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Intensive Glycemic Control in Cardiac Surgery

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Abstract Hyperglycemia has been found to be associated with increased morbidity and mortality in surgical patients, yet, the optimal glucose management strategy during the perioperative setting remains undetermined. While much has been published about hyperglycemia and cardiac surgery, most studies have used widely varying definitions of hyperglycemia, methods of insulin administration, and the timing of therapy. This has only allowed investigators to make general conclusions in this challenging clinical scenario. This review will introduce the basic pathophysiology of hyperglycemia in the cardiac surgery setting, describe the main clinical consequences of operative hyperglycemia, and take the reader through the published material of intensive and conservative glucose management. Overall, it seems that intensive control has modest benefits with adverse effects often outweighing these advantages. However, some studies have indicated differing results for certain patient subgroups, such as nondiabetics with acute operative hyperglycemia. Future studies should focus on distinguishing which patient populations, if any, would optimally benefit from intensive insulin therapy.

Keywords Hyperglycemia · Cardiac surgery · Glucose management · Outcomes

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Introduction

The optimal management of glucose levels for hyperglycemic cardiac surgery patients has been widely debated, with conflicting evidence from various observational and randomized controlled studies. Due to multiple proposed factors, hyperglycemia is seen in up to 80 % of patients after cardiac surgery [1, 2] and 40 % of patients with acute coronary syndrome and heart failure [3]. With this vast prevalence, investigating the potential negative impact of hyperglycemia and the benefits or drawbacks of intensive glycose control on clinical outcomes is of particular importance. Diabetes mellitus is a known independent predictor for increased morbidity and mortality following cardiac surgery [4–7]. Hyperglycemia has been found to be associated with increased rates of morbidity and mortality in both medical and surgical patients [8–13]. However, there is no consensus on how hyperglycemia should be controlled in a cardiovascular inpatient setting. Part of this controversy stems from the lack of a clear definition of glycemic cut-off values in the field [10].

As of 2009, the Society of Thoracic Surgeons (STS) guidelines recommend continuous insulin infusion with a treatment goal of glucose <180 mg/dL intraoperatively [14, 15]. Most of the existing research in the field attempts to establish whether intensive or conventional glycemic control results in better clinical outcomes. The lower limits of intensive glycemic control have been defined as 80 to 100 mg/dL, and the upper limits have been defined as 100 to 140 mg/dL. For conventional glycemic control, the lower and upper limits have ranged from 110 to 141 mg/dL and 140 to 200 mg/dL, respectively. Thus, what is considered intensive control by some studies is regarded as conventional by others. The various different parameters used in these studies have created difficulty in determining a consensus on optimal glucose levels for cardiac surgery patients.

As such, this review aims to elucidate the effects of hyperglycemia and provide an integrated review of the most relevant studies on conservative versus intensive glycemic control specifically in cardiac surgery patients.

Pathophysiology of Hyperglycemia

Until recently, hyperglycemia during critical illness was perceived as a harmless or beneficial adaptive stress response [10, 16, 17]. Often, high glucose levels were not treated until they exceeded the renal threshold of 220 mg/dL [10]. This elevation in glucose was postulated to be a normal phenomenon caused by the interplay of various regulatory factors including cortisol, glucagon, growth hormone, and cytokines [16, 17]. It was even proposed that stress hyperglycemia was associated with lower ICU mortality mainly in patients with septic shock and cardiac comorbidities [17].

However, a vast body of contemporary evidence shows that dysglycemia has multifactorial effects on the metabolic and inflammatory states of the myocardium and the body as a whole that may contribute to adverse clinical outcomes [18]. In addition to causing direct cellular toxicity and increased apoptosis, hyperglycemia can have negative consequences for immunity, vascular function, metabolism, and wound healing [10]. Cells that uptake glucose independent of insulin, such as those comprising the nervous system, liver, vasculature, and immune system, are most drastically affected [10].

Inflammation is the underlying mechanism of the adverse cellular effects of hyperglycemia. By forming advanced glycation end products, hyperglycemia triggers a systemic inflammatory response [19]. There is then increased the production of pro-inflammatory cytokines such as TNF-α and IL-6 [20]. This inflammation impacts vascular function by causing endothelial dysfunction and thrombogenesis [13]. Hyperglycemia creates an imbalance between nitric oxide bioavailability and creation of damaging reactive oxygen species in the mitochondria [10, 13]. Overall metabolism is additionally altered by impaired free fatty acid processing leading to acute dyslipidemia [13]. Furthermore, altered leukocyte function including impaired neutrophil adhesion and phagocytosis as well as glycation of circulating immunoglobulins increases the risk of sepsis and infection [10, 21].

Hyperglycemia and Cardiopulmonary Bypass

Hyperglycemia has been commonly noted in cardiac surgery patients, especially those undergoing cardiopulmonary bypass (CPB) [10, 22–24]. A combination of surgical stress, release of catecholamines, increased catabolism, and treatment with glucose-containing cardioplegia predisposes these patients to dysglycemia [10, 22]. Studies comparing on-pump and off-pump coronary artery bypass graft (CABG) show that CPB has a negative influence on glucose homeostasis and that hypothermia exacerbates this effect [25]. Glucose range, peak glucose level, and percent of patients with very high glucose levels were all adversely affected by the use of CPB in both diabetic and non-diabetic patients [25]. The amount of exogenous insulin required to maintain the same blood glucose level is reduced in patients receiving CABG without CPB [26].

The trauma of surgery itself causes increased cortisol secretion, which promotes hyperglycemia through its effects on glycolysis, gluconeogenesis, lipolysis, and proteolysis [27]. Additionally, CPB in cardiac surgery causes increased catabolism, metabolic uncoupling, and inflammation [26, 28, 29]. Changes in the insulin-like growth factor (IGF) system may explain these changes in catabolism [26]. CPB generates reactive oxygen species leading to mitochondrial dysfunction and metabolic uncoupling that creates a positive feedback cycle between hyperlactemia and hyperglycemia [28]. The systemic inflammation that CPB initiates is mediated by the release of cytokines such as IL-6, IL-8, and TNF-α [29].

Interestingly, the intensity of the inflammatory response is positively correlated with surgical complexity, suggesting that this effect is particularly important in patients with multiple comorbidities [29]. Although these mechanisms have all been implicated in the dysregulation of glucose balance after cardiac surgery, studies have implicated a complex, multifactorial relationship between inflammation and CPB that requires further elucidation [29].

Clinical Consequences of Hyperglycemia

Many reports have substantiated the detrimental effects of hyperglycemia on clinical outcomes in postoperative and critically ill patients [10, 30, 31]. Longer duration and higher levels of hyperglycemia have been associated with increased morbidity and mortality [10].

Mortality

Hyperglycemia is a predictor of mortality in all hospital-admitted patients, including those undergoing cardiac and general surgery as well as those requiring intensive care [30, 32–34]. For all admitted patients, those with new hyperglycemia had a higher in-hospital mortality of 16 % compared with 3 % for those with a history of diabetes and 1.7 % for those with normoglycemia [32]. Whitcomb et al. found that in ICU patients there was 10.4 % mortality in those with hyperglycemia and 8 % mortality in those without hyperglycemia [30]. The overall unadjusted odds ratio for death based on the presence of hyperglycemia was 1.42 (95 % confidence interval = 1.09, 1.86) [30]. Patients with hyperglycemia receiving gastric and colon surgery also had a higher rate of unadjusted mortality (1.5 vs. 0.6 %) [33]. In cardiac surgery patients, mortality was less than 2 % when peak glucose level remained

below 360 mg/dL [34]. However, when peak glucose levels exceeded 360 mg/dL, mortality rates tripled [34]. This association between mortality and hyperglycemia was seen both in patients with and without pre-existing diabetes [34].

Morbidity

Studies have found an association between hyperglycemia and multiple adverse outcomes including sepsis, mediastinitis, prolonged mechanical ventilation, cardiac arrhythmias, longer ICU stay, and longer hospital stay [10]. Other negative effects of hyperglycemia include reduced ischemic preconditioning, impaired development of collaterals post-myocardial infarction, cerebral edema, and disruption of the blood brain barrier [8, 10, 35]. Umpierrez et al. studied 1886 hospital-admitted patients and found that hyperglycemic patients were more likely to be admitted to the ICU than normoglycemic patients (29 vs. 9 %) and had a longer length of stay (9.7 ± 0.7 days vs. 4.5 ± 0.1 day) [32]. Kwon et al. showed a similar correlation in general surgery patients, with hyperglycemic patients having a longer length of stay (6 ± 8.5 days vs. 5.3 ± 7.4 days) and lower likelihood of being discharged to home (91.5 vs. 94.9 %) [33]. Hyperglycemia was also associated with a twofold higher risk of infection and a higher rate of reoperative intervention (4.4 vs. 3.1 %) [33].

For cardiac surgery patients in particular, blood glucose level has been shown as a predictor of negative clinical outcomes in both diabetic and non-diabetic patients such as stroke, infection, and myocardial infection [34]. Gandhi et al. found that above a concentration of 100 mg/dL, each 20 mg/dL increase in mean intraoperative glucose showed a greater than 30 % increase in the occurrence of adverse events including pulmonary and renal complications [31]. There was a linear relationship between glucose level and likelihood of postoperative complications with an event rate of 38 % for glucose less than 100 mg/dL and 76 % for glucose greater than 200 mg/dL [31]. Another study correlated immediate postoperative glucose levels with risk of infection, atrial fibrillation, heart failure, myocardial infarction, pericarditis, neurologic complications, and pulmonary complications [36]. Patients with glucose levels <200 mg/dL had a 13 % risk of complications, while those with ≥200 mg/dL had a 36 % risk, and those with ≥250 mg/dL had a 63 % risk [36].

Hypoglycemia

Although hyperglycemia has detrimental effects, the opposite extreme of hypoglycemia can be equally dangerous. Similar to hyperglycemia, hypoglycemia causes a pro-inflammatory state and an increased sympathoadrenal response with the release of catecholamines and production of cytokines [8, 37]. Hypoglycemia also results in endothelial dysfunction, coagulation changes, and activation of the renin-angiotensin-aldosterone system with accompanying vasoconstriction, tachycardia, and vascular remodeling [8]. Adrenergic symptoms and cognitive dysfunction begin to occur at glucose levels of 55 and 45 mg/dL, respectively [23]. Likely due to these physiological alterations, hypoglycemia is independently associated with increased mortality, longer hospital stay, higher rates of ICU admission, increased infection risk, impaired wound healing, and increased occurrence of cardiac arrhythmias in critically ill patients [8, 35, 37–39].

Maintaining a Balance: Intensive versus Conventional Glucose Control

Evidence in Critically Ill Patients

Since both hyperglycemia and hypoglycemia are linked to adverse clinical outcomes, the optimal management of glucose concentrations in critically ill patients has been controversial. Part of this controversy has stemmed from the wide variety of study designs and diverse definitions of hypoglycemia and hyperglycemia.

In 2001, the prospective, randomized, controlled Leuven Surgical Trial triggered a period of protocols that favored intensive glucose control [13]. This study included 1548 patients in the surgical intensive care unit, with 63 % of the cohort receiving cardiac surgery [2]. Hyperglycemia was defined as a glucose concentration above 215 mg/dL for the conventional group and 110 mg/dL for the intensive group [2]. Insulin infusions were adjusted to maintain a range of 180 to 200 mg/dL for the conventional group and 80 to 110 mg/dL for the intensive group [2]. Van den Berghe et al. found a 32 % reduction in mortality of critically ill patients with intensive glucose control when compared with conventional glucose control (4.6 vs. 8 %) [2]. Additionally, intensive glucose control showed reduced duration of intensive care, decreased necessity of prolonged ventilation, and lower risk of sepsis [2]. After this study, insulin infusion therapy for tight glucose control became the standard of care for critically ill patients [13].

This standard ended in 2009 when the NICE-SUGAR study came to the forefront [13]. In contrast to the results produced by van den Berghe et al., the NICE-SUGAR investigators found that intensive glucose control actually increased mortality in medical and surgical ICU patients [40]. The NICE-SUGAR study was a prospective, randomized, controlled trial with 6104 patients (37 % surgical patients). Intensive glucose control was defined as blood glucose of 81 to 108 mg/dL and conventional glucose control as blood glucose of less than 180 mg/dL. The intensive group had 27.5 % 90-day mortality while the conventional group had 24.9 % 90-day mortality ($p = 0.02$) [40]. However, there were no differences in other clinical outcomes including length of stay, organ failure rate, days of mechanical ventilation, or transfusion.

The implications in the NICE-SUGAR trial led many clinicians to favor a more conservative approach to blood sugar management in recent years.

There are several theories that strive to explain the discrepancy among the Leuven and NICE-SUGAR trials. The NICE-SUGAR study used a unique treatment algorithm that was standardized via central servers at multiple institutions [40]. This may have produced a specific effect not seen in other studies. The authors of NICE-SUGAR also observe that their trial had a longer follow-up period and greater statistical power than most other trials, suggesting that detrimental effects may require time to appear. Finally, patients in the NICE-SUGAR trial received predominantly enteral nutrition whereas patients in the Leuven study received a high percentage of parenteral nutrition, implying differential results based on method of nutrition [40].

Supporting this theory, a meta-analysis by Marik et al. analyzed seven randomized controlled trials in ICU settings with a total of 11,425 patients [41]. Marik et al. found that intensive glycemic control did not reduce incidence of 28-day mortality, blood stream infections, or renal replacement therapy [41]. Additionally, the rate of hypoglycemia was significantly higher in patients with intensive glucose control. Interestingly, a meta-regression showed a significant correlation between proportion of parenteral calories and 28-day mortality ($p = 0.005$) [41]. In fact, when the Leuven trials were excluded from the meta-analysis, mortality was lower in the conventional control patients (OR = 0.90; 95 % CI = 0.81–0.99. $p = 0.04$) [41]. This perhaps suggests that intensive glucose control can be harmful in patients receiving enteral nutrition.

Evidence in Surgical Patients

There have been some studies conducted in gastric, gynecologic, and transplant surgery patients regarding optimal glucose control. Two previous studies in gastrectomy patients both used intensive glucose parameters of 80 to 110 mg/dL and a conventional glucose parameter of <200 mg/dL [42, 43]. Yuan et al. included 212 diabetic patients who received enteral nutrition while Cao et al. included 248 non-diabetic patients who received parenteral nutrition. Yuan et al. found that surgical site infection rates were lower in the intensive control group (4.7 vs. 13.2 %, $p < 0.03$) [42]. However, rates of mortality, bleeding, delayed gastric emptying, obstruction, hepatic dysfunction, renal dysfunction, and circulatory complications were the same in the intensive and conventional groups [42]. In contrast, Cao et al. showed that the intensive glucose therapy decreased overall postoperative complications (25.2 vs. 13.6 %, $p = 0.024$) including wound infection, intra-abdominal infection, sepsis, urinary tract infection, pneumonia, pseudomembranous colitis, and anastomotic leakage [43]. The authors postulated that the suppression of insulin resistance and upregulated expression of HLA-DR on monocytes accounted for the improved outcomes of intensive control [43].

Similarly, Al-Niaimi et al. conducted a study in 372 patients undergoing gynecologic oncology surgery [44]. Patients who had diabetes or who has blood glucose >150 mg/dL postoperatively received intensive control using continuous IV insulin infusion with a target of 90 to 139 mg/dL [44]. This group was compared to patients who received conventional sliding scale insulin with a target of <200 mg/dL [44]. Patients treated with intensive insulin therapy had a lower rate of surgical site infection than those treated with conventional therapy (19 vs. 29 %, $p = 0.001$) [44].

In 104 renal transplant patients with diabetes or impaired glucose tolerance, Hermayer et al. found that intensive insulin control resulted in no significant difference in delayed graft function [45]. However, nine out of the 11 observed rejection episodes occurred in the intensive control group.

Evidence in Cardiac Surgery

Given the clearly conflicting results in critically ill patients and patients undergoing surgery other than cardiac described above, it is perhaps not surprising that consensus is far from reached in cardiac surgery in terms of glucose management. The current guidelines for glycemic control in a hospital setting vary by organization [15]. The American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE) recommend initiating insulin therapy for glucose >180 mg/dL with a target level of 140 to 180 mg/dL [46]. Under this guideline, they suggest that more strict goals of 110 to 140 mg/dL may be appropriate for some patients [46]. The American College of Physicians recommends against intensive insulin control and suggests a target glucose of 140 to 200 mg/dL [47]. The Critical Care Society, on the other hand, states that patients with glucose >150 mg/dL should be treated to maintain a glucose <150 mg/dL [48]. Specific to adult cardiac surgery patients, the Society of Thoracic Surgeons (STS) recommends continuous insulin infusion with a treatment goal of glucose <180 mg/dL during surgery [14].

For cardiac surgery in particular, there is mixed evidence indicating the benefits and drawbacks of intensive blood glucose control. Among these studies, there have been multiple patient populations, blood glucose targets, and strategies for control. Patient populations include diabetics and non-diabetics; blood glucose targets change by the study; and strategies for control compare continuous versus subcutaneous insulin. The methodology and aims of each study are so different that comparison becomes difficult. Some of the key studies and their findings are summarized in Table 1.

Table 1 A summary of main studies of intensive vs conservation glucose management in cardiac surgery patients

Study	Number of patients	Type of surgery	Diabetic/Non-diabetic	Glucose targets (mg/dL)	Mode of treatment: continuous insulin infusion (CII)/ subcutaneous (SC)	Main findings
Furnary 2003	3554	CABG	Diabetic	SC: <200 CII: 1991–1998 150–200; 1999–2000 125–175; 2001 100–150	CII vs. SC	CII (2.5 %) had reduced mortality compared to SC (5.3 %), $p < 0.0001$
Blaha 2015	2383	CABG, AVR, MVR, TVR, thoracic aortic surgery, pulmonary endarterectomy	Both	80–110	CII	Initiating insulin perioperatively (23.2 %) reduced complications compared to postoperatively (34.1 %), RR = 0.68
Gandhi 2007	400	Procedures with CPB	Both	Intensive: 80–100 Conventional: <200	CII	Morbidity, length of ICU/hospital stay same for intensive vs conventional control
Mulla 2014	1325	CABG, valve replacementrepair	Both	Intensive: 80–110 Conventional: 110–140	CII	30-day mortality, long-term mortality, complication rates same for intensive vs conventional control
Saager 2015	198	Procedures with CPB	Both	Intensive: 80–110 Conventional: <150	CII	Delirium more likely in intensive control (RR = 1.89, $p = 0.03$)
Desai 2012	189	CABG	Both	Intensive: 90–120 Conventional: 121–180	CII	Prolonged ventilation, deep sternal wound infection, pneumonia, perioperative renal failure, operative mortality same for intensive vs conventional control
Pezzella 2014	189	CABG	Both	Intensive: 90–120 Conventional: 121–180	CII	No difference in 40 month mortality or health-related quality of life for intensive vs. conventional control
Lazar 2011	82	CABG	Diabetic	Intensive: 90–120 Conventional: 120–180	CII	No difference in incidence of major adverse events for intensive vs conventional control. Increased incidence of hypoglycemia with intensive control (4 vs. 30, $p < 0.0001$)
Umpierrez 2015	302	CABG	Both	Intensive: 100–140 Conventional: 141–180	CII	Complications, length of stay, readmission rates same for intensive vs conventional control; Non-diabetic patients had lower complication rate with intensive (34 %) vs. conventional (55 %) control, $p = 0.008$

Trials Comparing Continuous Infusion with Sliding Scale Insulin

In several studies, a continuous insulin infusion protocol has been compared with a conventional sliding scale method. The use of continuous insulin infusion was found to be associated with lower mortality and significant reduction in the incidence of deep sternal wound infection for diabetics after cardiac surgery [18, 49]. Furnary et al. conducted a retrospective review of 3554 diabetic patients undergoing isolated CABG and found continuous insulin infusion to be more effective in controlling postoperative hyperglycemia than subcutaneous insulin injections. Patients who received continuous insulin infusion had a 57 % reduced perioperative absolute mortality (2.5 vs. 5.3 %, $p < 0.0001$) [18]. Cardiac-related mortality occurred at a significantly higher rate in the subcutaneous insulin group (4.2 vs. 1.6 %, $p < 0.001$), suggesting that the myocardium may underlie the mechanism behind the effect of insulin control on mortality. However, it should be noted that patients enrolled in this study were treated sequentially (subcutaneous insulin was used in years 1987–91 whereas continuous infusion in years 1991–2001), and there were several changes in the protocol spanning the study period, so confounding factors were likely present.

Despite these concerns, the findings reported by Furnary et al. have been supported by a recent meta-analysis of ten studies comprised of four randomized controlled trials and seven cohort studies [50], including diabetic cardiac surgery patients. The meta-analysis found that using a continuous insulin infusion to maintain blood glucose levels ≤200 mg/dL significantly decreased postoperative infection rates after cardiac surgery (OR = 0.35, $p < 0.00001$) [50]. In some studies, continuous insulin infusion was associated with a trend indicating lower 30 day readmission rates [50]. The studies included in this meta-analysis had protocols initiating insulin treatment in all stages of the perioperative period. Many of them were conducted at single institutions on small sample sizes with the patient population consisting of mostly middle-aged men (62 to 80 % male, average age 57 to 67.4 years) [50]. Therefore, care should be taken in generalizing these results to a broader patient population.

Trials Comparing Timing of Insulin Administration

Few studies have sought to determine the optimal timing for initiation of insulin therapy [51]. Blaha et al. conducted a single center randomized controlled trial with 2383 cardiac surgery patients undergoing CABG, aortic valve replacement, mitral valve replacement, tricuspid valve replacement or repair, thoracic aortic surgery, and pulmonary endarterectomy [51]. The patients were divided into two groups, either receiving treatment perioperatively or postoperatively with a target glucose range from 80 to 110 mg/dL [51]. In the perioperative protocol, insulin was started when glucose reached over 110 mg/dL at any time from the beginning of surgery [51]. In the postoperative protocol, insulin was started after admission to the ICU and when glucose reached over 180 mg/dL intraoperatively [51]. For both groups, insulin therapy was given until the end of the ICU stay or until oral intake was restored. Blaha et al. discovered that initiating therapy perioperatively reduced postoperative complications (23.2 vs. 34.1 %, 95 % CI = 0.60–0.78) [51]. This effect was seen most prominently in non-diabetic patients with a risk reduction of 37 % (21.3 vs. 33.7 %, RR = 0.63, 95 % CI = 0.54–0.74) [51]. However, there was no significant benefit in diabetic patients [51]. The reduction in complications was attributed to a decrease in neurological and infectious factors. These findings imply that glucose control intraoperatively and timing of insulin therapy may have important consequences for clinical outcomes.

Trials Comparing Intensive versus Conventional Glucose Targets

When directly comparing intensive versus conventional glucose control, multiple studies have showed no significant differences in clinical measures. Gandhi et al. randomly assigned 400 cardiac surgery patients undergoing on-pump procedures to intraoperative intensive continuous insulin infusion with glucose levels between 80 to 100 mg/dL or conventional insulin therapy with glucose levels under 200 mg/dL [23]. To ensure that any differences were only due to intraoperative glucose levels, all patients received intensive control postoperatively. The authors showed that intensive control had no effect on morbidity and length of ICU or hospital stay. In fact, there was an increased in incidence of death, stroke, and pacemaker requirement in the intensive control group [23].

Since guidelines for insulin infusion protocols changed in 2009 after the NICE trial, Mulla et al. investigated how this change would impact outcomes [12]. This was a retrospective review of 1325 patients undergoing CABG with and without valve replacement or repair between September 2007 and April 2011 [12]. Two groups of patients were stratified into insulin control parameters of 80 to 110 mg/dL and 110 to 140 mg/dL [12]. The study found no difference in 30 day mortality, long-term mortality, or complication rates including deep sternal wound infection, pulmonary, renal, cardiac, neurological complications, and readmission within 30 days [12]. The higher glucose target provided fewer instances of hypoglycemia [12]. Furthermore, Saager et al. randomized 198 patients undergoing cardiac surgery with CPB to either intensive or conventional intraoperative glucose control [52]. The intensive control was defined as glucose levels of 80 to 110 mg/dL, and the conventional control was defined as glucose levels <150 mg/dL [52]. Each group consisted of 30 % diabetic patients. Delirium was assessed twice a day in each

patient for 5 days postoperatively. Saager et al. reported that after adjusting for preoperative calcium channel blocker use and ASA score, patients receiving intensive control were more likely to be diagnosed with delirium (RR = 1.89, $p = 0.03$) [52].

In two smaller reports, Desai et al. and Pezzella et al. also showed no significant differences in clinical outcomes between liberal and strict glucose control [53, 54]. Desai et al. enrolled 189 patients receiving first-time isolated coronary artery bypass graft procedures and randomized them to intensive postoperative control with glucose 90 to 120 mg/dL or conventional postoperative control with glucose 121 to 180 mg/dL [53]. Intraoperatively, blood glucose was maintained between 100 and 180 mg/dL for all patients. In terms of clinical outcomes, the conventional control group was noninferior to the intensive control group with respect to prolonged ventilation, deep sternal wound infection, pneumonia, perioperative renal failure, or operative mortality [53]. For both groups, there were no incidences of myocardial infarction, permanent stroke, or leg infection [53]. Subsequently, Pezzella et al. used the same patient population to assess long-term survival data in those randomized to intensive versus conventional control [54]. After discharge, patients with diabetes resumed their previous glycemic control regimen. Neither group received any further intervention as a part of the study. Pezzella et al. found no difference in survival between the intensive (95.5 %) and conventional (93.5 %) groups over a 40 month period ($p = 0.57$) [54]. There was also no difference in improvement of health-related quality of life among the two groups [54]. Thus, the study was supportive of the 2009 STS guidelines that blood glucose be maintained <180 mg/dL.

Specifically studying diabetic patients, Lazar et al. randomized 82 patients undergoing CABG to intensive control with a glucose target of 90 to 120 mg/dL or conventional control with a glucose target of 120 to 180 mg/dL [55]. Continuous insulin infusion was started at induction of anesthesia and continued for 18 h after surgery. They found no significant differences in the incidence of major adverse events including 30-day mortality, myocardial infarction, neurologic events, deep sternal infection, and atrial fibrillation between the two groups. However, the incidence of hypoglycemic events was higher in the intensive compared to the conventional control group (4 vs. 30, $p < 0.0001$) [55]. On the other hand, Lazar et al. observed that levels of free fatty acids were lower in patients with intensive control ($p = 0.043$), potentially indicating reduced perioperative inflammation. Overall, in diabetic patients, it appeared that intensive glycemic control offered no clinical improvement and increased the risk of hypoglycemia.

Recently, Umpierrez and colleagues from Emory University conducted a randomized study of 302 CABG patients in the GLUCO-CABG trial [56••]. They included patients with diabetes and those without diabetes but with perioperative hyperglycemia defined as glucose >140 mg/dL. All of the patients underwent CABG and 14.9 % had concomitant valve surgery. Patients were randomized to intensive postoperative control of glucose 100 to 140 mg/dL or conventional postoperative control of glucose 141 to 180 mg/dL. Both groups were managed using continuous insulin infusion. Continuous insulin therapy was discontinued after the patient was able to eat or transferred out of the ICU. After discontinuation, all patients received treatment with a glucose aim of <140 mg/dL before meals while inpatient and 90 days post-discharge. In the ICU, the mean glucose was 132 ± 14 in the intensive group and 154 ± 17 in the conventional group ($p < 0.001$) [56••].

The two groups in the GLUCO-CABG trial had no significant difference in episodes of hypoglycemia. No significant differences in complication rates for intensive versus conventional control were reported (42 vs. 52 %, $p = 0.08$), including a composite measure of complications including mortality, wound infection, pneumonia, bacteremia, respiratory failure, acute kidney injury, and major cardiovascular events [56••]. There was also no significant difference in hospital length of stay, ICU readmission, or readmission after hospital discharge. However, on subgroup analysis, there was a differential effect for diabetic and non-diabetic patients. Consistent with the group as a whole, intensive control had no difference when compared with the conventional control for complication rates in diabetic patients (49 vs. 48 %, $p = 0.87$) [56••]. On the other hand, patients without diabetes showed a lower rate of complications in the group receiving intensive control (34 vs. 55 %, $p = 0.008$) [56••]. This suggests that perhaps a lower blood glucose target is needed for patients without diabetes, whereas a higher target is permissible for those with diabetes.

Taken altogether, studies on intensive versus conventional glucose targets in cardiac surgery patients have discovered a myriad of effects that are specific to certain patient subgroups. A combination of randomized controlled trials and retrospective reviews over several time periods has sought to determine optimal glucose parameters. Most of these studies have focused on CABG patients and have widely varying insulin therapy protocols. As such, each study has contributed knowledge of particular patient populations as well as specific outcomes that are investigated.

Conclusion

Hyperglycemia has been shown to have negative clinical effects on all critically ill patients, including those undergoing cardiac surgery. On the opposite end, hypoglycemia also triggers a cascade of harmful cellular events. The pendulum of glycemic control was first pushed to the side of intensive control by the landmark Leuven study describing better outcomes with tighter glucose parameters. Since then, several

large studies have caused the practice guidelines to swing the other way, favoring conventional control. The paradox of a large body of evidence outlining frequent incidence of hyperglycemia in cardiac surgery patients; the well-documented adverse effects of hyperglycemia in the critically ill and surgical patient alike; yet the conflicting evidence regarding how aggressively hyperglycemia should be managed in the operative setting remains an enigma.

Research in the field has explored the optimal timing, delivery route, and glucose targets that clinicians should strive to maintain. Each study has focused on a different element and analyzes different populations. Therefore, the various parameters create significant difficultly establishing a consensus on management. Ultimately, in the general population, the benefits of intensive glucose control are modest and the adverse effects of hypoglycemia may overshadow them. However, some patient subgroups show significant benefits from intensive glucose control. Based on the available evidence, we recommend beginning continuous insulin infusion prior to surgical intervention rather than postoperatively. Although there is no clear consensus, it appears that diabetic patients can be managed with a more liberal glycemic control strategy, with blood glucose allowed up to 180 mg/dL. However, in non-diabetic patients, there is increasing evidence that intensive control, with blood glucose of less than 140 mg/dL, is beneficial. It is of paramount importance that future large clinical studies focus on identifying differences in subgroups and determining how each of them should be optimally managed.

Compliance with Ethical Standards

Conflict of Interest Lillian L. Tsai, Hanna A. Jensen, and Vinod H. Thourani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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