Is it time to abandon glucose control in critically ill adult patients?

James S. Krinsley[a] *and Jean-Charles Preiser*[b]

Purpose of review
To summarize the advances in literature that support the best current practices regarding glucose control in the critically ill.

Recent findings
There are differences between patients with and without diabetes regarding the relationship of glucose metrics during acute illness to mortality. Among patients with diabetes, an assessment of preadmission glycemia, using measurement of Hemoglobin A1c (HgbA1c) informs the choice of glucose targets. For patients without diabetes and for patients with low HgbA1c levels, increasing mean glycemia during critical illness is independently associated with increasing risk of mortality. For patients with poor preadmission glucose control the appropriate blood glucose target has not yet been established. New metrics, including stress hyperglycemia ratio and glycemic gap, have been developed to describe the relationship between acute and chronic glycemia.

Summary
A 'personalized' approach to glycemic control in the critically ill, with recognition of preadmission glycemia, is supported by an emerging literature and is suitable for testing in future interventional trials.

Keywords
critically ill, diabetes, glucose control, hyperglycemia, mortality

INTRODUCTION

The era of blood glucose control in critically ill patients began quietly, in the cardiovascular surgery division of a hospital in Portland, Oregon, in which a forward-thinking surgeon started treating diabetes patients with insulin in the late 1980's and demonstrated, over time, sequential reduction in mortality and reduction in infections and cost of care over a period of decades [1,2]. The interest in this intervention exploded with the publication in 2001 of the first randomized controlled trial (RCT) of intensive insulin therapy (IIT), from Leuven, Belgium, conducted in a predominantly cardiac surgery population, reporting substantial reduction in mortality and morbidities [3]. These findings were largely confirmed in a before and after nonrandomized trial from a mixed medical-surgical ICU published 3 years later [4] and, less conclusively, in a second trial from Leuven conducted in a medical ICU cohort [5]. Two subsequent multicenter RCT's of IIT were terminated prematurely, without demonstrating benefit. Among the potential reasons for the discrepancies between the results of these studies a lower rate of achievement of the blood glucose range [6] and very high rates of hypoglycemia in the interventional arm of the trial [7] were suggested. Importantly, the amount of intravenous glucose given in the two Leuven studies [3,5] was much higher than in the other trials. Finally, the largest RCT of IIT, NICE-SUGAR, a multicenter study including 6104 patients from 42 institutions, found that IIT was associated with higher 90-day mortality than was conventional blood glucose management [8]. The publication of this study led to a change in blood glucose control guidelines [9,10], away from 'tight' blood glucose control (targeting 80–110 mg/dl) to 'moderate' control, generally with a 140–180 mg/dl target.

[a]Department of Medicine, Stamford Hospital, Columbia Vagelos College of Physicians and Surgeons, Connecticut, USA and [b]Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Belgium

Correspondence to James S. Krinsley, MD, FCCM, FCCP, Stamford Hospital, Stamford, Columbia Vagelos College of Physicians and Surgeons, CT 06902, USA. Tel: +1 203 348 2437;
e-mail: jkrinsley@stamhealth.org

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KEY POINTS

- The failure of randomized controlled trials of intensive insulin therapy completed after the original successful trials conducted in Leuven can be attributed to the 'single center' effect, high rates of hypoglycemia, low time in targeted blood glucose range, different amounts of intravenous glucose, and perhaps to the use of a single blood glucose target in all interventional patients.
- For patients with diabetes and well controlled preadmission glycemia based on HgbA1c levels and patients without diabetes, increasing mean glycemia during ICU stay is independently associated with increasing risk of mortality.
- For patients with diabetes and poor preadmission glycemic control there is no clear association between mean ICU glycemia and mortality.
- The metrics of stress hyperglycemia ratio and glycemic gap describe the relationship between acute and chronic glycemia.
- A blood glucose target of 80–140 mg/dl during ICU stay for patients without diabetes and diabetes patients with well-controlled glycemia before acute illness is supported by available data from observational and randomized trials. For patients with diabetes and poorly controlled glycemia before ICU admission the appropriate blood glucose target has not yet been established.

What happened? How can we explain the difference in outcomes among these various investigations? Is it time to give up on the notion that blood glucose levels in critically ill patients should be monitored and treated with insulin?

This review article will attempt to answer these questions. It will include an analysis of the factors underlying the failure of later trials to replicate the findings of the first Leuven trial and the important advances that have occurred in the decade as publication of the NICE-SUGAR trial, learnings that have helped shape a new paradigm, that of personalized glycemic control in the critically ill. It will not explore the numerous pathophysiologic mechanisms that underlie the deleterious impact of dysglycemia on the critically ill. For this purpose, the interested reader is directed to two outstanding recent reviews [11▪▪,12▪].

WHY WERE THE FINDINGS OF LEUVEN 1 NOT REPLICATED IN SUBSEQUENT RANDOMIZED CONTROLLED TRIALS OF INTENSIVE INSULIN THERAPY?

The single center effect

The investigations with positive findings – the 2 Leuven trials and the nonrandomized trial conducted at Stamford Hospital in the United States – were conducted in a single ICU. Why is this important? Blood glucose control in the critically ill is a complex, dynamic process, requiring frequent monitoring, reassessment of the patient's status, and dose adjustments of insulin over a period of days to weeks. The success of this intervention depends largely on the clinical team's ability to safely and effectively adhere to the treatment protocol, requiring training, practice, and leadership. Compare this intervention to the administration of aspirin in the treatment of acute myocardial infarction. In this latter example, all that is required is for an order to be given and the medication to be administered once, a process that would be associated with high compliance. Table 1 reports the number of patients in the interventional arms of the trials described above, as well as the percentage of patients who sustained at least one occurrence of severe hypoglycemia (blood glucose < 40 mg/dl) in the interventional and control arms of the trials. The small number of included patients raises the possibility that the centers participating in the GLUCONTROL, VISEP, and NICE-SUGAR trials did not have the opportunity to achieve optimal success with insulin infusion protocol performance.

Table 1. Number of patients in interventional trials of intensive insulin therapy, and percentage of patients with at least one episode of severe hypoglycemia

Study (references)	Year published	Number of patients in interventional arm, per center	Percentage of patients with severe hypoglycemia
Leuven 1 [3]	2001	765	5.3 vs. 0.8
Leuven 2 [5]	2006	595	18.7 vs. 3.1
VISEP [7]	2008	15	17.0 vs. 4.1
GLUCONTROL [6]	2009	26	8.7 vs. 2.7
NICE-SUGAR [8]	2009	73	6.8 vs. 0.5
Stamford [4] [a]	2004	800	1.5 vs. 1.5

[a]nonrandomized.

Table 2. Inferred time in targeted blood glucose range in the interventional trials of intensive insulin therapy

Study (reference)	Mean (SD) AM BG	Time in range (%)[a]
Leuven 1 [3]	103 (19)	53.1
Leuven 2 [5]	111 (29)	35.5
VISEP [7]	112 (18)	45.4
GLUCONTROL [6]	110 (99–124)[b]	42.8[c]
NICE-SUGAR [4]	118 (25)	31.0

BG, blood glucose.
[a]inferred using Standard Normal Distribution Table. Each of the studies had BG target 80–110 mg/dl in the interventional arm.
[b]median (IQR).
[c]reported in manuscript.

Hypoglycemia

Hypoglycemia is independently associated with increased risk of death in critically ill patients, a finding that has been demonstrated in numerous observational studies [13–17], as well as in the Leuven and NICE-SUGAR RCT's [18,19]. This association has been observed regardless of whether hypoglycemia occurs spontaneously or is associated with treatment with insulin [20]. Notably, 25% of the patients undergoing IIT for 5 days or more in the second Leuven trial sustained at least one episode of severe hypoglycemia [5]. Hypoglycemia can be particularly detrimental in brain-injured patients, as suggested by the higher rate of 'energy crisis [21].'

Low time in targeted blood glucose range

Time in targeted blood glucose range (TIR) may be considered a unifying metric of glycemic control, as it encompasses the three frequently described 'domains' of hyperglycemia, hypoglycemia, and glucose variability, all independently associated with mortality in the critically ill. Chase and coworkers [22,23] demonstrated that TIR (72–136 mg/dl) more than 70% was independently associated with survival and more than 50% was independently associated with less organ system dysfunction in single center observational studies. In a 3247 patient cohort from Stamford Hospital, TIR 70–140 mg/dl was independently associated with survival in patients without diabetes, but not in those with diabetes [24]. A multicenter observational investigation from Intermountain Health in Utah, the United States demonstrated that this same range of TIR was independently associated with survival in patients with and without diabetes, though the association was stronger among patients without diabetes [25].

The major interventional trials of IIT targeted blood glucose 80–110 mg/dl. Were these trials successful in achieving this goal? Only one trial – GLUCONTROL, involving 1078 medical and surgical patients from 21 predominantly European ICU's – explicitly reported TIR [6]. Table 2 reports TIR data from the trials, suggesting that the highest TIR was achieved in the first Leuven trial and the lowest in NICE-SUGAR; the standard normal distribution table is used in conjunction with the reported median (interquartile range) morning blood glucose results to estimate TIR (adapted from Ref. [26]).

It is reasonable to consider that if achieving the stated blood glucose target was necessary to establish a beneficial effect of the intervention, the low TIR achieved in the trials contributed to their lack of success.

Was 'one size fits all' the correct approach?

Consider an RCT that reports a 4% net reduction in mortality because of a specific intervention. This benefit may have been because of a 25% reduction in mortality in 20% of the patients in the trial, no change in mortality in 70% and a 10% increase in mortality in the remaining 10%. Is it possible that IIT had a differential effect on patients enrolled in the trial? Table 3 presents evidence that diabetes status confounded the results of the RCT of IIT (adapted from reference [27]).

In each case, the interventional arm demonstrated greater benefit (or in the case of NICE-SUGAR, less harm) among patients without diabetes than among those with diabetes.

Table 3. Mortality percent stratified by diabetes status in interventional trials of intensive insulin therapy

			No diabetes		Diabetes	
Study (reference)	*n*	Diabetes %	Control	Rx	Control	Rx
Leuven 1 [3]	1548	13.2	8.4	5.8	4.7	4.0
Leuven 2 [5]	1200	16.9	40.9	35.1	36.8	39.6
NICE-SUGAR [8]	6021	20.7	24.3	27.7	26.5	31.7
Stamford [27] [a]	5365	20.1	18.7	13.5	22.6	19.2

[a]nonrandomized.

These data raise the possibility that diabetes status impacts the association between glycemic control and mortality in critically ill patients. The next section of this review will explore the available data supporting this idea.

DIABETES STATUS IMPACTS THE RELATIONSHIP BETWEEN GLYCEMIC CONTROL IN THE CRITICALLY ILL AND MORTALITY

The relationship between mean glycemia during ICU stay and mortality is distinctly different when comparing patients with and without diabetes. A number of observational cohort studies have demonstrated that for patients without diabetes the lowest mortality is seen in patients with mean blood glucose in the 80–110 mg/dl range during ICU stay, with a modest increase associated with mean blood glucose 110–140 mg/dl and progressively higher mortality rates observed with mean blood glucose 140–180 mg/dl and higher [28–32]. In contrast, for patients with diabetes, there is a 'blunted' [28,30], or even absent [29,31,32], relationship between mean blood glucose above 80–110 mg/dl and mortality. None of the RCT of IIT reported the relationship between mean glycemia, in distinct bands, and mortality, either for the entire cohort, or stratified by diabetes status.

The relationship between diabetes status and outcome in patients with sepsis or acute bacteremia was evaluated in a retrospective cohort study of 128 222 patients admitted with sepsis over a 5 year period to 83 Dutch ICU's [33]. Among patients with diabetes, only hypoglycemia in the absence of severe hyperglycemia was independently associated with risk of death. In contrast, for patients without diabetes, hyperglycemia and hypoglycemia were independently associated with increased risk of death, as was their combination. In a cohort of 317 patients with *Acinetobacter baumannii* complex bacteremia, the lowest mortality among patients without and with diabetes the lowest mortality was seen with mean blood glucose 70–100 mg/dl and 100–140 mg/dl, respectively [34]. Increasing glucose variability was independently associated with risk of death only for patients without diabetes.

The studies describing the relationship between mean glycemia and mortality also confirmed the strong association of hypoglycemia with death in critically ill patients with and without diabetes; those with mean blood glucose during ICU stay less than 80 mg/dl sustained the highest mortality [28–32]. Recently published work suggests that the independent association of hypoglycemia with death may even be stronger in patients with diabetes than in those without [35].

Several observational cohort studies have demonstrated that high glucose variability is independently associated with risk of death in patients without diabetes [31,32,36,37]. In contrast, for patients with diabetes there was no association between high glucose variability and risk of death in three of these studies [31,32,36]; in one, there was a positive association, but it was not as strong as for those without diabetes [37]. A recently published multicenter observational cohort study included 90 644 septic patients, 5127 with insulin-treated diabetes [38▪] evaluated glucose metrics in the first 24 h of ICU admission. Patients with insulin-treated diabetes had lower adjusted hospital mortality with higher peak blood glucose levels whereas those without diabetes had increased mortality with higher peak blood glucose. For patients without diabetes, increasing glucose variability was associated with increased risk of death; in contrast, there was no association between increasing glucose variability and risk of death for patients with insulin-treated diabetes.

THE CRITICALLY ILL DIABETES COHORT IS NOT UNIFORM

Acute and chronic glycemia

Egi and coworkers [39] evaluated the relationship between acute and chronic glycemia in 415 patients with diabetes admitted to two Australian ICU's. Chronic glycemia was characterized by Hemoglobin A1c (HgbA1c) levels obtained on admission. There was no significant difference in mean blood glucose or mean HgbA1c levels between survivors and nonsurvivors. However, for patients with low HgbA1c levels, increasing mean ICU glycemia was associated with increased risk of death and for patients with high HgbA1c levels low mean ICU glycemia was associated with increased risk of death. This landmark study suggested that for patients with well-controlled diabetes prior to admission, reflected by low HgbA1c levels, the relationship between mean ICU glycemia and mortality was similar to that seen among patients without diabetes, and that for patients with poorly controlled diabetes prior to admission higher blood glucose targets may be reasonable and appropriate.

These findings were corroborated in a single-center 1000 patient study (22% with previously diagnosed diabetes) in which peak glycemia during the first 48 h of admission was associated with mortality, stratified by the patient's HgbA1c level upon admission [40]. For patients without diabetes or with diabetes and HgbA1c level less than 6%, there was a 20% increase in risk of death for every 18 mg/dl

increase in peak glycemia. For patients with diabetes and HgbA1c 6–7% there was a positive, but less significant, relationship between peak glycemia and mortality. For diabetes patients with HgbA1c at least 7% there was no relationship between peak glycemia and mortality.

Importantly, HgbA1c, considered to be a measure of glycemia for 3 months preceding its measure, is not affected by acute illness [41].

New metrics describing acute and chronic glycemia in the critically ill

An emerging literature has described the relationship of the difference between acute and chronic glycemia to morbidity and mortality in various cohorts of critically ill patients. These studies all define chronic glycemia using HgbA1c levels obtained at admission or just before admission and converting this value to mean chronic blood glucose level using a formula derived by Nathan [42]. The 'stress hyperglycemia ratio' (SHR) was defined as the quotient of admission blood glucose level and HgbA1c-derived chronic glycemia.

The 'glycemic gap' was defined as the difference between admission blood glucose level and the HgbA1c-derived chronic blood glucose level. In each of these studies, increasing values of the new derived metric was strongly associated with morbidity and/or mortality, in contrast to admission blood glucose, which was associated with deleterious outcomes only in patients with normal preadmission glycemia.

Roberts and coworkers [43] created the metric SHR to describe the association of admission glycemia with hospital death or need for ICU care; on multivariable analysis SHR, but not admission glycemia, was independently associated with adverse outcomes. These findings were confirmed in a single center mixed ICU ($n = 311$ patients), in which a U-shaped relationship between the SHR and ICU mortality was observed, with nadir with SHR in the 0.97–1.2 quartile [44]. Yang and colleagues [45▪▪] corroborated these findings in a large multicenter observational cohort study of Korean patients undergoing percutaneous coronary intervention, demonstrating that SHR was independently associated with a composite of death, myocardial infarction, and stroke. Suh and colleagues [46] evaluated the ratio (termed in their investigation 'Glucose to HbA1c Ratio' [GAR]) in 661 patients with initial blood glucose more than 500 mg/dl presenting to a single emergency room. GAR, but not initial blood glucose, was independently associated with risk of hospital death, ICU admission and need for mechanical ventilation. A group of Taiwanese investigators conducted a series of multicenter studies that evaluated the utility of glycemic gap in various groups of diabetes patients: pyogenic liver abscess [47]; a mixed critically ill population [48]; community-acquired pneumonia [49]; and myocardial infarction [50]. These investigators demonstrated consistently that glycemic gap, but not admission blood glucose, was independently associated with adverse outcomes and added prognostic value to severity scoring, such as with the APACHE II model. Finally, this same group evaluated both SHR and glycemic gap and found that each was independently associated with adverse outcomes in a cohort of 309 patients presenting to a single emergency department with acute ischemic stroke [51].

Taken together, this group of investigations demonstrates that relative, but not absolute, hyperglycemia is independently associated with risk of morbidity and mortality in critically ill patients, and raises the possibility that blood glucose targets for patients with diabetes should be based at least in part on a determination of preadmission glycemic status. The availability of point-of-care meters to determine HbA1c could represent a major advance in this field [52▪].

WHAT IS THE APPROPRIATE BLOOD GLUCOSE TARGET IN CRITICALLY ILL PATIENTS?

For patients with diabetes, how high is too high?

A group of Australian investigators has tested the hypothesis that permissive hyperglycemia is not harmful to patients with diabetes. In 2 'exploratory' before and after studies they compared glucose metrics of 40 diabetes patients treated with 'conventional' blood glucose target (108–180 mg/dl) to 40 diabetes patients treated with 'liberal' blood glucose target (180–252 mg/dl) [53,54]. They measured glycemic gap similarly to the studies described above defined 'relative hypoglycemia' as a gap of more than 30% from preadmission glycemia, determined by measurement of HgbA1c on admission [53]. Not surprisingly, significantly more patients treated with the lower blood glucose target had higher rates of relative hypoglycemia and more insulin administration than did those treated with the liberal blood glucose target. In addition, they found numerically fewer episodes of moderate and severe hypoglycemia and lower glucose variability in the cohort treated with the higher blood glucose target [54]. These studies were underpowered to evaluate clinical outcomes. The same group has recently published two additional studies with a significantly

larger cohort. A before-and-after study including a total of 350 patients in each group found no differences in serum creatinine, white blood cell count, days of mechanical ventilation, ICU days [55▪]. Mean glycemia was considerably higher during the 'liberal' era and there was a trend toward lower rates of hypoglycemia. The study was not adequately powered to assess the association of the intervention with mortality; nevertheless, there was a trend toward higher mortality in the group treated with the higher blood glucose target. A second study identified no difference in the overall number of hospital-acquired cardiovascular, renal, and neurological complications in a subset of patients from the first investigation [56]. A secondary analysis suggested a relationship between increasing mean glycemia as well as increasing glucose variability and mortality among patients with HgbA1c less than 7%.

A single center proof-of-concept study

A single center 1979 patient before-and-after study was recently completed at Stamford Hospital that assessed the impact of blood glucose targets based on preadmission glycemia [57▪]. In year 1, all patients were treated with blood glucose target 90–125 mg/dl. In year 2, patients without diabetes or with hx diabetes but with HgbA1c level less than 7% were treated with blood glucose target 80–140 mg/dl. Patients with diabetes and HgbA1c at least 7% were treated with blood glucose target 110–160 mg/dl. There were very low rates of hypoglycemia. Among patients without diabetes there was no difference in the observed:expected mortality ratio (using APACHE IV mortality prediction model) between the 2 years. However, for patients with diabetes there was a significant decrease in the observed:expected mortality ratio in the second year, driven largely by the patients with diabetes treated with the looser blood glucose target.

CONCLUSION

It should be clear that we do not believe that glucose control in the critically ill should be abandoned. Instead, there needs to be a more nuanced approach. The wealth of randomized trial and observational data suggest that it is the 'one size fits all' approach that needs to be abandoned.

Important unresolved issues include, in part: the role of nutritional support and its integration with glucose control; and how differences in patient characteristics other than diabetes status, such as diagnostic category, age, and sex may impact the relationship of glucose control to clinical outcomes.

For patients without diabetes, and for those patients with diabetes who have well-controlled preadmission glycemia, a blood glucose target of 80–140 mg/dl is supported by available data. For patients with less well-controlled preadmission glycemia (HgbA1c $\geq$ 7%) the appropriate blood glucose target remains unclear and further studies will be needed to clarify this important question. The available studies exploring 'liberal' blood glucose targets in patients are likely underpowered to uncover clinically important signals of morbidity and mortality [53,54,55▪,56], especially in view of the well-described pathophysiologic basis of the deleterious impact of dysglycemia in the critically ill [11▪▪].

Patient safety is paramount. Clinical teams must develop the expertise to perform insulin therapy with low rates of hypoglycemia. High measurement frequency is mandatory, and the development of continuous or near-continuous blood glucose monitoring devices, beyond the scope of this review, promises to be very useful in this regard [58▪]. A recently completed multicenter observational study in a cohort of patients with cardiovascular disease was notable not only for the very low rates of hypoglycemia but also for lower mortality in patients treated with the 'tight' target (80–110 mg/dl) compared to those treated with a 'moderately tight' target (90–140 mg/dl) [59▪▪]. Excellent glycemic control, achieved by experienced teams utilizing protocols with high measurement frequency led to excellent clinical outcomes.

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Conflicts of interest

There are no conflicts of interest.

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