COMPARISON OF COMPUTER AND PAPER-BASED PROTOCOLS
FOR MANAGING HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

By

Andrew T. Peckham

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CERTIFICATE OF APPROVAL

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This is to certify that the Master's Thesis of

Andrew Peckham

has been approved

_____
William Lambert, PhD
Mentor/Advisor

_____
Daniel Hagg, MD
Member

_____
Dawn Peters, PhD
Member

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ABSTRACT

Title: Comparison of Computer and Paper-Based Protocols for Managing Hyperglycemia in Critically Ill Patients

Introduction: The purpose of this study was to compare a computer-based insulin protocol against two paper-based protocols to control hyperglycemia in intensive care unit (ICU) patients. A safe and effective protocol must minimize hyperglycemia and glucose variability while also avoiding hypoglycemia, all of which are associated with increased risk of death. In theory, computer-based protocols that base insulin dosing on the individual patient's record of response offer better performance by adjusting to each patient's sensitivity to insulin. **Methods:** This is a retrospective cohort study on 1896 patients admitted to four ICUs (surgical, medical/cardiac, trauma, and neuroscience) at an academic tertiary care hospital. We included all adult patients from January 2012 to October 2013 on one of three continuous insulin protocols for at least eight hours. The two paper-based protocols (Cardiothoracic Surgery (CTS) and Adult ICU) had a target glucose of 140-180 mg/dL. The computer-based insulin protocol (EndoTool) targeted a glucose of 150 mg/dL. All cardiothoracic surgery patients were automatically started on the CTS or EndoTool protocol, regardless of whether they had developed hyperglycemia; whereas all the other patients were started on either the Adult ICU or EndoTool protocol after developing hyperglycemia of 180 mg/dL or greater. In our analyses, the primary exposure was the type of insulin protocol (computer- vs. paper-based), and the primary outcome was performance in maintaining glucose control.

Results: Among cardiothoracic surgery patients who were automatically placed on an insulin protocol without necessarily developing hyperglycemia, the mean glucose in the EndoTool group (130.9 mg/dL) was lower than the CTS group (138.8 mg/dL) ($p<0.0001$). The proportion of

patients in each group with 10% or higher of measurements at a severe hyperglycemia level (≥200 mg/dL) in the EndoTool group (6.2%) was lower than the CTS group (15.5%) (p=0.0092).The standard deviation in the EndoTool group (23.1 mg/dL) was not significantly lower than that observed in the CTS group (24.3 mg/dL). The incidence of hypoglycemia in the EndoTool group (5.83 hypoglycemic measurements/100 person-protocol days) was higher than in the CTS group (3.57) (RR=1.63, 95% CI 0.99-2.59; p=0.041). Among the patients who were put on an insulin protocol after developing hyperglycemia, the mean glucose in the EndoTool group (141.5 mg/dL) was lower than in the Adult ICU group (159.9 mg/dL) (p<0.0001). The proportion of patients in each group with 10% or higher of measurements at a severe hyperglycemia level (≥200 mg/dL) in the EndoTool group (35.2%) was lower than the Adult ICU group (64.1%) (p<0.0001). The standard deviation of glucose in the EndoTool group (32.3 mg/dL) was lower than in the Adult ICU group (39.5 mg/dL) (p=0.0001). There was a higher overall incidence of hypoglycemia in the EndoTool group (5.02 hypoglycemic measurements/100 person-protocol days) compared to the Adult ICU group (3.17) (RR=1.58, 95% CI 1.02-2.41, p=0.031). Severe hypoglycemia (<40 mg/dL) did not occur in either of the EndoTool groups, and was rare in both the CTS group (2/595 (0.34%)), and the Adult ICU group (2/580 (0.34%)).

Conclusions: Overall, the computer-based protocol performed better than the paper-based protocols with respect to decreasing mean glucose and avoiding hyperglycemia. There was a higher incidence of moderate but not severe hypoglycemia associated with the computer-based protocol. With the exception of cardiothoracic surgery patients, the computer-based protocol also was associated with decreased glucose variability.

INTRODUCTION

Stress-induced hyperglycemia is present in approximately 30-50% of patients admitted to an intensive care unit,[1,2] and has a strong association with increased risk of mortality and complications such as infection and multiple organ dysfunction.[3,4] Stress-induced hyperglycemia commonly occurs among patients without a prior history of diabetes, though up to 20% of patients have previously undiagnosed diabetes or pre-diabetes (with an admissions HbA1c > 6.1%), and up to 60% of patients with new hyperglycemia will be diagnosed with diabetes within 1 year.[5]

Critically ill patients have deranged metabolism, including increased blood glucose levels, insulin resistance, inflammation, and dyslipidemia.[6] Stress-induced hyperglycemia leads to impaired immune system functioning, leading to increased susceptibility to infections.[7,8] Hyperglycemia can also lead to mitochondrial dysfunction, impairing energy production, and possibly leading to tissue damage in kidneys and other organs.[9] Intensive insulin therapy may reduce mortality by countering the harmful effects of hyperglycemia. Insulin can also help other metabolic abnormalities, such as lowering harmful dyslipidemia, and weakening the catabolic response to severe illness or injury. Insulin therapy may also have anti-inflammatory effects.[10] In addition to developing hyperglycemia, two other general categories of disrupted glucose metabolism are thought to be harmful: glucose variability and hypoglycemia. These three domains of glucose control have been collectively referred to as "dysglycemia."[11]

Moderate stress-induced hyperglycemia has been considered a beneficial stress response in critically ill patients, and up until 2001 it was common to allow patients' blood glucose to be as high as 160-200 mg/dL without being treated with insulin.[12] The Portland Diabetic Project, begun in 1987 at Providence St. Vincent Medical Center, has been credited with being the first to establish an association between hyperglycemia and increased mortality and morbidity in diabetic cardiac surgery patients.[13] This prospective observational study of 5,510 patients found a

dramatic 60% relative risk reduction in mortality, and also demonstrated a decreased incidence of infection and hospital length of stay after using continuous insulin infusions to achieve tight perioperative glucose control. Initially a target glucose range of 150-200 mg/dL was used, but this was lowered to 70-110 mg/dL by 2005.

Hyperglycemia was also observed to be a risk factor for mortality and heart failure in patients admitted for acute myocardial infarction.[14] In 1995 the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial was published, showing a mortality benefit in patients who received a combined insulin-glucose infusion after being admitted for acute myocardial infarction.[15] This was a randomized control trial of 620 patients who had hyperglycemia of greater than 200 mg/dL; patients either received an insulin-glucose infusion for 24 hours or conventional therapy. At 24 hours after randomization the intensive insulin group had lower blood glucose than the control group, though it was still at a hyperglycemic level (173 mg/dL vs 210 mg/dL). There was a high incidence of hypoglycemia (<54 mg/dL) in the intensive insulin group (18%). After 3.4 years of follow-up, multivariable Cox regression showed a 28% relative reduction in mortality associated with the intensive insulin treatment group. However the second DIGAMI trial, a randomized trial of 1,253 patients, failed to demonstrate a reduction in mortality, as were other studies.[16]

The first randomized control trial comparing insulin protocols with different target blood glucoses was conducted by Van den Berghe et al. in 2001 with 1,548 patients in a surgical ICU in Leuven, Belgium. A significant 42% reduction in mortality (4.6% vs 8.0%) was observed in patients treated with a very aggressive insulin protocol with a low and narrow target glucose (80-110 mg/dL). Patients in the conventional control group were only started on insulin after developing hyperglycemia >215 mg/dL, and then treated to a much higher target of 180-200 mg/dL. In addition to lower mortality, there was a 46% reduction in blood stream infections, a 41% reduction in acute renal failure, and other improvements associated with the intensive insulin

therapy group, including fewer red blood cell transfusions.[17] After this landmark study was published, ICUs around the world began adopting similar intensive insulin therapy protocols. This became the standard of care after the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) published recommendations in 2004 for strict glucose targets of < 110 mg/dL for critically ill patients.[18]

The treatment provided in the original Leuven study by Van den Berghe et al. had some differences from conventional treatment in other sites, such as having a fairly relaxed threshold for initiating treatment in the control group (only for hyperglycemia greater than 215 mg/dL) and a higher percentage of patients receiving parenteral nutrition, which caused some speculation that the benefit experienced by the intensive insulin therapy group was due to insulin protecting these patients from the harmful effects of hyperglycemia induced by parenteral nutrition.[19] Also of note, the mortality benefit was only seen in patients with ICU length of stays greater than 5 days. Subsequent studies produced differing results, with several showing that tight glucose control had no improvement in mortality,[20] and one reporting an association between tight glucose control and increased mortality.[21]

In 2006, Van den Berghe and colleagues conducted another randomized control trial using the same protocol as the first Leuven study but with 1,200 patients in a medical ICU. In contrast to the 2001 study in a surgical ICU, there was no overall reduction in mortality associated with the intensive insulin group, however there was still reduction in morbidity such as decreased renal failure, decreased mechanical ventilation, and decreased ICU and hospital length of stay. Among the subgroup of patients admitted to the ICU for three days or more, there was a significantly lower mortality associated with the intensive insulin group (43.0% 52.5%, p=0.009). There was a high rate of severe hypoglycemia (≤ 40 mg/dL), occurring in 18.7% of the intensive insulin group compared to 3.1% in the control group, and increasing to 25% in the intensive insulin group in patients admitted in the ICU for 3 days or more.[22]

A pivotal randomized control trial called the NICE-SUGAR trial was published in 2009, leading to a major change in glucose control. [23] This study involved 6,104 patients in over 40 ICUs (both medical and surgical) in different countries. Patients were randomized either to an intensive glucose control group (target glucose 81-108 mg/dL) or to a "conventional" glucose control group (target glucose 144-180 mg/dL). This study found increased 90-day mortality in the intensive control group, with a 2.6% absolute increase in mortality from 24.9% in the conventional control group compared to 27.5% in the intensive control group (OR 1.14, 95% CI 1.02-1.28, $p = 0.02$). Of note, the "conventional" glucose control group had a more moderate target glucose (144-180 mg/dL) compared to the conventional control group in the first Leuven study. There was a much higher incidence of severe hypoglycemia (≤ 40 mg/dL) in the intensive insulin group, occurring fourteen times as often (6.8% vs 0.5%). This increased incidence of severe hypoglycemia was hypothesized to be an explanation for the higher mortality seen in the intensive insulin group.

Insulin protocols that have lower target blood glucose ranges naturally have increased risk of glucose dropping low enough to result in hypoglycemia. Hypoglycemia appears to be quite harmful, being independently associated with increased mortality.[24,25] Multiple meta-analyses have been conducted from randomized control trials comparing intensive insulin therapy (usually with target glucose <110 mg/dL or <150 mg/dL) to conventional therapy (usually target glucose <180 mg/dL or <200 mg/dL). For example, Griesdale et al. included data from the NICE-SUGAR study and found that that the majority of studies comparing tight glucose control to moderate glucose control found a significantly increased incidence of hypoglycemia in the tight glucose control groups, with a pooled relative risk of 6.0. In this meta-analysis there was evidence that patients in surgical ICUs may benefit from tight glucose control, but otherwise tight glucose control was not associated with an overall improved mortality.[26] In 2009, the ADA and AACE updated their guidelines to recommend a target of 140-180 mg/dL for most critically ill patients.[27]

Three subsequent meta-analyses failed to show any mortality benefit from intensive insulin therapy in surgical patients or any other subset of patients.[28,29,30]

The apparent lack of benefit and potentially increased harm associated with tight glucose control may be explained by the significantly increased risk of hypoglycemia, which may outweigh the benefits of avoiding hyperglycemia. One of the important remaining questions is whether tight glucose control, if achieved through a protocol that avoids hypoglycemia, reduces morbidity and mortality. There is some evidence that the use of computer-based insulin protocols has been able to achieve tighter glucose control while avoiding increasing the risk of hypoglycemia in comparison to paper protocols with the same glucose targets.

Variability of glucose control, in addition to the mean and range of glucose control, has been recognized as an independent risk factor for morbidity and mortality.[31,32] High variability in glucose levels has been found in some studies to be a stronger predictor of mortality than mean blood glucose.[33,34] It is possible that the association between glucose variability and mortality is connected to the level of attention the patient received during their care or is related to a higher severity of illness.[35] However, increased glucose variability has also been associated with more significant metabolic changes than sustained hyperglycemia, with worsened oxidative stress and inflammation[36] High glucose variability has been associated with increased oxidative stress and impairment of mitochondrial, neuronal, and coagulation function.[37,38] Because many of the studies comparing different blood glucose goals have not included measures of variability of blood glucose, it is not clear whether the differences in mortality are associated with differences in incidence of hypoglycemia, variability of glucose control, level of attention provided to patients, or other unmeasured differences.

Interestingly, having a preexisting diagnosis of diabetes appears to have moderate protective effect from some of the harmful effects of dysglycemia. In a study of over 45,000 patients, Krinsley et al. (2013) reported an interaction between diabetes and the relationship

between dysglycemia and mortality.[39] This study found evidence that having diabetes was protective against the harmful effects of both hyperglycemia and increased glucose variability, but not hypoglycemia. The authors also found that increased variability of glucose control (coefficient of variation $\geq$ 20%) was only associated with increased mortality for patients without a diagnosis of diabetes after controlling for other confounding variables. In support of this finding, Plummer et al. (2014) prospectively evaluated 1,000 consecutive patients admitted to an ICU and discovered that the association between acute hyperglycemia and mortality was only present if the patient had baseline hyperglycemia (defined by hemoglobin A1c of $\geq$ 7%) before admission.

The use of computer-based protocols which are adaptive to the individual patient's sensitivity to insulin promise to allow more precise adjustments in insulin doses to maintain glucose within the target range for longer periods of time, reduce variability, and also minimize hypoglycemia.[40] Computer software algorithms also simplify the process of administering insulin by clinical staff by automatically doing the calculations. Several computer software programs are now available and have been adopted by many institutions. However, computer-based protocols may require more frequent blood glucose testing which may increase the workload of providers, with one study finding an extra 30 minutes of work for nurses per day per patient with a computer protocol compared to a paper-based protocol.[41]

Background at Oregon Health & Science University (OHSU)

Oregon Health & Science University (OHSU) is a tertiary care academic hospital that has four adult ICUs. After the first Leuven study was published by Van den Berghe et al. in 2001, OHSU began developing an intensive insulin therapy protocol with a target glucose of 80-110 mg/dL that was implemented in 2002. When the NICE-SUGAR study was published in 2009, OHSU relaxed the target glucose range to a moderate glucose control target of 140-180 mg/dL.

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During this time there was a separate insulin protocol for cardiothoracic surgery patients that was used in a more prophylactic manner, with every cardiothoracic surgery patient being started on insulin whether they had developed hyperglycemia or not. In contrast, other ICU patients were only started on an insulin protocol after developing hyperglycemia. In 2012, a computer-based insulin protocol called EndoTool® (Monarch Medical Technologies, Charlotte, NC) was purchased with the hope of improving glucose control. Up until this point, paper-based protocols were being used. The standard paper-based protocol had a set rate of insulin infusion for a given blood glucose level, without different doses for different categories of suspected insulin resistance. The computer protocol was designed to individually calculate insulin infusion rates for each patient based on their current degree of insulin resistance, that was calculated using all their prior insulin infusion rates and glucose levels and the rate at which they changed.

Significance

Numerous studies have been conducted attempting to determine the optimal level of glucose control that minimizes the toxicity associated with stress-induced hyperglycemia and protects the patient from the harmful effects of hypoglycemia, while delivering the insulin in a way in which is not overly burdensome or time-intensive for the ICU staff. Some studies have demonstrated significant benefit from tight blood glucose control compared to moderate glucose control, whereas other studies have shown no mortality benefit, and increased complications from hypoglycemia. Various blood glucose targets have been used, and more evidence is needed to determine how strict of a protocol is needed to best protect patients and improve outcomes.

Few studies have been published comparing the EndoTool computer-based insulin protocol to other protocols.[42] A randomized control trial done in 2008 with 300 patients comparing the EndoTool protocol to a paper-based protocol found a significantly higher percentage of measurements within target range and decreased variability of glucose control.[43] In

this study there was a small but not statistically significant reduction in number of hypoglycemic measurements; the time to achieve target range did not differ significantly and incidence of mortality was not reported.[44] Another study by Cochran et al. evaluated the EndoTool protocol after it was implemented in 2003, replacing a traditional paper-based protocol, and found it was effective at achieving tight glucose control with low incidence of hypoglycemia, but a direct comparison to the paper-based protocol was not performed.[45]

Stress-induced hyperglycemia is a common problem in the ICU, and when it is not well managed, it is associated with increased risk of death and other poor outcomes. The unique data set from critically ill patients at OHSU provides the opportunity to evaluate outcomes for patients on the computer-based protocol (EndoTool) versus two paper-based protocols. Our analysis will include almost two thousand patients in four different types of adult ICUs. Our analysis may provide evidence that will be useful to guide decisions about what type of protocol is most effective in controlling blood glucose, as well as explore potential differences in patient outcomes for different degrees of glucose control and differences between patients with and without diabetes.

METHODS

Overview of Design

This is a retrospective cohort study comparing the level of glucose control among adult ICU patients at OHSU with stress-induced hyperglycemia who were treated with two similar paper-based protocols that had a goal of keeping blood glucose within the range of 140-180 mg/dL, versus a computer-based protocol that had a goal of maintaining glucose at 150 mg/dL, making continuous corrections based on each individual's previous responses to insulin. The primary exposure of interest is the type of insulin protocol, and the primary outcome of interest is level of glucose control, as measured by mean blood glucose, variability of glucose, and

incidence of hypoglycemia and hyperglycemia. Secondary outcomes include infection and acute kidney injury, which have been associated with hyperglycemia,[46] and ICU and hospital length of stay. All adult patients in the four OHSU ICUs were added to a registry if they were on continuous insulin therapies for at least eight hours during the study period (January 2012-October 2013). Exposure was determined by which insulin protocol was recorded in the patient's electronic medical record (EMR). Patients were stratified based on whether they were in the surgical ICU or one of the other ICUs, and whether they underwent cardiothoracic surgery or not, since the protocols were initiated differently for cardiothoracic surgery patients compared to other patients.

At the start of the study period in 2012, patients were on one of two paper-based insulin protocols, each with a target blood glucose range of 140-180 mg/dL. Patients were started on the Adult ICU protocol if they had a blood glucose higher than 180 mg/dL. Another protocol called the "Cardiothoracic Surgery (CTS) protocol" was specifically used for patients who underwent cardiothoracic surgery. Patients were automatically placed on this protocol after surgery, regardless of their blood glucose level. In June of 2013, the EndoTool computer-based insulin protocol began to be implemented for all adult patients in any of the four ICUs, replacing both paper protocols. The target glucose for the EndoTool protocol was 150 mg/dL, with continual adjustments to the insulin infusion rate in an attempt to maintain the blood glucose at 150 mg/dL. Criteria for starting patients on the EndoTool protocol was the same as that used for the Adult ICU and CTS protocols, with all cardiothoracic surgery patients automatically starting EndoTool post-operatively, and other patients starting it if their blood glucose went above 180 mg/dL.

Specific Aim 1: Identify all of the patients in the four adult intensive care units at OHSU between January 2012 – October 2013 who were on a continuous insulin infusion protocol for at least eight hours.

Inclusion Criteria

Patients were included if they were adults (age 18 or greater) who were admitted to one of the four adult ICUs at OHSU and were on an insulin protocol for at least eight hours. Only patients during the years 2008-2013 were included.

Exclusion Criteria

Patients were excluded if they received less than 8 hours of IV insulin, or were less than 18 years of age. Patients with missing outcomes data were excluded. For comparing glucose control measures, patients were excluded if they had less than 5 blood glucose measurements. Repeat admissions for the same patient were excluded for this study.

Specific Aim 2: Compare outcomes for the EndoTool computer-based protocol against the Cardiothoracic Surgery (CTS) paper-based protocol used for cardiothoracic surgery patients within a surgical ICU who were automatically started on an insulin protocol after surgery (regardless of the level of their blood glucose). The cardiothoracic surgery patients will be considered separately because a different method of glucose control was used. As soon as these patients were transferred to the surgical ICU from the operating room, they had a blood glucose measurement and an insulin infusion was begun, whether they had developed hyperglycemia or not. Consequently, these patients would be expected to have their glucose controlled within the target range much sooner and with less variability than patients who started a continuous insulin protocol after developing hyperglycemia.

The primary outcome was degree of glucose control:

2.a) Glucose control measures (mean glucose, percentage of glucose measures within target range, variability of glucose, and incidence of hypoglycemia and hyperglycemia)

2.b) Morbidity associated with hyperglycemia (infection and renal failure), ICU length of stay, and mortality

Other variables associated with glucose control, such as receiving glucocorticoids, various forms of nutrition, glucose level on admission, and underlying severity of illness were tested for confounding and adjusted for as needed. Additional outcomes associated with hyperglycemia (infection and renal failure) were compared, along with ICU and hospital length of stay and mortality.

Specific Aim 3: Compare outcomes for the EndoTool computer-based protocol versus the Adult ICU paper-based protocol among patients in the medical/cardiac ICU, trauma ICU, and neuroscience ICUs who were started on an insulin protocol if their blood glucose went above 180 mg/dL. Patients in these three ICUs were combined because the general method of initiating an insulin protocol was the same for them, with patients starting an insulin protocol only after developing hyperglycemia, in contrast to the cardiothoracic surgery patients in the surgical ICU. We expected that it should take longer to get these patient's glucose under control within the target range and that there would be higher variability in comparison to the post-operative cardiothoracic surgery patients.

Outcome Variables
- Overall mean/median of glucose measurements
- Variability of glucose control: standard deviation (SD) and coefficient of variation (CV = SD/mean)
- Percent of total number of glucose measurements that were within target range (140-180 mg/dL)
- Moderate Hypoglycemia: Proportion of patients who had at least one moderate hypoglycemic measurement (<70 mg/dL), and incidence of hypoglycemia per 100 patient protocol days. Definition of hypoglycemia based on AACE/ADA definition[47] and also the study of hypoglycemia and risk of death done by NICE-SUGAR trial investigators (2012)[48] and a recent paper by Krinsley et al. (2014).[49]

- Severe Hypoglycemia: Proportion of patients who had at least one severe hypoglycemic measurement (<40 mg/dL). Definition of severe hypoglycemia based on convention and multiple studies including Krinsley et al. (2014).[50]
- Percentage of patients who had 10% or more of their glucose measurements at a severe hyperglycemic level (glucose ≥ 200 mg/dL). This cutoff of 10% of measurements at a hyperglycemic level represents approximately the top tertile (34%) of all patients in our study. For the purpose of this study, 200 mg/dL or higher will be considered "severe" hyperglycemia. According to the ADA/AACE consensus statement on inpatient glycemic control, any glucose of 140 mg/dL or higher is defined as hyperglycemia.[51] A threshold of 200 mg/dL is the more general threshold used by the ADA/AACE to define hyperglycemia for random blood glucose measurements. A recent study by Plummer et al. (2014)[52] considered 200 mg/dL as the threshold for defining "critical illness associated hyperglycemia."

Potential confounding variables were measured that may be associated with exposure to an insulin protocol and causally related to the outcomes of interest, but not in the causal pathway between exposure and outcome. Previous research done at OHSU with cardiovascular surgery patients identified several variables that influence insulin resistance in patients, including diabetic status, steroids, and adrenergic medications.[53] Degree of insulin resistance is directly related to glucose control. Administration of glucocorticoids affects glucose metabolism, leading to hyperglycemia through increased hepatic production and peripheral insulin resistance.[54] We adjusted for other potential confounding variables that are known to influence glucose metabolism, including receiving total parenteral nutrition[55] and vasopressors.[56]

Covariates adjusted for potential confounding
- Diagnosis of diabetes (2 levels (binary) and 4 levels: None, Pre-diabetes, Type 1, & Type 2)
- Received glucocorticoids (binary)
- Received total parenteral nutrition (TPN) (binary)
- Received tube feed (binary)
- Received nutrition by mouth (binary)
- Received vasopressor (binary)
- Glucose level on admission (continuous)
- Severity of illness: Day 1 SOFA score, delta SOFA from Day 1 → Day 2, and highest SOFA score during admission. Both the change in SOFA score from Day 1 to Day 2 and the max SOFA score have been found to predictors of mortality.[57]

Secondary Outcomes

- Presence of infection documented (not specified whether present on admission)
- Presence of acute kidney injury/acute renal failure documented (not specified whether present on admission)
- ICU length of stay & hospital length of stay
- ICU mortality & hospital mortality: proportion and incidence rate (per 1,000 patient-ICU days or 1,000 patient-hospital days)

Hypotheses

- The mean glucose will be higher in patients on the paper-based protocols (because insulin doses are not as well individualized for the patients degree of insulin resistance). Additionally, the glucose target range was higher in the paper protocols (140-180 mg/dL) than in the computer-based protocol that had a target of maintaining glucose at 150 mg/dL, so I expect this to result in a lower mean glucose.

- Glucose variability will be less in the computer-based protocol (because it has a narrower target and utilizes multiple algorithms that take into account the individual patients sensitivity to insulin, which should allow more precise control).

- EndoTool computer protocol will better control the three main glucose domains: (1) hyperglycemia, (2) glucose variability, and (3) hypoglycemia.

- Receiving glucocorticoids and TPN will be associated with higher mean glucose.

- Patients with worse underlying severity of illness, as quantified by maximum SOFA score and delta SOFA score from day 1 to day 2, will have higher variability of glucose control.

Specific Aim 4: Assess whether there is an interaction between diabetes diagnosis and insulin protocol that influences the association between insulin protocol and glucose control outcomes.

In a large study of almost 45,000 patients conducted by Krinsley et al. (2013), the associations hyperglycemia, hypoglycemia, and glucose variability with mortality were modified by the diagnosis of diabetes. Patients with preexisting diabetes have altered glucose metabolism, with varying degrees of insulin resistance. It seems biologically plausible that patients with

diabetes may respond differently to a computer-based protocol that provides individualized insulin doses compared to a paper protocol that is less individualized for different degrees of insulin resistance.

Hypotheses

- Patients with diabetes will have worse measures of glucose control measures, specifically higher mean glucose, more hyperglycemia, more hypoglycemia, and more glucose variability.

- The degree of influence of the computer protocol compared to the paper protocols on glucose control will differ by presence of diabetes diagnosis. There will be a stronger interaction between diabetes and the paper insulin protocols modifying the relationship between the protocol and the outcome of glucose control measures compared to the computer insulin protocol. I expect the computer protocol to provide a better individualized insulin dose for each patient, minimizing the differences between diabetic and non-diabetic patients in their responses to the protocol.

Hypothetical Example to Demonstrate Potential Interaction

	Mean Glucose (mg/dL)	
No Interaction:	EndoTool	Adult ICU
Diabetic (50%)	145	165
Non-Diabetic (50%)	135	155
Total	140	160
With Interaction:	EndoTool	Adult ICU
Diabetic (50%)	142	170
Non-Diabetic (50%)	138	150
Total	140	160

Table 1. Hypothetical example of mean glucoses in two protocols, stratified by diabetes, with evidence of an interaction of diabetes by protocol on mean glucose
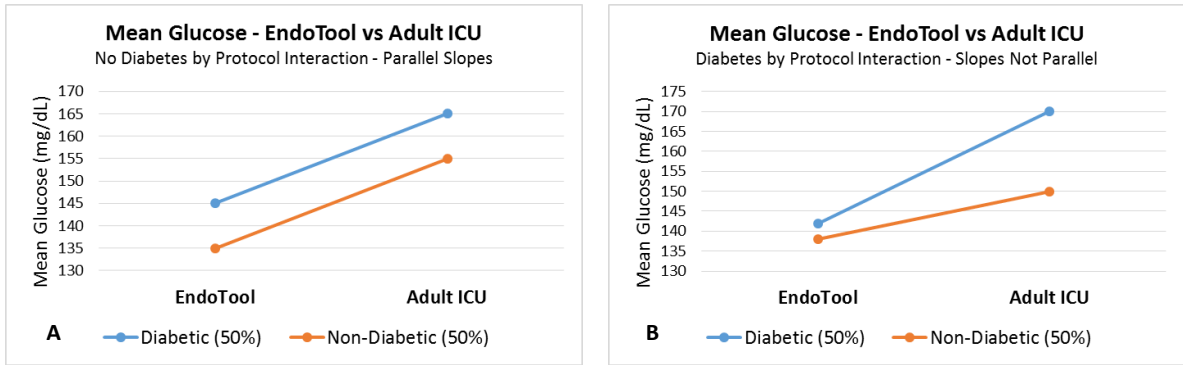
Figure 1. Hypothetical example showing no diabetes by protocol interaction in Graph A (parallel slopes), in contrast with Graph B, which has evidence of a diabetes by protocol interaction (slopes not parallel).

In the hypothetical example without an interaction, diabetic patients are consistently 10 mg/dL higher than non-diabetics in both insulin protocols, and the EndoTool protocol lowers mean glucose by 20 mg/dL in both diabetics and non-diabetics in comparison to the Adult ICU protocol. Diabetes has a significant relationship with mean glucose, with diabetics having mean glucoses 10 mg/dL higher, but this relationship is not changed by which insulin protocol the patient is on. In the example with an interaction occurring, the mean glucoses in the EndoTool group and Adult ICU groups are the same as in the first scenario, with the EndoTool protocol being associated with a 20 mg/dL lower mean glucose, however the relationship between diabetics and mean glucose is different in the EndoTool protocol compared to the Adult ICU protocol. The EndoTool protocol lowered the mean glucose by 28 mg/dL for diabetics, and only 12 mg/dL for non-diabetics, even though overall it lowered mean glucose by the same amount (20 mg/dL) as in the example without an interaction. Additionally, in the EndoTool group, there is much less spread between the diabetics and non-diabetics, with only a 4 mg/dL difference. In the Adult ICU group, there is a much greater difference of 20 mg/dL between the diabetics and non-diabetics. This is evidence of an interaction occurring, where the insulin protocol modifies the relationship between diabetes and the outcome of mean glucose. The interaction can be thought

of either as the relationship between diabetes and outcome being modified by insulin protocol, or as the relationship between insulin protocol and outcome being modified by diabetes.

Directed Acyclic Graph
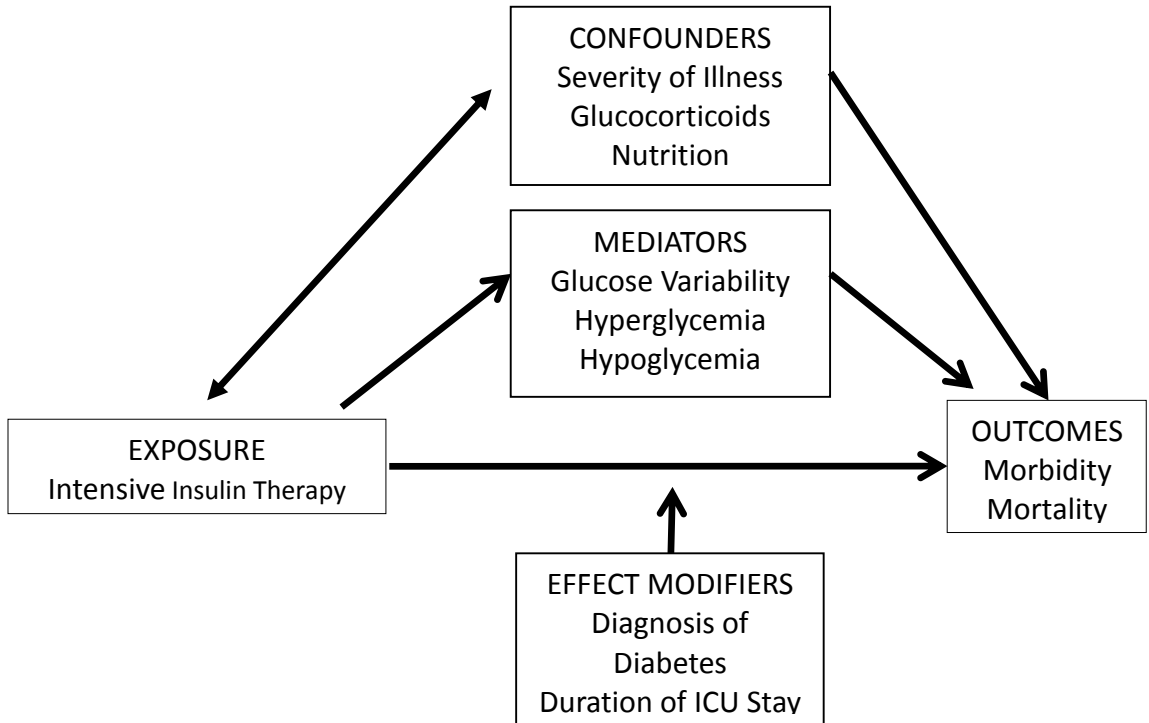
Figure 2. Directed acyclic graph showing the proposed relationship between insulin therapy (exposure) and morbidity & mortality (outcome), including potential confounders, effect modifiers, and mediators.

Dataset

Data Collection

Data collection for the registry began at OHSU in October of 2008. Data were abstracted from the electronic medical records (EMR) of all adult patients in the four adult ICUs who were on a continuous insulin protocol for at least 8 hours. A large group of volunteers participating in the Critical Care Academic Associates Program (CCAAP) were trained to use a data collection

protocol. These volunteers would work shifts in the ICUs, abstracting data onto paper forms and then later entering this into an electronic database.

The data included demographics, admission labs, mechanical ventilation, central line, types of nutrition, inotropes, pressors, blood transfusions, renal failure, infection, and hourly information on insulin doses, glucose measurements (averaged for each hour), dextrose infusions, and glucocorticoids. For at least a few patients, a daily measure of severity of illness was calculated (either a sequential organ failure assessment (SOFA) score, or an Acute Physiology and Chronic Health Evaluation (APACHE) score). These data were then entered into an electronic database.

Throughout 2011, various combinations of variables for different subgroups of patients were exported into dozens of Excel spreadsheets. In almost all of the files that contained hourly info, the midnight hour was missing. Diabetes status was either never recorded, or never exported from the electronic database. Sometime in 2011, it was decided that the data should be transferred to a different electronic database system called Research Electronic Data Capture (REDCap). Unfortunately, there were problems that occurred during exporting the data, and it was never transferred into REDCap. At the time of working on this thesis, the original electronic database was no longer supported and no longer accessible. The only accessible data from 2008-2011 was the collection of Excel files with different patients and different variables exported at different times.

Beginning in January of 2012, patient data were entered into the REDCap database and complete data was available until the end of the study period, October 2013. These data were able to be exported into a format that could be used with Stata statistical software (Stata Intercooled, version 13). Because data were missing from the earlier time period, only the data collected in REDCap from this time period was used for this study.

Quality Control

   Several quality control activities were conducted to ensure validity and reliability. First, each patient's data entry was audited by a second staff member to independently confirm the integrity of the data. Discrepancies were referred to the study coordinator, who made the final decision. Second, each abstractor was trained to follow standardized methods for chart review. Clear definitions for each data element were used to limit ambiguity and the need for interpretation of the medical record by the volunteers doing chart review.

   An audit of each recorded glucose measurement was performed on 27 randomly selected patients to estimate the frequency of hypoglycemic events missed by the use of the one-hour average measurement to represent blood glucose status. A total of 862 recorded glucose values were reviewed (average of 32 per patient) and hourly glucose values were averaged 49 times (5.2% of values). Of these 49 instances where hourly glucose values were averaged, only one hypoglycemic measurement (64 mg/dL) was lost by averaging (2.0%). When all the glucose values that were lost by averaging were included, the mean glucose was only changed by an average of 2.4% and the standard deviation was changed by an average of 11.0%.

   In the process of auditing 27 patients, it was discovered that ICU unit type was misclassified for three patients. In each case, the misclassification occurred because patients were initially were admitted to the medical ICU, had cardiac surgery, and then were transferred to the surgical ICU and started on an insulin protocol. The correct ICU location while receiving an insulin protocol was updated for these patients.

   An audit was was performed for all 172 patients in the surgical ICU on the EndoTool protocol, because it had not been recorded whether the EndoTool patients in the surgical ICU were cardiothoracic surgery patients that had insulin started prophylactically, or whether they were in the category of patients who had the insulin protocol started only after developing hyperglycemia. This allowed the cardiothoracic surgery (CTS) paper protocol to be compared to

the EndoTool protocol. Two thirds of the patients in the surgical ICU on the EndoTool protocol were cardiothoracic surgery patients. See **Appendix F** for a breakdown of the different types of surgeries the patients underwent.

Data Cleaning

Glucose measurements were dropped if they were <20 mg/dL. Glucose values <20 mg/dL were thought to be erroneous, significantly below even the severe hypoglycemia range. A random sample of 10 glucose values <20 was audited and none of them were true values. Most of the values less than 20 were even less than 10, and many had decimal places recorded, whereas the data collection protocol instructed glucose measurements to be averaged to the nearest whole number. The majority of the values were equivalent to the insulin doses that were being given at the time. A total of 238 glucose values <20 were changed to missing in the dataset. There were only eight severe hypoglycemic measurements (<40 mg/dL) that remained after dropping values that were <20. All eight of these values were looked up in the electronic medical record, and only 4 of them were true glucose values. Glucose values were also dropped if they were >2,000, which was only two values. There were an additional six glucose values that were between 1,000-2,000, but these were left in the dataset.

Statistical Analysis

Descriptive Statistics

The pattern of distribution was evaluated for all variables to be used in the analysis, using histograms, box plots, and comparisons of means and medians (see **Appendix E**). Information on the type of distribution was used to determine what type of statistical tests were most appropriate. Baseline characteristics were compared for patients on the three insulin protocols (stratified by ICU) to check for similar distributions of potential confounding variables such as history of diabetes, receiving glucocorticoids or vasopressors, type of nutrition received, and measures of severity of illness (see **Tables 3-5**).

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Univariable Analysis

Linear regression was performed for the primary glucose control measures of mean blood glucose and standard deviation of glucose, with the primary predictor being the insulin protocol as a categorical variable. Linear regression was appropriate because the two dependent variables of interest (mean and standard deviation of glucose) are continuous variables. To meet the assumption of independence, only the first of multiple hospital admissions recorded for the same patient was kept in the dataset. The dependent variables (means and standard deviations of glucose) appeared approximately normal but had some right skew. The mean and standard deviation of glucose were log transformed (natural log), and analysis using both the original and transformed variables was compared.

After performing regression, residuals were calculated and tested for normality so that the assumption of a normal distribution of the dependent variable given the values of the independent variables could be tested. Scatter plots of the residuals versus predicted values were constructed to test the assumption of equal variance of the dependent variable at different values of the independent variables. These residual plots and other diagnostics showed that log-transformed mean glucose and log-transformed standard deviation better met the assumptions of normal distribution and homogeneity of error.

Potential confounding variables that may be associated with mean glucose and standard deviation of glucose were examined one at a time. Scatter plots of mean glucose and standard deviation of glucose versus each potential confounding variable that is continuous were done to test for evidence of a linear relationship. Model diagnostics included calculating residuals and examining residual plots, testing for influential points, and testing for multicollinearity. The normality of the residuals was tested with Q-Q plots and Shapiro Wilk tests (see **Appendix E**). Influential points were assessed by using Cook's distance, leverage, DFFITS, and DFBETAS. Linear regression was repeated with influential points (determined by DFBETAS) omitted, and

the overall fit of the model (e.g. as measured by adjusted r-squared) was improved but the estimates of the mean and standard deviation associated with the protocols was not significantly changed (data not shown). Multicollinearity was assessed by doing pairwise correlations and calculating variance inflation factors.

Potential interactions were assessed before testing and controlling for confounding. An interaction term was created to test whether the type of protocol modifies the association between diabetes and mean glucose and the relationship between diabetes and standard deviation of glucose, since this is one of the primary research questions. Interaction terms were created as the product of an indicator variable for diabetes and an indicator variable for the insulin protocol. The significance of adding the interaction term to the model was tested by a partial F test.

Indicator variables were created for the four ICUs so that we could adjust for ICU location. Prior studies have found differences in the relationship between insulin therapy and mortality depending on the type of ICU the patient is in, suggesting a possible interaction between the type of underlying illness and the harmful effects of altered glucose metabolism.

After testing for interaction, potential confounding was assessed. Covariates were added one at a time to the simple linear regression model containing the dependent variable (mean glucose or standard deviation of glucose) and protocol indicator variable. If the addition of the covariate resulted in 10% or greater change in the Beta coefficient of the protocol indicator variable, the variable was considered to be a confounder (see **Appendix D**).

Incidence of hypoglycemia was calculated as a rate per 100 person-protocol days for each protocol stratified by either cardiothoracic surgery, non-cardiothoracic surgery, or combined ICU group. These rates were used to calculate relative risks of hypoglycemia for each protocol.

Additional outcomes that are continuous and have approximately normal distributions, such as coefficient of variation and percentage of glucose measurements in target range were compared with t-tests. Categorical outcomes that are binary (hypoglycemia, hyperglycemia, acute

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kidney injury, and infection) were compared with two-sample tests of independent proportions. Continuous outcomes such as ICU length of stay that are not normally distributed were compared with Wilcoxon Rank Sum tests. Incidence rates of mortality per 1,000 person-ICU-days and 1,000 person-hospital days were calculated.

Multivariable Analysis

Multivariable linear regression models were built using various methods, including stepwise regression, forward selection, and backwards elimination. Nested regression was also done to test for the joint significance of the addition of multiple variables, such as the nutrition variables. Interaction terms that were not significant were not included in the final models.

In the final multivariable models used to estimate adjusted differences in mean glucose and standard deviation, all of the *a priori* identified potential confounders were included in the model, whether they met the rule of thumb for being a confounder or had significant p-values or not. The primary research questions were related to comparing the mean glucose and standard deviation associated with each insulin protocol, so this was the primary relationship of interest. Our goal was not to build the most parsimonious model in order to be able to accurately predict mean glucose and standard deviation of glucose. Please see **Appendix C** for details of the full multivariable models that were used.

Power and Sample Size Calculations

The overall mean of the mean blood glucose for all patients in the study combined was 148 mg/dL, with a standard deviation of 22. Using a two-sample *t*-test to compare two independent means, a sample size of 125 per group (250 total for two groups) is needed to have 80% power at a 5% significance level to detect a 10 mg/dL absolute difference in mean glucose, assuming equal standard deviations of blood glucose of 22 in each group. This study is more than adequately powered to detect this difference within the surgical ICU (8CSI), which has 415 patients in the Adult ICU paper protocol group, 650 patients in the Cardiothoracic Surgery paper

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protocol group, and 192 patients in the EndoTool computer protocol group. Power and sample size calculations were performed in Stata 13.1 IC (StatCorp LP, College Station, TX).

The overall mean of the standard deviation of glucose for all patients combined was 34 mg/dL, with a standard deviation of 19. Using a two-sample *t*-test to compare two independent means, a sample size of 90 per group (180 total for two groups) is needed to have 80% power at a 5% significance level to detect a 8 mg/dL absolute difference in mean glucose (approximately 24% relative reduction), assuming equal standard deviations of blood glucose of 19 in each group. Again, these estimates indicated a priori, adequate sample size and sufficient statistical power to detect clinically meaningful differences in standard deviation of glucose.

RESULTS

Patient Population

Within the study period (January 2012 – October 2013) a total of 2,452 patients admitted to one of the four adult ICUs at Oregon Health & Science University (OHSU) met inclusion criteria and had data collected. Patient entries that were missing important information such as ICU location, insulin protocol, or alive at ICU or hospital discharge were excluded. Repeat admissions for the same patient were also excluded in order to meet the assumption of independence. After this process, a total of 1,896 patients were included in the analysis (see **Figure 3**).

Demographic information was recorded for each patient, along with basic admission labs, admission glucose level, and other information such as whether the patient had a diagnosis of diabetes. A modified sequential organ failure assessment (SOFA) score was calculated for each patient on the first day of starting an insulin protocol and every day afterwards, and their day one SOFA score was used to compare the baseline severity of illness for five organ systems. Additional information included whether the patient was mechanically ventilated, received vasopressors or glucocorticoids, and the types of nutrition they received, although this was measured for the entirety of the duration of their insulin protocol, not necessarily at the start of their admission (see **Tables 3-5**).

Baseline characteristics were fairly similar with respect to demographic information for most of the subgroups being compared. There were some differences in the severity of illness on day one (as measured by day one SOFA score), and also some differences in the proportion of patients in each subgroup comparison that were diabetic. Admission glucose levels were fairly similar, along with information on mechanical ventilation, vasopressor and glucocorticoid use, and types of nutrition received (see **Tables 3-5**).

Baseline characteristics for diabetic and non-diabetic patients were also compared, showing non-diabetic patients in general to be older, have higher severity of illness, higher admission glucose levels, and be more likely to be intubated, receive vasopressors, and receive glucocorticoids (see **Table 5**). The distributions of ICUs represented by diabetic and non-diabetic patients was quite different, particularly with respect to more non-diabetic patients in the surgical ICU, which likely explains some of these differences.
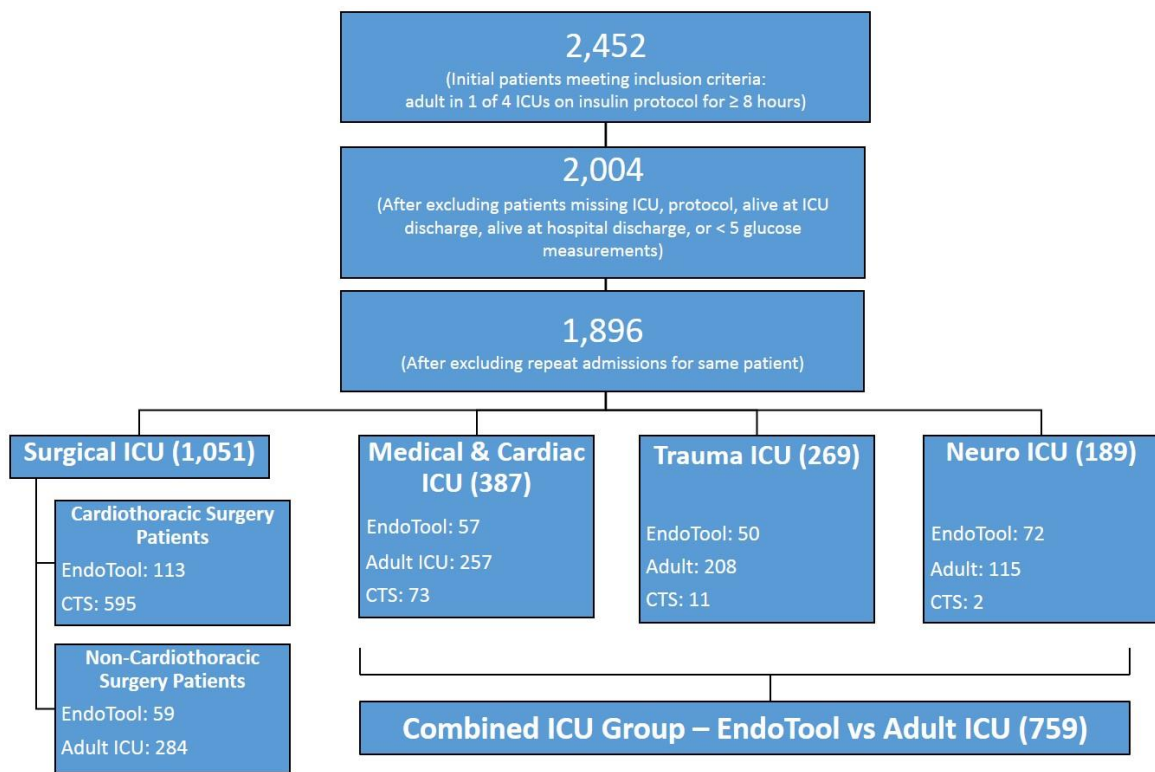
Figure 3. Patient inclusion and exclusion process, ICU distribution, and protocol distribution

Insulin Protocol	Surgical ICU	Medical/Cardiac ICU	Trauma ICU	Neuroscience ICU	Total
Cardiothoracic Surgery (CTS) (Paper)	595 (87.4%)	73 (10.7%)	11 (1.6%)	2 (0.3%)	681
Adult ICU (Paper)	284 (32.9%)	257 (29.8%)	208 (24.1%)	115 (13.3%)	864
EndoTool (Computer)	172 (49.0%)	57 (16.2%)	50 (14.2%)	72 (20.5%)	351
Total	1,051	387	269	189	1,896

Table 2. Exact breakdown of ICU and protocol divisions

Surgical ICU	Cardiothoracic Surgery Patients – Cardiothoracic Surgery Paper Protocol (Target 140-180 mg/dL)	Cardiothoracic Surgery Patients – EndoTool Computer Protocol (Target 150 mg/dL)	Non-Cardiothoracic Surgery Patients – Adult ICU Paper Protocol (Target 140-150 mg/dL)	Non-Cardiothoracic Surgery Patients – EndoTool Computer Protocol (Target 150 mg/dL)
Sample Size	595	113	284	59
Age - yrs (mean, SD)	63.3 yrs (14.5 yrs)	61.7 yrs (14.4 yrs)	62.4 (13.7 yrs)	61.5 yrs (12.5 yrs)
Female sex - no./total (%)	221/595 (37.1%)	40/113 (35.4%)	128/284 (45.1%)	21/59 (35.6%)
Day 1 SOFA Score – median, IQR	6 (5-7)	5 (4-7)	4 (2-5)	3 (1-6)
Day 1 organ failure or dysfunction - no./total (%)				
Pulmonary				
Dysfunction (SOFA 1–2)	213/595 (35.8%)	26/113 (23.0%)	78/284 (27.5%)	11/59 (18.6%)
Failure (SOFA 3–4)	252/595 (42.4%)	27/113 (23.9%)	65/284 (22.9%)	11/59 (18.6%)
Coagulatory				
Dysfunction (SOFA 1–2)	388/595 (65.2%)	73/113 (64.6%)	106/284 (37.3%)	22/59 (37.3%)
Failure (SOFA 3–4)	5/595 (0.8%)	0/113 (0%)	8/284 (2.8%)	0/59 (0%)
Hepatic				
Dysfunction (SOFA 1–2)	37/595 (6.2%)	5/113 (4.4%)	38/284 (13.4%)	6/59 (10.2%)
Failure (SOFA 3–4)	4/595 (0.7%)	0/113 (0%)	4/284 (1.4%)	1/59 (1.7%)
Cardiovascular				
Dysfunction (SOFA 1–2)	59/595 (9.9%)	13/113 (11.5%)	148/284 (52.1%)	23/59 (39.0%)
Failure (SOFA 3–4)	40/595 (6.7%)	3/113 (2.7%)	15/284 (5.3%)	2/59 (3.4%)
Renal				
Dysfunction (SOFA 1–2)	152/595 (25.5%)	28/113 (24.8%)	75/284 (26.4%)	19/59 (32.2%)
Failure (SOFA 3–4)	24/595 (4.0%)	5/113 (4.4%)	20/284 (7.0%)	2/59 (3.4%)
Intubated - no./total (%)	517/593 (87.2%)	90/113 (79.7%)	168/282 (59.6%)	35/59 (59.3%)
Vasopressors - no./total (%)	536/595 (90.1%)	108/113 (95.6%)	107/282 (37.9%)	29/59 (49.2%)
Glucocorticoids - no./total (%)	133/595 (22.4%)	30/113 (26.6%)	89/282 (31.6%)	14/59 (23.7%)
Diabetes – no./total (%)	191/595 (32.1%)	44/113 (38.9%)	122/284 (43.0%)	30/59 (50.9%)
Pre-diabetes - no./total (%)	8/191 (4.2%)	3/44 (6.8%)	2/122 (1.6%)	0/30 (0%)
Type 1 Diabetes - no./total (%)	17/191 (8.9%)	2/44 (4.5%)	10/122 (8.2%)	1/30 (3.3%)
Type 2 Diabetes - no./total (%)	152/191 (79.6%)	36/44 (81.8%)	96/122 (78.7%)	27/30 (90%)
Admission blood glucose – median (IQR)	130 mg/dL (112-153 mg/dL)	126 mg/dL (107-144 mg/dL)	155 mg/dL (129-180 mg/dL)	157 mg/dL (128-186 mg/dL)
Nutrition while on insulin protocol				
Nutrition by mouth - no./total (%)	537/595 (90.3%)	106/113 (93.8%)	143/282 (50.7%)	27/59 (45.8%)
TPN - no./total (%)	5/595 (0.8%)	5/113 (4.42%)	37/282 (13.1%)	13/59 (22.0%)
Tube Feed - no./total (%)	71/595 (11.9%)	12/113 (10.6%)	75/282 (26.6%)	18/59 (30.5%)

Table 3. Baseline Characteristics of Patients in Surgical ICU

Baseline Characteristics	Adult ICU Paper Protocol (Medical/Cardiac ICU)	EndoTool Computer Protocol (Medical/Cardiac ICU)	Adult ICU Paper Protocol (Trauma ICU)	EndoTool Computer Protocol (Trauma ICU)	Adult ICU Paper Protocol (Neuroscience ICU)	EndoTool Computer Protocol (Neuroscience ICU)
Sample Size	257	60	208	50	115	72
Age - yrs (mean, SD)	57.5 (15.6)	58.4 (14.7)	59.3 (13.9)	58.1 (13.1)	59.8 (14.7)	60.1 (13.3)
Female sex - no./total (%)	111/257 (43.2%)	24/60 (40%)	78/208 (37.5%)	20/50 (40.0%)	54/115 (47%)	42/72 (58.3%)
Day 1 SOFA Score – median, IQR	5 (2-8)	4 (2-7)	3 (1-6)	3 (1-6)	2* (1-4)	2* (1-4)
Day 1 Organ failure or dysfunction - no. (%)						
Pulmonary						
Dysfunction (SOFA 1–2)	40/257 (15.6%)	8/60 (13.3%)	65/208 (31.3%)	8/50 (16.0%)	24/115 (20.9%)	14/72 (19.4%)
Failure (SOFA 3–4)	66/257 (25.7%)	5/60 (8.3%)	34/208 (16.3%)	6/50 (12.0%)	20/115 (17.4%)	11/72 (15.3%)
Coagulatory						
Dysfunction (SOFA 1–2)	79/257 (30.7%)	15/60 (25.0%)	73/208 (35.1%)	25/50 (50.0%)	28/115 (24.3%)	12/72 (16.7%)
Failure (SOFA 3–4)	37/257 (14.4%)	13/60 (21.7%)	16/208 (7.7%)	5/50 (10.0%)	4/115 (3.5%)	0/72 (0%)
Hepatic						
Dysfunction (SOFA 1–2)	50/257 (19.5%)	10/60 (16.7%)	31/208 (14.9%)	10/50 (20.0%)	9/115 (7.8%)	3/72 (4.2%)
Failure (SOFA 3–4)	13/257 (5.1%)	5/60 (8.3%)	11/208 (5.3%)	2/50 (4.0%)	0/115 (0%)	0/72 (0%)
Cardiovascular						
Dysfunction (SOFA 1–2)	108/257 (42.0%)	20/60 (33.3%)	104/208 (50.0%)	23/50 (46.0%)	54/115 (47.0%)	29/72 (40.3%)
Failure (SOFA 3–4)	40/257 (15.6%)	9/60 (15.0%)	19/208 (9.1%)	2/50 (4.0%)	9/115 (7.8%)	3/72 (4.2%)
Renal						
Dysfunction (SOFA 1–2)	91/257 (35.4%)	15/60 (25.0%)	53/208 (25.5%)	17/50 (34.0%)	23/115 (20.0%)	7/72 (9.7%)
Failure (SOFA 3–4)	58/257 (22.6%)	11/60 (18.3%)	15/208 (7.2%)	2/50 (4.0%)	2/115 (1.7%)	4/72 (5.6%)
Intubated - no./total (%)	149/257 (58.0%)	31/60 (51.7%)	134/208 (64.4%)	34/50 (68.0%)	69/115 (60.0%)	40/72 (55.6%)
Vasopressors - no./total (%)	104/257 (40.5%)	24/60 (40.0%)	64/206 (31.1%)	12/50 (24.0%)	34/115 (29.6%)	17/72 (23.6%)
Glucocorticoids - no./total (%)	112/257 (43.6%)	25/60 (41.7%)	80/207 (38.7%)	16/50 (32.0%)	57/115 (49.6%)	29/72 (40.3%)
Diabetes - no./total (%)	162/257 (63.0%)	35/60 (58.3%)	86/207 (41.5%)	29/50 (58.0%)	72/115 (62.6%)	32/72 (44.4%)
Pre-diabetes - no./total (%)	2/162 (1.2%)	0/35 (0.0%)	3/86 (3.4%)	1/29 (3.4%)	1/72 (1.4%)	1/32 (3.1%)
Type 1 Diabetes - no./total (%)	23/162 (14.2%)	4/35 (11.4%)	6/86 (7.0%)	2/29 (6.9%)	6/72 (8.3%)	4/32 (12.5%)
Type 2 Diabetes - no./total (%)	120/162 (74.1%)	27/35 (77.1%)	64/86 (74.4%)	24/29 (82.8%)	56/72 (77.8%)	23/32 (71.9%)
Admission blood glucose – median (IQR)	195 (144-289)	209 (151–251)	176 (146-223)	184 (153-217)	189 (148-247)	172 (135-210)
Nutrition while on insulin protocol						
Nutrition by mouth - no./total (%)	151/257 (58.8%)	37/60 (61.7%)	114/207 (55.1%)	25/50 (50.0%)	57/115 (49.6%)	38/72 (52.8%)
TPN - no./total (%)	20/257 (7.8%)	3/60 (5.0%)	14/207 (6.8%)	2/50 (4.0%)	3/115 (2.6%)	3/72 (4.2%)
Tube Feed - no./total (%)	104/257 (40.5%)	18/60 (30.0%)	68/207 (32.9%)	20/50 (40.0%)	63/115 (54.8%)	36/72 (50.0%)

Table 4. Baseline Characteristics of Study Patients in Other ICUs (Medical/Cardiac, Trauma, Neuroscience)

* Modified SOFA score lacking neurologic component (based on Glasgow Coma Scale), particularly relevant for the Neuroscience ICU

Baseline Characteristics	Diabetic Patients	Non-Diabetic Patients
ICU Location Distribution	Surgical: 387/838 (46.2%) Medical/Cardiac: 223/838 (26.6%) Trauma: 122/838 (14.6%) Neuroscience: 106/838 (12.7%)	Surgical: 664/1,057 (62.8%) Medical/Cardiac: 164/1,057 (15.5%) Trauma: 146/1,057 (13.8%) Neuroscience: 83/1,057 (7.9%)
Age - yrs (mean, SD)	62.6 yrs (12.9 yrs)	59.6 yrs (15.5 yrs)
Female sex - no./total (%)	344/838 (41.1%)	418/1,057 (39.6%)
Day 1 SOFA Score – median, IQR	4 (2-7)	5 (3-7)
Day 1 Organ failure or dysfunction - no./total (%)		
Pulmonary		
Dysfunction (SOFA 1–2)	183/838 (21.8%)	328/1,057 (31.0%)
Failure (SOFA 3–4)	221/838 (26.4%)	319/1,057 (30.2%)
Coagulatory		
Dysfunction (SOFA 1–2)	316/838 (37.7%)	552/1,057 (52.2%)
Failure (SOFA 3–4)	28/838 (3.3%)	60/1,057 (5.7%)
Hepatic		
Dysfunction (SOFA 1–2)	93/838 (11.1%)	128/1,057 (12.1%)
Failure (SOFA 3–4)	8/838 (1.0%)	32/1,057 (3.0%)
Cardiovascular		
Dysfunction (SOFA 1–2)	320/838 (38.2%)	274/1,057 (25.9%)
Failure (SOFA 3–4)	57/838 (6.8%)	95/1,057 (9.0%)
Renal		
Dysfunction (SOFA 1–2)	268/838 (32.0%)	252/1,057 (23.8%)
Failure (SOFA 3–4)	86/838 (10.3%)	59/1,057 (5.6%)
Intubated - no./total (%)	506/836 (60.5%)	832/1,054 (78.9%)
Vasopressors - no./total (%)	407/837 (48.6%)	699/1,054 (66.3%)
Glucocorticoids - no./total (%)	252/837 (30.1%)	360/1,055 (34.1%)
Admission blood glucose – median (IQR)	164 (132-221)	140 (114-172)
Nutrition while on insulin protocol		
Nutrition by mouth - no./total (%)	615/837 (73.5%)	691/1,055 (65.5%)
TPN - no./total (%)	40/837 (4.8%)	67/1,055 (6.4%)
Tube Feed - no./total (%)	225/837 (26.9%)	277/1,055 (26.3%)

Table 5. Baseline characteristics of diabetic and non-diabetic patients in all ICUs combined

Cardiothoracic surgery patients in a surgical ICU

Cardiothoracic surgery patients were automatically placed on a continuous insulin infusion protocol post-operatively, regardless of their current glucose level. In contrast, patients in the medical and cardiac, surgical, and neuroscience ICUs were only started on an insulin protocol after developing hyperglycemia to 180 mg/dL. Since the method by which the insulin protocol was initiated was different for cardiothoracic surgery patients, the computer protocol (EndoTool) was compared to the paper protocol (Cardiothoracic Surgery, CTS) separately for these patients. The EndoTool protocol provided individualized insulin doses with the goal of maintaining glucose stable at 150 mg/dL, whereas the CTS protocol provided standardized doses with the goal of maintaining glucose between 140-180 mg/dL.

Cardiothoracic surgery patients on EndoTool had lower mean glucose levels than patients on the paper-based Cardiothoracic Surgery (CTS) protocol (median 130.9 mg/dL vs 138.8 mg/dL, respectively; $p<0.0001$). Patients on the EndoTool protocol had significantly fewer hyperglycemic measurements (≥ 200 mg/dL) than those on the CTS protocol, with only 6.2% of EndoTool patients having 10% or greater of their glucose measurements at a hyperglycemic level, compared to 15.5% of CTS patients. There was no significant difference in variability of glucose control, as measured by standard deviation and coefficient of variation (standard deviation/mean). The overall incidence of moderate (<70 mg/dL) or severe (<40 mg/dL) hypoglycemia combined, when measured as total number of hypoglycemic measurements per 100 person-protocol days was higher in the EndoTool group compared to the CTS group (5.83 vs 3.57, respectively; RR = 1.63 (95% CI 0.99-2.59), $p=0.041$). There was a trend towards a higher proportion of people in

the EndoTool group having at least one moderate or severe hypoglycemic measurement compared to the CTS group, but the difference was not statistically significant (13.3% vs 8.7% for moderate or severe hypoglycemia combined, p=0.13). Severe hypoglycemia (<40 mg/dL) was rare in the CTS group (2/595 (0.34%)) and did not occur in the EndoTool group (see **Table 6**).

Non-cardiothoracic surgery patients in a surgical ICU

Non-cardiothoracic surgery patients in the surgical ICU on the EndoTool protocol also had significantly lower mean glucoses than non-cardiothoracic surgery patients on the other paper protocol, Adult ICU (median 127.2 mg/dL vs 142.9 mg/dL, respectively; p<0.0001). Similarly to the cardiothoracic surgery patients, there was significantly fewer hyperglycemic measurements in the EndoTool group compared to the Adult ICU group (8.5% with 10% or more of measurements at a hyperglycemic level compared to 28.5%, p=0.0012). There was decreased glucose variability as measured by standard deviation after adjusting for potential cofounders (p=0.039), but not in the crude comparison. The other measure of glucose variability, coefficient of variation, did not show any difference. There was not a significant difference in incidence of hypoglycemia for non-cardiothoracic surgery patients, whether measured as a combined incidence per 100 person-ICU days, or as a proportion of patients who had at least one moderate or severe hypoglycemic measurement. Severe hypoglycemia did not occur in either group (see **Table 7**).

Combined ICU Group (Medical/Cardiac, Trauma, & Neuroscience)

Patients in the combined ICU group who were on the EndoTool protocol had significantly lower mean glucoses than patients on the Adult ICU paper protocol (median 141.5 mg/dL vs 159.9 mg/dL, respectively; p<0.0001). The proportion of patients on the EndoTool protocol who had 10% or more hyperglycemic measurements was significantly lower compared to patients on the Adult ICU protocol (35.2% vs 64.1%, p<0.0001). Variability of glucose control

as measured by standard deviation was significantly lower in the EndoTool group compared to the Adult ICU group (median 32.3 mg/dL vs 39.5 mg/dL, p=0.0001), but coefficient of variation was not significantly different. Combined incidence of moderate or severe hypoglycemia (per 100 person-protocol days) was significantly higher for patients on the EndoTool protocol (5.02 hypoglycemic measurements per 100 person-protocol days vs 3.17, RR=1.58 (95% CI: 1.02-2.41, p=0.031)). The crude proportion of people on each protocol with at least one moderate or severe hypoglycemic measurement was not significantly different (11.7% on EndoTool; 9.0% on Adult ICU). Severe hypoglycemia (<40 mg/dL) was rare in the Adult ICU group (2/580 (0.34%)) and did not occur in the EndoTool group (see **Table 8**).

In the combined ICU group, the incidence of moderate hypoglycemia (<70 mg/dL), as measured by number of hypoglycemic measurements per 100 person-protocol days, was higher in the EndoTool group compared to the Adult ICU group. The difference was most dramatic within the trauma ICU, and much smaller in the medical/cardiac and neuroscience ICUs. In terms of crude proportions of patients in each group who had one or more moderate hypoglycemic measurement, the EndoTool groups in each ICU except for the trauma ICU actually had less hypoglycemia. When taking into account the total number of hypoglycemic measurements and the at-risk time each patient contributed while on an insulin protocol, the incidence rate of moderate hypoglycemia was a little higher in each ICU subgroup (see **Table 9**).

Cardiothoracic Surgery Patients (Surgical ICU)	Cardiothoracic Surgery (CTS) Paper Protocol (Target 140-180 mg/dL) – N=595	EndoTool Computer Protocol (Target 150 mg/dL) – N=113	EndoTool vs CTS	EndoTool vs CTS (Adjusted*)
Mean Glucose - median (IQR)	138.8 mg/dL (132.7 – 146.5 mg/dL)	130.9 mg/dL (124.3 – 135.4 mg/dL)	EndoTool 7.3% lower than CTS (95% CI: 9.3% lower to 5.4% lower) p<0.0001	EndoTool 7.2% lower than CTS (95% CI: 8.7% lower to 5.6% lower) p<0.001
Standard Deviation - median (IQR)	24.3 mg/dL (18.8 – 32.4 mg/dL)	23.1 mg/dL (18.6 – 29.7 mg/dL	NS (p=0.18)	NS (p=0.14)
Coefficient of Variation - median (IQR)	17.8% (14.1% - 22.4%)	18.3% (14.7% - 23.1%)	NS (p=0.68)	---
Percent of glucose measurements between 140-180 mg/dL – mean (95% CI)	35.7% (34.5% - 36.9%)	24.0 (21.7% - 26.2%)	Absolute difference (EndoTool – CTS): EndoTool 11.7 percentage points lower than CTS (95% CI: 14.6 percentage points lower to 8.8 percentage points lower) p<0.0001	---
One or more moderate hypoglycemic measurements (<70 mg/dL) – no/total (%)	52/595 (8.7%)	15/113 (13.3%)	NS (p=0.13)	---
Incidence of Hypoglycemia/100 person-protocol days (95% CI)	3.57 (2.87 – 4.46)	5.83 (3.98 – 8.52)	Relative Risk (EndoTool/CTS): 1.63 (95% CI: 0.994 – 2.59) p=0.041	---
One or more severe hypoglycemic measurements (<40 mg/dL)	2/595 (0.34%)	0/113 (0%)	NS (p=0.54)	---
≥ 10% Severe Hyperglycemia (≥ 200 mg/dL) – no./total (%)	92/595 (15.5%)	7/113 (6.2%)	Absolute difference (EndoTool – CTS) EndoTool 9.27 percentage points lower than CTS (95% CI: 3.96 percentage points lower to 14.57 percentage points lower) p=0.0092	---

Table 6. Primary Outcomes – Cardiothoracic surgery patients in surgical ICU
*Adjusted for diabetes, admission glucose, nutrition (oral, tube feed, and TPN), glucocorticoid use, vasopressor use, and day 1 SOFA score.

Non-cardiothoracic Surgery Patients (Surgical ICU)	Adult ICU Paper Protocol (Target 140-180 mg/dL) – N=284	EndoTool Computer Protocol (Target 150 mg/dL) – N=59	EndoTool vs Adult ICU	EndoTool vs Adult ICU (Adjusted*)
Mean Glucose - median (IQR)	142.9 mg/dL (135.0 – 151.3 mg/dL)	127.2 mg/dL (119.6 – 135.5 mg/dL)	EndoTool 13.0% lower than Adult ICU (95% CI: 16.2% lower to 9.9% lower) p<0.0001	EndoTool 11.4% lower than Adult ICU (95% CI: 13.7% lower to 9.1% lower) p<0.001
Standard Deviation - median (IQR)	27.9 mg/dL (20.3 – 39.3 mg/dL)	27.3 mg/dL (17.5 – 33.0 mg/dL)	NS (p=0.075)	EndoTool 13.3% lower than Adult ICU (95% CI: 24.3% lower to 0.7% lower) p=0.039
Coefficient of Variation - median (IQR)	20.3% (14.8% - 25.9%)	21.3% (14.2% - 25.6%)	NS (p=0.92)	---
Percent of glucose measurements between 140-180 mg/dL – mean (95% CI)	35.7% (33.8% - 37.6%)	20.8% (16.9% - 24.8%)	Absolute difference (EndoTool – Adult ICU): EndoTool 14.9 percentage points lower than Adult ICU (95% CI: 19.4% percentage points lower to 10.3% percentage points lower)	---
One or more moderate hypoglycemic measurements (<70 mg/dL) – no/total (%)	24/284 (8.45%)	6/59 (10.17%)	NS (p=0.67)	---
Incidence of moderate hypoglycemia/100 person-protocol days (95% CI)	3.93 (2.95 – 5.24)	4.11 (2.17 – 7.79)	NS (p=0.87)	---
One or more severe hypoglycemic measurement (<40 mg/dL)	0/284 (0%)	0/59 (0%)	No Difference	---
≥ 10% Severe Hyperglycemia (≥ 200 mg/dL) – no./total (%)	81/284 (28.5%)	5/59 (8.5%)	Absolute difference (EndoTool - Adult ICU) 20.05 percentage points (95% CI: 11.21% lower to 28.88% lower) p=0.0012	---

Table 7. Primary Outcomes – Non-cardiothoracic surgery patients in surgical ICU
*Adjusted for diabetes, admission glucose, nutrition (oral, tube feed, and TPN), glucocorticoid use, vasopressor use, and day 1 SOFA score.

Combined ICU Group (Medical/Cardiac, Trauma, Neuroscience)	Adult ICU Paper Protocol (Target 140-180 mg/dL) – N=580	EndoTool Computer Protocol (Target 150 mg/dL) – N=179	EndoTool vs Adult ICU	EndoTool vs Adult ICU (Adjusted*)
ICU Location Distribution – no./total (%)	Medical/cardiac ICU: 257/580 (44.3%) Trauma ICU: 208/580 (35.9%) Neuroscience ICU: 115/580 (19.8%)	Medical/cardiac ICU: 57/179 (31.8%) Trauma ICU: 50/179 (27.9%) Neuroscience ICU: 72/179 (40.2%)	NA	NA
Mean glucose - median (IQR)	159.9 mg/dL (148.6 – 176.2 mg/dL)	141.5 mg/dL (131.6 – 150.4 mg/dL)	EndoTool 12.6% lower than Adult ICU (95% CI: 14.6% lower to 10.6% lower) p<0.0001	EndoTool 11.7% lower than Adult ICU (95% CI: 13.7% lower to 9.7% lower)
Standard deviation - median (IQR)	39.5 mg/dL (29.4 – 52.2)	32.3 mg/dL (24.6 – 45.2 mg/dL)	EndoTool 14.5% lower than Adult ICU (95% CI: 20.8% lower to 7.6% lower) p=0.0001	EndoTool 10.2% lower than Adult ICU (95% CI: 16.6% lower to 3.3% lower) p=0.005
Coefficient of variation - median (IQR)	25.0% (19.3% - 31.1%)	23.1% (18.3% - 31.4%)	NS (p=0.52)	---
Percent of glucose measurements between 140-180 mg/dL – mean (95% CI)	37.3% (36.0% - 38.6%)	28.5% (26.2% - 30.8%)	Absolute difference (EndoTool – Adult ICU): -8.78 percentage points (95% CI: 11.42 percentage points lower to 6.13 percentage points lower) p<0.0001	---
One or more moderate hypoglycemic measurements (<70 mg/dL) – no/total (%)	52/580 (8.97%)	21/179 (11.7%)	NS (p=0.27)	---
Incidence of moderate hypoglycemia/100 person-protocol days (95% CI)	3.17 (2.52-3.98)	5.02 (3.62-6.97)	Relative Risk (EndoTool/Adult ICU): 1.58 (95% CI: 1.02 – 2.41) p=0.031	---
One or more severe hypoglycemic measurement (<40 mg/dL)	2/580 (0.34%)	0/179 (0%)	NS (p=0.43)	---
≥ 10% Severe Hyperglycemia (≥ 200 mg/dL) – no./total (%)	372/580 (64.1%)	63/179 (35.2%)	EndoTool 28.9% lower than Adult ICU (95% CI: 20.9% lower to 37.0% lower) p<0.0001	---

*Adjusted for ICU location, diabetes, admission glucose, nutrition (oral, tube feed, and TPN), glucocorticoid use, vasopressor use, and day 1 SOFA score.
Table 8. Primary Outcomes – Combined ICU Group (Medical/Cardiac, Trauma, Neuroscience)

EndoTool vs Adult ICU – Primary Outcomes Stratified by ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Medical/Cardiac ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Medical/Cardiac ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Trauma ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Trauma ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Neuroscience ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Neuroscience ICU
Sample Size	257	57	208	50	115	72
Mean glucose - median (IQR)	166.8 mg/dL (151.2 – 181.1 mg/dL)	143.1 mg/dL (132.3 – 153.2 mg/dL)	156.9 mg/dL (146.8 – 166.9 mg/dL)	140.9 mg/dL (134.3 – 153.1 mg/dL)	158.8 mg/dL (148.5 – 170.4 mg/dL)	141.3 mg/dL (129.5 – 147.9 mg/dL)
Standard deviation - median (IQR)	44.9 mg/dL (32.3 – 60.5 mg/dL)	35.2 mg/dL (26.2 – 49.3 mg/dL)	36.5 mg/dL (27.9 – 45.7 mg/dL)	35.8 mg/dL (26.5 – 54.8 mg/dL)	38.4 mg/dL (28.4 – 48.1 mg/dL)	29.6 mg/dL (23.2 – 40.0 mg/dL)
Coefficient of variation - median (IQR)	27.0% (21.6% - 33.8%)	25.6% (18.6 – 32.7%)	23.6% (18.1% - 28.9%)	24.6% (20.4% - 34.6%)	23.4% (17.8% - 29.0%)	22.2% (16.7% - 28.2%)
Percent of glucose measurements between 140-180 mg/dL – mean (95% CI)	35.2% (33.3% - 37.0%)	27.4% (23.3% - 31.6%)	38.5% (36.3% - 40.7%)	26.8% (22.6% - 30.9%)	39.8% (36.9% - 42.8%)	30.6% (26.7% - 34.4%)
One or more moderate hypoglycemic measurements (<70 mg/dL) – no/total (%)	31/257 (12.1%)	6/57 (10.5%)	10/208 (4.8%)	9/50 (18.0%)	11/115 (9.6%)	6/72 (8.3%)
Incidence of Hypoglycemia/100 person-protocol days (95% CI)	4.29 (3.23 – 5.71)	4.62 (2.44 – 8.74)	2.18 (1.34-3.54)	7.51 (4.69-12.03)	2.24 (1.25-4.03)	3.35 (1.76 – 6.36)
At least one severe hypoglycemic measurement (<40 mg/dL)	1/257 (0.39%)	0/57 (0%)	1/208 (0.48%)	0/50 (0%)	0/115 (0%)	0/72 (0%)
≥ 10% Severe Hyperglycemia (≥ 200 mg/dL) – no./total (%)	182/257 (70.8%)	26/57 (45.6%)	123/208 (59.1%)	19/50 (38.0%)	67/115 (58.3%)	18/72 (25.0%)

Table 9. Primary outcomes stratified by the ICUs that make up the Combined ICU group

Secondary Outcomes

There were no significant differences in the three overall comparisons of patients in terms of ICU and hospital length of stay, ICU and hospital mortality, insulin protocol days, or infection (see **Table 10**, **Table 11**, and **Table 12**. Within the trauma ICU, which was one of the three ICUs in the combined ICU group, the mortality associated with the EndoTool protocol was much higher than the Adult ICU protocol (22.0% vs 11.5%), though it was not quite statistically significant (p=0.0524) (see **Table 13**).

In the combined ICU group, there was less renal failure in EndoTool group compared to the Adult ICU group, and this was true within each of the three ICUs individually. More people in the Adult ICU protocol groups had renal dysfunction or failure on day one of their insulin

protocol being started, as defined by day 1 SOFA scores. In addition, within the combined ICU group, the Adult ICU protocol had a higher representation of patients in the medical and cardiac ICU, which also had a higher prevalence of renal failure than the other two ICUs.

In order to evaluate for a general association between increasing mean glucose and increasing mortality, the entire cohort of patients was divided into six intervals of mean glucose, and the overall hospital mortality was compared for each of these subgroups. There was evidence of a consistent increase in mortality associated with increasing mean glucose achieved (see **Figure 4**). A Cochran-Armitage test for trend was highly significant (chi-square for trend = 36.8, p<0.0001).

When the patients in the study were divided into approximate quartiles of mean glucose achieved, and stratified into approximate tertiles of severity of illness based on day one SOFA scores, there was evidence of a dose response pattern of increased mortality as mean glucose increased within the same approximate level of severity of illness (see **Figure 5**). An extended Mantel-Haenszel test for trend, stratified by SOFA category, was significant (correlation statistic Q: 38.13, p<0.0001). A similar trend was seen when patients were divided into approximate quartiles of standard deviation of glucose and stratified by approximate tertiles of severity of illness (see **Figure 6**). Once again, an extended Mantel-Haenszel test for trend, stratified by SOFA category, was significant (correlation statistic Q: 47.50, p<0.0001). A similar process was done to compare mortality for patients with and without moderate hypoglycemia, stratified by approximate tertile of severity of illness. In this case, there was not a significant difference in mortality between those who had hypoglycemia compared to those without (see **Figure 7**).

Cardiothoracic Surgery Patients (Surgical ICU)	Cardiothoracic Surgery Paper Protocol (Target 140-180 mg/dL)	EndoTool Computer Protocol (Target 150 mg/dL)	EndoTool vs CTS
Sample Size	595	113	---
Insulin Protocol Days – median (IQR)	3 (2-4)	3 (2-4)	NS
ICU Length of Stay – median (IQR)	4 (3-7)	4 (3-5)	NS
Hospital Length of Stay – median (IQR)	8 (6-12)	8 (6-11)	NS
Renal Failure During Hospitalization – no./total (%)	121/595 (20.34%)	21/113 (18.58%)	NS (p=0.67)
Infection During Hospitalization – no./total (%)	70/595 (11.8%)	18/113 (15.9%)	NS (p=0.22)
Day 1 SOFA Score – median, IQR (Baseline Reference)	6 (5-7)	5 (4-7)	---
Delta SOFA (Day 1 → Day 2)			
Improved - no./total (%)	482/595 (81.0%)	85/113 (75.2%)	---
No Change - no./total (%)	58/595 (9.7%)	16//113 (14.2%)	---
Worsened - no./total (%)	55/595 (9.2%)	12/113 (10.6%)	---
Highest SOFA Score – median (IQR)	7 (5-8)	5 (4-7)	---
ICU Mortality – no./total (%)	12/595 (2.02%)	1/113 (0.88%)	NS (p=0.41)
ICU Mortality Incidence Rate per 1,000 person-ICU days (95% CI)	3.39 (1.92 – 5.97)	1.52 (0.21 – 10.76)	NS (p=0.48)
Hospital Mortality – no./total (%)	15/595 (2.52%)	2/113 (1.77%)	NS (p=0.63)
Hospital Mortality Incidence Rate per 1,000 person-hospital days (95% CI)	2.322 (1.400 – 3.851)	1.621 (0.405 – 6.481)	NS (p=0.69)

Table 10. Secondary outcomes - Cardiothoracic surgery patients in surgical ICU

Non-cardiothoracic Surgery Patients (Surgical ICU)	Adult ICU Paper Protocol (Target 140-180 mg/dL)	EndoTool Computer Protocol (Target 150 mg/dL)	EndoTool vs Adult ICU
Sample Size	284	59	NA
Insulin Protocol Days – median (IQR)	3 (2-4)	3 (2-4)	No difference
ICU Length of Stay – median (IQR)	3 (4-10)	3 (5-8)	No difference
Hospital Length of Stay – median (IQR)	11 (7-20)	10 (6-22)	NS (p=0.70) [Wilcoxon Rank-Sum Test]
Renal Failure During Hospitalization – no./total (%)	65/284 (22. 9%)	9/59 (15.3%)	NS (p=0.19)
Infection During Hospitalization – no./total (%)	118/284 (41.6%)	24/59 (40.7%)	NS (p=0.90)
Day 1 SOFA Score – median, IQR (Baseline Reference)	4 (2-5)	3 (1-6)	---
Delta SOFA (Day 1 → Day 2)			
Improved - no./total (%)	163/284 (57.4%)	35/59 (59.3%)	---
No Change - no./total (%)	72/284 (25.4%)	15/59 (25.4%)	---
Worsened - no./total (%)	49/284 (17.3%)	9/59 (15.3%)	---
Highest SOFA Score – median (IQR)	4 (2-7)	4 (2-6)	---
ICU Mortality – no./total (%)	19/284 (6.7%)	6/59 (10.2%)	NS (p=0.65)
ICU Mortality Incidence Rate per 1,000 person-ICU days (95% CI)	7.74 (4.94 – 12.14)	11.65 (5.23 – 25.93)	NS (p=0.39)
Hospital Mortality – no./total (%)	25/284 (8.8%)	8/59 (13. 6%)	NS (p=0.26)
Hospital Mortality Incidence Rate per 1,000 person-hospital days (95% CI)	5.45 (3.68 – 8.07)	8.69 (4.34 – 17.37)	NS (p=0.26)

Table 11. Secondary outcomes - Non-cardiothoracic surgery patients in surgical ICU

| Combined ICU Group (Medical/Cardiac, Trauma, Neuroscience)	Adult ICU Paper Protocol (Target 140-180)	EndoTool Computer Protocol (Target 150)	EndoTool vs Adult ICU
ICU Distribution – no./total (%)	Medical/Cardiac ICU: 257/580 (44.3%) Trauma ICU: 208/580 (35.9%) Neuroscience ICU: 115/580 (19.8%)	Medical/Cardiac ICU: 57/179 (31.8%) Trauma ICU: 50/179 (27.9%) Neuroscience ICU: 72/179 (40.2%)	NA
Insulin Protocol Days – median (IQR)	3 (2-4)	3 (2-4)	NS
ICU Length of Stay – median (IQR)	5 (3-11)	5 (3-12)	NS
Hospital Length of Stay – median (IQR)	11 (6-20)	11 (5-23)	NS
Renal Failure During Hospitalization – no./total (%)	176/580 (30.3%)	32/179 (17.9%)	p=0.0011
Infection During Hospitalization – no./total (%)	274/580 (47.2%)	87/179 (48.6%)	NS (p=0.75)
Day 1 SOFA Score – median, IQR (Baseline Reference)	4 (2-7)	3 (1-5)	---
Delta SOFA (Day 1 → Day 2)			
Improved - no./total (%)	326/580 (56.2%)	82/179 (45.8%)	---
No Change - no./total (%)	148/580 (25.5%)	64/179 (35.8%)	---
Worsened - no./total (%)	106/580 (18.3%)	33/179 (18.4%)	---
Highest SOFA Score – median (IQR)	5 (2-8)	4 (1-6)	---
ICU Mortality – no./total (%)	84/580 (14.5%)	25/179 (14.0%)	NS (p=0.86)
ICU Mortality Incidence Rate per 1,000 person-ICU days (95% CI)	16.96 (13.72 – 20.97)	16.31 (11.05 – 24.06)	NS (p=0.96)
Hospital Mortality – no./total (%)	104/580 (17.9%)	33/179 (18.4%)	NS (p=0.88)
Hospital Mortality Incidence Rate per 1,000 person-hospital days (95% CI)	11.26 (9.30 – 13.63)	11.89 (8.47 – 16.69)	NS (p=0.77)

Table 12. Secondary outcomes in Combined ICU group

EndoTool vs Adult ICU – Secondary Outcomes Stratified by ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Medical/cardiac ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Medical/cardiac ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Trauma ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Trauma ICU	Adult ICU Paper Protocol (Target 140-180 mg/dL) – Neuroscience ICU	EndoTool Computer Protocol (Target 150 mg/dL) – Neuroscience ICU
Sample Size	257	57	208	50	115	72
Insulin Protocol Days – median (IQR)	3 days (2-5 days)	2 days (2-4 days)	2 days (2-4 days)	3 days (2-4 days)	3 days (2-6 days)	3 days (2-5 days)
ICU Length of Stay – median (IQR)	6 days (3-10 days)	4 days (3-13 days)	4 days (3-9 days)	5 days (3-9 days)	8 days (4-15 days)	6 days (3-13 days)
Hospital Length of Stay – median (IQR)	10 days (6-18 days)	9 days (5-26 days)	10 days (7-19 days)	10 days (6-24 days)	13 days (6-25 days)	12 days (6-17 days)
Renal Failure During Hospitalization – no./total (%)	126/257 (49.0%)	22/57 (38.6%)	37/208 (17.8%)	6/50 (12.0%)	13/115 (11.3%)	4/72 (5.6%)
Infection During Hospitalization – no./total (%)	126/257 (49.0%)	28/57 (49.1%)	85/208 (40.9%)	28/50 (56.0%)	63/115 (54.8%)	31/72 (43.1%)
Day 1 SOFA Score – median, IQR (Baseline Reference)	5 (2-8)	4 (2-7)	3 (1-6)	3 (1-6)	2* (1-4)	2* (1-4)
Delta SOFA (Day 1 → Day 2)						
Improved - no./total (%)	146/257 (56.8%)	34/60 (56.7%)	125/208 (60.1%)	19/50 (38.0%)	55/115 (47.8%)	32/72 (44.4%)
No Change - no./total (%)	65/257 (25.3%)	22/60 (36.7%)	51/208 (24.5%)	16/50 (32.0%)	32/115 (27.8%)	26/72 (36.1%)
Worsened - no./total (%)	46/257 (17.9%)	4/60 (6.7%)	32/208 (15.4%)	15/50 (30.0%)	28/115 (24.4%)	14/72 (19.4%)
Highest SOFA Score – median (IQR)	6 (3-9)	5 (2-8)	4 (2-7)	4 (2-8)	3 (1-5)	3 (1-4)
ICU Mortality – no./total (%)	54/257 (21.0%)	8/57 (14.0%)	21/208 (10.1%)	8/50 (16.0%)	9/115 (7.8%)	9/72 (12.5%)
ICU Mortality Incidence Rate per 1,000 person-ICU days (95% CI)	24.58 (18.82 – 32.09)	16.26 (8.132 – 32.51)	13.40 (8.738 – 20.55)	20.36 (10.18 – 40.70)	7.576 (3.942 – 14.56)	14.71 (7.652 – 28.26)
Hospital Mortality – no./total (%)	64/257 (24.9%)	11/57 (19.3%)	24/208 (11.5%)	11/50 (22.0%)	16/115 (13.9%)	11/72 (15.3%)
Hospital Mortality Incidence Rate per 1,000 person-hospital days (95% CI)	15.70 (12.29 – 20.06)	11.42 (6.33 – 20.63)	7.68 (5.15 – 11.46)	13.13 (7.27 – 23.70)	7.86 (4.81 – 12.82)	11.29 (6.25 – 20.39)

Table 13. Secondary outcomes stratified by the ICUs that make up the Combined ICU group
* Modified SOFA score lacking neurologic component (based on Glasgow Coma Scale), particularly relevant for the Neuroscience ICU
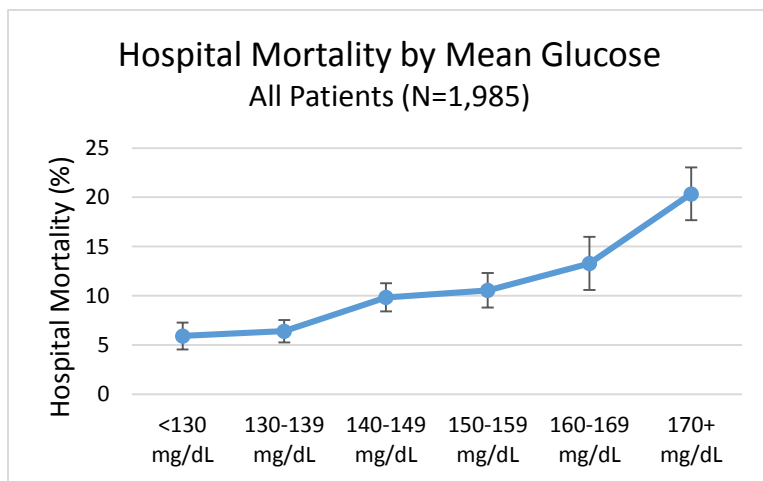
Figure 4. Hospital mortality for entire cohort divided into 6 intervals of mean glucose
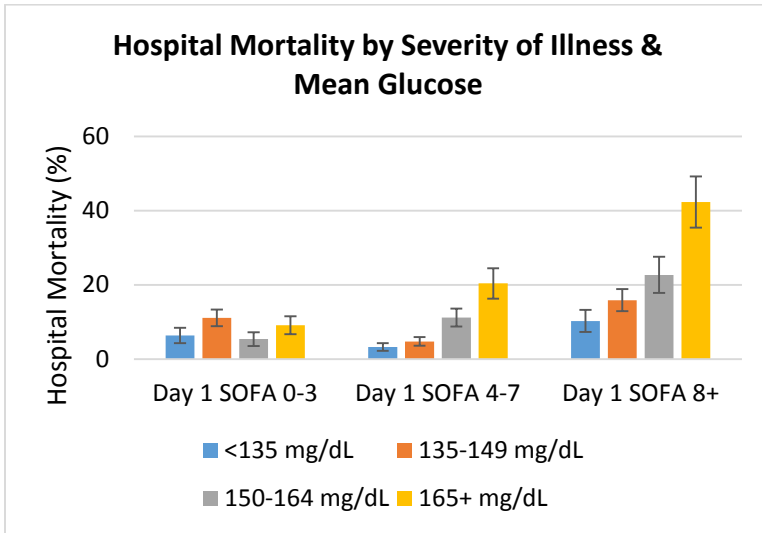
Figure 5. Hospital mortality by approximate quartile of mean glucose, stratified by approximate tertile of severity of illness on day 1 (SOFA score)
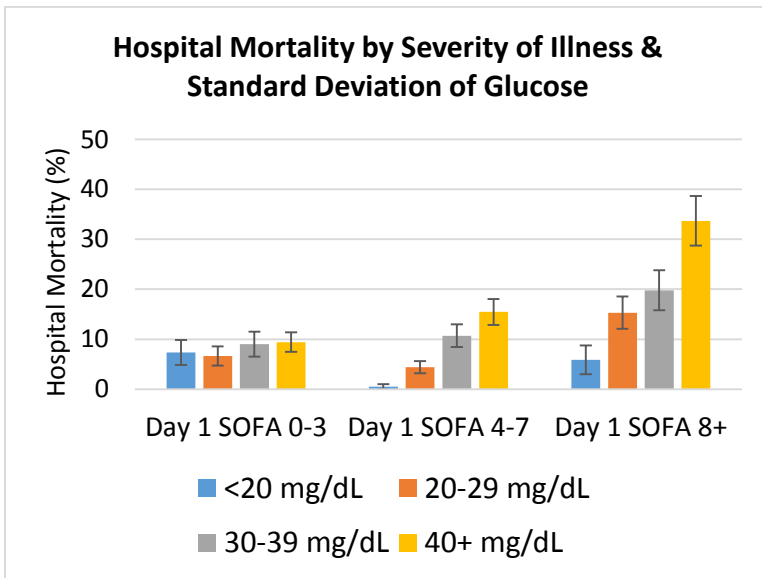
Figure 6. Hospital mortality by approximate quartile of standard deviation, stratified by approximate tertile of severity of illness on day 1 (SOFA score)
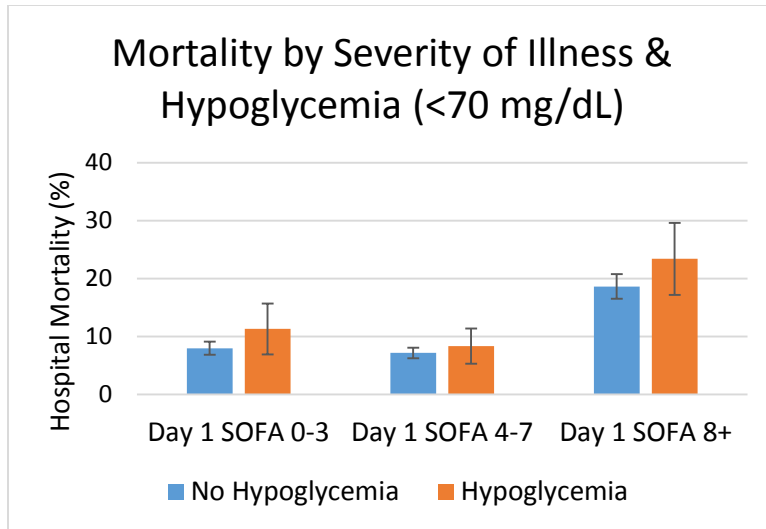
Figure 7. Hospital mortality by presence of one or more moderate hypoglycemic (<70 mg/d) measurement, stratified by approximate tertile of day one severity of illness (SOFA score).

Diabetics vs Non-diabetics

In order to explore the third primary research question of whether there was an interaction between insulin protocol and the relationship between diabetes and glucose control outcomes, an interaction term was created and tested in the six multivariable linear regression models (three protocol comparisons with two outcomes). Partial F tests for the addition of the interaction term were not significant in any of the six models at a 5% significance level (see **Appendix C**), so these interaction terms were not included in the multivariable regression models used to determine adjusted differences in means and standard deviations. The indicator variable for diabetes itself was significant in all of the six models, with diabetes consistently being associated with higher mean glucose and higher standard deviation. Diabetes was independently associated with a 5% increase in mean glucose in cardiothoracic surgery patients, 4% increase in non-cardiothoracic surgery patients, and a 3% increase in patients in the combined ICU group. Diabetes was independently associated with even greater increases in standard deviation, with a 24% increase in cardiothoracic surgery patients, 19% increase in non-cardiothoracic surgery patients, and 17% increase in the combined ICU group (see **Appendix C**).

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The primary outcomes were compared for diabetics and non-diabetics in *a priori* planned subgroup analyses. The four primary outcomes (mean glucose, standard deviation, hyperglycemia, and hypoglycemia) and mortality were compared for diabetics and non-diabetics within the same ICU and protocol groups (see **Table 14**). In all comparisons of diabetics and non-diabetics on the same protocol, whether a paper protocol or the computer protocol, the diabetic patients had worse glucose control measures. However, despite having worse glucose control measures, the diabetics had lower mortality than the non-diabetics in every group except for the cardiothoracic surgery patients.

The dose-response pattern that was observed in the association between increasing mean glucose and increasing hospital mortality was still seen in the diabetic and non-diabetic subgroups, however the trend appeared to be stronger among the non-diabetics (see **Table 16** and **Figure 8**). A Cochran-Armitage test confirmed a significant trend in both groups, but it was stronger in the non-diabetics compared to the diabetics (chi-square for trend: 43.9, $p<0.0001$; and chi-square for trend: 6.63, $p=0.010$).

Mortality was compared for diabetics and non-diabetics by dividing them into quartiles of both mean glucose (**Table 17**) and standard deviation (**Table 18**), and stratifying by approximate tertiles of day 1 SOFA scores in order to roughly control for severity of illness. In addition to a general dose-response relationship between increasing mean glucose and increasing mortality, and increasing standard deviation and increasing mortality, there was a fairly consistent increased mortality in non-diabetics compared to diabetics in each subgroup. These patterns were more evident in the top two tertiles of severity of illness and the top three quartiles of both mean glucose and standard deviation.

Diabetic patients were more likely to have moderate hypoglycemia (11.93% vs 7.95%, $p=0.0036$), however there was a much lower mortality associated with hypoglycemia in the diabetic group compared to the non-diabetic group (8.0% vs 19.1%, $p=0.0267$) (see **Table 19**).

There was not a significant difference in mortality for diabetics who had moderate hypoglycemia compared to diabetics without hypoglycemia. In contrast, there was a dramatic difference in mortality for non-diabetics, with almost twice the mortality in non-diabetics with moderate hypoglycemia compared to non-diabetics without hypoglycemia (19.1 vs 9.6%, p=0.0061) (see **Figure 9**).

Overall hospital mortality was not significantly different for diabetics compared to non-diabetics when patients from all ICUs were combined (see **Table 15**). However, the non-diabetic group consisted of a much higher percentage of surgical ICU patients than the diabetic group (63% vs 42%), and there was much lower hospital mortality in the surgical ICU in general (4.8% for all protocols combined) compared to the other ICUs (medical/cardiac ICU: 19.7%, trauma ICU: 13.0%, and neuroscience ICU: 14.8%). Cardiothoracic surgery patients, representing 67% of the surgical ICU, were also an exception in that they were the only subgroup in which non-diabetic patients had lower mortality than diabetic patients. Non-diabetic patients did have higher median day one SOFA scores (5 vs 4), but delta SOFA scores (change from day 1 to day 2) were similar between non-diabetics and diabetics. There was more renal failure in the diabetic group, but this was to be expected because there was more renal failure present on day one in the diabetic group, and diabetic nephropathy is a common complication of diabetes.

Diabetics vs Non-Diabetics

Primary Outcomes & Mortality	Mean		Standard Deviation		≥ 10% Severe Hyperglycemia (≥ 200 mg/dL)		Hypoglycemia (<70 mg/dL)		Hospital Mortality	
	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic
Cardio-thoracic Surgery	EndoTool: 133 mg/dL CTS: 145 mg/dL	EndoTool: 130 mg/dL CTS: 137 mg/dL	EndoTool: 27.0 mg/dL CTS: 30.4 mg/dL	EndoTool: 21.5 mg/dL CTS: 22.7 mg/dL	EndoTool: 11.4% CTS: 29.8%	EndoTool: 2.9% CTS: 8.7%	EndoTool: 15.9% CTS: 13.6%	EndoTool: 11.6% CTS: 6.4%	EndoTool: 0% CTS: 5.2%	EndoTool: 2.9% CTS: 1.2%
Non-Cardiothoracic Surgery	EndoTool: 131 mg/dL Adult ICU: 147 mg/dL	EndoTool: 126 mg/dL Adult ICU: 141 mg/dL	EndoTool: 30.5 mg/dL Adult ICU: 32.9 mg/dL	EndoTool: 21.3 mg/dL Adult ICU: 25.3 mg/dL	EndoTool: 16.7% Adult ICU: 41.8%	EndoTool: 0% Adult ICU: 18.5%	EndoTool: 10.0% Adult ICU: 10.7%	EndoTool: 10.34% Adult ICU: 6.8%	EndoTool: 13.3% Adult ICU: 7.4%	EndoTool: 13.8% Adult ICU: 9.9%
Combined ICU Group	EndoTool: 142 mg/dL Adult ICU: 165 mg/dL	EndoTool: 141 mg/dL Adult ICU: 156 mg/dL	EndoTool: 39.0 mg/dL Adult ICU: 44.0 mg/dL	EndoTool: 28.2 mg/dL Adult ICU: 34.7 mg/dL	EndoTool: 46.3% Adult ICU: 73.8%	EndoTool: 22.6% Adult ICU: 52.1%	EndoTool: 15.8% Adult ICU: 9.4%	EndoTool: 7.1% Adult ICU: 8.5%	EndoTool: 12.6% Adult ICU: 14.1%	EndoTool: 25.0% Adult ICU: 22.8%

Table 14. Primary outcomes and mortality compared for diabetics and non-diabetics

Secondary Outcomes - Diabetics vs Non-Diabetics	Diabetics	Non-diabetics	Diabetics vs Non-Diabetics
ICU Distribution – no./total (%)	Surgical: 387/838 (46.2%) Medical/Cardiac: 223/838 (26.6%) Trauma: 122/838 (14.6%) Neuroscience: 106/838 (12.7%)	Surgical: 664/1,057 (62.8%) Medical/Cardiac: 164/1,057 (15.5%) Trauma: 146/1,057 (13.8%) Neuroscience: 83/1,057 (7.9%)	NA
Insulin Protocol Days – median (IQR)	3 days (2-5 days)	3 days (2-4 days)	No difference
ICU Length of Stay – median (IQR)	4 days (3-8 days)	5 days (3-10 days)	p=0.0028 (z=2.99, Wilcoxon Rank-Sum)
Hospital Length of Stay – median (IQR)	9 days (6-15 days)	9 days (6-19 days)	No difference
Renal Failure During Hospitalization – no./total (%)	233/838 (27.8%)	218/1,057 (20.6%)	p=0.0003
Infection During Hospitalization – no./total (%)	290/838 (34.6%)	322/1,057 (30.5%)	NS (p=0.0554)
Day 1 SOFA Score – median, IQR (Baseline Reference)	4 (207)	5 (3-7)	---
Delta SOFA (Day 1 → Day 2)			
Improved - no./total (%)	517/838 (61.7%)	723/1,057 (68.4%)	---
No Change - no./total (%)	194/838 (23.2%)	190/1,057 (18.0%)	---
Worsened - no./total (%)	127/838 (15.2%)	144/1,057 (13.6%)	---
Highest SOFA Score – median (IQR)	5 (3-7)	6 (4-8)	---
ICU Mortality – no./total (%)	59/838 (7.0%)	89/1,057 (8.4%)	NS (p=0.27)
Hospital Mortality – no./total (%)	81/838 (9.7%)	109/1,057 (10.3%)	NS (p=0.64)

Table 15. Secondary outcomes for diabetics compared to non-diabetics

Mortality & Mean Glucose	<130 mg/dL	130-139 mg/dL	140-149 mg/dL	150-159 mg/dL	160-169 mg/dL	170+ mg/dL	Totals
All Patients (N=1,985)	18/304 (5.9%)	30/468 (6.4%)	43/437 (9.8%)	32/303 (10.6%)	21/158 (13.3%)	46/226 (20.4%)	190/1,895 (10.0%)
Diabetics (44%)	7/96 (7.3%)	9/130 (6.9%)	16/190 (8.4%)	15/160 (9.4%)	8/103 (7.8%)	26/159 (16.4%)	81/838 (9.7%)
Non-Diabetics (56%)	11/208 (5.3%)	21/338 (6.2%)	27/247 (10.9%)	17/143 (11.9%)	13/54 (24.1%)	20/67 (29.9%)	109/1,057 (10.3%)

Table 16. Hospital mortality divided by 6 intervals of mean glucose, stratified by diabetes
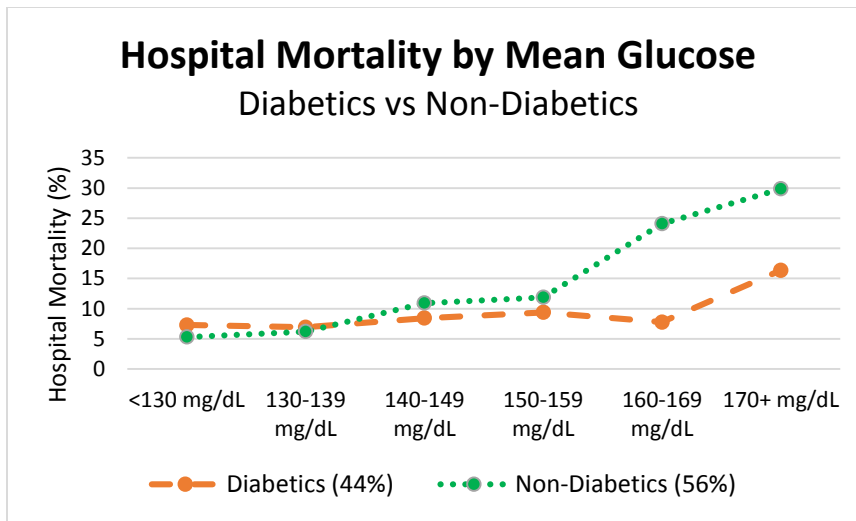
Figure 8. Hospital mortality for diabetics and non-diabetics divided into 6 intervals of mean glucose

Hospital Mortality	Mean <135 mg/dL	Mean 135-149 mg/dL	Mean 150-164 mg/dL	Mean 165+ mg/dL
Day 1 SOFA 0-3	Diabetic: 5/58 (8.6%) Non-Diabetic: 4/83 (4.8%)	Diabetic: 9/90 (10.0%) Non-Diabetic: 13/108 (12.0%)	Diabetic: 4/88 (4.6%) Non-Diabetic: 4/60 (6.7%)	Diabetic: 8/106 (7.6%) Non-Diabetic: 5/37 (13.5%)
Day 1 SOFA 4-7	Diabetic: 3/61 (4.9%) Non-Diabetic: 6/215 (2.8%)	Diabetic: 5/124 (4.0%) Non-Diabetic: 11/212 (5.2%)	Diabetic: 10/98 (10.2%) Non-Diabetic: 9/72 (12.5%)	Diabetic: 8/69 (11.6%) Non-Diabetic: 12/29 (41.4%)
Day 1 SOFA 8+	Diabetic: 3/30 (10.0%) Non-Diabetic: 8/77 (10.4%)	Diabetic: 7/53 (13.2%) Non-Diabetic: 17/98 (17.4%)	Diabetic: 6/31 (19.4%) Non-Diabetic: 11/44 (25.0%)	Diabetic: 13/30 (43.3%) Non-Diabetic: 9/22 (40.9%)

Table 17. Hospital mortality by approximate quartile of mean glucose and approximate tertile of day 1 SOFA score, stratified by diabetes

| Hospital Mortality	Standard Deviation <20 mg/dL	Standard Deviation 20-29 mg/dL	Standard Deviation 30-39 mg/dL	Standard Deviation 40+ mg/dL
Day 1 SOFA 0-3	Diabetic: 3/41 (7.3%) Non-Diabetic: 5/68 (7.4%)	Diabetic: 7/62 (11.3%) Non-Diabetic: 4/104 (3.9%)	Diabetic: 4/75 (5.3%) Non-Diabetic: 8/57 (14.0%)	Diabetic: 12/164 (7.3%) Non-Diabetic: 9/59 (15.3%)
Day 1 SOFA 4-7	Diabetic: 0/40 (0%) Non-Diabetic: 1/163 (0.6%)	Diabetic: 3/98 (3.1%) Non-Diabetic: 10/198 (5.1%)	Diabetic: 9/91 (9.9%) Non-Diabetic: 11/96 (11.5%)	Diabetic: 14/123 (11.4%) Non-Diabetic: 16/71 (22.5%)
Day 1 SOFA 8+	Diabetic: 2/17 (11.8%) Non-Diabetic: 2/51 (3.9%)	Diabetic: 3/33 (9.1%) Non-Diabetic: 16/91 (17.6%)	Diabetic: 10/48 (20.8%) Non-Diabetic: 10/53 (18.9%)	Diabetic: 14/46 (30.4%) Non-Diabetic: 17/46 (37.0%)

Table 18. Hospital mortality by approximate quartile of standard deviation and approximate tertile of day 1 SOFA score, stratified by diabetes

Hospital Mortality & Moderate Hypoglycemia	No Moderate Hypoglycemia	Moderate Hypoglycemia	Hypoglycemia vs No Hypoglycemia
Total	166/1,712 (9.70%)	24/184 (13.04%)	NS (p=0.15)
Diabetics	73/738 (9.89%)	8/100 (8.00%)	NS (p=0.55)
Non-Diabetics	93/973 (9.56%)	16/84 (19.05%)	p=0.0061
Diabetics vs Non-Diabetics	NS (p=0.82)	p=0.0267	

Table 19. Hospital mortality by moderate hypoglycemia, stratified by diabetes
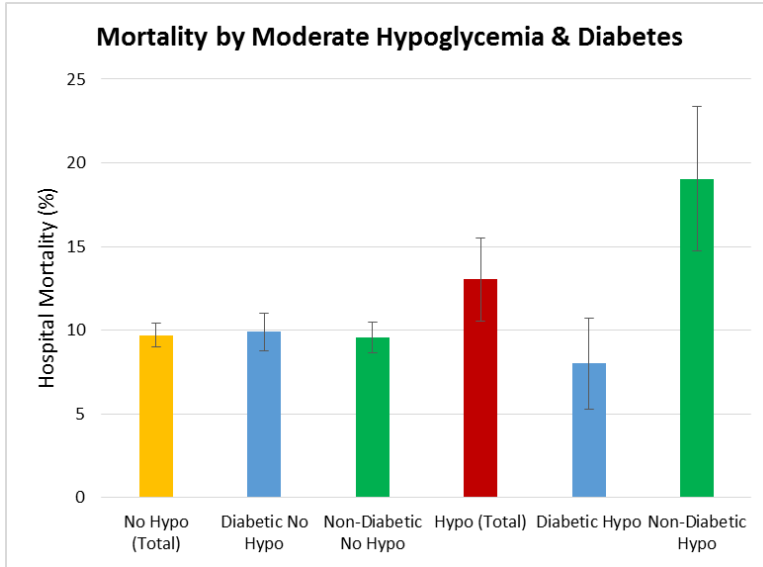
Figure 9. Hospital mortality by presence of moderate hypoglycemia, comparing diabetics and non-diabetics

DISCUSSION

The results of this study are consistent with other comparisons of computer protocols against paper protocols that have found improvements in several glucose control measures at the expense of increased incidence of hypoglycemia. In this study, however, the difference in hypoglycemia was only significant when measured as an incidence rate, and not when comparing crude proportions of patients in each group who had one or more hypoglycemic measurement. Additionally, there was no incidence of severe hypoglycemia associated with the computer protocol. Not only did the EndoTool groups have significantly lower mean glucose levels, but the

amount of severe hyperglycemia was also dramatically reduced. EndoTool was associated with decreased glucose variability (as represented by standard deviation) in all groups except for cardiothoracic surgery patients.

Surgical ICU & Cardiothoracic Surgery Patients

In this study we looked at outcomes for patients in the surgical ICU separately from the patients in the other ICUs. This allows direct comparison with the first Leuven study that found a dramatic reduction in mortality associated with aggressive glucose control in a surgical ICU.[58] The second Leuven study was conducted in a medical ICU and did not demonstrate the same mortality benefit.[59] Based on these studies and others, one meta-analysis concluded that aggressive glucose control targets may be beneficial for surgical ICU patients, but not others.[60] We also compared outcomes for cardiothoracic surgery patients separately from other surgical patients, because an insulin protocol was started prophylactically on these patients rather than reactively.

In the surgical ICU, there were much lower mean glucose levels and decreased glucose variability for both cardiothoracic surgery patients and non-cardiothoracic surgery patients compared to the other three ICUs. Incidence and proportion of moderate hypoglycemia were similar in the surgical ICU compared to the other ICUs. ICU and hospital mortality was much lower overall for surgical ICU patients, but there were no significant differences between protocols. Many of the patients who had cardiothoracic surgery had operations done on an elective basis, such as heart valve replacements or coronary artery bypass grafts. These patients were not admitted with acute illnesses, in comparison to most of the patients in the other ICUs. Being admitted to an ICU in a post-operative state may be expected to cause stress-induced hyperglycemia, but one might expect a less severe stress response in comparison to a patient admitted to the medical ICU with multiple organ failure. This, in combination with being placed

on an insulin protocol immediately regardless of whether hyperglycemia had developed, likely explains the improved indices of glucose control.

Among the cardiothoracic surgery patients, the patients on the CTS protocol had worsened organ dysfunction and failure on admission in comparison to the patients on the EndoTool protocol, which theoretically could explain some of the worse glucose control outcomes. However, even though it was hypothesized that higher severity of illness would be associated with worsened glucose control, neither day 1 SOFA scores or max sofa scores were found to be significantly associated with either mean glucose or standard deviation of glucose in multivariable linear regression. The remainder of their baseline characteristics were fairly equal (see **Table 3**).

Though cardiac surgery patients and surgical patients in general have been thought to benefit more from tight glucose control than other critically ill patients, there is not great evidence for this. One meta-analysis performed by Haga et al. in 2011 focused exclusively on randomized control trials (RCTs) of cardiac surgery patients.[61] Only six RCTs met their inclusion critieria, and only 3, with a total of 1,500 patients, could be used to compare mortality. The comparison was "tight" vs "normal" glucose control, defined differently in each study with a range of <110 mg/dL up to 125-200 mg/dL qualifying as "tight." Similar differences existed in the control groups, with "normal" glucose control defined as <180 mg/dL, <200 mg/dL, or <220 mg/dL. The pooled odds ratio for mortality was 0.52 (95% CI: 0.3-0.9). They also determined that tight glucose control was associated with decreased risk of atrial fibrillation, epicardial pacing, mechanical ventilation, and length of stay, but there was also significant heterogeneity in how these were measured in the RCTs used. The much larger NICE-SUGAR trial included surgical ICU patients, and actually found higher odds of mortality associated with tight glucose control among the surgical subgroup compared to the non-surgical subgroup.[62]

Maintaining mean glucose in a moderate range

According to the AACE/ADA Task Force on Inpatient Glycemic Control, the recommended target glucose for most patients in the ICU is 140-180 mg/dL, however, "Greater benefit may be realized at the lower end of this range."[63] A lower glucose target (110-140 mg/dL) may be used for select groups such as cardiac surgery patients or within ICUs that have a lot of experience with tight glucose control and high levels of nursing support.[64] One of the outcomes we selected for comparing the performance of the insulin protocols was the percentage of glucose measurements within the target range of 140-180. Considering that strategy used by the EndoTool protocol to reach the target glucose was a little different than the paper-based protocols, the comparison of percentage of glucose measurements within the target range of 140-180 mg/dL is misleading. Rather than calculating insulin doses in order to keep the glucose between 140-180, the EndoTool protocol attempts by design to keep the blood glucose right at 150. Therefore, it is not surprising that the percentage of glucose measurements between 140-180 was lower in the EndoTool groups compared to the paper protocol groups.

The median of the mean glucose of all patients on the EndoTool protocol (4 ICUs combined) was 134, and the median of the mean glucose of all patients on the Cardiothoracic Surgery protocol (4 ICUs combined) was 139, both of which are below the target range of 140-180. The median of the mean glucose of patients on the Adult ICU protocol was 154 mg/dL. Even though the "target glucose" range was 140-180 mg/dL during the time of the study, achieving the lower end of the range may still have been thought to be preferable.

Minimizing hyperglycemia

The computer protocol (EndoTool) substantially outperformed the paper protocols when it came to avoiding severe hyperglycemia. The degree of hyperglycemia has been consistently

associated with increasing mortality risk even after adjusting for severity of illness and other comorbidities.[65,66] In a large retrospective study of over 66,000 patients the risk of death associated with hyperglycemia appeared to have a J-shaped curve, with the lowest mortality associated with mean glucoses between 101-157 mg/dL, and increased mortality in the quartile below this and in the two quartiles above this.[67]

In our study, there was evidence of a dose-response effect of increasing mortality as mean glucose increased when looking at patients separated into six levels of mean glucose (see **Figure 4** and also **Figure 8**). To roughly control for severity of illness on admission patients were also divided into approximate tertiles of severity of illness based on day one SOFA scores. In **Figure 5**, a pattern of increasing mortality associated with increasing mean glucose is observed in the upper two tertiles of severity of illness.

Despite hyperglycemia being a well-established risk factor for mortality, it is still debated as to whether hyperglycemia is actually an "essential survival response."[68] As Marik and Bellomo discuss, hyperglycemia may actually be a beneficial physiological response, ensuring that the brain has an adequate supply of glucose for metabolism, and also ensuring a high concentration gradient to facilitate diffusion to tissues that have poor perfusion during critical illness. The association of hyperglycemia with mortality may only exist because it is a marker of underlying severity of illness.

Decreasing variability

The superiority of the computer protocol was most evident outside of the surgical ICU, particularly with respect to improvement of glucose variability. It was expected that the cardiothoracic surgery patients would have lower glucose variability because they were started on a continuous insulin infusion before developing hyperglycemia and would be expected to have their blood glucose controlled more quickly than other patients who were started on insulin after

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developing hyperglycemia. After adjusting for potential confounding variables, the standard deviation associated with EndoTool was estimated to be lower than the Adult ICU protocol for non-cardiothoracic surgery patients in the surgical ICU. Within the combined ICU group the difference between the standard deviation associated with the EndoTool protocol and the Adult ICU protocol was much larger than in the surgical ICU groups. Within each ICU (medical/cardiac, trauma, and neuroscience ICUs) separately the standard deviation was lower in the EndoTool group compared to the Adult ICU protocol.

In our study, there was evidence of a dose-response effect of increasing mortality as standard deviation increased, with crude adjustment for severity of illness on admission (see **Figure 6**). Glucose variability (most often measured by standard deviation) has consistently been shown to be an independent predictor of mortality, with an apparent dose-response relationship between increased variability and increased mortality.[69,70,71] High glucose variability has even been found to be a stronger predictor of mortality than mean glucose in some studies.[72,73] It is biologically plausible that high glucose variability could be causing harm, with large glucose fluctuations having been associated with increased oxidative stress, inflammation, endothelial dysfunction and other harmful effects.[74]

Since the target glucose for the EndoTool protocol was slightly different than the paper-based protocols, the standard deviation of the protocols may be a more valid comparison of the protocols' ability to control blood glucose levels. One would expect a smaller standard deviation for the EndoTool protocol, because by design it essentially had a narrower target "range" (150 mg/dL) than the paper-based protocols (140-180 mg/dL).

Avoiding hypoglycemia

The degree and frequency of hypoglycemia have both been shown to be strongly associated with mortality, even after adjusting for comorbidities and severity of illness.[75,76,77]

When tight glucose control targets were being studied, intensive insulin therapy was associated with very high incidences of severe hypoglycemia, ranging from 10-25%, and causing two large randomized control trials (VISEP and GLUCONTROL) to be stopped early.[78]

In this study which had a moderate glucose target (140-180 mg/dL), no patients in the EndoTool groups had a severe hypoglycemic measurement recorded. The EndoTool protocol was associated with a fairly low proportion of patients developing moderate hypoglycemia (13.3% of cardiothoracic surgery patients, and 11.7% of patients in the other three ICUs combined), but the rate at which this occurred was higher than in the paper protocol groups.

In our analysis, a blood glucose level below 70 mg/dL was used to classify hypoglycemia. This threshold was based on the ADA/AACE 2009 consensus statement on inpatient glycemic control and corresponds to the level at which counter-regulatory hormones are initially released. The ADA/AACE acknowledged that a threshold of <40 mg/dL has been used in many studies as a measure of "severe" hypoglycemia, but point out that glucose levels <50 mg/dL are associated with the beginnings of cognitive impairment.[79] The most common definition of hypoglycemia in the published literature historically has been <60 mg/dL, however there has been a trend in the more recent published studies to use a definition of <70 mg/dL.[80,81,82]

The increased mortality in the NICE-SUGAR trial observed in the tight glucose control group compared to the moderate glucose control group was hypothesized to be related to the increased incidence of hypoglycemia. In further analysis of their data, there was 23.5% mortality in patients without hypoglycemia, 28.5% mortality in patients with moderate hypoglycemia (41-70 mg/dL), and 35.4% mortality in patients with severe (≤ 40 mg/dL) hypoglycemia. The apparent dose-response pattern for increased mortality associated with moderate and severe hypoglycemia persisted after adjusting for possible confounders such as age, diabetes, reason for

admission, and severity of illness, with adjusted hazard ratios of 1.41 (95% CI: 1.21-1.62, p<0.001) and 2.10 (95% CI: 1.59-2.77, p<0.001), respectively.[83]

Few published studies have evaluated EndoTool specifically. One randomized control trial was conducted with 300 cardiac surgery patients comparing EndoTool to a paper-based protocol, using a target glucose of 80-150 mg/dL.[84] No patients in the EndoTool group experienced severe hypoglycemia (<40 mg/dL), while only two patients in the paper group had severe hypoglycemia. Moderate hypoglycemia (<60 mg/dL) occurred only seven times in the EndoTool group compared to 18 times in the paper group, but the difference was not significant.

Most other studies that have compared computer insulin protocols to paper insulin protocols have had lower glucose targets, and naturally experienced higher rates of hypoglycemia. In a small multicenter randomized control trial with a target glucose of 80-120 mg/dL, 153 patients in medical ICUs were assigned to either a computer protocol (Glucommander) or a paper protocol (Newton et al 2010)[85]. The computer protocol performed better at maintaining glucose within the target range, decreasing hyperglycemia, and decreasing glucose variability, without a significant difference in hypoglycemia. However, the incidence of severe hypoglycemia (<40 mg/dL) was 3.9%, and moderate hypoglycemia (<60 mg/dL) was 42.9%. In a retrospective study of 4,588 patients on a different computer insulin protocol (Clarian GlucoStabilizer) with a tight blood glucose control target of 80-110 mg/dL, Juneja et al. (2009) found severe hypoglycemia (<40 mg/dL) occurred in 4.25% of patients.[86]

In the trauma ICU, the incidence of hypoglycemia in the EndoTool group was more than triple that compared to the Adult ICU group (18.0% vs 4.8%, and 7.51 hypoglycemic measurements/100 person-protocol days vs 2.18). The EndoTool group in the trauma ICU also had double the hospital mortality (22%) in comparison to the Adult ICU group (11.5%), that is concerning for an association between increased hypoglycemia and increased mortality. Injury

severity scores (ISS) commonly used in trauma research were not recorded in our database, limiting our ability to compare trauma-specific severity of injury. Patients in the trauma ICU had the same median day 1 SOFA scores and maximum SOFA scores. On day one the EndoTool group had more dysfunction and failure of their coagulatory, hepatic, and renal organ systems, but had less dysfunction and failure of their pulmonary and cardiovascular organ systems in comparison to the Adult ICU group. The change in SOFA scores from day 1 to day 2 were dramatically different, with only 38% of the EndoTool group having improvement in comparison to 60% of the Adult ICU group, and with 30% of the EndoTool group developing a worsened SOFA score on day 2 in comparison to 15% of the Adult ICU group.

Within the trauma ICU, there was a higher percentage of diabetics in the EndoTool group (58%) compared to the Adult ICU group (42%), but if anything one would expect this to be associated with lower mortality in the EndoTool group because diabetic patients in general had lower mortality. In the trauma ICU diabetics had lower mortality compared to non-diabetics in both the EndoTool group (13.8% hospital mortality vs 33.3%) and the Adult ICU (7.0% mortality vs 14.9%). It is likely that only a portion of the difference in mortality is explained by the difference in hypoglycemia, but it warrants further investigation. There was a small sample size of only 50 patients total in the trauma ICU on the EndoTool protocol compared to 208 patients in the trauma ICU on the Adult ICU protocol, so there is higher risk of differences being seen by chance.

Kutcher and colleagues (2011)[87] conducted a retrospective analysis of 1,422 patients in a trauma ICU and calculated hypoglycemia as an incidence rate per 100 person-ICU days, allowing at least a crude comparison to our study. Outcomes were compared during three successive time periods spanning 9 years, and the authors evaluated three paper insulin protocols with different target glucose levels. Hypoglycemia was defined as <60 mg/dL. In the "relaxed" (target <180

mg/dL) group, the incidence of hypoglycemia was 0.77 per 100 person-ICU days, in the

"aggressive" (target 80-120 mg/dL) group it was 3.76, and in the "moderate" (target 80-140

mg/dL) group it was 1.45. In our study there was a higher incidence of hypoglycemia in both the

EndoTool group (7.51) and the Adult ICU group (2.18) compared to the "relaxed" group (0.77),

but we used a higher glucose cutoff (<70 mg/dL) and measured incidence of hypoglycemia per

100 person-protocol days, rather than person-ICU days. The median trauma ICU length of stay

was two days longer in our study than the median number of insulin protocol days, so when

combined with a higher cutoff for hypoglycemia, our measure of hypoglycemia incidence would

be higher than what was used in that study.

There is thought to be a difference in risk associated with spontaneous hypoglycemia that

occurs in the absence of insulin or other glucose-lowering medication, compared to hypoglycemia

associated with glucose-lowering medication ("iatrogenic" hypoglycemia).[88] Multiple risk factors

have been identified for developing hypoglycemia, including older age, sepsis, multiorgan failure,

type 1 diabetes versus type 2 diabetes, and prior history of hypoglycemia.[89] It makes sense that

the development of spontaneous hypoglycemia represents different underlying pathophysiology

and may be more of a marker of severity of illness rather than causing harm directly. Even in

cases of iatrogenic hypoglycemia, it has been argued that developing hypoglycemia is simply

"unmasking" the severity of illness of the patient that is predisposing them to have

hypoglycemia.[90]

In support of this hypothesis, one large retrospective cohort study of almost 32,000

hospitalized patients (admitted to general medicine and surgical wards, not ICUs) found that

although hypoglycemia ($\leq$ 70 mg/dL) was associated with increased mortality there was only an

increase in mortality in patients who had spontaneous hypoglycemia (HR=2.84, 95% CI: 2.14-

3.76, p<0.001) rather than hypoglycemia associated with antidiabetic medication. Furthermore,

after adjusting for comorbid conditions such as diabetes, congestive heart failure, chronic obstructive pulmonary disease, renal failure, stroke, and liver disease the association between spontaneous hypoglycemia and increased mortality was no longer significant (HR=1.11, 95% CI: 0.76-1.64, p=0.58).[91]

In most studies that were able to differentiate spontaneous and iatrogenic hypoglycemia, both types of hypoglycemia were associated with significantly increased mortality, however there was higher risk associated with spontaneous hypoglycemia compared to iatrogenic. In a study of 4946 medical and surgical ICU patients treated with a target glucose of 108-180 mg/dL, mild hypoglycemia (<81 mg/dL) occurred in 22.4% and severe hypoglycemia (<40 mg/dL) occurred in 2.1%.[92] Hypoglycemia was associated with severity of illness in general and also liver failure. Patients with moderate hypoglycemia had increased mortality compared to patients without hypoglycemia (36.6% vs 19.7%). Mortality increased as the severity of hypoglycemia increased, and in this study both spontaneous and insulin-associated hypoglycemia were independently associated with mortality. In our study hypoglycemia occurred on a day that the patient was receiving a continuous insulin infusion, so it is most likely that the hypoglycemia was iatrogenic.

Diabetics vs Non-Diabetics

Diabetic patients in this study had worse glucose control outcomes in comparison to non-diabetic patients. Diabetic patients had higher mean glucose, more severe hyperglycemia, higher standard deviation, and also more moderate hypoglycemia. In multivariable linear regression of mean glucose and standard deviation of glucose, diabetes was a significant predictor of increased mean glucose and increased standard deviation. We tested for the significance of a potential interaction between insulin protocol and the relationship between diabetes and glucose control outcomes with the use of an interaction term in multivariable regression, but this was not significant at the 5% level.

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Even though the interaction term was not statistically significant, when the primary outcomes for each group were stratified by diabetic status, there was a pattern consistent with a potential interaction for the outcome of mean glucose. If an interaction was present, we would expect to see a difference in the amount that the computer protocol improved the outcome for diabetics and non-diabetics compared to the paper protocols. Equivalently, if an interaction was present, the difference between diabetics and non-diabetics would be different in the EndoTool protocol compared to the paper protocols.

The EndoTool protocol was associated with a smaller difference in mean glucose between diabetic and non-diabetic patients compared to the paper protocol (either CTS or Adult ICU). Among cardiothoracic surgery patients there was a 3 mg/dL (2.3%) difference between diabetics and non-diabetics in the EndoTool group compared to an 8 mg/dL (5.5%) difference in the CTS group. Among the non-cardiothoracic surgery patients there was a 5 mg/dL (3.8%) difference between diabetics and non-diabetics in the EndoTool group compared to a 6 mg/dL (4.1%) difference in the Adult ICU group. Within the combined ICU group, there was a 1 mg/dL (0.7%) difference between diabetics and non-diabetics in the EndoTool group compared to a 9 mg/dL (5.5%) difference in the Adult ICU group. Though there was an appearance of a trend in the outcome of mean glucose, there was no consistent pattern in the other outcomes such as standard deviation (see **Table 14**). The fact that the difference in mean glucose between diabetics and non-diabetics was much less dramatic in the EndoTool protocol compared to either of the paper protocols provides support to the conclusion that the computer protocol performed better at determining the right insulin dose for individual patients based on their degree of insulin resistance.

In this study, diabetes was associated with worse dysglycemia, yet there was much greater mortality associated with dysglycemia in non-diabetics in comparison to diabetics. This

pattern was seen consistently when evaluating the strength of the association between all three domains of glucose control. This difference that we observed has been noted in many prior investigations. For example, several studies have found that hospitalized patients with pre-existing diabetes are less harmed by having their blood glucose at a hyperglycemic level[93,94,95,96,97] or by having high glucose variability[98] in comparison to non-diabetic patients who develop stress-induced hyperglycemia. It may be that patients who have diabetes have compensated for chronic hyperglycemia, and may not benefit as greatly from having their glucose level maintained at a lower level. Also, developing stress-induced hyperglycemia in non-diabetics may be more significant than when diabetics have hyperglycemia, because stress-induced hyperglycemia in non-diabetics may be an indicator of a higher severity of underlying illness that is disturbing their normal physiology.

The divergent response to hyperglycemia observed between diabetics and non-diabetics is well-described in the literature. In one study of over 7,000 critically ill patients of all types (medical, cardiac, surgical, trauma, and neurologic), there was lower mortality associated in multivariable analysis with diabetes in general, and the association between hyperglycemia and mortality and also between glucose variability and mortality was only significant in non-diabetics.[99] In another study of almost 5,000 patients admitted to medical and surgical ICUs, the association between hyperglycemia and mortality was strong for non-diabetics, but was not significant for patients known to have diabetes. [100] At one trauma center, admission hemoglobin A1c (HbA1c) levels were measured for all trauma patients and used to classify over 5,100 patients who developed hyperglycemia ≥ 200 mg/dL as having either stress-induced hyperglycemia or diabetic hyperglycemia.[101] Only in non-diabetics who had stress-induced hyperglycemia was there an increased mortality risk (RR 2.41, 95% CI 1.81–3.23). This pattern held true within a recent cohort study of over 3,300 abdominal, vascular, and spine surgery patients who had hyperglycemia ≥ 180 mg/dL.[102] The authors of this study found increased odds

of a composite endpoint of mortality and adverse events in a dose-response pattern for non-diabetic patients with hyperglycemia, but no significant increase in mortality for diabetic patients with hyperglycemia.

The results of our study are consistent with prior observations that critically ill patients without diabetes do worse in comparison to patients with diabetes when their glucose metabolism is altered. When we compared the primary outcomes of our study between diabetics and non-diabetics, diabetic patients consistently had worse glucose control outcomes (higher mean glucose, higher standard deviation of glucose, higher proportion with severe hyperglycemia, and higher proportion with hypoglycemia) in all subgroups, yet despite this the diabetic subgroup had much lower mortality (almost half) compared to non-diabetics in the combined ICU group (see **Table 14**). There was a similar pattern in the surgical ICU, with the exception that among cardiothoracic surgery patients on the CTS paper protocol, diabetics had higher mortality than diabetics (see **Table 14**). When evaluating the association between mortality and increasing mean glucose and also mortality and increasing standard deviation of glucose among patients from all ICUs combined, there was also a consistently higher mortality among the non-diabetics compared to the diabetics within the higher quartiles of both mean glucose and standard deviation of glucose (see **Table 17** and **Table 18**).

The overall hospital mortality was lower in diabetics compared to non-diabetics in the medical/cardiac ICU (EndoTool: 11.8% vs 30.4%; Adult ICU: 19.1% vs 34.7%), trauma ICU (EndoTool: 13.8% vs 33.3%; Adult ICU: 7.0% vs 14.9%), and neuroscience ICU (EndoTool: 12.5% vs 17.5%; Adult ICU: 11.1% vs 18.6%). In non-diabetics, stress-induced hyperglycemia that is high enough to require continuous insulin infusion is probably a result of a more severe insult to the body than that which may cause hyperglycemia in diabetic patients. In addition to hyperglycemia acting as a marker of underlying severity of illness, it seems plausible that non-

diabetics may have more severe responses to these acute changes in glucose in comparison to diabetics, who may have adapted over time to more extreme fluctuations in glucose, and that these derangements in glucose physiology may be more directly harmful in non-diabetics.

Not only is the risk of death associated with hyperglycemia substantially lower for diabetics compared to non-diabetics, but the level of glucose control that diabetics have before ICU admission also appears to change the risk of mortality. In a subgroup of 415 diabetic patients with hemoglobin A1c (HbA1c) measured, an interesting observation was made in patients admitted to ICUs at two Australian hospitals. If diabetics had poorly controlled diabetes before being admitted (based on elevated HbA1c), survival was actually associated with higher mean glucose, whereas in patients with well-controlled diabetes, survival was associated with lower mean glucose.[103] A similar phenomenon was seen by Plummer et al. in a prospective cohort of 1,000 consecutive ICU patients that had their HbA1c measured on admission. Hyperglycemia was only associated with increased mortality in diabetic patients with HbA1c below 7%, and not for diabetics with high HbA1c (≥7%).[104] Together these studies support a hypothesis that diabetics who have poorly controlled blood glucose may have adapted to having chronic hyperglycemia and are at less at risk of death if they have hyperglycemia during hospitalization for critical illness.

Strengths and Potential Limitations

Methods to Minimize Bias

Selection bias was minimized by including every adult patient in any of the four ICUs that was on insulin therapy for at least eight hours. In this study design, differential loss to follow-up was avoided because the outcomes of interest are defined during their hospital stay, and we have complete records for the entirety of their admission. OHSU is a tertiary referral center, so there is negligible risk of sicker patients being transferred to other hospitals, and being lost to

follow-up in this way. If there was loss to follow-up, it should have occurred roughly equally for the different years studied and therefore be non-differential, resulting in the same relative risk ratio (a sort of "compensating" bias).

There should not be risk of exposure identification bias since exposure status was determined objectively from the electronic medical record (EMR) according to which insulin protocol is recorded in the medication administration record (MAR). In order to minimize outcome identification bias, clear, standardized definitions of each outcome were used based on objective data readily available in the medical record. Outcome identification bias was further minimized through quality assurance and quality control. In order to improve quality assurance, individuals who collected the data went through training specifically developed for this study, and followed a detailed study protocol. To improve quality control, all of the data collected for each patient was audited by a more experienced staff member, increasing the reliability of the data. Disagreements were decided by the study coordinator. Though data collectors knew which insulin protocol each patient was on, and were aware of the general purpose of the study, they were not informed about any specific hypothesis as to which of the three insulin protocols was expected to be the best, so observer bias should be minimal.

Addressing Potential Confounding

Multivariable linear regression was performed for the primary outcomes that were continuous (mean glucose and standard deviation of glucose) in order to adjust for potential confounding variables that could be obscuring the relationship between insulin protocol and these outcomes. These potential confounders were chosen *a priori* based on known associations with the outcomes of interest, as discussed earlier. Some of these potential confounders met criteria as being confounders in at least some of the comparisons based on changing the β-coefficient of the insulin protocol variable by 10% or more (see **Appendix D**). Regression of the standard deviation

of glucose was more affected by confounders than regression of the mean glucose. Variables that were identified as having a stronger confounding relationship were admission glucose and diabetes. Admission glucose was expected to be strong confounders based on an observed Pearson's correlation coefficient of 0.5 for admission glucose and both mean glucose and standard deviation.

In general, the adjusted estimates for the differences between the computer and paper protocols were not very different than the crude estimates (see **Table 6**, **Table 7**, and **Table 8**), increasing our confidence that our estimates of the true differences between protocols are quite robust. In the non-cardiothoracic surgery comparison, the crude difference in standard deviation between the EndoTool and Adult ICU groups was not different, but after adjusting it reached statistical significance at the 5% level.

Alterations in glucose metabolism such as hyperglycemia, hypoglycemia, and increased variability, may actually be a manifestation of underlying organ dysfunction or organ failure. There is at least an association between multiple organ failure and these three disturbances in glucose control,[105] though it is not clear whether there is an actual causal relationship, and whether altered glucose physiology is causing organ failure, or organ failure is causing altered glucose physiology.

We controlled for severity of illness by using the Sequential Organ Failure Assessment (SOFA) score, because of concern that severity of illness may be associated with our primary outcome of glucose control. In multivariable regression, severity of illness on admission, as measured by the day 1 SOFA score, was not associated with mean glucose or standard deviation of glucose except for within the cardiothoracic surgery group (p=0.04). There was an estimated 1.5% increase in standard deviation in cardiothoracic surgery patients for every 1 point increase in day one SOFA score.

The SOFA score measures the severity of organ dysfunction for the major organ systems: respiratory, renal, hepatic, cardiovascular, and hematologic (neurologic status, measured by Glasgow Coma Score, was not recorded). We used the SOFA score on day one of starting an insulin protocol as a measure of baseline severity of illness. SOFA scores are calculated using the worst values over a 24 hour period, so the score could reflect the severity of illness at a point in time after the insulin protocol was begun, and the insulin protocol may have already changed the degree of organ dysfunction by that time. If the insulin protocol caused a change in organ dysfunction, and the degree of organ dysfunction also caused a change in glucose control outcomes, then there may be concern that by adjusting for the degree of organ dysfunction, one may be adjusting for a mediator and not a confounder.

A recent study by Plummer et al (2014) found that the association between acute hyperglycemia and mortality in critically ill patients disappeared after adjusting for severity of illness, suggesting that severity of illness is a confounder of the association between hyperglycemia and mortality.[106] This is likely because higher severity of illness is associated with higher blood glucose, and also causally related to mortality. Severity of illness may be associated with insulin protocol, and may be causally associated with hyperglycemia, hypoglycemia, and increased variability of glucose control. Severity of illness has been found to be a predictor of hypoglycemia,[107] and hypoglycemia is associated with mortality, but severity of illness could be directly causing both hypoglycemia and death. The primary outcomes of this study were measures of glucose control, rather than mortality. Given the strong associations between severity of illness and mortality, and dysglycemia and mortality, it made sense to adjust for variables that are either known to be causally related to hyperglycemia or other glucose measures, or to adjust for variables related to severity of illness.

Incidence of hypoglycemia is an important outcome for comparison. One potential limitation of this study is that when there were multiple glucose measurements during one hour, these values were averaged for that hour. This means that some hypoglycemic measurements could have been missed if a subsequent measure in the same hour was high enough to bring the average above the threshold. Typically if a patient has a hypoglycemic measurement, some type of intervention such as giving the patient dextrose will be done in order to bring the glucose level back to a normal range. The blood glucose would then be re-checked in order to confirm the intervention had been successful. Since this is a reasonable scenario that could result in a hypoglycemic measurement not being recorded, a random sample of twenty seven patients was audited. Rather than averaging multiple measurements for each hour, every single glucose measure was recorded. If any hypoglycemic or hyperglycemic measurements were lost to averaging, this was noted, and glucose summary measures such as mean and standard deviation were compared. This showed that approximately 5% of glucose values had been averaged, and only one hypoglycemic measurement was missed in the 49 instances where glucose values were averaged. Therefore the true number of hypoglycemic measurements is likely only slightly underestimated in this study.

One of the outcomes of interest is variability of glucose control. There are many factors which affect variability of glucose control that are hard to control for in comparing patients in different groups. For example, administration of glucocorticoids affects glucose metabolism, leading to hyperglycemia through increased hepatic production and peripheral insulin resistance,[108] which can interfere with glucose control. There is variability among patients as to whether they are able to begin eating while on an insulin protocol. Nutritional data was collected for each patient for each hour they were receiving insulin regarding whether they were receiving total parenteral nutrition (TPN), nutrition through a feeding tube, dextrose-containing intravenous

(IV) solutions, and whether they were eating food that day. Information about glucocorticoid administration was also recorded. We were only be able to control for these variables in a crude way with multivariable linear regression, considering these are time-varying covariates and the variables were converted to binary form. Therefore there is potential for residual confounding to exist that was not adjusted for.

In comparison to the NICE-SUGAR trial, which had over 6,000 patients and found an absolute difference in mortality of 2.6% between the conventional glucose control group (glucose <180 mg/dL) and the tight glucose control group (glucose 81-108 mg/dL), this study was underpowered to be able to detect a difference in mortality between the paper and computer protocol groups of a similar magnitude. Rather than comparing mortality as a primary outcome, the three most significant domains of glucose control that have been associated with mortality were compared. Differences in other binary outcomes such as incidence of hypoglycemia, renal failure, and infection could only be crudely compared with stratification to minimize confounding. Multivariable logistic regression would be required in order to better control for multiple confounders associated with these secondary outcomes.

One measure that has been used in other studies for comparison of different protocols is the time it takes to get a patient to their target glucose range. In this study protocol, day one did not begin until a patient had received 8 hours on insulin infusion during a 24 hour period starting at 0600 until 0559 of the next calendar day. This means that glucose measurements are missing for some days for some patients before they had at least 8 hours of insulin during one 24 hour period. Because of this, the time to target range cannot be calculated accurately for comparison. In addition, comparisons of glucose summary measures such as mean and standard deviation are affected in some patients by missing data for the first glucose measurements that may have been made but that were not recorded in the database.

One of the outcomes was presence of infection, but information on whether the infection developed after hospitalization or was present at time of admission was not recorded. Therefore it is not possible to make conclusions about differences in incidence of new infection as a secondary complication of hyperglycemia. Similarly, acute kidney injury was documented as being present or absent during the hospitalization without specifying whether it was present on admission or developed later during the hospitalization. However, collecting day 1 SOFA scores allowed comparison of the prevalence of renal dysfunction or failure on the first day of starting an insulin protocol. In the combined ICU group, the EndoTool protocol was associated with decreased renal failure in comparison to the Adult ICU protocol. The prevalence of renal dysfunction or failure in the EndoTool group on day one was lower in the medical/cardiac ICU, lower in the neuroscience ICU, but higher in the trauma ICU. The representation of each ICU in the combined ICU groups was not equal for the EndoTool and Adult ICU groups. In the combined ICU EndoTool group there was a smaller percentage of patients from the medical/cardiac ICU and trauma ICU, and a higher percentage of patients from the neuroscience ICU.

One of the limitations that has affected many studies attempting to determine the optimal glucose target range for critically ill patients is the inaccuracy of point-of-care glucometers and capillary blood glucose measurements. Capillary point-of-care blood glucose measurements may be up to 20% inaccurate compared to plasma level, especially with hypotension and anemia, which are common in the ICU.[109] Point-of-care glucometers are most inaccurate with very high and very low measurements, varying from central laboratory measurements by up to 32%.[110] Point of care measurements using capillary or venous blood while patients are receiving catecholamines (epinephrine, norepinephrine, or dopamine), which a significant number of these patients were receiving, have been shown to be inaccurate compared to central laboratory

measurements, varying by as much as 40 mg/dL in 40% of patients.[111] Data in this study included both point-of-care values and central laboratory measures.

Patients in this study were categorized as having no diagnosis of diabetes, or having either pre-diabetes, Type 1 diabetes, or Type 2 diabetes according to the documentation in their EMR. It has been demonstrated that a significant percentage (5.5% - 20%) of critically ill patients who develop stress-induced hyperglycemia actually have undiagnosed diabetes, as shown by having an elevated hemoglobin A1c.[112, 113] The patients in this study did not have an A1c checked on admission to see if they may have previously undiagnosed diabetes, so a portion of the patients categorized as not having diabetes probably actually did. Assuming that some patients were misclassified as not having diabetes, this would affect the observed relationship by underestimating the differences in glucose control measures and the differences in associated mortality.

Public Health & Clinical Implications

High prevalence & potential prevention of morbidity & mortality

The prevalence of hyperglycemia among critically ill patients is very high, affecting approximately 40-50% of patients admitted to intensive care units, and up to 80% of cardiac surgery patients.[114,115] Hyperglycemia is a well-established risk factor for mortality and is also a risk factor for many serious complications such as infection, renal failure, and prolonged mechanical ventilation and hospital length of stay. Some interventions that have decreased hyperglycemia have also decreased these outcomes.

Potential cost savings associated with improved glycemic control

Improved glycemic control has been associated with substantial cost savings in multiple studies. In a review done by the ADA and the AACE, cost savings were attributed to reductions in complications such as infection, decreased ICU and hospital length of stay, and decreased re-

admissions.[116] For example, the Portland Diabetic Project estimated a net savings of $5,580 per diabetic cardiac surgery patient treated with a continuous insulin protocol, attributed primarily to a 57% relative reduction in mortality and a 66% relative reduction in deep sternal wound infections compared to a historical cohort.[117]

In this study, the performance of a computer-based insulin protocol that had to be purchased was compared with two paper-based protocols. There is a high upfront cost of purchasing software and implementing its use, but if it can prevent the morbidity and mortality associated with hyperglycemia and hypoglycemia, it will more than pay for itself. Glycemic control measures are often considered quality and safety performance measures. The Centers for Medicare and Medicaid Services (CMS) has a list of "hospital-acquired conditions" that are theoretically preventable when evidence-based guidelines are followed. One of these categories is "manifestations of poor glycemic control," which includes hypoglycemia. These conditions may not get reimbursed, costing the hospital large expenses.[118]

Unclear benefits of interventions to improve glycemic control

Since much of the data showing strong associations between mortality and morbidity and markers of poor glycemic control have come from observational studies, there is the usual difficulty of sorting out correlation from causation. Each of the three main measures of glycemic control (hyperglycemia, glucose variability, and hypoglycemia) have all been disputed as to whether they actually cause harm or are simply markers of other underlying disease processes. Interventions that have successfully improved these glucose control measures have had mixed results as far as actual improved clinical outcomes.

Future Research

Optimal blood glucose targets may be different depending on whether patients have pre-existing diabetes or not. Future randomized controlled trials should use diabetic status, as

determined by admission hemoglobin A1c in order to not miss patients with undiagnosed

diabetes, to stratify patients into different treatment groups. Hemoglobin A1c should also be used

to assess chronic level of glucose control prior to admission. This may be important to determine,

because it is possible that patients with poorly controlled diabetes and chronic hyperglycemia

may need higher glucose targets to avoid harm from dramatically lowering their glucose to a

more "normal" range that is not normal for their bodies, which have adapted to hyperglycemia.

Another area of research that may be helpful is the use of continuous glucose monitors in

the ICU. Glucose control could theoretically be done more precisely by measuring glucose levels

in real-time. The use of continuous glucose monitoring devices should not only provide much

better data for computer software to fine-tune insulin doses for each patient, but should also

decrease the workload for nursing staff and decrease discomfort for patients from getting frequent

finger sticks. Perhaps more importantly, continuous monitoring would be able to provide instant

warning of developing hypoglycemia and could theoretically be automated to deliver dextrose to

treat the hypoglycemia immediately.

CONCLUSION

Hyperglycemia is very common among critically ill patients, and measures of glucose

control outside of the "normal" range have been associated with increased risk of mortality and

other complications such as infection and renal failure. The pendulum of glucose control has

swung from being very relaxed in allowing glucose levels to be at a hyperglycemic range, to

taking great effort to aggressively control glucose within a very low and narrow range, to now

attempting to control glucose within a moderate and wider range.

There is still much controversy over not only what the best glucose targets are for

different patient populations, but whether intervening to try to improve these different glucose

parameters really improves outcomes in the first place. Several meta-analyses have concluded

that intensive insulin therapy with a low and narrow range does not provide significant benefit, and is associated with much higher incidence of hypoglycemia which may actually increase mortality.

The three glucose control parameters evaluated in this study (hyperglycemia, hypoglycemia, and glucose variability) have all been well-established as independent risk factors for mortality. The use of a computer insulin protocol (EndoTool) was associated with much higher performance at minimizing severe hyperglycemia in comparison to two paper insulin protocols. The computer protocol was associated with a higher incidence rate of moderate hypoglycemia (<70 mg/dL), but not a higher proportion of patients developing one or more moderate hypoglycemic measurement. Additionally, the computer protocol was not associated with any severe hypoglycemic (<40 mg/dL) measurements, whereas this did occur rarely in the paper protocol groups (non-significant difference). The computer protocol was associated with significantly decreased standard deviation of glucose in the medical/cardiac, trauma, and neuroscience ICUs, but not for cardiothoracic surgery patients. There were no differences in the secondary outcomes of ICU and hospital mortality and length of stay, though the study was underpowered to detect a significant difference based on the effect size seen in previous studies. The computer protocol was associated with decreased renal failure outside of the surgical ICU.

Computer-based insulin protocols allow individualized doses of insulin to be given to patients by taking into account all their prior insulin doses, the response to those doses, the rate at which their glucose has been changing, and even taking into account other medications they are receiving that are influencing their glucose levels. There is evidence from multiple studies that computer-based insulin protocols are more effective than paper protocols at lowering mean glucose and decreasing variability of glucose, and even decreasing hypoglycemia or at least not increasing hypoglycemia. The EndoTool protocol in our study was associated with these same results except for an increased incidence, but not proportion, of moderate hypoglycemia (<70

mg/dL). The incidence of hypoglycemia associated with computer protocols is very important, because if there truly is benefit from improved glycemic control, this may be offset by increased harm from hypoglycemia.

In the last few years more attention has been paid to differences between critically ill patients with preexisting diabetes who develop hyperglycemia, and patients without diabetes who develop stress-induced hyperglycemia. Patients without diabetes appear to have higher risk associated with the incidence of altered glucose physiology while they are in a critically ill condition. The current body of evidence suggests that perhaps we should be more aggressive in glucose control for critically ill patients without pre-existing diabetes, for whom the development of stress-induced hyperglycemia, increased glucose variability, and hypoglycemia are associated with higher mortality. It is unclear whether the three main types of dysglycemia are simply indicators of higher severity of illness, but there are multiple physiological mechanisms that can explain how these processes can be harmful.

It may even be the case that critically ill diabetic patients that have had poor glucose control prior to becoming ill have become used to having chronic hyperglycemia and may be harmed by aggressively trying to decrease hyperglycemia during their hospitalization. This highlights the need for further research that evaluates different glucose control targets for diabetics and non-diabetics. For now, it is reasonable and prudent to follow the guidelines recommending moderate glucose control in order to protect patients from harm associated with both hyperglycemia and hypoglycemia.

Appendix A - Modified Sequential Organ Failure Assessment (SOFA) Score (missing Neurological system as measured by Glasgow Coma Scale).

Calculated using worst value over 24-hour period

Organ System	Dysfunction (Score 1 or 2)	Failure (Score 3 or 4)
Pulmonary	1 – PaO2/FiO2 ≤ 400 2 – PaO2/FiO2 ≤ 300	3 – PaO2/FiO2 ≤ 200 4 – PaO2/FiO2 ≤ 100
Coagulatory	1 – Platelets ≤ 150 2 – Platelets ≤ 100	3 – Platelets ≤ 50 4 – Platelets ≤ 20
Cardiovascular	1 – Mean Arterial Pressure <70 2 – Dopamine ≤ 5 or any dose of Dobutamine	3 – Dopamine >5, Epinephrine ≤ 0.1, or Norepinephrine ≤ 0.1 4 – Dopamine >15, Epinephrine > 0.1, or Norepinephrine > 0.1
Hepatic	1 – Bilirubin 1.2-1.9 2 – Bilirubin 2.0-5.9	3 – Bilirubin 6.0-11.9 4 – Bilirubin ≥ 12
Renal	1 – Creatinine 1.2-1.9 2 – Creatinine 2.0-3.4	3 – Creatinine 3.5-4.9 or Urine Output <500 mL 4 – Creatinine >5 or Urine Output <200 mL

Appendix B – Additional Results Figures & Tables
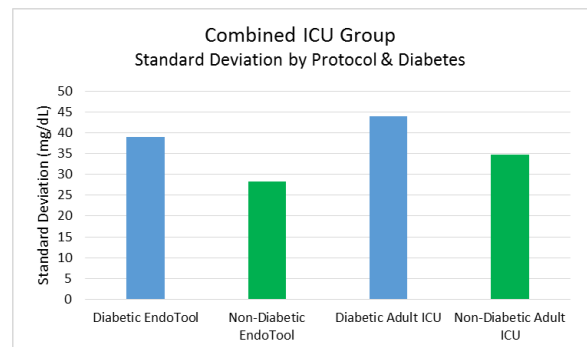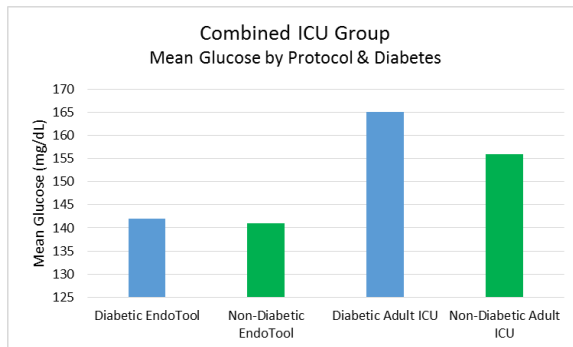
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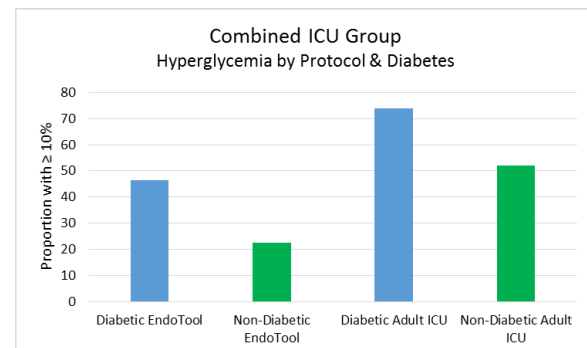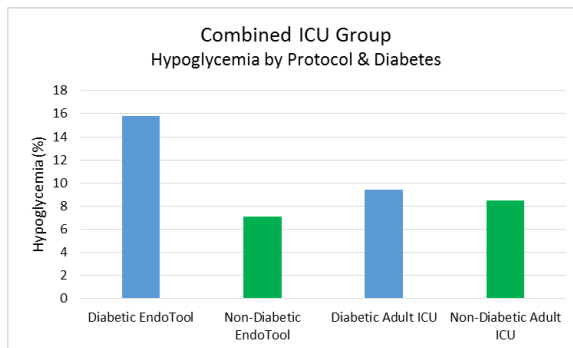
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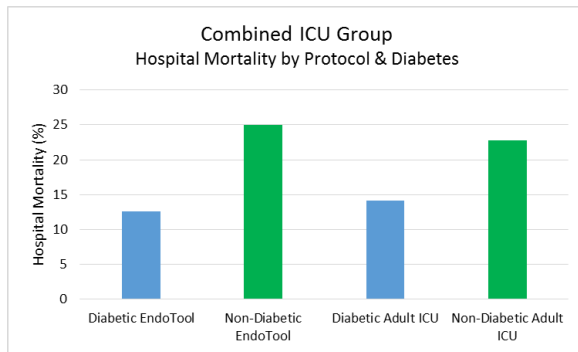
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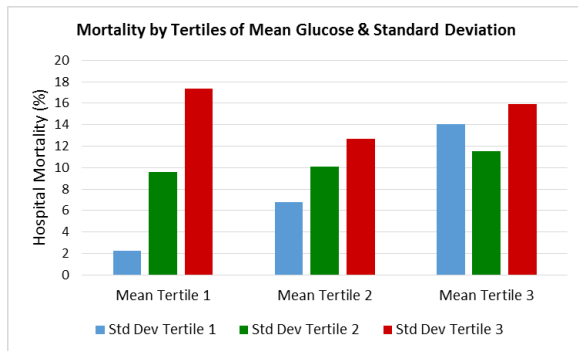
Comparison of Protocols (All ICUs Combined)	Cardiothoracic Surgery (CTS) – N=681	Adult ICU (MICU) – N=864	EndoTool (Computer) – N=351	EndoTool vs CTS – difference (95% CI)	EndoTool vs Adult ICU – difference (95% CI)	Adult ICU vs CTS – difference (95% CI)
Mean Glucose – mean (95% CI)	140.8 mg/dL (139.7 – 141.9)	157.5 mg/dL (155.9 – 159.1)	136.6 mg/dL (134.7 – 138.5)	-4.23 mg/dL (-6.3 to -2.2) [t=-4.02, p=0.0001]	-20.91 mg/dL (-23.7 to -18.1) [t=-14.8, p<0.0001]	16.68 mg/dL (14.6 – 18.7) [t=16.1, p<0.0001]
Standard Deviation of Glucose – Median (IQR) geometric mean (95% CI)	25.08 mg/dL (24.3 – 25.9 mg/dL)	35.00 mg/dL (33.9 – 36.2 mg/dL)	28.30 mg/dL (26.9 – 29.7 mg/dL)	Ratio (EndoTool/CTS): 1.128 (95% CI: 1.067 – 1.193) EndoTool 12.8% higher than CTS (95% CI: 6.7% higher to 19.3% higher) [t=4.25, p<0.0001]	Ratio (EndoTool/Adult ICU): 0.808 (95% CI: 0.760 – 0.860) EndoTool 19.2% lower than Adult ICU (95% CI: 24% lower to 14% lower) [t=-6.81, p<0.0001]	Ratio (Adult/CTS): 1.396 (95% CI: 1.332 – 1.462) Adult ICU 39.6% higher than CTS (95% CI: 33.2% higher to 46.2% higher) [t=14.04, p<0.0001]
Percent in Target Range (140-180 mg/dL) – mean (95% CI)	35.6% (34.5% - 36.7%)	36.8% (35.7% - 37.8%)	25.8% (24.2% - 27.3%)	-9.85 (-11.7% to -7.98%) [t=-10.3, p<0.0001]	-11.0% (-12.9% to -9.06%) [t=11.1, p< 0.0001]	1.15% (-0.39% to 2.7%) [t=1.46, p=0.14]
Proportion w 10% or Greater Hyperglycemic (>200 mg/dL)	16.45% (13.66% - 19.23%)	52.43% (49.10% - 55.76%)	21.37% (17.08% - 25.66%)	4.9% (-0.19% to 10%) [z=1.94, p=0.052]	-31.1% (-36.5% to -25.6%) [z=-9.9, p<0.0001]	36.0% (32% - 40%) [z=14.6, p<0.0001]
Number w at least one hypoglycemic measurement	9.69% (7.47% - 11.91%)	9.03% (7.12% - 10.94%)	11.97% (8.57% - 15.36%)	2.27% (-1.8% to 6.3%) [z=1.13, p=0.26]	2.94% (-0.96% to 6.8%) [z=1.56, p=0.12]	-0.66% (-3.6% to 2.3%) [z=-0.45, p=0.66]
Incidence of Hypoglycemia/100 person-protocol days (95% CI)	3.631 (2.975 – 4.433)	3.601 (3.027 – 4.283)	5.283 (4.206 – 6.636)	EndoTool vs CTS – Relative Risk (95% CI): 1.455 (95% CI: 1.051 – 2.005, p=0.019)	EndoTool vs Adult ICU – Relative Risk (95% CI): 1.467 (95% CI: 1.078 – 1.983, p=0.012)	Adult ICU vs CTS – Relative Risk (95% CI): 0.9915 (0.7513 – 1.312) [p=0.95]

Table ***. Summary of Comparisons of the Three Insulin Protocols and Glucose Control Measures

	8CSI – Surgical (Cardiothoracic & General)	12K – Medical & Cardiac ICU	7A - Trauma ICU	7N - Neuroscience ICU
N	1,051	390	269	189
Age – median (IQR)	65 (55-73)	60 (50-68)	60 (51-69)	62 (52-69)
Diabetes	386/1048 (36.8%)	224/390 (57.4%)	122/268 (45.5%)	106/189 (56.1%)
Admission Glucose – median (IQR)	136 (115-161)	180 (130-257)	178 (146-222)	183 (146-227)
Day 1 SOFA Score – median (IQR)	5 (4-7)	5 (3-8)	3 (1-6)	2 (1-4)
Insulin Protocol Days – median (IQR)	3 (2-4)	3 (2-5)	3 (2-4)	3 (2-5)
ICU LOS – median (IQR)	4 (3-7)	7 (4-12)	4 (3-9)	6 (3-14)
Hosp LOS – median (IQR)	8 (6-14)	11 (6-21)	10 (6-19)	13 (6-22)
ICU Mortality	38/1051 (3.6%)	63/387 (16.3%)	29/269 (10.8%)	18/189 (9.5%)
Hospital Mortality	50/1048 (4.8%)	77/390 (19.7%)	35/269 (13.0%)	28/189 (14.8%)
Positive Culture	229/1048 (21.9%)	174/390 (44.6%)	115/269 (42.8%)	94/189 (49.7%)
Renal Failure	214/1048 (20.4%)	174/390 (44.6%)	46/269 (17.1%)	17/189 (9.0%)

Table ***. Baseline Characteristics & Secondary Outcomes by ICU (all protocols combined)
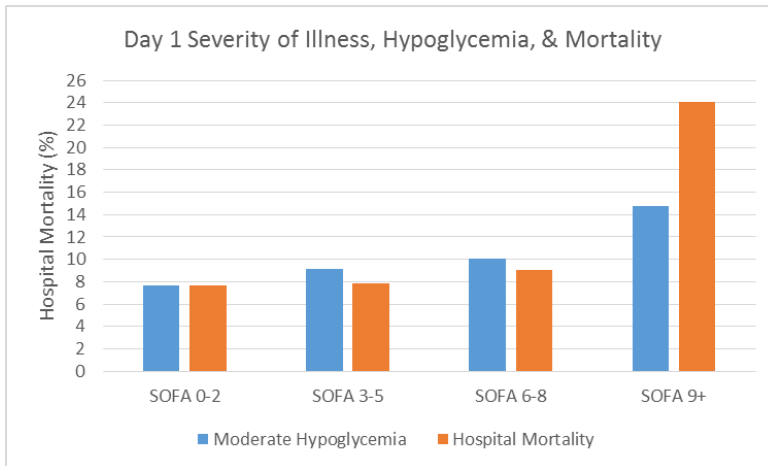

```
. table sofacat3, c(med mean med sd)

---------------------------------
Day 1    |
SOFA - 3 |
Levels   |   med(mean)      med(sd)
---------+-----------------------
    0-3 |   148.1367      32.46385
    4-7 |   141.9858      27.86071
     8+ |    141.925      30.00031
---------------------------------
```

```
. table deltasofacat3, c(med mean med sd)

------------------------------------
Delta SOFA - 4 |
Levels         |  med(mean)    med(sd)
---------------+--------------------
 No Change (0) |   153.8214   36.92693
     Improved  |   142.2529   27.98743
No Change (>0) |   147.7787   32.14431
     Worsened  |   144.8765   33.26395
------------------------------------



. table protocol, c(mean mean med mean mean median med median)

--------------------------------------------------------------------------------
      Protocol Name |   mean(mean)    med(mean)   mean(median)   med(median)
--------------------+-----------------------------------------------------------
Cardiac Surgery (CTS) |     140.838      138.875     138.0441          136
    Adult ICU (MICU) |    157.5198     153.8667      151.816          148
            EndoTool |    139.3752     137.2815     132.6492          131
        EndoTool-CTS |    130.7869     130.8824     127.3075        126.5
--------------------------------------------------------------------------------



. table protocol, c(mean mean med mean mean median med median) by(icu)

--------------------------------------------------------------------------------
Admitting ICU and    |
Protocol Name        |   mean(mean)    med(mean)   mean(median)   med(median)
---------------------+----------------------------------------------------------
Trauma (7A)          |
Cardiac Surgery (CTS) |    161.8798      152.875     157.9091        151.5
    Adult ICU (MICU) |    159.7194     156.9393     155.2043          152
            EndoTool |    145.3961      140.938       137.99       135.25
        EndoTool-CTS |
---------------------+----------------------------------------------------------
Neuro (7N)           |
Cardiac Surgery (CTS) |    150.3333     150.3333          145          145
    Adult ICU (MICU) |    160.4342     158.7727     154.1435          154
            EndoTool |    140.9025     141.3309     135.1875       135.25
        EndoTool-CTS |
---------------------+----------------------------------------------------------
Surgical (8CSI)      |
Cardiac Surgery (CTS) |    140.4105     138.7973     137.7874          136
    Adult ICU (MICU) |    143.7098     142.8606     139.8592          139
            EndoTool |    127.1242     127.2167     122.1271        121.5
        EndoTool-CTS |    130.7869     130.8824     127.3075        126.5
---------------------+----------------------------------------------------------
Medical (12K)        |
Cardiac Surgery (CTS) |    140.8913     138.7987     136.9521          137
    Adult ICU (MICU) |    169.6963     166.7857     161.2451          158
            EndoTool |    144.8454     143.1186     135.6491          134
        EndoTool-CTS |
--------------------------------------------------------------------------------
```

Appendix C – Multivariable Linear Regression Models

Variable Key:
Outcomes (dependent variables)
- logmean: natural log(mean)
- logsd: natural log(standard deviation)

Protocols
- endocts_v_cts: indicator variable for EndoTool (1) and CTS protocol (0) for cardiothoracic surgery Pts
- endononcts_v_adult: indicator variable for EndoTool (1) and Adult ICU protocol (0) for surgical ICU Pts
- endo_v_adult: indicator variable for EndoTool (1) and Adult ICU protocol (0) [used for combined ICU group]

Covariates
- logadmitgluc: natural log(admission glucose)
- diabetes: binary
- binarysteroid: received glucocorticoid (steroid) – binary
- binarypress: received vasopressor (binary)
- binaryeat: received oral nutrition (binary)
- binarytf: received tube feeding (binary)
- binarytpn: received total parenteral nutrition (binary)
- sofa1: day 1 sequential organ failure assessment score (measure of severity of illness)
- dum7a: indicator variable for Trauma ICU
- dum7n: indicator variable for Neuroscience ICU [in combined ICU group, reference group is medical/cardiac ICU]

Surgical ICU – Cardiothoracic Surgery Patients – EndoTool vs CTS

```
Stata 13.1 IC

reg logmean endocts_v_cts logadmitgluc diabetes binarysteroid /*
>        */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==1, eform("exp(B)")

      Source |       SS       df       MS              Number of obs =     692
-------------+------------------------------           F(  9,   682) =   35.32
       Model |  1.98608942     9  .220676602           Prob > F      =  0.0000
    Residual |  4.26140959   682  .006248401           R-squared     =  0.3179
-------------+------------------------------           Adj R-squared =  0.3089
       Total |  6.24749901   691  .009041243           Root MSE      =  .07905


------------------------------------------------------------------------------
     logmean |     exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
endocts_v_cts|   .9284412   .0079356    -8.69   0.000      .91299    .9441539
logadmitgluc |    1.10818   .0135421     8.41   0.000     1.081908   1.135091
    diabetes |   1.052437    .006914     7.78   0.000     1.038949   1.066101
binarysteroid|   1.043856   .0076749     5.84   0.000     1.028895   1.059034
 binarypress |   .9720946   .0117277    -2.35   0.019     .9493384   .9953962
   binaryeat |   1.051865   .0123039     4.32   0.000     1.027983   1.076303
    binarytf |   .9981542   .0103814    -0.18   0.859     .9779776   1.018747
   binarytpn |   .9889215   .0252529    -0.44   0.663     .9405611   1.039768
       sofa1 |   1.000495   .0015832     0.31   0.754     .9973918   1.003609
       _cons |   80.72788   4.969522    71.33   0.000      71.5371   91.09945
------------------------------------------------------------------------------
```

Surgical ICU – Cardiothoracic Surgery – EndoTool vs CTS: Regression of log(mean) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference).
Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.145**

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```
Stata 13.1 IC

reg logsd endocts_v_cts logadmitgluc diabetes binarysteroid /*
>          */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==1, eform("exp(B)")

      Source |       SS       df       MS              Number of obs =     692
-------------+------------------------------           F(  9,    682) =   16.71
       Model |  20.7038032        9  2.30042258        Prob > F      =  0.0000
    Residual |  93.8778698      682  .137650836        R-squared     =  0.1807
-------------+------------------------------           Adj R-squared =  0.1699
       Total |  114.581673      691  .165820077        Root MSE      =  .37101


--------------------------------------------------------------------------------
        logsd |     exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+------------------------------------------------------------------
endocts_v_cts |   .9426891   .0378182    -1.47   0.142     .8712841   1.019946
 logadmitgluc |   1.241652   .0712166     3.77   0.000     1.109408    1.38966
     diabetes |   1.241007   .0382658     7.00   0.000     1.168103   1.318461
binarysteroid |   1.270261   .0438359     6.93   0.000     1.187042   1.359313
  binarypress |    .993982   .0562844    -0.11   0.915     .8893923   1.110871
    binaryeat |   1.079303   .0592556     1.39   0.165      .969009   1.202151
     binarytf |   1.083027   .0528692     1.63   0.103     .9840407    1.19197
    binarytpn |   1.024236   .1227594     0.20   0.842     .8094654   1.295991
        sofa1 |    1.01537   .0075412     2.05   0.040     1.000671   1.030285
        _cons |   6.436176   1.859619     6.44   0.000     3.649649   11.35023
--------------------------------------------------------------------------------
```

Surgical ICU – Cardiothoracic Surgery – EndoTool vs CTS: Regression of log(standard deviation) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference)
Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.668**

Surgical ICU – Non-Cardiothoracic Surgery Patients – EndoTool vs Adult ICU

```
Stata 13.1 IC

. reg logmean endononcts_v_adult logadmitgluc diabetes binarysteroid /*
>          */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==1, eform("exp(B)")

      Source |       SS       df       MS              Number of obs =     331
-------------+------------------------------           F(  9,    321) =   16.56
       Model |   1.1930956        9  .132566178        Prob > F      =  0.0000
    Residual |  2.56969632      321  .008005284        R-squared     =  0.3171
-------------+------------------------------           Adj R-squared =  0.2979
       Total |  3.76279192      330   .0114024          Root MSE      =  .08947


--------------------------------------------------------------------------------
           logmean |    exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------------+------------------------------------------------------------
endononcts_v_adult |   .8859131   .0117835    -9.11   0.000     .8630312    .9094016
      logadmitgluc |   1.071898   .0174784     4.26   0.000     1.038057   1.106842
          diabetes |   1.038355    .010888     3.59   0.000     1.017154   1.059999
     binarysteroid |   1.005752   .0110578     0.52   0.602     .9842306   1.027744
       binarypress |   .9941633   .0125414    -0.46   0.643     .9697933   1.019146
         binaryeat |   1.042199    .011236     3.83   0.000     1.020326    1.06454
          binarytf |   1.033012   .0127643     2.63   0.009     1.008202   1.058432
         binarytpn |   1.044158   .0152029     2.97   0.003     1.014672   1.074501
             sofa1 |   .9991545   .0021866    -0.39   0.699     .9948619   1.003466
             _cons |   96.13446   7.994235    54.91   0.000      81.6259   113.2218
--------------------------------------------------------------------------------
```

Surgical ICU – Noncardiothoracic Surgery – EndoTool vs Adult ICU: Regression of log(mean) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference).
Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.335**

```
Stata 13.1 IC

. reg logsd endononcts_v_adult logadmitgluc diabetes binarysteroid /*
>          */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==1, eform("exp(B)")

      Source |       SS       df       MS                Number of obs =     331
-------------+------------------------------            F(  9,   321) =    7.55
       Model |  14.5132456        9  1.61258284         Prob > F      =  0.0000
    Residual |  68.5547787      321  .213566289         R-squared     =  0.1747
-------------+------------------------------            Adj R-squared =  0.1516
       Total |  83.0680242      330  .251721286         Root MSE      =  .46213

----------------------------------------------------------------------------------
            logsd |     exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
------------------+---------------------------------------------------------------
endononcts_v_adult |   .8670821   .0595689    -2.08   0.039     .7574622    .9925662
      logadmitgluc |    1.42154    .119725     4.18   0.000     1.204475   1.677723
          diabetes |   1.185593    .064212     3.14   0.002     1.065761   1.318899
      binarysteroid |   .9972417   .0566312    -0.05   0.961     .8918249   1.115119
        binarypress |   .9578364   .0624106    -0.66   0.509     .8425952   1.088839
          binaryeat |    1.18344   .0658999     3.02   0.003     1.060639   1.320458
           binarytf |   1.205224   .0769199     2.92   0.004     1.063009   1.366466
          binarytpn |   1.328638   .0999185     3.78   0.000     1.145911   1.540503
             sofa1 |   .9996088    .011299    -0.03   0.972     .9776247   1.022087
             _cons |   3.788838   1.627353     3.10   0.002     1.627499   8.820464
----------------------------------------------------------------------------------
```

Surgical ICU – Noncardiothoracic Surgery – EndoTool vs Adult ICU: Regression of log(standard deviation) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference)
Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.926**

Combined ICU Group (medical/cardiac, trauma, neuroscience) - EndoTool vs Adult ICU

```
Stata 13.1 IC

. reg logmean endo_v_adult dum7a dum7n logadmitgluc diabetes binarysteroid /*
>          */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==0, eform("exp(B)")

      Source |       SS       df       MS                Number of obs =     708
-------------+------------------------------            F( 11,   696) =   27.80
       Model |  4.77782096       11   .43434736         Prob > F      =  0.0000
    Residual |  10.8757708      696  .015626108         R-squared     =  0.3052
-------------+------------------------------            Adj R-squared =  0.2942
       Total |  15.6535918      707  .022140865         Root MSE      =    .125

----------------------------------------------------------------------------------
          logmean |     exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
------------------+---------------------------------------------------------------
      endo_v_adult |   .8830805   .0100596   -10.92   0.000     .8635489    .9030538
             dum7a |   .9690856   .0109073    -2.79   0.005     .9479053    .9907392
             dum7n |   .9680018   .0126469    -2.49   0.013     .9434869    .9931536
      logadmitgluc |   1.119954   .0130357     9.73   0.000      1.09465   1.145842
          diabetes |   1.026964    .010547     2.59   0.010     1.006464   1.047882
      binarysteroid |   1.030577   .0103657     2.99   0.003     1.010424   1.051131
        binarypress |   .9896114   .0120696    -0.86   0.392     .9661957   1.013595
          binaryeat |   .9937493   .0109725    -0.57   0.570     .9724379   1.015528
           binarytf |   .9827083   .0109305    -1.57   0.117     .9614802   1.004405
          binarytpn |   1.013766    .020727     0.67   0.504     .9738771   1.055289
             sofa1 |   .9987182   .0017727    -0.72   0.470     .9952438   1.002205
             _cons |   90.51282   5.803267    70.27   0.000      79.8068    102.655
----------------------------------------------------------------------------------
```

Combined ICU Group – EndoTool vs Adult ICU: Regression of log(mean) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference).
Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.137**

```
Stata 13.1 IC

. reg logsd endo_v_adult dum7a dum7n logadmitgluc diabetes binarysteroid /*
>          */ binarypress binaryeat binarytf binarytpn sofa1 if surgicu==0, eform("exp(B)")

      Source |       SS       df       MS              Number of obs =     708
-------------+------------------------------          F( 11,   696) =   17.61
       Model | 33.5510053    11  3.05009139           Prob > F      =  0.0000
    Residual | 120.548891   696   .17320243           R-squared     =  0.2177
-------------+------------------------------          Adj R-squared =  0.2054
       Total | 154.099897   707  .217963079           Root MSE      =  .41618

------------------------------------------------------------------------------
        logsd |     exp(B)   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
 endo_v_adult |   .8979973   .0340571    -2.84   0.005     .8335592    .9674167
        dum7a |    .928916   .0348084    -1.97   0.049     .8630274    .9998348
        dum7n |   .8804917   .0382988    -2.93   0.004     .8084181    .9589908
 logadmitgluc |   1.462113   .0566587     9.80   0.000     1.354997    1.577696
     diabetes |   1.168487   .0399529     4.55   0.000      1.09262    1.249623
binarysteroid |   1.069676   .0358199     2.01   0.045      1.00161    1.142367
  binarypress |   1.049684   .0426224     1.19   0.233     .9692493    1.136795
    binaryeat |   1.021252   .0375417     0.57   0.567     .9501409    1.097686
     binarytf |   1.025673   .0379818     0.68   0.494     .9537467    1.103023
    binarytpn |   1.040752   .0708431     0.59   0.558     .9105538    1.189566
        sofa1 |   .9981142   .0058982    -0.32   0.750     .9866007    1.009762
        _cons |   4.815817   1.027978     7.36   0.000     3.167065    7.322897
------------------------------------------------------------------------------
```

Combined ICU Group – EndoTool vs Adult ICU: Regression of log(standard deviation) and insulin protocol along with potential confounders – β-coefficients exponentiated for ease of interpretation (ratio, not difference)

Diabetes by Protocol (EndoTool) Interaction Term: Partial F-test for significance of addition of diabetes by protocol interaction term: **p=0.546**

Appendix D – Assessing Confounding

1. Run regression of primary outcome (dependent) variable with protocol indicator variable only
2. Add potential confounders one at a time and see how much the addition of the covariate changes the primary relationship of interest
3. Rule of thumb: if β-coefficient changes by 10% or greater, consider covariate a confounder

Surgical ICU - Cardiothoracic Surgery Pts – EndoTool vs CTS

Regression of log(mean)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.0708988	-0.0681939	3.815156251	3.966483806
diabetes	-0.0708988	-0.0751641	-6.016039764	-5.674650531
binarytpn	-0.0708988	-0.0713674	-0.660942075	-0.656602314
binarytf	-0.0708988	-0.070898	0.001128369	0.001128382
binarysteroid	-0.0708988	-0.0729652	-2.914576833	-2.832034998
binaryeat	-0.0708988	-0.0722512	-1.907507602	-1.871802821
binarypress	-0.0708988	-0.068893	2.82910289	2.911471412
sofa1	-0.0708988	-0.0722269	-1.873233397	-1.838788595

Regression of log(standard deviation)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.0557633	-0.0364483	34.63747662	52.99286935
diabetes	-0.0557633	-0.0725956	-30.18526522	-23.18639146
binarytpn	-0.0557633	-0.0606575	-8.776740257	-8.068581791
binarytf	-0.0557633	-0.0538691	3.39685779	3.516301553
binarysteroid	-0.0557633	-0.0669015	-19.97406897	-16.64865511
binaryeat	-0.0557633	-0.0556605	0.184350639	0.184691118
binarypress	-0.0557633	-0.0550834	1.219260697	1.234310155
sofa1	-0.0557633	-0.0427434	23.34851058	30.46060912

Surgical ICU – Non-Cardiothoracic Surgery – EndoTool vs Adult ICU

Regression of log(mean)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.1222415	-0.1141321	6.633917287	7.105275378
diabetes	-0.1222415	-0.1260504	-3.115881268	-3.021727817
binarytpn	-0.1222415	-0.1273057	-4.142782934	-3.977983704
binarytf	-0.1222415	-0.1243875	-1.755541285	-1.725253743
binarysteroid	-0.1222415	-0.1229648	-0.591697582	-0.588217116
binaryeat	-0.1222415	-0.1216614	0.474552423	0.476815161
binarypress	-0.1222415	-0.1221107	0.107001305	0.10711592
sofa1	-0.1222415	-0.122768	-0.430704793	-0.428857683

Regression of log(standard deviation)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.1283629	-0.1023429	20.27065453	25.4243333
diabetes	-0.1283629	-0.1452473	-13.15364486	-11.62458786
binarytpn	-0.1283629	-0.1596023	-24.33678267	-19.57327683
binarytf	-0.1283629	-0.1398782	-8.970894238	-8.232376453
binarysteroid	-0.1283629	-0.1334041	-3.927302982	-3.778894352
binaryeat	-0.1283629	-0.1272661	0.854452494	0.861816305
binarypress	-0.1283629	-0.1262326	1.659591673	1.687598925
sofa1	-0.1283629	-0.1306307	-1.766709852	-1.736039078

Combined ICU Group – EndoTool vs Adult ICU

Regression of log(mean)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.1351261	-0.1291237	4.442072997	4.648565678
diabetes	-0.1351261	-0.1339948	0.837217976	0.844286495
binarytpn	-0.1351261	-0.1347567	0.273374278	0.274123661
binarytf	-0.1351261	-0.1344374	0.509672077	0.51228304
binarysteroid	-0.1351261	-0.1344654	0.488950691	0.491353166
binaryeat	-0.1351261	-0.1343699	0.559625417	0.562774848
binarypress	-0.1351261	-0.1356517	-0.388970007	-0.387462892
sofa1	-0.1351261	-0.1368068	-1.243801161	-1.228520805

Regression of log(standard deviation)

variable	Theta (smaller model)	Beta (larger model)	% change (theta-beta)/theta	% change (theta-beta)/beta
admitgluc	-0.156278	-0.1364469	12.68963002	14.53393225
diabetes	-0.156278	-0.1511294	3.294513623	3.406749448
binarytpn	-0.156278	-0.1571832	-0.579224203	-0.575888517
binarytf	-0.156278	-0.1568767	-0.383099349	-0.381637299
binarysteroid	-0.156278	-0.157247	-0.620048887	-0.616227973
binaryeat	-0.156278	-0.1563715	-0.059829279	-0.059793505
binarypress	-0.156278	-0.1547085	1.004300029	1.014488538
sofa1	-0.156278	-0.1536864	1.658326828	1.686291045

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Appendix E – Additional Statistical Methods

Distributions of Important Variables
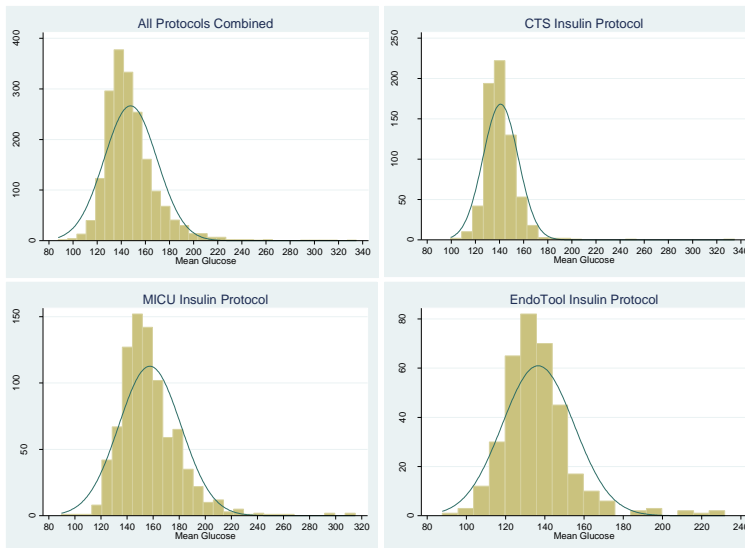
Distribution of Mean Glucose
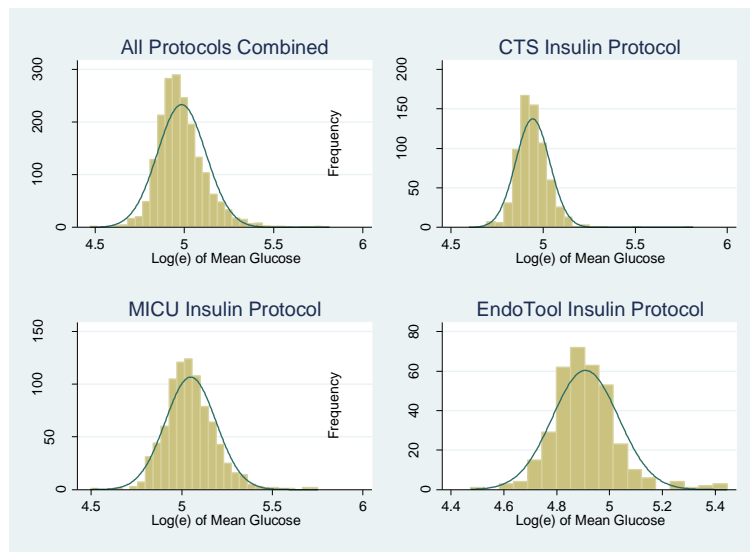
Distribution of log(e) transformed mean glucose
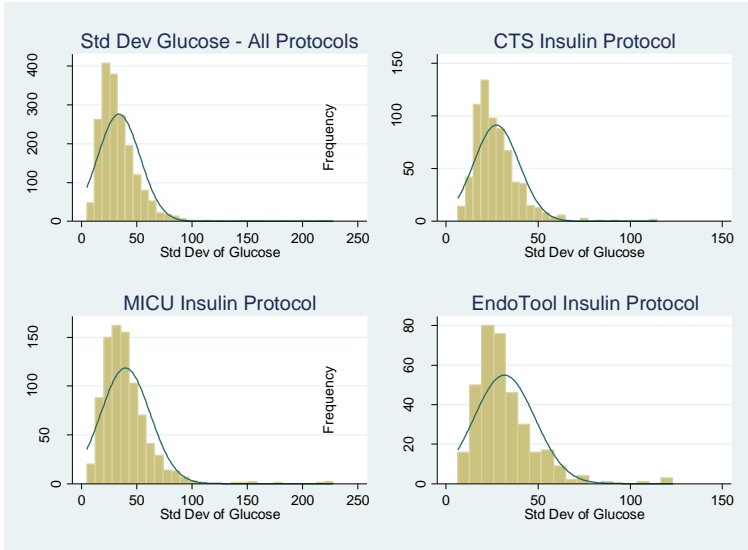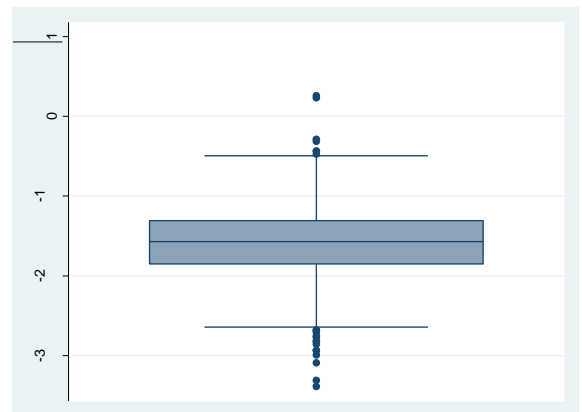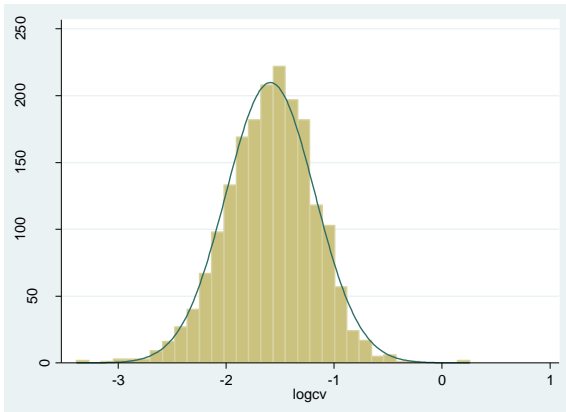
Distribution of standard deviation of glucose
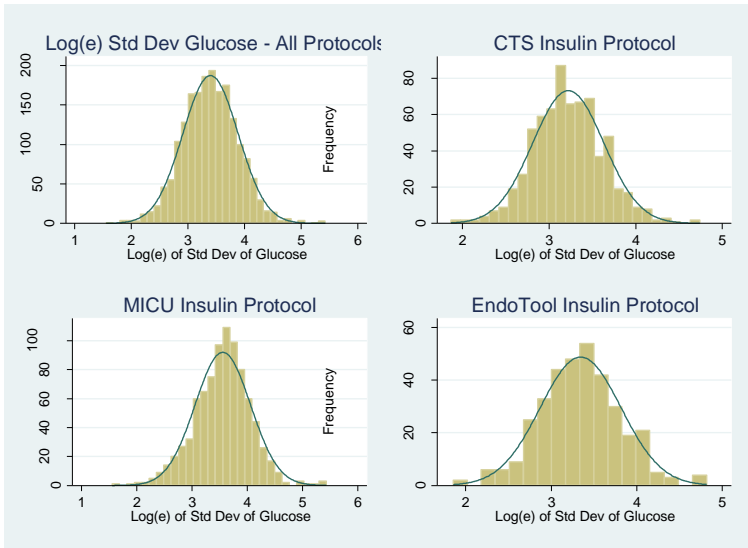
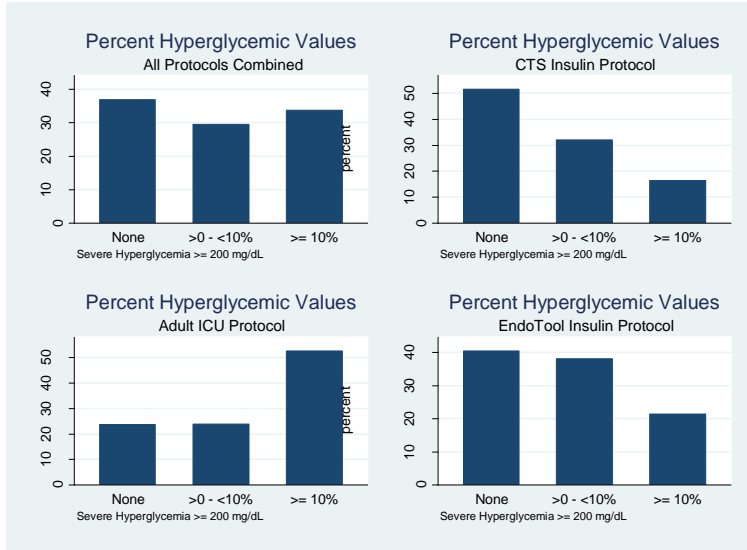Distribution of log(e) transformed standard deviation of glucose
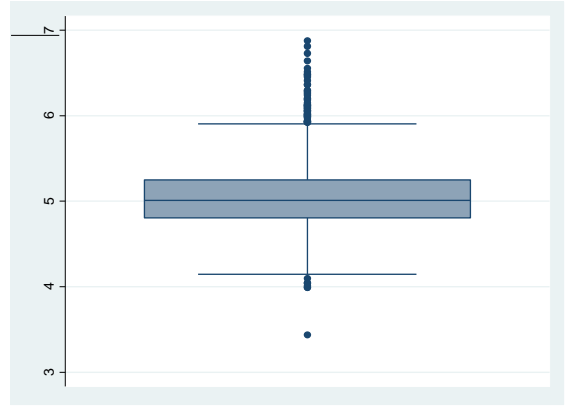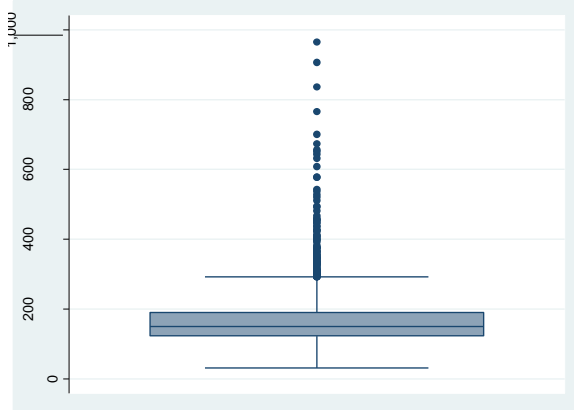
Boxplots of admission glucose & log(admission glucose)
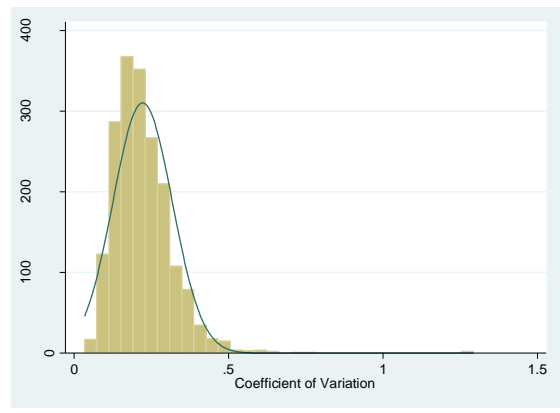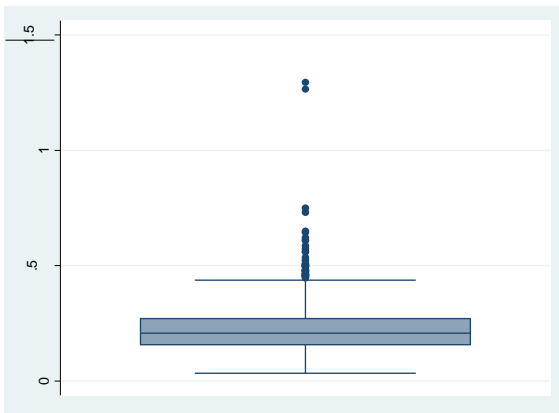
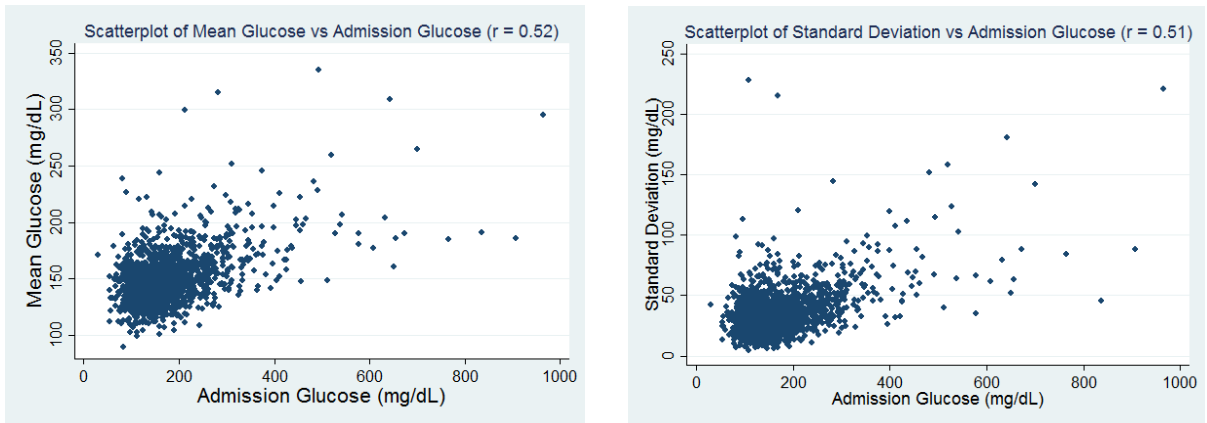Histogram & boxplot of coefficient of variation


Histogram & boxplot of log(coefficient of variation)

Approximate tertiles of percentage of glucose measurements at a hyperglycemic (>= 200 mg/dL) level

Correlation between outcome variables and covariates (potential confounders)

Scatterplots of mean glucose and standard deviation vs admission glucose, with corresponding Pearson's correlation coefficients
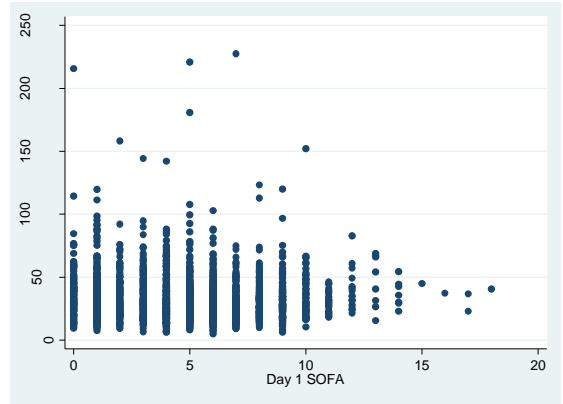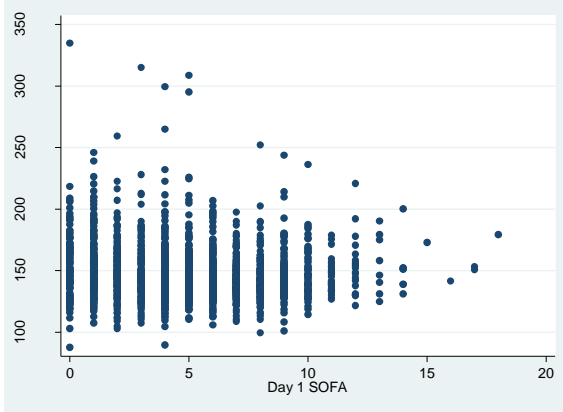
Scatterplots of mean and standard deviation vs severity of illness on day 1 (SOFA score)

Residual Plots & Other Model Diagnostics

Untransformed (Top) vs Log Mean & Log Admit Glucose (Bottom)

Untransformed (Top) vs Log Mean & Log Admit Glucose (Bottom)

_____
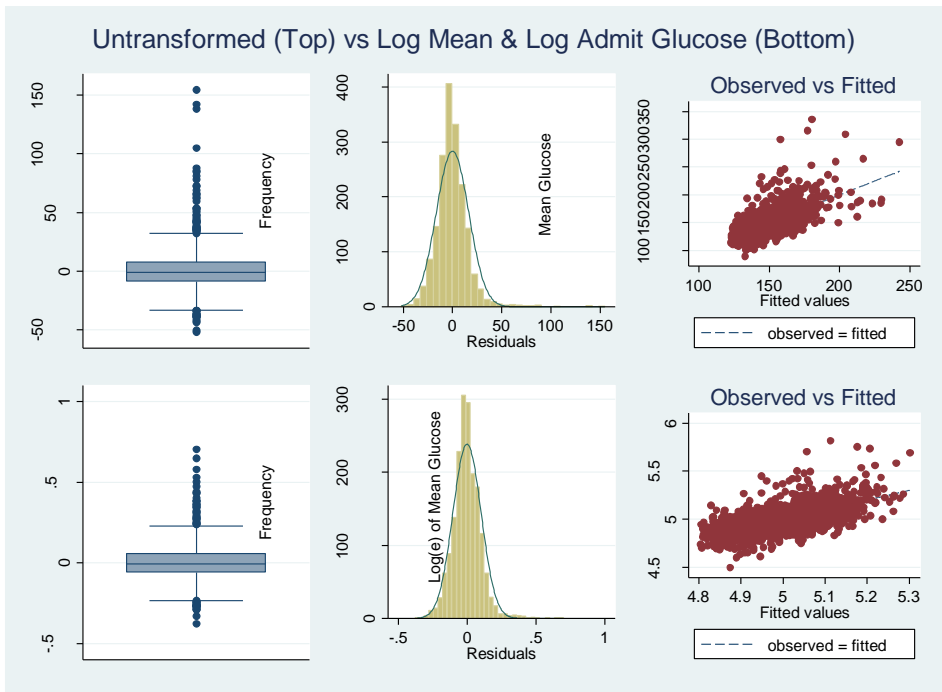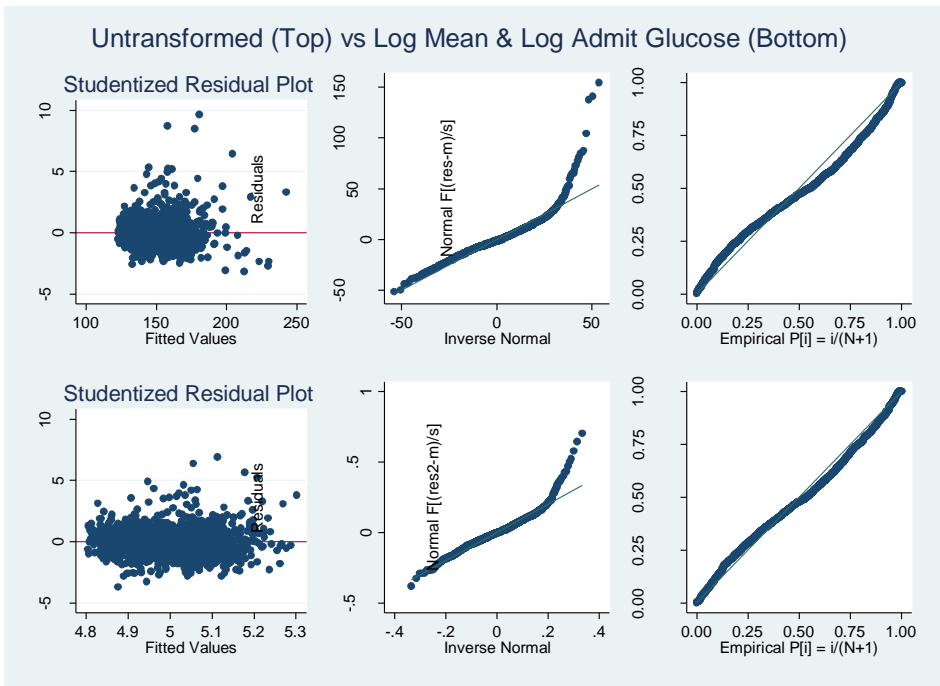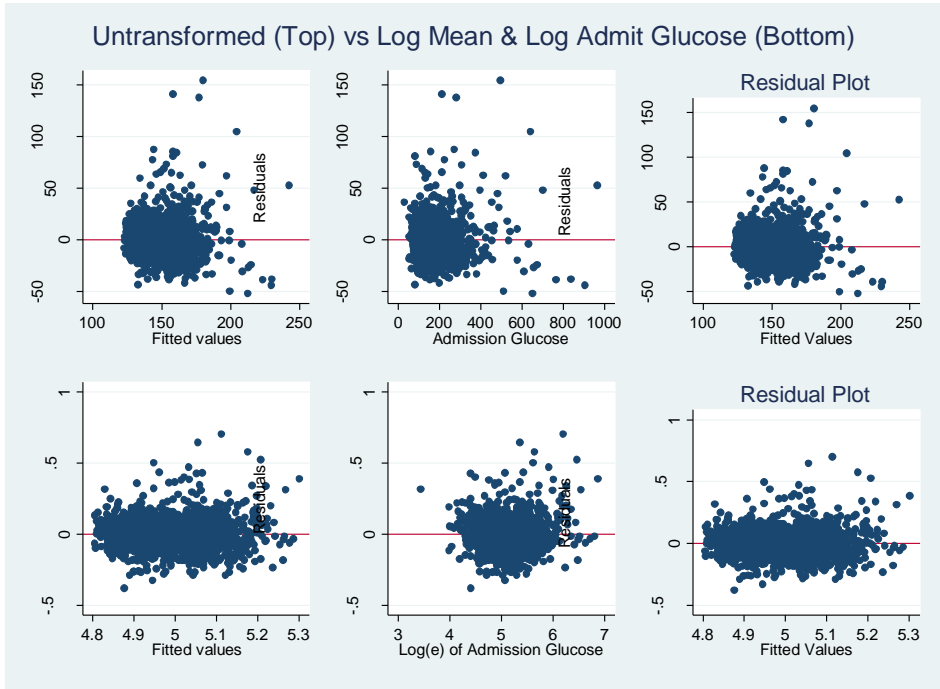
Shapiro-Wilk Test of Normality

```
. swilk mean logmean admitgluc logadmitgluc res res2 res3

                Shapiro-Wilk W test for normal data

    Variable |    Obs        W         V         z      Prob>z
-------------+------------------------------------------------
        mean |   1896    0.86969   147.223    12.673    0.00000
     logmean |   1896    0.94893    57.700    10.295    0.00000
   admitgluc |   1817    0.74413   278.088    14.266    0.00000
logadmitgluc |   1817    0.96740    35.428     9.043    0.00000
         res |   1813    0.88373   126.110    12.260    0.00000
        res2 |   1813    0.95190    52.171    10.023    0.00000
        res3 |   1813    0.95737    46.234     9.717    0.00000
```

None are normally distributed according to Shapiro-Wilk test (p > 0.05), even after log(e) transformation.

_____

Partial F test to test significance of addition of vasopressor use to model

The partial F test has a test statistic

$$F = \frac{\frac{RSS_{RED} - RSS_{FULL}}{df_{RED} - df_{FULL}}}{\frac{RSS_{FULL}}{df_{FULL}}}$$

Under the null hypothesis that the RED model is true (all the predictor coefficients for the suspected group are zero), F has an $F(df_{RED} - df_{FULL}, df_{FULL})$ distribution. (Lindsey C & Sheather S. Variable selection in linear regression. Stata Journal 2010)

RSS (reduced)	df (reduced)	RSS (full)	df (full)	numerator	denominator	partial F	F df 1	F df 2	p
492348	1796	491231	1794	558.5	273.8188406	2.03967	2	1794	0.13
reduced: reg mean admitgluc binaryeat ib3.protocol##ib3.icu diabetes##ib3.protocol									
full: reg mean admitgluc binaryeat binarypress ib3.protocol##ib3.icu diabetes##ib3.protocol									

. di Ftail(2,1794,2.0397)
.13036925
Addition of pressor variable is not significant

Appendix F – Audit of EndoTool Patients in Surgical ICU

EndoTool Patients in Surgical ICU:

- Cardiothoracic surgery: 113/172 (65.7%)
- No CTS: 59/172 (34.3%)

CABG	50/113 (44.2%)
Valves	38/113 (33.6%)
CABG and valves	8/113 (7.1%)
LVAD	2/113 (1.8%)
Transplant	4/113 (3.5%)
Ascending Aortic Aneurysm	3/113 (2.7%)
Chest	4/113 (3.5%)
Other	4/113 (3.5%)

Table *** Cardiothoracic surgery patients in surgical ICU on the EndoTool Protocol

Abdominal	23/59 (39.0%)
Pancreas	10/59 (16.9%)
Colon	3/59 (5.1%)
Gastric	2/59 (3.4%)
Other	8/59 (13.4%)
Head and Neck	13/59 (22.0%)
Vascular	12/59 (20.3%)
Spine	2/59 (3.4%)
Other Surgery	1/59 (1.7%)
Other Nonsurgical	8/59 (13.6%)

Table *:** Non-cardiothoracic surgery patients in surgical ICU on the EndoTool Protocol

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