very tight and/or tight glycaemic control may exert some positive effects on at least one of the subgroups in all of the outcomes. However, these results should be interpreted with caution due to the significant level of heterogeneity in some of the meta-analysis. A number of implications for practice and research have been identified which can be helpful for future practice.

5.1 Implications for practice

It is difficult to formulate clear recommendations from the findings of this systematic review. All graded findings were graded low quality evidence except for two which were graded moderate. However, the evidence supports the following guidance for clinicians managing patients during the perioperative period of cardiac surgery which can be useful in their clinical practice:

For all patients undergoing cardiac surgery:

Very tight glycaemic control may be effective in reducing all-cause mortality (although this should be interpreted with caution) and most of the outcomes of morbidity except time in mechanical ventilation, renal failure and deep sternal infection.

Tight glycaemic control is effective in reducing all-cause mortality and most of the outcomes of morbidity except time in mechanical ventilation and renal failure.

For diabetic patients undergoing cardiac surgery:

Very tight glycaemic control is not effective in reducing all-cause mortality but is effective in reducing most of the outcomes of morbidity except time on mechanical ventilation, stroke, deep sternal infection and re-infarction.

Tight glycaemic control is effective in reducing all-cause mortality and most of the outcomes of morbidity except stroke and renal failure.

However, blood glucose levels should be monitored routinely and carefully in all groups to avoid the incidence of hypoglycaemia.

5.2 Implications for research

Researchers should design adequately powered, rigorously conducted and methodologically sound randomized control trials in patients undergoing cardiac surgery to determine the role of perioperative insulin use and of tight glycaemic control. The trials should focus on the optimal glycaemic range to confer the best outcomes, the most appropriate duration of intervention (intraoperative or postoperative or both) and the most effective way of glucose administration, and to identify the population at risk. A clearly defined and accepted glycaemic range is required which is suitable for perioperative patients undergoing cardiac surgery to achieve the best possible outcomes. Additional research needs to be done to identify the frequency of hypoglycaemic events and the best method of glucose measurement during the perioperative period and the role of preoperative glycated haemoglobin (HbA1c) levels in determining postoperative outcomes after cardiac surgery. Further investigation is required to identify the effects on nondiabetic patients individually. Long term outcomes need to be looked at in addition to those immediately after surgery.

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Appendix I: Search strategy

Search strategy for PubMed run on July 02, 2014

No	Search	Result
1	"clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields] "random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomized"[All Fields] "randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields] "blood glucose"[MeSH Terms] OR ("blood"[All Fields] AND "glucose"[All Fields]) OR "blood glucose"[All Fields] "prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "control"[All Fields] OR "control groups"[MeSH Terms] OR ("control"[All Fields] AND "groups"[All Fields]) OR "control groups"[All Fields] "insulin"[MeSH Terms] OR "insulin"[All Fields] "therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] "glucose"[MeSH Terms] OR "glucose"[All Fields] "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields] "thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) OR "cardiac surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields]	1276

	AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) "coronary artery bypass"[MeSH Terms] OR ("coronary"[All Fields] AND "artery"[All Fields] AND "bypass"[All Fields]) OR "coronary artery bypass"[All Fields] "cardiovascular surgical procedures"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiovascular surgical procedures"[All Fields] OR ("cardiovascular"[All Fields] AND "surgery"[All Fields]) OR "cardiovascular surgery"[All Fields] "thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("heart"[All Fields] AND "surgery"[All Fields]) OR "heart surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("heart"[All Fields] AND "surgery"[All Fields])	

Search strategy for Embase run on July 02, 2014

No	Search	Result
1	'blood'/exp OR blood AND ('glucose'/exp OR glucose) AND [1990-2014]/py	228,297
2	blood AND glucose AND control AND [1990-2014]/py	71,597
3	tight AND blood AND glucose AND control AND [1990-2014]/py	1,733
4	intensive AND blood AND glucose AND control AND [1990-2014]/py	5,001
5	insulin AND therapy AND [1990-2014]/py	161,717
6	insulin AND protocol AND [1990-2014]/py	7,125
7	intensive AND insulin AND therapy AND [1990-2014]/py	8,926
8	glucose AND management AND [1990-2014]/py	27,785
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	343,657
10	clinical AND trial AND [1990-2014]/py	1,120,873

11	randomised AND [1990-2014]/py	80,755
12	randomized AND [1990-2014]/py	587,452
13	randomized AND controlled AND trial AND [1990-2014]/py	429,366
14	#10 OR #11 OR #12 OR #13	1,293,961
15	cardiac AND surgery AND [1990-2014]/py	164,003
16	coronary AND artery AND bypass AND [1990-2014]/py	69,124
17	cardiovascular AND surgery AND [1990-2014]/py	182,183
18	heart AND surgery AND [1990-2014]/py	319,018
19	#15 OR #16 OR #17 OR #18	427,463
20	#9 AND #14 AND #19	3,409

Search strategy for Cochrane (Central) run on July 02, 2014

No	Search	Results
1	Blood glucose	21667
2	Blood glucose control	21500
3	Tight blood glucose control	207
4	Intensive blood glucose control	1549
5	Insulin therapy	13,541
6	Intensive insulin therapy	1286
7	Insulin protocol	1795
8	Glucose management	2457
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	27,583
10	Cardiac surgery	10,862
11	Coronary artery bypass	7,993
12	Heart surgery	13,683

13	Cardiovascular surgery	7,624
14	#10 or #11 or #12 or #13	23,701
15	Clinical trial	516,293
16	Randomized	497,383
17	Randomised	497,383
18	Randomized controlled trial	56
19	#15 or #16 or #17 or #18	649,720
20	#9 and #14 and #19	1072

Search strategy for CINAHL run on July 02, 2014

No	Search	Result
S1	Blood glucose	22,023
S2	Blood glucose control	9,279
S3	Tight blood glucose control	313
S4	Intensive blood glucose control	831
S5	insulin therapy	11,052
S6	Intensive insulin therapy	941
S7	Insulin protocol	449
S8	Glucose management	2,989
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	29,279
S10	Cardiac surgery	9,566
S11	Coronary artery bypass	7,713

S12	Heart surgery	16,132
S13	Cardiovascular surgery	5,388
S14	S10 OR S11 OR S12 OR S13	26,926
S15	Clinical trial	41,973
S16	Randomized	67,653
S17	Randomised	17,963
S18	randomized controlled trial	24,202
S19	S15 OR S16 OR S17 OR S18	96,862
S20	S9 AND S14 AND S19	74

Search strategy for ProQuest run on August 03, 2014

No	Search	Result
1	(Blood glucose OR Blood glucose control OR Tight blood glucose control OR Intensive blood glucose control OR Insulin therapy OR intensive insulin therapy OR insulin protocol OR glucose management) AND (Cardiac surgery or coronary artery bypass OR Heart surgery or cardiovascular surgery) AND (Clinical trial or Randomized OR Randomised or randomized controlled trial)	519

Search strategy for Science Direct run on August 03, 2014

No	Search	Result
1	date > 1989 and TITLE-ABSTR-KEY(blood glucose control) and TITLE-ABSTR-	43

	KEY(cardiac surgery)	
2	date > 1989 and TITLE-ABSTR-KEY(Insulin therapy) and TITLE-ABSTR-KEY(cardiac surgery)	66
3	date > 1989 and TITLE-ABSTR-KEY(Tight blood glucose control) and TITLE-ABSTR-KEY(Coronary artery bypass)	6
4	date > 1989 and TITLE-ABSTR-KEY(Insulin protocol) and TITLE-ABSTR-KEY(Cardiovascular surgery)[	4
5	Total	119

Search strategy for Web of Science run on August 03, 2014

No	Search	Result
1	Blood glucose	601,498
2	Blood glucose control	222,709
3	Tight Blood glucose control	1,736
4	Intensive Blood glucose control	10,295
5	Insulin therapy	337,186
6	Intensive insulin therapy	16,084
7	insulin protocol	20,023
8	Glucose management	63,860
9	#8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	880,779
10	Cardiac surgery	299,877
11	Coronary artery bypass	155,040
12	Cardiovascular surgery	528,587
13	Heart surgery	510,646
14	#13 OR #12 OR #11 OR #10	868,926
15	clinical trial	1,813,297
16	randomised	1,877,069

17	randomized	1,877,069
18	randomized controlled trial	860,407
19	#18 OR #17 OR #16 OR #15	3,000,339
20	#19 AND #14 AND #9	1,082

Search strategy for Google Scholar run on August 03, 2014

No	Search	Results
1	(((((clinical trial) OR randomised) OR randomized) OR randomized controlled trial)) AND ((((((((((blood glucose) OR blood glucose control) OR tight blood glucose control) OR intensive blood glucose control) OR insulin therapy) OR insulin protocol) OR intensive insulin therapy) OR glucose management)) AND ((((cardiac surgery) OR coronary artery bypass) OR cardiovascular surgery) OR heart surgery))	100

Appendix II: Appraisal instruments

MAStARI appraisal instrument

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix lll: Data extraction instruments

MAStARI data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT	☐	Quasi-RCT	☐	Longitudinal	☐
Retrospective	☐	Observational	☐	Other	☐

Participants

Setting

Population

Sample size

Group A _____ Group B _____

Interventions

Intervention A

Intervention B

Authors Conclusions:

Reviewers Conclusions:

Appendix IV: Included studies

MAStARI

Study	Methods	Participants	Intervention A	Intervention B	Outcomes	Notes
Asida 2013[61]	RCT	Diabetic patient above 18 years old admitted for cardiac surgery.	Tight glycaemic control is defined 80-110 mg/dl was targeted with a CII in saline (50 units of rapidly acting insulin (actrapid) in 50 ml syringe) at a rate of 1–2 units/h if blood glucose between 110 and 150 mg/dl. If blood glucose level was between 150 and 200 mg/dl we in creased the rate of insulin infusion to 4–6 units/h. And if it exceeded 200 mg/dl then the insulin infusion rate was 6–9 units/h. Patients received insulin infusion intraoperatively and continued in the ICU until complete recovery from anaesthesia.	There was no tight glycaemic control. Patients in this group followed the same protocol of insulin infusion only if their perioperative blood glucose level exceeded 180 mg/dl.	Delayed recovery (length of hospital stay, pulmonary problems, cardiac problems, renal problems, neurological problems, surgical problems.	The study had a small sample size and it was a single centre study.

Azarfarin 2011[62]	RCT	Adult (above 18 years old) nondiabetic patients admitted for elective CABG surgery.	A modified insulin therapy protocol was used to maintain blood glucose level between 110mg/dl and 126mg/dl. Before induction of anaesthesia, fasting blood glucose level is obtained. After induction of anaesthesia, an insulin infusion (1U/ml in normal saline) was initiated and blood glucose testing was done every 30 minutes in the operating room and every 2 hours (or every hour if >50 mg/dl differences) in ICU. All intravenous fluids were free of glucose.	No intervention was done unless the blood glucose level exceeded 200mg/dl which was treated by bolus insulin. Blood glucose level monitored every 30 minutes during operation and thereafter every 2 hours postoperatively up to 48 hours in ICU.	Blood glucose level (baseline, intraoperative, postoperative), postoperative complications (cardiac pulmonary, neuropsychological, renal, infectious, rethoractomy for bleeding.	The intervention (insulin therapy) was limited to intraoperative period only. When the patients were in ICU the study protocol was no longer being continued.
Chan 2009[63]	RCT	Both diabetic and nondiabetic adult (above 21 years of age) patients from both	Intensive glycaemic control is defined 80-130 mg/dl targeted by maintaining CII through a central venous catheter using an infusion device. The standard concentration was 100 IU of Actrapid HM in 100 ml of 0.9% NaCl. When the blood	Conventional glycaemic control had a target blood glucose level of 160-200 mg/dl where insulin infusion was initiated at an initial dose of 1IU/dl when the blood glucose level	Primary outcomes were clinical outcomes, including time of mechanical ventilation,	

		genders admitted for open-heart surgery requiring cardiopulmonary bypass.	glucose level exceeded 130 mg/dl, insulin was started at 2IU/hr (4IU/hr if the first blood glucose level exceeded 220mg/dl). When the next blood glucose reading was >150 mg/dl, the insulin dose was increased by 1-2 IU/hr. When the subsequent blood glucose level was 110-140 mg/dl, insulin was increased by 0.5 to 1 IU/hr. When blood glucose approached 80-110 mg/dl, insulin was adjusted by 0.1 to 0.5 IU/hr. When the blood glucose level was 80-110 mg/dl, the insulin dose was unaltered. Dose adjustments were always proportionate to the observed change in blood glucose. During intraoperative period and during the first 24 hours after admission in ICU, measurement of blood glucose was advised every one to two hours until the targeted level of blood glucose was achieved.	exceeded 200 mg/dl. When a control blood glucose level was >200 mg/dl, the insulin dose was increased by increments of 1 IU/hr. Once the blood glucose level was between 180-200 mg/dl, the insulin dose was maintained constant. When blood glucose level <180 mg/dl, insulin infusion was decreased until the blood glucose level was between 180-200 mg/dl. The insulin dose was further reduced and eventually stopped completely when blood glucose levels decreased further. Insulin infusion was restarted when blood glucose exceeded 200 mg/dl.	length of stay in the intensive care unit, infection, hypoglycaemia, renal or neurological dysfunction, blood transfusion and length of stay in the hospital. The secondary outcome was a combined end-point (mortality at 30 days, infection or length of stay in the intensive care unit of more than 3 days).	

			Thereafter, blood glucose was measured every four hours, unless dramatic decreases or increases in blood glucose level occurred.			
Desai 2012[64]	RCT	Both diabetic and nondiabetic adult (above 18 years of age) patients undergoing first-time isolated coronary artery bypass grafting in whom hyperglycaemia developed.	Strict glycaemic control is defined as blood glucose 90-120 mg/dl. Intraoperative glucose measures and interventions were under the preview of the anaesthesiologist whose goal was to maintain a blood glucose level between 100 and 180 mg/dl. Maintenance of blood glucose level according to their randomized arm was started in ICU using the programmed Glucommander (a FDA approved computer software system for controlling blood glucose designed to assist clinicians in obtaining and then maintaining glucose control by calculating the insulin dose required to achieve the target range in response to measurement of blood glucose at the patient's	Liberal glycaemic control is defined as blood glucose level 121-180 mg/dl. If the randomization scheme determined the patient was to be in the liberal arm, then an order was written in the chart to change the Glucommander parameters for a target glucose range of 121-180 mg/dl.	Renal failure, atrial fibrillation, pneumonia, deep sternal wound infection, prolonged ventilation, major adverse cardiac events (MACE), length of stay, operative mortality.	This was not a blinded study, which could introduce bias into study.

			bedside, but does not administer the insulin) to adjust the blood glucose level to patients' assigned range. Hourly blood glucose was monitored with blood obtaining from a patient's arterial line and analysed by point of care testing through Glucose Accu-Chek Advantage with the AccuData GTS/GTS manufactured by Roche. Blood glucose levels less than 40 mg/dl or greater than 500mg/dl were sent to the laboratory for further analysis; however, treatment was initiated for low blood glucose if indicated. Patients were maintained on the electronic-based protocol of intravenous insulin for a minimum of 72 hours perioperatively. If the randomization scheme determined the patient was to be in the strict arm, then the patient continued on the standard CABG postoperative			

			orders, mandating strict glycaemic control with a target glucose range of 90-120 mg/dl.			
Gandhi 2007[65]	RCT	Adults with and without diabetes who were undergoing on-pump cardiac surgery.	Intensive glycaemic control is defined as blood glucose level between 4.4(80 mg/dl) and 5.6 mmol/l(100mg/dl) was targeted with a continuous intravenous insulin infusion, 250 units of NovoLin R (Novo Nordisk, Princeton, New Jersey) in 250 ml of 0.45% sodium chloride, when their blood glucose levels exceeded 5.6 mmol/l (>100 mg/dl0). The infusions were adjusted to maintain blood glucose levels between 4.4(80 mg/dl) and 5.6 mmol/l(100mg/dl). The doses were adjusted according to a standardised algorithm used by anaesthesiologists. Intensive glycaemic control was maintained during both intraoperative and postoperative period.	Patients in conventional group did not receive insulin during surgery unless their glucose level exceeded 11.1 mmol/l(>200 mg/dl). If glucose concentration was between 11.1 (200mg/dl) and 13.9 mmol/dl (250mg/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 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/l9 (<150	Glycaemic control (intraoperative and in ICU), length of stay in ICU and in hospital, death,	

				mg/dl). Arterial blood glucose monitored every 30 minutes during surgery. Intravenous insulin infusion started in this group on their arrival in ICU. Therefore, both group treated identically when they were in ICU. The target blood glucose 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).	stroke, deep sternal infection, cardiac arrest, heart block requiring pacemaker, new onset atrial fibrillation, acute renal failure, prolonged intubation.	
Giakoumidakis 2013[66]	Randomised quasi-experimental study	Both diabetic and nondiabetic adult (above 18 years of age) patients admitted for different	Intensive blood glucose control is defined as 120-160 mg/dl, aimed to maintain with continuous intravenous infusion of fast acting insulin solution (100 IU of Actrapid HM in 100 ml of 0.9% NaCl) through a central venous catheter using a volumetric infusion pump	Conventional blood glucose control is defined as 161-200 mg/dl, targeted with a CII when blood glucose level exceeded 200 mg/dl during the first 24 hours after surgery. The infusion rate was adjusted based on the	Mean blood glucose, mean duration of tracheal intubation, severe hypoglycaemia, mean ICU length	This is a single centre study with small sample size which has a quasi-experimental design,

		types of cardiac surgery.	during the first 24 hours after surgery. Patients in the therapy group received insulin when their blood glucose level exceeded 160 mg/dl. The infusion rate was adjusted based on the predetermined insulin infusion protocol while aiming to maintain blood glucose level between 120 mg/dl and 160 mg/dl. The infusion was stopped when blood glucose levels were <160 mg/dl. Measurement of blood glucose levels (baseline values) on ICU admission and every 2 hours thereafter during the first 24 hours of ICU stay.	predetermined insulin infusion protocol while aiming to maintain blood glucose levels between 160 mg/dl and 200 mg/dl. The infusion was stopped when blood glucose levels were less than or equal to 200 mg/dl.	of stay, mean postoperative hospital length of stay, postoperative infection, in-hospital mortality, 30-day mortality.	selection bias and lack of both allocation concealment.
Hoedemaeker 2005[67]	RCT	Adult (above 18 years old) nondiabetic patients undergoing elective coronary	Intensive glycaemic control is defined as 80-110 mg/dl targeted with continuous insulin (Actrapid HM; Novo Nordisk, Copenhagen,Denmark) infusion when the blood glucose level exceeded 110 mg/dl. The treatment	In conventional treatment group, 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	Time between	The sample size used in this study was small.

		artery bypass grafting (CABG) were included. Patients undergoing off-pump cardiac surgery were excluded.	started immediately on admission to the ICU. The maximal dose of insulin was arbitrarily set at 50 IU per hour. 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 analyser (ABL700, Radiometer Medical, Copenhagen)	pump (Perfusor-FM, B. Braun, Melsungen, Germany), was started only if the blood glucose level exceeded 200 mg/dl and the infusion was adjusted to maintain the level at a value between 180 and 200 mg/dll (10.0 and 11.1 mmol/l).	end of surgery and admission to ICU, Time in ICU, Time in ventilator, creatine kinase, erythrocyte transfusion, platelet transfusion.	
Ingels 2006[68]	Pre-planned sub-analysis and follow-up study of a RCT	Adult (above the age of 18 years) diabetic and nondiabetic patients admitted for different types of high risk cardiac surgery.	Strict blood glucose control below 6.1 mmol/L (110 mg/dL) with intensive insulin therapy when patients admitted in surgical ICU. An insulin infusion was started if the blood glucose level exceeded 110 mg per decilitre, and the infusion was adjusted to maintain normoglycaemia (80 to 110 mg/dl [4.4 to 6.1 mmol/l]). The maximal dose of insulin was arbitrarily set at 50 IU per hour. Adjustments of the	Conventional approach which was only recommended insulin therapy when blood glucose levels exceeded 12 mmol/L (220 mg/dL). 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.	Mortality analysis: Death during intensive care, causes of death in ICU, In-hospital death, long term mortality(2,3,4 years after ICU admission); ICU morbidity analysis:	This was performed in a single centre. There was no baseline analysis performed of the Karnofsky score or the NHP questionnaire.

			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 analyser (ABL700, Radiometer Medical, Copenhagen).	Braun, Melsungen, Germany), was started only if the blood glucose level exceeded 215 mg/dl and the infusion was adjusted to maintain the level at a value between 180 and 200 mg per decilitre (10.0 and 11.1 mmol/l).	Extubated within 48 h after surgery, duration of ventilatory support, duration of intensive care, dialysis, hyperbilirubinaemia, bloodstream infection, electromyographic evidence of critical illness, polyneuropathy, red cell transfusions, highest level of C-reactive protein, cumulative TISS-28	
Kirdemir 2008[69]	RCT	Adult (above 18 years old) diabetic	Continuous insulin infusion(CII) was initiated and maintained to lower the blood glucose level to	In this group, subcutaneous insulin was injected every 4 hours in an attempt to	Perioperative and postoperative	

		patients admitted for coronary artery bypass graft(CABG).	100 to 150 mg/dl in this patient group. The patients received a CII titrated per protocol in the perioperative period (Portland protocol).The CII was initiated in the operating room (before sternotomy and after induction of anaesthesia), continued during cardiopulmonary bypass (CPB), and was maintained until the third postoperative day, even for patients who were transferred out of the intensive care unit (ICU). Serum potassium levels were maintained between 4.0 and 5.5 mmol/L through the administration of exogenous potassium. In the ICU, this was accomplished through the intravenous administration of potassium according to a standardized protocol.	maintain blood glucose levels below 200 mg/dL. Sliding scale dosage of insulin was titrated to each patient's glycaemic response during the prior 4 hours. These sliding scale subcutaneous injections were continued every 4 hours throughout the patients' hospital course, even after the resumption of their preoperative glucose control regimen.	outcomes were: CPB time (min) cross-clamp time, distal anastomosis, low cardiac output, IABP positive inotropic drug requirement, renal failure needing dialysis, reoperative surgery, tamponade, bleeding ventilation longer than 48 hrs, sternal dehiscence, TIA, stroke, sternal wound infection, mediastinitis, internal mammary artery,	

					postoperative glucose level, mortality, ICU stay, hospital stay, SVT, atrial fibrillation, atrial flutter, sinus tachycardia, multifocal atrial tachycardia.	
Lazar 2004[70]	RCT	Adult diabetic patients undergoing primary or reoperative coronary artery bypass grafting (CABG) performed on cardiopulmo	Tight glycaemic control defined as 125-200 mg/dl targeted to maintain by a modified Glucose-insulin-potassium (GIK) infusion through a central line consisting of 500 mL DW with 80 U of regular insulin and 40 mEq of KCl infused at 30 mL/h, prepared by a research pharmacist. The GIK was started just before anaesthetic induction and continued until cardiopulmonary bypass was instituted. It was then discontinued and restarted after the aorta was unclamped and	Standard therapy is defined as blood glucose <250 mg/dl which was maintained by DW infused at 30 mL/h. Blood glucose and potassium were also monitored every hour, and the scale which was used to administer subcutaneous insulin in this group:351-400 mg/dL - 8 U SC regular insulin; 300-350 mg/dL - 6 U SC regular insulin; 250-299 mg/dL - 4 U SC regular	30-day mortality, myocardial	

		nary bypass.	continued for 12 hours after arrival in the Intensive Care Unit (ICU). Blood glucose and potassium were monitored every hour. Adjustments in the rate of the GIK infusion were made on the basis of the scale which was: >270 mg/dL - 8 U regular insulin IV bolus; increase GIK by 6 mL/h; 201-270 mg/dL - Increase GIK by 3mL/h; 126-200 mg/dL - No change;75-125 mg/dL - Decrease GIK by 6 mL/h; <75 mg/dL - Hold GIK for 15 minutes; recheck blood glucose every 15minutes until >125 mg/dL; after blood glucose >125mg/dL, restart GIK at 6 mL/h less than previous rate.	insulin; 80-249 mg/dL - No insulin coverage. After the 18-hour study period, patients resumed their preoperative diabetic regimens (oral agents or insulin) titrated to keep blood glucose <200 mg/dL.	infarction, pacing, atrial fibrillation, infections (pneumonia and wound), time on ventilators, maximum weight gain, inotropic score, ICU stay, postoperative hospital stay.	
Lazar 2011[71]	RCT	Adult diabetic patients with diabetes mellitus undergoing	Aggressive glycaemic control was defined as 90-120 mg/dl maintained by a CII 100 units of regular insulin in 100 mL of 0.9% normal saline was initiated at 3 mL/hour and titrated to maintain the	Moderate glycaemic control was defined as 120-180 mg/dl using the same insulin infusion used for aggressive control. The algorithm was: blood glucose >240 mg/dl -		The study was performed in a single centre. There was a small sample size and the

		coronary artery bypass surgery (CABG) on cardiopulmonary bypass.	targeted glucose level on the basis of the algorithm which was: Blood glucose 240-300 mg/dl - Give 6 units IV regular insulin bolus and increase infusion by 1 unit/hour; 201-240 mg/dl - Give 3 units IV regular insulin bolus and increase infusion by 1 unit/hour; 151-200 mg/dl - Give 2 units IV regular insulin bolus and increase infusion by 1 unit/hour; 121-150 mg/dl- Increase infusion by 0.5 unit/hour; 80-120 mg/dl - No change; 60-79 mg dl- Discontinue insulin infusion. Give 25 mL of D50% dextrose IV and recheck glucose in 30 minutes. If glucose >80 mg/dL, restart insulin infusion, but decrease by 1 unit/hour from previous infusion rate. The study protocol continued during the periods of cardiopulmonary bypass and cardioplegic arrest, after the discontinuation of bypass and for	Increase infusion by 2 units/hour and give 3 units IV regular insulin bolus; 180-240 mg/dl - Increase infusion by 2 units/hour; 121-180 mg/dl - no change; 81-120 mg/dl - Decease infusion by 2 units/hour; <80 mg/dl - Decrease infusion by 2 units/hour and give 25 ml 50% dextrose IV; recheck glucose in 30 minutes. If glucose level exceeds 120, restart insulin infusion, but decrease by 1 unit/hour from previous infusion rate.	Primary outcomes were major adverse events (30-day mortality, myocardial infection, neurologic events, deep sternal infections and atrial fibrillation), incidence of hypoglycaemia.	clinicians were not blinded to the treatment group.

			18 hours in the ICU. After the 18-hour ICU period, patients were transitioned off the insulin drip using either short or long acting insulin agents and ultimately back to their preoperative diabetic regimens maintaining a fasting glucose level less than 120 mg/dL and 4 PM glucose levels less than 180 mg/dL.		Secondary outcomes were time on ventilator, weight gain, inotropic score>1%, ICU, hospital length of stay, amount of insulin.	
Rujirojindakul 2014[72]	RCT	Adult both diabetic and nondiabetic patients having various types of surgery using cardiopulmonary bypass.	In the intensive group, a hyperinsulinemic normoglycaemic clamp with modified glucose insulin potassium (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	In the control group, 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.		This study conducted in a single centre and terminated early because of hypoglycaemia.

			magnesium sulphate 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 scale: 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. Arterial blood glucose levels were measured with an Accu-Chek glucose monitor (Roche Diagnostics, Basel, Switzerland) every 30 min after arterial cannulation until the end of surgery. By design, both groups had 12-h post-operative blood glucose controlled levels at less		Infection, stroke, new atrial fibrillation, heart block requiring pacemaker, acute kidney injury, cardiac arrest, death, median duration of mechanical ventilation, median length of ICU stay, safety outcome, hypolycaemia	

			than 11.1 mmol/l to make sure that any observed differences in outcome would be due to the effects of intraoperative glycaemic control.			

Appendix V: Excluded Studies and reasons for exclusion

1. Bhamidipati, Castigliano M, LaPar, Damien J, Stukenborg, George J, Morrison, Christine C, Kern, John A, Kron, Irving L, Ailawadi, Gorav. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2011; 141(2): 543-551.

Reason for exclusion : This study was a retrospective one.

2. Subramaniam, B., Panzica, P. J., Novack, V., Mahmood, F., Matyal, R., Mitchell, J. D., Sundar, E., Bose, R., Pomposelli, F., Kersten, J. R., Talmor, D. S.. Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. Anesthesiology. 2009; 110(5): 970-977.

Reason for exclusion: This trial included patients undergoing vascular surgery rather than cardiovascular surgery.