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The effectiveness of tight glycemic control on decreasing surgical site infections and readmission rates in adult patients with diabetes undergoing cardiac surgery: A systematic review

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ABSTRACT

Objective: A systematic review of the effects of tight glycemic control with a continuous insulin infusion to achieve blood glucose levels ≤ 200 mg/dL on surgical site infections and readmission rates in adult patients with diabetes after cardiac surgery.
Methods: A quantitative systematic review of the literature. Databases, including PubMed, CINAHL, EMBASE, and CENTRAL, were searched for relevant studies from database inception through August 2014. Randomized and quasi-experimental studies were included.
Results: A meta-analysis of ten studies demonstrated that glycemic control with a continuous insulin infusion to achieve blood glucose levels ≤ 200 mg/dL significantly reduced surgical site infection rates (odds ratio 0.35, 95% confidence interval 0.25-0.49; $Z = 6.0$, $P < 0.00001$) compared with standard diabetes management.
Conclusions: Maintaining blood glucose levels ≤ 200 mg/dL with a continuous insulin infusion in all stages of the perioperative period in cardiac surgery patients with diabetes can reduce the incidence of surgical site infections.

Introduction

As of 2012, 29.1 million people, representing 9.3% of the United States' (US) population, have been diagnosed with diabetes mellitus (DM).[1] Patients with DM have a 2- to 4- fold greater risk for developing coronary heart disease (CHD) compared to patients without DM and suffer more multi-vessel CHD that leads to invasive revascularization procedures including coronary artery bypass surgery (CABG).[2]

Of the approximately 397,000 CABG procedures performed in the US,[3] as many as 31% of patients develop hospital acquired infections within 30 days of the operation.[4] DM, obesity, high preoperative serum glucose levels (>200 mg/dL), and female gender are among the risk factors for surgical site infections following CABG surgery.[5] Serum glucose levels > 200 mg/dL in the immediate (<48 h) postoperative period contribute to increased risk of surgical site infections.[6,7] Poor glycemic control prior to surgery contributes to poor control after hospital discharge and increases the incidence of complications such as poor wound healing and higher rates of surgical site infections, and ultimately readmission to the hospital and increased mortality.[8]

Increased hospital readmissions can be used as indicators of poor quality care and are major concerns for health care organizations due to substantial incurred losses in revenue.[9,10] A readmission can be the result of incomplete treatment, poor care of the underlying problem, poor discharge coordination of services, incomplete discharge planning, and/or inadequate access to care.[11,12] Hannan et al[13] showed a 16.5% all-cause readmission rate within 30 days of CABG surgery and Li et al[14] showed a 13.2% readmission rate. The authors of both studies identified postoperative infection as the most common reason for readmission.

Abbreviations: AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; ICU, Intensive care unit; JBI-MAStARI, Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument; NA, not applicable; N, no; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SCIP, surgical care improvement project; SE, standard error; U, unclear; US, United States; Y, yes.

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To address the problem of poor glycemic control in acutely ill patients with diabetes, the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) recommend intravenous insulin infusions for achieving and maintaining tight glycemic control in critically ill patients who have DM.[15] The recommendation is to initiate the insulin infusion at a blood glucose threshold no greater than 180 mg/dL for the treatment of persistent hyperglycemia in critically ill inpatients with a target blood glucose of 140–180 mg/dL for the majority of these patients.[15,16] The 2015 ADA practice guidelines[16] suggest that a target of 110–140 mg/dL may be appropriate for select critically ill patients when there is no increased risk of hypoglycemia and recommended the use of subcutaneous insulin with basal and corrective doses in non-critically ill patients, with the goal of a preprandial glucose of <140 mg/dL. However, there are no uniform guidelines defining a desired target range for optimal postoperative blood glucose. The Surgical Care Improvement Project (SCIP), which was developed in 2003 as a national quality partnership of organizations committed to improving the safety of surgical care through the reduction of postoperative complications, developed a core measure to maintain blood glucose at a level ≤ 180 mg/dL during the perioperative and postoperative period based on evidence of decreased surgical site infections with this target.[17,18] The Society of Thoracic Surgeons also recommends a target of ≤180 mg/dL in the immediate postoperative period.[19] In contrast, the Portland Diabetic Project[20] evaluated the effects of the Portland Protocol, a now widely used intravenous insulin protocol to maintain blood glucose < 150 mg/dL, in a randomized controlled trial (RCT) of 5510 cardiac surgery patients with DM. It was demonstrated that the use of this protocol was safe and led to a 77% reduction in surgical site infections.[20]

Despite the current recommendations, the most recent systematic review of the effects of tight glycemic control in the postoperative period after surgical procedures was published in 2009[21] and included five RCTs involving 773 adult patients with DM who underwent a variety of surgical procedures. The authors concluded that there was insufficient evidence to support the use of tight glycemic control with continuous insulin infusions to reduce surgical site infections.

Due to the absence of consistent evidence of the effects of tight glycemic control during the postoperative period after cardiac surgery, the purpose of this systematic review was to identify and synthesize the best available evidence on the effectiveness of tight glycemic control interventions using a continuous insulin infusion to achieve blood glucose levels ≤200 mg/dL on decreasing surgical site infections and readmission rates in adult patients with DM undergoing cardiac surgery.

Methods

We considered studies on the effectiveness of tight glycemic control interventions in which a continuous insulin infusion was used to control blood glucose to levels ≤200 mg/dL, for inclusion in this review. The goal of tight glycemic control in the adult patient with DM after cardiac surgery is to obtain a steady serum glucose level to reduce the risk of postoperative complications such as surgical site infections. While current guidelines recommend a target glucose of ≤180 mg/dL,[16,18,19] some of the studies these guidelines were based on include target ranges up to 200 mg/dL; therefore, a serum glucose target of ≤200 mg/dL was chosen for this review to capture all studies evaluating tight glycemic control interventions.

We considered studies that compared tight glycemic control interventions with continuous insulin infusions to standard care. Standard care included the administration of bolus dose insulin subcutaneously on a sliding scale regimen for elevated glucose levels or the administration of diabetes medications in oral form to control serum glucose levels.

Studies included the following outcome measures:

- Surgical site infections within one year after cardiac surgery. For this review a surgical site infection was defined as purulent drainage from the deep incision; an organism isolated from an aseptically obtained wound culture; wound dehiscence; the need for surgical wound revision; or the presence of fever (>38 °C), localized pain or tenderness, an abscess, or any other observable evidence of infection on direct examination, reoperation, histopathology, or radiologic examination.[4,22]
- All cause readmission rates to the same hospital, a different hospital, or another acute care facility within one-year post discharge from the index admission in which the patient underwent cardiac surgery.

Search strategy

To find both published and unpublished studies, we conducted a comprehensive search of the literature in three steps: 1) We conducted an initial limited search of PubMed and CINAHL using the following initial key words: diabetes, glycemic control, cardiac surgery, insulin, and surgical wound infection. To develop a comprehensive list of key words, we analyzed the text words contained in the title and abstract and the index terms used to describe an article. 2) We conducted a second search across all included databases using all identified keywords and index terms. The databases searched included: PubMed, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Health Source: Nursing/Academic Edition, and Scopus. The search for unpublished studies included: New York Academy of Medicine, ProQuest Dissertation & Thesis, Google Scholar, Virginia Henderson International Library, and the European Society of Cardiology. 3) We searched the reference lists of all identified articles for additional studies. We considered studies published in the English language from the inception of each database through August 2014 for inclusion in this review. Fig. 1 details the PubMed search strategy.

Study selection

The comprehensive search of the literature yielded 1755 potentially relevant articles. We removed 14 duplicate records and excluded 1701 additional articles after review of the titles and key words. We retrieved 40 full text articles for further review, because additional information beyond the abstract was needed to determine if the article met the inclusion criteria for this review. After reviewing the full text papers for eligibility, we excluded 27 studies that did not meet the inclusion criteria. We identified 13 articles for inclusion in this systematic review. Fig. 2 outlines the stages of the process for identifying relevant studies for inclusion in this systematic review.

Assessment of methodological quality

Two authors independently assessed each quantitative paper selected for retrieval for methodological quality prior to inclusion in the review. We used standardized critical appraisal instruments from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI).[23]

Data extraction

Two authors independently extracted data from the included studies using the standardized data collection tool from

#1	"diabetes mellitus"[MeSH Terms] OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields] OR "diabetes mellitus type 2"[All Fields] OR "maturity onset diabetes"[All Fields] OR "type 2 diabetes"[All Fields] OR "noninsulin dependent diabetes"[All Fields] OR "non-insulin dependent diabetes"[All Fields] OR "niddm"[All Fields]
#2	"coronary surgery" OR CABG OR "thoracic surgical procedures"[MeSH Terms] OR “thoracic surgical procedure”[All Fields] OR “thoracic surgical procedures”[All Fields] OR "thoracic surgery"[All Fields] OR "thoracic surgery"[MeSH Terms] OR "cardiac surgical procedures"[MeSH Terms] OR “cardiac surgical procedure”[All Fields] OR “cardiac surgical procedures”[All Fields] OR "coronary artery bypass"[MeSH Terms] OR "coronary artery bypass"[All Fields] OR "heart surgery" OR "cardiac surgery"
#3	"insulin"[MeSH Terms] OR "insulin"[All Fields] OR "hemoglobin a, glycosylated"[MeSH Terms] OR "glycosylated hemoglobin a"[All Fields] OR "hemoglobin a, glycosylated"[All Fields] OR "glycemic control" OR "insulin infusion" OR “hypoglycaemic agent”[All Fields] OR “hypoglycaemic agents”[All Fields] OR "hypoglycemic agents"[MeSH Terms] OR “hypoglycemic agent”[All Fields] OR “hypoglycemic agents”[All Fields] OR “hypoglycemic drug”[All Fields] OR “hypoglycemic drugs”[All Fields] OR “antidiabetic drug”[All Fields] OR “antidiabetic drugs”[All Fields] OR “antidiabetic agent”[All Fields] OR “antidiabetic agents”[All Fields] OR "hemoglobin a1c"[All Fields] OR "hba1c"[All Fields] OR “hypoglycaemic drug”[All Fields] OR “hypoglycaemic drugs”[All Fields] OR "glycaemic control" OR "haemoglobin a, glycosylated"[All Fields] OR "glycosylated haemoglobin a" OR "haemoglobin a1c"
#4	"surgical wound infection"[MeSH Terms] OR "surgical wound infection"[All Fields] OR "surgical wound infections"[All Fields] OR "infection"[MeSH Terms] OR "infection"[All Fields] OR "infections"[All Fields] OR "intraoperative complications"[MeSH Terms] OR "intraoperative complications"[All Fields] OR "intraoperative complication"[All Fields] OR "postoperative complications"[MeSH Terms] OR "postoperative complications"[All Fields] OR "postoperative complication"[All Fields] OR "surgical site infection"[All Fields] OR “surgical site infections”[All Fields] OR readmission[All Fields] OR readmissions[All Fields] OR "patient readmission"[MeSH Terms] OR "patient readmission"[All Fields] OR readmit[All Fields] OR readmits[All Fields] OR readmitted[All Fields] OR admit[All Fields] OR admits[All Fields] OR admitted[All Fields] OR admission[All Fields] OR admissions[All Fields] OR hospitalisation[All Fields] OR hospitalization[MeSH Terms] OR hospitalization[All Fields] OR rehospitalisation[All Fields] OR rehospitalisations[All Fields] OR rehospitalization[All Fields] OR rehospitalizations[All Fields]
#5	#1 and #2 and #3 and #4

Fig. 1. PubMed search strategy.

JBI-MAStARI.[23] The data extracted included specific details about the population, intervention, study methods, and outcomes of significance to the review question and specific objectives. Any discrepancy between the authors in the assessment or data extraction process was resolved through discussion.

Data synthesis

Quantitative data were, when possible, pooled in statistical meta-analysis using the Cochrane Collaboration's Review Manager 5 software.[24] Effect sizes expressed as odds ratios (OR) and their 95% confidence intervals (CI) were calculated using a random effects model for analysis. We used the standard Chi^2 and the I^2 to assess for statistical heterogeneity; in addition, subgroup analyses based on the different study designs included in this review were explored. Where statistical pooling was not possible, the findings were presented in narrative form.

Results

Thirteen articles describing 11 studies, four RCTs and seven cohort studies, were included in this review. Three articles[7,25,26] detailed the results from a 17-year prospective cohort study at different time points (1993, 1997, and 2003). All studies

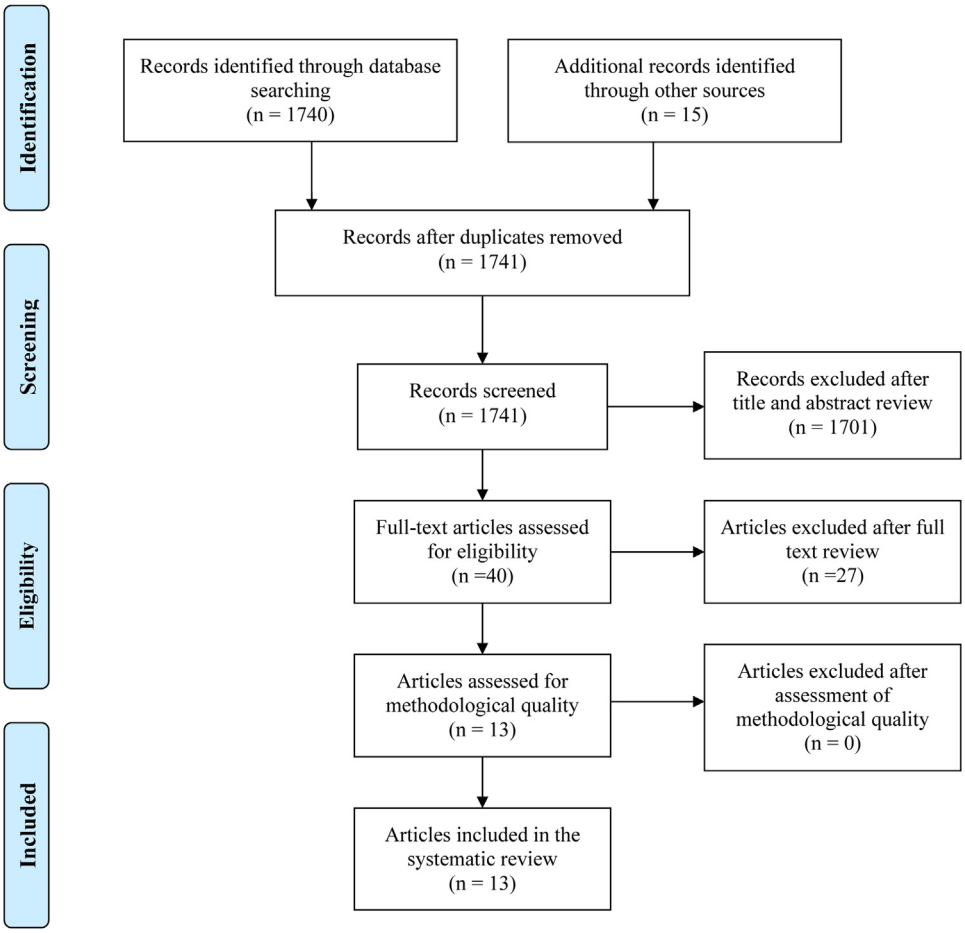

Fig. 2. Flow diagram illustrating the process of identifying articles for inclusion.

investigated tight glycemic control using a continuous insulin infusion on reducing surgical site infections in the adult patient with DM undergoing cardiac surgery. Ten of these studies[7,27–35] included a control group that received standard care. Eight studies[7,27–33] described standard care as the use of subcutaneous insulin dosed by sliding scale; two studies[34,35] did not provide details on the standard care received in the control group. One cohort study[36] used a single arm without a control group. Table 1 displays the characteristics and results of the included RCTs and Table 2 displays the characteristics and results of the cohort studies.

The studies included samples that ranged from 24 to 4864 patients. The populations were 62–80% men with an average age of 57–67.4 years and a mean body mass index ranging from 25.2 to 30.2 kg/m^2. Seven of the included studies were conducted in the US,[7,29–31,33,34,36] one in Saudi Arabia,[28] one in Jordan,[32] one in Israel,[35] and one in Brazil.[27] Seven of the included studies[7,30–34,36] defined the surgical site infection as a sternal wound infection within one-year post cardiac surgery. One study[28] reported the outcome of wound infections without specifying the site. Three studies[27,29,35] reported postoperative infection outcomes that included surgical site infection data in combination with other sources of infection, such as pneumonia and urinary tract infections. While this was not the outcome identified at the outset of this review, we decided to include these studies to get a more complete understanding of the effects of tight glycemic control interventions on postoperative infections. Only two of the included studies[27,35] evaluated the effects of tight glycemic control interventions on readmission rates.

Quality assessment

The results of the quality assessment of the four included RCTs are presented in Table 3. de Barcellos et al[27] used building block allocation time stratified by sex for participant randomization. The authors clearly identified the blinding of participants, allocators and those assessing outcomes. The authors of the other three RCTs[28–30] did not report the method of participant randomization. Methods for blinding were unclear or not mentioned in two RCTs[28,29] and blinding was not used in one RCT.[30] We agreed to include these studies because the other aspects of quality were satisfied.

The results of the quality assessment for the seven cohort studies are presented in Table 4. The authors of all of the included cohort studies used objective criteria for assessing outcomes. We were unable to determine if the samples used in these single center cohort studies were representative of the population as a whole as they were all convenience samples of mostly male patients with limited information provided regarding racial/ethnic characteristics and other comorbid conditions. Samples included patients with DM not on medication, on oral medication, or on insulin at the time of admission, indicating that the patients were at different points in the disease course; the authors of two studies[33,35] did not provide data related to this factor. Follow up occurred for one year in four studies[7,32,33,35]; the authors of the other three studies[31,34,36] did not include the length of follow up used. The authors of two studies[34,36] provided minimal details on the statistical analysis used. Given the limited number of studies

Table 1
Description of randomized controlled trials.

Author, year	Setting/inclusion period	Patient population	Intervention	Control	Results
de Barcellos et al, 2007[27]	Passo Fundo, Brazil. January 2002–June 2003	24 patients with DM who underwent CABG. Mean age: 59.6 years Men: 62% Mean BMI: 28.1 kg/m^2	($n = 12$) Continuous insulin infusion started 1 h prior to the induction of anesthesia and continued for up to 12 h postoperatively. Target glucose 126–200 mg/dL	($n = 12$) Subcutaneous insulin per sliding scale. Target glucose 80–160 mg/dL.	Postoperative infectious complications (deep and superficial surgical site infections, pneumonia, and urinary tract infections) were less frequent in the intervention group compared with control (3 [25%] versus 10 [80%], respectively; RR 0.30; 95% CI 0.11–0.83; $p = 0.01$). One patient in the control group was readmitted within 30 days follow up compared to none in the intervention group.
Eman et al, 2010[28]	Dhahran, Saudi Arabia. 2005–2008	120 patients with DM who underwent cardiac surgery. Mean age: 57 years Men: 80% Mean BMI: 30.2 kg/m^2	($n = 80$) Continuous insulin infusion started the evening before surgery and continuing until 7:00 am on postoperative day 3. Target glucose 100–150 mg/dL	($n = 40$) Subcutaneous insulin per sliding scale. Target glucose <200 mg/dL.	There were no surgical site infections in the intervention group compared to 5 in the control group (test of significance not reported by study authors).
Lazar et al, 2004[29]	Boston, MA, USA. (Inclusion period not identified by study authors)	141 patients with DM who underwent CABG. Mean age: 63.6 years Men: 62%	($n = 72$) Continuous insulin infusion started prior to the induction of anesthesia and continued for 12 h postoperatively. Target glucose 125–200 mg/dL	($n = 69$) Subcutaneous insulin per sliding scale. Target glucose <250 mg/dL.	There were no postoperative infectious complications (surgical site infections or pneumonia) in the intervention group compared to 9 in the control group ($p = 0.01$).
Li et al, 2006[30]	Houston, TX, USA. January 2001–January 2003	93 patients with DM who underwent CABG. Mean age: 63.6 years Men: 63% Mean BMI: 25.2 kg/m^2	($n = 51$) Continuous insulin infusion started on arrival to the ICU and continued until the patient was tolerating oral feedings. Target glucose 150–200 mg/dL	($n = 42$) Subcutaneous insulin per sliding scale. Target glucose 150–200 mg/dL.	There were 2 sternal wound infections in both the intervention and control groups (3.9% versus 4.8%, respectively: $p = 0.587$). There was 1 (2%) leg wound infection in the intervention group compared to none in the control group ($p = 0.548$).

BMI, Body mass index; CABG, Coronary artery bypass graft; CI, Confidence interval; DM, Diabetes mellitus; ICU, Intensive care unit; RR, Relative risk.

identified for inclusion, the limitations in quality assessment due to inadequate reporting of study methods, and the fact that bias is inherent in any cohort study, we decided not to exclude studies based on quality. While bias may exist, the outcomes of the included studies add to the discussion on the effectiveness of tight glycemic control on reducing surgical site infections in patients with DM undergoing cardiac surgery.

Tight glycemic control to reduce surgical site infections

Four RCTs and seven cohort studies that reported on the outcome of surgical site infections rates were combined in the meta-analysis. One cohort study[36] was not included in the analysis but is presented in narrative form due to the absence of a control group and reporting of dichotomous outcome data. As it was not possible to extrapolate results on surgical site infections alone from all studies, the meta-analysis reported on postoperative infections, which include surgical site infections.

Six postoperative infections were reported in the four combined RCT intervention groups ($n = 215$), in which all received continuous insulin infusions to maintain blood glucose levels $\leq$ 200 mg/dL. Twenty-six postoperative infections were reported in the combined RCT control groups ($n = 163$), in which all received subcutaneous insulin as needed. The meta-analysis (Fig. 3) of the four RCTs that compared tight glycemic control interventions using continuous insulin infusions with subcutaneous insulin by sliding scale showed an overall OR of 0.13 (95% CI 0.02–0.82; $Z = 2.17$, $p = 0.03$).

While clinical heterogeneity was present in the intervention protocols, there was no statistical heterogeneity as indicated by Chi^2 (7.28, df = 3, $p = 0.06$) but a moderately high level of heterogeneity as indicated by I^2 (59%). Three of the studies[27–29] demonstrated a statistically significant reduction in postoperative infections. The study by Li et al[30] was the only study in which the results trended toward the subcutaneous insulin by sliding scale group over the continuous insulin infusion group, but these results were not statistically significant (OR 1.25, 95% CI 0.20–7.85). In this study,[30] there were two sternal wound infections in both the intervention and control groups (3.9% versus 4.8% respectively; $p = 0.587$) and one (2%) leg wound infection in the intervention group compared to none in the control group ($p = 0.548$).

There were 59 postoperative infections in the combined cohort intervention groups ($n = 5994$), who received continuous insulin infusions to maintain blood glucose levels $\leq$ 200 mg/dL. There were 111 postoperative infections in the combined cohort control groups ($n = 3369$) (Fig. 3). The control group participants in four of the cohort studies[7,31–33] received subcutaneous insulin as needed, but the authors of two studies[34,35] did not provided details related to the control group. The results of all of the cohort studies[7,31–35] included in this meta-analysis favored the continuous insulin infusion group with an overall OR of 0.37 (95% CI 0.27–0.52; $Z = 5.71$, $p < 0.00001$). While there was clinical heterogeneity in the intervention protocols used, there was no significant statistical heterogeneity (Chi^2 = 0.61, df = 5, $p = 0.99$; $I^2 = 0\%$).

In the combined RCT and cohort study subgroups, there were 65 postoperative infections in the intervention (continuous insulin infusion) group ($n = 6209$) and 137 postoperative infections in the control (subcutaneous insulin/usual care) group ($n = 3532$) (Fig. 3). Continuous insulin infusions to maintain a blood glucose of $\leq$200 mg/dL demonstrated a statistically significant reduction in overall postoperative infection rates (OR 0.35, 95% CI 0.25–0.49; $Z = 6.0$, $p < 0.00001$). There was no statistical heterogeneity in the combined meta-analysis of both subgroups (Chi^2 = 9.49, df = 9, $p = 0.39$; $I^2 = 5\%$).

Table 2
Description of cohort studies.

Author, year	Setting/inclusion period	Patient population	Intervention	Control	Results
Abelev et al, 2011[31]	New York, NY USA. January 1999–January 2008	517 patients with DM who underwent CABG. Mean age: 65.6 years Men: 67.7% Mean BMI: 28.5 kg/m^2	($n = 285$) Continuous insulin infusion started postoperatively and continued for a minimum of 24 h. Target glucose 90–150 mg/dL.	($n = 232$) Subcutaneous insulin per sliding scale. Target glucose <150 mg/dL. If glucose >150 mg/dL within the first 4 postoperative hours, continuous insulin infusion was started and continued for a minimum of 3 days.	There were 2 (0.7%) surgical site infections in the intervention compared to 3 (1%) in the control group ($p = 0.66$).
Carr et al, 2005[36]	Boston, MA, USA. November 2002–August 2004	737 patients (314 with known DM) who underwent CABG. Mean age: 67.4 years Men: 79.3%	($n = 737$) Continuous insulin infusion started intraoperatively for glucose > 125 mg/dL. Trigger for continuous insulin infusion initiation in the ICU was decreased in 3 phases. Phase 1 trigger was glucose >150 mg/dL, phase 2 > 125 mg/dL, and phase 3 > 110 mg/dL. Target glucose <130 mg/dL.	No control group.	Annual postoperative surgical site infection rate per 100 cardiac surgeries fell from 1.6% prior to the use of the protocol to zero in phase 3 of the protocol ($p = 0.003$).
Harahsheh et al, 2012[32]	Amman, Jordan. (Inclusion period not identified by study authors)	265 patients with DM who underwent CABG. Mean age: 59.1 years Men: 71.7%	($n = 120$) Continuous insulin infusion started intraoperatively and continued until discharge from the ICU. Target glucose 120–150 mg/dL.	($n = 145$) Subcutaneous insulin per sliding scale. Target glucose not specified.	There were no deep surgical site infections in the intervention group compared to 2 (1.3%) in the control group. There were 4 (3.3%) superficial surgical site infections in the intervention group compared with 9 (6.2%) in the control group ($p < 0.05$).
Hruska et al, 2005[33]	Cincinnati, OH, USA. January 1997–December 1998	246 patients with DM who underwent CABG. Mean age: 64 years Men: 65%	($n = 102$) Continuous insulin infusion started intraoperatively and continuing for 48 h postoperatively. Target glucose 120–160 mg/dL.	($n = 144$) Subcutaneous insulin per sliding scale. Target glucose not specified.	In patients with a history of DM, there were 2 surgical site infections in the intervention group compared with 11 in the control group. There was a significant decreased in surgical site infection in patients with DM compared to those without DM ($p = 0.0092$).
Kramer et al, 2010[34]	Portland, ME, USA. January, 2004–December, 2006	3065 patients who underwent cardiac surgery. (The number of patients with DM was not identified by study author.)	($n = 1388$) Continuous insulin infusion started intraoperatively and continued until the morning of postoperative day 3. Target glucose 80–120 mg/dL.	($n = 1677$) Usual care, which was not defined by the study authors.	Postoperative surgical site infections were lower in the intervention group compared to the control group (1% versus 2.6%, $p < 0.001$).
Leibowitz et al, 2010[35]	Jerusalem, Israel. January 2008–June 2009.	406 patients with DM or random glucose >150 mg/dL who underwent cardiac surgery. Mean age: 63.7 years Male: 63.8% Mean BMI: 27.8 kg/m^2	($n = 203$; patients with DM, $n = 72$) Continuous insulin infusion started postoperative and continued until taking food by mouth or discharge from the ICU. Target glucose 110–150 mg/dL.	($n = 203$ patients with DM, $n = 79$) Usual care, which was not defined by the study authors.	There was a lower incidence of any infection in the intervention group compared with the control group (10 [5%] versus 23 [11%], $p = 0.018$). This difference remained significant in patients with a history of DM (5 [7%] versus 16 [20%], respectively; $p = 0.018$). In the total population there was no difference in 30 day readmission rates (intervention 31 [15%], control 36 [18%]; $p = 0.5$). In patients with a history of DM, the intervention was associated with a trend toward a lower 30 day readmission rate when compared to the control (9 [12%] versus 19 [24%], respectively; $p = 0.052$).

Zerr et al, 1997[25]; Furnary et al, 1999,[26] 2004[7]	Portland, OR, USA. January 1987 – September 2003	4864 patients with DM who underwent cardiac surgery. Mean age: 65.6 years Men: 67.7% Mean BMI: 28.5 kg/m^2	(n = 3896) Continuous insulin infusion titrated according to the Portland protocol. Phase 1 (1992–1994): infusion started postoperatively and continued until transfer out of the ICU. Phase 2 (1995–2003): expended to start infusion preanesthesia and continued until 7:00 AM on postoperative day 3. Target glucose levels decreased over 3 phases: 1991–1998, target glucose 150–200 mg/dL; 1999–2000, target glucose 125–175 mg/dL; 2001–2003, target glucose 100–150 mg/dL.	(n = 968) Subcutaneous insulin per sliding scale. Target glucose <200 mg/dL.	Surgical site infections were lower in the intervention group compared to the control group (0.7% versus 2.0%, respectively; RR 0.39, $p < 0.01$).

BMI, Body mass index; CABG, Coronary artery bypass graft; DM, Diabetes mellitus; ICU, Intensive care unit; RR, Relative risk.

One cohort study[36] was not included in the meta-analysis due to changes in many factors throughout the study period (changes in antibiotic prophylaxis, surgeon, operating room draping, and the trigger for initiation of intravenous insulin). The study authors did not provide the number of surgical site infections, but reported the infection rates during each phase of the study. The annual surgical site infection rates per 100 cardiac surgeries fell from 1.6% prior to the use of the continuous insulin infusion protocol to zero in phase 3 of the protocol ($p = 0.003$). However, given the many changes in clinical care, it is difficult to evaluate this outcome.

We used a funnel plot to explore the potential for publication bias (Fig. 4). The treatment effect estimates for the included studies are plotted on the horizontal axis against the standard error (SE) of the estimates on the vertical axis. The symmetry of the individual effect estimates around the overall treatment effect indicates that there may be minimal publication bias in the included studies.

Tight glycemic control to reduce readmissions

Only two of the included studies[27,35] included readmissions as outcome measures. There was one readmission in the subcutaneous insulin group compared to none in the continuous insulin infusion group during a 30 day follow up in an RCT.[27] The continuous insulin infusion intervention did not lead to statistically significant differences in 30 day readmission rates between groups (intervention 31 [15%], control 36 [18%]; $p = 0.5$) in a cohort study.[35] In this study,[35] the continuous insulin infusion intervention was associated with a trend toward a lower 30 day readmission rate in the subgroup of patients with a history of DM when compared to the control (9 [12%] versus 19 [24%] respectively; $p = 0.052$).

Discussion

We identified four RCTs and seven cohort studies that evaluated the effects of tight glycemic control with continuous insulin infusions to maintain blood glucose ≤200 mg/dL on the rates of surgical site infections among patients with DM during the early postoperative period after cardiac surgery. A meta-analysis of 10 of these studies provides evidence that this intervention significantly reduced surgical site infection rates compared with standard DM management. Only one study[30] failed to show a reduction in surgical site infections. This may have been due to the small sample size in the study, the inability of one third of the intervention group to achieve the target glucose levels, or the early discontinuation of the insulin infusion after the patient began oral feedings when less control over oral intake occurred.

The results of the included studies suggest that the beneficial effects of continuous insulin infusion on surgical site infection may vary depending on the phase of the perioperative period in which the insulin infusion was initiated, the duration of the infusion, or the target glucose levels. The three studies[27–29] that demonstrated the most benefit included protocols in which the insulin infusion was started prior to surgery. In one study[28] the insulin infusion was started the evening prior to surgery and continued for three days postoperatively. In two studies[27,29] the insulin infusion were started prior to the induction of anesthesia and continued for 12 hours postoperatively. All three of these interventions had small sample sizes (≤150 patients) but were able to demonstrate statistically significant reductions in surgical site infections. The intervention detailed across the articles by Zerr et al[25] and Furnary et al[7,26] also used a protocol in which the insulin infusion was started prior to anesthesia and continued until postoperative day three and was able to demonstrate a statistically significant reduction in surgical site infections within one year in a large sample of patient ($n = 4864$). Furnary et al[7] noted that the patients who had glucose

Table 3
Critical appraisal of randomized control trials.

Study	Assignment to treatment groups was truly random.	Participants were blinded to treatment allocation.	Allocation to groups was concealed from allocator.	Outcomes of people who withdraw were described and included in the analysis.	Those assessing outcomes were blinded to the treatment allocation.	Groups were comparable at entry.	Groups were treated identically other than for the named intervention.	Outcomes were measured in the same way for all groups.	Outcomes were measured in a reliable way.	Appropriate statistical analysis was used.
de Barcellos et al, 2007[27]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Emam et al, 2010[28]	U	U	U	Y	U	Y	Y	Y	Y	Y
Lazar et al, 2004[29]	U	U	U	U	U	Y	Y	Y	Y	Y
Li et al, 2006[30]	U	N	N	Y	N	Y	Y	Y	Y	Y
%	25.0	25.0	25.0	75.0	25.0	100	100	100	100	100

Y, Yes; N, No; U, Unclear.

Table 4
Critical appraisals of cohort studies.

Study	Sample is representative of patients in the population as a whole.	The patients are at a similar point in the course of their condition.	Bias has been minimized in relation to selection of cases and controls.	Confounding factors were identified and strategies to deal with them were stated.	Outcomes were assessed using objective criteria.	Follow up was carried out over a sufficient time period.	Outcomes of people who withdrew were described and included in the analysis.	Outcomes were measured in a reliable way.	Appropriate statistical analysis was used.
Abelev et al, 2011[31]	U	N	N/A	N	Y	U	N	Y	Y
Carr et al, 2005[36]	U	N	N/A	N	Y	U	Y	Y	U
Harahsheh, 2012[32]	U	N	N/A	Y	Y	Y	Y	Y	Y
Hruska et al, 2005[33]	U	U	N/A	Y	Y	Y	Y	Y	Y
Kramer et al, 2008[34]	U	N	N/A	N	Y	U	N	Y	U
Leibowitz et al, 2010[35]	U	U	N/A	Y	Y	Y	N	Y	Y
Zerr et al, 1997[25]; Furnary et al, 1999,[26] 2004[7]	U	N	N/A	Y	Y	Y	Y	Y	Y
% Yes	0	0	N/A	57.1	100	57.1	57.1	100	71.4

Y, Yes; N, No; U, Unclear; N/A, Not applicable.

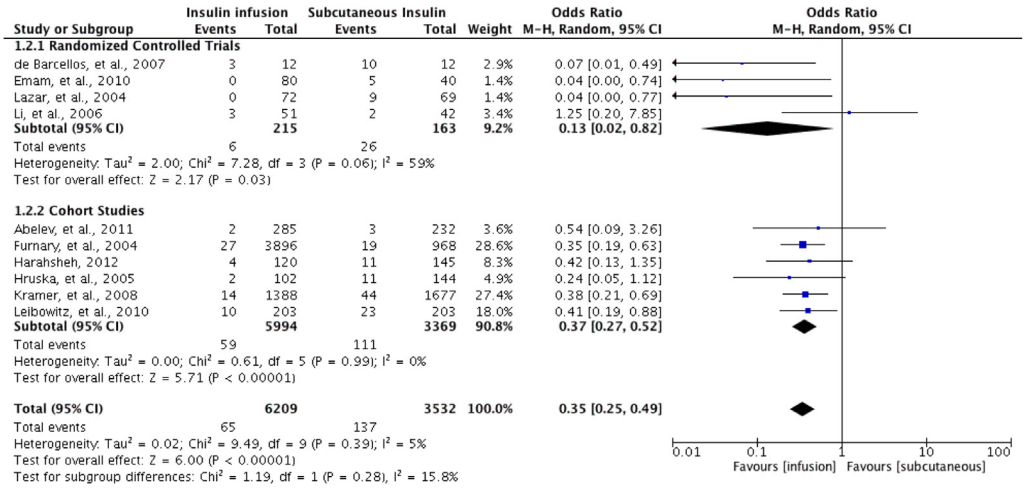

Fig. 3. Effects of tight glycemic control with a continuous insulin infusion compared with subcutaneous insulin on postoperative infections in patients with DM undergoing cardiac surgery.

levels >150 mg/dL on postoperative day two had the highest risk for deep sternal wound infections. Emam et al[28] confirmed the importance of maintaining adequate glucose control during the first 48 postoperative hours to reduce the risk of surgical site infections.

The studies included in this systematic review highlight the importance of postoperative glucose control to reduce the incidence of postoperative infections. Preoperative glucose control has also been linked to worse postoperative outcomes.[19] However, none of the studies evaluated the effects of the degree of preoperative glycemic control and the use of a continuous insulin infusion postoperatively on surgical site infections or readmissions. Emam et al[28] started continuous insulin infusions on all patients the evening prior to surgery but those with preoperative glucose >150 mg/dL were started even earlier in the preoperative period (specific time point not indicated by study authors). Although there were no surgical site infections in patients receiving the infusions, it is not known whether the earlier insulin infusion start time influenced these results. Halkos et al[37] demonstrated that a preoperative hemoglobin A1c level ≥8.6% was associated with an increase in surgical site infections and mortality. However, tight glycemic control was not routinely achieved postoperatively. Lazar et al[38] demonstrated that when glucose was maintained <180 mg/dL in the postoperative period, preoperative hemoglobin A1c levels were not predictive of 30 day morbidity and mortality. Therefore, further research is needed to determine the effects of preoperative control on postoperative outcomes.

Targeting a lower glucose range does not necessarily improve outcomes. Studies comparing intensive glycemic control (target blood glucose < 120 mg/dL) in critically ill patients to a control group whose target was <180 mg/dL were effective in achieving treatment outcomes; however, the lower targets carried a greater risk for hypoglycemia and subsequent higher mortality.[36,39,40] Lazar et al[38] found that aggressive glycemic control in patients with DM undergoing CABG surgery with a target blood glucose of 90–120 mg/dL resulted in more episodes of hypoglycemia without any improvement in other clinical outcomes when compared with a target glucose of 120–180 mg/dL. The ability to frequently monitor blood glucose measurements during the first 48 h of the postoperative period is crucial to safe achievement of lower blood glucose targets.[36]

Two studies[27,35] showed lower readmission rates after cardiac surgery when continuous insulin infusions were instituted to target postoperative blood glucose ≤200 mg/dL. However, we cannot conclude that this reduction in readmissions was the direct results of the tight glycemic control intervention or other factors related to postoperative patient care. Therefore, further studies are needed to address this outcome.

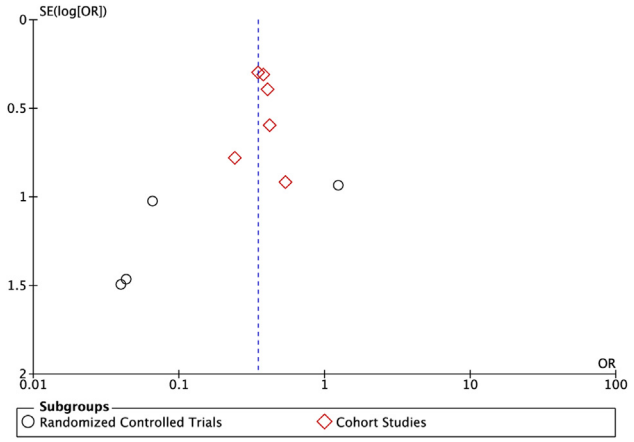

Fig. 4. Funnel plot of tight glycemic control interventions.

Limitations

Limitations of this review included limiting the search to articles published in English. Although international studies were included, it is unknown if there are additional studies in other languages that could have added to the evidence base. The most recent study identified was published in 2012 and the most recent RCT was published in 2007; however, questions remain as to the most effect target glucose range and insulin infusion protocol to achieve optimal postoperative outcomes. Many of the included studies were conducted on small samples and in single centers that may limit the generalizability or statistical power of the findings. The samples included mostly middle-aged men, consistent with demographic characteristics of the typical patient undergoing CABG surgery, but may overlook women and aged individuals who may undergo CABG.

The clinical heterogeneity that is present in the protocols used in the included studies could suggest that the effect sizes may vary

according to different aspects of the protocol such as when in the perioperative period the insulin infusion was started, the duration of the infusion, and the target glucose level used. While this clinical heterogeneity may weaken the results of the meta-analysis, we believe the findings from this systematic review provide useful information for stakeholders concerned with reducing surgical site infection rates in patients with DM undergoing cardiac surgery.

The findings of this review suggest the benefit of maintaining blood glucose levels ≤200 mg/dL with continuous insulin infusions. The authors of many of the studies highlighted the need to arrive at a generally accepted range; however, the variations among study protocols make it difficult to recommend one target range or infusion protocol. Beyond the evidence to support maintaining blood glucose to a level ≤200 mg/dL, a target range for optimal control of blood glucose that balances the need for normoglycemia versus the risk of hypoglycemia, an optimal level remains to be defined.

Implications for practice

Continuous insulin infusion protocols to achieve postoperative glucose levels ≤200 mg/dL in patients undergoing cardiac surgery should be implemented into practice. There may be a need for a learning period as clinicians gains confidence in the safety of achieving lower target glucose levels to prevent adverse outcomes. Hyperglycemia can be a greater risk for negative outcomes, including increased mortality and longer ICU lengths of stay, than mild hypoglycemic episodes.[41] Careful monitoring and follow up of blood glucose must occur to prevent moderate to severe hypoglycemia (blood glucose 70–41 mg/dL or ≤ 40 mg/dL, respectively) with the use of continuous insulin infusion protocols as these levels have also been associated with increased length of stay and mortality in critically ill patients.[39,41,42] Failure to properly implement an established protocol leaves the patient with DM who undergoes cardiac surgery at high risk for poor outcomes.

Implications for research

The evidence presented in this systematic review underscores the need for continued research to identify an ideal target glucose range and clinical protocol for optimal control of blood glucose to reduce surgical site infections and readmission rates in patients with DM undergoing cardiac surgery. The Society of Thoracic Surgeons is expected to update their perioperative glycemic control guidelines in the near future; however, there have been no additional RCTs published since their last guideline[19] was developed in 2009 to inform future recommendations in this area. While the benefits of maintaining postoperative glucose ≤200 mg/dL are clearly supported by this review an optimal range has not been determined; some studies have demonstrated worse outcomes with even tighter glucose targets (<120 mg/dL).[36,39,40] In addition, the Portland Protocol[20] is one of the most widely adapted postoperative glycemic control protocols. While the benefits have been documented in a large prospective cohort study,[7,25,26] this study was conducted in a single center limiting the generalizability of the findings. Future research should include well designed, large, multicenter RCTs on diverse patient populations to determine an ideal range for control of blood glucose as well as the optimal protocol including timing for starting the insulin infusion, frequency of glucose checks, dose adjustments, and the duration of infusion to reduce postoperative complications. Additional research is needed to identify methods for maintaining optimal blood glucose control after discontinuation of the continuous insulin infusion in patients with DM undergoing cardiac surgery.

Conclusion

Maintaining blood glucose levels ≤200 mg/dL with continuous insulin infusions in patients with DM who undergo cardiac surgery reduces the incidence of surgical site infections. While there is great variability in the management of tight glycemic control protocols, the use of continuous insulin infusions during all phases of the perioperative period were superior to subcutaneous insulin injections in controlling blood glucose levels.

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References

1. National Center for Chronic Disease Prevention and Health Promotion. *National Diabetes Statistics Report, 2014 [Internet]*. Atlanta, GA: Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf; 2014.
2. Deb S, Wijeysundera HC, Ko DT, et al. Coronary artery bypass graft surgery vs percutaneous intervention in coronary revascularization: a systematic review. *J Am Med Assoc*. 2013;310(19):2086–2095.
3. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29–e322.
4. The Center for Disease Control and Prevention. *Surgical Site Infection (SSI) Event [Internet]*. Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf?agree=yes&next=Accept; 2015.
5. Fowler VG, O'Brian SM, Muhlbaier LH, et al. Clinical predictors of major infections after cardiac surgery. *Circulation*. 2005;112(suppl 1):I358–I365.
6. Lee P, Min L, Mody L. Perioperative glucose control and infection risk in older surgical patients. *Curr Geriatr Rep*. 2014;3(1):48–55.
7. Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland diabetic project. *Endocr Pract*. 2004;10(suppl 2):21–32.
8. Engoren M, Schwann TA, Habib RH. Elevated hemoglobin A1c is associated with readmission but not complications. *Asian Cardiovasc Thorac Ann*. 2014;22(7):800–806.
9. Jencks SF, Williams MV, Coleman E. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009;360(14):1418–1428.
10. van Walraven C, Bennett C, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. *CMAJ*. 2011;183(7):E391–E402.
11. Halfon P, Eggli Y, Pretre-Rohrbach I, et al. Validation of potentially avoidable hospital readmission rate as a routine indicator of the quality of hospital care. *Med Care*. 2006;44(11):972–981.
12. Goldfield NI, McCullough EC, Hughes JS, et al. Identifying potentially preventable readmissions. *Health Care Financ Rev*. 2008;30(1):75–91.
13. Hannan EJ, Zhong Y, Lahey SJ, et al. 30-day readmissions after coronary artery bypass graft surgery in New York State. *JACC Cardiovasc Interv*. 2011;4(5):569–576.
14. Li Z, Armstrong EJ, Parker JP, Danielsen B, Ramano PS. Hospital variation in readmission after coronary artery bypass surgery in California. *Circ Cardiovasc Qual Outcomes*. 2012;5(5):729–737.
15. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract*. 2009;15(4):1–11.
16. American Diabetes Association. Standards of medical care in diabetes-2015. *Diabetes Care*. 2015;38(suppl 1):S1–S93.
17. Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for having surgery. *Clin Infect Dis*. 2006;43(3):322–330.
18. The Joint Commission. *Surgical Care Improvement Project. [Internet]*. Available from: http://www.jointcommission.org/surgical_care_improvement_project/; 2014.
19. Lazar HL, McDonnell M, Chipkin S, et al. The Society of Thoracic Surgeons practice guideline series: blood glucose management during adult cardiac surgery. *Ann Thorac Surg*. 2009;87(2):663–669.
20. Furnary AP, Wu Y. Clinical effects of hyperglycemia in the cardiac surgery population: the Portland Diabetic Project. *Endocr Pract*. 2006;12(suppl 3):22–26.
21. Kao LS, Meeks DA, Moyer VA, Lally KP. Peri-operative glycaemic control regimens for preventing surgical site infections in adults. *Cochrane Database Syst Rev* 2009;(3):CD006806.
22. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for the prevention of surgical site infection, 1999. Hospital infection control practices advisory committee. *Infect Control Hosp Epidemiol*. 1999;20(4):247–278.

23. Joanna Briggs Institute. *Joanna Briggs Institute Reviewers' Manual: 2014 Edition*. Adelaide, South Australia: The Joanna Briggs Institute; 2014.
24. *Review Manager (RevMan) [Computer Program]*. Version 5.3. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration; 2014.
25. Zerr KJ, Furnary AP, Grunkemeier GL, et al. Glucose control lowers the risk of wound infection in diabetes after open heart operations. *Ann Thorac Surg*. 1997;63(2):356–361.
26. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg*. 1999;67(2):352–362.
27. de Barcellos CS, Wender OCB, Azambuja PC. Clinical and hemodynamic outcome following coronary artery bypass surgery in diabetic patients using glucose-insulin-potassium (GIK) solution: a randomized clinical trial. *Rev Bras Cir Cardiovasc*. 2007;22(3):275–284.
28. Emam IA, Allan A, Eskander K, et al. Our experience of controlling diabetes in the peri-operative period of patients who underwent cardiac surgery. *Diabetes Res Clin Pract*. 2010;88(3):242–246.
29. Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation*. 2004;109(12):1497–1502.
30. Li JY, Sun S, Wu SJ. Continuous insulin infusion improves post-operative glucose control in patients with diabetes mellitus. *Tex Heart Inst J*. 2006;33(4):445–451.
31. Abelev Z, Seth A, Patel R, et al. Continuous insulin infusion is associated with a reduced post-surgical length of stay, but not with the complication rate, in patients with diabetes mellitus undergoing coronary artery bypass graft. *J Endocrinol Invest*. 2011;34(10):770–774.
32. Harahsheh BS. Strict glycemic control improves outcomes after coronary artery bypass grafting (CABG). *Pak J Med Sci*. 2012;28(1):27–30.
33. Hruska LA, Smith JM, Hendy MP, Fritz VL, McAdams S. Continuous insulin infusion reduces infectious complications in diabetics following coronary surgery. *J Cardiovasc Surg*. 2005;20(5):403–407.
34. Kramer R, Groom R, Weldner D, et al. Glycemic control and reduction of deep sternal wound infection rates. *Arch Surg*. 2008;143(5):451–456.
35. Leibowitz G, Raizman E, Brezis M, et al. Effects of moderate intensity glycemic control after cardiac surgery. *Ann Thorac Surg*. 2010;90(6):1825–1832.
36. Carr JM, Sellke FW, Fey M, et al. Implementing tight glucose control after coronary artery bypass surgery. *Ann Thorac Surg*. 2005;80(3):902–909.
37. Halkos ME, Puskas JD, Lattouf OM, et al. Elevated preoperative hemoglobin A1c level is predictive of adverse events after coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2008;136(3):631–640.
38. Lazar HL, McDonnell MM, Chipkin S, et al. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. *Ann Surg*. 2011;254(3):458–463.
39. The NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283–1297.
40. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*. 2006;55(11):3151–3159.
41. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc*. 2003;789(12):1471–1478.
42. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and the risk of death in critically ill patients. The Nice-Sugar Study Investigators. *N Engl J Med*. 2012;367(1):105–115.