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Don’t Sugar Coat It: Glycemic Control in the ICU

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Abstract

Stress hyperglycemia is the transient increase in blood glucose as a result of complex hormonal changes that occur during critical illness. It has been described in the critically ill for nearly two hundred years; patient harm, including increases in morbidity, mortality, and lengths of stay, have been associated with hyperglycemia, hypoglycemia and glucose variability. However, there remains a contentious debate regarding the optimal glucose ranges for this population, most notably within the past 15 years. Recent landmark clinical trials have dramatically changed the treatment of stress hyperglycemia in the ICU. Earlier studies suggested that tight glucose control improved both morbidity and mortality for ICU patients, but later studies have suggested potential harm related to the development of hypoglycemia. Multiple trials have tried to elucidate potential glucose target ranges for special patient populations, including those with diabetes, trauma, sepsis, cardiac surgery, and brain injuries, but there remains conflicting evidence for most of these subpopulations. Currently, most international organizations recommend targeting moderate blood glucose concentration to levels less than 180 mg/dL for all patients in the intensive care unit. In this review, the history of stress hyperglycemia and its treatment will be discussed including optimal glucose target ranges, devices for monitoring blood glucose, and current professional organizations’ recommendations regarding glucose control in the intensive care unit.

INTRODUCTION

Hyperglycemia has been described in the critically ill for nearly two hundred years; the observation that glucose levels rise during critical illness was initially described by Bernard and Lefevre in 1855[1]. Claude Bernard also described hyperglycemia in the setting of hemorrhagic shock in 1878[2]. In the 1930’s, Norman Cruikshank reported increased glycosuria in patients who had recently suffered myocardial infarctions[3]. These studies formed our early understanding of stress hyperglycemia, which is often seen in critically ill patients.

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While stress hyperglycemia has been a clearly described entity in critically ill patients, its monitoring and treatment remains controversial. Until 2001 hyperglycemia was generally underappreciated in the intensive care unit (ICU); however, the landmark trial by van den Berghe, et al. set the foundation for a more aggressive approach[4]. This study revealed that tight glucose control was associated with a lower ICU mortality as well as other clinical benefits. However, the results were not met without criticism and multiple additional studies failed to replicate those benefits[5, 6]. The largest randomized clinical trial conducted in response to those critiques was the Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Trial, which, in direct contrast to the van den Berghe study found an increase in hypoglycemic events as well as mortality was associated with intensive insulin therapy[7].

Multiple additional studies have been conducted to further elucidate which target range is most appropriate for sub-patient populations, including patients with diabetes, trauma, brain injury, sepsis, and those who are recently post-cardiac surgery, however there currently remains little consensus amongst providers[8–21]. Despite intensive research for nearly twenty years, much debate still exists regarding the management and treatment of patients with stress hyperglycemia. Perhaps an important technological advancement to aid ICU personnel in treating these patients is the continuous glucose monitor (CGM), which may identify dangerous levels of blood glucose in patients with critical illness earlier than standard intermittent monitoring.

THE STRESS RESPONSE TO CRITICAL ILLNESS

The body’s primary response to stress is generated via the hypothalamic-pituitary-adrenal (HPA) axis. In the shock state, there are dramatic elevations in both epinephrine and norepinephrine as a result of the actions of the adrenal medulla[22]. These two hormones allow for hepatic gluconeogenesis and glycogenolysis[23]. In addition, norepinephrine induces lipolysis, thus increasing the amount of glycerol delivered to the liver. Furthermore, during times of stress the body experiences elevated levels of cortisol[23]. This occurs not only as a result of the release from the adrenal glands, but also due to an elevation of circulating free cortisol secondary to a decrease in serum cortisol binding protein. Cortisol works to increase serum glucose concentration by activating enzymes in the gluconeogenesis pathway as well as inhibiting glucose uptake[23]. Other mediators such as cytokines TNF-alpha, IL-1, IL-6, and CRP as well as altered release of adipokines from adipose tissue also induce insulin resistance in peripheral tissues[23].

ADVERSE EFFECTS OF HYPERGLYCEMIA

Numerous studies have demonstrated the link between the elevated blood glucose levels seen in critical illness and adverse clinical outcomes[23–25]. In a study of nearly 6,000 critically ill patients, glucose values <120 mg/dL and >162 mg/dL were associated with an increased risk of death[26]. A retrospective analysis of more than 55,000 non-cardiac surgical ICU patients found that high concentrations of glucose in the first 24 hours of the post-operative period increased the incidence of infections irrespective of pre-operative HbA_{1c}[27]. Krinsley reported that even small increases of mean glucose levels in the ICU were

associated with a large increased risk for in-hospital mortality[28]. Similarly, Umpierrez, et al. found that hyperglycemia occurred in 38% of patients admitted to the hospital, of which only 26% had known diabetes. Those who had no history of diabetes experienced higher rates of in-hospital mortality, longer lengths of stay, and a higher admission rate to the ICU compared with those with diabetes and those with normoglycemia[29].

ADVERSE EFFECTS OF HYPOGLYCEMIA

In contrast to hyperglycemia, hypoglycemia is also related to an increased risk of death. An observational study of 4946 ICU patients revealed that patients who experienced even mild hypoglycemia (72–81 mg/dL) were at a higher risk of mortality than those who maintained normoglycemia, and the more pronounced the hypoglycemia, the greater the mortality risk[30]. In an analysis of 6,240 critically ill patients, an increase in length of stay was associated with hypoglycemic events, and the greater the number of hypoglycemic events, the longer the length of stay[31]. Even a singular episode of hypoglycemia (<70 mg/dL) resulted in a substantially longer length of stay independent of the severity of illness[31].

ADVERSE EFFECTS OF GLUCOSE VARIABILITY

Unfortunately, glucose variability is also associated with an increased mortality rate. Krinsley, et al found that large glucose variability, based on standard deviation, was associated with an increased risk of mortality[32]. Those patients who had the lowest variability also experienced the lowest risk of mortality[32]. In another retrospective analysis of ICU patients treated with a computerized-based sliding scale, authors used both standard deviation and mean absolute glucose change per hour to evaluate glucose variability. It was reported that high glucose variability in combination with high average glucose levels was associated with the highest mortality in the ICU. Furthermore, low variability appeared to have a protective effect, even in the face of hyperglycemia[33].

INTENSIVE INSULIN THERAPY: LEUVEN I

In the past 15–20 years, multiple important clinical trials have been conducted regarding intensive vs. conventional glucose control and what constitutes the optimal glycemic target range. Prior to 2001, a strategy of permissive hyperglycemia was typical. At that time, insulin infusions were not initiated unless serum glucose reached the “renal threshold” of hyperglycemia, which is the critical turning point where glycosuria and hypovolemia occur. However, in 2001, van den Berghe, et al published a landmark study in which intensive insulin therapy (IIT) targeting blood glucose to a range of 80–110 mg/dL revealed a reduction in both morbidity and mortality amongst surgical ICU patients[4]. This study is often referred to as the Leuven study.

In this study, 1,548 primarily surgical ICU patients were randomized to receive either intensive or conventional glucose control; approximately 60% of the patients were post cardiac surgery. The intensive insulin therapy group were initiated on an insulin infusion when blood sugar rose to 110 mg/dL and targeted to a glucose range of 80–110 mg/dL[4]. The conventional treatment group received an insulin infusion only if blood glucose rose to the

renal threshold of 215 mg/dL, and the infusion was then titrated to a level of 180–200 mg/dL. Adjustments were made based on arterial blood measurements according to an algorithm and the assistance of non-clinical physician[4]. All patients were given intravenous (IV) dextrose initially, but parenteral or enteral feeding was administered whenever possible; however, many patients required parenteral feeding. The primary outcome was all cause mortality in the ICU, and secondary outcomes included in-hospital mortality, ICU length of stay, and the need for ventilatory or vasopressor support or renal-replacement therapy[4].

Nearly all patients in the intensive treatment group required insulin infusion compared with 39% of the conventional group. Additionally, hypoglycemia occurred in 39 patients in the intensive group versus 6 in the conventional[4]. In total, of the patients admitted to the ICU for >5 days and treated with intensive therapy, only 35 patients died compared with 63 in the conventional treatment group. Similar reductions were seen regarding in-hospital mortality as well[4]. Furthermore, the IIT group was at lesser risk for sepsis and the need for prolonged ICU care, ventilatory support, and renal replacement therapy[4].

This marked the first time that intensive insulin therapy was associated with positive clinical outcomes including a reduction in morbidity, mortality, and length of stay. However, the study was not without limitations. Firstly, it was conducted at a single institution with its own possible institutional biases. Also, it was not strictly blinded due to the nature of glucose monitoring, but the authors attempted to mitigate this by involving a non-clinical study physician to aid with glucose adjustments. Lastly, the results may not be generalized to the greater population as it was conducted primarily in cardiac surgery patients.

The benefits from TGC have been observed elsewhere too. For example, in a meta-analysis of 7 trials that did not include the Leuven I study, an overall reduction in ICU mortality with tight glucose control protocols. Furthermore, the authors noted a decrease in the overall length of stay and use of mechanical ventilation[34].

MODERATE GLUCOSE CONTROL: NICE-SUGAR

In the next few years following the initial Leuven study, there was a paucity of multi-center studies regarding tight glucose control. The studies that had been conducted failed to replicate all the clinical benefits seen in the Leuven study and were often criticized for study design[5, 6]. NICE-SUGAR sought to address these questions and was an international collaboration between multiple groups and hospitals from Australia, New Zealand, and Canada[7].

In all, 6,104 medical and surgical patients were enrolled and randomized to either intensive or conventional glucose control. The IIT group was targeted to a range of 81–108 mg/dL and the conventional to a glucose level <180 mg/dL. Blood glucose control was attained by use of an insulin infusion and adjustments were made via a validated protocol. While arterial blood measurements were used whenever possible, both venous and capillary blood measurements were also accepted[7]. The primary outcome analyzed was all cause mortality within 90 days of randomization, as well as multiple secondary and tertiary outcomes that included cause of death, duration of mechanical ventilation or renal replacement therapy,

and ICU and in-hospital length of stay amongst others[7]. The authors noted that 90 days following randomization, the patients in the IIT group were more likely to have died than those in the conventional therapy group, particularly from cardiovascular causes. This remained true even after adjustment for severity of illness[7]. Additionally, those in the IIT were more likely to experience severe hypoglycemia (glucose <40 mg/dL), and they failed to replicate the morbidity benefits seen in the first Leuven study[7].

While this study served to answer lingering questions regarding intensive insulin therapy in the ICU, it too was not without limitations. Again, the study was not strictly blinded given the nature of glucose management. Additionally, only 15% of patients who were admitted qualified for the study, which may have led to staff unfamiliarity with protocol design. Glucose measurements were also not standardized, and therefore measurements other than arterial blood were utilized. Studies in critically ill patients have suggested that capillary measurements may not effectively correlate with arterial measurements in patients in shock requiring vasopressor support[35].

Subsequent studies have provided similar results to NICE-SUGAR[36]. A prospective cohort study by Al-Tarifi, et al randomized more than 500 medical and surgical patients into six different glucose target ranges. The lowest mortality was noted for the group maintaining blood glucose between 129–145 mg/dL, and this was also associated with a lower risk of hypoglycemia[36].

OPTIMAL GLUCOSE TARGET RANGES

Leuven vs. NICE-SUGAR

Clearly, the Leuven and NICE-SUGAR studies reported contrasting results[4, 7]. The most significant of these was the reduction in mortality amongst patients receiving intensive insulin therapy in the Leuven study, and an increase in mortality amongst the same cohort in NICE-SUGAR. However, in addition to differences in results, these studies also have dramatically different study designs as summarized in table 1. Firstly, targeted glucose ranges were different in the control groups. The Leuven study aimed to keep blood glucose 180–200 mg/dL but only treated at levels above the renal threshold, while NICE-SUGAR study aimed to keep glucose <180 mg/dL. Moreover, while Leuven involved a single center, only 15% of the multicenter cohort qualified for NICE-SUGAR, thus limiting its broader applicability. Additionally, the Leuven study incorporated primarily cardiac surgery patients compared to primarily medical patients in the NICE-SUGAR study. Differences also exist regarding types of nutritional support and blood glucose measurements. Therefore, it may be difficult to perform a direct comparison of these studies given their significant differences in design[4, 7].

Effects on practice

In a study published in JAMA in 2015, authors investigated more than 350,000 patients admitted to more than 100 ICU's via the United States APACHE database to understand the effects that the Leuven and NICE-SUGAR studies had on management[37]. This was done by analyzing day 1 glucose control. The authors noted that in the pre-Leuven era 17.2% of

patients had tight glucose control and 40% were hyperglycemic. In the post-Leuven era, they found increases in both tight glucose control and hypoglycemia. However, following NICE-SUGAR, the authors did not note significant changes in glucose control nor the frequency of hypoglycemic events[37].

In contrast, a survey-based study of ICUs in the Netherlands found that six out of seven had changed their guidelines after the publication of NICE-SUGAR and began targeting moderate glucose control[38]. As such, they reported an increase in the patients maintaining normoglycemia and a decrease in those with hypoglycemia[38].

In a study conducted in Australia and New Zealand, more than 175,000 patients' day 1 glucose level were evaluated both before and after NICE-SUGAR to better understand study effects on practice[39]. Authors found that none of the 49 centers were utilizing intensive insulin therapy before the publication of NICE-SGUAR but that the average first day glucose levels increased following its release. Similarly, they found a reduction in hypoglycemic events as well[39].

Targeted blood glucose in special populations

There are several sub-patient populations for which it is conceivable that targeting different blood glucose levels than the general population may be advantageous. These may include but are not limited to patients with sepsis, diabetes, cardiac surgery, trauma, and brain injury. Their key risks and benefits are summarized in table 2.

The initial Leuven study was repeated in 1,200 medical ICU patients of which the majority were admitted with a diagnosis of sepsis[8]. While there was a reduction in morbidity including acute kidney injury, prolonged mechanical ventilation, and in-hospital length of stay, the authors were unable to replicate the mortality benefits seen in the original study. They theorized that these differences may be related to the organ damage with which many of the medical patients were presenting[8]. This is in contrast to a small 127 patient retrospective study that evaluated the most appropriate glucose target range for patients with sepsis and septic shock. A blood glucose of 120 mg/dL or below was an independent risk factor for 14-day mortality[9]. A subgroup analysis revealed that this was only true for patients who did not previously carry a diagnosis of diabetes prior to admission[9]. Similarly, in a multicenter, randomized prospective study of patients with severe sepsis, patients were randomized to either receive intensive insulin therapy targeted to blood glucose levels between 80–110 mg/dL or conventional therapy. This trial was stopped prematurely for safety reasons, as the patients in the intensive treatment group experienced increased rates of hypoglycemia[10]. However, at 28 days, there was no difference between the two groups with regards to mortality or organ failure development[10].

It is conceivable that patients who maintained their blood glucose at higher than average concentrations prior to ICU admission, may require higher than average blood glucose targets in the ICU. In support of this idea, a post-hoc analysis of the Leuven studies revealed that the only subgroup that did not demonstrate a survival benefit from tight glucose control were those patients who carried a known diagnosis of diabetes prior to admission[8]. Similarly, Egi, et al noted that blood glucose concentrations in patients with elevated

HbA_{1c}'s was higher in those who survived than in those who did not[12]. They also reported that the higher the HbA_{1c} upon admission, the higher the risk of death with hypoglycemia[12]. Krinsley, et al noted a mortality benefit with targeted glucose to a range of 110–160 mg/dL for patients with a HbA_{1c} >7 compared with a targeted range of 80–140 mg/dL[13].

There is less consensus on the treatment of hyperglycemia in patients with acute coronary syndrome (ACS). The first of these studies was the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial[14]. In this study, patients who were admitted with acute myocardial infarction and either a history of diabetes or an elevated blood glucose of more than 200 mg/dL were randomized to either intensive insulin therapy or conventional control. The control group was only managed with subcutaneous insulin at the discretion of a CCU physician[14]. The authors noted no difference in mortality at three months; however, there was a mortality reduction at 1, 3½, and 20 years for those treated with intensive therapy when compared to the conventional therapy [14]. One of the more recent studies is the BIOMarker Study to Identify the Acute Risk of a Coronary Syndrome 2 (BIOMArCS-2)[15]. This was a prospective, single centered study of 294 patients with ACS and a serum glucose between 140–290 mg/dL who were randomized to receive either intensive insulin therapy (85–110 mg/dL) or targeted to a blood glucose of <290 mg/dL[15]. They used both high sensitivity troponin and the extent of myocardial injury at 6 weeks to evaluate infarct size. There was no difference between the two groups with regards to either biomarker[15].

Regarding appropriate blood glucose targets in patients following cardiac surgery, it is of course important to reference back to the Leuven study in which nearly two thirds of patients were post-cardiac surgery where there was improved survival and morbidity with intensive glucose control[4]. In a 17-year prospective non-randomized study of nearly 5,000 patients with diabetes who underwent cardiac surgery, when blood glucose was targeted to <150 mg/dL with continuous insulin infusion, there was a significant reduction in mortality, deep sternal wound infections, and hospital LOS[16] Another study evaluated changes of inflammatory and oxidative stress markers and their association with glucose control following coronary artery bypass grafting[17]. In this study, 302 patients were randomized to receive intensive or conservative glucose targets and levels of plasma cortisol, CRP, TNF-alpha, IL-6, as well as several other biomarkers were measured prior to treatment and at 3, 5, and 30 days[17]. There was no difference in the stress markers with either treatment group[17].

Trauma patients represent another unique group who may benefit from intensive glucose control. A retrospective review of 2,028 trauma patients admitted to the SICU at a level 1 trauma center evaluated 2-year data of patients pre- and post-insulin therapy[18]. Intensive insulin therapy of 80–110 mg/dL was associated with multiple benefits that included both mortality and in-hospital length of stay[18]. The most significant results were found in patients with moderate and severe injuries and those aged 40 and older[18]. Another retrospective analysis of 1,422 trauma patients evaluated patient outcomes after receiving one of three targets ranges: >180 mg/dL, 80–120 mg/dL, or 80–140 mg/dL[19]. They found a correlation with hyperglycemia and mortality and that moderate (80–140 mg/dL) glucose control was associated with the fewest hypoglycemic events; however, there were similar outcomes between both moderate and aggressive treatment[19].

Glucose is a necessary molecule in brain metabolism[40]; therefore, it is reasonable to consider alternative glucose target ranges in patients with brain injury. A subgroup of patients from the NICE-SUGAR study with traumatic brain injury were followed for two years post randomization and evaluated for both neurological outcome and mortality[21]. The authors found that while the intensively treated patients did experience more frequent hypoglycemic events, they were not at increased risk for adverse neurological outcomes nor mortality[21]. In contrast, in a subgroup analysis of patients with brain injury from the first Leuven study, authors noted that intensive insulin therapy was associated with improved morbidity including a reduction in ICP, need for vasopressors, fewer seizures, and improved 1-year functional status[20]. Additional studies are needed to fully understand appropriate target ranges of patients with sepsis, diabetes, ACS, cardiac surgery, trauma, and brain injury.

RECOMMENDATIONS BY PROFESSIONAL ORGANIZATIONS

Most international professional organizations recommend the use of moderate glucose control in critically ill patients with stress hyperglycemia as outlined in table 3. For example, according to the American Association of Clinical Endocrinologists and the American Diabetes Association, ICU patients with hyperglycemia should be treated at 180 mg/dL and targeted to a range of 140–180 mg/dL[41, 42]. Additional suggestions by the same groups include the consideration for different target ranges for different sub-patient groups and the implementation of a hypoglycemia management protocol[41, 42]. Similarly, the Surviving Sepsis Campaign has also recently revised their guidelines, recommending treating stress hyperglycemia at a level of 180 mg/dL[43]. Further recommendations include values should be measured every 1–2 hours during insulin infusion preferably by arterial measurements[43].

PROTOCOLS

Following the above described studies, many protocols have been designed to modulate glucose control. One such example of this is the specialized relative insulin nutrition tables (SPRINT) protocol that helps clinicians tighten glycemic control. In a study of 371 patients treated under the SPRINT protocol, authors evaluated whether the protocol improved glycemic control or mortality compared with 413 case matched controls[44]. The authors noted that those patients treated under the SPRINT protocol achieved a higher level of glycemic control and were at a lesser risk for mortality than case matched controls[44]. Multiple other protocols have been developed with varying accuracy, perhaps one of the most widely used is the Yale protocol[45]. A study that compared the Yale protocol to the protocol used in the Leuven studies revealed that patients treated under the Yale protocol had better than average glucose control with less hypoglycemic events[46]. However, a major drawback of using protocols for glucose control is that it requires a large time commitment from clinical staff and is associated with increased costs[47].

CONTINUOUS GLUCOSE MONITORING

Intensive care units across the country still utilize point of care (POC) devices to measure blood glucose and modulate insulin requirements. However, the use of these devices has

raised concerns regarding their accuracy due to the changes in hematocrit, oxygenation, and pH to which critically ill patients are predisposed[48, 49]. Furthermore, studies have revealed fewer discrepancies associated with arterial blood measurements than capillary measurements, and thus it has become the standard of care[50, 51]. However, arterial measurement can be laborious and often capillary measurements are recorded. In response to these concerns, continuous glucose monitors are in development. These devices offer the benefit of prevention of large swings in glucose levels. In a randomized study of 124 mechanically ventilated patients, authors found that continuous glucose monitoring significantly reduced hypoglycemic events compared with conventional intermittent glucose monitoring although it did not improve overall glycemic control[52].

More than $700 million has been spent on the development of the continuous monitors, but despite this, they are not widely adopted by American ICU's[53, 54]. While several of the devices have been approved in noncritically ill patients, only one has approval in the critically ill and is not in clinical use at this time. Overall, clinician concern with cost, clinical burden, accuracy, and reliability are the limiting factors to the wide spread use of continuous glucose monitoring[54]. Despite the resources and interest invested in the development of these products, accuracy remains a problem with many devices failing to meet the mean absolute relative difference point accuracy standard[54, 55]. A panel of experts on the field of inpatient glucose management released a consensus statement indicating that while they believe CGM may be of utility in the future, the evidence is currently lacking to institute widespread use of the devices[56].

CONCLUSIONS

Hyperglycemia occurs as a result of physiologic stress irrespective of baseline blood sugar levels prior to hospitalization. Many studies have suggested that there is an increased risk for morbidity and mortality associated with hypoglycemia, hyperglycemia, and large blood glucose variation. The scientific evidence behind optimal blood glucose control is mixed and somewhat controversial with earlier studies suggesting a positive effect for strict glucose control of 80–110 mg/dL with later studies suggesting a more moderate control of 140–180 mg/dL. A large part of this controversy is as a result of variations in study design including patient populations, levels targeted, and how levels were measured. Most professional organizations currently recommend maintaining blood glucose levels in the ICU between 140–180 mg/dL. However, there is some evidence that certain groups of patients may benefit from tighter control, including cardiac surgery and trauma patients. Much time and money has been invested in the development of continuous glucose monitors to ameliorate concerns regarding the accuracy of point of care devices in the critically ill population. However, these devices have limited use in the United States due to concerns over the clinical burden created, reliability, and cost. More evidence is needed to further guide treatment of patients in these populations, especially given the morbidity and mortality associated with glucose abnormalities in the intensive care population.

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Abbreviations:

ICU	intensive care unit
NICE-SUGAR	Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation
CGM	continuous glucose monitor
HPA	hypothalamic–pituitary–adrenal
IIT	intensive insulin therapy
TGC	tight glucose control
CRP	c-reactive protein
TNF-a	tumor necrosis factor alpha
IL-6	interleukin-6
ICP	intracranial pressure
POC	point-of-care
IV	intravenous
ACS	acute coronary syndrome
DIGAMI	Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction
BIOMArCS-2	BIOMarker Study to Identify the Acute Risk of a Coronary Syndrome 2
SPRINT	specialized relative insulin nutrition tables

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Table 1.

Comparison of essential data between Leuven I study and NICE-SUGAR.

Leuven	**NICE-SUGAR**
Single centered	Multi-centered
Surgical patients	Medical and surgical patients
TG control vs <215 mg/dL	TG control vs. 140–180 mg/dL
Majority enrolled	15% enrolled
Enteral and parenteral nutrition	Enteral nutrition only
Arterial measurement	Arterial, venous, and capillary measurement

Abbreviations: TG = tight glucose control

Table 2.

Risks and benefits of intensive glucose control in various sub-patient populations.

Sepsis	DM	ACS	CTS	Trauma
• Conflicting: – Reduced Morbidity – Increased hypoglycemia – ?lncreased mortality	• No mortality benefit • May require higher glucose targets	• Conflicting: – Mortality reductions – No change in infarct size or injury	• Conflicting: – Decrease in mortality, LOS, and infection – No change in inflammation	• Conflicti – –

Abbreviations: DM = diabetes mellitus, ACS = acute coronary syndrome CTS = cardiothoracic surgery, TBI = traumatic brain injury, LOS = length of stay

Table 3.

Recommendations by professional organizations for treatment threshold and glucose targets for critically ill patients.

Year	Organization	Treatment Threshold	Glucose Target
2016	American Association of Clinical Endocrinologists and American Diabetes Association	180 mg/dL	140–180 mg/dL
2016	Surviving Sepsis Campaign	180 mg/dL	<180 mg/dL
2008	American Heart Association	180 mg/dL	140–180 mg/dL