

January 2012

The Effect of Tight Glycemic Control on Surgical Site Infection Rates in Patients Undergoing Open Heart Surgery

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The Effect of Intraoperative Tight Glycemic Control on Surgical Site Infection Rates in
Patients Undergoing Open-heart Surgery

by

Sierra Gower

A dissertation submitted in partial fulfillment
of the requirements for the degree of
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Date of Approval:
October 24, 2012

Keywords: Cardiac Surgery, Postoperative Wound Infection, Hyperglycemia

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Abstract

The purpose of this study was to investigate the effects of three different glycemic control conditions (tight, conventional, and standard) in the intraoperative period on: 1) postoperative surgical site infections, and 2) postoperative procalcitonin, and C-reactive protein levels in patients undergoing open-heart surgery. Secondary aims of the study were to investigate the effects of the three glycemic treatment conditions on: 1) intraoperative blood glucose; 2) intraoperative glycemic stability; and 3) intensive care unit length of stay, in patients undergoing open-heart surgery.

An experimental design with a multilevel, single factor, within-subjects design was utilized. Patients were nested within anesthesia provider teams. The design was counterbalanced by means of a Latin square, where each of three anesthesia provider teams dispensed each of three glycemic control conditions once. Thirty-seven participants were randomized to either tight glycemic control ($n=15$), which maintained blood glucose 110-149 mg/dl via continuous intravenous insulin infusion, conventional glycemic control ($n=11$), which maintained blood glucose 150-180 mg/dl via continuous intravenous insulin infusion, or standard glycemic control ($n=11$) which maintain blood glucose 150-180 mg/dl via intravenous bolus injections of insulin.

The main findings of this study were that there were no significant differences between the three glycemic interventional treatment groups in 1) thirty-day surgical site infections, 2) postoperative C-reactive protein or procalcitonin concentrations 3) intensive care unit length of stay, 4) intraoperative blood glucose levels, or 5) glycemic

stability. An association between intraoperative peak blood glucose and surgical site infection was established. Participants that experienced higher peak blood glucose levels intraoperatively exhibited increased surgical site infections. Procalcitonin levels were significantly elevated in participants that experienced a surgical site infection, but C-reactive protein showed no significant difference between participants with or without a surgical site infection. Coronary artery bypass graft surgery concomitant with valve replacement surgery was associated with a higher rate of surgical site infections compared coronary artery bypass graft surgery or valve surgery independently.

In conclusion, an association was found between higher peak intraoperative blood glucose levels and increased surgical site infections, therefore maintaining intraoperative blood glucose levels below 180 mg/dl via a continuous intravenous infusion of insulin, may reduce postoperative surgical site infections in the open-heart patient. The use of tight glycemic control during the intraoperative period can be achieved safely, with the use of judicious protocols, but its benefits remain unproven. Inflammatory biomarker procalcitonin was predictive of infection, where C-reactive protein was not. The addition of procalcitonin to routine postoperative blood work, in open-heart patients, may benefit providers in the diagnosis and early treatment of surgical site infections. This study was underpowered. Further studies with appropriate sample size, may be able to determine if tight glycemic control, compared to moderate glycemic control, in the intraoperative period is of benefit to patients undergoing open-heart surgery.

Chapter One

Introduction

According to the American Heart Association [AHA] there were 555,000 total open-heart surgeries performed in the United States in 2009 (Roger et al., 2012). Coronary artery bypass graft surgery (CABG) accounted for 416,000 of these procedures and cardiac valve replacements accounted for 139,000 (Roger et al., 2012). While there were 416, 000 CABG surgical procedures, these were performed on only 242,000 patients (Roger et al., 2012). Open-heart surgery, while very successful in the alleviation of chest pain due to coronary heart disease (CHD) and/or valvular disease carries risks. One risk is that of infection including median sternotomy site infections, surgical harvest site infections, pneumonias, urinary tract infections, and bacteremia (Ariyaratnam, Bland, & Loubani, 2010; Baillot, et al., 2010; Borger et al., 1998; El Oakley et al., 1997; Furnary, Wu & Bookin, 2004; Latham, Lancaster, Covington, Pirolo & Thomas, 2001; Lola et al., 2011; Mannien, Wille, Klock, & van Benthem, 2011; Spelman et al., 2000, Trick et al., 2000a; Trick et al., 2000b; Zerr et al., 1997).

Surgical site wound infection, after open-heart surgery, is associated with increased hospital stays, increased costs and substantial morbidity and mortality (Athanasίου et al., 2003; El Oakley et al., 1997; Fowler et al., 2005; Jonkers, Elenbaas, Terporten, Nieman, & Stobberingh, 2003; Knapik et al., 2009; L'Ecuyer, Murphy, Little,

& Fraser, 1996; Lola et al., 2011; Vuorisalo, Haukipuro, Pokela, & Syrjala, 1998; Yun et al., 2005).

Previous studies suggest a link between poor glycemic control and surgical site infection rates (Borger et al., 1998; El Oakley et al., 1997; Estrada, Young, Nifong, & Chitwood, 2003; Fowler et al., 2005; Furnary et al., 2004; Latham et al., 2001; Trick et al., 2000b; Zerr et al., 1997). Deep sternal site wound infection, after open-heart surgery, is associated with substantial morbidity and a mortality rate as high as 14% (El Oakley et al., 1997; Fowler et al., 2005; Knapik et al., 2009; Lola et al., 2011). Harvest surgical site infections are the most common surgical site infection associated with CABG surgery, with rates as high as 15.4% (Athanasίου et al., 2003; Jonkers et al., 2003; L'Ecuyer et al., 1996; Vuorisalo et al., 1998; Yun et al., 2005). While these infections are associated with lower morbidity and mortality than deep sternal wound infections they can have severe clinical consequences, such as limb amputations (Lee & Reinstein, 1998; Paletta, et al., 2000).

There is evidence that aggressive glycemic control for critically ill hospitalized patients improves clinical outcomes, especially for surgical patients and patients with CHD (Furnary et al., 2004; Trence, Kelly, & Hirsch, 2003; Trick et al., 2000b; Van den Berghe, et al., 2001). However, these data have been challenged by more recent studies that suggest there is no improvement in clinical outcomes, or possibly worse outcomes for the critically ill patient who is treated with aggressive glycemic control (Arabi et al., 2008; Chan et al., 2009; Finfer, et al., 2009; Gandhi et al., 2007; Griesdale, et al., 2008; Lazar et al., 2011; Wiener, Wiener, & Larson, 2008).

Studies that have explored glycemic control for open-heart surgery specifically in the perioperative period (intra- and postoperative), have also reported conflicting results on the benefits of tight glycemic control (Furnary, Zerr, Grunkemeier, & Starr, 1999; Furnary et al., 2003; Furnary et al., 2004; Gandhi et al., 2007; Goldberg, Siegel, & Sherwin, 2004; Guvener, Pasaoglu, Demircin, & Mehmet, 2002; Lazar et al., 2004; Schmeltz et al., 2007; Smith, Grattan, Harper, Royston, & Riedel, 2002; Zerr et al., 1997). While there is consensus that hyperglycemia should be avoided in the perioperative period in patients undergoing open-heart surgery, it remains unclear how tight the glycemic control should be. A few studies have reported good results with tight glycemic control (80-120 mg/dl) in the intraoperative period, showing improved outcomes including improved myocardial function (Lazar et al., 2004), decreased wound infections (Carr et al., 2005; Emam et al., 2010; Furnary et al., 1999), and decreased morbidity and mortality (Furnary et al., 2003). Other studies reported no improvement in mortality and morbidity with tight glycemic control (80 -110 mg/dl), and potentially worse outcomes (Chan et al., 2009; Gandhi et al., 2007; Lazar et al., 2011).

Results from more recent research has triggered national associations to amend their guidelines to more conservative glucose parameters. Currently, the Institute for Healthcare Improvement (IHI, 2011) recommends cardiovascular surgery patients, who are at a high risk for complications from hyperglycemia, maintain blood glucose levels below 180 mg/dl for the first two postoperative days. The American Diabetes Association (ADA, 2012) recommends initiating insulin therapy for persistent hyperglycemia starting at a threshold of no greater than 180 mg/dl. Once insulin therapy is initiated, blood glucose levels in critically ill patients should be maintained from 140-

180 mg/dl (ADA, 2012). More stringent goals, such as 110-140 mg/dl may be appropriate for selected patients, as long as this is achieved without significant hypoglycemia (ADA, 2012).

Further research utilizing randomized controlled trials is needed to investigate whether tight or moderate glycemic control in the intraoperative period substantially improves clinical outcomes such as postoperative infection. It is also important to determine the incidence of intra- and postoperative hypoglycemia experienced with tight glycemic control.

Statement of the Problem

Postoperative surgical site infection in the open-heart patient population is a significant problem for cardiothoracic surgical teams and hospitals. There is paucity of literature concerning the impact of intraoperative glycemic control on surgical site wound infections in patients undergoing open-heart surgery, including CABG surgery and/or cardiac valve surgery. Limited research is available to support which insulin protocol and/or blood glucose value, in the intraoperative period, is the safest and most effective for glycemic stability or preventing surgical site infections (SSIs). A greater understanding of glycemic control in the intraoperative period, and its impact on postoperative surgical site infection is needed for patients undergoing open-heart surgery.

Purpose of the Study

The purpose of this study was to investigate the effects of three different glycemic control conditions (tight, conventional, and standard) in the intraoperative period on: 1) thirty-day postoperative surgical site infections; and 2) postoperative procalcitonin, and C-reactive protein levels in patients undergoing open-heart surgery. Secondary aims of

the study were to investigate the effects of the three glycemic treatment conditions on: 1) intraoperative blood glucose; 2) intraoperative glycemic stability; and 3) intensive care unit (ICU) length of stay (LOS) in patients undergoing open-heart surgery.

The three protocols were tight glycemic control (blood glucose levels 110-149 mg/dl) via continuous intravenous infusion of insulin, conventional glycemic control (blood glucose levels 150-180 mg/dl) via continuous intravenous infusion of insulin, and standard glycemic control (blood glucose levels 150-180 mg/dl) via intravenous bolus injections of insulin.

Specific aims.

The specific primary aims of this study were to compare the effect of three intraoperative glycemic control protocols on:

1. Thirty-day postoperative wound infection rates in open-heart surgical patients; and
2. Procalcitonin and C-reactive protein levels in the immediate postoperative period (5 days) in open-heart surgical patients.

The specific secondary aims of this study were to compare the effect of three intraoperative glycemic control protocols on:

1. Intraoperative blood glucose levels;
2. Intraoperative glycemic stability; and
3. Intensive care unit length of stay.

Hypotheses for aim 1.

The hypotheses for aim 1 are as follows:

1. It was hypothesized that patients undergoing open-heart surgery, who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative phase would demonstrate fewer 30 day sternal and harvest surgical site wound infections compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

2. It was hypothesized that patients undergoing open-heart surgery, who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative phase would have lower procalcitonin levels and lower C-reactive protein levels in the first five days of the postoperative period compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

Hypotheses for aim 2.

The hypotheses for aim 2 are as follows:

1. It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative period would have significantly lower blood glucose levels during this period compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

2. It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for glycemic control, whether tight control (blood glucose 110-149 mg/dl) or conventional control (blood glucose 150-180 mg/dl), during the intraoperative phase would have significantly improved glycemic stability in the intraoperative period compared to patients who received the standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

3. It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative phase would demonstrate a shorter length of stay in the intensive care unit compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

Definition of Terms

The following terms were defined and used throughout the study. The study definitions were derived partially from their use in previous research and are established in open-heart surgery, glycemic control, and postoperative wound infection

Intraoperative Tight Glycemic Control

Intraoperative tight glycemic control was defined as the maintenance of blood glucose level between 110-149 mg/dl by means of a continuous intravenous infusion of regular insulin throughout the intraoperative period.

Intraoperative Conventional Glycemic Control

Intraoperative conventional glycemic control was defined as the maintenance of a blood glucose level between 150-180 mg/dl by means of a continuous intravenous infusion of regular insulin throughout the intraoperative period.

Intraoperative Standard Glycemic Control

Intraoperative standard glycemic control was defined as the maintenance of blood glucose level between 150-180 mg/dl by means of bolus intravenous injections of regular insulin throughout the intraoperative period.

Intraoperative Glycemic Stability

Intraoperative glycemic stability was defined by the maintenance of blood glucose levels in the preset target ranges for each group, or normal blood glucose range, during the intraoperative period. Target ranges include 110-149 mg/dl for the tight glycemic control, 150-180 mg/dl for the conventional glycemic control, and for the standard glycemic control. Glycemic stability was considered achieved if blood glucose levels were maintained within the preset target range and/or in the normal range for blood glucose (80-110 mg/dl). Variation of abnormal blood glucose levels outside of the preset target range could occur as long as it was less than three consecutive blood glucose levels (< 1.5 hours). Blood glucose levels were monitored and recorded every thirty minutes in the intraoperative period.

Intraoperative Glycemic Instability

Intraoperative glycemic instability was defined as three consecutive blood glucose levels that were abnormal and outside of the preset target ranges, whether above or below the limits during the intraoperative period. Target ranges included 110-149 mg/dl for the

tight glycemic control, 150-180 mg/dl for the conventional and standard glycemic control. Blood glucose levels were monitored and recorded every thirty minutes in the intraoperative period.

Coronary Artery Bypass Graft Surgery

Coronary artery bypass graft surgery (CABG) was defined as surgery performed with a median sternotomy incision using cardiopulmonary bypass (CPB). Myocardial preservation is provided by cardioplegic arrest. The procedure involves bypassing coronary blockages with a variety of conduits (Bojar, 2005). Coronary artery bypass graft surgery is used to augment restricted coronary blood flow, including collateral pericardial blood flow to epicardial arteries and implantation of the internal mammary artery (IMA) with unligated side branches into the left ventricular muscle. The technique involves a bypass to a narrowed or occluded epicardial coronary > 1 mm in diameter with a small diameter conduit (usually reversed saphenous vein or IMA) distal to the narrowed segment, with the proximal arterial inflow source being the ascending aorta (Mitchell, Shumway, Garman, & Siegel, 2004).

Off-Pump Coronary Artery Bypass Graft

Off-pump CABG was defined as a surgical procedure that completes revascularization of the heart without cardiopulmonary bypass. The surgery uses a median sternotomy incision with deep pericardial sutures to stabilize the heart allowing for positioning of the heart without hemodynamic compromise (Bojar, 2005).

Cardiac Valve Surgery: Aortic Valve

Aortic valve replacement was defined as a surgical procedure, on full CPB, performed through a median sternotomy. The rheumatic, stenotic valve, including aortic

annulus, is excised and all calcified areas are debrided to allow the prosthetic valve to be securely seated. After excision of the valve leaflets and debridement, the annulus is measured and appropriate valve prosthesis is placed. Interrupted sutures are placed through the annulus for its entire circumference, than passed through the sewing ring of the prosthesis. The prosthesis is lowered into the annulus and securely tied in place (Mitchell et al., 2004).

Cardiac Valve Surgery: Mitral Valve

Mitral valve surgery was defined as a surgical procedure, on full CPB, performed through a median sternotomy. The atrium, atrial appendage and mitral valve are inspected and a decision is made to repair or replace the valve. Repair of regurgitant valves used primarily by posterior leaflet problems is usually possible. Similarly, annular dilatation secondary to left ventricular enlargement is also usually possible by means of a ring annuloplasty. Valve replacement is performed after excising the valve leaflets and debridement, the annulus is rimmed with interrupted sutures, passed through the sewing ring of the valve prosthesis. The prosthesis is carefully positioned and the sutures are tied (Mitchell et al., 2004).

Coronary Artery Bypass Graft/Valve Surgery

Coronary artery bypass graft/valve surgery was defined as surgery that includes CABG surgery in conjunction with a valve repair or replacement. It is performed with a median sternotomy incision using cardiopulmonary bypass. Myocardial preservation is provided by cardioplegic arrest. The procedure involves bypassing coronary blockages with a variety of conduits (Bojar, 2005). The left internal thoracic artery is used as a pedicled graft to the left anterior descending artery and is supplemented by saphenous

vein grafts or radial artery grafts interposed between the aorta and coronary arteries (Bojar, 2005). In addition to the CABG surgery a valve repair or replacement is performed. The valve is replaced after excising the valve leaflets and debridement, the annulus is rimmed with interrupted sutures, passed through the sewing ring of the valve prosthesis. The prosthesis is carefully positioned and the sutures are tied (Mitchell et al., 2004).

Hypoglycemia

Hypoglycemia was defined as a condition that occurs when blood glucose is lower than 70 mg/dl (ADA, 2012; Moghissi et al., 2009). Signs include hunger, nervousness, shakiness, perspiration, dizziness or light-headedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. It is also known as an insulin reaction if induced by excessive doses of insulin (ADA, 2009). In this study the operational definition of hypoglycemia was defined as a blood glucose level of less than 70 mg/dl at any time during the intraoperative period or within the first six hours postoperatively.

Superficial Incisional Surgical Site Infection

Superficial incisional surgical site infection was defined according to the Center of Disease Control (CDC) and the National Healthcare Safety Network (NHSN) (Horan, Andrus, & Dudeck, 2008). A superficial incisional surgical site infection (SSI) must meet the following criterion: Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and the patient has at least one of the following

- purulent drainage from the superficial incision;

- organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision; and in addition at least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision that is deliberately opened by the surgeon and is culture positive or not cultured (A culture-negative finding does not meet this criterion); or
- a diagnosis of superficial incisional SSI by the surgeon or attending physician (Horan et al., 2008).

There are 2 specific types of superficial incisional SSI, they include:

- 1) superficial incisional primary defined as a superficial incisional SSI that is identified in the primary incision in a patient who has had an operation with one or more incisions (chest incision for CABG surgery); and
- 2) superficial incisional secondary defined as a superficial incisional SSI that is identified in the secondary incision in a patient who has had an operation with more than one incision (donor site incision for CABG surgery) (Horan et al., 2008).

Deep Incisional Surgical Site Infection

Deep incisional surgical site infection was defined according to the Center of Disease Control (CDC) and the National Healthcare Safety Network (NHSN) (Horan et al., 2008). A deep incisional SSI must meet the following criterion: Infection occurs within 30 days after the operative procedure if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operative procedure, and involves deep soft tissues (fascial and muscle layers) of the incision. In addition, the patient must have at least one of the following:

- purulent drainage from the deep incision but not from the organ/space component of the surgical site;
- a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive, or not cultured when the patient has at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$), or localized pain or tenderness;
- an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination; or
- a diagnosis of a deep incisional SSI by a surgeon or attending physician (Horan et al., 2008).

There are 2 specific types of deep incisional SSI, they include:

1. deep incisional primary defined as a deep incisional SSI that is identified in a primary incision in a patient who has had an operation with one or more incisions (chest incision for CABG surgery); and
2. deep incisional secondary defined as a deep incisional SSI that is identified in the secondary incision in a patient who has had an operation with more than one incision (donor site incision for CABG surgery) (Horan et al., 2008).

Potential Infectious State

Potential infectious state was defined as one of the following: 1) Persistent elevations of procalcitonin (PCT) > 1.5 ng/ml past the second postoperative day; 2) sustained or increased PCT blood levels (> 1 ng/ml) past the fourth postoperative day; 3)

a persistent elevated C-reactive protein (CRP) level of > 100 mg/L past the fourth postoperative day; or 4) a PCT blood level > 1 ng/ml combined with a CRP blood level > 100 mg/L past the fourth postoperative day.

Perioperative Period

Perioperative period was defined as the time of arrival to the pre-anesthesia holding area through the operative period and the postoperative or intensive care unit (ICU) period, ending upon transfer out of the ICU. It was measured in days.

Intraoperative Period

Intraoperative period was defined as the time of arrival to the operating room until the departure of the operating room, measured in minutes.

Length of Intensive Care Unit Stay

Length of intensive care unit stay was defined as the arrival to the intensive care unit from the operating room suite until discharge to the ward, measured in days. A qualifier was noted if surgeons document that the patient was medically ready to be transferred from the ICU to the ward, but logistically the transfer could not be completed. This may have occurred when hospital beds on the transferring wards were full and not capable of receiving transferring patients.

Significance to Nurse Anesthesia

The literature reflects that patients who experience postoperative wound infections after open-heart surgery are at greater risk for increased morbidity and mortality. Postoperative wound infections also increase hospital LOS and increase costs. Because of the high morbidity and mortality associated with open-heart postoperative

infections, and the financial cost to institutions, there is a need to identify ways to reduce the incidence of these infections.

Previous studies investigating surgical site infections in open-heart surgery have suggested a link between poor glycemic control and surgical infection rates. Many of these studies are observational designs without randomization or control groups. Research investigating the perioperative glycemic control is limited, and results of these studies are divergent. It is uncertain if tight glycemic control in the perioperative period is beneficial and safe in open-heart surgery. Before implementation of practice protocols for glycemic control can be considered for evidence-based practice, further studies, in the form of randomized controlled trials, are needed. Research is needed to investigate if the relationship between hyperglycemia and surgical site infection is a causal relationship, and determine what effect tight glycemic control has on postoperative surgical wound infections. Investigation of tight glycemic control in the diabetic population verses the non-diabetic population related to postoperative infections also needs to be examined, as well as the identification of blood glucose ranges that produces optimal patient outcomes in both the diabetic and non-diabetic patients. Finally, there is a need to determine if a continuous infusion of intravenous insulin is more effective in glycemic control than intravenous bolus injections of insulin to control blood glucose levels during the perioperative period.

This study attempted to explore glycemic control, specifically in the intraoperative period, by the delivery of varied insulin protocols, and the effects on postoperative wound infection in open-heart patients. The specific aim of this study was to compare the effect of three glycemic control protocols (tight, conventional, and

standard) on postoperative surgical wound infections, procalcitonin and C-reactive protein levels. Secondary outcomes that were investigated included the effect of three glycemic control protocols on blood glucose levels intraoperatively, glycemic stability intraoperatively, and ICU LOS. The next chapter presents the literature supporting the study of glycemic control on surgical site infection rates in patients undergoing open-heart surgery.

Chapter Two

Review of Literature

This chapter presents a review of empirical literature pertinent to intraoperative glycemic control on surgical site infection rates in patients undergoing open-heart surgery. The literature review focused on the incidence and impact of surgical site infections in open-heart surgical patients, biomarkers currently utilized to identify surgical site infections, the influence of hyperglycemia and diabetes in surgical site infections, and current studies related to glycemic control in the postoperative, perioperative and intraoperative period. Existing gaps in research to date were also reviewed.

Databases utilized for literature search included: Cumulative Index to Nursing and Allied Health Literature (CINAHL); PubMed; Cochrane Database; and MD Consult. Search terms for glucose included “blood glucose”, “blood glucose level”, “glycemic control”, “hyperglycemia”, and “hypoglycemia”. Search terms for infection included “deep sternal wound infection (DSWI)”, “harvest site infection (HSI)”, and “surgical site infection (SSI)”. Search terms for open-heart surgery included “cardiac surgery”, “open-heart surgery”, “coronary artery bypass grafting (CABG)”, “cardiovascular surgery”, and “cardiac valve surgery”. Search terms for glycemic control intervention included “insulin infusion”, “insulin drip”, “glucose-insulin-potassium drip”, “insulin protocols”, and

“insulin intervention”. Search terms for biomarkers of infection included “infectious biomarkers”, “C-reactive protein”, “procalcitonin”, and “postoperative markers of infection”.

Published studies examining postoperative wound infections and open-heart surgical patients with diabetes or hyperglycemia were found primarily in medical journals, specifically, the specialty areas of endocrinology, cardiothoracic surgery and anesthesiology. The search was limited to adult human studies specifically looking at blood glucose levels, in the pre-, intra- and postoperative period; and wound infections in the cardiac surgical patient. While cardiovascular surgery was the major focus of this search, other studies related to glycemic control in the critically ill were reviewed and incorporated. Research studies were further restricted to those published in the English language and had a publication date of 1997 or later.

Incidence of Surgical Site Infection

The incidence and impact of surgical site infection (SSI) in open-heart surgical patients has been studied at length (Al-Zaru, AbuAlRub, & Musallam, 2011; Ariyaratnam et al., 2010; Baillot et al., 2010; El Oakley et al., 1997; Fowler et al., 2005; Hollenbeak et al., 2000; Lola et al., 2011; Mannien et al., 2011; Matros et al., 2010; Olsen et al., 2002; Paul et al., 2007; Ridderstolpe, Granfeldt, Ahlfeldt, & Rutberg, 2001; Rosmarakis et al., 2007; Tokmakoglu, 2010; Vogel, Dombrovskiy, & Lowry, 2010 & Zerr et al., 1997). The National Nosocomial Infections Surveillance (NNIS) monitors reported trends in health care associated infections in participating United States acute care hospitals. Surgical site infections have been estimated by NNIS to occur in approximately 4-16% of all hospitalized patients (NNIS, 2004). The CDC estimates that 1.7 million healthcare

associated infections occur annually, of which 290,485 are surgical site infections (Scott, 2009). The estimated cost of SSIs range from \$11,874 to \$41,559 per infection and cost \$3.45-10 billion per year nationally in the USA (Al-Zaru et al., 2011; Scott, 2009). Mortality associated with healthcare associated infections in U.S. hospitals is estimated at 98,987; of these 8,205 were related to SSIs (Klevens et al., 2007).

When open-heart surgery was evaluated, the National Healthcare Safety Network (NHSN) reported an overall infection rate of sternal and harvest site wounds of approximately 0.35-8.5% for patients with a cardiac risk index of zero to three, respectively (Edwards et al., 2009). The NNIS risk index is operation-specific, and applied to prospectively collected surveillance data (Mangram, Horan, Pearson, Silver, & Jarvis, 1999). The index values range from 0 to 3 points and are defined by three independent and equally weighted variables (Mangram et al., 1999). One point is scored for each of the following when present: 1) American Society of Anesthesiologists (ASA) Physical Status Classification of greater than 2; 2) either contaminated or dirty/infected wound classification; and 3) length of operation in excess of T hours, where T is the approximate 75th percentile of the duration of the specific operation being performed (Mangram et al., 1999). Studies reflect the incidence of mediastinitis or deep sternal wound infection (DSWI) post open-heart surgery ranges 0.4-2.7% (Ariyaratnam et al., 2010; Baillot, et al., 2010; El Oakley et al., 1997; Fowler et al., 2005; Hollenbeak et al., 2000; Lola et al., 2011; Mannien et al., 2011; Matros et al., 2010; NNIS, 2004; Olsen et al., 2002; Ridderstolpe et al., 2001; Rosmarakis et al., 2007; Tokmakoglu, 2010; Vogel et al., 2010; Zerr et al., 1997).

Risk Factors Associated with Surgical Site Infection

Many studies investigated SSIs related to CABG surgery in an attempt to identify risk factors for SSI. Related risk factors included a diagnosis of diabetes mellitus (Ariyaratnam et al., 2010; Borger et al., 1998; Harrington et al., 2004; Ji et al., 2009; Lola et al., 2011; Paletta et al., 2000; Spelman et al., 2000; Toumpoulis, Anagnostopoulos, DeRose, & Swistel, 2005; Vuorisalo et al., 1998), obesity (Ariyaratnam et al., 2010; Olsen et al., 2002; Harrington et al., 2004), advanced age exceeding 65 years (Ariyaratnam et al., 2010; Borger et al., 1998; Ji et al., 2009), male gender (Borger et al., 1998; Spelman et al., 2000), female gender (Paletta et al., 2000; Harrington et al., 2004), chronic obstructive pulmonary disease (COPD) (Al-Zaru et al., 2011; Ariyaratnam et al., 2010) and renal dysfunction (Toumpoulis et al., 2005). The predominant risk factors that were identified for SSIs in the open-heart patient included obesity and diabetes mellitus diagnosis. These studies will be described in detail in the next section as they also investigated the impact of SSIs.

Impact of Surgical Site Infections

Studies that investigated the impact of the infectious process on the outcome variable mortality in the open-heart surgery suggested infection was associated with increased mortality (Ariyaratnam et al., 2010; Baillot et al., 2010; Coskun, Aytac, Aydinli, & Bayer, 2005; El Oakley et al., 1997; Fowler et al., 2005; Hollenbeak et al., 2000; Lola et al., 2011; Olsen et al., 2002; Paul et al., 2007; Rosmarakis et al., 2007; Tokmakoglu, 2010; Vogel et al., 2010; Zerr et al., 1997). One study outcome showed infected patients had a decreased mortality when compared to patients without infection (Ridderstolpe et al., 2011). They attributed this decreased mortality to the additional

surveillance methods and aggressive treatment management in patients with infection, while the patients without infections may not have been followed as closely. Several studies reviewed the impact of infection on length of stay (LOS) and all studies suggested the presence of a postoperative SSI increased hospital and/or intensive care unit (ICU) LOS (Al-Zaru et al., 2011; Coskun et al., 2005; El Oakley et al., 1997; Fowler et al., 2005; Graf et al., 2009; Hollenbeak et al., 2000; Paul et al., 2007; Rosmarakis et al., 2007; Vogel et al., 2010).

Deep sternal site infection or mediastinitis, post open-heart, is associated with substantial morbidity and with a mortality rate as high as 34.5% (Ariyaratnam et al., 2010; Baillot et al., 2010; Coskun et al., 2005; El Oakley et al., 1997; Fowler et al., 2005; Hollenbeak et al., 2000; Lola et al., 2011; Olsen et al., 2002; Paul et al., 2007; Ridderstolpe et al., 2001; Rosmarakis et al., 2007; Vogel et al., 2010; Zerr et al., 1997). Deep chest surgical site infections following open-heart surgery were also associated with significant increases in LOS, and hospitalization costs (Coskun et al., 2005; El Oakley et al., 1997; Fowler et al., 2005; Graf et al., 2009; Hollenbeak et al., 2000; Paul et al., 2007; Rosmarakis et al., 2007; Vogel et al., 2010).

In a Swedish retrospective study of 3,008 adults, Ridderstolpe et al. (2001) investigated the incidence of superficial sternal wound complications and deep sternal infections or mediastinitis after open-heart surgery. They aimed to identify preoperative, intraoperative and postoperative factors that could influence the risk of SSI after open-heart surgery (Ridderstolpe et al., 2001). Patients were followed from 1996 through 1999 for the identification of infection by means of telephone questionnaires to patients at 2 weeks and 6 weeks postoperatively, as well as follow up visits with the respective

patient's cardiologists at 2 and 6 months postoperatively (Ridderstolpe, et al., 2001). Forty-two preoperative, intraoperative and postoperative variables were evaluated and 24 were found to be associated with increased risk of SSIs by univariate analysis (Ridderstolpe et al., 2001). Follow up multivariate analysis identified age 75 years, obesity, insulin dependent diabetes, smoking, peripheral vascular disease, a New York Heart Association NYHA classification of III-IV, use of bilateral internal mammary arteries for grafts, and prolonged ventilator support as independent predictors of superficial sternal wound complications and deep sternal wound complications (Ridderstolpe et al., 2001).

Ridderstolpe et al. (2001) found a sternal wound infection rate of 9.7%, with patients that underwent CABG surgery experiencing the highest rate of infection (10.6%), followed by CABG with valve combined surgery (8.4%), and cardiac valve surgery yielding the lowest rate of infection (7.2%). The researchers also revealed that superficial wound complication occurred in 194 patients (6.4%), deep sternal wound infections occurred in 47 patients (1.6%), and 50 patients (1.7%) experienced mediastinitis (Ridderstolpe et al., 2001). The impact of infection in this study revealed a 30-day mortality rate of 2.7% for patients without sternal wound complications and 0.7% for patients with sternal wound complication. Of the patients that experienced a sternal wound complication, the mortality rate was 0.5% for superficial sternal wound complications and 1.0% for deep sternal infections/mediastinitis (Ridderstolpe et al., 2001). The one-year mortality rate was 4.8% for patients without sternal wound complications and 3.8% for those subjects with sternal wound complications, and while not statistically significant, it is interesting that mortality was lower for patients who

suffered a sternal wound infection. The researchers attributed the lower mortality rate for infected subjects to dedicated follow-up of patients, earlier recognition of infection, and aggressive treatment (Ridderstolpe et al., 2001). Limitations of the study included a retrospective design and single site study.

Paul et al. (2007) conducted a prospective observational study of 809 consecutive patients undergoing CABG surgery, with and without cardiopulmonary bypass (CPB), and CABG valve combination surgery, with a purpose to assess the ability of the NNIS risk index, the Euro SCORE, and the Society of Thoracic Surgeons (STS) risk score to predict infection and mortality after open-heart surgery. Surveillance for infection revealed an overall rate of SSI at 3.6 % (29/809) (Paul et al., 2007). Thirty-four percent of these infections were diagnosed after discharge, and 10% were diagnosed more than 30-days post discharge (Paul et al., 2007). Results of the study implied that the NNIS risk index only provided moderate discrimination for infection, and a poor ability to stratify patients into infection risk group (Paul et al., 2007). The researchers found the Euro SCORE predicted infection, 30-day mortality, and 6-month mortality rate with good discrimination (Paul et al., 2007). The preoperative and intraoperative STS risk scores showed good discrimination for SSI and excellent discrimination for early and late mortality (Paul et al., 2007). Results of multivariate analysis revealed COPD, an operation combined with CABG, and diabetes mellitus were significantly associated with SSI (Paul et al., 2007).

Hospital LOS was greatly increased in subjects that experienced a SSI. Subjects with a diagnosed SSI had average hospital LOSs of 27 ± 19.9 days compared with 7.3 ± 7.4 days for subjects without a SSI (Paul et al., 2007). Six-month all-cause mortality rates

were 34.5% in subjects with a SSI compared to 7.6% for subjects without a SSI (Paul et al., 2007). Limitations of the study included a single-center study, small cohort of patients with infection, and lack of randomization (Paul et al., 2007).

A five-year multicenter study conducted in the Netherlands described the Dutch surveillance methods for SSI post open-heart, and results of data collected between 2002 and 2007 (Mannien et al., 2011). The study aimed to identify the feasibility of surgical site infection surveillance as well as identify patients at high risk for the development of SSI after cardiothoracic surgery (Mannien et al., 2011). The study incorporated surveillance of surgical site infections from 8 hospitals on 4,066 patients undergoing CABG surgery, valve surgery or a combination of CABG surgery with concomitant valve surgery (Mannien et al., 2011). The study surveillance period included post discharge surveillance period of 45 days. Registration of sternal SSI within the 45-day period was mandatory but registration of any harvest SSIs was voluntary (Mannien et al., 2011).

In total, 4,066 surgical procedures and 183 SSIs were registered (Mannien et al., 2011). Fifty-three deep sternal SSIs (1.3%), and 44 superficial sternal SSIs (1.1%) were identified, revealing a rate of 2.4% for sternal SSIs (Mannien et al., 2011). Harvest sites for CABG surgery were performed in 2,691 patients, of which 3.2% (86/2691) developed a SSI, thirteen deep infections (0.5%) and 73 superficial (2.7%) (Mannien et al., 2011). Of note, sixty-one percent of all SSIs were recorded after discharge from medical centers (Mannien et al., 2011).

Utilizing multilevel multivariate analysis, the significant risk factors identified for sternal SSIs were re-thoracotomy (odds ratio [OR] = 5.2, 95% CI [2.5, 10.6], $p = .001$); diabetes (OR = 2.5, 95% CI [1.1, 5.5], $p = .03$); preoperative LOS > 3 days (OR = 2.1,

95% CI [1.1, 4.1], $p = .04$); and obesity (OR = 2.0, 95% CI [1.0, 3.8]), $p = .04$ (Mannien et al., 2011). Prolonged extracorporeal circulation (ECC) greater than 123 minutes was the only identified risk factor for the development of harvest SSIs (OR= 1.8, 95% CI [0.9, 3.7]), $p = .08$ (Mannien et al., 2011). Limitations of the study were related to remarkable differences in patient and procedure characteristics between hospitals, including use of ECC, median time of ECC, use of bilateral thoracic arteries, and patient body mass index (Mannien et al., 2011). Harvest site infection rates post patient discharge may have been underestimated since registration of these infections were voluntary and three hospital did not volunteer this data (Mannien et al., 2011).

Vogel et al. (2010) identified that infection rates for CABG surgery increased significantly with increased preoperative LOS. The investigators sought to evaluate the association of in-hospital delay of elective procedures and the subsequent impact on infectious complications after surgery. The study observed infection rates for three surgical procedures CABG surgery, colon resection, and lung resection (Vogel et al., 2010). The study utilized a nationwide inpatient sample queried between 2003 and 2007, and patients who developed a postoperative infectious complication were identified via ICD-9 CM Codes. A total of 87,318 CABG surgeries were evaluated (Vogel et al., 2010).

Results of the study revealed total infection rates significantly increased after elective surgery delays in all three surgeries. Infection rates for CABG surgery increased each day surgery was delayed ranging from an infection rate of 6.68% when surgery was delayed one day to 18.24% when surgery was delayed 6-10 days (Vogel et al., 2010). Trends for increasing infections with increase preoperative LOS were significant for pneumonia and sepsis for all procedures ($p < .001$); and urinary tract infections and SSIs

significantly increased after CABG surgery (Vogel et al., 2010). Postoperative hospital mortality rate was also greater, and mean cost of hospital stay increased with increased preoperative LOS in all procedures (Vogel et al., 2010). Mean hospital costs for CABG surgery increased every day surgery was delayed, costing \$28,962 for surgery delayed 1 day to \$42,055 when surgery was delayed 6-10 days; $p < .001$ (Vogel et al., 2010).

El Oakley et al. (1997) conducted an observational risk analysis to identify variables significant for developing postoperative mediastinitis in patients that underwent CABG surgery in a four-year period. Twenty-one out of 4,043 consecutive patients that underwent open-heart surgery with CPB developed mediastinitis (0.4%), valve endocarditis occurred in 0.1% and superficial wound infection occurred in 3.3% of cases (El Oakley et al., 1997). Results of multivariate regression analyses identified that diabetes, obesity, re-exploration for bleeding, blood transfusions in excess of 3 units, and associated leg wound infections increased the risk of mediastinitis/DSWIs (El Oakley et al., 1997). The impact of mediastinitis included significantly higher hospital mortality rates as compared to those who had no mediastinitis (14% vs. 3.8%), $p < .05$ (El Oakley et al., 1997). Mean hospital LOS was longer in the patients with mediastinitis compared to patients with no infection (36 days vs. 7 days), $p < .01$ (El Oakley et al., 1997).

In a retrospective study investigating postoperative outcomes in obese females undergoing CABG surgery, Tokmakoglu (2010) found no difference in infection rates among females with normal body mass index (BMI) versus morbidly obese females. The study covered a period of four years and reviewed 427 female patients were allocated into three groups: 1) severe obese with a BMI $> 35 \text{ kgm}^2$; 2) obese patients with a BMI $> 30 \text{ kgm}^2$; 3) normal-slightly obese with a BMI $< 30 \text{ kgm}^2$ (Tokmakoglu, 2010).

The study revealed an overall infection rate of 9.6% and an overall hospital mortality rate of 0.7%, yet no statistical difference was noted between the three groups for infection or mortality (Tokmakoglu, 2010). The study did find that while the overall re-hospitalization rate was 10%, subjects with a BMI $> 35 \text{ kgm}^2$ had significantly higher readmission rate (16.1%) than females with a BMI $< 35 \text{ kgm}^2$ (9.8%) and a BMI $< 30 \text{ kgm}^2$ (6.5%), $p = .02$ (Tokmakoglu, 2010). There were a greater number of patients that had a diagnosis of diabetes in the group of subjects with a BMI > 35 , and they experienced more urgent surgeries than the other two groups, which may have influenced results since this difference was not controlled for (Tokmakoglu, 2010).

Using a prospective design Ariyaratnam et al. (2010) investigated the risk factors and mortality associated with DSWI. Data was collected on 7,602 patients undergoing CABG with or without valve surgery, between April 1999 and September 2009 (Ariyaratnam et al., 2010). The study used the 13 STS risk-scoring variables in a logistic regression analysis to identify factors that increased DSWI (Ariyaratnam et al., 2010). Forty-four (0.59%) patients developed DSWI, and experienced a higher mortality rate when compared to patients without DSWI (9.6% vs. 2.6%), $p = .03$ (Ariyaratnam et al., 2010). Logistic regression identified age (OR=1.055, 95% CI [1.016, 1.095], $p = .005$), BMI (OR = 1.076, 95% CI [1.015, 1.141], $p = .01$), diabetes (OR = 2.00, 95% CI [1.07, 3.75], $p = .03$), and COPD (OR = 2.47, 95% CI [1.24, 4.92], $p = .01$) as significant independent determinants of DSWI from the variables considered (Ariyaratnam et al., 2010).

A prospective observational study investigating the risk factors for postoperative infections following open-heart surgery was reported by Lola and colleagues (2011). One

hundred seventy-two patients that underwent open-heart surgery over a 2 year period were evaluated for preoperative, intraoperative and postoperative variables that may increase risk for postoperative wound infections (Lola et al., 2011).

The overall incidence of infection was 13.95% (24/172), including eight superficial sternal wound infections (4.65%), five central line infections (2.9%), four incidences of pneumonia (2.32%), nine incidences of bacteremia (5.23%), one urinary tract infection (0.58%) and one harvest surgical site infection (0.58%; Lola et al., 2011). The total mortality attributed to infection in the study was 3.48% (6/172), and mortality among subjects diagnosed with infection was 25% (6/24; Lola et al., 2011).

In a backward stepwise multivariable logistic regression analysis Lola and colleagues identified diabetes mellitus (OR = 5.92, 95% CI [1.56, 22.42], $p = .009$); duration of mechanical ventilation (OR = 1.30, 95% CI [1.005, 1.69], $p = .046$); development of severe complications in the ICU (OR = 18.66, 95% CI [3.36, 103.61], $p = .001$); and re-admission to the CVICU (OR = 8.59, 95% CI [2.02, 36.45], $p = .004$) as independent risk factors associated with development of nosocomial infection after open-heart surgery (Lola et al., 2011). Limitations to the study included an observational design and the small sample size in a single institution.

Fowler et al. (2005) utilized the STS National Cardiac Database and analyzed 331,429 CABG surgeries to identify the frequency of major infection, identify determinants of major infection, and to convert these determinants into a bedside scoring system to estimate a patient's risk of major infection after CABG surgery. Two logistic regression models were developed to estimate the risk of major infection after CABG surgery, one with preoperative patient characteristics, and the other with preoperative

patient characteristics as well as intraoperative variables (Fowler et al., 2005). Major infection occurred in 3.51% (11,636/331,429) of patients, including an incidence of mediastinitis of 25.1%, saphenous harvest site infections 32.6%, and sepsis incidence of 35% (Fowler et al., 2005). Patients with major infection had significantly higher mortality (17.3% vs. 3.0%), $p < .01$ and postoperative LOS > 14 days (47% vs. 5.9%), $p < .01$ than patients without major infection (Fowler et al., 2005).

Both the preoperative model and the combined model successfully discriminated between high and low risk patients (Fowler et al., 2005). A simplified risk scoring system of 12 variables accurately predicted risk for major infection (Fowler et al., 2005). Several variables were identified as particularly important risk factors including morbid obesity (BMI > 40 kgm²), CPB time > 300 minutes, placement of an intra-aortic balloon pump, and the presence of 3 or more distal anastomoses (Fowler et al., 2005). Diabetes mellitus and obesity were identified as independent risk factors for major infection in the preoperative model (Fowler et al., 2005). A limitation included the use of broader definitions for infection, and a potential for underreported infectious complications, including infections detected post discharge, or more than 30 days after surgery (Fowler et al., 2005). Due to the nature of a retrospective analysis, the study was unable to control for, or even have the ability to process detailed data of the surgical case, such as type and timing of antibiotics, or the use of insulin infusions for glycemic control (Fowler, et al., 2005).

Mediastinitis in diabetic patients after open-heart surgery increases operative mortality two to threefold (Zerr et al., 1997; Olsen et al., 2002). Olsen et al. (2002) sought to determine risk factors for deep and superficial chest wound infections after

CABG surgery to develop a predictive model. The researchers retrospectively analyzed data collected on 1,980 consecutive patients undergoing CABG surgery from 1996 to 1999, using the STS database (Olsen et al., 2002). They found deep chest infections occurred in 1.9% (37/1,980), and superficial chest SSIs occurred in 2.3% (46/1,980) of patients (Olsen et al., 2002). Multivariate logistic regression revealed obese, diabetic patients had a 7.7-fold increased risk of deep chest infections after controlling for intra-aortic balloon pump use, and postoperative transfusions (Olsen et al., 2002). Independent risk factors for superficial SSIs included obesity, diabetes in persons 65 years of age or older and current smoking history (Olsen et al., 2002). Patients with deep chest infections suffered an increased post one-year mortality rate compared with that seen in uninfected patients (21.6% vs. 7.1%, $p = .004$). However, this was not noted in patients with superficial chest infections (15.2% vs. 7.1%), $p = .75$ (Olsen et al., 2002).

Hollenbeak et al. (2000) examined how deep chest surgical SSIs following CABG surgery impacted hospital inpatient LOS, costs, and mortality. They reported a 2.7% (41/1,519) deep chest SSI rate in patients who underwent CABG and CABG/valve surgery over a two-year period. This prompted an aggressive surveillance protocol and the collection of clinical data to determine impact, costs and risk factors. A retrospective review of all CABG patients who developed deep chest infection ($n = 41$) was compared to a set of control patients ($n = 160$) systematically selected as every tenth uninfected CABG patient (Hollenbeak et al., 2000). Variables that significantly increased the risk of deep chest SSI included obesity, renal insufficiency, connective tissue disease, re-exploration for bleeding, and antibiotic prophylaxis greater than 60 minutes before incision (Hollenbeak et al., 2000).

The one-year mortality rate was 22% for patients with deep sternal SSIs versus 0.6% for uninfected patients ($p < .001$), and hospital LOS was increased by 20 days for infected patients ($p < .001$). Patients who developed deep sternal SSI incurred \$20,012 in additional costs in the first year ($p < .001$). Infected patients who died incurred on average three times the cost compared to infected patients who survived ($p = .034$) (Hollenbeak et al., 2000). Limitations of the study included a single center study with a retrospective observational design.

Similarly, Coskun et al. (2005) found an increase in hospital LOS, hospital costs and mortality rates when patients suffered infectious complications. Coskun et al. (2005) sought to determine the mortality rate, LOS, and cost of sternal SSIs for 176 patients that underwent CABG surgery from January 1999 to December 2002. The study utilized an active prospective and laboratory based surveillance program to identify patients with nosocomial infections (Coskun et al., 2005). The sample included 52 patients with deep sternal SSIs, 36 patients with superficial sternal SSIs, and 88 in a randomly selected uninfected control (Coskun et al., 2005). Mortality rates in the deep sternal SSI group was significantly greater (19.2%, $p < .01$) when compared to the superficial sternal SSI group (0%) and the uninfected control group (4.5%). Hospital LOS was significantly different between groups, with the deep sternal SSI group having the greatest compared to the superficial sternal SSI group (47 days vs. 33 days, $p < .001$), respectively, and uninfected group (47 days vs. 12 days), $p < .01$ (Coskun et al., 2005). Identified limitations of the study were a single site center study and an observation study design.

A European case-control study conducted by Graf et al. (2009) examined the economic aspects of DSWIs comparing the ICU and hospital LOS, as well as the total

costs for patients undergoing CABG surgery depending upon the occurrences of subsequent DSWI. Two control patients without any signs or symptoms of an infection were matched to each case by 1) type of surgery according to their diagnosis related group (DRG), 2) age \pm 5 years, 3) gender, and 4) duration of preoperative hospital LOS \pm 2 days (Graf, et al., 2009). Seventeen CABG patients with DSWI and 34 matched controls were included during January 2006 and March 2008 (Graf et al., 2009). Findings reflected that LOS in the hospital was doubled and costs almost tripled with the development of a DSWI, $p < .001$ (Graf et al., 2009).

Infectious complications have been reported with off-pump CABG surgery as well as with CABG surgery with CPB. Rosmarakis et al. (2007) conducted a non-interventional prospective cohort study including 360 subjects to evaluate the frequency, characteristics, and risk factors of nosocomial infections. The study also examined the role of laboratory tests C-reactive protein (CRP) and procalcitonin (PCT), and the role of sternal wound cultures in the diagnosis of sternal wound infection (Rosmarakis et al., 2007). Patients were followed for six months postoperatively and infectious complications were recorded (Rosmarakis et al., 2007). Eighteen of the 360 subjects (5%) developed postoperative infections including 1.9% sternal wound infections, 1.7% superficial wound infections, 0.3% mediastinitis, 1.4% pneumonia, and 1.1% bacteremia (Rosmarakis et al., 2007). C-reactive protein levels increased significantly from the day before surgery to postoperative day 1 through 3 in patients with and without infection (Rosmarakis et al., 2007). However, CRP levels measured on postoperative day one and two after CABG without CPB, were significantly higher in patients with postoperative infection compared to patients without infection, $p < .05$ (Rosmarakis et al., 2007).

Procalcitonin levels increased significantly from the day before surgery to postoperative day 1 and 2 after surgery in patients with and without infection (Rosmarakis et al., 2007). Procalcitonin levels measured on postoperative day (POD) 1-3, in patients, that underwent CABG without CPB, were significantly higher in patients with postoperative infections compared to patients without infection, $p < .05$ (Rosmarakis et al., 2007). The investigators also found PCT to be superior to CRP in discriminating infection after open-heart surgery.

A backward stepwise multivariate logistic regression model revealed that independent risk factors of postoperative infection included a history of major nervous system disorder, history of left ventricular heart failure, an emergent operation, blood transfusions in ICU, and duration of central venous catheter placement in ICU (Rosmarakis et al., 2007). The mortality rate for patients with infection was 11.1% compared to 0.6% for patients without infection, $p < .05$ (Rosmarakis et al., 2007). Limitations of this study included a single site center study, and a small sample size of infected patients (18) that may not reflect true statistical association between a variable and the outcome of interest (Rosmarakis et al., 2007). Many cases were also missing CRP and PCT values which may have altered results of the study (Rosmarakis et al., 2007).

In contrast, Singhal, Mahon, and Riordan (2010) found no difference in mortality, stroke, renal dysfunction, atrial fibrillation, or DSWI between off pump and on pump CABG surgical patients. They did find that off pump CABG surgical patients received less blood transfusions and required less inotropic support than patients with CPB (Singhal et al., 2010).

While the incidence of DSWI continues to occur, Matros et al. (2010) demonstrated a significant reduction in DSWI incidence the last 5 years of a 15-year study period. Matros et al. (2010) conducted a retrospective longitudinal analysis, and reviewed all median sternotomies performed at a single institution from 1991 through 2006. Two cohorts were separated into periods from 1992 through 2001 and 2002 through 2006 to identify longitudinal trends in risk factors for DSWI (Matros et al., 2010). Univariate and matched multivariable analyses were performed (Matros et al., 2010). Overall, the study population had increased comorbidities associated with DSWI including obesity, diabetes, and advanced age (Matros et al., 2010). The overall DSWI rate was 1.35% (285/21,000), with a noted reduction in infection rates from 1.57% to 0.88% in the latter 5-year period (Matros et al., 2010). The rate of DSWI among the patients with diabetes decreased from 3.2% to 1.0% in the last 5 years (Matros et al., 2010). Multivariable analysis revealed a diagnosis of diabetes and smoking, while risk factors in the first cohort, were not risk factors in the second cohort (Matros et al., 2010). Prolonged CPB time was the only identified risk factor independently associated with DSWI for the entire study period (Matros et al., 2010). Limitations of the study included the longitudinal design opening concerns of practices changes over time.

Baillot et al. (2010) examined the outcome of patients with DSWI treated with vacuum-assisted closure (VAC) therapy as a bridge to sternal osteosynthesis with horizontal titanium plate fixation. Over a 15-year period (1992-2007) a consecutive cohort of patients were divided into conventional (1992-2001) and contemporary (2002-2007) groups. Retrospective data in the conventional group (non-VAC) received a treatment of debridement/drainage with primary closure and irrigation ($n = 118$), or

debridement/drainage, open packing followed by pectoralis myocutaneous flaps ($n = 81$). The contemporary group was a prospective design in which subjects received a variety of treatments including non-VAC and pectoralis myocutaneous flaps ($n = 24$), VAC treatment and pectoralis myocutaneous flap ($n = 33$), VAC and osteosynthesis and pectoralis myocutaneous flap ($n = 92$), or treatment of the VAC therapy alone ($n = 125$) (Baillot et al., 2010).

Results of the Baillot study revealed a 1.1% DSWI rate overall with 0.9% in the first conventional period and 1.4% in the second contemporary period, $p = .001$ (Baillot et al., 2010). Hospital mortality was 10.25% overall in the study with no statistical difference between groups (Baillot et al., 2010). However, it was noted that VAC therapy ($n = 125$) was associated with a lower mortality (4.8% vs. 14.1%), $p = .001$ (Baillot et al., 2010). Risk factors identified for DSWI included prolonged intubation in the ICU, use of bilateral internal thoracic artery grafting, diabetes, reoperation for bleeding and BMI > 30 kgm² (Baillot et al., 2010).

Studies have shown that the harvest site or donor site is a common surgical site infection associated with CABG surgery, with rates reported as high as 35% (Jonkers et al., 2003; Olsen et al., 2003; Rosenfeldt et al., 2003; Swenne, Lindholm, Borowiec, & Carlsson, 2004). Surgical site infections may have a delayed diagnosis up to 30 to 90 days post-surgery (Jonkers et al., 2003; Olsen et al., 2003; Rosenfeldt et al., 2003; Swenne et al., 2004). Rosenfeldt et al. (2003) investigated two different dressing techniques and the impact on saphenous vein harvest site infections. One hundred fifty two consecutive patients were randomly assigned to receive either standard postoperative leg dressings (control group) or a wrap dressing (interventional group) (Rosenfeldt et al.,

2003). Results revealed an infection rate of 35% in the patients that had the standard leg dressing for harvest surgical sites verses an infection rate of 14% for patients that had the interventional wrap dressing, $p = .006$ (Rosenfeldt et al., 2003). Rosenfeldt et al. (2003) also found that 97% of infections were detected after the patient had been discharged from the hospital; only one control group patient had an infection documented while in the hospital (3%).

A retrospective analysis of data from 1,980 subjects obtained over 4 years from the institutional STS database was conducted to determine independent risk factors for leg harvest SSIs after CABG surgery (Olsen et al, 2003). The analysis showed 76 patients (4.5%) developed leg harvest site infections, of which the impact was a significantly longer hospital LOS (10.1 days) compared to those patients without an infection (7.1 days), $p < .01$ (Olsen et al., 2003). Eight patients (11.9%) developed saphenous harvest infections, which were primarily superficial infections (86%) (Olsen et al., 2003). Independent risk factors for leg harvest site infection included previous cerebrovascular accident, postoperative blood transfusions in excess of 5 units, obesity, and an age of 75 years or older (Olsen et al., 2003). The study was limited by a small sample size and a retrospective design.

The incidence of SSIs may be underreported. Studies that have investigated delayed diagnosis of SSIs have shown that often infections are not present until after hospital discharge (Berg et al., 2011; Hannan et al., 2011; Jonkers et al., 2003; Swenne et al., 2004). Swenne et al. (2004) investigated surgical wound infections within 30 and 60 days of CABG surgery for 374 patients, 197 with diabetes and 199 patients without diabetes. The study design was a prospective, post-discharge evaluation of surgical

wound infections at 30 and 60 days after surgery (Swenne et al., 2004). The study attempted to control for known risk factors for infection including preoperative preparation of the skin, antibiotics within one hour of surgical incision, intravenous infusion for glucose control during the operation and the first 24 hours postoperatively (Swenne et al., 2004). The study revealed a SSI rate of 30.5% (114/374), of which 17.7% were harvest site infections, and 12% were superficial sternal infections (Swenne et al., 2004). The incidence of mediastinitis was low (0.1%). Almost all surgical wound infections of the sternum (93.3%), and most harvest wound infections (73%) were diagnosed within 30 days. Significant risk factors identified for surgical wound infections included low preoperative hemoglobin, obesity, and female sex (Swenne et al., 2004).

Jonkers et al. (2003) studied the prevalence of sternal wound infection and harvest site infections during hospitalization as well as 30 and 90 days after open-heart surgery. The prospective study included a total of 1,885 patients who underwent open-heart surgery from September 1996 to August 1998 (Jonkers et al., 2003). During hospitalization, following open-heart surgery, as well as during re-hospitalization, infection data were collected using medical records, bacteriological results and infection control surveillances (Jonkers et al., 2003). After discharge patients visited the outpatient clinic for follow up at 2 and 6 weeks, and the medical attendants completed a wound healing questionnaire. Patients completed a wound healing questionnaire at 90 days postoperatively (Jonkers et al., 2003).

The infection rate for the entire study period was 9.0% for sternal wounds and 7.9% for harvest sites (Jonkers et al., 2003). Of the sternal wound infections 1.3% were categorized as deep infections, and 7.7% were categorized as superficial infections

(Jonkers et al., 2003). More SSIs were diagnosed at the 30-day post discharge compared to during hospitalization (11.4% vs. 6.2%), respectively (Jonkers et al., 2003). The 90-day post discharged had an even higher rate of SSIs than the 30 day post discharge period (16.3% vs. 11.4%) (Jonkers et al., 2003).

A retrospective analysis by Hannan et al. (2011) looked at 30-day re-admissions for 33,936 patients in New York State during a two-year period. Findings showed that postoperative infections (16.9%) were the most common reason for readmission after CABG surgery (Hannan et al., 2011). They also found a slight correlation between the risk-adjusted 30-day readmission rate of hospitals, and risk-adjusted in-hospital 30-day mortality rate, which was 0.32 ($p = .047$). Factors that were associated with readmission included advanced age, female sex, African-American race, obesity, Medicare or Medicaid status, longer LOS with original surgery. These patients were also sicker, having multiple co-morbidities, and experiencing postoperative complications with initial surgery, specifically renal failure and surgical re-exploration (Hannan et al., 2011).

Saphenous vein and/or donor site infections have been reported to have severe clinical consequences including non-healing ulcers, cellulitis that require debridement, skin graft, and/or amputation (Paletta et al., 2000; Young, Washer, & Malani, 2008). Young et al. (2008) reviewed and discussed risk factors and management strategies for SSIs among older adults undergoing surgery, including open-heart surgery. They noted that SSIs were an important source of morbidity and mortality in the older patient, and treatment of significant infections often requires prolonged courses of parenteral and/or oral antimicrobial therapy, as well as surgical interventions.

Paletta et al. (2000) presented the experience in treating 23 patients with major leg wound complications after saphenous vein harvest for coronary revascularization. A retrospective review of 3,525 bypass procedures over a 10 year period was conducted, and results showed that lower extremity wound complications occurred in 4.1% (145/3,525) of patients undergoing open-heart surgery (Paletta et al., 2000). Of the patients that experienced a postoperative lower extremity wound infection, 0.65% (23/3,525) required additional surgical interventions (Paletta et al., 2000). Surgical procedures that were required included 32 wound debridements, 8 skin grafts, 11 vascular procedures, 5 amputations, 3 fasciotomies, 2 free tissue transfers, and 1 fascio-cutaneous flap (Paletta et al., 2000).

The introduction of endoscopic harvest of the saphenous vein has decreased harvest site complications to an overall complication rate of 2-4% (Athanasίου et al., 2003; Bonde, Graham, & MacGowan, 2002; Yun et al., 2005). Yun et al. (2005), using a randomized control trial (RCT), compared angiographic patency rates, of greater saphenous veins removed during CABG surgery, in patients who had endoscopic vein harvest technique or open vein harvest technique. Two hundred patients undergoing CABG surgery with CPB, were randomized to receive endoscopic or traditional saphenous vein harvest during a six month trial (Yun et al., 2005). The researchers found leg wound complications were significantly reduced in the endoscopic vein harvest group compared to the open harvest vein group (7.4% vs. 19.4%) respectively, $p = .014$ (Yun et al., 2005).

Bonde et al. (2002) investigated, in a prospective RCT, the quality of wound healing in 60 patients with saphenous vein harvests performed either by endoscopic

technique or traditional open technique. In a three month period patients were randomized to either the endoscopic vein harvest group ($n = 30$) or the open long saphenous vein harvest group ($n = 30$). Infection rate was determined by the additional treatment, serous discharge, erythema, purulent exudates, separation of deep tissue, isolation of bacteria, stay duration as inpatient (ASEPSIS score; Bonde et al., 2002). In the open vein harvest group the ASEPSIS score was 15 (range 2-38) indicating a disturbance of wound healing compared to 2.13 (range 1-3) in the endovascular vein harvest group, $p < .01$ (Bonde et al., 2002). Investigators also found that patients with the endoscopic approach to vein harvesting had a statistically significant lower infection rate and postoperative pain score than patients who underwent the traditional open vein harvest technique, $p = .001$ (Bonde et al., 2002).

Athanasίου et al. (2003) conducted a meta-analysis of studies that investigated the effect of traditional vein harvest versus endoscopic vein harvest on wound healing and hospital LOS. When considering randomized studies, the total number of non-infective wound disturbances was lower in minimally invasive endoscopic vein harvest (4%) compared to the traditional open vein harvest (13%) group (Athanasίου et al., 2003). Hospital LOS was significantly reduced in the endoscopic minimally invasive group in comparison to the traditional open harvest group (Athanasίου et al., 2003).

In summary, studies investigating the incidence and impact of postoperative infection in open-heart surgery were observational, primarily retrospective. These studies inferred the presence of postoperative infection increases morbidity and mortality, as well as an increasing hospital LOS. The observational research also suggested an association between postoperative infections and risk factors of obesity and a diagnosis of diabetes

mellitus. However, while an association exists between certain risk factors and poor patient outcomes, it does not implicate these risk factors as a cause for poor patient outcomes.

Infectious Biomarkers

This section summarizes studies examining biomarkers utilized in identification of postoperative SSIs for open-heart surgery, specifically C-reactive protein (CRP) and procalcitonin (PCT). While there is an increasing body of evidence supporting the use of biomarkers for diagnosis of infection and sepsis, evidence of its use in cardiac surgery is limited.

C-reactive protein.

It has been known for several years that C- reactive protein (CRP) is one of the non-specific acute phase reactants that is elevated during the inflammatory response process (Ho, 2009). C- reactive protein belongs to the pentraxin family of proteins; having five subunits that form a pentameric structure (Ho, 2009). The gene for CRP is located on chromosome 1, and baseline CRP variability between individuals can be as high as 40% (Ho, 2009). C-reactive protein plays an important role during the innate immune response to infection. It belongs to the humoral response of the immune system and functions by activating opsonization and the complement system, and in modulation of platelet activation (Moodley, 2012; Neumaier & Scherer, 2008). It is a marker of general tissue damage in addition to inflammation, and bacterial infection (Neumaier & Scherer, 2008).

The production of CRP occurs almost exclusively in the liver by hepatocytes as part of the acute phase response upon stimulation by interleukin-6 (IL-6), and to a lesser

extent tumor necrosis factor alpha (TNF α), and IL-1-Beta originating at the site of inflammation (Ho, 2009; Welsch et al., 2007). The plasma half-life is approximately 19 hours and clearance of CRP from the plasma occurs entirely by the liver (Ho, 2009). C-reactive protein has been used as a prognostic indicator in a variety of clinical scenarios from primary care to surgery and critical care.

Studies on how CRP concentrations are affected by uncomplicated surgery have produced a general consensus that a rise in CRP occurs as a result of surgical trauma, and peaks at 48 hours postoperatively (Cole, Watts, Scott-Coombes, & Avades, 2008). Patients who exhibit higher than normal CRP concentrations (0.5 mg/L) preoperatively have been shown to experience later peak CRP levels and prolonged elevation in CRP postoperatively (Cole et al., 2008). Specific to cardiac surgery Meng et al. (2008) conducted a study aimed at assessing the release and timing of cardiac biochemical and inflammatory markers in patients undergoing elective CABG with CPB. Forty patients had blood samples collected for biochemical measurements at time points: prior to induction of anesthesia, 1, 6, 12, and 24 hours after initiation of CPB (Meng et al., 2008). The results of the study showed serum high-sensitivity CRP levels started to elevate 12 hours after CPB ($p < .01$) and continued to increase 24 hours after CPB (Meng et al., 2008). C-reactive protein is one of the biochemical markers that if monitored could help to determine implementation of protective interventions during CABG with CPB (Meng et al., 2008). This is consistent with the findings of Franke et al. (2005), who found CRP elevated 4-6 hours post surgery (with or without CPB) peaking on day 3 and lasting to postoperative day five. Parolari et al. (2007) found that high sensitivity CRP increased after surgery up to eight days postoperatively in patients with and without CPB.

While several studies exist investigating CRP and surgery, its role in open-heart surgery has been limited to primarily risk stratification related to preoperative CRP levels and to a lesser extent intra and postoperative blood values alone, or in combination of other inflammatory biomarkers for evidences of adverse outcomes. The majority of studies have investigated the use of preoperative or baseline CRP values for identification of postoperative adverse events in cardiac surgery and/or identification of patient populations that have higher baseline levels (Biancari et al., 2003; Cappabianca et al., 2006; De Lorenzo, Pittella, & Rocha, 2012; Elenbaas et al., 2010; Fellahi et al., 2009; Gaudino et al., 2002; Kangasniemi et al., 2006; Kim et al., 2009; Lo, Fijnheer, Nierich, Bruins, & Kalkman, 2005; Perry et al., 2010; Xu et al., 2010).

Of the studies investigating preoperative CRP most have found that patients with higher baseline CRP have increased postoperative risks, including an increase risk for cerebrovascular complications (Biancari et al., 2003; Kim et al., 2009), renal dysfunction (Kim et al., 2009), prolonged ventilation (Kim et al., 2009), myocardial infarction, low cardiac output (Biancari et al., 2003; Fellahi et al., 2009), atrial fibrillation (Lo et al., 2005), re-exploration and/or re-vascularization (Fellahi et al., 2009; Kim et al., 2009; Xu et al., 2010), increased platelets and fibrinogen levels (Gaudino et al., 2002), increased hospital LOS (Perry et al., 2010), long-term mortality (Fellahi et al., 2009; Kangasniemi et al., 2006; Perry et al., 2010), 30 day mortality (Biancari et al., 2003; Cappabianca et al., 2006; De Lorenzo et al., 2012), and DSWI or infection (Cappabianca et al., 2006; Elenbaas et al., 2010; Kim et al., 2009). In addition, it was found that patients with a preoperative diagnosis of diabetes mellitus, history of myocardial infarction (MI), peripheral vascular disease (PVD), low cardiac output states, and emergent surgery had

higher preoperative CRP concentrations than patients without these co-morbidities (Biancari et al., 2003).

Padayachee, Rodseth, and Biccard (2008) conducted a meta-analysis of the utility of pre-operative CRP in predicting early (< 30 days), intermediate (30-180 days), and long term (> 180 days) mortality, and major adverse cardiac events, cardiac mortality, and non-fatal MI following vascular surgery. Meta-analysis revealed that a preoperative CRP level of in excess of 3 mg/L was associated with mortality ($p = .02$), cardiac death ($p = .005$), and major adverse cardiac events ($p = .004$) (Padayachee et al., 2008).

Perry et al. (2010) examined the value of preoperative CRP levels less than 10 mg/L for predicting long-term, all cause mortality and hospital LOS in 914 surgical patients undergoing primary, non-emergent CABG surgery. Preoperative CRP was stratified into four categories (< 1, 1-3, 3-10, and > 10 mg/L) in a prospective study. Patients in the higher CRP categories (3-10 mg/L and > 10 mg/L) were more likely to be women, current smokers, have a higher BMI, have a higher incidence of recent MI, and have longer CPB times (Perry et al., 2010). Results revealed that the two groups with higher preoperative CRP values, 3-10mg/L and > 10mg/L, experienced greater long-term all cause mortality (hazards ratios = 2.5, CI [1.22, 5.16], $p = .01$; and 2.66, CI [1.21-5.80], $p = .02$), respectively and extended hospital LOS (1.32, CI [1.07-1.63], $p < .001$ and 1.27, CI [1.02-1.62], $p = .001$), respectively (Perry et al., 2010).

However, there are a few studies that have shown no difference in patient outcomes of renal dysfunction (Gaudino et al., 2002), incidence of postoperative atrial fibrillation (Ahlsson, Bodin, Lundblad, & Englund, 2007), or postoperative mortality, MI, or stroke for those patients with higher preoperative CRP levels (> 5 mg/L)

compared to those with lower CRP values preoperatively (Gaudino et al., 2002; Xu et al., 2010). The cutoff value for CRP classified as high varied in the studies from as low as 3 mg/L to as high as 10 mg/L, reflecting a significant variability in the high-risk category of patients.

Only three studies investigated preoperative CRP and relationship with postoperative wound infection. All three studies found that higher preoperative CRP concentrations yielded more postoperative infectious complications (Cappabianca et al., 2006; Kim et al., 2009; Elenbaas et al., 2012). Preoperative CRP was identified as a risk factor for the development of postoperative infectious complications in a study conducted by Cappabianca et al. (2006). The study evaluated the effect of preoperative inflammatory status, via CRP on short-term and mid-term outcome after cardiac surgery. A secondary outcome was to verify the effect of preoperative inflammatory status on in-hospital mortality and morbidity (Cappabianca et al., 2006). Five-hundred ninety seven patient records were reviewed in a retrospective study in which patients were separated into a high inflammatory state ($n = 243$, $\text{CRP} \geq 0.5 \text{ mg/dl}$), and a low inflammatory state ($n = 354$, $\text{CRP} < 0.5 \text{ mg/dl}$). Results showed that median CRP values were significantly higher in the high inflammatory state group than the lower inflammatory state group for all 5 time points preoperative, day of surgery and postoperative day (POD) 1, 2 and 4 (1.1 mg/dl vs. 0.2 mg/dl, $p < .001$; 2.2 mg/dl vs. 0.3 mg/dl, $p = .001$; 11.6 mg/dl vs. 7.3 mg/dl, $p = .001$; 20.3 vs. 17.8 mg/dl, $p = .02$; and 18.6 mg/dl vs. 13.6 mg/dl, $p = .008$), respectively (Cappabianca et al., 2006). Differences in preoperative clinical status showed the high inflammatory state group had a significantly greater number of co-morbidities including hypertension, carotid stenosis exceeding 50%, and creatinine level

exceeding 2 mg/dl (Cappabianca et al., 2006). Results on postoperative outcomes showed the high inflammatory status group experienced a higher incidence of in hospital mortality (8.2% vs. 3.4%, $p = .01$), death from sepsis (2.9% vs. 0.3%, $p = .007$), death from bleeding (1.2% vs. 0%, $p = .04$), acute renal failure (3.7% vs. 1.4%, $p = .07$), overall infections (16.5% vs. 5.1%, $p = < .001$), sternal wound infections (10.7% vs. 2.8%, $p < .001$), and sepsis (3.2% vs. 0.8%, $p = .03$) compared to low inflammatory group, respectively (Cappabianca et al., 2006).

Kim et al. (2009) conducted a prospective study to investigate the predictive value of preoperative high sensitivity CRP (hsCRP) concentration for major postoperative complications following off-pump CABG surgery. The study included 185 subjects undergoing elective CABG during the year 2007. Subjects were allocated to a low CRP group ($n = 137$, < 0.3 mg/dl) and a high CRP group ($n = 48$, $\text{CRP} > 0.3$ mg/dl). The study found no significant differences between the groups for postoperative CRP concentrations with both peaking on the second day postoperative. However, the white blood cell count (WBC) was statistically significantly higher in the high CRP group on POD 2. Univariate analysis of preoperative variables showed that reduced ejection fraction, history of MI or stroke or renal failure and baseline $\text{hsCRP} > 0.3$ mg/dl were risk factors for major postoperative complications (Kim et al., 2009). In a follow-up multivariate logistic regression adjusting for significant univariate predictors, preoperative renal failure and baseline $\text{hsCRP} > 0.3$ mg/dl remained significant independent predictors of major complications including MI, prolonged ventilation, DSWI, stroke and renal dysfunction (Kim et al., 2009). The study also is consistent with other studies that indicated an inflammatory process is present in off-pump as well as on-

pump CABG surgery. This speaks to the significant acute inflammatory response as a result of surgical trauma and warm regional myocardial ischemia that occurs with off-pump CABG surgery (Raja & Berg, 2007). Unfortunately, the only infectious outcome measure was DSWI, which is the least prevalent of all postoperative infectious complications. Considering this, with the finding that patients with high preoperative hsCRP also had significantly greater leukocytosis on POD 2, it leaves questions to the possibility of undiagnosed superficial infections.

Elenbaas et al. (2010) analyzed data from all patients undergoing CABG surgery from 1998 to 2008 to determine risk factors for the development of postoperative mediastinitis. Mediastinitis was present in 100 out of the 11,748 patients (Elenbaas et al., 2010). Patients that developed postoperative mediastinitis were older, had more COPD, PVD, diabetes, atrial fibrillation, a BMI greater than 35 kg/m², and a higher preoperative CRP level (Elenbaas et al., 2010). Univariate and multivariate logistic regression analyses were performed to investigate the effect of biomedical variables on the development of mediastinitis (Elenbaas et al., 2010). Preoperative atrial fibrillation and preoperative CRP level were important independent predictors of the development of mediastinitis (Elenbaas et al., 2010).

Use of postoperative CRP as a marker for infection in cardiac surgery has not been explored extensively. Corral et al. (2009) conducted a prospective, clinical cohort study to determine the possible correlation between inflammatory activation after cardiac surgery with CBP, measured by postoperative CRP. Two hundred sixteen consecutive patients, that underwent CABG, valve surgery or a combination of valve and CABG, were included in the study. Results showed that postoperative CRP concentrations did not

correlate with variables reflective of outcomes and therefore, was not a useful marker in predicting outcome after 48 hours in the post cardiac ICU (Corral et al., 2009).

Unlike PCT, CRP is influenced, and increased, by extraneous factors, such as advanced age, male gender, diagnosis of diabetes, hypertension, and operation site and time; therefore may not be as useful in diagnosing postoperative infection as PCT (Chung et al., 2011). C-reactive protein does not differentiate specifically enough between patients developing an infection and those exhibiting an acute phase response following cardiac surgery. However, it does increase the specificity for identifying infections when used in addition to PCT levels (Rothenburger et al., 1999). Rothenburger et al. (1999), in a prospective study, investigated if PCT was more helpful than CRP in identifying infection from a normal acute phase response following open-heart surgery (Rothenburger et al., 1999). In a one year period, 7 out of 563 patients (1.2%) developed systemic infections after open-heart surgery, and an additional 8 patients (1.4%) had local wound infections requiring surgical therapy (Rothenburger et al., 1999). Blood samples for PCT and CRP measurement were taken preoperatively, at the onset of infection, as well as on the 3rd, 5th, and 7th day following diagnosis of infection (Rothenburger et al., 1999). Forty-four randomly selected patients undergoing open-heart surgery without clinical signs of infection served as a control to assess the PCT and CRP contribution to acute phase response (Rothenburger et al., 1999). The researchers found that a pattern of high PCT levels and high CRP levels were indicative of systemic infection, while low PCT levels and high CRP indicated either acute phase response or local wound problems, but no systemic infection (Rothenburger et al., 1999). A PCT level > 4 ng/ml combined

with a CRP level > 170 mg/L was indicative of a systemic infection in patients following cardiopulmonary bypass (Rothenburger et al., 1999).

Simon, Gauvin, Amre, Saint-Louis, and Lacroix (2004) performed a meta-analysis to evaluate the accuracy of determination of PCT and CRP levels for the diagnosis of bacterial infection. The analysis included published studies that evaluated CRP and PCT for the diagnosis of bacterial infections in hospitalized patients (Simon et al., 2004). Findings included that the PCT level was more sensitive 88%, (95% CI [80, 93]) versus 75%, (95% CI [62, 84]) and more specific 81%, (95% CI [67, 91]) versus 67%, (95% CI [56, 77]) than the CRP level for differentiating bacterial from non-infective causes of inflammation (Simon et al., 2004).

Procalcitonin.

Procalcitonin is a 116-amino acid polypeptide precursor to the calcium regulatory hormone calcitonin, and has a molecular weight of 13 kDa (Becker, Snider, & Nylen, 2008; Oczenski, Fitzgerald & Schwarz, 1998; Schneider & Lam, 2007). It is the precursor protein of the hormone calcitonin which consists of 32 amino acids known to be produced in the thyroid gland, and is composed of three sections: the amino terminus (N-ProCT), immature calcitonin, and katacalcin (Becker et al., 2008; Oczenski, et al., 1997; Schneider & Lam, 2007). The Calc-1 gene located on chromosome 11 regulates synthesis of PCT. In healthy individuals production of PCT and subsequently calcitonin is restricted to the thyroid C-cells (Becker et al., 2008; Schneider & Lam, 2007). The normal healthy patient, without infection or inflammation, usually has very low PCT concentrations in circulating blood, < 0.05 ng/mL. (Karlsson et al., 2010; McGee & Baumann, 2009; Reinhart, Meisner, & Brunkhorst, 2006). The half-life of PCT is

approximately 24 hours, with peak levels occurring at 12-16 hours after initial stimulus, and decreasing half daily when host immune system controls insult (Becker et al., 2008; Brunkhorst, Heinz & Forycki, 1998; McGee & Baumann, 2009; Schuetz, Albrich & Mueller, 2011).

Literature supports that a number of stimuli, such as endotoxin, and proinflammatory cytokines, induce PCT, raising values reflective of the severity of the insult and/or bacterial load (Becker, Nylen, White, Muller, & Snider, 2004; Christ-Crain et al., 2006; Muller et al., 2010; Muller et al., 2007; Schuetz et al., 2011; van Nieuwkoop et al., 2010). Several observational studies support the use of PCT as a diagnostic marker for infection and or complications in various clinical situations. Evidence supports the use of PCT differential diagnosis in cases of bacteremia (Muller et al., 2010; Schuetz, Mueller & Trampuz, 2007; van Nieuwkoop et al., 2010), endocarditis (Knudsen et al., 2010; Mueller et al., 2004), pyelonephritis and urinary tract infection (Pecile et al., 2004; van Nieuwkoop et al., 2010), abdominal infections (Gurda-Duda, Kusnierz-Cabala, Nowak, Naskalski & Kulig, 2008; Markogiannakis et al., 2011; Sand et al., 2009), and postoperative fever (Hunziker et al., 2010).

There have also been several RCTs conducted investigating the role of PCT in differential diagnosis for pulmonary infections (Christ-Crain et al., 2006; Kristoffersen et al., 2009; Long et al., 2011; Schuetz et al., 2009; Stolz et al., 2009), postoperative infections (Hochreiter et al., 2009; Schroeder et al., 2009), and sepsis (Bouadma et al., 2010; Nobre, Harbarth, Graf, Rohner, & Pugi, 2008), and its benefit in reduction in the use of antibiotic therapy (Bouadma et al., 2010; Christ-Crain et al. 2006; Hochreiter et

al., 2009; Jensen et al., 2011; Kristoffersen et al., 2009; Long et al., 2011; Schroeder et al., 2009; Schuetz et al., 2009; Stolz et al., 2009).

Studies have shown that PCT can be induced after surgery, when no bacterial infection is present, and is reflective of the type and severity of the surgical trauma (Chung et al., 2011; Hunziker et al., 2010; Meisner, Tschaikowsky, Hutzler, Schick, & Schuttler, 1998; Meisner et al., 2002; Prat et al., 2008). Different mechanisms may be involved in inducing this non specific acute inflammatory response, including the use of CPB, the surgical trauma, transfusions including cell saver, blood loss, ischemia-reperfusion and endotoxin release, and hypothermia (Cremer et al., 1996; Delannoy, Guye, Slaiman, Lehot & Cannesson, 2009; Falcoz et al., 2005; Laffey, Boylan & Cheng, 2002; Meisner et al., 2002). This non-specific systemic inflammatory response syndrome (SIRS), a term proposed to identify non-specific generalized inflammatory process independently from any causative factor, makes early diagnosis of postoperative infectious process difficult to identify in open-heart patients (Delannoy et al., 2009; Prat et al., 2008).

Procalcitonin has been used as a reliable diagnostic parameter to detect and to monitor postoperative complications including infection, morbidity and mortality, with a predictive PCT concentration level 0.5 ng/ml to 1.5 ng/ml suggestive of complications (Falcoz et al., 2005; Jebali et al., 2007; Macrina et al., 2005; Meisner et al., 2002; Prat et al., 2008; Sinning et al., 2010). A slow decrease or further increases in PCT values after the second or third postoperative day may indicate that systemic inflammation or infection complication is likely (Oczenski et al., 1997; Whicher, Bienvenu, & Monneret, 2001). While PCT does increase with systemic inflammatory response syndrome (SIRS),

it occurs in modest increases, whereas significant increases in levels of PCT are correlated with an infectious process and sepsis (Falcoz et al., 2005; Jebali et al., 2007; Macrina et al., 2005; Meisner et al., 1998; Whicher et al., 2001).

Falcoz et al. (2005) investigated the utility of PCT in the early detection of infection after thoracic surgery, specifically lung surgery. A twofold aim of the prospective study was to assess the accuracy of PCT as a marker of postoperative infection after thoracic surgery, and to compare it with CRP (Falcoz et al., 2005). The sample consisted of 157 patients who were classified as non-infected ($n = 132$) or infected ($n = 25$; Falcoz et al., 2005). Results included a mean PCT value that was significantly higher in patients with postoperative infection than in those with no postoperative infection (3.6 ± 5.5 vs. 0.63 ± 0.62 ng/ml), $p < .001$ (Falcoz et al., 2005). The onset of infection most frequently occurred on postoperative day 2 (43% of patients); maximum PCT and CRP concentrations most frequently appeared on postoperative day 1 (56% of patients) and day 2 (63% of patients), respectively (Falcoz et al., 2005). The best cutoff value for detection of infection with PCT was 1 ng/ml, and with CRP, 100 mg/L (Falcoz et al., 2005). Procalcitonin was better than CRP for detecting postoperative infection (Falcoz et al., 2005).

A prospective observational study conducted by Macrina et al. (2005) investigated the predictive role of PCT and CRP changes during the immediate postoperative period. Thirty-two patients that underwent CABG surgery were enrolled and followed up to the 7th postoperative day (Macrina et al., 2005). At the end of follow-up, patients were divided into two groups, one if they had an uncomplicated course and the other if they experienced a complicated postoperative course (Macrina et al., 2005).

Postoperative complications included re-sternotomy, need of an intra-aortic balloon pump postoperatively, or intestinal ischemia (Macrina et al., 2005). The researchers found that serum PCT concentrations increased from baseline in both groups during the first two days after surgery (Macrina et al., 2005). The increase in serum PCT concentration was significantly greater in the group with a complicated course than the group without complications (Macrina et al., 2005). The study defined a perioperative PCT value of > 0.5 ng/ml as abnormal (Macrina et al., 2005). Preoperatively and immediate postoperatively the PCT values were below 0.5 ng/ml in patients without complications compared to > 0.5 ng/ml in patients that experience a complication. (Macrina et al., 2005). An absolute PCT concentration change of 0.20, 0.40, and 0.60 ng/ml carried an approximate risk of 5, 26, and 69%, respectively of postoperative complications in the first week post surgery (Macrina et al., 2005).

Jebali et al. (2007) in a prospective study investigated the accuracy of PCT to diagnose postoperative infection after cardiac surgery with CPB and compared it with CRP, WBCs, and IL 6 and IL 8 (Jebali et al., 2007). Blood samples of 100 patients were taken before surgery and each day over the 7-day postoperative period. A blinded expert panel of individuals determined diagnosis of infection. Of the 16 patients diagnosed with infection, PCT concentrations were significantly higher versus those without infection (Jebali et al., 2007). A PCT value of > 1.5 ng/ml beyond the second day diagnosed postoperative infection with a sensitivity of 0.93 (95% CI [0.70, 0.99]) and a specificity of 0.80 (95% CI [0.70, 0.87]). Procalcitonin was also significantly higher in patients who died compared to patients who survived (27.5 vs. 1.2 ng/ml), $p < .001$ (Jebali et al., 2007).

Sponholz, Sakr, Reinhart and Brunkhorst (2006) conducted a systematic review of the literature with the aims of: 1) describing the evolution of serum PCT levels after uncomplicated cardiac surgery; 2) characterizing the role of PCT as a tool in discriminating infection; 3) identifying the relation between PCT, organ failure, and severity of sepsis syndromes; and 4) assessing the possible role of PCT in detection of postoperative complications and mortality. Results of the review revealed uncomplicated cardiac surgery induces a postoperative increase in serum PCT levels, with peak PCT levels reached within 24 hours postoperatively, and return to normal levels within the first week (Sponholz et al., 2006). Although PCT values reported in infected patients are generally higher than in non-infected patients after cardiac surgery, the cutoff point for discriminating infection ranged from 1 to 5 ng/ml, and the dynamics of PCT levels over time may be more important than absolute values (Sponholz et al., 2006).

Prat et al. (2008) attempted to establish the baseline levels of PCT after cardiac surgery in order to analyze a possible induction of the inflammatory response that might interfere with the diagnosis of infection by PCT. Patients were separated into 3 groups, sixty-nine patients undergoing CABG with CPB, sixty-nine patients undergoing valve replacement with CPB, and thirteen patients undergoing CABG surgery without the use of CPB. A control group consisted of 24 healthy subjects not undergoing cardiac surgery. Procalcitonin levels were collected, in 151 patients undergoing open-heart surgery, on admission to the ICU and the first two PODs (Prat et al., 2008). Results revealed the mean PCT values were significantly higher in the first POD in all groups except the control group. While all patients experienced a slight and transient increase in PCT postoperatively, only patients who presented with postoperative complications had

significantly increased PCT values (> 3 mg/mL) immediately after surgery ($p = .004$), in the first POD ($p < .001$), and in the second POD ($p < .001$) with respect to those who recovered uneventfully (Prat et al., 2008). Procalcitonin values were not related to duration of CPB, or to aortic clamp time, and there was no difference in PCT values for those patients that were on CPB compared to those patients off CPB (Prat, et al., 2008). Studies reviewed in this section showed CRP and PCT are significantly increased in patients with infection or postoperative complications. The use of these biomarkers may be beneficial in the early detection of postoperative complication and infection.

The Influence of Diabetes in Surgical Site Infections

This section will review the influence of diabetes in SSIs in open-heart surgical patients. Patients with diabetes after open-heart surgery have increased hospital LOS, poorer wound healing, higher infection rates, and higher mortality rates than patients without diabetes (Brown, Edwards, O'Conner, Ross, & Furnary, 2006; Bucerius et al., 2003; Carson et al., 2002; Guvener et al., 2002; Ji et al., 2009; Woods, Smith, Sohail, Sarah, & Engle, 2004). Brown et al. (2006) conducted a retrospective review of two large registries: the STS database and the Northern New England Cardiovascular Disease Study Group (NNECDSG) to benchmark diabetic outcomes prior to the widespread use of glycemic control in 2001. The STS database revealed 30-day mortality rates were higher for diabetic patients when compared to non-diabetic patients regardless of the type of open-heart surgery (Brown et al., 2006). Results showed lower mortality for non-diabetic patients compared to patients with diabetes in isolated CABG surgery (2.82% vs. 3.96%, $p < .01$), aortic valve replacement (AVR) (3.57% vs. 6.53%, $p < .01$), and mitral valve replacement (MVR) (5.52% vs. 11.07%), $p < .01$. The NNECDSG reported similar

findings in mortality in non-diabetic patients compared to diabetic patients undergoing isolated CABG (2.96% vs. 3.93%, $p < .01$), concomitant CABG/valve (9.55% vs. 15.81%, $p < .01$), AVR (5.48% vs. 8.51%, $p < .05$), and MVR (7.76% vs. 13.01%), $p < .05$ (Brown et al., 2006).

The STS database was used to identify DSWI rates at 30 days after open-heart surgery and found patients with diabetes had nearly twice the number of DSWIs as patients without diabetes, regardless of the procedure (Brown et al., 2006). The specific rates for non-diabetic patients versus diabetic patients showed isolated CABG (0.45% vs. 1.02%, $p < .01$), AVR (0.41% vs. 0.78%, $p < .01$), and MVR (0.35% vs. 0.72%, $p < .01$). The NNECDSG database revealed rates of infection were significantly higher for diabetic patients than non-diabetic patients undergoing isolated CABG (1.97% vs. 1.16%, $p < .01$), but not higher for diabetics undergoing CABG/valve, or valve only procedures (Brown et al., 2006).

On average, diabetic patients were more likely to have longer hospital LOS following open-heart surgery (Brown et al., 2006). In the STS database, the mean post procedure LOS for non-diabetic patients and diabetic patients was 7.08 and 8.05 days, respectively for CABG; 8.28 and 10.03 days for AVR; 9.86 and 12.82 days for MVR (all $p < .01$; Brown et al., 2006). The NNECDSG postoperative LOS was similar when comparing non-diabetic patients to diabetic patients for isolated CABG at 7.60 versus 8.87 days; 11.91 versus 15.12 days for CABG/valve; 9.54 versus 17.67 for AVR; and 10.52 versus 16.25 days for MVR (all $p < .01$; Brown et al., 2006).

Guvener et al. (2002) studied the relationship between perioperative glycemic control and infectious complications in diabetic and non-diabetic patients. A total of

1,090 adults (400 diabetic and 690 non-diabetics) who underwent CABG surgery in a five year period were included in a retrospective cohort study based on chart review (Guvener et al., 2002). Intraoperative and postoperative blood glucose levels in diabetic patients were manipulated by means of a continuous insulin infusion to maintain blood glucose levels between 150-200 mg/dl; non-diabetic patients received no standard insulin treatment (Guvener et al., 2002).

Mean blood glucose levels for the diabetic patient on postoperative day 1 was significantly higher (191 ± 36 mg/dl) compared to the patient without diabetes (140 ± 24 mg/dl), $p = .003$ (Guvener et al., 2002). In the diabetic group, 5% (20/400) of patients developed a postoperative infection, which included superficial sternal SSI (0.75%), harvest site SSI (1%), mediastinitis (1.25%), urinary tract infection (1.5%), and lung infection (0.5%). The diabetic group had a significantly higher prevalence of mediastinitis, harvest SSI, urinary tract infection, and total infection as compared to the non-diabetic group ($p = .048$, $.013$, $.009$, and $.044$), respectively (Guvener et al., 2002). In diabetic patients who developed an infection, the mean glucose level two days preoperative was significantly higher (201 ± 47 mg/dl) compared to diabetic patients who did not develop an infection (165 ± 37 mg/dl). High preoperative mean glucose levels, in the first and second preoperative days, were the main risk factor for the development of postoperative infection ($p = .012$ and $p = .028$), respectively (Guvener, et al., 2002). Mortality was higher among diabetic patients than in non-diabetic patients (3% vs. 1.73%), $p = .048$ (Guvener et al., 2002).

An eight year prospective cohort design by Woods et al. (2004) investigated postoperative outcomes and operative mortality of 6,711 patients (2,178 diabetic and

4,522 non-diabetics) who underwent CABG surgery to determine if any outcome differences existed. Univariate analysis comparing diabetic status with demographic variables and co-morbidities found that the diabetic population was significantly more likely to be women, have left ventricular hypertrophy, have a history of cerebrovascular disease, hypertension, COPD, obesity, higher creatinine levels, more likely to be African-American, and less of a history of tobacco use compared to non-diabetic patients (all $p < .05$; Woods et al., 2004). The researchers found that patients with diabetes experienced significantly higher mortality than patients without diabetes (OR = 1.67, 95% CI [1.20, 2.30], $p < .004$). However, there was no difference between diabetic and non-diabetic patients in the incidence of postoperative morbidity (Woods et al., 2004).

Bucerius et al. (2003) conducted a prospective observational study aimed to delineate the prevalence and the impact of diabetes on perioperative outcomes on 16,184 patients undergoing open-heart surgery over a 5 year period (Bucerius et al., 2003). They found the prevalence of diabetes mellitus was 33.3% (5,389/16,184), and compared to non-diabetic patients the group with diabetes mellitus was older ($p < .001$), and had a significantly lower ejection fraction ($p < .001$). The researchers also found diabetes to be an independent predictor for seven postoperative outcome variables including prolonged ICU stay, sternal SSI, sternal revision, respiratory insufficiency, postoperative delirium, perioperative stroke, renal dysfunction, and postoperative re-intubation (Bucerius et al., 2003).

In a retrospective cohort study of 434 hospitals in North America, researchers sought to determine the impact of diabetes mellitus on short term mortality and morbidity in patients undergoing CABG surgery (Carson et al., 2002). The study sample included

146,786 patients who underwent CABG surgery during 1997, of which 41,663 were diagnosed with diabetes and 105,123 without diabetes (Carson et al., 2002). The researchers found the 30-day mortality was 3.7% in patients with diabetes mellitus and 2.7% in patients without diabetes (Carson et al., 2002). Morbidity and infections occurred more commonly in diabetic patients and were associated with an adjusted risk approximately 35% higher in diabetic patients than non-diabetic patients, particularly among insulin treated diabetics (Carson et al., 2002). Limitations of the study included the retrospective design with a historical control.

Similarly, Ji et al. (2009) found patients with diabetes had a higher rate of infection post-CABG surgery. In a retrospective chart review investigators analyzed 393 elderly patients (121 with diabetes) evaluating the impact of diabetes mellitus on patients undergoing CABG surgery (Ji et al., 2009). Intensive insulin therapy was used in the perioperative period, with a target glucose level of 80 to 110 mg/dl for both diabetic and non-diabetic patients (Ji et al., 2009). Patients with diabetes were less likely to have undergone previous percutaneous coronary intervention ($p = .012$), compared with patients without diabetes mellitus (Ji et al., 2009). Univariate and multivariate logistic regression analysis showed that patients with diabetes had a higher rate of deep sternal SSIs (OR = 2.28, 95% CI [1.29, 6.84], $p = .002$), while sharing similar rates for other morbidities and mortality compared with the patients without diabetes mellitus despite maintaining tight glycemic control (Ji et al., 2009). While studies showed a diagnosis of diabetes mellitus increased the risk of SSIs, hyperglycemia with or without a diagnosis of diabetes has also been implicated as a risk factor for SSIs.

The Influence of Hyperglycemia in Surgical Site Infections

Hyperglycemia, preoperatively, intraoperatively and postoperatively, has been implicated in more infectious complications, longer hospital stays, higher morbidity, mortality and increased resource utilization after open-heart surgery (Ascione, Rogers, Rajakaruna, & Angeline, 2008; Doenst et al., 2005; Estrada et al., 2003; Gandhi et al., 2005; Imran et al., 2010; Knapik, Ciesla, Filipiak, Knapik, & Zembala, 2011; Knapik et al., 2009; Ouattara et al., 2005; Sato et al., 2010; Swenne, Lindholm, Borowiec, Schnell & Carlsson, 2005; Umpierrez et al., 2002).

The American Diabetes Association (ADA) has recommended the use of glycohemoglobin (HbA1c) as a method of assessing long-term glycemic control in diabetic patients, and recommends levels are maintained less than 7% (ADA, 2012). Glycosylated hemoglobin, indicates a patient's blood glucose control during the previous 3 to 4 months and is formed when glucose in the blood binds irreversibly to hemoglobin to form a stable glycated hemoglobin complex (Halkos et al., 2008). Glycosylated hemoglobin is not affected by short-term glycemic lability; it allows a reflection of longer term glucose control.

Preoperative hyperglycemia, as evidenced by preoperative blood glucose, or HbA1c, significantly contributes to morbidity and mortality after cardiac surgery (McAlister, Man, Bistriz, Amad & Tandon, 2003; Halkos et al. 2008; Imran et al., 2010; Knapik et al., 2011; Sato et al., 2010). Sato et al. (2010) conducted a prospective cohort study, of 143 non-diabetic and 130 diabetic patients, to assess the association between the quality of preoperative glycemic control, intraoperative insulin sensitivity, and adverse events after cardiac surgery. Results showed that diabetic patients with poor glycemic

control had a greater incidence of major complications ($p = .010$) and minor infections ($p = .006$). They also received more blood products and spent more time in the intensive care unit ($p = .030$) and the hospital ($p < .001$) than non-diabetic patients (Sato et al., 2010).

In a prospective observational study, Halkos et al. (2008) investigated if preoperative HbA1c was a predictor of adverse outcomes after CABG surgery. In-hospital mortality for all patients was 1% (31/3,089). An elevated HbA1c level predicted in hospital mortality after CABG surgery (OR = 1.40 per unit increase, $p = .019$) (Halkos et al., 2008). Receiver operating characteristic curve analysis revealed that HbA1c greater than 8.6% was associated with a 4-fold increase in mortality (Halkos et al., 2008). For every unit increase in HbA1c, there was a significantly increased risk of MI, and DSWI. By using receiver operating characteristic value thresholds, renal failure (threshold 6.7, OR = 2.1), stroke (threshold 7.6, OR = 2.24), and DSWI (threshold 7.8, OR = 5.29) occurred more commonly in patients with elevated HbA1c (Halkos et al., 2008).

Knapik et al. (2011) conducted a retrospective review of 2,665 patients, 782 (29%) of which had diabetes mellitus, to determine the prevalence of elevated HbA1c among diabetic patients scheduled for CABG surgery and if this influenced postoperative outcomes. Patients with preoperative normal or elevated HbA1c ($> 7\%$) were compared regarding their hospital mortality, morbidity, and LOS (Knapik et al., 2011). Results showed elevated HbA1c levels were present in 38.4% of diabetic patients, 57.1% of patients among insulin-dependent diabetics, 27.3% of patients on oral medication, and in 7.7% of patients whose diabetes was treated with diet only (Knapik et al., 2011). There

was no difference between mortality, or LOS, whether ICU or hospital, and the only significant difference was perioperative MI. Patients with an elevated HbA1c had significantly more perioperative MIs than patients with normal preoperative HbA1c, particularly if the patients had insulin dependent diabetes (Knapik et al., 2011).

Glycosylated hemoglobin has also been used as a predictor of postoperative glucose variability and hyperglycemia in CABG surgery patients (Masla, Gottschalk, Durieux & Groves, 2011).

Masla et al. (2011) investigated the relation of HbA1c and/or a prior diagnosis of diabetes mellitus and intra- and postoperative hyperglycemia and glycemic variability. The retrospective data analysis looked at 120 patients undergoing isolated CABG surgery and found that diabetics and/or patients with elevated HbA1c had higher postoperative glucose levels, a higher standard deviation, and a higher coefficient of variation of glucose values (Masla et al., 2011). However, higher glucose variability was not associated with higher rates of complication, and intraoperative glucose values and variation did not differ significantly between groups (Masla et al., 2011). Increased mean blood glucose values were associated with and increased risk of infection. Additionally, this study found that preoperative fasting glucose could better predict intraoperative hyperglycemia than HbA1c (Masla et al., 2011). Other studies have investigated preoperative blood glucose and found a significant increase in morbidity in patients undergoing CABG surgery (Imran et al., 2010).

A Canadian study by Imran et al. (2010) investigated the impact of admission serum glucose level on outcomes in CABG surgery. A prospective observational study collected data on 2,856 consecutive patients undergoing CABG surgery and divided them

into two groups, those patients with admission blood glucose levels below 9.2 mmol/L (167 mg/dl) 76.3% of patients, and those patients with an admission blood glucose level ≥ 9.2 mmol/L (167 mg/dl) 23.7% of patients. Patients with elevated admission glucose levels tended to be females, have diabetes, preoperative renal failure, an ejection fraction less than 40%, triple vessel disease or left main disease, and a prior MI within 21 days of surgery (Imran et al., 2010). There was no difference between the two groups in-hospital mortality rates ($p = 0.12$). However, patients admitted with higher blood glucose levels were more likely to suffer major morbidity postoperatively, as measured by a composite measure, than patients with admission blood glucose below 9.2 mmol/L (167 mg/dl). Morbidity, as measured by composite, included outcomes of stroke, MI, sepsis, DSWI, acute renal failure, increased inotropic support, and prolonged ventilation (Imran et al., 2010). Patients who were not diabetic but had admission blood glucose levels ≥ 9.2 mmol/L did not experience an increase in morbidity as the diabetic patients with preoperative hyperglycemia did (Imran et al., 2010). This is in contrast to a study completed by Ascione et al. (2008), which found poor blood glucose control led to increase mortality and morbidity, whether the patient was a diabetic or non-diabetic.

Ascione et al. (2008) prospectively investigated the effect of blood glucose control (BGC) in 8,727 patients on clinical outcomes after open-heart surgery. The highest blood glucose level recorded over the first 60 hours postoperatively was used to classify patients as having good (< 200 mg/dl), moderate (200-250 mg/dl), or poor (> 250 mg/dl) BGC (Ascione et al., 2008). They found 85% (7,547) of patients had good BGC, 10 % (905) had moderate BGC, and 4% (365) had poor BGC (Ascione et al., 2008). Diabetic patients comprised 52% of the poor control category with, 31% having moderate

control, and 8% good BGC (Ascione et al., 2008). Inadequate BGC, but not a diagnosis of diabetes, was associated with in-hospital mortality (good BGC 1.8%, moderate BGC 4.2%, poor BGC 9.6%). Additionally, inadequate BGC was associated with postoperative MI, pulmonary and renal complications in patients without known diabetes mellitus (Ascione et al., 2008).

The association between perioperative hyperglycemia and outcomes in patients, with and without diabetes mellitus undergoing CABG surgery, was investigated by Estrada et al. (2003). A retrospective historical study of 1,574 patients, 545 (34.6%) with diabetes and 1,029 patients without diabetes was conducted for patients that underwent CABG surgery over a year time period (Estrada et al., 2003). The researchers found that every 50 mg/dl blood glucose increase, regardless of diabetic status, was associated with increased hospital LOS by 0.76 days (95% CI [0.36, 1.17], $p < .01$); increased hospitalization charges to patients by \$2,824 (95% CI [1,599, 4,049], $p < .01$); and increased hospitalization cost by \$1,769 (95% CI [928, 2,610], $p < .01$). They also found that infections occurred more frequently in patients with diabetes (6.6% vs. 4.1%, $p = .03$) than patients without diabetes (Estrada et al., 2003).

Umpierrez et al. (2002) in a retrospective review of 2,030 patients aimed to determine the prevalence of in-hospital hyperglycemia, survival rates, and functional outcome of patients who experienced hyperglycemia with and without a history of diabetes. Results revealed hyperglycemia (fasting blood glucose level > 126 mg/dl, or random blood glucose > 200 mg/dl) was present in 38% of patients admitted to the hospital, of whom 26% had a known history of diabetes, and 12% had no history of diabetes before the admission (Umpierrez et al., 2002). Hyperglycemia in previously

undiagnosed patients was associated with higher in-hospital mortality rate (16%) compared with those patients with a prior history of diabetes (3%) and patients with normoglycemia (1.7%; both $p < .01$). This indicated that in-hospital hyperglycemia was an important marker of poor clinical outcome and mortality in patients with and without diabetes (Umpierrez et al., 2001).

A retrospective review of 374 patient charts was performed by Swenne et al. (2005) to determine the significance of postoperative blood glucose control as a risk factor for surgical wound infection in open-heart surgery. The sample included patients with and without diabetes that underwent CABG surgery over four years (Swenne et al., 2005). Analysis of blood glucose concentrations postoperatively and patient's evaluation of infection 30 and 60 days post-surgery revealed no difference in the risk factor for surgical wound infections between patients that were diabetic and patients that were hyperglycemic (Swenne et al., 2005). However, the study did show that hyperglycemia in patients without a preoperative diagnosis of diabetes was associated with an increased risk of mediastinitis compared to patients with a diagnosis of diabetes (Swenne et al., 2005).

A retrospective observational study examined the relationship between intraoperative glucose concentration and postoperative complications in 409 consecutive patients who underwent open-heart surgery (Gandhi et al., 2005). The primary independent variable was the mean intraoperative glucose concentration, and the primary end point was a composite of death, and operative complications developing within 30 days postoperative (Gandhi et al., 2005). They found that patients experiencing a primary end point were more likely to be male, older, have diabetes mellitus, undergo CABG

surgery, and receive insulin during surgery (Gandhi et al., 2005). Atrial fibrillation ($n = 105$), prolonged pulmonary ventilation ($n = 53$), delirium ($n = 22$), and urinary tract infection ($n = 16$) were the most common complications (Gandhi et al., 2005). The initial, mean and maximal intraoperative glucose concentrations were significantly higher in patients experiencing the primary end point ($p < .01$ for all comparisons; Gandhi et al., 2005). In a multivariable analysis, mean and maximal glucose levels remained significantly associated with outcomes after adjusting for potentially confounding variables, including postoperative glucose concentration (Gandhi et al., 2005). Intraoperative hyperglycemia was identified as an independent risk factor for complications, including death, after open-heart surgery (Gandhi et al., 2005).

Knapik et al. (2009) in a retrospective review of 814 patients investigated the influence of CPB on postoperative glucose and insulin consumption in patients with and without diabetes mellitus undergoing CABG surgery. Additionally, the study investigated if a marked hyperglycemia in the early postoperative period was a factor associated with early mortality and morbidity (Knapik et al., 2009). Outcome variables for the study included difficult glycemic control (postoperative blood glucose levels > 11.0 mmol/L or 200 mg/dl), hospital mortality, and morbidity.

Results of the study revealed glycemic control was significantly worse in patients who underwent CABG surgery with CPB, in comparison to patients who underwent CABG surgery without CPB (Knapik et al., 2009). Patients with difficult glycemic control had more serious postoperative complications and higher mortality (2.5% vs. 0.4%), $p = .02$ (Knapik et al., 2009). Multivariate analysis revealed difficult glycemic control was significantly associated with a female sex, presence of diabetes, and the

usage of CPB (OR = 2.36, 2.22 and 1.81), respectively (Knapik et al., 2009). Mortality was significantly associated with left ventricular dysfunction, difficult glycemic control, and previous stroke (OR = 7.38, 7.06, and 5.66), respectively (Knapik et al., 2009). Difficult glycemic control was also significantly associated with postoperative morbidity (OR = 1.87; Knapik et al., 2009). The retrospective design of the study is a limitation of the study.

A retrospective study by Reyes, Jensen, Stewart and Kidd (2008) examined the relationship between preoperative and postoperative blood glucose levels and outcomes in cardiac surgery patients with and without diabetes mellitus. Specifically, they investigated if maintaining preoperative blood glucose below a value of 11 mmol/L (198 mg/dl) made a difference in postoperative outcomes in diabetic and non-diabetic patients. Results revealed no difference in postoperative outcomes between patients with and without diabetes, however patients with diabetes did have a significantly longer LOS in the ICU (3.6 ± 6.4 vs. 2.2 ± 2 days, $p = .03$) and hospital LOS (18 ± 18.9 vs. 12.8 ± 9.5 days, $p = .01$) than patients without a diagnosis of diabetes (Reyes et al., 2008). Interestingly, preoperative and postoperative blood glucose values did not correlate with LOS in the ICU ($r = 0.05$, $p = .29$; $r = .03$, $p = .61$), respectively, or hospital ($r = 0.03$, $p = .63$; $r = 0.07$, $p = .20$), respectively (Reyes et al., 2008). Elevated preoperative and postoperative blood glucose levels > 11 mmol/L was associated with increased BMI ($p < .001$ and $p = .001$), respectively. Factors affecting increased hospital LOS included increased age ($p < .01$). Factors that increased ICU LOS included longer aortic cross clamp time and CPB time ($p = .01$, $p = .001$), respectively, and elevated HbA1c values, p

= .001 (Reyes et al., 2008). Factors that affected both ICU and hospital LOS included undergoing combined CABG and valve surgery, $p = .004$ (Reyes et al., 2008).

Studies reviewed in this section suggest hyperglycemia with or without a diagnosis of diabetes mellitus is associated with increased risk of postoperative complications, and mortality. Thereby supporting the need for further research focused on prevention of hyperglycemia and glycemic control in the pre-, intra-, and postoperative period are important.

Glycemic Control

Glycemic control in the postoperative period.

Postoperative glycemic control has been a main focus in the ICU setting to decrease mortality and morbidity, including infectious complications. A variety of continuous insulin infusion protocols have been published and many modifications of these protocols have been instituted in ICU settings, across the nation. Studies that have reported beneficial results with the use of continuous intravenous insulin infusions for glycemic control in the ICU have resulted in improved glucose control; reduce infections, reduced morbidity and mortality (Hruska, Smith, Hendy, Fritz, & McAdams, 2005; Van den Berghe et al., 2001; Zerr et al., 1997; Zimmerman, Mlynarek, Jordan, Rajda, & Horst, 2004).

In a retrospective observational study of 1,585 diabetic patients who underwent open-heart operations, Zerr et al. (1997) aimed to determine the rate of infection between diabetic and non-diabetic patients, and to evaluate the effects of an insulin infusion in the postoperative period on wound infection. The study utilized a historical cohort (first cohort) of patients ($n = 990$, 1987-1991) that received subcutaneous insulin to maintain

blood glucose levels between 150 and 200 mg/dl (Zerr et al., 1997). However, recorded blood glucoses in this cohort ranged from 175-240 mg/dl (Zerr et al., 1997). From 1991 through 1998, an intravenous insulin protocol was utilized, for a second cohort of diabetic patients ($n = 595$), to maintain blood glucose levels < 200 mg/dl in the postoperative period (Zerr et al., 1997). The rate of DSWI in diabetic patients dropped from 2.8% in the historic cohort to 0.74% in the second cohort treated with intravenous insulin. The overall mortality rate in the diabetic population was 5.7% (90/1,585). Of those patients who died, 6.7% (6/90) had DSWI, and patients with DSWIs had a mortality rate of 18% (6/33; Zerr et al., 1997). Blood glucose levels were significantly associated with deep wound infections ($p < .002$). Infected diabetic patients had a higher mean blood glucose level through the first 2 postoperative days than non-infected patients (208 ± 7.1 vs. 190 ± 0.8 mg/dl); $p < .01$ (Zerr et al., 1997). The study inferred the use of a continuous insulin infusion, to maintain blood glucose levels below 200 mg/dl, in the postoperative period for patients undergoing open-heart surgery significantly reduced major infectious morbidity (Zerr et al., 1997). Limitations of the study included the nature of the retrospective, historical control group.

Van den Berghe et al. (2001) in a RCT attempted to determine whether normalization of blood glucose levels with intensive insulin therapy reduced mortality and morbidity among critically ill patients. Of the 1,548 adults patients admitted to a surgical ICU 62% were post open-heart surgical patients, who were receiving mechanical ventilation (Van den Berghe et al., 2001). Patients were randomly assigned to receive either intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dl) or conventional treatment (infusion of insulin only if the blood glucose level

exceeded 215 mg/dl, and then blood glucose level was maintained between 180 and 200 mg/dl; Van den Berghe et al., 2001).

Results of the study showed that the mortality rate in the intensive insulin therapy group was 4.6% compared to 8% in the conventional treatment, $p < .04$ (Van den Berghe et al., 2001). This observed reduction in mortality with intensive insulin therapy occurred exclusively in patients with an ICU LOS > 5 days (10.6% mortality in the intensive insulin group vs. 20.2% in the conventional group), $p = .005$ (Van den Berghe et al., 2001). Intensive insulin therapy when compared to conventional therapy reduced overall in-hospital mortality by 34%. Intensive insulin therapy also reduced bloodstream infections by 46% compared to the conventional therapy (Van den Berghe et al., 2001). Bloodstream infections in the intensive insulin group was 4.2% (32/765) versus 7.6% bloodstream infection rate in the conventional group (61/738), $p = .003$ (Van den Berghe et al., 2001). Acute renal failure requiring dialysis or hemofiltration was also reduced by intensive insulin therapy by 41% (Van den Berghe et al., 2001). The intensive insulin group renal failure rate was 4.8% (37/765) versus the conventional therapy group renal failure rate of 8.2% (64/738), $p = .007$; and the median number of blood transfusions was reduced by 50%, ($p = .001$). They also found that patients receiving intensive insulin therapy were less likely to require prolonged mechanical ventilation (Van den Berghe et al., 2001). Conclusions of the study included intensive insulin therapy to maintain blood glucose at or below 110 mg/dl reduced morbidity and mortality among critically ill patients in the surgical ICU (Van den Berghe et al., 2001).

Hruska et al. (2005) conducted an observational study aimed to evaluate the effects of a continuous insulin infusion protocol on postoperative infection and mortality.

The sample consisted of 761 patients who underwent CABG surgery from January 1997 through December 1998 (Hruska et al., 2005). The conventional group included patients who underwent CABG surgery in 1997 ($n = 436$) and were treated with subcutaneous insulin sliding scale to control postoperative hyperglycemia (Hruska et al., 2005). The insulin infusion group included patients who underwent CABG surgery in 1998 ($n = 325$), and were treated with an insulin drip protocol to maintain blood glucose levels between 120 mg/dl and 160 mg/dl in the immediate postoperative period (Hruska et al., 2005).

Researchers found that the overall wound infection rate for all patients was 3% (23/761; Hruska et al., 2005). In the conventional therapy group the infection rate was significantly higher in diabetic patients than non-diabetic patients, $p < .001$ (Hruska et al., 2005). Initiation of an insulin infusion protocol and the subsequent tight control of blood glucose levels in the immediate postoperative period reduce the incidence of wound infection in the diabetic population to that of the non-diabetic population (Hruska et al., 2005). There was no significant difference between the two groups in the mortality rate of patients with diabetes (conventional group 4% vs. tight control group 5%), $p = .575$ (Hruska et al., 2005). Limitations of the study included a single center, observational design with a historical cohort comparison group and the use of different insulin delivery methods between groups.

A large international RCT investigated the use of an algorithm to determine if intensive glucose control reduced mortality at 90 days (Finfer et al., 2009). The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study included 6,104 patients admitted to surgical and

medical ICUs of 42 hospitals (38 academic tertiary care hospitals and 4 community hospitals). Adults who were expected to require more than 3 days of intensive care were randomized to either conventional control therapy ($n = 3,050$) or intensive control therapy ($n = 3,054$) for blood glucose control (Finfer et al., 2009). The conventional glucose control therapy consisted of an insulin infusion to maintain blood glucose between 140-180 mg/dl, while the intensive insulin therapy group consisted of an insulin infusion to maintain blood glucose levels between 80-108 mg/dl (Finfer et al., 2009).

The study had an overall mortality rate of 13.58% (829/6,104), with 27.5% in the intensive group and 24.9% in the conventional control group (Finfer et al., 2009). The absolute difference in mortality was 2.6 percentage points 95% CI [0.4, 4.8], and death with intensive control (OR = 1.14 95% CI [1.02, 1.28]), $p = .02$ (Finfer et al., 2009). Severe hypoglycemia (blood glucose < 40 mg/dl) was reported in 6.8% of the intensive control group compared to 0.5% in the conventional control group, $p < .01$ (Finfer et al., 2009). The intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg/dl or less resulted in lower mortality than did a target of 81-108 mg/dl (Finfer et al., 2009). Representation of open-heart patients enrolled in the was not reported.

Leibowitz et al. (2010) investigated the impact of intensive insulin therapy on the clinical outcomes of hospitalized patients subsequent to cardiac surgery. Diabetic patients, or patients with a blood glucose level > 150 mg/dl post cardiac surgery were treated in the ICU with an intravenous insulin protocol to maintain blood glucose levels between 110 to 150 mg/dl (Leibowitz et al., 2010). The study utilized a historical control ($n = 207$) in which insulin treatment ranged from insulin infusion to subcutaneous

injections. The interventional group ($n = 203$) received intravenous insulin in all patients, with or without a diagnosis of diabetes. Results showed the intervention group had a lower mean blood glucose in the ICU and ward compared to the control group (151 ± 19 vs. 166 ± 27 mg/dl and 157 ± 32 vs. 184 ± 46 mg/dl), respectively, $p < .001$ (Leibowitz et al., 2010). There was no significant difference in the number of hypoglycemic events that occurred. The intensive insulin treatment decreased the risk for infection from 11% to 5% (56% reduction, $p = .018$), mainly by reducing the incidence of graft harvest site infection (6.9% vs. 2.5%, $p = .034$). The incidence of atrial fibrillation after CABG decreased from 30% to 18% (39% risk reduction) $p = .042$ (Leibowitz et al., 2010).

Studies reviewed in this section suggest that patients with and without diabetes with persistently elevated blood glucose levels (> 180 mg/dl) would benefit from intravenous insulin therapy to maintain levels below 180 mg/dl while in the ICU (Lazar et al., 2009). Evidence also suggested critically ill patients requiring vasopressor support, prolonged ventilation and extended ICU stays may benefit if blood glucose levels are kept below 150 mg/dl (Lazar et al., 2009). Debate remains to what the lower limits of glycemic control should be. Studies have shown mixed results on the benefits of tight glycemic control when blood glucose levels are allowed at normoglycemic levels (80-110 mg/dl) in the postoperative ICU period.

Glycemic control in the perioperative period.

Several studies support the use of intensive insulin therapy in the perioperative period (intraoperative and postoperative) for open-heart patients, in both diabetic and non-diabetic patients, suggesting that aggressive glycemic control decreased overall mortality, cardiac related mortality, and infection in patients (Carr et al., 2005; Furnary et

al., 2004; Lazar et al., 2004). Furnary et al. (2004) analyzed data from The Portland Diabetic Project, which included prior published studies of Zerr et al. (1997); Furnary et al. (1999), and Furnary et al. (2003). The Portland Diabetic Project was an ongoing study that involved 3,554 diabetic patients who underwent open-heart surgery from 1987 to 2001(Furnary et al., 2004). Patients were divided into three different cohorts based on the years of surgery and the blood glucose values targeted in the interventional group (Furnary et al., 2004). The first cohort was treated from 1987 to 1991 and consisted of patients who received subcutaneous insulin, given every 4 hours to keep serum blood glucose between 150 and 200 mg/dl (Furnary et al., 2004). From 1991 to 1998 the second cohort of patients received a continuous insulin infusion to maintain blood glucose levels between 150-200 mg/dl (Furnary et al., 2004). In 1998 the third cohort of patients received continuous insulin infusion to maintain blood glucose levels between 100-150 mg/dl (Furnary et al., 2004). The use of continuous insulin infusions significantly lowered mean blood glucose levels and glycemic control was significantly better in the second and third cohorts than in the historic first cohort that received subcutaneous insulin (Furnary et al., 2004). Furnary et al. (1999) found that the mean blood glucose levels on the day of operation through the third POD were significantly lower within the second cohort that received continuous insulin infusion than the first cohort that received subcutaneous insulin therapy (183 ± 12 vs. 213 ± 41 mg/dl, $p < .01$). Furnary et al. (2003) found mean blood glucose levels on the day of the operation through the third POD were significantly lower in the third cohort that received continuous insulin infusion than the first cohort that received subcutaneous insulin therapy (177 ± 30 vs. 213 ± 41), $p < .01$ (Furnary et al., 2003).

Use of perioperative continuous intravenous insulin infusion reduced major infectious morbidity such as DSWIs compared to subcutaneous insulin therapy (Furnary et al., 2004). Furnary et al. (1999) found that the patients in the second cohort that received a continuous insulin infusion had a significant reduction in the incidence of DSWI 0.8% (12/1,499) compared to those patients in first cohort that received subcutaneous insulin group 2.0% (19/968), $p = .01$ (Furnary et al., 1999). Observed mortality with continuous insulin infusion was also significantly lower than with subcutaneous insulin, reducing mortality by 50% (Furnary et al., 2004). Furnary et al. (2003) observed mortality in the third cohort that received a continuous insulin infusion 2.5% ($n = 65/2612$) was significantly lower than with the first cohort that received subcutaneous insulin therapy 5.3%, ($n = 50/942$, $p < .01$). From 2001 to 2005 the researchers developed a new method to assess glycemic control in which the average of all glucose values obtained on the day of surgery, the first and second PODs determined a “3-BG” score. An increase in 3-BG score was an independent predictor of perioperative mortality (Furnary et al., 2004). The mortality for patients with 3-BG level > 200 mg/dl was 6.0% compared to patients with a 3-BG level < 200 mg/dl the mortality was 1.6%, $p < .001$ (Furnary et al., 2004). Indicating the risk of post open-heart mortality is doubled for each 50 mg/dl increase in 3-BG value (Furnary et al., 2004). Limitations of the study included a retrospective design, with a historical cohort utilizing different treatment modalities for glycemic control.

Ouattara et al. (2005) conducted a prospective observational study of 1,146 open-heart patients (18% with diabetes) to evaluate the role hyperglycemia (blood glucose level > 200 mg/dl), in 200 patients with diabetes, on postoperative outcomes; and to

determine whether poor intraoperative glycemic control was associated with increased in-hospital morbidity. A standard insulin protocol based on subcutaneous insulin was given the morning of surgery and intravenous insulin therapy was initiated intraoperatively for blood glucose concentrations > 180 mg/dl and titrated according to a predefined protocol (Ouattara et al., 2005). Poor intraoperative glycemic control was defined as four consecutive blood glucose concentrations greater than 200 mg/dl despite aggressive insulin therapy (Ouattara et al., 2005). All patients received the same postoperative insulin therapy to maintain blood glucose concentrations below 140 mg/dl (Ouattara et al., 2005).

Results of the study revealed an overall in-hospital morbidity rate of 29% (Ouattara et al., 2005). During the intraoperative period, an insulin infusion was initiated in 71 patients (36%), among these 71 patients, 35 (50%) had poor intraoperative glycemic control despite aggressive insulin therapy (Ouattara et al., 2005).

Hyperglycemia was significantly more frequent in patients with severe postoperative morbidity (37% vs. 10%, $p < .01$) when compared to those without hyperglycemia (Ouattara et al., 2005). Morbidity in this study was defined as at least one of the following adverse outcomes: low cardiac output, hypotension needing intra-aortic balloon pump support, malignant arrhythmia, mechanical ventilation > 48 hours, neurologic deficit, acute renal failure, infectious outcome including sternal or leg infection, and/or septic shock (Ouattara et al., 2005). Multivariate analysis identified poor glycemic control as an independent risk factor of severe morbidity along with pulmonary hypertension, increased intraoperative blood transfusion, hypothermic CPB, preoperative plasma creatinine, and CPB time (Ouattara et al., 2005). In diabetic patients who

exhibited poor intraoperative glycemic control, the overall in-hospital mortality rate was significantly higher (11.4% vs. 2.4%, $p < 0.05$), and a prolonged ICU LOS was more frequently observed (46% vs. 19%, $p < .01$) compared to diabetic patients with achieved glycemic control (Ouattara et al., 2005). Limitations with the study included an observational design.

Lecomte et al. (2008) retrospectively analyzed two groups of consecutive patients undergoing cardiac surgery with CPB to determine the effect of intraoperative and postoperative glycemic control on renal function after cardiac surgery based on the risk, injury, failure, loss and end-stage kidney failure (RIFLE) criteria, and on the need for acute postoperative dialysis. The historic control group ($n = 305$) received insulin when blood glucose levels exceeded 150 mg/dl, and the tight glycemic group ($n = 745$) received insulin to a target blood glucose level 80-110 mg/dl in the intraoperative and postoperative period. Results showed that in patients without diabetes, tight glycemic control was associated with decreased incidence of renal impairment ($p = .01$) and failure ($p = .02$) scoring according to the RIFLE criteria, as well as a reduced incidence of acute postoperative dialysis (from 3.9% in control to 0.7% in tight group), $p < .01$ (Lecomte et al., 2008). Additionally, the 30-day mortality rate was lower in the tight glycemic group compared to the control group (1.2% vs. 3.6%), $p = .02$ (Lecomte et al., 2008).

Doenst et al. (2005) performed a multivariate logistic regression analysis on all diabetic ($n = 1,579$) and non-diabetic ($n = 4,701$) patients undergoing open-heart surgery in a two year period to determine the effect of hyperglycemia, during CPB, on perioperative morbidity and mortality (Doenst et al., 2005). Boluses of insulin were given during CPB when the glucose levels exceeded 270 mg/dl, when the serum potassium

level exceeded 6.0 mmol/L, or both (Doenst et al., 2005). Overall mortality was 1.8% (115/6,280). Comparison of those patients with peak serum glucose levels during CPB of less than and greater than 360 mg/dl in non-diabetic patients revealed those patients with severe hyperglycemia (> 360 mg/dl) had significantly more preoperative risk factors than patients with peak glucose levels of less than 360 mg/dl (Doenst et al., 2005). In contrast, the risk profiles of diabetic patients with peak glucose levels of greater than or less than 360 mg/dl were not different from non-diabetic patients (Doenst et al., 2005).

Overall preoperative risk factors were higher in the diabetic than in the non-diabetic patients (Doenst et al., 2005). These risk factors included hypertension, preoperative MI, triple vessel disease, peripheral vascular disease, and low ejection fraction (Doenst et al., 2005). Preoperative risk factors associated with severe hyperglycemia in the non-diabetic population included congestive heart failure, cardiogenic shock, renal failure, undergoing a second CABG, any subsequent open-heart surgery (Doenst et al., 2005). Although mortality was less than 2% when the peak glucose levels remained less than 360 mg/dl, the incidence tripled when the peak glucose level exceeded this value for both diabetic patients and non-diabetic patients (Doenst et al., 2005). In both patient populations, peak glucose level was an independent predictor of death, in patients with diabetes (OR = 1.20, 95% CI [1.08, 1.32], $p < .005$); and for non-diabetic patients (OR = 1.12, 95% CI [1.06, 1.19], $p < .01$). A high glucose level during CPB was also an independent predictor of all major adverse events in both patient groups (Doenst et al., 2005). All adverse events included stroke, infection, myocardial infarction, and cardiac syndromes that produced a low ejection fraction (Doenst et al., 2005).

Lazar et al. (2004) used a RCT to determine the relationship between tight glycemic control, with modified glucose-insulin-potassium (GIK) solution, in diabetic patients undergoing CABG surgery, and perioperative outcomes. One hundred forty one diabetic patients were randomized to tight glycemic control (blood glucose 125-200 mg/dl) with GIK in the intraoperative period, and 12 hours postoperatively or standard therapy (serum glucose < 250 mg/dl) using intermittent subcutaneous insulin in the intraoperative period and continuing for 12 hours postoperatively (Lazar et al., 2004). Results showed GIK treated patients achieved significantly better glycemic control, immediately before CPB than the standard therapy (169 ± 4.9 vs. 209 ± 5.3 mg/dl), $p < .01$ (Lazar et al., 2004). Twelve hours postoperative glycemic control was significantly better in the GIK group than the standard group (134 ± 3.7 vs. 266 ± 6.3 mg/dl), $p < .001$ (Lazar, et al., 2004). Patients in the GIK group also experienced a lower incidence of atrial fibrillation postoperatively (16.6% vs. 42%, $p = .0017$), a shorter postoperative LOS (6.5 ± 0.1 vs. 9.2 ± 0.3 days, $p = .003$), and less incidence of pneumonia and wound infections (0% vs. 13%, $p = .010$) than those in standard group (Lazar et al., 2004). In the 5 year follow up study, the interventional GIK group experienced less episodes of recurrent ischemia (5% vs. 19%, $p = .01$), and developed fewer recurrent wound infections (1% vs. 10%, $p = .03$) when compared to the standard therapy group (Lazar et al., 2004).

In a retrospective analysis of the implementation of a strict insulin protocol to achieve tight glucose control in open-heart surgical patients, Carr et al. (2005) aimed to determine if tight glycemic control would decreased the incidence of postoperative wound infection. Prior to the initiation of an insulin protocol, blood glucose levels of 200

mg/dl were acceptable. With the initiation of the protocol, diabetic patients were given an insulin infusion when blood glucose values reached 125 mg/dl; non-diabetic patients received insulin intravenous bolus for the same value (Carr et al., 2005). In the ICU patients were treated with a continuous insulin infusion protocol when blood glucose levels reached a trigger value. Over a period of two years the researcher adjusted the trigger value in ICU as follows: phase I-150 mg/dl, phase II-125 mg/dl, and phase III-110 mg/dl (Carr et al., 2005). Good blood glucose control was defined as a glucose level of < 130 mg/dl more than 50% of the measured time (Carr et al., 2005). The team found of 818 patients that underwent CABG surgery, 737 (90%) received insulin, even though only 43% of patients had a diagnosis of diabetes mellitus (Carr et al., 2005). They found that the factor that was most predictive of glucose being well controlled was the protocol with the 110 mg/dl trigger value for initiation of insulin infusion (Carr et al., 2005). The researchers also found the rate of mediastinitis decreased from 1.6% to 0% (Carr et al., 2005).

Chan et al. (2009) investigated, in a RCT the relationship between different target levels of glucose and the clinical outcomes of patients undergoing open-heart surgery with CPB. One hundred and nine patients were randomized to either the tight glycemic control ($n = 55$), which maintained blood glucose levels between 80-130 mg/dl or the conventional glycemic control ($n = 54$), which maintained blood glucose levels between 160-200 mg/dl (Chan et al., 2009). Blood glucose levels were maintained during the intraoperative period and 36 hours postoperatively by means of a continuous intravenous insulin infusion. All patients also received an intravenous glucose infusion of 8-12 g/hr during the intraoperative and first 24 hours postoperatively, after which enteral feedings

started (Chan et al., 2009). The researchers found that mean blood glucose levels in the tight glycemic group were significantly lower than the conventional glycemic group (126.69 vs. 168.21 mg/dl), $p < .0016$ (Chan et al., 2009). However, there was no significant difference between groups regarding clinical outcomes, including the duration of mechanical ventilation, ICU LOS, number of blood transfusions, occurrence of postoperative infections, hypoglycemic events, neurological dysfunction or 30 day mortality rates (Chan et al., 2009). The study may have been under powered due to a small sample size, especially for dichotomous variables as infections.

Pittas, Siegel and Lau (2004) conducted a meta-analysis of RCT studies that investigated insulin therapy for critically ill patients. They discovered that in the trials that administered insulin perioperatively for open-heart surgery, no benefit of insulin administration was noted (Pittas et al., 2004). They also discovered that most RCTs utilized GIK solutions as opposed to insulin in normal saline, and when all GIK studies were combined, there was a trend for GIK to reduce mortality, but it did not reach statistical significance (Pittas et al., 2004). In contrast, studies that administered insulin by a method other than GIK (i.e. insulin in normal saline), there was a statistically significant relative risk mortality reduction of 27% with insulin therapy (Pittas et al., 2004).

Lazar et al. (2011) conducted a RCT to determine whether more aggressive glycemic control would result in more optimal clinical outcomes and less morbidity than can be achieved with moderate control in patients with diabetes mellitus undergoing CABG surgery. Eighty-two diabetic patients were randomized to aggressive glycemic control (90-120 mg/dl) or moderate glycemic control (120-180 mg/dl) using continuous

insulin infusion starting at induction of anesthesia and continuing for 18 hours after surgery. Results revealed no difference in the incidence of major adverse events between the groups (17/42 moderate vs. 15/40 aggressive, $p = .91$). Major adverse events included 30-day mortality, MI, neurologic events, DSWIs, and atrial fibrillation. Patients with aggressive control had lower mean glucose at the end of 18 hours of insulin infusion compared to moderate control (103 ± 17 vs. 135 ± 12 mg/dl), respectively, $p < .001$ (Lazar et al., 2011). Those patients in the aggressive control group had a higher incidence of hypoglycemic events (blood glucose < 80 mg/dl) than the moderate control group (30/42 vs. 4/40), $p < .001$ (Lazar et al., 2011). These findings are similar to the findings of Bhamidipati et al. (2011) that found moderate glycemic control was superior to tight glycemic control for patients undergoing isolated CABG surgery.

Bhamidipati et al. (2011) stratified 8,662 patients who underwent isolated CABG surgery into 3 arbitrary postoperative glycemic groups, based on 3-day average postoperative serum glucose levels. The tight group was composed of patients with average serum glucose not more than 126 mg/dl, the moderate group was composed of patients with average serum glucose levels of 126.1 to 179.9 mg/dl, and the liberal group was composed of patients with a mean serum glucose of at least 180 mg/dl (Bhamidipati et al., 2011). Statistical analysis revealed more patients in the tight group had preoperative renal failure ($p = .001$), and underwent more emergent operations ($p = .007$). However, use of the STS prediction model revealed mortality risk was lower in the tight groups, $p < .001$ (Bhamidipati et al., 2011). The STS model considers the type of surgery, preoperative co-morbidities, and intraoperative risks to determine overall risk of poor outcomes. Results showed the moderate glycemic group had the lowest mortality (tight

2.9%, 4/134; moderate 2.0%, 56/2785; liberal 3.4%, 59/1739), $p = .02$. In addition, the moderate group had the lowest incidence of major complications (tight 19.4%, 26/134; moderate 11.1%, 308/2785; liberal 14.2%, 247/1739), $p < .001$ (Bhamidipati et al., 2011). Limitations of this study include a retrospective design, and a concern that the tight glycemic arm was under powered, having only 134 participants compared to the moderate glycemic group of 2,785 and the liberal group having 1,739 participants.

Emam et al. (2010) conducted a prospective study of 120 subjects with a diagnosis of diabetes, undergoing open-heart surgery randomized to either a control group, simple sliding scale ($n = 40$) to keep blood glucose < 200 mg/dl or the Braithwaite protocol ($n = 80$) to maintain tight control of 100 to 150 mg/dl. Results of the study showed that subjects in the interventional Braithwaite group had blood glucose levels less than 200 mg/dl at the end of the 48 hour postoperative, compared to the control group, which did not obtain a blood glucose level of less than 200 mg/dl, 48 hours postoperatively, in all subjects in the control group ($p < .01$). There was a significant reduction in hospital stay in the tight group compared to the control group (mean in days 9.1 ± 2.3 vs. 12.3 ± 7.6 days), $p < .001$. There was also no wound infection in the tight control group compared to 12% (5/40) in the control group (Emam et al., 2010).

Glycemic control in the intraoperative period.

Studies that have investigated the use of intensive insulin therapy exclusively in the intraoperative period are very limited. Two studies investigated the effects of glycemic control in the intraoperative period on patient outcomes (Azarfarin, Sheikhzadeh, Mirinazhad, Bilehjani, and Alizadehasl, 2011; Gandhi et al., 2007). Gandhi et al. (2007) compared outcomes of intensive insulin therapy during cardiac surgery with

those of conventional intraoperative glucose management. In a RCT, with blinded assessment, 400 patients undergoing cardiac surgery with CPB were randomized to receive intensive insulin therapy ($n = 199$) or conventional treatment ($n = 201$; Gandhi et al., 2007). Patients in the intensive insulin therapy group received a continuous intravenous infusion of regular insulin implemented when patient blood glucose levels exceeded 100 mg/dl; blood glucose levels were maintained between 80 and 100 mg/dl during the intraoperative period (Gandhi et al., 2007). The conventional treatment groups received insulin during the surgery when their blood glucose levels exceeded 200 mg/dl via intravenous bolus injections of 4 units of regular insulin every hour until levels were below 200 mg/dl (Gandhi et al., 2007). If the blood glucose level exceeded 250 mg/dl in the conventional group, patients were placed on a continuous insulin infusion that was continued until the blood glucose levels were less than 150 mg/dl (Gandhi et al., 2007).

The mean glucose concentrations were significantly lower in the intensive treatment group post- CPB compared to the conventional group (123 ± 24 vs. 148 ± 35 mg/dl), $p < .01$ (Gandhi et al., 2007). Blood glucose concentrations were significantly lower at the end of surgery in the intensive treatment group compared to the conventional group (114 ± 29 vs. 157 ± 42 mg/dl), $p < .01$ (Gandhi et al., 2007). There was no difference between the groups in the number of hypoglycemic events, ICU LOS, or hospital LOS (Gandhi et al., 2007). More deaths (4 vs. 0, $p = .061$) and strokes (8 vs. 1, $p = .020$) occurred in the intensive treatment group as compared to the conventional group (Gandhi et al., 2007). The authors concluded that the intensive insulin therapy during cardiac surgery failed to reduce perioperative death or morbidity (sternal wound

infections, prolonged ventilation, cardiac arrhythmias, stroke, acute renal failure), and may increase the risk for morbidity (Gandhi et al., 2007).

Azarfarin et al. (2011) investigated, in a RCT, the effect of blood glucose control with insulin in preventing hyperglycemia during and after CABG surgery in non-diabetic patients. One hundred seventeen patients were randomized to a control group ($n = 58$), which received bolus insulin coverage only if blood glucose levels exceeded 200 mg/dl, or experimental group ($n = 59$), which received an insulin infusion to maintain blood glucose levels between 110 to 126 mg/dl (Azarfarin et al., 2011). Insulin therapy was limited to intraoperative period, but blood glucose levels during surgery and up to 48 hours after surgery, and early postoperative complications were compared between the study and control groups (Azarfarin et al., 2011). Results of the study, showed peak intraoperative blood glucose levels in the experimental group were significantly lower than in the control group (126.4 ± 17.9 vs. 137.3 ± 17.6 mg/dl, $p = .024$). The frequency of severe hyperglycemic (blood glucose > 180 mg/dl) events during the intraoperative period was greater in the control group compared to the experimental group, (32.7%) 19/58 versus (10.1%) 6/59, respectively, $p = .002$ (Azarfarin et al., 2011). There was no difference between the groups in the postoperative peak blood glucose, and neither group experienced hypoglycemic events (Azarfarin et al., 2011). Early postoperative complications composite was greater in the control group than the experimental group, (32.7%) 19/58 versus (16.9%) 10/59, respectively, $p = .047$. The complication composite was composed of major complications in cardiac, pulmonary, neuropsychological, renal, infectious, and re-exploration.

Chaney, Nikolov, Blakeman, and Bakhos (1999) attempted to develop an insulin administration protocol to maintain normoglycemia in patients undergoing cardiac surgery and to study the effects of intraoperative blood glucose management on serum levels of creatine phosphokinase isoenzyme BB (CK-BB) and S-100 protein. Twenty patients without diabetes mellitus diagnosis were randomized to receive either tight glycemic control intraoperatively ($n = 10$), or to receive no control of blood glucose intraoperatively ($n = 10$).

Results showed that despite the tight glycemic group receiving insulin both groups experienced similar significant increases in blood glucose levels during hypothermic CPB (Chaney et al., 1999). The tight glycemic group had significantly lower blood glucose levels at sternal closure and ICU admission time (125.4 ± 53.1 and 84.7 ± 41 mg/dl), respectively, compared to the group receiving no insulin treatment (237.6 ± 61.2 , and 201.4 ± 67.5 mg/dl), respectively, $p < .001$ (Chaney et al., 1999). There was no difference in peak intraoperative blood glucose level between the tight glycemic group from the control group (301.6 ± 104 vs. 312.6 ± 100.7 mg/dl). Forty percent of patients in the tight control group required treatment in the ICU for hypoglycemia (blood glucose level < 60 mg/dl) compared to zero patients in the no control group (Chaney et al., 1999).

Hypoglycemia

Intensive insulin therapy has become a major therapeutic target in cardiac surgical patients. It has, however, been associated with an increased risk of hypoglycemia. A few studies have investigated hypoglycemia related to cardiac surgery (Chaney et al., 1999; Stamou et al., 2011; Wiener, Wiener, & Larson, 2008). Stamou et al. (2011) sought to

identify the factors predisposing to hypoglycemia with intensive insulin therapy and investigate its effect on early clinical outcomes after cardiac surgery. A concurrent cohort study of 2,538 consecutive patients undergoing cardiac surgery over a 5 year period was carried out (Stamou et al., 2011). Multivariate logistic regression analysis and propensity score matching were used to identify the risk factors for developing hypoglycemia (blood glucose < 60 mg/dl) after cardiac surgery, and to compare major morbidity, operative mortality, and actuarial survival between patients in whom hypoglycemia developed ($n = 77$) and those in whom it did not ($n = 2461$). To improve balance for analysis, a propensity score analysis was used, which included 61 patients in whom hypoglycemia developed and 305 patients in whom it did not (1 to 5 matching; Stamou et al., 2011).

Results showed risk factors for hypoglycemia included female gender (OR = 2.3, 95%CI = [1.4, 3.7], $p < .001$), diabetes (OR = 2.8, 95% CI = [1.7, 4.5], $p < .001$), hemodialysis (OR=3.0, 95% CI [1.3-6.8], $p = .009$), intraoperative blood transfusion (OR = 2.0, 95% CI [1.2, 3.4], $p = .010$), and an earlier date of surgery (historic cohort) (OR=2.1, 95% CI [1.2, 3.7], $p = .007$). Hypoglycemia, compared to normoglycemia, increased the risk for operative mortality in univariate (10% vs. 2%; $p < .001$), but not in propensity score-adjusted analysis (OR = 2.5, 95% CI [0.9, 6.7], $p = .11$). The propensity score-adjusted analysis demonstrated a significant increase in hemorrhage-related re-exploration ($p = .048$), pneumonia ($p < .001$), reintubation and prolonged ventilation ($p < .001$), and ICU and hospital LOS ($p < .001$) for hypoglycemic compared with normoglycemic patients (Stamou et al., 2011).

Zimmerman et al. (2004) examined the performance of a postoperative insulin infusion protocol to maintain tight glycemic control, defined as a blood glucose level of

80–150 mg/dl, in cardiothoracic surgical patients, with and without diabetes mellitus. In this retrospective cohort study, two periods of measurement were performed: a 6-month baseline period prior to the initiation of the insulin infusion protocol ($n = 174$) followed by a 6-month intervention period in which the tight glycemic protocol was utilized in the postoperative period ($n = 168$). The researchers found that blood glucose measurements occurred with greater frequency in the tight control group (baseline group 47%, tight control group 67%), $p = .01$ (Zimmerman et al., 2004). They also found that the median time to obtain a blood glucose level < 150 mg/dl was 2.1 hours in the tight control group and 9.4 hours in the baseline group, $p < .001$ (Zimmerman et al., 2004). The occurrence rate of hypoglycemia (blood glucose < 65 mg/dl) was 9.8% in the baseline group versus 16.7% in the tight control group; while more episodes of hypoglycemia occurred in the tight control group it was not significant (Zimmerman et al., 2004). The study showed that an insulin infusion protocol designed to achieve a goal blood glucose range of 80–150 mg/dl efficiently and significantly improved tight glycemic control in postoperative cardiothoracic surgery patients without significantly increasing the incidence of hypoglycemia (Zimmerman et al., 2004).

Summary of Research for Glycemic Control

The understanding of the importance of glycemic control in the preoperative, intraoperative and postoperative period and its impact on surgical site infections is imperative to improve the quality of care for patients undergoing open-heart surgery. There is a consensus that surgical site infections have a significant impact on postoperative outcomes in the open-heart surgical patients. Mortality, from surgical site infection, is increased 3-5 times compared to individuals without infection, and hospital

length of stay is increased 2-4 times that of non-infected patients. There are ample observational studies that suggest surgical site infections increase mortality and morbidity of patients, as well as increase resource utilization of hospitals that must treat these infections. Multiple observational studies, and a few interventional studies have suggested that diabetes and hyperglycemia, in the perioperative period, are associated with more infectious complications, longer hospital stays, higher morbidity, mortality and increased resource utilization after open-heart surgery. The few randomized controlled trials have been more controversial on the benefits of tight glycemic control. Some studies showing benefit, some showing no difference in tight glycemic control compared to moderate control and some studies showing worse outcomes with tight glycemic control.

Studies that investigated biomarkers CRP and PCT revealed that patients who experienced postoperative complications, including infection, have significantly higher values of both CRP and PCT in the preoperative, and immediate postoperative period. The studies reviewed reported a wide range of discriminating CRP values in the identification of an infectious process and/or postoperative complications. The CRP values suggestive of infection ranged from 96 to 170 mg/L in the immediate postoperative period, and/or a baseline preoperative high sensitive CRP value of > 3 -5 mg/L (> 0.3 -0.5 mg/dl). Studies also showed a wide range of discriminating PCT values in the identification of infection and/or postoperative complications. Procalcitonin values ranged from 0.5-5 ng/dl in the immediate postoperative period. However, PCT values have been identified in multiple studies to be superior to CRP in detection of infection and sepsis in the postoperative period.

Studies have investigated interventions to reduce infection in open-heart surgery including controlling hyperglycemia with continuous insulin infusions. Few studies supporting the use of intensive insulin therapy in open-heart patients to improve patient outcomes, as infection, are randomized controlled trials. Evidence is primarily derived from observational studies that cannot determine a causal link, and these studies have had diverse results. Of the studies that utilized randomized controlled trials, most are in the perioperative or postoperative period, leaving glycemic control during the intraoperative period essentially unstudied. The blood glucose levels maintained in the intensive insulin groups varied amongst the studies, with some studies using a value of 80-110 mg/dl and other using 120 -150 mg/dl as their definition of tight control. Of the studies using the lower glucose target values of 80-130 mg/dl, only the study performed in the postoperative period showed improved patient outcomes of reduced mortality and reduced infection. The intraoperative and perioperative studies with the tight glycemic control (80-130 mg/dl) did not produce improved patient outcomes, and one had potentially worse patient outcomes. Of interest, the study conducted in the perioperative period that showed improved patient outcomes maintained higher blood glucose levels (125-200 mg/dl) in the intensive insulin group. Inferences from these studies would suggest that tighter blood glucose control (80-130 mg/dl) may be most effective in the postoperative period, and more moderate blood glucose levels should be maintained in the intraoperative period.

Current Gaps in Research for Glycemic Control in Open-heart Surgery

Lack of randomized controlled trials, which address the causal nature of the relationship between hyperglycemia and surgical site infections in open-heart surgery

patients, is an identified gap in knowledge, which must be addressed. If hyperglycemia is the cause of surgical site infections then it is reasonable to infer that blood glucose levels maintained more closely to normal, throughout the perioperative period, would improve infection rates. However, if hyperglycemia is only a reflection of the severity of the stress response, maintaining euglycemia may not be of benefit, and could be potentially detrimental.

The use and/or benefits of CRP and/or PCT testing in the early identification of infection for open-heart patients have yet to be determine. Specific discriminative values that identify infection in the early postoperative period are needed, and until more RCT studies can be completed decisions for early intervention in the treatment of postoperative infection should be based on the entire clinical presentation of the patient and not strictly on pre-set biomarker values. It is still undetermined if the use of both PCT and CRP biomarkers should be utilized in the identification of postoperative infection, as opposed to each individually; or the trending of biomarkers that may give practitioners better evidence in infectious identification and decision making regarding treatment.

The optimal perioperative glycemic range that improves patient outcomes, such as reduced infection rates, with minimal risk of hypoglycemia has yet to be identified. Closure of this gap is imperative before standardization and/or recommendations of intraoperative glycemic protocols are instituted for open-heart surgery. Future studies also need to investigate one element of glycemic control, either the route of insulin administration, intravenous or subcutaneous, with the same glycemic end target or studies that investigate the level of glycemic control, tight or conventional, utilizing the same method of insulin delivery, either subcutaneous or intravenous. Until more randomized

controlled trials can be conducted, it remains unclear if perioperative tighter blood glucose control will improve patient outcomes postoperatively.

The next chapter discusses the study sample, design, research questions, and hypothesis for the effect of intraoperative tight glycemic control on surgical site infection rates in patients undergoing open-heart surgery.

Chapter Three

Methods

Introduction

This chapter describes the methods that were used to investigate the effects of various insulin protocols on intraoperative glycemic control in the open-heart surgical patient, and on postoperative surgical site wound infection. The study design, sample characteristics, interventional protocols, measures, data collection and instrumentation are described. This is followed by a description of the data analysis plan.

The primary study aims were to investigate the effects of three different glycemic treatment conditions (tight, conventional, and standard) in the intraoperative period on postoperative surgical site infection (SSI) rates, and postoperative biomarkers, procalcitonin (PCT), and C-reactive protein (CRP), in patients undergoing open-heart surgery. Secondary aims were to examine the effects of three glycemic treatment conditions on perioperative blood glucose, intraoperative glycemic stability, and intensive care unit (ICU) length of stay (LOS) in patients undergoing open-heart surgery.

Research Design

A multilevel, single factor, within-subjects design was utilized. Patients were nested within anesthesia provider teams. The design was counterbalanced by means of a Latin square, where each of three anesthesia provider teams dispensed each of three glycemic treatment conditions once. This arrangement spread any practice effects over

the three treatment conditions equally. The study used a three-group randomized clinical trial design to determine if there was a difference on 1) postoperative surgical site infection rates; 2) infection biomarker levels procalcitonin and C-reactive protein; 3) blood glucose levels; 4) glycemic stability; and 5) intensive care unit length of stay in open-heart surgical patients (Figure 1).

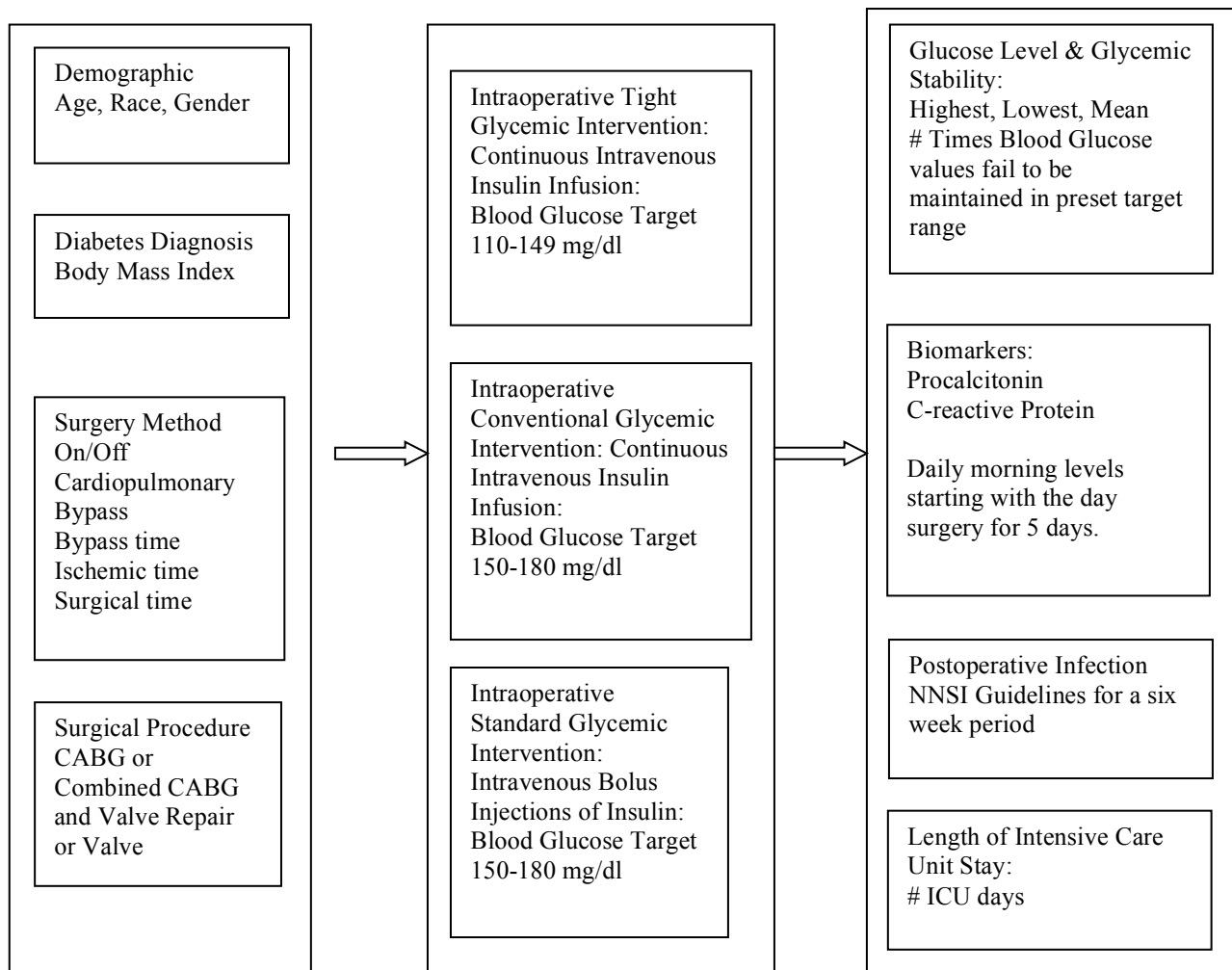


Figure 1. Research Design

Setting

The study was conducted in the operating room suites at a major Veterans Affairs Medical Center in Tampa Florida. A convenience sample for this study was drawn from the adult population who were scheduled to undergo coronary artery bypass grafting (CABG) surgery, CABG combined with valve repair, or valve repair/replacement surgery from June 2010 through June 2011.

Sample

A convenience sample of 112 participants was recruited. Inclusion criteria included: 1) over the age of 21; 2) on cardiopulmonary bypass (CPB) or off CPB; 3) elective or urgent CABG, with or without combined valve surgery; and 4) valve surgery. Participants were excluded from the study if they were: 1) chronically immunosuppressed, such as steroid dependent, diagnosed with any autoimmune disease, or human immunodeficiency virus; 2) suffered from end-stage organ disease such as end stage renal or liver disease; 3) currently had active infections such as increased white blood cell count, fevers, or productive coughs; 4) underwent emergent or salvage CABG surgery where risk for infection is higher; 5) had an implanted insulin pump; or 6) were in another interventional clinical trial. After exclusions ($n = 35$), and patient refusals to participate ($n = 40$), a total of 37 subjects were enrolled in the study over a period over 12 months, and randomized to the three glycemic control conditions.

Interventions

The study used three different glycemic control interventions, during the intraoperative period, in an attempt to determine if maintaining blood glucose levels

closer to normal values via a continuous infusion would reduce postoperative wound infections.

Intervention group I: tight glycemic control.

Patients randomized to the tight glycemic group received a continuous intravenous infusion of regular insulin in the intraoperative period titrated per a modified Portland Protocol from Vanderbilt University Medical Center, Tennessee. The initial bolus of insulin and insulin infusion therapy was initiated prior to induction of anesthesia if the morning blood glucose is greater than 149 mg/dl or any time intraoperatively that the blood glucose elevated above 149 mg/dl (Table 1).

Table 1. Initial Insulin Infusion Tight Glycemic Intervention Group

Blood Glucose (mg/dl)	Bolus dose of Insulin (units)	Insulin Infusion Rate (unit/hour)
150-180	5	5
181-200	10	10
201-250	15	15
251-350	20	20

The subsequent titration of insulin infusion therapy for the tight glycemic group maintained blood glucose levels between 110-149 mg/dl throughout the intraoperative period (Table 2). The intraoperative maintenance of blood glucose was monitored, recorded and titrated to blood glucose levels sampled every 30 minutes by arterial line drop sample, and started 30 minutes after entry into the surgical suite. Upon transfer to the ICU the intraoperative protocol ended and all subjects received the standardized

glycemic control for the ICU. An insulin infusion of 100 units of regular insulin in 100 ml of normal saline was used for the study.

Table 2. *Titration of Insulin Infusion Protocol Tight Glycemic Group*

Responders Blood Glucose level	Defined as a decrease in blood glucose level in response to initial insulin treatment
> 149 mg/dl	Maintain insulin infusion at current rate
110-149 mg/dl	Adjust insulin infusion to 10 units /hour or half of initial infusion rate (whichever is lower)
Non Responders	Defined as no change or an increase in blood glucose level in response to initial insulin treatment
< 200 mg/dl	Increase infusion rate by an additional 10 units /hour
> 200 mg/dl	Double infusion rate up to a maximum of 50 units/ hour and double the initial bolus up to a maximum of 25 units.
Hypoglycemia Treatment	
If blood glucose level < 80mg/dl	10-15 ml 50% Dextrose (D50) Recheck blood glucose in 15 minutes Repeat with 20 ml 50% Dextrose if repeat blood glucose less than 80 mg/dl

Intervention group II: conventional glycemic control.

Patients randomized to the conventional glycemic group received a continuous intravenous infusion of regular insulin in the intraoperative period titrated per a modified Portland Protocol from Vanderbilt University Medical Center, Tennessee. The initial insulin bolus and infusion was initiated prior to induction of anesthesia if the morning blood glucose was greater than 180 mg/dl or any time intraoperatively that the blood glucose elevated above 180 mg/dl (Table 3).

Table 3. *Initial Insulin Infusion for Conventional Glycemic Group*

Blood Glucose (mg/dl)	Bolus dose of Insulin (units)	Insulin Infusion Rate (unit/hour)
180-200	5	5
201-250	10	10
251-300	15	15
> 300	20	20

The insulin infusion was titrated throughout the intraoperative period to maintain blood glucose levels between 150-180 mg/dl (Table 4). The intraoperative blood glucose was monitored, recorded and titrated to blood glucose levels sampled every 30 minutes by arterial line drop sample method. Intraoperative blood glucose monitoring started 30 minutes after entry into the surgical suite. Upon transfer to the ICU the intraoperative protocol ended and all subjects received the standardized glycemic control for the ICU. The insulin infusion consisted of 100 units of regular insulin in 100 ml of normal saline.

Intervention group III: standard glycemic control, control group.

Patients randomized to the standard glycemic group received intravenous injections of regular insulin in the intraoperative period titrated per the usual care protocol utilized at the study site (Table 5). The initial bolus of insulin was initiated prior to induction of anesthesia if the morning blood glucose was greater than 180 mg/dl or any time intraoperatively that the blood glucose elevated above 180 mg/dl (Table 5).

Measures

Data collection at baseline included the following measures:

Demographics.

Demographic variables including age, sex, height, weight, race and ethnicity was measured and recorded at baseline during the preoperative interview (Appendix A).

Table 4. *Titration of Insulin Infusion for Conventional Glycemic Group*

Responders Blood Glucose	Defined as a decrease in blood glucose level in response to initial insulin treatment
>180 mg/dl	Maintain insulin infusion at current rate
150-180 mg/dl	Adjust insulin drip to 10 units /hour or half of initial infusion rate (whichever is lower)
Non Responders	Defined as no change or an increase in blood glucose level in response to initial insulin treatment
< 200 mg/dl	Increase infusion rate by an additional 10 units /hour
> 200 mg/dl	Double infusion rate up to a maximum of 50 units/ hour and double the initial bolus up to a maximum of 25 units.
Hypoglycemia Treatment	
If blood glucose level < 80 mg/dl	10-15 ml 50% Dextrose (D50) Recheck blood glucose in 15 minutes Repeat with 20 ml 50% D50, if repeat blood glucose less than 80 mg/dl

Table 5. *Standard Glycemic Treatment Group Intravenous Insulin Bolus*

Blood Glucose Level mg/dl	Bolus of insulin given U
180-200	5
201-250	10
251-300	15
> 300	20

Medical history.

The following variables were collected by chart review at baseline by the principle investigator or co-investigator obtaining the patient informed consent. Historical variables included type of preoperative diabetic control (insulin, oral, diet or none), smoking history (never, past, current), historical co-morbidities (hypertension, congestive heart failure, history of myocardial infarction, history of stroke, renal insufficiency, and peripheral vascular disease), and American Society of Anesthesiologists (ASA) classification (Appendix A).

Surgical clinical variables.

Surgical variables measured included the surgeon of record, type of surgery, number and type of harvest site grafts, Society of Thoracic Surgeons operative status (elective, urgent), first or subsequent surgery, surgery time, bypass time, aortic cross clamp time (ischemic time), and ICU length of stay. In addition to standard cardiac laboratory studies a preoperative glycosylated hemoglobin (HbA1c) was collected during the preoperative visit. The HbA1c was the baseline data for measure of preoperative glycemic control. Measures collected the day of surgery included fasting blood glucose and glucose every 30 minutes after entry into the surgical suite. (Appendix A)

Primary outcome variables.

The presence or absence of deep, or/and superficial sternal wound infection and deep, superficial harvest site infection within in six weeks postoperatively was a primary outcome variable. Infection assessment was performed during the intensive care phase, at hospital discharge, two-week post hospital discharge and six-week post hospital discharge by independent blinded researchers that were part of the cardiothoracic team.

Procalcitonin and CRP concentrations were collected in addition to clinical signs for indications of infection. These biomarker concentrations were collected the morning of surgery, after successful separation from CPB, and every morning for five days postoperatively. Values were drawn by anesthesia providers and ICU registered nurses or laboratory personnel with the standard morning blood work, and trended over the six-day period.

Secondary outcome variables.

Blood glucose values were obtained every 30 minutes in the intraoperative period, and were drawn and recorded by the certified registered nurse anesthetist (CRNA) performing the anesthetic. Blood glucose levels were also monitored every 30 minutes for the first six hours in the postoperative period. Blood glucose values obtained in the postoperative period were drawn and recorded by the primary ICU registered nurse caring for the patient.

Intraoperative glycemic stability was operationalized as how often blood glucose levels were maintained as normal or maintained in the preset target ranges for each group. If intraoperative blood glucose levels fell outside of normal or, the preset target ranges, for each protocol, 3 consecutive blood glucoses (1.5 hours) despite insulin therapy a marker of inadequate glycemic control was recorded. Length of ICU stay was measured by the total number of days each patient stayed in the ICU. (Appendix A).

Procedures

Protection of human subjects.

Approval for the study was obtained through the research and development center at the study site and the University of South Florida Institutional Review Board.

Screening and recruitment.

A member of the anesthesia team during the preoperative interview screened patients for inclusion and exclusion criteria. Recruitment of patients occurred Monday through Friday for any patient scheduled to undergo CABG, combined CABG/valve, or valve surgery from June 1, 2010 through May 31, 2011. One hundred and twelve potential subjects were screened for the study. The refusal rate was 35.7% (40/112) and 31% (35/112) patients were ineligible to participate due to exclusion criteria leaving a total of 37 subjects that were enrolled in the study.

Informed consent and enrollment.

The principal investigator or co-investigators explained the study to all open-heart surgery patients during the preoperative anesthesia visit, which was usually within the week prior to the scheduled surgery. Patients were also given the opportunity to read the informed consent and have all questions answered prior to any decisions to participate in the study. Informed consent included the potential risks associated with participating with the study with the most likely risk of transient hypoglycemia. In addition, patients were informed of any additional blood work that would be drawn, which included PCT and CRP blood work upon separation from CPB and every morning for 5 postoperative days. Informed consent was signed the morning of surgery after the anesthesia care team reviewed all laboratory results and before any sedation occurred.

Randomization.

The anesthesia provider teams were randomly assigned to the treatment condition in the Latin square (Table 6). The random assignment dictated the rotation of anesthesia care teams. The team was scheduled in advanced on a monthly basis in accordance with

the Latin square design. This design provided a permuted block in which each team was scheduled every 3 days, this allowed for each team to receive equal numbers of patients.

Table 6. *Latin Square Design*

	Months 1-4	Months 5-8	Months 9-12
Anesthesia Team 1	Standard Current Glycemic Control Treatment for blood glucose 150-180 mg/dl via IV bolus insulin	Tight Glycemic Control Blood Glucose 110-149 mg/dl via insulin infusion	Conventional Glycemic Control Blood glucose 150-180 mg/dl via insulin infusion
Anesthesia Team 2	Tight Glycemic Control Blood Glucose 110-149 mg/dl via insulin infusion	Conventional Glycemic Control Blood glucose 150-180 mg/dl via insulin infusion	Standard Current Glycemic Control Treatment for blood glucose 150-180 mg/dl via IV bolus insulin
Anesthesia Team 3	Conventional Glycemic Control Blood glucose 150-180 mg/dl via insulin infusion	Standard Current Glycemic Control Treatment for blood glucose 150-180 mg/dl via IV bolus insulin	Tight Glycemic Control Blood Glucose 110-149 mg/dl via insulin infusion

Each anesthesia provider team included a minimum of one anesthesiologist and two CRNAs, and each team dispensed one of three treatment conditions for a 4-month period before rotating to the next glycemic treatment condition per the Latin square. This provider structure ensured the Latin square design was followed, regardless of individual practitioner circumstances, such as being on-call. The intervention was implemented in the intraoperative period only. Postoperative glycemic control was the same for all groups. The postoperative glycemic control was the standard protocol utilized in the surgical intensive care unit at the study site. This intensive care protocol is a modification

of the Yale protocol published by Goldberg et al. (2004) and is considered a strict glycemic control protocol maintaining blood glucoses less than 150 mg/dl.

Intraoperative protocol.

The day of surgery, patients were met and evaluated in the preoperative holding area where standard lines were placed, a baseline morning laboratory studies (blood glucose, PCT, CRP) were drawn and standard preoperative medications given.

Demographical data, historical data and baseline blood work was collected by one of the cardiac anesthesia providers. The patients were then taken to the operating suite where standard ASA monitors were placed and induction of anesthesia ensued. If glucose levels met criteria for treatment, for each protocol, interventions were initiated upon entry into the surgical suite. The majority of surgical parameters remained constant through the entire study period including infection prophylaxis, antibiotic coverage, Chloraprep skin preparation, and normal preoperative electrolytes values. One surgical parameter for standard cardiac protocol did change during the study period. In January 2011 all cardiac patients were given Chloraseptic mouth rinse prior to entry into the operating room suite, in an attempt to reduce the risk of postoperative infection. The Latin Square design controlled for this factor. Specific intraoperative procedures other than the study protocol, including monitoring, laboratory testing and treatment, and anesthetic technique were determined by the standard protocols and the discretion of the anesthesia care team. This protocol ended with the transport of the patient out of the operating room en route to the ICU.

Postoperative protocol.

Upon delivery of the patients to the ICU, all patients received the same glycemic control, which was the standard ICU glycemic protocol, an intravenous insulin infusion protocol based on the Harvard glycemic protocol. Data collection on blood glucose levels was continued every 30 minutes, from entry to the unit, for six hours into the postoperative period. The intensive care team members were blinded to the intraoperative interventions.

Data collection.

The day of surgery the anesthesia care team collected routine blood work and study blood work; results were documented in the patient electronic chart and the study work sheet. Blood glucose was measured every 30 minutes by means of the intraoperative I-Stat monitor with arterial line blood samples. Upon transfer to the ICU data collection of blood glucose levels occurred every 30 minutes utilizing a designated glucometer monitor; results were documented in the patient's electronic chart, and ICU study worksheet by ICU nurses. The purpose of six hours postoperative blood glucose data collection was to evaluate evidence of hypoglycemia that may occur with reversal of cardiopulmonary induced insulin resistance. Six hours after admission into the ICU data collection for glycemic control ended (Appendix B). Procalcitonin, and CRP levels were collected every morning for five days starting with the day of surgery.

Data on infection status were collected during the ICU phase, at hospital discharge; two weeks post hospital discharge, and at a 30-day follow-up appointment. An advanced registered nurse practitioner, or member of the cardiothoracic team performed wound Infection assessment; all members were blinded to the intraoperative intervention

that patients received. Data collection on the outcome variable intensive care length of stay was determined from the documented day of discharge from the intensive care unit.

Statistical analysis.

Statistical analyses included descriptive statistics on all demographic, and surgical variables. Statistical analysis also included the development of a logistic regression model to determine the effect of intraoperative glycemic control method (tight, conventional or standard) on the dichotomous outcome of postoperative wound infection controlling for demographics and covariates (See Figure 1). A series of repeated measures analyses of variances was performed on each continuous outcome variable, PCT, CRP levels, and intraoperative blood glucose levels. Analysis of variance was performed on intensive care length of stay after adjusting for other known preoperative risk factors. Outcome variables were postoperative infection rate, postoperative PCT levels, postoperative CRP levels, intraoperative glycemic stability, intraoperative blood glucose levels (high, low and mean) and length of intensive care stay. All data were analyzed run using SPSS software, version 16 (SPSS, Inc, Chicago, Ill).

Chapter Four

Results

Introduction

Chapter four includes a description of participant's characteristics and demographics, and the data analyzed to address the aims and hypotheses described in chapter three. In addition findings from exploratory analyses will be presented.

Demographics and Clinical Characteristics of Participants

A total of 112 Veterans, scheduled for open-heart surgery were screened for recruitment; thirty-seven Veterans agreed to participate and 35 Veterans completed the study. One participant was lost to follow up and one participant died prior to the final wound visit. Forty Veterans refused participation and 35 Veterans did not meet inclusion/exclusion criteria. Data from 37 participants were used in statistical analyses for surgical site infections (SSIs) since only the final wound assessment data was missing. Inspection of data revealed wound visit 3 and 4 were consistent in all participants. Therefore, if no infection was noted at prior visits it was reasoned that there would have been no wound infection in the fourth and final visit. Data from three treatment groups, group 1 tight glycemic control (n = 15), group 2 conventional glycemic control (n = 11), and group 3 standard glycemic control (n = 11) were analyzed (Figure 2).

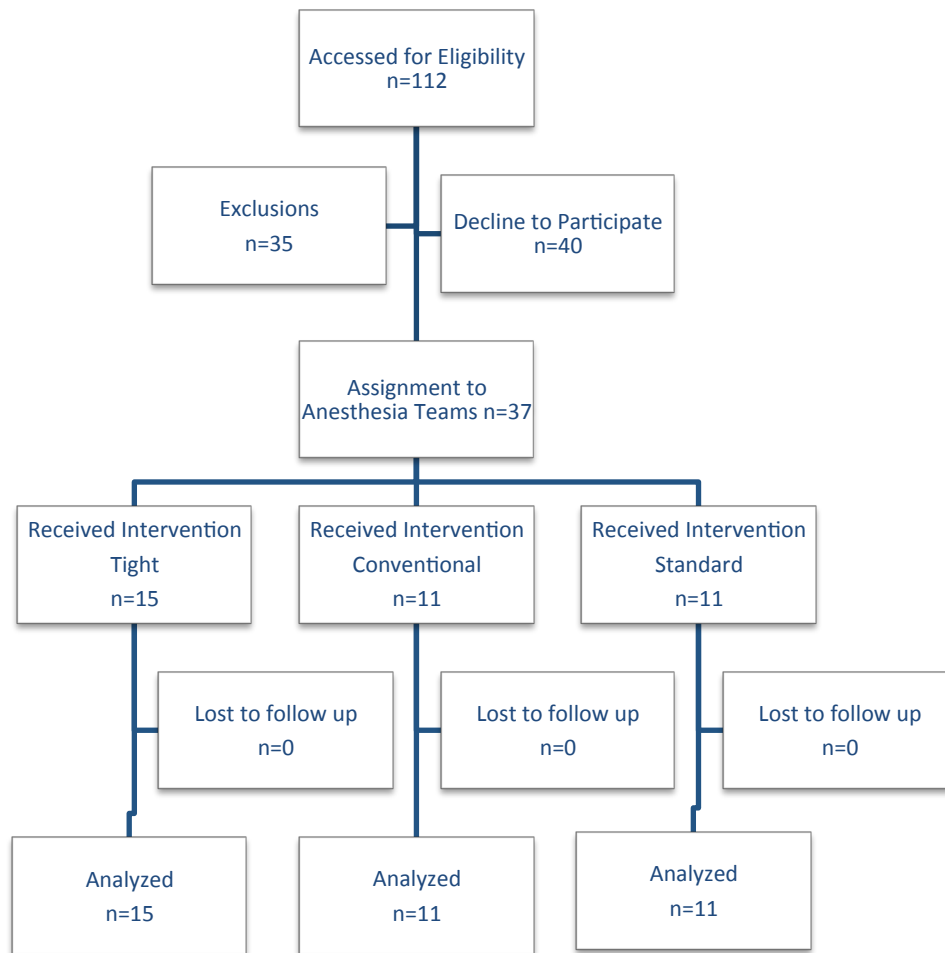


Figure 2. Flow of Subjects Through the Study

Table 7 summarizes the sample of primarily male non- Hispanic Caucasians with a mean age of 65 (\pm 5) years. Common co-morbidities of the sample included hypertension (92%, 34/37), chronic obstructive pulmonary disease (COPD) (43%, 16/37), and prior myocardial infarction (38%, 14/37). Characteristics of the randomized groups were analyzed for pre-intervention differences using chi-square (χ^2) for categorical

variables and analysis of variance (ANOVA) for continuous variables. The groups were not significantly different at baseline on any participant demographics.

Table 7. Baseline Participant Characteristics by Treatment Groups

Characteristic	Glycemic Control			F/ χ^2	p
	Tight n =15	Conventional n =11	Standard n =11		
Age, mean (SD)	64 (6.9)	66 (7.4)	66 (4)	F = .629	.539
Male, n (%)	15 (100)	11 (100)	11 (100)		
Race, n (%)				$\chi^2 = 2.43$.297
Caucasian	15 (100)	11 (100)	10 (90)		
African American	0 (0)	0 (0)	1 (10)		
Ethnicity, n (%)				$\chi^2 = .921$.631
Hispanic	1 (6.7)	2 (18.2)	1 (9.1)		
Non- Hispanic	14 (93.3)	9 (81.8)	10 (90.9)		
Hypertension, n (%)	13 (87)	10 (91)	11 (100)	$\chi^2 = 1.54$.464
COPD, n (%)	7 (47)	4 (36)	5 (46)	$\chi^2 = .306$.858
PVD, n (%)	2 (13)	1 (9)	3 (27)	$\chi^2 = 1.49$.474
CRI, n (%)	1 (6.7)	3 (27.3)	3 (27.3)		
Diabetes, n (%)				$\chi^2 = 2.66$.851
Type I	0 (0)	1 (9)	1 (9)		
Type II ^a	4 (27)	3 (27)	4 (36)		
Type II ^b	2 (13)	1 (9)	2 (18)		
MI, n (%)	6 (40)	5 (45)	3 (27)	$\chi^2 = 4.01$.405
CVA, n (%)	1 (6)	0 (0)	1 (9)	$\chi^2 = .967$.616

Notes: ^a=oral agent controlled; ^b=insulin and oral agent controlled; COPD=chronic obstructive pulmonary disease; CRI = chronic renal insufficiency; CVA= cerebral vascular accident; MI= myocardial infarction; PVD= peripheral vascular disease.

Surgical Characteristics of Participants

Table 8 describes the surgical characteristics for the three intervention groups. Coronary artery bypass graft (CABG) surgery made up the majority of surgical cases (62%, 23/37). Among the 37 participants that underwent open-heart surgery, 32 procedures were elective in nature (86%) and 35 cases utilized cardiopulmonary bypass (CPB) (95%). Surgical times including total operating room times, CPB times, and aortic cross clamp time were similar across the three interventional groups. Three cardiothoracic surgeons participated in the research study. While the number of surgical procedures was not equally distributed amongst the surgeons, the dispersion of treatment groups was similar. There was no significant difference in any baseline characteristics, nor were there any differences in glycohemoglobin (HbA_{1c}), glucose, C-reactive protein (CRP), procalcitonin (PCT) or white blood count (WBC).

Research Hypotheses

The study had two aims, the first aim had two hypotheses investigating SSI and biomarkers for SSI, and the second aim had three hypotheses investigating glycemic control in the operating room and length of stay (LOS) in the intensive care unit (ICU).

Hypotheses for aim 1.

1.1 It was hypothesized that patients undergoing open-heart surgery, who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative phase would demonstrate fewer thirty-day sternal and harvest SSIs at four time points: in ICU, at hospital discharge, at 2 weeks post hospital discharge, and at 6 weeks post hospital discharge, compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control

(blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

Cross tabulation with statistical testing chi-square and Cramer's V was performed on infection outcomes to determine if there was any difference in surgical site infections between the interventional treatment groups in a thirty-day observation period. In total, fourteen of the 37 (37.8%) participants experienced some form of SSI. The majority of SSIs were diagnosed 2 weeks post hospital discharge (57%). Two patients diagnosed with a SSI at visit 2 (discharge from hospital) continued with a residual SSI at visit 3 (2 week post-hospital discharge). Of these two patients, one continued with a superficial sternal and the other had noted improvement from a deep harvest SSI to a superficial harvest SSI. Four patients continued with superficial harvest infections diagnosed on wound visit 3 (2 weeks post-hospital discharge) to wound visit 4 (6 weeks post-hospital discharge). The majority of infections were superficial in nature (32%, 11/37) occurring in harvest sites (27%, 10/37). Deep infections occurred in only three of the 37 participants (8.1%) and only 4 participants suffered sternal wound infections (10.8%, 4/37). One participant required multiple sternal debridement surgeries, and a pectoral flap for sternal reconstruction. Results of statistical analysis revealed no statistical difference in overall SSIs among the three treatment groups (Table 9).

A logistic regression model was applied to assess the simultaneous effect of multiple variables on the dichotomous dependent variable, infection. The independent variables shown in Table 7 and Table 8 were initially analyzed by univariate and bivariate analysis. Correlational analyses were used to examine the relationship between all variables and SSI.

Table 8. *Surgical Characteristics of Participants by Treatment Group*

Characteristic	Glycemic Control			F/ χ^2	p
	Tight n =15	Conventional n=11	Standard n =11		
Surgery Type, n (%)				$\chi^2 = 3.177$.529
CABG	9 (60)	6 (54.5)	8 (72.7)		
Valve Surgery	4 (26.7)	5 (45.5)	2 (18.2)		
CABG & Valve	2 (13.3)	0 (0)	1 (9.10)		
CPB, n (%)	14 (93.3)	10 (90.1)	11 (100)	$\chi^2 = .967$.616
Priority, n (%)				$\chi^2 = .390$.823
Elective	13 (86.7)	9 (81.8)	10 (90.9)		
Urgent	2 (13.3)	2 (18.2)	1 (9.1)		
Surgeon, n (%)				$\chi^2 = 1.670$.796
Surgeon A	6 (40)	6 (54.5)	7 (63.6)		
Surgeon B	6 (40)	3 (27.3)	3 (27.3)		
Surgeon C	3 (20)	2 (18.2)	1 (9.1)		
Cross-Clamp Time, (SD), minutes	77 (34)	77 (19)	80 (30)	F = 0.281	.757
CPB Time, m (SD)	104 (39)	109 (31)	110 (36)	F = 0.463	.634
HbA1c, % (SD)	6.33 (0.97)	7.07 (1.53)	6.85 (1.66)	F = 0.955	.395
Glucose, mg/dl (SD)	116 (24)	135 (39)	117 (42)	F = 1.160	.327
CRP, mg/L (SD)	0.55 (0.31)	0.26 (0.23)	0.51 (0.51)	F = 2.153	.133
PCT, ng/ml (SD)	0.05 (.008)	0.06 (.015)	0.05 (.012)	F = 0.107	.899
WBC, x10 ⁹ /L (SD)	6.6 (1.7)	7.4 (2.3)	6.7 (1.8)	F = 0.581	.565

Notes: CABG=coronary artery bypass grafting; CPB=cardiopulmonary bypass; CRP = C-reactive protein pre operative; HbA1c = glycohemoglobin preoperative; OR Time = operating room time; PCT = procalcitonin preoperative; SD=standard deviation; WBC = white blood count preoperative; X-Clamp = aortic cross clamp.

Table 9. *Surgical Site Infection Rates by Treatment Groups*

	Glycemic Control			χ^2	<i>p</i>	Cramer's <i>V</i>
	Tight	Conventional	Standard			
	<i>n</i> =15	<i>n</i> =11	<i>n</i> =11			
Total SSI, n (%)	4 (26.7)	5(45.5)	5(45.5)	1.34	.512	.190
Superficial SSI, n (%)	4(26.7)	4(36.4)	4(36.4)	.383	.826	.102
Deep SSI, n (%)	0 (0)	1(9.1)	2(18.2)	2.84	.242	.277
Harvest SSI, n (%)	3(20)	3(27.3)	4(36.4)	.862	.650	.153
Sternal SSI, n (%)	1(6.7)	2(18.2)	1(9.1)	.921	.631	.158

Notes: SSI = surgical site infections.

Table 10 reflects variables that were significantly correlated with SSI. There was a moderate positive correlation between experiencing a SSI and peak intraoperative blood glucose, and PCT levels on postoperative days 3, 4, and 5 (Table 10). Procalcitonin levels on postoperative day 3, 4 and 5 were associated with each other with a Pearson's correlation greater than .70. Therefore, in an effort to limit the risk of multicollinearity, a two predictor logistic model was designed using the independent variables peak intraoperative blood glucose, and the PCT level on postoperative day three.

A two-predictor logistic model was the best fit to predict occurrence of SSIs for open-heart patients using the peak intraoperative blood glucose levels and the PCT blood value on postoperative day 3 as predictors. The peak intraoperative blood glucose levels had a mean value of 178 mg/dl (S.D. 29), and a blood glucose range of 119 to 235 mg/dl.

Table 10. *Correlations Surgical Site Infection, Peak Intraoperative Blood Glucose and Procalcitonin n=37*

		SSI	High BG	PCT 3	PCT 4	PCT 5
SSI	r	1	.454**	.406*	.462**	.455**
	p		.006	.016	.005	.006
High BG	r		1	.252	.307	.225
	p			.144	.073	.193
PCT 3	r			1	.876**	.827**
	p				.000	.000
PCT 4	r				1	.920**
	p					.000
PCT 5	r					1

Notes: N=35 Listwise, ** Correlation at 0.01 (2-tailed), * Correlation at 0.05 (2-tailed), SSI=surgical site infection, HIGHBG=highest intraoperative blood glucose, PCT 3= procalcitonin postoperative day 3, PCT 4= procalcitonin postoperative day 4, PCT 5= procalcitonin postoperative day 5.

Postoperative day 3 PCT level ranged from 0.06 to 3.22 µg/L with a mean of 0.83 µg/L (S.D. 0.815). A test of the full model against a constant only model was statistically significant, indicating that the predictors reliably distinguished between participants with infection and participants without infection ($\chi^2=10.179$, $p = .006$ with $df = 2$). Of the two-predictor variables only one was statistically significant, peak intraoperative blood glucose. Participants that experienced a higher peak blood glucose level intraoperatively exhibited an increase likelihood of exhibiting a SSI.

The model explained 36.0% (Nagelkerke $R^2 = .359$) of the variance in SSI and correctly classified 73.0% of cases. Sensitivity was 54%, specificity was 85%, positive

predictive value was 70% and negative predictive value was 73.9%. The Wald criterion demonstrated that only the peak intraoperative blood glucose values made a significant contribution to predication ($p = .034$). The PCT blood value was not a significant predictor ($p = .127$), indicating that participants that experienced higher peak blood glucose levels were associated with an increased likelihood of developing a SSI. A rise in peak intraoperative blood glucose level by one unit (1 mg/dl), had an odds ratio of 1.04, indicating patients were 1.04 times more likely to develop a SSI.

While there was no statistically significant difference for infection rates among the intervention groups, exploration of the data revealed a significant difference in the overall SSI rates depending on the type of surgery performed (Table 11). Surgical site infections occurred in 34.8% (8/23) of patients after CABG surgery; 18% (2/11) of patients after heart valve surgery; and 100% (3/3) of patients after combined CABG and valve surgery. Chi-square analysis with Cramer's V showed participants who underwent combined CABG and valve surgery had significantly higher rates of SSI compared to CABG surgery or valve surgery alone ($\chi^2 = 6.927$, $p = .031$ with 2 df ; $V = .433$), respectively.

1.2 It was hypothesized that patients undergoing open-heart surgery, who received a continuous intravenous insulin infusion for tight glycemic control during the intraoperative phase would have lower PCT levels and lower CRP levels in the first five days of the postoperative period compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

Table 11 *Surgical Site Infection Rates by Type of Surgery*

	CABG <i>n</i> =23	Cardiac Valve <i>n</i> =11	Combined CABG & Valve <i>n</i> =3	χ^2	p
Total SSI, n (%)	8(34.8)	2(18)	3(100)	6.927	.031
Superficial SSI, n (%)	9(39)	1(9)	2(66.7)	4.810	.090
Deep SSI, n (%)	1(4.3)	1(9)	1(33)	3.013	.222
Harvest SSI, n (%)	6(26)	1(9)	2(66.7)	4.348	.114
Sternal SSI, n (%)	2(8.7)	1(9)	1(33)	1.719	.423

Notes: CABG=coronary artery bypass grafting; SSI = surgical site infection.

Preliminary analysis was conducted to validate of the relationship of the biomarkers CRP and PCT to SSIs. The research design used biomarkers PCT and CRP, as continuous measures, and predictors of infection. Selection of PCT and CRP as significant biomarkers for infection was based upon prior research.

Procalcitonin.

Data were evaluated for missing values, outliers, and normality. Investigation of PCT data revealed 6 participants with more than 50% non-random missing data. These participants were dropped from any data analyses involving PCT. All other missing data for PCT were completely random, and therefore, derived variables were calculated for replacement. Calculations for derived PCT levels were based upon knowledge of typical trends post surgery. Procalcitonin rises and peaks at 24 hours post-surgery, and then declines to normal values, usually, by the third or fourth day postoperatively. Missing values were calculated by taking the mean of the precedent and post PCT surrounding the missing value.

Procalcitonin was screened for outliers and the assumption of normality using boxplot and Shapiro-Wilk's test ($p < .05$) respectively. Results showed a data distribution that was substantially positively skewed; therefore, data were transformed using the log transformation. In addition, severe outliers were corrected by replacing them with the next largest or smallest value. The assumption of normality for PCT levels was satisfied after transformation, as assessed by Shapiro-Wilk's and inspection of normal Q-Q Plots.

Descriptive data on PCT levels collected over six time points is noted in Table 12. The baseline blood value for PCT taken the morning of surgery showed no pre-intervention differences between the three treatment groups $F(2, 35) = 0.134, p = .875$. Procalcitonin levels were drawn across six time periods; the first level was drawn upon successful separation from CPB in the operating room followed by daily morning levels for five postoperative days.

Preliminary analysis of procalcitonin as a significant biomarker for infection.

A repeated measures analysis of variance (RM ANOVA) with a Greenhouse-Geisser correction was conducted to determine if PCT levels drawn over time (separation from CPB, daily POD 1-5) were significantly related to SSI. One of the assumptions in RM ANOVA procedure is that of sphericity. Mauchly's test of sphericity, which tests for the equivalence of the hypothesized and observed variance/covariance patterns, was conducted.

Result of the Mauchly's test was highly significant ($W = .003, \chi^2 = 159.536, p < .000$ with $df=14$), suggesting that the observed matrix does not have approximately equal

variances and covariance. In order to reduce the likely inflation of Type I errors, the Greenhouse-Geisser epsilon correction was applied ($\epsilon = .309$).

Table 12. *Procalcitonin Post Cardiopulmonary Bypass, and Postoperative Days 1-5*

Glycemic Control		Post CPB	POD 1	POD 2	POD 3	POD 4	POD 5
Tight, n = 11	Mean	0.067	0.949	0.770	0.496	0.303	0.211
	Standard Deviation	0.032	1.07	0.803	0.461	0.218	0.101
Conventional, n = 10	Mean	0.052	2.47	1.66	1.21	0.881	0.631
	Standard Deviation	0.006	2.03	1.30	1.01	0.862	0.680
Standard, n = 10	Mean	0.071	1.30	0.993	0.864	0.590	0.339
	Standard Deviation	0.035	0.990	0.902	0.859	0.463	0.236
Total, n = 31	Mean	0.640	1.55	1.13	0.845	0.582	0.388
	Standard Deviation	0.029	1.53	1.06	0.829	0.601	0.437

Notes. Post CPB = post separation from cardiopulmonary bypass; POD = postoperative day.

The between subjects RM ANOVA performed on PCT means indicated that there was a significant SSI main effect between the two groups, with or without infection, $F(1, 29) = 5.655, p = .024$. Figure 3 reflects that at all time observations, PCT blood levels were higher in the presence of a SSI. Therefore, a RM ANOVA was conducted to determine if there was any difference in PCT blood levels over time (post CPB, POD 1-5) between the three glycemic treatment groups.

Procalcitonin differences between treatment groups.

A 3 X 6 ANOVA with a Greenhouse-Geisser correction was employed to test if there was any significant difference in blood levels of biomarkers PCT values over time (separation from CPB, daily POD 1-5), for participants randomly assigned to the tight glycemic group compared to the convention or standard glycemic group treatments.

These data are shown in Figure 4. The assumption of sphericity was violated, as assessed Mauchly's Test of Sphericity therefore a Greenhouse-Geisser correction was applied (Table 13).

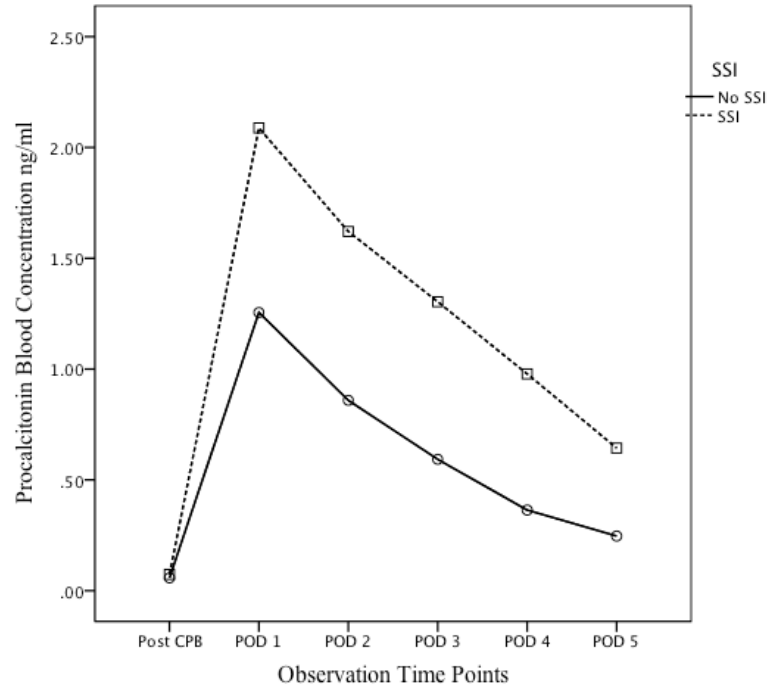


Figure 3. Procalcitonin in Participants With and Without Surgical Site Infections. Notes $n = 31$, CPB = cardiopulmonary bypass, POD = postoperative day.

Table 13. *Mauchly's Test of Sphericity Measure Procalcitonin*

Within Subjects Effect	Mauchly's W	$\approx \chi^2$	df	p	Epsilon		
Time	.003	153.478	14	.000	Greenhouse-Geisser .319	Huynh-Feldt .359	Lower-Bound .200

Results of the univariate analysis with epsilon correction, Greenhouse-Geisser, for within subjects effects determined that the overall mean PCT concentrations differed significantly across the six time points $F(5, 140) = 40.00, p < .001, \eta^2_p = .588$. The interaction between the intervention groups and time was not significant $F(10, 140) = 1.758, p = .166, \eta^2_p = .112$.

The between subjects analyses showed there was not a significant treatment arm main effect between the groups $F(2, 28) = 2.649, p = .088, \eta^2_p = .159$. The tight glycemic control was not statistically significantly different in PCT concentration over the postoperative time period compared to the conventional or standard glycemic treatment. Although not statistically significant, Figure 4 reflects a consistent pattern of PCT concentrations among the three glycemic control groups. Except for post CPB separation, all other observations of postoperative PCT concentrations for the tight glycemic group were consistently lower than the conventional and the standard treatment groups.

C-reactive protein.

Data was evaluated for missing data, outliers, and normality. Six participants had non-random missing CRP values greater than 50%. Data from these participants were dropped from further analyses involving CRP. Outliers were few, and they were confirmed as valid, therefore, included in the analysis; they were not expected to materially affect the results. C-reactive protein data was normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$).

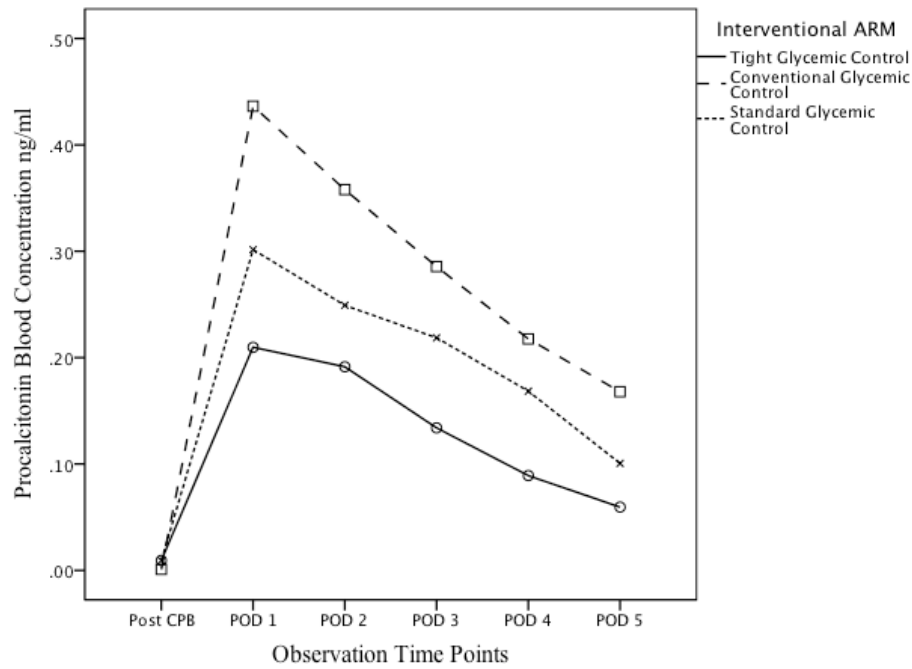


Figure 4. Postoperative Procalcitonin Concentrations by Treatment Groups. Note CPB = cardiopulmonary bypass, POD = postoperative day

Descriptive data on CRP concentrations in the three glycemic treatment groups collected in the five-day postoperative period is noted in Table 14. The baseline blood value for CRP taken the morning of surgery showed no pre-intervention differences between the three treatment groups $F(2, 34) = 2.15, p = .133$. C-reactive protein levels were drawn across six time periods; the first level was drawn upon successful separation from CPB in the operating room followed by daily morning levels for five postoperative days. Descriptive data of CRP concentrations for participants with and without SSI is noted in Table 15.

Table 14. *C-reactive Protein Concentrations By the Treatment Groups.*

Glycemic Control		Post CPB	POD 1	POD 2	POD 3	POD 4	POD 5
Tight, n = 11	Mean, mg/L	0.352	7.745	19.29	20.47	16.91	13.90
	Standard Deviation	0.199	2.25	3.09	5.28	5.20	5.12
Conventional, n = 10	Mean, mg/L	0.144	6.81	16.17	17.60	13.10	12.00
	Standard Deviation	0.158	1.84	2.82	5.06	4.51	6.51
Standard, n = 10	Mean, mg/L	0.317	7.17	20.64	22.72	19.53	13.50
	Standard Deviation	0.341	2.32	6.27	6.95	5.50	3.96
Total, n = 31	Mean, mg/L	0.274	7.26	18.72	20.27	16.52	13.16
	Standard Deviation	0.253	2.12	4.57	5.99	5.58	5.18

Notes. CPB = cardiopulmonary bypass, POD = postoperative day.

Preliminary analysis of C-reactive protein as a significant biomarker for infection.

A repeated measures analysis of variance (RM ANOVA) with a Greenhouse-Geisser correction was conducted to determine if CRP levels drawn over time (separation from CPB, daily POD 1-5) were significantly related to SSI. The assumption of sphericity was violated, as assessed Mauchly's Test of Sphericity, ($W = .117$, $\chi^2 = 58.230$, $p < .000$ with $df=14$). Therefore a Greenhouse-Geisser correction was applied ($\epsilon = .644$). The CRP concentration was statistically different over the postoperative time, as noted by the within subjects tests $F(5, 145) = 126.177$, $p < .000$. However, there was no significant difference in CRP concentrations whether or not a SSI was present, as noted in the between subjects tests $F(1, 29) = 1.170$, $p = .288$. Figure 5 reflects CRP

concentrations postoperatively between participants with and without SSI. C-reactive protein was not a significant predictor of SSI. Therefore, no further analyses of CRP and its relationship to infection was conducted.

Table 15. *C-reactive Protein in Participants With and Without Surgical Site Infections in the Postoperative Period.*

		Post CPB	POD 1	POD 2	POD 3	POD 4	POD 5
No SSI, n = 20	Mean, mg/L	0.299	7.26	18.88	20.54	17.35	14.46
	Standard Deviation	0.269	2.38	4.60	5.77	4.79	4.74
SSI Present, n = 11	Mean, mg/L	0.228	7.26	18.42	19.78	15.02	10.79
	Standard Deviation	0.226	1.63	4.73	6.62	6.78	5.31
Total, n = 31	Mean, mg/L	0.274	7.26	18.72	20.27	16.52	13.16
	Standard Deviation	0.253	2.12	4.57	5.99	5.58	5.18

Notes. CPB = cardiopulmonary bypass, POD = postoperative day, SSI = surgical site infection.

Hypotheses for aim 2.

Intraoperative blood glucose levels.

2.1 It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative period would have significantly lower blood glucose levels during this period compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

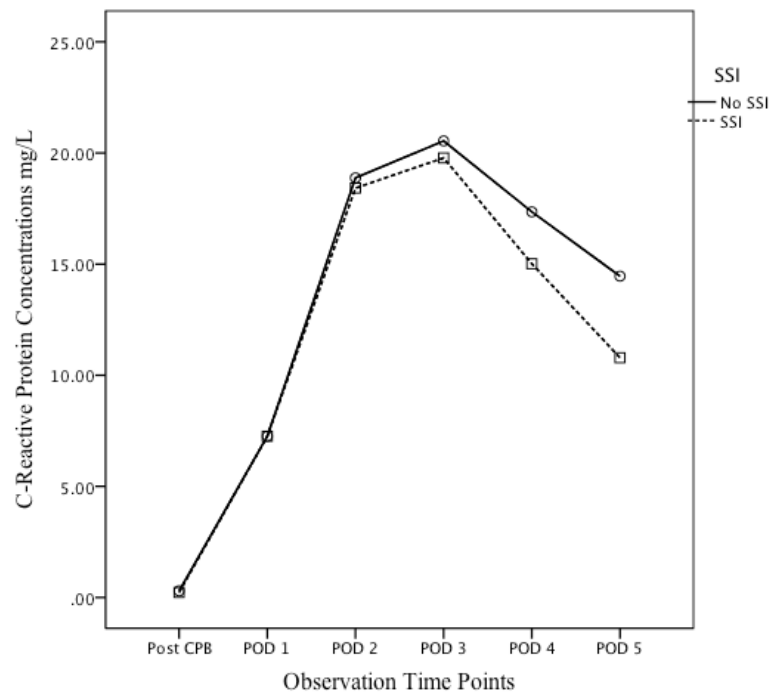


Figure 5. C-reactive Protein in Participants With and Without Surgical Site Infections. Notes CPB = cardiopulmonary bypass, POD = postoperative day.

Investigation of data revealed non-random missing data for the variables reflecting intraoperative blood glucose levels. Participants varied on the number of blood glucose values collected in the operating room because of varying operating room times. Blood glucose data was collected on all participants up to the sixth observation (BG 6) intraoperative (180 minutes). Five participants were missing two to three data observations at 210 and 240 minutes intra-operatively. Thirty-minute observations on all participants continued into the ICU period for six hours. Therefore, data missing from the intraoperative period were replaced with the first two or three observations from the ICU data. Inspection of these blood glucose levels was found to be lower than levels that would have initiated ICU insulin intervention. Data analysis incorporating intraoperative

blood glucose levels was conducted utilizing blood glucose levels up to the ninth observation in the operating room, yielding 37 participants. Outliers were few, and they were confirmed as true values, therefore included in the analysis; they were not expected to materially affect the results. Blood glucose levels during the intraoperative period were normally distributed, as assessed by Shapiro-Wilk's test ($p > .05$).

Descriptive data on blood glucose levels was collected every 30 minutes during the intraoperative period. The baseline blood value for blood glucose taken the morning of surgery showed no pre-intervention differences between the three groups. Table 16 reflects the mean blood glucose values every 30 minutes across 240 minutes of intraoperative time. The majority of all participants' blood glucose values were well controlled, regardless of which treatment arm they were randomized to. The tight glycemic treatment group blood glucose means ranged from 120 to 144 mg/dl, the conventional glycemic treatment group ranged from 137 to 154 mg/dl, and the standard glycemic treatment group ranged from 124 to 173 mg/dl.

Repeated measures ANOVA with Greenhouse-Geisser correction was employed to determine if open-heart surgical participants randomly assigned to the tight glycemic control group yielded lower blood glucose levels in the intraoperative period (every 30 minutes for 240 minutes) than participants who were assigned to conventional glycemic control treatment or the standard glycemic control treatment.

Assumption of compound symmetry was not met based on a significant Mauchly's test of Sphericity ($W = .001$, $\chi^2 = 218.738$, $p < .001$ with $df = 35$). Results of the univariate analysis with epsilon correction ($\epsilon = .334$), Greenhouse-Geisser, for within

subjects effects determined that the overall mean blood glucose concentrations differed significantly across the six time points $F(8, 272) = 7.240, p = .001, \eta^2 = .176$.

Table 16. *Intraoperative Blood Glucose Levels by Treatment Groups*

Glycemic Control		Intraoperative Blood Glucoses Every Thirty Minutes , mg/dl								
		BG 1	BG 2	BG 3	BG 4	BG5	BG 6	BG 7	BG 8	BG 9
Tight, n =15	Mean	125	120	123	123	131	134	139	138	144
	S. D.	32.79	20.15	19.03	17.9	16.33	23.82	23.19	16.23	28.95
Conventional, n = 11	Mean	137	140	142	144	143	139	145	154	146
	S.D.	50.33	43.06	26.17	20.9	20.33	23.93	33.92	22.78	24.93
Standard, n = 11	Mean	124	126	129	142	137	145	163	173	171
	S.D.	40.50	36.58	34.21	41.6	32.38	33.74	35.32	34.03	27.98
Total, n = 37	Mean	128	128	131	135	136	139	148	153	152
	S.D.	40.13	33.40	26.76	28.7	23.18	26.80	31.22	27.92	29.46

Note: BG 1 = blood glucose at operating room entry, BG 2 – BG 9 = blood glucose values every 30 minutes after BG 1.

The main effect between subjects for blood glucose differences was not statistically significant $F(2, 34) = 2.154, p = .132, \eta^2 = .112$. While the results are not significant, there was a moderate effect size. The interaction subject effects for interventional treatments across time was not significant $F(16, 272) = 1.484, p = .196, \eta^2 = .08$. As with the between subjects main effect, the interaction effect is not significant but has close to a moderate effect size. There was no statistically significant difference between the three glycemic treatment groups on blood glucose levels, or blood glucose variability during the intraoperative period. Results for above analyses may have been significant if the study was not underpowered.

Glycemic stability.

2. 2 It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for glycemic control, whether tight control (blood glucose 110-149 mg/dl) or conventional control (blood glucose 150-180 mg/dl), during the intraoperative phase would have significantly improved glycemic stability in the intraoperative period compared to patients who received the standard glycemic control via intravenous bolus injections of insulin (blood glucose 150-180 mg/dl).

Intraoperative glycemic instability was defined as three consecutive blood glucose values that were not within the preset limits of the protocol and outside of normal glucose values. Only four participants of the 37 (11%) experienced glycemic instability, and each of these participants only experienced one episode of glycemic instability. Of the four participants 2 were in the tight glycemic treatment group, and one participant each was in the conventional and standard group. All participants returned to the predetermined target range for their group by the fourth blood glucose indicating that all three protocols brought blood glucose levels under control within 2 hours. Additionally, no participants in the group had excessive blood glucose values (> 250 mg/dl). The two events of glycemic instability, in the tight glycemic group measured peak intraoperative blood glucose levels of 167 mg/dl and 184 mg/dl respectively. The peak blood glucose value, for the glycemic instability event, in the conventional glycemic treatment group was 223 mg/dl, and the peak glucose value, for the glycemic instability event, in the standard treatment group was 213 mg/dl. With so few episodes of glycemic instability, no tests of significance were possible.

Figure 6 reflects that, while not statistically significantly different, the tight glycemic treatment group trended the lowest blood glucose values of the three groups, for the majority of the intraoperative period (240 minutes). The two interventional groups that delivered the insulin via continuous intravenous infusion (tight glycemic treatment group and conventional glycemic treatment group) maintained blood glucose levels within a closer range than the interventional group that delivered insulin via intravenous bolus injections (standard glycemic treatment group). This overall pattern, while not statistically significant, suggests continuous intravenous infusion may produce better glycemic stability during the rewarming period of CPB (BG 7). Additionally, the pattern of blood glucose concentrations in participants with and without SSI, suggest patients with patients with SSI have higher intraoperative blood glucose concentrations. Figure 7 reflects that, while not statistically significant, the pattern of blood glucose concentrations in infected participants is higher, for all points, save one, than blood glucose concentrations for the non-infected participants.

Intensive care length of stay

2.3 It was hypothesized that patients undergoing open-heart surgery who received a continuous intravenous insulin infusion for tight glycemic control (blood glucose 110-149 mg/dl) during the intraoperative phase would demonstrate a shorter length of stay in the intensive care unit compared to patients who received continuous intravenous infusion of insulin for conventional glycemic control (blood glucose 150-180 mg/dl) or standard glycemic control via intravenous bolus injections (blood glucose 150-180 mg/dl).

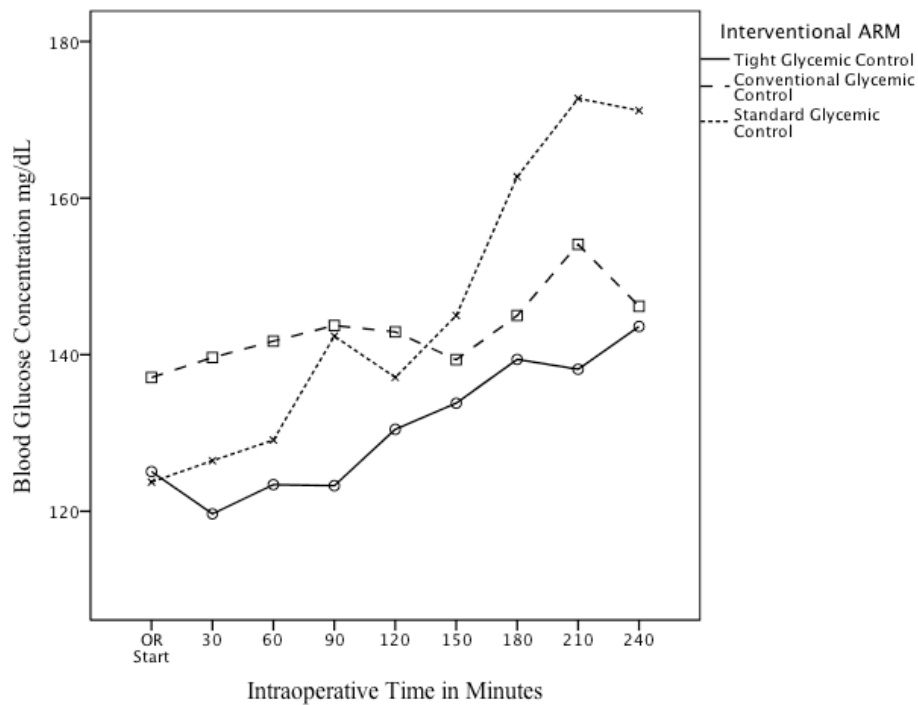


Figure 6. Intraoperative Blood Glucose Levels By Treatment Groups. Note OR = operating room.

A one-way ANOVA was used to determine if participants randomized to the tight glycemic control group had shorter ICU LOS than participant randomized to the conventional or standard glycemic treatment groups. There was homogeneity of variances, as assessed by Levene's test of homogeneity of variance ($p = .531$). There was no statistically significant difference in the ICU LOS between the different glycemic treatment groups $F(2, 34) = .096, p = .908$.

Table 17 reflects descriptive statistics for ICU LOS revealing that all three interventional groups had similar length of stay in the ICU. Results of the cross tabulation with Chi-square revealed there was no significant difference in total ICU LOS whether or not there was a SSI present ($\chi^2 = 17.920, p = .267$ with $df = 15$).

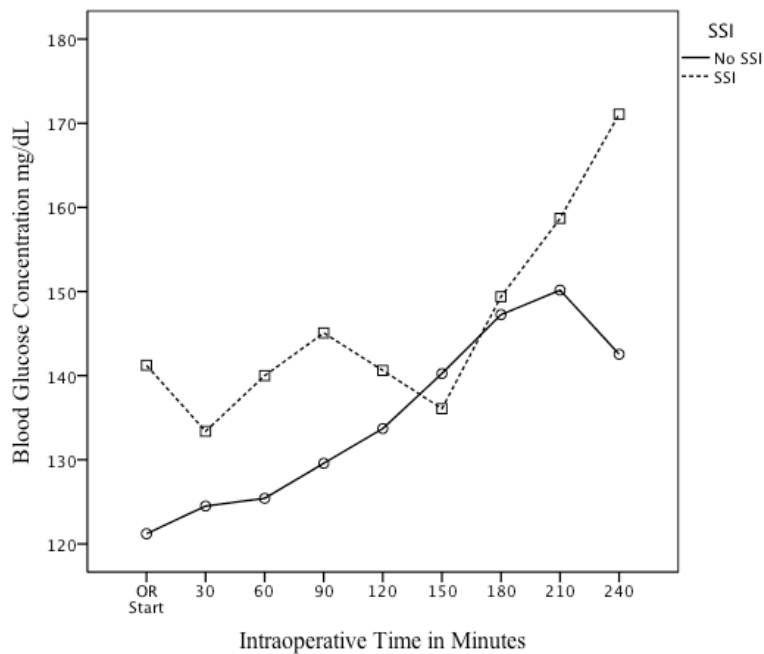


Figure 7. Intraoperative Blood Glucose Levels in Participants With and Without Surgical Site Infections. Note OR = operating room.

Table 17. *Intensive Care Unit Length of Stay by Treatment Groups*

Glycemic Control	Total Intensive Care Unit Days, m, (SD)
Tight, <i>n</i> = 15	7.00 (5.29)
Conventional, <i>n</i> = 11	6.18 (4.90)
Standard, <i>n</i> = 11	7.18 (6.03)
Total, <i>n</i> = 37	6.81 (5.26)

Summary of Research Findings

The aims of the study were to determine if maintaining intraoperative blood glucose levels in a tight range lowered the rate of surgical site infection (SSI), postoperative biomarkers of infection, PCT, CRP, and intraoperative glucose levels

compared to moderate glycemic control in patients undergoing open-heart surgery. Additionally, the study hypothesized that maintaining intraoperative tight glycemic control in open-heart surgical patients, with a continuous insulin infusion would provide better glycemic stability during the intraoperative period compared to insulin bolus injection technique. Lastly, it was hypothesized that use of intraoperative tight glycemic control, in open-heart patients, would decrease patient LOS in the ICU.

The primary findings of this randomized controlled trial revealed no significant difference in the three glycemic interventions on the outcomes SSI, ICU LOS, or postoperative plasma concentrations in markers of infection including CRP and PCT. Additional findings showed no significant difference between the three glycemic interventions on blood glucose levels, or glycemic stability during the intraoperative period. While tight glycemic control of blood glucose failed to show a reduction in postoperative SSIs, patients with higher peak intraoperative glucose levels during the intraoperative period had a higher incidence of postoperative SSI. Procalcitonin was significantly elevated in participants that developed a SSI compared to participants without a SSI, while CRP was not significantly related to SSI. Surgical site infections were significantly higher in patients that underwent combined CABG and valve repair surgery compared to participants who underwent either CABG surgery or valvular surgery independently.

Chapter Five

Discussion

Introduction

This chapter provides a discussion of the major findings of the study. The findings of this study are compared and contrasted to findings of relevant published literature.

Clinical implications and recommendations for future research are provided.

Research Aims of the Study

This study sought to determine whether open-heart surgical participants who were randomly assigned to tight glycemic control during the intraoperative period, compared to participant assigned to either the conventional or standard glycemic control treatments, would have significantly 1) lower thirty-day surgical site infections (SSIs), and 2) lower postoperative procalcitonin (PCT) and C-reactive protein (CRP) plasma levels. In addition, the study sought to determine if participants randomized to the tight glycemic control group, compared to the conventional or standard glycemic group, would have significantly lower intraoperative blood glucose levels, and a shorter length of stay (LOS) in the intensive care unit (ICU). Finally, the study sought to determine if the use of a continuous intravenous infusion of insulin compared to intravenous bolus injections of insulin would result in improved glycemic stability during the intraoperative period.

Major Findings of the Study

The main findings of this study were that there were no significant differences between the three glycemic interventional treatment groups in 1) thirty-day SSIs; 2)

postoperative CRP or PCT concentrations; 3) intraoperative blood glucose levels; 4) glycemic stability; or 5) ICU LOS. An association between intraoperative blood glucose and SSI was established. Participants that experienced higher peak blood glucose levels intraoperatively exhibited an increased likelihood of exhibiting a SSI. Procalcitonin levels were significantly elevated in participants that experienced a SSI, but CRP showed no significant difference between participants with or without a SSI. Participants that underwent coronary artery bypass graft surgery (CABG) with concomitant valve surgery had a significantly higher rate of SSIs postoperatively compared to participants that had either CABG surgery or valve surgery.

Effect of tight glycemic control on postoperative surgical site infections.

This study found no significant difference in SSIs between any of the three glycemic groups. These findings were consistent with the majority of randomized controlled trials (RCTs) that have been conducted related to glycemic control, and postoperative wound infections (Azarfari et al., 2011; Chan et al., 2009, Emam et al., 2010; Gandhi et al., 2007; Lazar et al., 2004; Lazar et al., 2011). Of the six RCTs that were similar to this study, four reported results consistent with the findings of this study (Azarfari et al., 2011; Chan et al., 2009; Gandhi et al., 2007; Lazar et al., 2011) and two had contrasting results (Emam et al., 2010; Lazar et al., 2004).

Chan et al. (2009) investigated the effect of tight glycemic control in patients undergoing open-heart surgery with cardiopulmonary bypass (CPB) on postoperative outcomes. They defined of tight glycemic control via continuous infusion ($n = 55$) as blood glucose levels from 80-130 mg/dl, and the conventional group via continuous infusion ($n = 54$) as blood glucose levels of 160-200 mg/dl. The study showed no

difference between the two glycemic groups in any clinical outcomes including the occurrence of postoperative infections (Chan et al., 2009).

Similarities between Chan et al. (2009) and this study included a similar patient sample (patients with and without a diagnosis of diabetes mellitus), the use of continuous insulin infusion for both the tight glycemic and control group, and comparable results, that of no significant difference in SSIs between the groups. Their study differed from this study in that the intervention was carried out in perioperative period and they used different blood glucose parameters. They used a much lower limit in their tight glycemic control group compared to this study (80-130 vs. 110-149 mg/dl), respectively, and a much higher limit for the control group compared to this study (200 vs. 150-180 mg/dl), respectively.

Gandhi et al. (2007) investigated the effects of tight glycemic control, during the intraoperative period, on postoperative adverse outcomes, including deep sternal wound infection. Patients with and without a diagnosis of diabetes mellitus were enrolled in a RCT, that compared tight glycemic control ($n=185$), which maintained blood glucose levels between 80 - 110 mg/dl via continuous insulin infusion, to conventional glycemic control ($n = 186$), which instituted insulin therapy when blood glucose levels exceeded 200 mg/dl via intravenous bolus injections of insulin, and for blood glucose levels exceeding 250 mg/dl patients received a continuous infusion (Gandhi et al., 2007). Gandhi et al. (2007) found no significant difference in sternal wound infections between the two groups.

The current study shared similarities with Gandhi and colleagues (2007) including that both studies intervention period was during the intraoperative period exclusively and

the inclusion of patients with and without diabetes mellitus. Both studies also showed that there was no significant difference in SSIs between treatment groups. The research by Gandhi and colleagues differed from the current study by using lower parameters in their tight glycemic group compared to this study (80-100 vs. 110-149 mg/dl), and a higher limit for the control group (200 vs. 180 mg/dl). They also included only patients that underwent CABG surgery with CPB, and the outcome was exclusively deep sternal wound infections and not harvest or superficial sternal wounds.

Lazar et al. (2011) enrolled patients, with a diagnosis of diabetes, undergoing CABG surgery with CPB to a tight or moderate glycemic treatments, in the perioperative period, to determine if tight glycemic control resulted in more optimal postoperative clinical outcomes. Patients randomized to the tight glycemic group ($n = 42$) had blood glucose levels maintained between 90-120 mg/dl and the moderate glycemic group ($n = 40$) maintained blood glucose levels between 120-180 mg/dl. Their study showed no significant differences in the incidence of deep sternal wound infection between the two treatment groups (Lazar et al., 2011).

As in the current study, Lazar et al. (2011) found no difference in SSIs between treatment groups. Other similarities included the insulin delivery method of continuous infusions for treatment groups. The current study differed from Lazar et al. in that it included all types of open-heart surgery, and Lazar et al. (2011) used lower parameters in the tight glycemic group compared to this study (90-120 vs. 110-149 mg/dl), and slightly lower limit for the control group compared to this study (120-180 vs. 150-180 mg/dl). Finally, their outcome was exclusively deep sternal wound infections.

Azarfarin et al. (2011) investigated the effect of blood glucose control with insulin in preventing hyperglycemia during and after CABG surgery, with and without CPB, in non-diabetic patients to determine the which protocol optimized outcomes. They measured a postoperative composite of various complications, that included SSI, and found it was significantly less in the tight glycemic group ($n=59$), which used a continuous insulin infusion to maintain blood glucose between 110-126 mg/dl, compared to the control group ($n=58$), which used intravenous bolus injections of insulin to treat blood glucose levels greater than 200 mg/dl (Azarfarin et al., 2011). The study did not find a significant difference in SSI between the two groups when evaluated independently, only when SSI was combined in a composite.

The current study had similar aspects to Azarfarin and colleagues (2011) like an exclusive intraoperative intervention with one group receiving continuous infusion and the other receiving intravenous bolus injections as a method of insulin delivery. The studies also had similar findings of no significant difference in postoperative SSI between treatment groups, when SSI was analyzed independently. The current study varied from Azarfarin et al. in surgical procedures, patient population sampled, as well as the parameters of intraoperative blood glucose levels. They used lower parameters for the tight glycemic group compared to the current study (110-126 vs. 110-149 mg/dl), and a higher limit for the control group (200 mg/dl vs. 150-180 mg/dl). Lastly, Azarfarin et al. (2011) only investigated deep sternal wound infections.

In contrast to the findings of the current study, other RCTs investigating perioperative glycemic control found a significant decrease in postoperative complications, including SSI (Emam et al., 2010; Lazar et al., 2004). Emam et al. (2010)

conducted a prospective RCT of 120 subjects with a diagnosis of diabetes, undergoing open-heart surgery to determine a glycemic protocol to produce the best postoperative outcomes. Subjects were randomly assigned to either a control group, simple sliding scale ($n = 40$) to keep blood glucose < 200 mg/dl or the Braithwaite protocol ($n = 80$) to maintain tight glycemic control between 100-150 mg/dl. The trial was started on admission to the hospital, 24 hours prior to surgery, and carried through postoperative day (POD) 2. They found no wound infections in the tight glycemic group compared to a 12.5% rate of infection (5/40) in the control group (Emam et al., 2010). Specifically, patients with a mean 48 hour blood glucose level greater than 200 mg/dl had a 2.2 times higher risk of deep sternal wound infection (Emam et al., 2010).

The current study was similar to Emam et al. (2010) in several aspects including the intraoperative interventional treatment arms included one with continuous infusion insulin and one with intravenous bolus injection, and glycemic parameters for the tight intervention were the same (110-149 mg/dl). Differences between the current study and the study by Emam et al. (2010) included blood glucose values for the control group compared to the current study (200 vs. 150-180 mg/dl), they also only included only patients with a diagnosis of diabetes mellitus for open-heart surgery requiring CPB. Additionally, the interventional period for Emam et al. (2010) was started 24 hours preoperatively through POD 2, much longer than the current study. Findings between the current study and Emam and colleagues was Emam et al. found significantly lower SSIs in patients that were randomized to the tight glycemic group compared to the control group.

Lazar et al. (2004), in a RCT, sought to determine whether tight glycemic control ($n = 69$, 125-200 mg/dl), via a continuous infusion of glucose-insulin-potassium, in diabetic patients, undergoing CABG surgery would improve perioperative outcomes compared to standard glycemic therapy ($n = 72$, < 250 mg/dl) via subcutaneous bolus injections of insulin. They found tight glycemic control produced a 13% lower incidence of postoperative infections, which included pneumonia and SSIs, compared the standard glycemic group (0/72, 0% vs. 9/89), respectively.

Unlike the current study, Lazar and colleagues (2004) included patients with diabetes undergoing CABG surgery with CPB. Lazar et al. (2004) also used a higher limit for the tight glycemic group compared to the current study (125-200 vs. 110-149 mg/dl), respectively, and a higher limit for the control group, with subcutaneous bolus injections, compared to the current study (250 mg/dl vs. 150-180 mg/dl), respectively. Lastly, Lazar and colleagues (2004) found significantly lower SSIs in patients that were randomized to the tight glycemic group compared to the control group.

In summarizing the comparisons between previous RCTs in literature with the current study, several themes are identified. The current study showed tight glycemic control did not significantly reduce postoperative SSIs, which is consistent with the other RCTs that investigated the effect of tight glycemic control on postoperative SSIs and maintained blood glucose levels below 200 mg/dl in the control group. Of the six RCTs investigating the effects of tight glycemic control on postoperative SSIs compared to conventional therapy two showed a significant reduction in SSIs with tight glycemic therapy (Emam et al., 2010; Lazar et al., 2004), three showed tight glycemic therapy slightly reduced the incidence of SSIs, but not significantly (Azarfarin et al., 2010; Chan

et al., 2009; Gandhi et al., 2007), and 1 showed no difference with tight glycemic control, as there were no SSIs in the tight control group or the conventional group (Lazar et al., 2011).

Possible reasons for the different findings may rest with different operational definitions for the tight glycemic group and the acceptable level of hyperglycemia permitted in the control groups for the studies. Of the two RCTs that showed a significant decrease in SSIs, with the use of tight glycemic control, both studies permitted the control groups to experience mean blood glucose levels consistently higher than 200 mg/dl during the perioperative period (Emam et al., 2010; Lazar et al., 2004). Lazar and colleagues (2004) permitted blood glucose levels, for patients in the control group, to elevate up to 250 mg/dl before intervention with subcutaneous bolus injections of insulin. As such, blood glucose levels during the intraoperative period were consistently close to 250 mg/dl and never below 200 mg/dl.

Similarly, Emam et al. (2010) permitted blood glucose levels greater than 200 mg/dl in patients in the control group before intervention with intravenous bolus injections of insulin. While they did attempt to maintain blood glucose levels below 200 mg/dl during the perioperative period, their protocol of intravenous bolus injections was inadequate to achieve this. Mean serum glucose levels during intraoperative and the first 24 hours postoperative period were greater than 220 mg/dl consistently. Allowing the blood glucose levels to exceed severe hyperglycemic levels (> 200 mg/dl), and utilizing the bolus injection method of insulin delivery may contribute to the significant difference in SSIs between the two glycemic treatments that these studies found.

The only other study that utilized intravenous bolus injections for glycemic management in the control group was Azarfarin and colleagues (2010). They were successful in achieving blood glucose levels below 200 mg/dl with intravenous bolus injections during the intraoperative period. The difference between Azarfarin and colleagues from Emam et al. (2010) and Lazar et al. (2004) was the patient population selection. Azarfarin et al. only included patients without a diagnosis of diabetes, and the other two studies included only patients with a diagnosis of diabetes. It is well established that patients with a diagnosis of diabetes mellitus have greater insulin resistance and difficult glycemic control in open-heart surgery, especially with the use of CPB (Ascione et al., 2008; Knapik et al., 2011).

Effect of tight glycemic control on procalcitonin and C-reactive protein.

In the current study the tight glycemic group did not significantly reduce the postoperative serum concentrations of PCT. Analysis of tight glycemic control on CRP was not conducted because preliminary analysis of CRP failed to show a significant relationship with infection. The current study did show that patients in the tight glycemic control group had consistently lower postoperative PCT values compared to the other two groups that maintained moderate glycemic control, and while not significant, there was a moderate effect size. This is the first study to investigate if tight glycemic control reduces the response of the inflammatory biomarker PCT. Only two studies were identified in research that investigated the effects of tight glycemic control, in open-heart surgery, on inflammatory biomarkers. These two studies investigated biomarkers CRP, interleukins (IL), and free fatty acid levels (Koskenkari et al., 2006; Visser et al., 2005).

In a RCT of 21 patients, Visser et al. (2005) utilized glucose-insulin-potassium therapy via a hyperinsulinaemic normoglycemic clamp for glycemic control, in CABG patients, and found this method attenuated the systemic inflammatory response, as measured by IL-6, IL-8, and IL-10, and CRP compared to standard treatment. The glucose-insulin-potassium group received a high dose of continuous insulin with a variable rate of glucose and potassium to maintain blood glucose between 4.0-5.5 mmol/L (72-99 mg/dl), during the intraoperative period, and 24 hours after the release of the aortic cross clamp. The control group received the standard institutional treatment, which was not described. Visser and colleagues (2005) showed the interventional insulin group had an overall lowering effect on CRP levels compared with the control group, and on the first POD.

Koskenkari et al. (2006) hypothesized that high dose glucose-insulin-potassium treatment could suppress the systemic inflammatory reaction and attenuate myocardial ischemia reperfusion injury in patients with unstable angina pectoris after urgent CABG surgery. Forty patient were randomized to receive either high-dose insulin treatment with a separate glucose potassium infusion or a control treatment. Both groups maintain blood glucose levels between 6-8 mmol/L (108-144 mg/dl) during the intraoperative period and 14 hours postoperatively. Koskenkari and colleagues found the high dose insulin treatment was associated with significantly lower CRP and lower free fatty acid levels compared to the control group. While these studies suggest tight glycemic control attenuated systemic inflammatory response, they do not discuss reduction in bacterial infection or SSI, or any clinical outcome benefits.

The studies conducted by Visser et al. (2005) and Koskenkari et al. (2006) vary from the current study in many respects. Primarily, the current study utilized insulin only as a method to control blood glucose levels and not for the immunomodulatory effects it may exert. Additionally, different inflammatory biomarkers were investigated and outcomes investigated differed.

Effect of tight glycemic control on blood glucose levels.

In the current study, there was no significant difference on intraoperative blood glucose levels between the three treatment groups. Serum glucose values increased in all three groups during the surgery, with peak blood glucose values occurring during rewarming on CPB. However, all three glycemic protocols were effective in maintaining mean blood glucose levels within their preset target range. The tight glycemic group did have consistently lower blood glucose levels during the intraoperative period compared to the moderate glycemic groups, and while the results were not significant, there was a moderate effect size. The current study did not find significantly lower intraoperative blood glucose levels in the tight glycemic group. This finding is in contrast to all other previous RCTs investigating the use of tight glycemic control on postoperative outcomes of wound infections (Azarfarin et al., 2011; Chan et al., 2009; Emam et al., 2010; Gandhi et al., 2007; Lazar et al., 2004; Lazar et al., 2011). A possible reason for this difference in the finding includes the difference in the treatment protocol ranges. The current study had the most narrow treatment window, between the tight glycemic group and control group, compared to other similar RCTs. The narrow treatment range, effectively decreased the effect size for this study. Moreover, this study had a much smaller sample size ($n = 37$) than any of the other comparable RCTs with sample sizes ranging from 82-

400 (Azarfarin et al., 2011; Chan et al., 2009; Emam et al., 2010; Gandhi et al., 2007; Lazar et al., 2004; Lazar et al., 2011). This study, with an insufficient sample size, was underpowered, which may have contributed to the lack of significance in intraoperative blood glucose levels between the three glycemic groups.

Effect of tight glycemic control on glycemic stability.

In this study, episodes of glycemic instability were too few to conduct analysis on the effect of continuous insulin infusion on intraoperative glycemic stability compared to intravenous bolus injection method. Intraoperative glycemic instability was defined as three consecutive blood glucose values that were not within the preset limits of the protocol and outside of normal glucose values. Only four participants of the 37 (11%) experienced glycemic instability, and each of these participants only experienced one episode of glycemic instability. Of the four participants 2 were in the tight glycemic treatment group, and one participant each for the conventional and standard group. All participants returned to the predetermined target range for their group by the fourth blood glucose indicating that all three protocols brought blood glucose levels under control within 2 hours. Utilizing this definition there were too few episodes of glycemic instability to analyze for significant differences between the three groups. However, evaluating the variability of intraoperative glycemic control showed the intravenous bolus injection group experienced twice the variability of the groups that received insulin via the continuous insulin infusion method.

In addition, both the conventional glycemic group and the standard glycemic group attempted to maintain intraoperative blood glucose levels between 150-180 mg/dl. Yet, during the rewarming phase of CPB, the conventional glycemic intervention via

continuous insulin infusion appeared to perform superior to the standard glycemic group, via intravenous bolus injections, in maintaining a more stable glucose level. Patients in the standard glycemic group experienced an larger increase in the blood glucose levels during rewarming on CPB (BG6 = 145 mg/dl to BG8 = 173 mg/dl) compared to the conventional treatment group (B6 = 139 mg/dl to BG8 = 154 mg/dl), a pattern, while not significant, suggestive that continuous infusion of insulin provides better glycemic control when insulin resistance is greatest.

The effect of tight glycemic control on intensive care length of stay.

This study found no significant difference in ICU LOS between the three glycemic protocols. This finding is consistent with other similar RCTs that found no significant difference in ICU LOS (Azarfarin et al., 2011; Chan et al., 2009; Emam et al., 2010; Gandhi et al., 2007; Lazar et al., 2011). Emam et al. (2010) while not finding a significant decrease in ICU LOS, did find a significant decrease in hospital LOS for patients who received tight glycemic control compared to the conventional glycemic control. In contrast, Lazar et al. (2004) found patients who received tight glycemic control via a continuous insulin infusion had shorter ICU LOSs compared to patients who received conventional therapy, subcutaneous bolus injections of insulin. Reasons for the difference in findings are likely the same that were discussed in tight glycemic effects on SSIs that of allowing the blood glucose levels in the control group to exceed 200 mg/dl, and an inadequate method of insulin delivery for the control group.

Exploratory findings

Hypoglycemia.

Investigation into the incidence of intraoperative hypoglycemia was not a primary aim of this study, yet it is a critical area of recent research that has shown negative impact on postoperative outcomes (Stamou et al., 2011). The current study showed no difference in the incidence of hypoglycemic events between the three glycemic control groups. There was only one patient, in the standard glycemic group, that experienced two episodes of hypoglycemia (< 70 mg/dl) during the intraoperative and 6 hours postoperative period; the episode occurred on arrival to the operating room, and was treated with intravenous dextrose successfully.

The finding that there was no significant difference in hypoglycemic events between the tight glycemic group and control group was consistent with the majority of previous RCTs that investigated tight glycemic control on postoperative outcomes of wound infection (Azarfarin et al., 2011; Chan et al., 2009; Emam et al., 2010; Gandhi et al., 2007; Lazar et al., 2004). Only one RCT, Lazar et al. (2011), reported a significantly higher incidence of hypoglycemia in the tight glycemic group compared to the conventional group. While they experienced significantly greater numbers of hypoglycemic events in the tight glycemic control group, there was no significant difference in major adverse events (Lazar et al., 2011). Reasons for the different findings is likely due to the varying definitions used for hypoglycemia in the studies. Lazar et al. (2011) defined hypoglycemia as a blood glucose level of 80 mg/dl. This is in contrast to other studies that used a lower value to define hypoglycemia, such as 50 mg/dl (Chan et al., 2009; Emam et al., 2010), and 60 mg/dl (Azarfarin et al., 2011; Gandhi et al., 2007).

This current study defined hypoglycemia as 70 mg/dl, congruent with the definition designated by the American Diabetes Association (2012).

Procalcitonin and C-reactive protein relationship to infection.

The selection of inflammatory biomarkers PCT and CRP was made with the expectation that they were reliable precursors to infection. Therefore exploratory analysis of CRP and PCT and their relationship to SSIs was conducted. The data indicated that PCT was a reliable predictor of infection, but CRP was not.

After surgery, CRP increased significantly compared with baseline in both participants with and without SSI. Peak serum concentration occurred on POD 3, whether a SSI was present or not. There was no significant difference in serum CRP concentrations between participant with and without a SSI, even for patients requiring longer ICU LOS. This was in contrast to Lannergard and colleagues (2003), who investigated several biomarkers for the detection of infection in open-heart surgery, and found IL-6 and CRP were significantly higher in patients that developed postoperative infections compared to patients without postoperative infections. Biomarkers and laboratory markers investigated by Lannergard et al. (2003) included CRP, white blood cells, IL-6, and human neutrophil lipocalin. In this prospective observational trial, they monitored laboratory markers every day for six postoperative days after open-heart surgery. Postoperative bacterial infections were diagnosed in 17 of 54 patients needing at least 3 days of ICU postoperatively; patients discharged from the ICU in less than 3 PODs were excluded from the study (Lannergard et al., 2003). While Lannergard and associates found that surgical trauma and CPB elicited a certain degree of an acute-phase response, resulting in elevation of IL-6, CRP and white blood cells, a significant

difference between patients with and without infection was noted for CRP on POD 2 and 3.

In the current study, CRP was not predictive of SSI, which is consistent with the results of other studies (Corral et al., 2009; Macrina et al., 2005). Corral et al. (2009), in a prospective observational study of 216 open-heart patients found postoperative CRP was not a useful biomarker in the immediate outcome after cardiac surgery with CPB. C-reactive protein was not correlated with postoperative outcomes and did not predict early complications, including infectious complications. Macrina et al. (2005), prospectively enrolled 32 post-CABG surgery patients and at the end of the 7th POD, the patients were divided into two groups, those with a complicated course and those with an uncomplicated postoperative course. C-reactive protein levels were drawn after induction of anesthesia (baseline), at the end of surgery, and daily until POD 2. After surgery they found CRP values increased significantly compared to the baseline in both the uncomplicated and complicated groups, determining that postoperative CRP values did not contribute in prediction of postoperative outcomes (Macrina et al., 2005). Evidence that CRP was predictive of SSI was not established; as such, no further investigation on the impact of tight glycemic control on CRP levels was conducted.

While Macrina et al. (2005) did not find CRP to be of value in predicting postoperative complications, they did find that absolute changes in PCT values of 0.20, 0.40, and 0.60 ng/ml carried an approximate risk of 5, 26 and 69% for postoperative complications, respectively. Macrina and colleagues did not specify SSI as a specific postoperative complication, only a category for all surgical complications requiring re-sternotomy, which may or may not have included sternal SSIs.

In the current study, postoperative PCT serum concentrations were significantly higher in the presence of a SSI compared to participants without a SSI. Procalcitonin values, in participants without a SSI, increased and peaked on the first postoperative day, followed by a return to near normal values by POD 5, compared to preoperative PCT levels. Procalcitonin values in participants that experienced an SSI, exhibited the same pattern, peaking on the first postoperative day and trending down. However, these values were significantly higher compared to participants without SSIs. Results of the current study, nor previous research studies, were able to verify a precise value or range for PCT that identifies an infectious process compared to an inflammatory process. Specifically, in this study PCT levels in patients without a SSI peaked on POD 1 and were less than 1.5 ng/ml, and in patients who experienced a SSI, PCT values on POD 1 were just above 2 ng/ml. Yet, elevated PCT concentrations greater than 2 ng/ml have been observed after CPB in cases of systemic inflammatory response syndrome without any postoperative complications, including infection (Meisner et al., 2002; Rothenburger et al., 1999). Other studies have shown PCT levels with a value of 1 ng/ml in the presence of postoperative fever was reliable for detecting infection in open-heart patients (Aouifi et al., 2000). In another study, Jebali et al. (2007) found a PCT value greater than 1.5 ng/ml beyond the second POD diagnosed postoperative infection with a sensitivity of 0.93 (0.70-0.99) and a specificity of 0.80 (0.70-0.87).

The patterns of postoperative PCT exhibited in this study are consistent with previous studies that have reported a moderate increase and peak on the first postoperative day in adults, with and without CPB, followed by a steady return to normal (Aouifi et al., 2000; Meisner et al., 2002; Prat et al., 2008; Sponholz et al., 2006).

Additionally, the results that PCT levels were significantly higher in participants that experienced a SSI compared to those without a SSI is concordant with other studies investigating the value of PCT in predicting postoperative complications, such as infection (Nahum et al., 2012; Macrina et al., 2005).

Nahum et al. (2012) utilized a nested case control study to investigate the use of procalcitonin to differentiate between bacterial and nonbacterial cause of fever of children who underwent cardiac surgery. Of 665 children that underwent cardiac surgery, 126 had postoperative febrile episodes, 47 with proven infection and 79 without bacterial infection. Procalcitonin levels were collected preoperative, post surgery and on POD 1, 2, and 5; and on the day a fever occurred. Sixty-eight children developed fevers during PODs 1-5, of which procalcitonin levels at fever day was significantly higher in those with bacterial infections ($n=16$) than in those without bacterial infection ($n=52$). Similarly, in 58 children whom fever occurred after the 5th POD a significant difference was found in procalcitonin level at fever day between those children with ($n=31$) and those without ($n=27$) bacterial infection (Nahum et al., 2012).

Surgical site infection and type of surgical procedure.

A one-way ANOVA was conducted to determine if there was a difference in the rate of SSIs between the three types of surgery that were performed. While there was no statistically significant difference for infection rates among the three treatment groups, exploration of the data revealed a significant difference in the overall SSI rates depending on the type of surgery performed. This study showed participants who underwent combined CABG and valve surgery had significantly higher rates of SSI compared to CABG surgery or valve surgery alone. This is consistent with Farzan et al. (2009) and

Sakamoto, Fukuda, Oosaka, and Nakata (2003), who found combined CABG and valve surgery was an independent risk factor for deep sternal wound infections. Combined procedures of CABG and valvular replacement or repair involve longer CPB times and aortic ischemic times. As such, this increased time on CPB increases the risks of complications, such as hypothermia, coagulopathies and bleeding that may add to increase SSIs postoperatively. This is yet another area for continued research.

Strengths

The experimental design was a major strength of the current study. The design was a multilevel, single factor, within-subjects design with patients nested within anesthesia provider teams. By counterbalancing the design with a Latin square, where each of three anesthesia provider teams dispensed each of three glycemic treatment conditions once, practice effects over the three treatment conditions occurred equally. There was no statistical difference, between the three glycemic protocol groups, in participant demographic characteristics, surgical characteristics, or preoperative baseline values for glycemic control. To minimize bias, the study team evaluating patients for SSIs, and ICU nurses were blinded to the glycemic treatment the patient received intraoperatively.

Limitations

There are noted limitations to the study. First, this study was conducted in a single center and the homogeneity of sample, primarily White, non-Hispanic males, limits the generalizability of the findings to the broader population. It is acknowledged that statistical power was not sufficient to draw conclusions on the effect of tight glycemic control on postoperative outcomes including SSI, CRP, PCT and ICU LOS. Recruitment

objectives were not met, and thus the sample size of 37 was insufficient. It is possible that with an appropriately powered study the use tight glycemic control would have yielded significantly lower PCT concentrations postoperatively and significantly lower SSIs. Since the present study was limited to the clinical usefulness of PCT for early detection of infection, variables that may explain this mechanism, such as plasma levels of endotoxin and cytokines, were not evaluated. The current study, for reasons of safety, used current ADA/AACE guidelines to define tight glycemic control compared to prior studies that defined tight glycemic control much lower. As such, this study had a smaller effect size between the tight and moderate glycemic protocols, and thereby lower statistical power.

Implications for Clinical Practice and Future Research

Effect of tight glycemic control on surgical site infections.

Despite a lower intraoperative mean blood glucose values in the tight glycemic group, there was no statistically significant difference in the SSIs between the treatment groups. While, the possibility that the current study was underpowered does exist, the findings are consistent with similar RCT (Chan et al., 2009; Gandhi et al., 2007; Lazar et al., 2011). Clearly, evidence supports maintaining perioperative blood glucose levels below 200 mg/dl, and several studies help make the argument that below 180 mg/dl is prudent. However, further investigation is needed to determine if the benefits of perioperative euglycemia (80-110 mg/dl) surpass the benefits of tight glycemic control (110-149 mg/dl), or even moderate glycemic control (150-180 mg/dl), and/or outweigh the risks of hypoglycemia. This study does add support that a tight glycemic control, defined as 110-149 mg/dl, can be safely achieved, during the intraoperative period, in

open-heart patients with little to no risk of hypoglycemia, if a judicious protocol is followed.

Effect of tight glycemic control on procalcitonin.

The effects of tight glycemic control on postoperative serum concentrations of PCT are currently unexplored in research. While this study did not show a significant difference in PCT concentrations between the three glycemic groups, the study was underpowered. A type II error may have occurred secondary to an insufficient sample size. The pattern produced, that of consistently lower procalcitonin levels in the tight glycemic group compared to the moderate glycemic groups, and an effect size that was moderate to large warrants further investigation with an appropriate sample size before conclusions are drawn. Replication of this study with an appropriate sample size would offer insight if tight glycemic control reduces postoperative procalcitonin levels, and if so, to what clinical benefit.

Additionally, the etiology for PCT induction in open-heart surgery is not completely understood. Generally, infection and/or bacterial endotoxins are a main stimulus for the induction of PCT. There is extensive array of possible stimuli, other than infection, that may contribute to PCT induction in open-heart surgery. Additional studies are needed to explore the impact of CPB on the immune response and activation of proinflammatory cytokines, as well as dysglycemia and risk of infection in open-heart patients.

Several studies have investigated the role of PCT as a predictor of postoperative complications like infection, in open-heart surgery. However, the cutoff value of PCT as a marker of infection remains a matter of debate. Prior research has shown conflicting

results with postoperative SSIs being diagnosed with PCT concentrations as low as 1 ng/ml, and no SSIs found in patients with PCT concentration exceeding 2 ng/ml.

Unfortunately, this study does not help to identify a reliable PCT concentration for the diagnosis of postoperative infection. Further RCTs are needed to determine the ideal PCT threshold, and timing, for the identification of postoperative SSIs compared to non-infectious systemic inflammatory response.

Finally, this study monitored postoperative SSIs until the sixth week post discharge, and found the majority of SSIs were superficial harvest site infections diagnosed post hospital discharge. Future studies are needed to investigate why PCT, an acute phase inflammatory biomarker, with a short half life, would be elevated in the immediate postoperative period (POD 1-5), when an infection did not surface until 3-7 weeks post the surgical event.

Effect of tight glycemic control on blood glucose levels.

Although this study was not able to conclude that tight intraoperative glucose control produced less postoperative SSIs, it should be noted that by introducing intraoperative blood glucose control, intraoperative hyperglycemia was avoided, which is an independent risk factor for mortality (Doenst et al., 2005). Furthermore, blood glucose levels on admission to the ICU, a surrogate of subsequent glucose control (Egi et al., 2006) was lower with the continuous insulin infusion groups compared to the intravenous insulin bolus group. By maintaining tight glycemic control with continuous insulin infusion in the operating room, ICU target blood glucoses are already at target or are reached more quickly (Lecomte et al., 2008) compared to several studies that focused

on glucose control only in the postoperative period (Goldberg et al., 2004; Van den Berge et al., 2001).

Additionally, there remains uncertainty if there is a time period more crucial for maintaining the tight glycemic control, whether preoperative, intraoperative, postoperative or post-hospital discharge. In this study, patients received the interventional treatments only during the intraoperative period, with all patients receiving the same glycemic protocol during the ICU phase. While the study monitored blood glucose levels during the intraoperative period and 6 hours postoperatively, it did not monitor the glycemic control throughout the rest of the hospitalization, nor post discharge. Because the majority of our participant's SSIs were diagnosed post hospital discharge, it is possible that glycemic control during ICU, ward, or post hospital discharge may have impacted the outcome of SSI.

Studies have investigated glycemic control in the preoperative, intraoperative, perioperative, and postoperative period, but there is yet to be a RCT that investigates glycemic control throughout all of these periods. It is not unreasonable to consider that it is the glycemic control throughout the entire pre, intra, and complete postoperative period that holds the key to improved outcomes. After all, even if plasma glucose levels are tightly controlled during a five hour surgery, what real impact will this have if the patient has poor glycemic control in longer periods preoperatively, postoperatively, and post-hospital discharge? Clearly, research supports that avoidance of severe hyperglycemia is important not only in the perioperative period, but also in the preoperative and late postoperative period, as patients' transition to the ward.

While this study investigated the effect of tight glycemic control on SSIs in open-heart surgery, it did not investigate the impact of insulin on the systemic immune response, which may offer critical insight to this research area. Studies have yet to elucidate if it is the plasma glucose level that offers the greatest impact or the amount of insulin delivered that produces improved outcomes. Studies have suggested that it is not the prevention of hyperglycemia that produces better postoperative outcomes, but rather the use of high doses of insulin that are utilized in providing tight glycemic control. Dandona, Thusu, Hafeez, Abdel-Rahman and Chaudhuri (1998) showed that 2 hours of insulin administration (2 IU/ hr) had similar anti-inflammatory effects as 100 mg of intravenous hydrocortisone. Chaudhuri et al. (2004) found low dose insulin had an anti-inflammatory, antioxidant and pro-fibrinolytic effect, independent of decreased blood glucose levels in patients with acute myocardial infarction. In the current study, the total amounts of insulin delivered to participants, were not measured. Of the three glycemic protocols, the tight glycemic protocol was designed to deliver higher doses of insulin compared to the conventional or standard group, but even so no clinical benefit was noted that would have suggested anti-inflammatory effects of insulin. Further research is needed in this area.

Lastly, the history of glycemic control in critically ill patients, including open heart patients, provides us with much to consider on how practitioners should critically assess changes made in the national standards of care and practice guidelines. The widespread acceptance of tight glycemic control, and the extrapolation of successful postoperative protocols into the perioperative period, in 2004, was based primarily on observational studies. Observational studies have inherent problems, most serious of

which is selection bias, which may lead to biased estimates of the treatment effects. Even the best observational designs, that attempt to control for selection bias, cannot control for unobserved differences in patient characteristics.

With the addition of a greater number of RCTs, in the last 5 years, it has become increasingly evident that tight glycemic control, actually euglycemia, advocated in 2004 may have been too precipitous. The dramatic clinical improvements seen with tight glycemic control in observational designs has not been reproducible with RCTs. Until more evidence, in the form of RCTs, is available prudent recommendation are for more conservative glycemic control in the critically ill patient, including open-heart surgery. Currently, ADA and AACE joint statement is to maintain serum blood glucose levels between 110-180 mg/dl.

Conclusion

Tight glycemic control, during the intraoperative period, did not reduce the incidence of postoperative SSIs; decrease ICU LOS, or lower serum concentrations of inflammatory biomarker PCT. Intraoperative tight glycemic control also did not significantly lower blood glucose levels or improve glycemic stability during the intraoperative period. Elevated intraoperative peak blood glucose levels were associated with an increased risk of SSI. As such, this study offers support to current guidelines that recommend maintaining blood glucose levels below 180 mg/dl with the use of continuous insulin infusion compared to intravenous bolus injections in open-heart surgical patients. Additionally, this study showed the use of tight glycemic control during the intraoperative period can be achieved safely, with the use of judicious protocols. Patients that undergo combined CABG and valve surgery are at an increased risk of developing a

SSI compared to patients who undergo CABG or valve replacement surgery alone. This study also showed PCT was an early marker of infection, where CRP was not. Addition of PCT to routine postoperative blood work in open-heart patients may benefit providers in the diagnosis and early treatment of SSIs.

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APPENDICES

Appendix A: Biographical Data & Intraoperative Worksheet

ID #: _____

Data Collector _____

Date: _____

Age: _____

Initial Vital Signs: (data taken morning of surgical day)

BP _____ HR _____ Respiration _____ Pulse oximetry _____ Temp _____

Height _____ (in) Weight _____ (Kg) Date of Birth _____

1. Interventional Arm

[1] Tight

[2] Conventional

[3] Standard

2. Race

[1] Caucasian

[2] African American

[3] Asian

[4] American Indian/Alaska Native

[5] Native Hawaiian/ Pacific Islander

[6] Mixed (please specify) _____

[7] Other (please specify) _____

3. Ethnicity

[1] Hispanic

[2] Non Hispanic

4. Gender

[1] Male

[2] Female

Only list the disease process if the patient has been diagnosed in computerized patient record system (CPRS)

5. Diabetes Mellitus Diagnosis

[0] None

[1] Type I

[2] Type II Oral Agent

[3] Type II Oral Agent & Insulin

[4] Type II Insulin only

6. MI History

[0] No

[#] Yes

Total # _____

Date of Last MI _____

7. PVD History

[0] No

[1] Yes

8. Cerebral Vascular Disease

[0] No

- [#] Yes
 Total # _____
 Date of Last CVA _____
9. Hypertension History
 [0] No
 [1] Yes
10. Chronic Obstructive Pulmonary Disease (COPD)
 [0] No
 [1] Yes
11. Renal Insufficiency History (creatinine > 1.5 mg/dl)
 [0] No
 [1] Yes
12. Prior Open-heart Surgery
 [0] No
 [#] Yes
 Total # _____
 Date of Last OHS _____
13. Pre operative Labs: Hemoglobin _____
 Hematocrit _____
 WBC _____
 RBC _____
 Platelets _____
 Sodium _____
 Potassium _____
 Chloride _____
 Glucose _____
 BUN _____
 Creatinine _____
 Calcium _____
 Alkaline Phosphatase _____
 AST _____
 ALT _____
 Cholesterol _____
 Triglycerides _____
 HbA1C _____
14. DOS Labs: ISTAT ABG pH _____
 PaO2 _____
 PaCO2 _____
 HCO3 _____
 ABE _____
 Sodium _____
 Potassium _____
 Calcium _____
 Glucose _____

16. Hospital Admission Date _____
17. Surgery Date _____
18. ICU Admission Date _____
19. ICU Discharge Date _____
20. Hospital Discharge Date _____

21. Preoperative Medication for Diabetes

22. Surgeon's Preoperative Mortality _____ %

Total # grafts_____

27. CABG Bypass Harvest Site

- [0] None
- [1] IMA
- [2] Radial
- [3] Saphenous (open technique)
- [4] Saphenous (endoscopic technique)
- [5] IMA/ Saphenous (open technique)
- [6] IMA/Saphenous (endoscopic technique)
- [7] IMA/ Radial
- [8] IMA/ Radial/Saphenous (open)
- [9] IMA/ Radial/Saphenous (endoscopic)
- [10] Radial/Saphenous (open)
- [11] Radial/Saphenous (endoscopic)

28. ASA Classification

- [1] ASA 1
- [2] ASA 2
- [3] ASA 3
- [4] ASA 4
- [5] ASA 5

29. Surgical Priority

- [1] Elective
- [2] Urgent

30. Operating Room Start Time _____

31. Operating Room Stop Time _____

Please circle 1-3 if the patient is on inotropic or vasopressor support in the post bypass period. This is defined as when the patient leaves the operating room. If the patient needed a vasopressor or inotrope temporarily to wean from bypass but is off the agent prior to leaving the operating room circle 0 for no support needed.

32. Inotropic or vasopressor support postoperatively

- [0] None
- [1] 1 agent
- [2] 2 agents
- [3] more than 2 agents

33. Cardiopulmonary Bypass

- [0] No
- [1] Yes
 - [1a] planned
 - [1b] unplanned

34. Cardiopulmonary Start Time _____

35. Cardiopulmonary Stop Time _____

36. Aortic Clamp Start Time _____

37. Aortic Clamp Stop Time _____

Intraoperative Phase: Blood Glucose (BG) testing begins with the first BG drawn immediately after induction of anesthesia in the operating room (30 minutes post blood

glucose drawn in pre-anesthesia holding area). Blood glucose levels will be drawn every 30 minutes after with ISTAT monitoring.

BG 1	Intervention
BG2	Intervention
BG3	Intervention
BG 4	Intervention
BG 5	Intervention
BG 6	Intervention
BG 7	Intervention
BG 8	Intervention
BG 9	Intervention
BG 10	Intervention
BG 11	Intervention
BG 12	Intervention
BG 13	Intervention
BG 14	Intervention
BG 15	Intervention
BG 16	Intervention
BG 17	Intervention
BG 18	Intervention
BG 19	Intervention
BG 20	Intervention

C-reactive Protein (CRP) and Procalcitonin (PCT) will be drawn upon successful separation from cardiopulmonary bypass. If cardiopulmonary bypass is not utilized in the open-heart surgical procedure CRP and PCT will be drawn at the end of surgery

31. CRP Post pump

32. PCT Post pump

Appendix B: Postoperative Intensive Care Worksheet

Data Collector _____

Date _____

ID # _____

Please complete the following vital statistics data upon admission to the ICU.

1. Blood Pressure _____
2. Heart Rate _____
3. Respiration _____
4. Pulse oximetry _____
5. Temperature _____

Blood Glucose (BG) should be measured immediately upon arrival into ICU and every 30 minutes after for six hours. Blood glucose testing should be completed by utilizing blood drawn from the arterial line and tested with the designated study glucometer. Intervention for glycemic control will be the standard ICU protocol that is currently approved.

- | | |
|-----------------------------------|--------------------|
| 1. BG initial _____ | Intervention _____ |
| 2. BG 30 minutes _____ | Intervention _____ |
| 3. BG 60 minutes (1 hr) _____ | Intervention _____ |
| 4. BG 90 minutes (1.5 hr) _____ | Intervention _____ |
| 5. BG 120 minutes (2 hr) _____ | Intervention _____ |
| 6. BG 150 minutes (2.5 hr) _____ | Intervention _____ |
| 7. BG 180 minutes (3 hr) _____ | Intervention _____ |
| 8. BG 210 minutes (3.5 hr) _____ | Intervention _____ |
| 9. BG 240 minutes (4 hr) _____ | Intervention _____ |
| 10. BG 270 minutes (4.5 hr) _____ | Intervention _____ |
| 11. BG 300 minutes (5 hr) _____ | Intervention _____ |
| 12. BG 330 minutes (5.5 hr) _____ | Intervention _____ |
| 13. BG 360 minutes (6 hr) _____ | Intervention _____ |

ICU Labs will be drawn upon admission into the ICU from the surgical suite and sent to the main laboratory at the study site.

1. Hemoglobin _____
2. Hematocrit _____
3. WBC _____
4. RBC _____
5. Platelets _____
6. Sodium _____
7. Potassium _____
8. Chloride _____
9. Glucose _____
10. BUN _____
11. Creatinine _____

Appendix C: Postoperative Worksheet Wound Visit

Data Collector _____

Date _____

ID # _____

Vital statistic to be measured the visit day.

1. Blood Pressure _____
2. Heart Rate _____
3. Respiration _____
4. Pulse oximetry _____
5. Temperature _____
6. Postoperative Visit Phase
 - [1] ICU (immediate postop)
 - [2] Ward (prior to hospital discharge)
 - [3] Clinic Visit 1 (2 weeks postop)
 - [4] Clinic Visit 2 (6 weeks postop)

The following questions should be based on the superficial or deep surgical site infection criteria set by the CDC.

7. Harvest Surgical Site Infection
 - [0] No
 - [1] Yes
8. Harvest Surgical Site Infected
 - [0] No
 - [1] Saphenous
 - [2] Radial
9. Sternal Surgical Site Infection
 - [0] No
 - [1] Yes
10. Superficial Surgical Site Infection (please select all criteria that apply)
 - [0] No
 - [1] Superficial Infection: Purulent drainage from superficial incision
 - [2] Superficial Infection: organisms isolated from aseptic culture of tissue/fluid
 - [3] Superficial Infection: Pain at the surgical site
 - [4] Superficial Infection: Tenderness at the surgical site
 - [5] Superficial Infection: Redness at the surgical site
 - [6] Superficial Infection: Heat at the surgical site
 - [7] Superficial Infection: Incision opened by surgeon and/or culture positive
 - [8] Superficial Infection: A diagnosis of superficial Incision Infection by surgeon
11. Superficial Infection: Primary (A superficial incisional infection that is identified in the primary incision in a patient who has had an operation with one or more incisions (chest incision for CABG surgery with a donor site))
 - [0] No
 - [1] Yes

12. Superficial Infection: Secondary: A superficial incisional secondary infection that is identified in the secondary incision in a patient who has had an operation with more than one incision (donor site incision for CABG)

[0] No

[1] Yes

13. Deep Surgical Site Infection (Please select all criteria that apply)

[0] No

[1] Purulent drainage from superficial incision

[2] Deep Infection: organisms isolated from aseptic culture of tissue/fluid

[3] Deep Infection: Spontaneous dehiscence

[4] A diagnosis of deep Incision Infection by surgeon

[5] Abscess by histopathologic, radiologic

[6] Deep Infection: Incision opened by surgeon and/or culture positive

If one of the following signs are present

[a] Fever

[b] Localized Pain

[c] Localized Tenderness

14. Deep Infection: Primary. A deep incisional infection that is identified in the primary incision in a patient who has had an operation with more than one incision (chest incision for CABG surgery with a donor site)

[0] No

[1] Yes

15. Deep Infection: Secondary. A deep incisional secondary infection that is identified in the secondary incision in a patient who has had an operation with more than one incision (donor site incision for CABG)

[0] No

[1] Yes

16. Labs

Hemoglobin _____

Hematocrit _____

WBC _____

RBC _____

Platelets _____

Sodium _____

Potassium _____

Chloride _____

Glucose _____

BUN _____

Creatinine _____

Calcium _____

Appendix D: Postoperative Laboratory and Temperature Monitoring

Please document the peak temperature in a 24 hour period starting on postoperative day (POD) 1 and continuing through POD 6. The 24 hour period will start at 6:00 am the morning after surgery and end at 5:59 am the second day after surgery.

1. POD 1 Peak Temperature _____
2. POD 2 Peak Temperature _____
3. POD 3 Peak Temperature _____
4. POD 4 Peak Temperature _____
5. POD 5 Peak Temperature _____
6. POD 6 Peak Temperature _____

C-reactive Protein (CRP) will be drawn with the scheduled morning laboratory collection starting postoperative day 1 continuing through postoperative day 6.

7. CRP 1 _____
8. CRP 2 _____
9. CRP 3 _____
10. CRP 4 _____
11. CRP 5 _____

Procalcitonin (PCT) will be drawn with the scheduled morning laboratory collection starting postoperative day 1 and continuing through postoperative day 6.

12. PCT 1 _____
13. PCT 2 _____
14. PCT 3 _____
15. PCT 4 _____
16. PCT 5 _____

Appendix E: Institutional Review Board Approval



April 25, 2008

Sierra Gower, CRNA, MS, ARNP
College of Nursing
MDC 22

RE: **Full Board Approval** for Initial Review

IRB#: 106219

Title: *The Effect of Intraoperative Tight Glycemic Control on Surgical Site Infection Rates in Patients Undergoing Coronary Artery Bypass Graft Surgery*

Study Approval Period: 04/15/2008 to 01/26/2009

Dear Ms. Gower:

On January 28, 2008, Institutional Review Board (IRB) reviewed and **APPROVED** the above application **for the period indicated above** including the following:

- 1) Informed Consent Form (Rev #5 revision date 2-22-08).
- 2) Research proposal.

Please note, if applicable, the **enclosed informed consent/assent documents are valid during the period indicated by the official, IRB-Approval stamp located on page one of the form.** Valid consent must be documented on a copy of the most recently IRB-approved consent form. Make copies from the enclosed original.

Please reference the above IRB protocol number in all correspondence regarding this protocol with the IRB or the Division of Research Integrity and Compliance. In addition, we have enclosed an Institutional Review Board (IRB) Quick Reference Guide providing guidelines and resources to assist you in meeting your responsibilities in the conduction of human subjects research. Please read this guide carefully. It is your responsibility to conduct this study in accordance with IRB policies and procedures and as approved by the IRB.

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