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SAFETY AND EFFICACY OF PERSONALIZED GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS: A 2 YEAR BEFORE AND AFTER INTERVENTIONAL TRIAL

James S Krinsley MD, FCCM[1]; Jean-Charles Preiser MD[2], PhD; Irl B. Hirsch MD[3]

Running title: Personalized glucose control

From: [1]Division of Critical, Department of Medicine; Stamford Hospital and Columbia University College of Physicians and Surgeons; Stamford, CT 06902; [2]Department of Critical Care, Erasme University Hospital, Universite Libre de Bruxelles, 808 route de Lennik, B-1070 Brussels, Belgium; [3]University of Washington School of Medicine, Department of Medicine, Division of Metabolism, Endocrinology, & Nutrition, Seattle, WA 98105.

Correspondence address: James S Krinsley MD, FCCM[1]

Stamford Hospital

1 Hospital Plaza

Stamford, CT 06902

Email: james.krinsley@gmail.com

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Conflicts of interests

JS Krinsley: Consulting/Advisory Board for Edwards Life Sciences, Medtronic, Optiscan Biomedical, Roche Diagnostics

JC Preiser: Consulting/Advisory Board for Edwards Life Sciences, Medtronic, Optiscan Biomedical

IB Hirsch: Consulting: Abbott Diabetes Care, Roche, Intarcia

Abstract

Objective

To determine the safety and efficacy of a change in blood glucose (BG) control protocol from a single target to 2 targets based on diabetes status and glycated hemoglobin (A1C) in a cohort of critically ill patients.

Methods

This investigation includes 1,979 patients admitted to a single intensive care unit between September 16, 2013 and September 15, 2015. The BG target was 90-120 mg/dL in the PRE era and 80-140 mg/dL for patients without diabetes (NON) and diabetes patients (DM) with A1C < 7%

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and 110-160 mg/dL for DM with A1C ≥ 7% (TIGHT and LOOSE protocols) in the POST era. The primary efficacy outcome were the observed:expected mortality ratios.

Results

Among NON, mean BG was slightly lower in the POST era: 118 (106-132) vs 115 (101-120) mg/dL (p=0.0003). Among DM, mean BG was 139 (123-160) mg/dL in the PRE era vs 136 (119-149) and 159 (138-171) mg/dL for TIGHT and LOOSE in the POST era (p=0.0668 and 0.0001, respectively). 11.0% and 11.8% of the patients had at least one BG level < 70 mg/dL in the 2 eras (p=0.68). Observed:expected mortality for NON and DM for the 2 eras were 0.75 vs. 0.74 (p=0.51) and 0.69 vs 0.52 (p<0.001) respectively, and among DM with A1C ≥ 7% was 0.74 vs 0.52 (p=0.004) .

Conclusions

This hypothesis-generating investigation suggests the need for additional prospective interventional studies assessing the outcomes of patients randomized to personalized glucose targets.

Key words: glucose control; critically ill; diabetes; mortality; Hemoglobin A1C; hyperglycemia

Abbreviations:

APACHE = Acute Physiology and Chronic Health Evaluation; **AIC =** hemoglobin A1C; **BG =** blood glucose; **CV =** coefficient of variation; **DM =** patients with diabetes; **ICU =** intensive care unit; **NON =** patients without diabetes.

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Introduction

Our understanding of the relationship of glycemia to outcomes of critically ill patients has evolved considerably in the 15 years since publication of the first randomized trial of intensive insulin therapy.[1] Observational[2-10] and randomized trial data[11,12] have demonstrated that hyperglycemia, hypoglycemia and increased glucose variability are independently associated with mortality. In addition, an emerging body of literature has highlighted differences in the relationship of glucose metrics to outcomes when comparing patients with and without diabetes[13-16] and a review of the interventional trials of intensive insulin therapy suggested greater benefit of treatment among patients without diabetes.[17]

Observational data has underscored the importance of preadmission glycemia. Among a cohort of critically ill diabetic patients, those with A1C levels $\geq$ 7% had higher probability of death with lower mean BG levels during ICU stay and higher probability of survival with higher mean BG levels during ICU stay while patients with A1C levels < 7% fared better with lower BG levels during ICU stay.[18] Similarly, another observational study reported that early hyperglycemia was associated with death only in patients with A1C < 6.5%.[19] Finally, in a multi-center cohort the relationship between hypoglycemia and mortality was strongest among those with the highest A1C comparing those with and without DM.[20]

While the major interventional trials of intensive insulin therapy targeted “euglycemia,” 80-110 mg/dL, these data suggest that a single glycemic target may not be suitable for all patients admitted to the ICU. Two small before and after observational studies, including a total of 80 and 82 patients, respectively, have recently reported results of implementing 2 BG targets in cohorts of patients with diabetes.[21,22]

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This current investigation evaluates the safety and feasibility of implementation of 2 BG targets in a much larger cohort of patients admitted to a single mixed medical-surgical ICU. In the first year all patients were treated with the same BG target; in the second year patients were treated to a personalized BG target based on preadmission glycemia. We hypothesized that this strategy would be safe and would be associated with reductions in mortality.

Patients and methods

Patients and Setting

This is a retrospective review of prospectively collected data involving 1,979 patients admitted consecutively to the Stamford Hospital Intensive Care Unit (ICU) between September 16, 2013 and September 15, 2015, comparing glucose metrics and mortality before and after a change in blood glucose (BG) management. Stamford Hospital is a 305-bed university affiliated teaching hospital; the 16 bed ICU treats a wide variety of medical, surgical, and trauma patients. Orders in the ICU are written by medical and surgical house staff supervised by a team of medical and surgical intensivists. The nurse:patient ratio is 1:2 or 1:1 depending on patient acuity. This analysis excluded patients admitted to the ICU following cardiovascular surgery since all patients continued to be treated with the more intensive glucose management protocol during the interventional era, irrespective of the diabetes status. In addition, we excluded patients admitted to the ICU with a diagnosis of diabetic ketoacidosis or hyperosmolar coma (see Figure 1).

Glucose control

Between September 16, 2013 and September 15, 2014 (PRE era) the BG target was 90-120 mg/dL using a nurse driven protocol using subcutaneous and intravenous insulin for all patients;

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A1C values were not obtained routinely. Between September 16, 2014 and September 15, 2015 (POST era) the BG target was 80-140 mg/dL for all patients without diabetes (NON) and for patients with diabetes (DM) with A1C values obtained at the time of ICU admission < 7% ("TIGHT" protocol). The BG target was 110-160 mg/dL in the POST era for DM with A1C $\geq$ 7% ("LOOSE" protocol). Diabetes status was assigned at the time of admission for all patients based on all available information, including medical history and electronic databases of outpatient medication administration. Nurses treat hyperglycemia using guidelines embedded into the electronic medical record (PRE and POST guidelines found in Supplemental files 1a-c) and record data and insulin treatment in the electronic medical record. The insulin treatment protocols used in the ICU are nurse-driven, allowing a degree of discretion about insulin dosing. Blood glucose monitoring is performed at a minimum of every 3 hours; if a patient requires continuous insulin infusion the monitoring frequency is increased to hourly. The majority of BG testing is performed on bedside point of care devices (AccuChek Inform II, Roche Diagnostics, Indianapolis, IN); these are calibrated daily by comparison to central laboratory analyzers. The A1C testing is performed in the central laboratory using the Siemens Advia 1800 analyzer (Siemens USA, Buffalo Grove, IL). The mean turnaround time for obtaining A1C value is approximately 30 minutes, including mean run time for each test of 10 minutes. Patients are treated with the TIGHT protocol until A1C levels are available unless diabetes status and recent A1C levels are available indicating that the LOOSE protocol would be appropriate. The predominant blood source for measurement is capillary; the remainder, especially in patients requiring vasopressors or with marked edema, is venous or arterial. Approximately 5-10% of the BG measurements are made using arterial blood gas monitors. Continuous infusion of insulin is triggered by BG > 180 mg/dL on 2 consecutive measures. For lesser degrees of hyperglycemia (140-180 mg/dL, except for the patients treated with the LOOSE protocol, where this range is 160-180 mg/dL) patients receive subcutaneous rapid acting insulin (insulin lispro) at every 3 hour intervals. During the entire period of the investigation the nurses received regular feedback about aggregate rates of hyperglycemia and hypoglycemia in the ICU.

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Rationale for choice of BG targets

We chose the BG target of 90-120 mg/dL in the PRE area based on the results of the trial of intensive insulin therapy conducted in Leuven, Belgium[1] and the results of an earlier before and after interventional trial of intensive insulin therapy conducted at our own institution[23], as well as observational data demonstrating the lowest mortality in critically ill patients who had mean BG levels during ICU stay in this approximate range.[3,4] The range of 90-120 mg/dL was used instead of the original randomized controlled trial's target of 80-110 mg/dL as a safety measure to minimize the risk of hypoglycemia. However, more recent observational data suggested a different relationship between mean glycemia and mortality for patients with and without DM.[13-18] In particular, a large multi-center investigation demonstrated that mean glycemia 80-140 mg/dL was independently associated with decreased risk of mortality among patients without DM but was independently associated with increased mortality among patients with DM.[13] We based our decision to choose different BG targets for patients with DM based on A1C values on an observational study conducted in critically ill diabetic patients.[18] Finally, we chose the target of 110-160 mg/dL for the "LOOSE" DM cohort for practical reasons; by choosing an upper limit of 160 mg/dL we hoped to minimize BG excursions above 180 mg/dL, a level of glycemia associated with increased risk of morbidity and mortality in multiple studies of patients with and without DM.

Statistical methods

We compared clinical characteristics and glucose metrics of patients in the entire PRE and POST cohorts and we also analyzed these data stratified by diabetes status. We calculated Acute Physiology and Chronic Health Evaluation (APACHE) II and IV scores as well as APACHE IV predicted mortality (%) prospectively as part of routine care.[24,25] We analyzed glucose metrics, including mean BG (mg/dL), severe and moderate hypoglycemia (defined as proportion of patients in whom at a least one BG value < 40 or 70 mg/dL was recorded), and glucose

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variability, defined as coefficient of variation (%), calculated as the standard deviation of the mean BG/mean BG), for the NON and DM cohorts in the PRE and POST eras. We calculated the percentage of time spent in the BG bands of < 80, 80-140, 140-180, 110-160 and >180 mg/dL for each point, assuming linear interpolation of consecutive values. We analyzed in-hospital mortality, defined as status at hospital, discharge, associated with levels of mean BG (80-110 mg/dL, 110-140 md/dL, 140-180 md/dL and >180 mg/dL), hypoglycemia (<70 mg/dL) and glucose variability (CV<20%, 20%-30% and >30%), for patients, stratified by diabetes status. We compared mortality of patients with mean BG 80-140 vs. $\geq$ 140 mg/dL of those with and without diabetes in the 2 eras, as well as those treated with the TIGHT vs. the LOOSE protocol in the POST era. We calculated observed:expected mortality ratios, using APACHE IV predicted mortality and compared them using the Z-test for independent proportions for between group comparisons.[26]

We report continuous data as median (interquartile range [IQR]) or mean (standard deviation [SD]) and compare groups using Mann-Whitney rank sum test or Student's t-test, as appropriate. We report categorical data as percentages and compare groups using the Chi-square test. We assigned the threshold for statistical significance as $p<0.05$.

We used the MedCalc statistical package (Brussels, Belgium) version 14.10.2 for statistical analysis.

The Stamford Hospital Institutional Review Board approved this study and in view of the observational nature of the study waived the need for individual informed consent.

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Results

Figure 1 describes reasons for exclusion from the final analysis.

Clinical characteristics

Table 1a details clinical characteristics of the 2 cohorts. There was a similar distribution of diagnostic categories, percentage of patients with diabetes, age and severity of illness scores. ICU length of stay (LOS) was 7 hours longer in the POST era, likely in part due to the slightly higher percentage of patients with medical service admissions during this period. Supplementary Table 1 details results of multivariable analysis for mortality, demonstrating that ICU LOS was not independently associated with mortality in either era. Table 1b describes clinical characteristics of NON and DM. Severity of illness did not differ significantly for NON or for DM when comparing the PRE and POST eras. Patients with diabetes were older and had higher severity of illness compared to patients without diabetes in both eras.

Insulin treatment and glucose metrics

Table 2 includes details about glucose metrics and insulin treatment of the cohorts. Among NON, the POST era was associated with a lower A1C, a slightly lower mean BG, lower maximum BG and lower minimum BG. Among DM, glucose metrics were similar when comparing PRE and the entire POST group. However, during the POST era patients treated with the LOOSE target had higher mean BG levels, higher maximum BG levels, higher glucose variability, and tended to have less hypoglycemia than those treated with the TIGHT protocol. Among DM, more than 4/5 received insulin in both periods, while approximately ½ of NON received insulin.

A total of 692 patients had at least one BG $\geq$ 180 mg/dL. Of these, 625 (90.3%) received sc insulin and 252 (36.4%) received IV insulin. Overall, 647 of patients with at least one BG $\geq$ 180

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mg/dL, (93.5%) received insulin. Among the 45 who did not receive any insulin, 4 had 2 values ≥ 180 mg/dL (not consecutive) and 41 had only a single BG value ≥ 180 mg/dL.

Relationship of glucose metrics to mortality

Figures 2a and 2b illustrate the relationship between mean BG and mortality for NON and DM, respectively, and Table 3 compares mortality for patients with mean BG 80-140 mg/dL vs. ≥ 140 mg/dL. For patients without diabetes and those treated with the TIGHT protocol in the POST era lower mortality was observed with mean BG 80-140 mg/dL. For the entire group of patients with diabetes mortality was similar for the 2 groups. However, for patients with A1C ≥ 7% and those treated with the LOOSE protocol mortality was higher among patients with mean BG 80-140 mg/dL than it was among those with mean BG ≥ 140 mg/dL.

Supplementary Table 2 describes the association of moderate (< 70 mg/dL) and severe (< 40 mg/dL) hypoglycemia with mortality in the cohorts.

Supplementary Figures 2a and 2b demonstrate that increasing glucose variability was strongly associated with mortality among NON in both eras (p for trend < 0.0001) but not among DM in either era.

Mortality in the 2 eras

Mortality was 12.1% and 11.3% in the 2 eras for the entire cohort (p=0.60) with O:E ratios 0.74 and 0.68 (p=0.004). Among NON mortality and O:E ratios were nearly identical in the 2 periods: 11.9% and 11.4% (p=0.84) and 0.75 vs. 0.74 (p=0.51). In contrast, among those with diabetes, there was a nonsignificant 17.3% reduction in mortality during the POST era, from 13.3% to

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11.0% (p=0.57) and a significant reduction in the O:E ratio from 0.69 to 0.52 (p<0.001). Finally, among DM with A1C ≥ 7% there was a nonsignificant 29.8% reduction in mortality during the POST era, from 14.1% vs. 9.9% (p=0.53) and a significant reduction in the O:E ratio from 0.74 to 0.52 (p=0.004).

Conclusions

This before and after interventional investigation evaluated the impact of a change in hyperglycemia management protocol from a single BG target to 2 targets, based on preadmission glycemia and diabetes status, on glucose metrics and mortality in a large cohort of heterogeneous adult patients admitted to a single university affiliated teaching hospital. The intervention was found to be safe, with low rates of moderate hypoglycemia (< 70 mg/dL) and very low rates of severe hypoglycemia (< 40 mg/dL) in both eras. Among those with diabetes in the POST era, those treated with the "TIGHT" protocol had significantly lower mean ICU glycemia, reflected by mean BG as well as time in BG range, than did those treated with the "LOOSE" protocol. Comparing the 2 eras, mortality of NON patients was nearly identical, as was the observed:expected mortality ratio, using APACHE IV methodology. In contrast, among patients with diabetes there was a nonsignificant 17.3% reduction in mortality during the 2nd era, as well as a significant reduction in the observed:expected mortality ratio from 0.69 to 0.52 (p<0.001); for diabetes patients with A1C ≥ 7% the corresponding values were 29.8% and 0.74 to 0.52 (p=0.004).

An evolving literature describing differences in outcomes of critically ill patients associated with preadmission glycemic control provided the rationale for the design of this investigation. The

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major interventional trials of insulin therapy targeted “euglycemia” – 80-110 mg/dL.[1,27-30] However, subsequent analysis of these trials suggests that the benefit of “tight” glycemic control is demonstrated more clearly among patients without diabetes.[17] A randomized trial of intensive vs. moderate glycemic control in patients undergoing cardiovascular surgery demonstrated reduced morbidity among patients without diabetes, but not those with diabetes, who were treated with the intensive regimen.[31] Moreover, a number of observational cohort studies reported that among those without diabetes mortality is lower in patients with mean ICU glycemia in the 80-140 mg/dL range, compared to higher ranges, while among those with diabetes the opposite is seen: higher mortality is associated with lower ICU glycemia, and lower mortality is observed among patients with higher ICU glycemia.[11,13-16] The data from the current investigation corroborate this finding. Finally, other reports suggest that preadmission glycemic control modulates the association between ICU glycemia and mortality; patients with well controlled diabetes before ICU admission, reflected by A1C[19], tolerate ICU hyperglycemia similarly to those without diabetes.

The association of preadmission glycemia with ICU glycemic control and mortality has biologic plausibility. Hyperglycemia is ubiquitous in critically ill patients, due to a number of endogenous factors, especially a complex interplay of counter-regulatory hormones, cytokine release and hormonal derangements, as well as exogenous factors such as the nature of nutritional support and its intensity, corticosteroid administration and insulin treatment.[2,32] However, chronic hyperglycemia may induce a degree of cellular conditioning that attenuates the deleterious impact of acute hyperglycemia.[2,32,] This is also true for hypoglycemia and glucose variability, both seen in those with diabetes who receive sulfonylureas or insulin and both of which can induce a similar inflammatory response as seen with hyperglycemia. Our association of mortality with glucose variability in the NON group but not those in the DM group is consistent with this important concept.

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In addition, a recently published multi-center observational study suggested that preadmission glycemia modulates the relationship between hypoglycemia and death in critically ill patients.[20] First, patients with higher pre-admission A1C levels were at significantly greater risk of hypoglycemia while in ICU than were those with lower levels of preadmission glycemia. Notably, there was a direct correlation between the degree of chronic hyperglycemia before ICU admission and mortality rate among patients who experienced hypoglycemia during ICU treatment.

The strengths of this investigation include the comprehensive nature of the dataset, especially detailed glucose metrics and outcome analysis, including severity adjusted mortality, as well as the large size of the cohort. We acknowledge several important limitations. First, this is a single center study, therefore potentially limiting its external validity, and the number of patients with diabetes was relatively small. Second, we cannot report data regarding nutritional support or insulin therapy, important factors that certainly modulate the relationship between ICU glycemia and outcomes. Third, BG values were obtained using point of care glucose meters, as is the standard of care in most ICU's in the United States. This technology is associated with greater analytic inaccuracy than are BG values obtained using arterial blood gas analyzers[33], as well as the likelihood of "missed" episodes of hypoglycemia and hyperglycemia due to the intermittent nature of monitoring.[34,35] Fourth, for those with diabetes we do not have data on pre-admission medications. We speculate that some of the newer diabetes therapies, either directly, or indirectly, (specifically the incretins and SGLT2 inhibitors) could impact outcomes due to each agent's different impact on inflammatory activation and hormonal changes (including brain naturetic peptide).[36] Fifth, the investigation uses A1C measurements to stratify patients and their treatment. This measurement can be variable dependent on ethnicity and can be unreliable in patients with hematologic conditions such as hemolytic anemia or hemoglobinopathies, as well as in those with mechanical heart valves, hypothyroidism or taking certain medications.[37] Moreover, and perhaps most importantly, differential glycation rates may lead to variability in A1C levels.[37]

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Finally, this is a before and after, rather than randomized, investigation. Therefore, any conclusions must be considered hypothesis generating, and not as proof of causality.

Important questions remain. Consistent with other studies[10,13-16] these data support a BG target of 80-140 mg/dL for patients without diabetes, and perhaps, as well, for patients with diabetes who have excellent preadmission glycemic control, reflected by a low A1C or potentially other biomarkers if there is a "glycation gap".[37] Nevertheless, the appropriate BG target for diabetic patients, especially of those with A1C levels $\geq$ 7%, is less clear. Available data suggest the need for a higher BG target in these patients than that used to treat those without diabetes.[13-16] However, should this target range be 110-160 mg/dL, 140-180 mg/dL, or even higher? The "moderately loose" target of 110-160 mg/dL for those with A1C levels $\geq$ 7% in this study was chosen with the intent of avoiding glucose excursions above 180 mg/dL, the usual threshold for glucosuria[38] and a level of hyperglycemia associated with increased risk of death in observational data in unselected individuals with diabetes[4,13] as well as increased risk of nosocomial infection.[39] Carefully designed randomized trials, using new technologies providing or near-continuous monitoring of blood glucose values[40], will be needed to answer this important question. What is becoming clearer is the concept of "personalized medicine" appears to be relevant to BG control in critically ill patients, similar to what has been developed for outpatient diabetes management.[41]

In summary, this large before and after trial demonstrated the safety and efficacy of implementation of 2 BG targets, based on preadmission glycemia, in a large cohort of critically ill patients. The higher BG target in those with diabetes and A1C levels $\geq$ 7% was associated with moderately higher glycemia during ICU stay and a reduction in their O:E mortality ratios. This hypothesis-generating investigation suggests the need for additional prospective interventional studies assessing the outcomes of patients randomized to personalized glucose targets.

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JSK conceived the design, researched data, wrote the original draft of the manuscript, performed statistical analysis, contributed to revisions and takes responsibility for study design, access to data and decision to publish.
JCP reviewed and edited the manuscript and contributed important intellectual content.
IBH reviewed and edited the manuscript and contributed important intellectual content.

Conflicts of interests

JS Krinsley: Consulting/Advisory Board for Edwards Life Sciences, Medtronic, Optiscan Biomedical, Roche Diagnostics

JC Preiser: Consulting/Advisory Board for Edwards Life Sciences, Medtronic, Optiscan Biomedical

IB Hirsch: Consulting: Abbott Diabetes Care, Roche, Intarcia

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Figure legends

Figure 1
Reasons for exclusion of patients from the analysis in the 2 eras

Figure 2a
Mortality of patients without diabetes, stratified by mean BG, during the 2 eras

Figure 2b
Mortality of patients with diabetes, stratified by mean BG, during the 2 eras

Supplemental Figure 1a
Mortality of patients without diabetes, stratified by coefficient of variation, during the 2 eras

Supplemental Figure 1b
Mortality of patients with diabetes, stratified by coefficient of variation, during the 2 eras

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Table 1a

Clinical characteristics of the patients: entire cohort

	PRE	POST	P value
ENTIRE COHORT			
Number	1005	974	
Age (years)	67 (53-79)	67 (53-79)	0.78
Diabetes (%)	19.5	21.6	0.27
Diagnostic category (%)			
Medical	65.1	69.5	0.04
Surgical	24.3	20.4	0.04
Trauma	10.7	10.1	0.74
APACHE II score	13 (9-19)	13 (9-19)	0.65
APACHE IV score	46 (33-66)	47 (33-66)	0.60
APACHE IV PM (%)	16.5 (23.2)	16.7 (22.4)	0.84
Ventilation (%)	32.7	32.3	0.89
ICU LOS (days)	1.4 (0.8-2.8)	1.7 (0.9-3.5)	0.02

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Table 1b
Clinical characteristics of patients with and without diabetes

	PATIENTS WITHOUT DIABETES			PATIENTS WITH DIABETES					
	PRE	POST	P value	PRE	POST	P value	TIGHT	LOOSE	P value
Number	809	764		196	210		104	106	
Age (years)	66 (50-79)	66 (51-79)	0.95	70 (60-80)	71 (61-80)	0.55	74 (65-83)	68 (58-79)	0.0032
APACHE II score	12 (9-18)	13 (9-19)	0.73	16 (11-22)	15 (11-22)	0.88	16 (12-22)	15 (11-23)	0.49
APACHE IV score	44 (32-64)	45 (31-64)	0.97	51 (37-71)	55 (39-73)	0.34	57 (41-71)	54 (38-75)	0.44
APACHE IV PM (%)	15.8 (22.8)	15.4 (21.6)	0.75	19.3 (25.0)	21.2 (24.7)	0.44	21.7 (24.1)	20.6 (25.4)	0.76
Ventilation (%)	31.7	31.6	0.91	37.2	35.7	0.83	41.4	30.2	0.12
ICU LOS (days)	1.4 (0.9-2.8)	1.6 (0.9-3.2)	0.25	1.5 (0.8-2.8)	2.0 (1.0-4.0)	0.005	2.5 (1.0-4.7)	1.9 (1.0-3.5)	0.09

PRE – patients admitted between September 16, 2013 and September 15, 2014, with a single BG target
POST – patients admitted between September 16, 2014 and September 15, 2015, with 2 BG targets based on preadmission diabetes status: TIGHT 80-140 mg/dL; LOOSE 110-160 mg/dL
NON – patients without diabetes
DM – patients with diabetes
APACHE – Acute Physiology and Chronic Health Evaluation
LOS – length of stay
PM – predicted mortality
MR – mortality ratio

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Table 2a

Glucose metrics and insulin treatment: PRE vs POST, patients without diabetes

	PRE	POST	P value
Number	809	764	
A1C (%)	5.8 (5.5-6.1)[1]	5.6 (5.2-5.9)[2]	<0.0001
Mean BG (mg/dL)	118 (106-132)	115 (101-128)	0.0003
CV (%)	15.3 (10.7-20.7)	15.4 (10.9-21.0)	0.82
Maximum BG (mg/dL)	153 (129-186)	148 (127-175)	0.02
Minimum BG (mg/dL)	91 (80-103)	88 (77-102)	0.009
Hypo < 70 mg/dL (% of patients)	11.00	11.78	0.68
Hypo < 40 mg/dL (% of patients)	0.99	0.39	0.26
Number of BG tests	10 (5-24)	11 (5-25)	0.40
Number of BG tests/24 hours	7 (5-8)	7 (5-8)	0.20
Insulin treatment			
SC insulin (% of pts)	56.4	37.6	<0.0001
IV insulin (% of pts)	10.5	5.9	0.0013
Any insulin (% of pts)	57.7	38.5	<0.0001
Insulin/24 hrs (units)	5.0 (2.0-12.0)	3.2 (1.3-8.0)	<0.0001

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Table 2b

Glucose metrics and insulin treatment: PRE vs POST, patients with diabetes

				POST era		
	PRE	POST	P value	TIGHT	LOOSE	P value
Number	196	210		104	106	
A1C (%)	7.1 (6.4-8.5)[3]	6.8 (6.1-8.0)[4]	0.04	6.2 (6.0-6.6)[1]	8.0 (7.1-9.1)[2]	<0.0001
Mean BG (mg/dL)	139 (123-160)	146 (128-165)	0.15	136 (119-149)	159 (138-177)	<0.0001
CV (%)	22.1 (15.0-32.7)	22.7 (15.8-30.1)	0.91	20.7 (15.6-27.3)	24.2 (17.3-34.2)	0.02
Maximum BG (mg/dL)	206 (172-270)	224 (179-272)	0.20	205 (157-253)	244 (200-299)	<0.0001
Minimum BG (mg/dL)	91 (76-109)	89 (75-111)	0.70	87 (74-104)	92 (77-118)	0.05
Hypo <70 mg/dL*	17.86	17.14	0.95	20.19	14.15	0.33
Hypo <40 mg/dL*	1.02	0.48	0.96	0.00	0.94	0.99
Number of BG tests	13 (6-30)	17 (8-53)	0.004	18 (8-56)	17 (8-49)	0.75
Number of BG tests/24 hrs	8 (6-10)	8 (7-12)	0.07	8 (6-11)	9 (8-14)	0.01
INS Rx						
SC insulin (% of pts)	83.1	77.7	0.21	75.0	81.1	0.37
IV insulin (% of pts)	26.2	39.8	0.0051	32.7	47.2	0.0451
Any insulin (% of pts)	84.6	80.6	0.35	76.9	84.9	0.19
Insulin/24 hrs (units)	16.7 (6.1-36.9)	18.6 (6.7-36.8)	0.97	9.8 (4.7-25.4)	25.0 (10.6-48.3)	<0.0001

[1]n=343
[2]n=646
[3]n=116
[4]n=192
PRE – patients admitted between September 16, 2013 and September 15, 2014, with a single BG target
POST – patients admitted between September 16, 2014 and September 15, 2015, with 2 BG targets based on preadmission diabetes status
NON – patients without diabetes
DM – patients with diabetes
CV – coefficient of variation
Maximum BG – maximum BG (mg/dL) during ICU stay
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Minimum BG – minimum BG (mg/dL) during ICU stay
Hypo 70 – percentage of patients with at least one BG value < 70 mg/dL
Hypo 40 – percentage of patients with at least one BG value < 40 mg/dL
Pts – patients
Rx – treatment
*percentage of patients

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Table 3 Comparison of mortality for patients with mean BG 80-140 mg/dL vs ≥ 140 mg/dL

Cohort	Mortality (%) 80-140	N	Mortality (%) ≥140	N	P value
NON PRE	9.0	679	26.0	124	<0.0001
NON POST	10.2	665	19.4	93	0.0144
DM PRE	13.9	101	12.8	94	0.99
DM POST	10.3	87	11.4	123	0.98
DM POST, TIGHT protocol	7.0	57	10.9	46	0.73
DM POST, LOOSE protocol	17.2	29	11.7	77	0.67
All A1C < 7.0%*	10.5	936	18.2	170	0.0060
All A1C ≥ 7.0%*	20.8	48	11.8	136	0.19

*includes patients in both eras

BG targets in POST era: TIGHT 80-140 mg/dL for NON and DM with A1C < 7%; 110-160 for DM with A1C ≥ 7%

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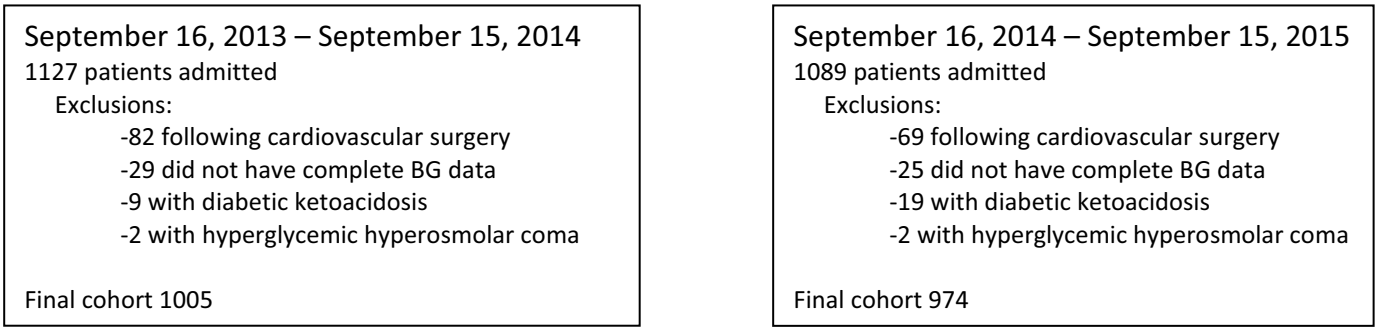
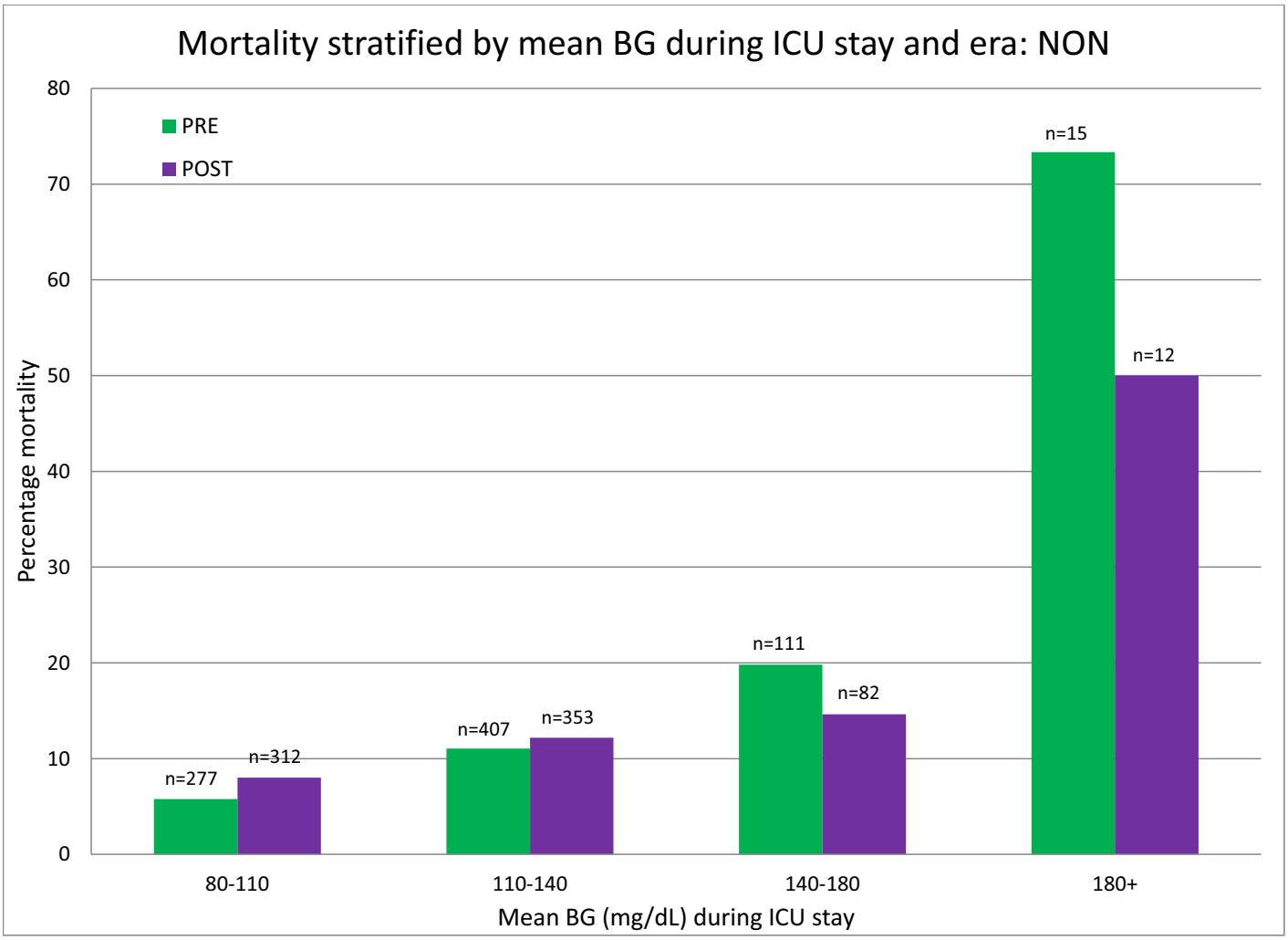
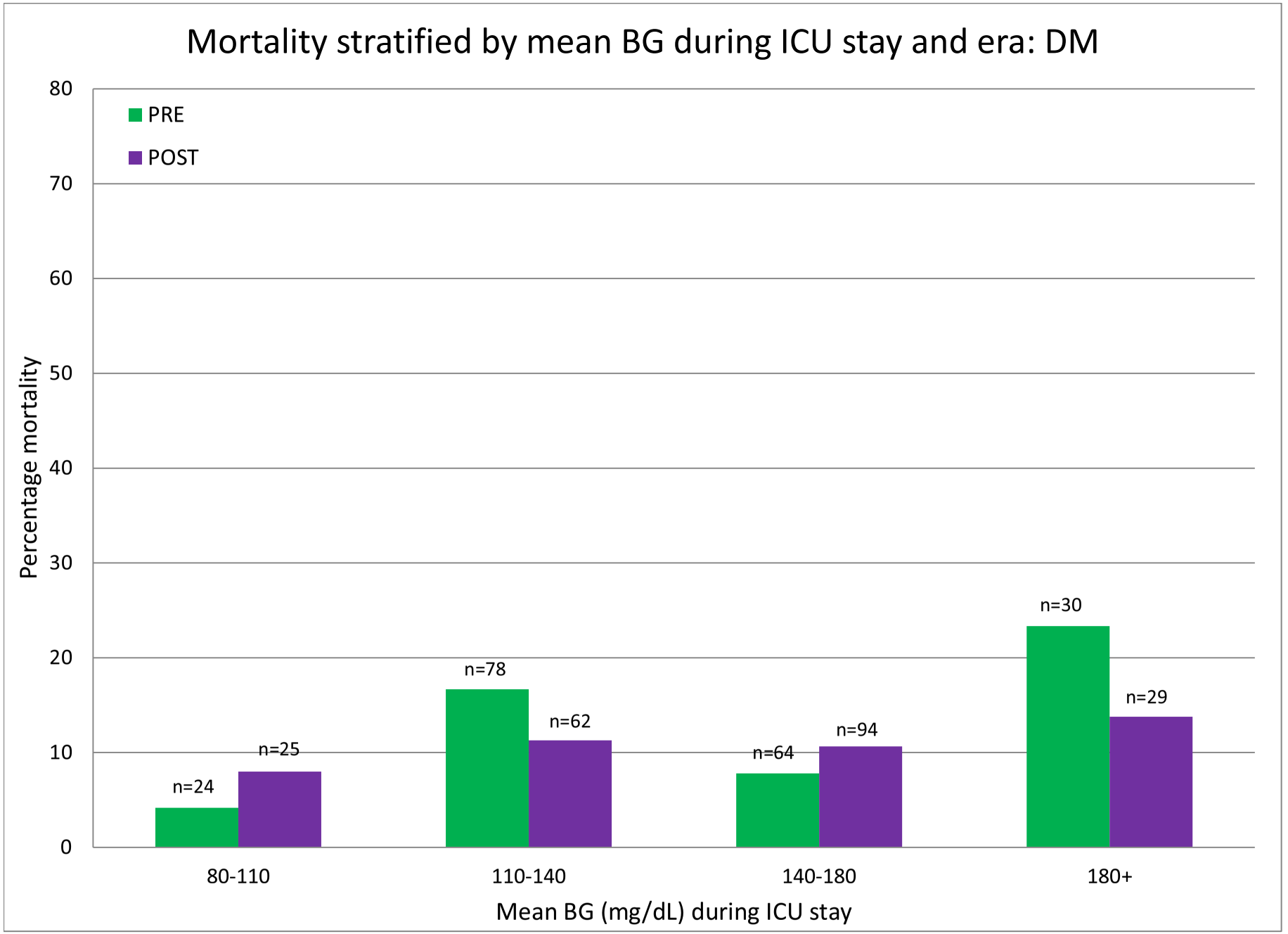
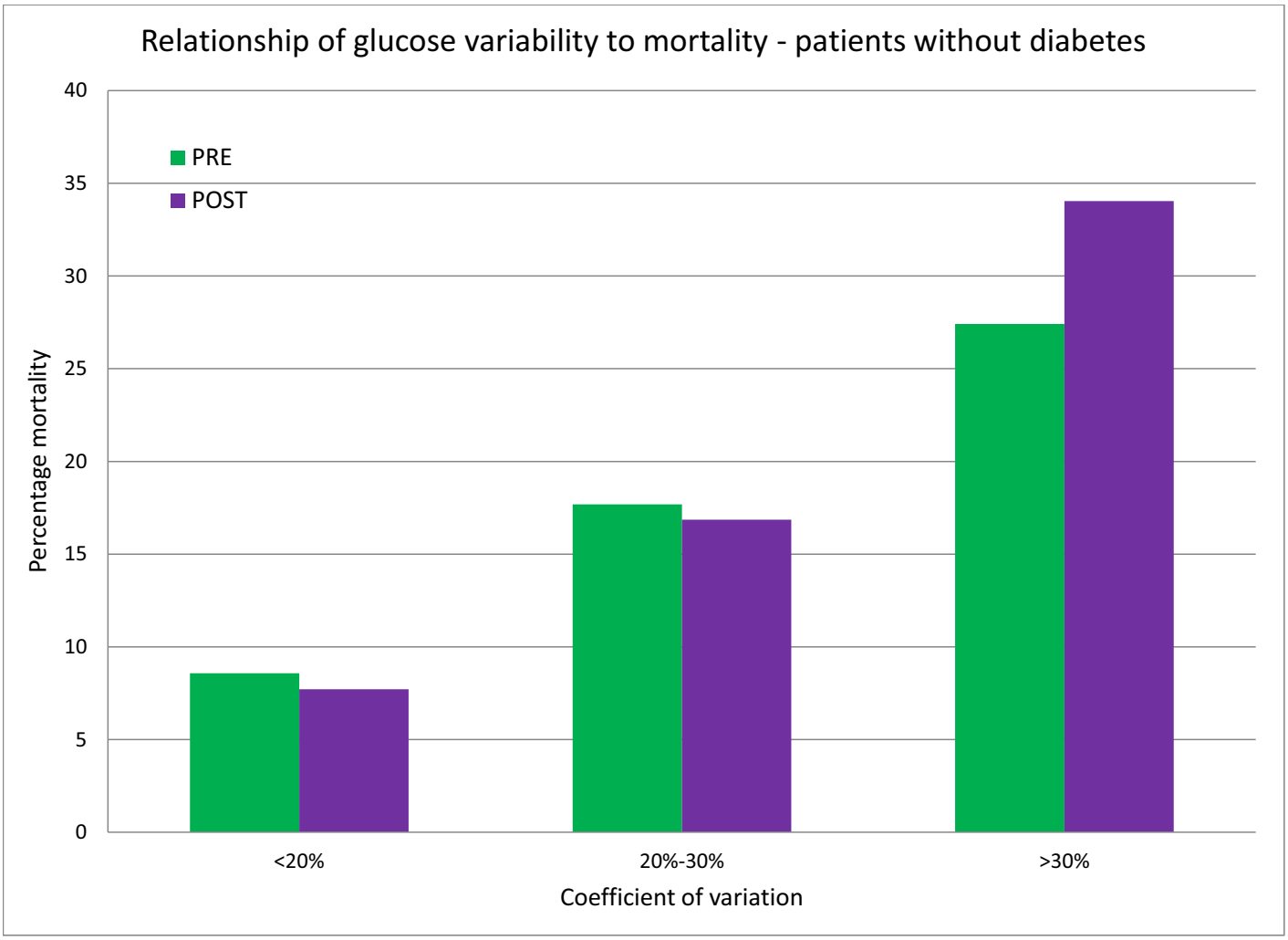
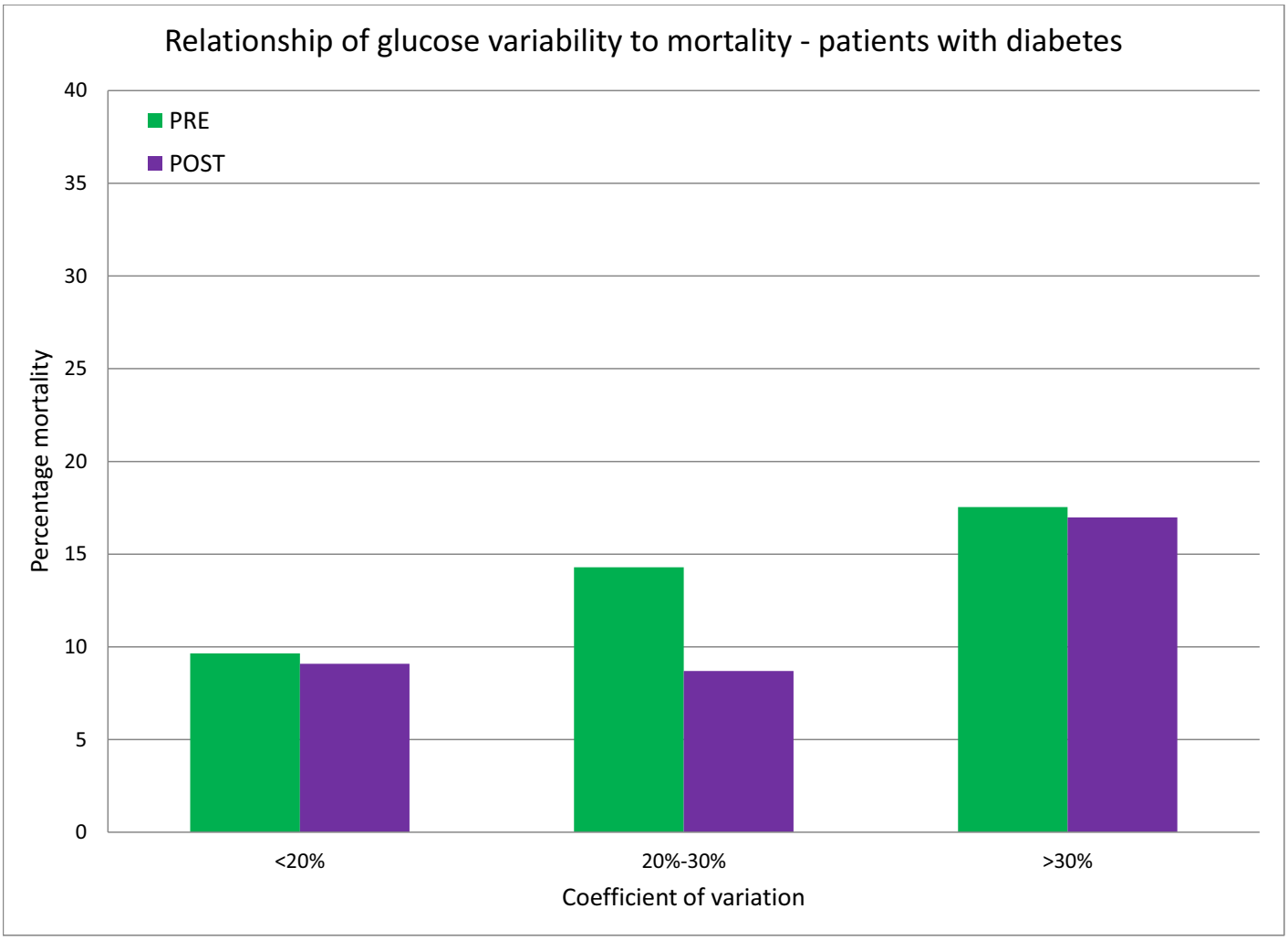
Figure 1


September 16, 2013 – September 15, 2014
1127 patients admitted
Exclusions:
-82 following cardiovascular surgery
-29 did not have complete BG data
-9 with diabetic ketoacidosis
-2 with hyperglycemic hyperosmolar coma
Final cohort 1005
September 16, 2014 – September 15, 2015
1089 patients admitted
Exclusions:
-69 following cardiovascular surgery
-25 did not have complete BG data
-19 with diabetic ketoacidosis
-2 with hyperglycemic hyperosmolar coma
Final cohort 974


Mortality stratified by mean BG during ICU stay and era: NON
Percentage mortality
80
70
60
50
40
30
20
10
0
PRE
POST
n=277
n=312
n=407
n=353
n=111
n=82
n=15
n=12
80-110
110-140
140-180
180+
Mean BG (mg/dL) during ICU stay


Mortality stratified by mean BG during ICU stay and era: DM
PRE
POST
Percentage mortality
80
70
60
50
40
30
20
10
0
n=24
n=25
n=78
n=62
n=64
n=94
n=30
n=29
80-110
110-140
140-180
180+
Mean BG (mg/dL) during ICU stay


Relationship of glucose variability to mortality - patients without diabetes
Percentage mortality
40
35
30
25
20
15
10
5
0
PRE
POST
<20%
20%-30%
>30%
Coefficient of variation


Relationship of glucose variability to mortality - patients with diabetes
PRE
POST
Percentage mortality
40
35
30
25
20
15
10
5
0
<20%
20%-30%
>30%
Coefficient of variation

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ICU Insulin Drip Protocol

Goal: To bring blood glucose (BG) to a level between 90-120 mg/dl

BG (mg/dL)	Insulin Gtt Rate units/hr
> 400	12
350-399	10
300-349	9
275-299	8
250-274	7
225-249	6
200-224	5
180-199	4
150-179	3
135-149	2
120-134	1.5

Important Points:

- Protocol is initiated by RN, when there is one BG > 300, or two consecutive BG ≥ 180. MD must be notified regarding initiation of insulin drip. IV regular insulin is administered at concentration of 1unit/mL.
- All patients receiving continuous insulin with a BG <200 must receive a continuous source of glucose, either via D5W, D10W, TPN or enteral feeds.
- BG monitoring frequency is Q1 hr.
- Patients with severe shock or severe edema should have BG monitored using venous or arterial blood, rather than fingerstick capillary blood.
- If BG has not decreased after 2 BG, insulin dose should be increased.
- If BG control stabilizes (4 consecutive BG between 90-120 mg/dl) on the infusion, monitoring frequency can be decreased to Q2hours.
- Variances to the protocol are documented by the RN in Meditech and the MD is notified.

When BG rate of change >50 mg/dL:

- If BG is between 200-300 with greater than 100 BG drop since the previous BG, decrease drip rate by 50% recheck in 1 hour.
- If BG is between 150-200 with greater than 50 BG drop since the previous BG, decrease drip rate by 50% recheck in 1 hour.

BG (mg/dL)	Management of BG <120 mg/dL on an Insulin Drip
80-119	Continue insulin infusion at 1 unit/hr.
60-79	Stop insulin infusion, recheck in 1 hr
40-59	Stop infusion and initiate D10 at 100ml/hr recheck BG in 30min and 60 min. Stop infusion when BG >79.
<40	Stop infusion, give1/2 amp D50 give recheck in 30 min

Transition to Subcutaneous Therapy
- For patients with **low (requiring < 1 units/hr)** but stable (90-119 mg/dl) insulin requirement turn off insulin drip. - For patients with **high (requiring > 2 units/hr)** but stable insulin requirement on Insulin drip, calculate previous 24 hour total insulin given and divide by 2 to calculate dose of Lantus. Give 50% of calculated dose at 0800 or 2000, then turn off Insulin drip 2 hours after giving lantus dose.
Shut off D5W once insulin drip is shut off. Check blood sugar in 2 hrs and begin subcutaneous insulin protocol.
The transition to subcutaneous therapy is based on the patient's overall clinical status, not just the degree of BG control. Unstable patients (eg shock) should have the insulin infusion continued even if excellent BG control has been achieved with a low insulin infusion rate.

ICU Subcutaneous Insulin Protocol

Goal: To bring blood glucose (BG) to a level between 90-120 mg/dl

BG (mg/dL)	SC Aspart Insulin Units
> 300	Insulin gtt
250-299	10
200-249	8
180-199	6
150-179	4
135-149	2
120-134	1.5

Important Points:

- Protocol is initiated upon patient's admission to ICU, or transition from IV insulin drip. Aspart insulin is the designated sc insulin.
- BG monitoring frequency is Q3 hr unless the patient is on po diet, in which case BG is monitored AC/HS.
  -Patients with severe shock or severe edema should have BG monitored using venous or arterial blood, rather than fingerstick capillary blood.
- If the daily Aspart dose exceeds 15 units, addition of Glargine insulin should be considered. Glargine should be administered Q12 hrs. The starting Glargine dose should be 33% - 50% of the previous day's total Aspart dose.
- Oral hypoglycemic agents should not be used in the ICU.
- If patient's BG remains in the 90-120 mg/dL range without iinsulin requirement for 48 hours, BG monitoring frequency can be decreased to Q6hrs.
- Variances to the protocol are documented by the RN in Meditech and the MD is notified.

When BG rate of change >50mg/dL:

- If BG is between 200-300 with greater than 100 BG drop since the previous BG, decrease insulin dose by 50% and recheck BG in 1 hour.
- If BG is between 150-200 with greater than 50 BG drop since the previous BG decrease insulin dose by 50% and recheck BG in 1 hour.

BG (mg/dL)	Management of BG <80mg/dl on sc Insulin
60-79	If patient is asymptomatic, recheck BG in 1 hour. If symptomatic, treat patient using the 40-59 mg/dl guideline.
40-59	If patient is ordered for PO intake, give 120ml of apple juice, if NPO initiate D10 at 100ml/hr and recheck BG in 30 min and 60 min. Stop infusion when BG >79.
<40	Give 1/2 amp D50, check BG in 30min. Notify MD.

RISK OF HYPOGLYCEMIA INCREASES:

- In patients not receiving nutrition. Consider holding insulin in this case.
- In patients with ESRD or liver failure. Treat initially with 50% suggested insulin dose and consider increasing the frequency of BG monitoring.

This protocol is not to be used for patients being treated for diabetic ketoacidosis.

These guidelines can be modified if the patient requires more or less intensive therapy.

NON DIABETICS, DIABETICS w/ A1C <7, CV SURGERY

ICU GLYCEMIC CONTROL PROTOCOL

Goal: To bring and maintain blood glucose (BG) **80-140 mg/dL**

Subcutaneous Insulin Guidelines

BG (mg/dL)	Subcutaneous Insulin (units)
300+	**Insulin gtt**
250-299	**8**
200-249	**6**
170-199	**4**
140-169	**3**
80-139	**No treatment**
70-79	If asymptomatic, check BG in 1 hour. If symptomatic, treat using 40-69 mg/dL guidelines.
40-69	If ordered for PO intake, give 120mL of apple juice. If NPO initiate D10 @ 100mL/hr and check BG in 30 min and 60 min. Stop D10 infusion when BG >89 mg/dL.
<40	Give 1/2 amp D50. Check BG in 30 min. Notify MD.

Important points:

-Protocol is initiated upon patient's admission to ICU, or transition from IV insulin drip.
- Novolog insulin is the designated SC insulin.
- BG monitoring frequency is **Q3H** unless the patient is on PO diet, in which case BG is monitored **AC/HS**.
- If patient's BG remains in the 80-140 mg/dL range without insulin requirement for 48 hours, BG monitoring frequency can be decreased to Q6H.

Insulin Drip Guidelines

BG (mg/dL)	Insulin Drip Rate (units/hr)
400+	**10**
300-399	**8**
250-299	**6**
200-249	**4**
170-199	**3**
140-169	**2**
90-139	**1**
70-89	Stop insulin infusion. Check BG Q1H x 2 hours.
40-69	Stop insulin infusion: initiate D10 @ 100mL/hr. Check BG in 30 min and 60 min. Stop D10 infusion when BG >79.
<40	Stop insulin infusion. Give1/2 amp D50. Check BG in 30 min. Notify MD.

Important points:

- Protocol is initiated by RN when there is **one BG > 300 mg/dL, or two consecutive BG ≥ 180 mg/dL.** Notify MD.
- **CV SURGERY – insulin drip initiated during surgery will be maintained until 24 hours after ICU admission**
- All patients receiving continuous insulin with a BG <220 must receive a continuous source of glucose, either via D5W, D10W, TPN or enteral feeds.
- BG monitoring frequency is **Q1H**.
- If there is no decrease after two consecutive BG, titrate insulin drip according to your ***nursing judgment.***
- If the patient has 4 consecutive BG between 80-140 mg/dL on the infusion, monitoring frequency can be decreased to Q2H.
- Prior to discontinuation of insulin drip, address potential need for Lantus dosing with MD

DIABETICS w/ A1C ≥7
ICU GLYCEMIC CONTROL PROTOCOL

Goal: To bring and maintain blood glucose (BG) **110-160 mg/dL**

Subcutaneous Insulin Guidelines:	
BG (mg/dL)	**Subcutaneous Insulin (units)**
300+	**Insulin gtt**
250-299	**8**
200-249	**6**
180-200	**4**
161-179	**2**
110-160	**No treatment**
70-109	If asymptomatic, check BG in 1 hour. If symptomatic, treat using 40-69 mg/dL guidelines. Notify MD.
40-69	If ordered for PO intake, give 120 mL of apple juice. If NPO initiate D10 @ 100mL/hr and check BG in 30 min and 60 min. Stop D10 infusion when BG >89 mg/dL. Notify MD.
<40	Give 1/2 amp D50. Check BG in 30 min. Notify MD.

Important points:

- Protocol is initiated upon patient's admission to ICU, or transition from IV insulin drip.
- Novolog insulin is the designated SC insulin.
- BG monitoring frequency is **Q3H** unless the patient is on PO diet, in which case BG is monitored **AC/HS**.
- If patient's BG remains in the 110-160 mg/dL range without insulin requirement for 48 hours, BG monitoring frequency can be decreased to Q6H.

Insulin Drip Guidelines:	
BG (mg/dL)	**Insulin Drip Rate (units/hr)**
400+	**10**
300-399	**8**
250-299	**6**
200-249	**4**
180-200	**3**
161-179	**2**
110-160	**1**
70-109	Stop insulin infusion. Check BG Q1H x 2 hours.
40-69	Stop insulin infusion: initiate D10 @ 100mL/hr. Check BG in 30 min and 60 min. Stop D10 infusion when BG >79. Notify MD.
<40	Stop insulin infusion. Give1/2 amp D50. Check BG in 30 min. Notify MD.

Important points:

- Protocol is initiated by RN when there is **one BG > 300 mg/dL, or two consecutive BG ≥ 180 mg/dL.** Notify MD.
- All patients receiving continuous insulin with a BG <250 must receive a continuous source of glucose, either via IVF, TPN or enteral feeds.
- BG monitoring frequency is **Q1H**.
- If there is no decrease after two consecutive BG, titrate insulin drip according to your ***nursing judgment.***
- If the patient has 4 consecutive BG between 110-160 mg/dL on the infusion, monitoring frequency can be decreased to Q2H.
- Prior to discontinuation of insulin drip, address potential need for Lantus dosing with MD.

Supplementary Table 1

Multivariable analysis: mortality

	OR (95% CI)	P value
NON		
APACHE IV predicted mortality (%)	1.06 (1.05-1.07)	<0.0001
ICU LOS	0.99 (0.95-1.03)	0.5402
POST era	1.04 (0.71-1.53)	0.8251
DM		
APACHE IV predicted mortality (%)	1.06 (1.05-1.08)	<0.0001
ICU LOS	1.04 (0.96-1.12)	0.3157
POST era	0.54 (0.24-1.22)	0.1386
A1C < 7.0*		
APACHE IV predicted mortality (%)	1.06 (1.05-1.07)	<0.0001
ICU LOS	0.99 (0.95-1.04)	0.8490
POST era	1.00 (0.63-1.57)	0.9936
A1C $\geq$ 7.0^		
APACHE IV predicted mortality (%)	1.05 (1.03-1.07)	<0.0001
ICU LOS	1.07 (0.97-1.19)	0.1681
POST era	0.64 (0.23-1.75)	0.3848

*n=1113; 373 PRE, 740 POST
^n=184; 87 PRE, 97 POST
LOS – length of stay
PRE – patients admitted between September 16, 2013 and September 15, 2014, with a single BG target
POST – patients admitted between September 16, 2014 and September 15, 2015, with 2 BG targets based on preadmission diabetes status: TIGHT 80-140 mg/dL; LOOSE 110-160 mg/dL

Supplementary Table 2 Hypoglycemia and mortality

Minimum BG

	<40 mg/dL		<70 mg/dL		No Hypo		
	Mortality (%)	N	Mortality (%)	N	Mortality (%)	N	P value*
NON PRE	87.5	8	30.3	89	9.6	721	<0.0001
NON POST	33.3	3	24.4	90	9.7	673	0.0001
DM PRE	100.0	2	20.0	35	11.9	160	0.3164
DM POST	100.0	1	19.4	36	9.1	175	0.1298

*comparison of No hypo and Hypo < 70 mg/dL