

Acute Glycemic Control in Hospitalized Patients: Evidence Published Since the American College of Endocrinology Position Statement

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ABSTRACT

Background: In a 2004 position statement, the American College of Endocrinology (ACE) recommended that the plasma glucose level be ≤ 110 mg/dL (fasting) and <180 mg/dL (postprandial) for hospitalized patients not in the intensive care unit (ICU) and 80 to 110 mg/dL for hospitalized patients in the ICU, whether or not they had documented diabetes mellitus.

Objective: This paper reviews published studies on this topic, with focus on those appearing after the ACE statement.

Methods: Relevant studies were identified by a MEDLINE search of references and studies and by extensive familiarity with the topic.

Results: The results of observational studies have been mixed and are complicated by uncertainty as to whether hyperglycemia is simply a marker of illness severity or is causally related to adverse clinical outcome.

Conclusions: Intriguing evidence from randomized controlled trials suggests that tight glycemic control in the hospitalized patient improves mortality and morbidity, although the above-recommended glucose target values have not been met in some studies. (*Insulin*. 2007;2:12–23) Copyright © 2007 Excerpta Medica, Inc.

Key words: critical care, insulin, hyperglycemia, hypoglycemia.

INTRODUCTION

Hyperglycemia occurs frequently in hospitalized patients. In a recent review of nationally representative Medicare data on 29,016 elderly patients hospitalized between 1994 and 1996 with acute myocardial infarction (AMI) and admission glucose levels >240 mg/dL, Kosiborod et al¹ found that 26% of patients were not recognized to have diabetes mellitus (DM). Only 73% of those known to have DM, and 22% of those without diagnosed DM, received insulin during their hospitalization. Another study of hospitalized patients with AMI showed that 31% had previously undiagnosed DM,² and a similar study of stroke patients showed that 16% were newly found to have DM.³

In January 2004, the American College of Endocrinology (ACE) position statement on inpatient DM and metabolic control,⁴ based on a December 2003 consensus conference sponsored jointly with several other professional societies, recommended fasting glucose levels ≤ 110 mg/dL and postprandial glucose levels <180 mg/dL in patients not in the intensive care unit (ICU) and 80 to 110 mg/dL in patients in the ICU, with or without a diagnosis of DM.

The following month, Clement et al⁵ published a comprehensive analysis of evidence as an American Diabetes Association (ADA) Technical Review, suggesting potential benefit of aggressive treatment of hyperglycemia and offering detailed practical approaches for managing DM and hyperglycemia in the hospitalized patient. The authors did not define target glucose values, suggesting that additional interventional clinical trials were needed to establish whether aggressive glycemic control in the hospitalized patient improves outcomes. A difficulty was recognized in that hyperglycemia in the hospitalized patient may be a marker for DM, or for the severity of DM, or for the severity of the patient's underlying condition requiring hospitalization, with or without DM being present; conversely, hyper-

Hyperglycemia in the hospitalized patient may be a marker for DM, or for the severity of DM, or for the severity of the patient's underlying condition requiring hospitalization, with or without DM being present.

glycemia itself, in conjunction with relative hypoinsulinemia, may be pathogenic.

The ACE recommendations⁴ (Table 1) have been controversial because the cited clinical trial data are inconclusive. Furthermore, few institutions have treatment protocols established that achieve the proposed strict standards for inpatient glucose management, although much progress has been made. This paper reviews recent developments in the field, emphasizing information of particular relevance to clinicians.

Table 1. Upper limits for in-hospital glycemia as recommended by the American College of Endocrinology.

Setting	Upper Limit (mg/dL)
Intensive care unit	110
Noncritical care unit	
Preprandial	110
Maximal glucose	180
Prelabor in pregnancy	
Preprandial	100
1-Hour postprandial	120
Labor and delivery	100

METHODS

Relevant studies were identified by a MEDLINE search of references and studies and by extensive familiarity with the topic.

RANDOMIZED CONTROLLED TRIALS

The ACE position statement,⁴ in discussing what glycemic targets to attain in hospitalized patients, cites reductions in mortality in 2 prospective, randomized trials in ICUs: a trial of intensive insulin therapy at the Catholic University of Leuven in Belgium, and the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Both research groups have recently published the results of subsequent randomized controlled trials, as disclosed below.

The Leuven Trials

In the original Leuven trial, 1548 patients receiving mechanical ventilation in a surgical ICU were randomly assigned to intensive insulin therapy, with the goal of maintaining glucose levels at 80 to 110 mg/dL, or to a control protocol in which insulin was started only for glucose levels >215 mg/dL, with a target of 180 to 200 mg/dL. The primary outcome, death during intensive care, occurred in 4.6% of the intensive-treatment group compared with 8.0% in the control group, a relative risk (RR) reduction of 42% (95% CI, 22%–62%; $P < 0.04$). Overall in-hospital mortality was reduced by 34%. Most of the patients (63%) were recruited after cardiac surgery, but similar benefits were observed in ICU patients who had not undergone cardiac surgery. A recent update reported the survival benefit to be maintained over 4 years of follow-up.⁶

Intensive treatment decreased morbidity, with significantly fewer episodes of septicemia, a significantly lower rate of development of polyneuropathy and significantly less need for prolonged ventilatory support, renal replacement therapy, or transfusion, whether or not DM or hyperglycemia was documented at admission.⁷

Although intensive insulin therapy was associated with reduced in-hospital mortality regardless of length of ICU stay, the mortality benefit was attributable to its effect among patients who remained in the ICU >5 days, comprising 27% of the intensive-treatment group and 31% of the conventional-treatment group. Mortality rates in the ICU were 10.6% and 20.2% ($P = 0.05$), and in-hospital mortality rates were 16.8% and 26.3% ($P = 0.01$), respectively.⁷ Similar observations have been suggested from uncontrolled studies. Furnary et al,⁸ in an observational study of patients with DM undergoing cardiac surgery, established that continuous insulin infusion should be maintained for ≥ 3 postoperative days.

The Leuven group performed a second trial of intensive insulin therapy in a medical ICU. They hypothesized that benefit would accrue to patients with an ICU stay of ≥ 3 days, and powered the study accordingly.⁹ The 1200 patients enrolled had already been admitted to the ICU and were considered to require ≥ 3 days of intensive care. Again, patients were randomly assigned to strict glycemic control (target 80–110 mg/dL) or to conventional therapy (insulin administered only if glucose levels were >215 mg/dL, with the infusion tapered when glucose levels declined to <180 mg/dL).

The primary outcome measure was in-hospital mortality among all patients. In the intent-to-treat analysis, intensive insulin therapy did not reduce either in-ICU or in-hospital mortality (Figure 1). However, it did reduce some measures of morbidity: the incidence of newly acquired kidney injury (8.9% in the control group vs 5.9% in the intensive-treatment group, $P = 0.04$), duration of mechanical ventilation (hazard ratio [HR], 1.21; 95% CI, 1.02–1.44; $P = 0.03$), length of ICU stay (HR, 1.15; 95% CI, 1.01–1.32; $P = 0.04$), and length of hospital stay (HR, 1.16; 95% CI, 1.00–1.35; $P = 0.05$).⁹

Mortality among patients with a prolonged ICU stay, the group hypothesized to benefit based on the first study, was a prespecified subgroup outcome measure. Among the 767 patients who stayed in the ICU for ≥ 3 days, in-hospital mortality was significantly lower in the intensive-treatment group (43.0%) than in the control group (52.5%) ($P = 0.009$).⁹ However, of the 433 patients who stayed in the ICU for <3 days, 56 patients in the intensive-treatment group died, compared with 42 in the conventional-treatment group. The latter finding has been interpreted to suggest that adverse effects of intensive glycemic control are as likely as benefits, with the author of the editorial that accompanied the study report suggesting targeting glucose values <150 mg/dL during the first 3 days in the ICU and then considering 80 to 110 mg/dL as the goal if critical illness persisted.¹⁰ He based this recommendation¹¹ on a published international consensus statement about the management of severe sepsis.¹²

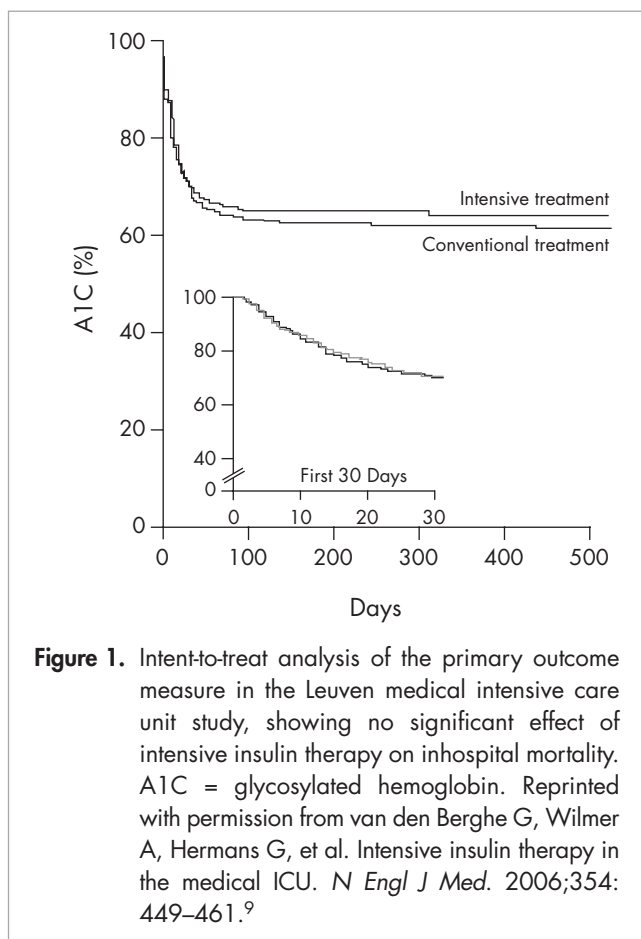


Figure 1. Intent-to-treat analysis of the primary outcome measure in the Leuven medical intensive care unit study, showing no significant effect of intensive insulin therapy on in-hospital mortality. A1C = glycosylated hemoglobin. Reprinted with permission from van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354:449–461.⁹

The editorial also noted that the subgroup analysis may have been biased by survivor effects, since patients were not enrolled until they had survived for 2 days in the ICU.¹¹ The most ill patients may have died prior to study entry. Furthermore, early deaths in the intensive-treatment group may have affected the morbidity results by protecting against the development of renal failure and prolonged use of mechanical ventilation. It should be noted, however, that the apparent adverse effect on survival with intensive glycemic treatment in the short-stay group lost significance after correction for a set of baseline risk factors comprising the severity of illness scores (Acute Physiology and Chronic Health Evaluation II¹³ and Therapeutic Intervention Scoring System-28 scores), history of DM, presence of active cancer or kidney failure before admission to the ICU, and baseline plasma urea level and C-reactive protein level both >150 mg/dL. Thus, this important study strongly supports the hypothesis that aggressive insulin therapy benefits patients who require a prolonged ICU stay when it is given from the start of ICU admission, but it does not benefit patients with less severe illness and shorter ICU stay.

DIGAMI and DIGAMI 2 Studies

The multicenter DIGAMI study involved 620 patients with type 1 or type 2 DM who had experienced AMI and

had glucose levels >198 mg/dL.¹⁴ Patients were randomly assigned to receive insulin-glucose infusion for ≥ 24 hours, followed by multidose subcutaneous insulin for ≥ 3 months or conventional antidiabetes therapy at the physician's discretion. After 1 year, mortality was 18.6% in the infusion group and 26.1% in the control group ($P = 0.027$). The survival benefit was maintained over a mean follow-up period of 3.4 years: mortality was 33% in the infusion group and 44% in the control group ($P = 0.011$)—a relative mortality reduction of 28% (95% CI, 8%–45%).¹⁵

The DIGAMI study¹³ could not indicate, however, whether the survival benefit was due to the acute infusion, the use of insulin for metabolic control, or both. The purpose of DIGAMI 2 was to distinguish the in-hospital benefits of intensive glucose control from the long-term benefits.¹⁶ A total of 1253 patients with type 2 DM, suspected AMI, and either established type 2 DM or admission blood glucose >198 mg/dL were randomly assigned to 1 of 3 management strategies: 24-hour insulin-glucose infusion followed by subcutaneous insulin-based long-term glucose control (group 1); 24-hour insulin-glucose infusion followed by standard glucose control (group 2); or routine metabolic management (group 3). In group 1, the treatment goals were fasting glucose level of 90 to 126 mg/dL and nonfasting glucose level <180 mg/dL. The protocol did not define target values for groups 2 and 3.

The primary outcome of DIGAMI 2 was negative: there were no significant differences in mortality or morbidity between groups 1 and 2. However, as the investigators noted, the study was markedly underpowered, with only 1274 of the anticipated 3000 patients recruited. More important, the study did not achieve its treatment goals. Apart from the earliest glucose values, glycemic control was no better in group 1 or 2 than in the control group, with group 1 failing even during the initial period to meet the target glucose range, despite the protocol-defined treatment strategy and treatment by physicians with a special interest in the care of patients with DM and AMI. The investigators concluded that “this goal may be difficult to accomplish” and that “the interpretation must be that there is no evidence to support a beneficial effect of insulin if sufficient amounts are not given to achieve a difference in glucose levels.”¹⁶

It is difficult to argue with these conclusions. Certainly, a study that failed to show the benefit of glycemic control must be considered meaningless if glycemic control improved only minimally. Thus, although this report has been interpreted to suggest that efforts to aggressively treat DM in patients with AMI are unnecessary,¹⁷ it is the opinion of the current authors that it should simply be disregarded.

Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicas Latin America Study Group (CREATE-ECLA)

Another recent randomized study of AMI patients also had a neutral result, explicable by its failure to achieve any

glycemic goal. Conducted in low- and middle-income regions of the world, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicas Latin America Study Group (CREATE-ECLA) evaluated a low-cost, simple regimen for AMI patients: a 24-hour infusion of high-dose glucose-insulin-potassium (GIK). At 470 centers, 20,201 patients with acute ST-segment elevation myocardial infarction were randomly assigned to GIK infusion or to usual care, without a glucose target in either group.¹⁸

As in DIGAMI 2, the primary outcome of CREATE-ECLA was negative, without a significant difference between groups with respect to death from any cause within 30 days. Neither were there significant differences between groups with regard to secondary outcome measures: the composites of death or nonfatal cardiac arrest, death or cardiogenic shock, and death or reinfarction, or any of these outcomes individually. The investigators concluded that GIK “is unlikely to be of any material value” in patients with STEMI.¹⁸

As was the case in DIGAMI 2, CREATE-ECLA failed to meet its goal of glycemic control. In fact, in CREATE-ECLA the mean glucose concentration in the treatment group worsened during the infusion and was higher than that in the control group. Furthermore, the investigators found that higher baseline glucose concentrations were associated with higher 30-day mortality, which, contrary to their interpretation of the study, suggests that the premise of benefit of glycemic control is actually correct. GIK infusion is probably not practical in most circumstances because it tends to cause hyperglycemia and is difficult to use, particularly compared with variable-rate insulin infusion, because the volume of fluid infused, the degree of heart failure, and whether the patient is eating influence outcomes.¹⁹

As was the case in DIGAMI 2, CREATE-ECLA failed to meet its goal of glycemic control.

Patel and Pittas²⁰ have written that the results of CREATE-ECLA may simply indicate that insulin therapy that does not achieve normoglycemia does not affect outcomes, as appears to have been the case with DIGAMI 2. Pittas et al²¹ recently conducted a meta-analysis of data from 35 randomized trials that evaluated the effect of insulin therapy initiated during hospitalization on mortality in adults with a critical illness (eg, AMI, stroke, cardiac surgery, or an illness requiring admission to the ICU). The results suggested that targeting normoglycemia is the main determinant of the benefit of insulin therapy (RR, 0.73; 95% CI, 0.57–0.94).

The combined analysis showed that insulin therapy decreased short-term mortality by 15%. Subgroup analyses showed that insulin therapy decreased mortality in patients in surgical ICUs, when the aim of therapy was glucose control (RR, 0.58; 95% CI, 0.22–0.62), and in patients with DM (RR, 0.76; 95% CI, 0.62–0.92), but not in patients with AMI. Patel and Pittas²⁰ recommend a fasting glucose level

<145 mg/dL in all hospitalized patients, with stricter targets for critically ill patients, especially those with cardiac disease.

STUDIES COMPARING PATIENTS WITH OR WITHOUT KNOWN DIABETES MELLITUS

Clement et al⁵ distinguished among 3 categories of hyperglycemic inpatients, adapting terms from an ADA-sanctioned classification²²:

- Medical history of DM: DM diagnosed and acknowledged by the patient’s treating physician.
- Unrecognized DM: Hyperglycemia (fasting blood glucose ≥ 126 mg/dL or random blood glucose ≥ 200 mg/dL) occurring during hospitalization and confirmed as DM after hospitalization by standard diagnostic criteria, but unrecognized as DM by the treating physician during hospitalization.
- Hospital-related hyperglycemia: Hyperglycemia occurring during hospitalization that reverts to normal after discharge.

Recent studies suggest that the second and third categories of patients are at greater risk of death than patients with known DM, but otherwise are not in a stress state such as those typically causing hyperglycemia in hospitalized persons without DM.²³

In the study by Kosiborod et al,¹ among persons with admission glucose levels >240 mg/dL, both those with and without diagnosed DM showed increased crude 30-day and 1-year mortality rates with increasing admission glucose levels. However, even after adjustment for multiple risk factors, the mortality risk increased much more steeply for patients without diagnosed DM than for those known to have DM. As the investigators noted, it remains unclear whether hyperglycemia is a mediator or marker of adverse outcome. In any patient, with DM or not, hyperglycemia during AMI presumably in part reflects the severity of illness due to excess inflammatory mediator and counterregulatory hormone release.¹

A body of evidence suggests that pharmacologic levels of insulin itself, rather than achievement of euglycemia, may mediate some of the benefits of intensive insulin therapy protocols.^{24,25} Rady et al²⁶ have speculated that early resolution of acute illness, rather than control of glucose values with insulin, may be the principal explanation for improved glycemic control and survival in the original Leuven trial. The investigators in that trial attributed the beneficial effect of intensive insulin therapy principally to metabolic control rather than to the infused insulin dose.^{7,27}

Rady et al²⁶ observed that glucose levels fluctuated above the target range in a subset of the intervention group, while some participants in the control group achieved the target glycemic range with conventional management. However, the analysis of the Leuven study by van den Berghe et al²⁷ shows that mortality in patients requiring >5 -day stays in the ICU was substantially lower in patients achieving glucose levels <110 mg/dL compared with those with glucose levels

110 to 150 mg/dL or >150 mg/dL, so that the hypothesis that insulin itself is a protective factor remains unproved.

Finney et al²⁸ conducted a prospective observational trial in the ICU of a United Kingdom referral center for cardio-respiratory surgery and medicine where the practice was to maintain glucose levels between 90 and 145 mg/dL using insulin infusion. Multivariate regression analysis showed that, regardless of the prevailing glucose level in the range of 111 to 144 mg/dL, increased administration of insulin was positively and significantly associated with mortality (odds ratio, 1.02; 95% CI, 1.01–1.04). Based on a survival analysis according to how much time patients spent in various “bands” of glucose values, Finney et al recommend 145 mg/dL as a conservative upper limit for glucose control.

To clarify the relationship between patient characteristics and mortality after intensive insulin control, Rady et al²⁶ conducted a case-control study of patients admitted to a multi-disciplinary ICU (medical, surgical, and coronary care) at the Mayo Clinic in Scottsdale, Arizona. Approximately 2 months before data collection began, a protocol was established to guide nurses in giving short-acting insulin, subcutaneously or as a continuous intravenous infusion, to patients with glucose levels >150 mg/dL. Of the 7285 patients treated over a 5-year period, 2826 required insulin, of whom 1083 had a diagnosis of DM before hospitalization.

A principal finding of the study was that the presence or absence of diagnosed DM modifies the relationship between

glucose ranges, insulin dose, and mortality. Among the patients who required insulin, the mortality rate was 10% in hyperglycemic patients without diagnosed DM and 6% in patients with diagnosed DM ($P < 0.001$), despite the lower median glucose values in the group without diagnosed DM. The investigators attribute the higher mortality in patients without DM to their increased severity of illness, as evidenced by higher scores on the Sequential Organ Failure Assessment (SOFA).²⁶ Interestingly, in this study persons requiring large amounts of insulin had increased in-hospital mortality, further suggesting a stress effect.

Rady et al²⁶ also compared patients with and without DM who did not receive insulin. Mortality rates were similar in these 2 groups, even though patients with DM had higher median glucose levels and higher SOFA scores. Mortality increased with both increased median glucose levels and increased dose of insulin required (Figure 2). The authors also found that the adverse effect of insulin was more pronounced in patients without DM than in those with DM. Among persons without DM, acute insulin resistance with poor glycemic control was associated with poor outcome because of the severity of concurrent illness, while in patients with DM, insulin resistance was associated with a large body mass index, which would be likely to have less influence on mortality. The investigators concluded that the appropriate target glucose value for patients with DM may differ from that for hyperglycemic patients without diag-

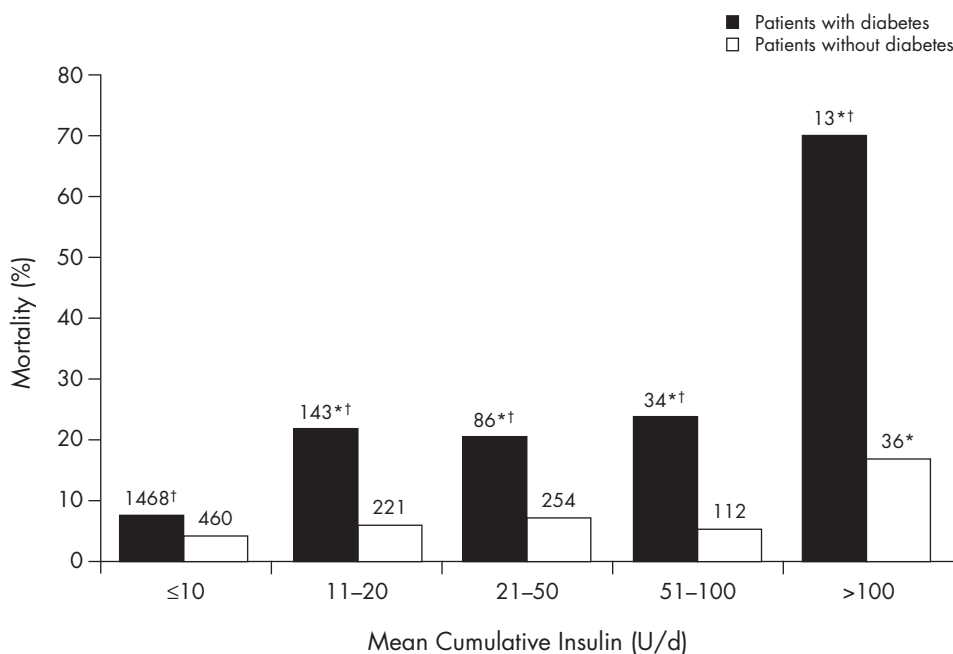


Figure 2. Relationship between mortality and mean cumulative insulin dose given during hospitalization. The number of patients in each subgroup is depicted above the bar. * $P < 0.001$ between dosage subgroups; † $P < 0.001$ for patients with and without diabetes mellitus. Reprinted with permission from Rady MY, Johnson DJ, Patel BM, et al. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc.* 2005;80:1558–1567.²⁶

nosed DM, although one must recognize that it is difficult to make conclusions on causality in such analyses. Although useful for generating hypotheses, it is probably inappropriate to derive recommendations for management from such data without referring to clinical trial evidence.

HYPOGLYCEMIA

The limiting nature of hypoglycemia in optimizing glycemic control has long been recognized in the outpatient management of persons with diabetes,²⁹ and it is not surprising that it may similarly restrict the ability to optimize outcome in persons with critical illness.³⁰ Potential adverse effects of insulin include hypoglycemia, sympathetic stimulation, increased stroke volume, shifts in intracellular potassium and phosphate levels, and the mitogenic actions of insulin, which might cause proliferation of abnormal blood vessels. Even mild hypoglycemia (50 mg/dL) increases epinephrine levels 100-fold.

There has been increasing recognition that in-hospital hypoglycemia may be a marker for adverse outcome,³¹ further raising concern that intensive glycemic treatment will increase the likelihood of hypoglycemia. However, it has long been appreciated that hypoglycemia-predisposing factors include renal, cardiac gastrointestinal, and hepatic insufficiency, malnutrition, and sepsis, all of which are associated with adverse outcome. Thus, in a fashion parallel to that discussed above regarding hyperglycemia, hypoglycemia may be a marker of worsened physiologic state, rather than directly mediating adverse outcome. In a retrospective cohort study of 2272 persons requiring ICU stay,³² 156 (6.9%) had ≥ 1 glucose level < 45 mg/dL. Risk factors for such episodes included sepsis, requirement for inotropic support, and requirement for bicarbonate administration. Persons with DM were more likely to experience hypoglycemia, and 2 insulin treatment-related conditions appeared to explain part of the risk of hypoglycemia: the simultaneous administration of octreotide, which would reduce levels of counterregulatory hormones, and reduction in enteral or parenteral nutrition without adjustment of insulin infusion rates.

Further analyses of this data set in a case-control study showed that although 2 persons with hypoglycemia developed coma and 1 had seizure, there was no increased mortality in this group. In a study of 713 persons with DM and acute coronary syndrome, there was a 2.66-fold increase in mortality for the highest versus lowest quartile of admission blood glucose level, but a 1.77-fold increase in mortality for persons experiencing any hypoglycemia during hospitalization.³³

The Leuven study did report a 7% incidence of brief episodes of hypoglycemia (< 40 mg/dL). Despite not finding specific evidence of hypoglycemia-induced adverse events, it was noted that those persons who did experience hypoglycemia had increased risk of death on multivariate logistic regression analysis.^{32,34} In the subsequent Leuven medical ICU study, intensive insulin therapy increased the incidence of marked glucose < 40 mg/dL to 18.7% from the 3.1% fre-

quency among persons not receiving such treatment, with regression analysis again showing such episodes to be associated with increased mortality.^{9,32}

A German multicenter study of intensive insulin therapy in patients with severe sepsis was suspended by the safety monitoring board because of excess severe hypoglycemia without improvement in survival,³⁵ further suggesting the need for well-validated protocols to allow glycemic control without hypoglycemia. We have reviewed a number of studies to assess the potential for hypoglycemia with intensive insulin treatment in the ICU setting (Table II).^{7,9,36-40} Clearly, there is a wide range of such episodes, with a 15% to 20% range appearing typical of studies that include persons receiving intensive insulin treatment and a comparator group. Despite heterogeneity in the trials reviewed, meta-analysis shows a 5-fold increase in the likelihood of hypoglycemia among persons receiving intensive insulin treatment.

The assessment suggests that a number of steps may be taken to minimize hypoglycemia. Persons with extremely low expected survival may be at particular risk, while those with very good prognosis who are likely to require < 3 days of intensive care are less likely to attain benefit. It may thus be important to develop approaches to recognize those persons at intermediate risk and likely to have a long ICU stay, who might realize the greatest benefit from intensive insulin management while not being at risk of hypoglycemia-related complications. Other factors, including institutional variances, may lead to better outcome in some settings and to less benefit in others, so that it is important to take measures to minimize the frequency of hypoglycemia, with appropriate glucose sampling rates, and avoid insulin treatment, with nutrition discontinuation and other nursing errors being important.

"REAL-LIFE" PROTOCOLS

How to deliver continuous insulin infusion safely and feasibly in busy ICUs is a long-standing, widespread concern. Even before the ACE released its position statement, numerous insulin infusion protocols had been published to facilitate communication between physicians and nurses. In most protocols, orders to "titrate drip" are given to achieve a target glucose range, and nurses use an established algorithm or apply mathematical rules to determine whether the infusion rate should be changed. A problem with some of the protocols, notably the ones used in the Leuven trials and DIGAMI, is that their complexity makes them suitable for use only by very highly trained ICU nurses.

How to deliver continuous insulin infusion safely and feasibly in busy ICUs is a long-standing, widespread concern.

Table III lists studies of simpler nurse-driven protocols for continuous insulin infusion that have been published since the ACE position statement was issued.⁴²⁻⁴⁸ It is inter-

Table II. Hypoglycemia with intensive insulin treatment.

Reference*	No. of Patients	Hypoglycemia Frequency in Conventional-Treatment Group, %	Hypoglycemia Frequency in Intensively Treated Group, %	Relative Risk
van den Berghe et al ⁷	1548	0.80	5.10	6.3
Brunkhorst et al ³⁶	488	2.10	12.10	5.8
van den Berghe et al ⁹	1200	3.90	25.10	6.5
Toft et al ³⁷	271	4	14	3.7
Kanji et al ³⁸	100	16	4	0.3
Plank et al ³⁹	60	7	0	—
Grey and Perdrizet ⁴⁰	61	7.40	32	4.7
Summary	3728			5.0

*All studies include comparator groups. All are randomized controlled trials with the exception of Toft et al³⁷ and Kanji et al,³⁸ which were observational studies with prospective components. The glucose target for the intensive-treatment group was 110 mg/dL in all studies except Grey and Perdrizet,⁴⁰ which used a target of 120 mg/dL. The cutoff for definition of hypoglycemia was 40 mg/dL in all studies except Plank et al,³⁹ which used 54 mg/dL, and Grey and Perdrizet,⁴⁰ which used 60 mg/dL. The overall relative risk⁴¹ is 5.0, with 95% CI range of 3.6 to 6.8 ($P < 0.001$).

Table III. Recent reports on nurse-driven protocols for continuous insulin infusion (CII).

Reference	Target Population	Summary of Algorithm	BG Threshold for Starting CII
Goldberg et al ⁴²	Medical ICU at Yale University	Determine current BG value Use a 5-column table to determine rate of change from prior BG level Use a 3-column table to determine the change in infusion rate	>200 mg/dL (not strictly enforced)
Goldberg et al ⁴³	Cardiothoracic ICUs at Yale University and Yale New Haven Hospital	As above	>150 mg/dL × 2 consecutive readings
Ku et al ⁴⁴	University of Washington—critical care, medical/surgery, solid organ transplant, oncology	Determine current BG value Depending on the result, choose 1 of 4 algorithms for determining the new infusion rate	Not reported
Lien et al ⁴⁵	Medical ICU and general surgical ICU at Duke University	Use a 15-column table to identify a multiplier, based on current and prior BG values Multiply the current infusion rate by the multiplier to determine the new infusion rate	>250 mg/dL × 24 h despite q6h SC insulin >200 × 48 h despite active increase of q6h SC insulin
Davis et al ⁴⁶	Intermediate-care general medicine units at Duke University	As above	Not reported
Osburne et al ⁴⁷	ICU (medical, surgical, trauma) at Atlanta Medical Center	Determine current BG value Use an 11-column table to determine the new infusion rate	>180 mg/dL despite basal SC insulin
Smiley and Umpierrez ⁴⁸	Perioperative patients at Emory University	Determine current BG value Use a 2-column table to determine the change in infusion rate	>140 mg/dL ≥70 mg/dL for patients with type 1 DM or type 2 DM treated with insulin

BG = blood glucose; ICU = intensive care unit; DM = diabetes mellitus.

esting to see how many different hospital settings are being addressed and the range of glucose thresholds used. One of the papers simply presents a protocol,⁴⁸ but the others report favorable preliminary data on improvement in glycemic control, safety with respect to hypoglycemia, and/or nurse accuracy in small numbers of patients. One paper⁴⁷ notes that ICU nurses expressed concerns about increased workload, insufficient numbers of glucose monitors, and patient discomfort given the number of fingersticks required. An example of a standardized intravenous insulin infusion appears in the **Appendix**.⁴⁹

Davidson et al⁵⁰ recently published the first peer-reviewed efficacy and safety data using a computer program they named "Glucommander," a system that calculates the infusion rate for continuous insulin based on glucose level, the patient's insulin sensitivity, and the target glucose range specified by the ordering physician. Depending on the rate of change in glucose level, the system notifies a nurse every 20 to 120 minutes that another glucose measurement is needed. The authors analyzed a database of 120,618 glucose values measured in 5808 runs, supervised by nonspecialized nurses in all units of >100 general hospitals. The mean glucose level reached <150 mg/dL in 3 hours, and the prevalence of hypoglycemia <40 mg/dL was 2.6% of all runs.

Even more useful would be a closed-loop, continuous monitoring system that would automatically regulate the dose of insulin based on the system's own glucose measurements, providing tight glycemic control without adding to nurse workload and preventing hypoglycemia-induced side effects. In Europe, members of the Closed Loop Insulin Infusion for Critically Ill Patients project are working to develop such a system for ICUs. As a first step, a computerized algorithm, originally developed for use in an artificial pancreas, was tested in a randomized pilot study in 3 cardiac surgery ICUs. The results showed that the algorithm was as safe and effective as routine care in controlling glycemia, with no episodes of hypoglycemia <54 mg/dL recorded in the investigational group.³⁹ The algorithm relies on a dose optimizer that proposes future insulin infusion rates and adjusts them until the predicted glucose excursion is as desired. The inputs are insulin dose, carbohydrate intake, and glucose concentration; for now, the latter must be input every 60 minutes. Unlike classic algorithms, which use feedback control to *respond* to hypoglycemia and hyperglycemia, the optimized algorithm is designed to *prevent* these conditions.

Other recent publications include protocols for converting continuous insulin infusion to subcutaneous insulin^{51,52} and for using subcutaneous insulin to treat patients with DM on general medical^{53,54} and general surgical⁵⁴ units without using sliding-scale insulin. Sliding-scale insulin treats hyperglycemia after it has occurred, instead of preventing it, and can also result in high rates of hypoglycemia and iatrogenic diabetes ketoacidosis.^{4,5} Yet another challenge for hospitals is to learn how best to manage patients who received insulin pump therapy before admission.⁵⁵

It is no longer acceptable to ignore glucose measurement or to tolerate marked hyperglycemia in hospitalized persons.

A large, prospective, multicenter study now under way is expected to provide more information about appropriate glucose targets. The NICE-SUGAR trial (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) is expected to enroll 6000 patients in diverse critical care settings in Australia and Canada.⁵⁶ Patients will be randomly assigned to receive insulin therapy that controls glucose between 80 and 110 mg/dL or to have insulin infused only if glucose levels exceed 180 mg/dL, adjusted to maintain glucose at 145 to 180 mg/dL. Results from this and other well-designed randomized trials are eagerly awaited.

CONCLUSIONS

It is no longer acceptable to ignore glucose measurement or to tolerate marked hyperglycemia in hospitalized persons. Target glucose values remain to be established for both hospitalized patients without critical illness, a group for which there are no randomized trial data, and for patients requiring ICU treatment. Focused research is also needed to explore whether acute hyperglycemia causes poor clinical outcomes or is a marker of more severe illness, whether strict control of glycemia is the principal factor contributing to improved mortality and morbidity outcomes with insulin therapy, and how insulin can be used more safely in hyperglycemic patients with and without diabetes.

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Appendix. Example of a standardized intravenous insulin infusion.

General Guidelines: Goal BG = Usually 80–180 mg/dL

Standard drip: 100 units/100 mL 0.9% NaCl via an infusion device.

Surgical patients who have received an oral diabetes medication within 24 hours should start when BG >120 mg/dL. All other patients can start when BG ≥70 mg/dL.

Insulin infusions should be discontinued when a patient is eating AND has received first dose of subcutaneous insulin.

Intravenous Fluids:

Most patients will need 5–10 g of glucose per hour.

D₅W or D₅W1\2NS at 100–200 mL/hr or equivalent (TPN, enteral feeding, etc)

Initiating the Infusion:

Algorithm 1: Start here for most patients.

Algorithm 2: For patients not controlled with Algorithm 1, or start here if s/p CABG, s/p solid organ transplant or islet cell transplant, receiving glucocorticoids, or patient with diabetes receiving >80 units/d of insulin as an outpatient.

Algorithm 3: For patients not controlled on Algorithm 2. NO PATIENTS START HERE without authorization from the endocrine service

Algorithm 4: For patients not controlled on Algorithm 3. NO PATIENTS START HERE.

Patients not controlled with the above algorithms need an endocrine consult.

Algorithm 1		Algorithm 2		Algorithm 3		Algorithm 4	
BG	Units/h	BG	Units/h	BG	Units/h	BG	Units/h
<60 = Hypoglycemia (See below for treatment)							
<70	Off	<70	Off	<70	Off	<70	Off
70–109	0.2	70–109	0.5	70–109	1	70–109	1.5
110–119	0.5	110–119	1	110–119	2	110–119	3
120–149	1	120–149	1.5	120–149	3	120–149	5
150–179	1.5	150–179	2	150–179	4	150–179	7
180–209	2	180–209	3	180–209	5	180–209	9
210–239	2	210–239	4	210–239	6	210–239	12
240–269	3	240–269	5	240–269	8	240–269	16
270–299	3	270–299	6	270–299	10	270–299	20
300–329	4	300–329	7	300–329	12	300–329	24
330–359	4	330–359	8	330–359	14	>330	28
>360	6	>360	12	>360	16		

Moving from Algorithm to Algorithm:

Moving Up: An algorithm failure is defined as BG outside the goal range (see above goal), and BG does not change by ≥60 mg/dL within 1 hour.

Moving Down: When BG is <70 mg/dL × 2

Patient Monitoring:

Goal BG = 80–180 mg/dL

(continued)

Appendix. (Continued)

Check capillary BG every hour until it is within goal range for 4 hours, then decrease to every 2 hours for 4 hours, and if remains stable may decrease to every 4 hours.

Hourly monitoring may be indicated for critically ill patients even if they have stable BG

Treatment of Hypoglycemia (BG <60 mg/dL)

Discontinue insulin drip AND

Give D₅₀W IV

Patient awake: 25 mL (1/2 amp)

Patient not awake: 50 mL (1 amp)

Recheck BG every 20 minutes and repeat 25 mL of D₅₀W IV if <60 mg/dL. Restart drip once BG is >70 mg/dL × 2 checks. Restart drip with lower algorithm (see moving down)

Notify the physician:

For any BG change >100 mg/dL in 1 hour.

For BG >360 mg/dL

For hypoglycemia that has not resolved within 20 minutes of administering 50 mL of D₅₀W IV and discontinuing the insulin drip.

BG = blood glucose; TPN = total parenteral nutrition; CABG = coronary artery bypass surgery; IV = intravenous.

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