Inpatient Management of Diabetes and Hyperglycemia

Magdalena Bogun, MD; and Silvio E. Inzucchi, MD

Section of Endocrinology, Yale University School of Medicine, New Haven, Connecticut

ABSTRACT

Illness, particularly when severe, leads to increased concentrations of counter-regulatory factors which induce insulin resistance and predispose patients to stress hyperglycemia. Elevated glucose concentrations are common in hospitalized patients, both those with as well as without recognized diabetes. Substantial data has emerged over the past decade that quality glucose management in these individuals actually improves clinical outcomes. Controlling glucose in this setting is challenging, given the phenotypic variability amongst patients, with fluctuating courses of acute illnesses and unpredictable nutritional schedules. We review the evidence basis that has informed national standards and glucose targets in both critically and non-critically ill patients. In the intensive care setting, insulin infusions are now widely endorsed to quickly achieve and maintain glucose control. On the hospital wards, physiological subcutaneous insulin therapy, incorporating both basal and nutritional components, is emerging as the optimal treatment strategy. The transition to outpatient care is another important aspect of any hospital glycemic management program. (*Clin Ther.* 2013;35: 724–733) © 2013 Published by Elsevier HS Journals, Inc.

Key words: diabetes, hyperglycemia, hospital, inpatient, critical care, insulin infusion

INTRODUCTION

Hyperglycemia in hospitalized patients with or without overt diabetes presents complex management issues. Questions arise about the degree of intensity to which glucose levels should be maintained in the critical care setting, step-down units, and general medical-surgical wards, as well as the optimal strategies for subsequent transitions to outpatient care.

Glucose Control During Critical Care

There is a well-recognized relationship between glucose levels and adverse clinical outcomes in the critically ill. In 2003, Krinsley et al[1] reported that in a mixed medical-surgical intensive care unit (ICU), mortality increased progressively as mean blood glucose concentrations increased. For example, mortality was 9.6% in patients whose mean ICU glucose concentration fell between 80 and 99 mg/dL but was >4-fold higher (42.5%) in those whose mean glucose exceeded 300 mg/dL. Similarly, Kosiborod et al[2] in 2008 reported that in patients hospitalized for acute myocardial infarction (AMI), mortality increased progressively with every 10-mg/dL glucose increase above 120 mg/dL, after controlling for a variety of important clinical variables (**Slide 1**). This relationship was particularly striking in those without an antecedent history of diabetes. These data were consistent with those from an early observational study from Umpierrez et al[3] involving 2030 ICU patients, which concluded that those with newly identified hyperglycemia had significantly higher mortality (31%) than did patients with known diabetes (11%). Notably, in the Kosiborod analysis,[4] an increase in mortality was also seen when mean blood glucose fell below 70 mg/dL.

These studies raise the possibility that controlling blood glucose in the setting of critical illness may improve clinical outcomes but also that overly intensive approaches might be counterproductive. Yet observational data alone can be misleading and are influenced by confounding factors that are either not easily assessed or not initially considered to be relevant by the investigators. So, it remained unknown as to whether hyperglycemia merely serves as a marker of poor clinical outcomes or represents a true mediator of these adverse events. It is well-recognized that illness by itself, particularly when severe, leads to "stress hyperglycemia" through the activation of counter-regulatory hormones, primarily cortisol and epinephrine, which increase endogenous glucose production and decrease glucose uptake into peripheral tissues, while also elevating circulating levels of free fatty acids

Accepted for publication April 19, 2013.
http://dx.doi.org/10.1016/j.clinthera.2013.04.008
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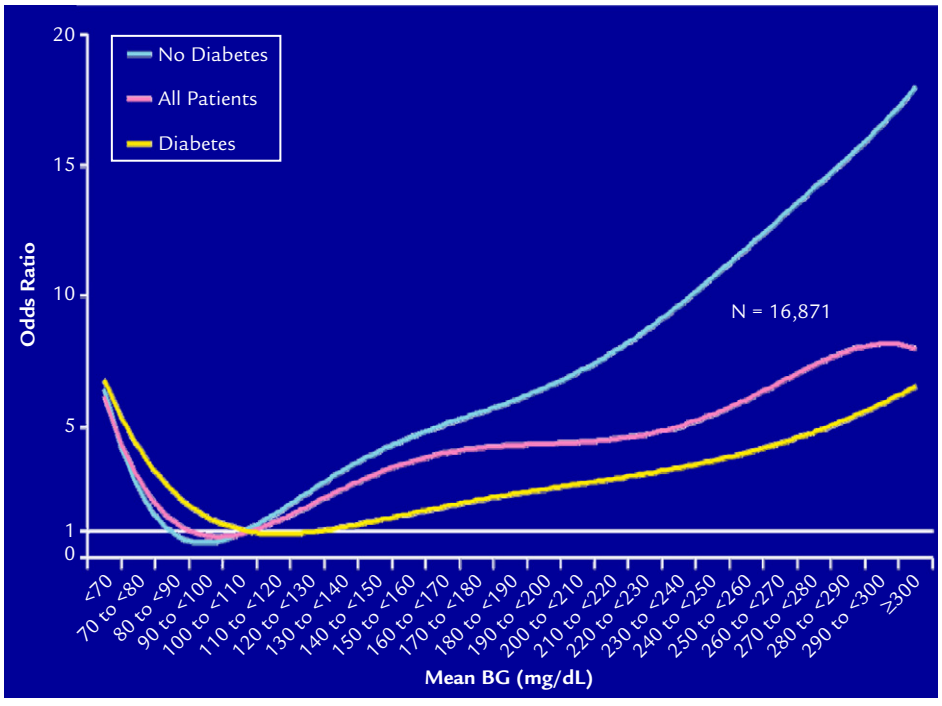
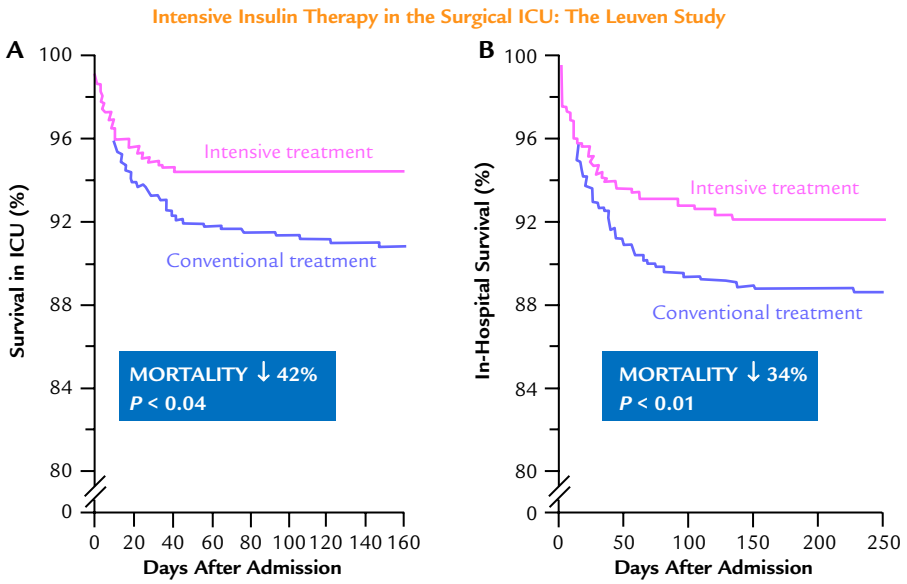


Slide 1. Relationship between mean glucose levels and mortality during hospitalization for nearly 17,000 acute myocardial infarction patients. Hyperglycemia is associated with more adverse outcomes, especially in nondiabetic individuals. Reprinted with permission from Kosiborod M *et al. Circulation* 2008;117:1018–1027.[2]

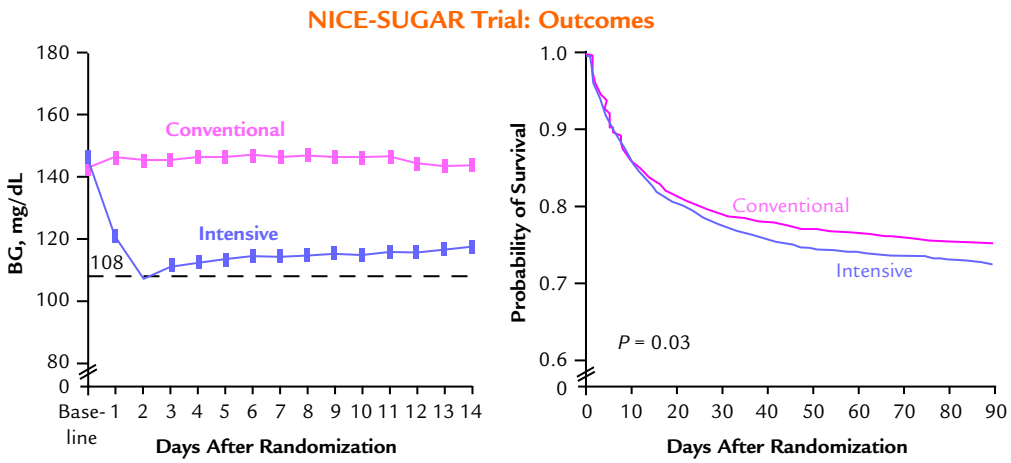
through the stimulation of lipolysis (Slide 2). Conversely, increased glucose and fatty acids may secondarily exacerbate illness through altered tissue metabolism, oxidative stress, hypercoagulability, and suppressed immunity and wound healing.

The first study to explore the notion of controlling glucose in the ICU to improve patient outcomes was conducted by cardiothoracic surgeons, led by Funary.[5] In this nonrandomized trial, patients undergoing cardiac surgery were placed on an insulin-infusion regimen for 3 days postoperatively, targeting a glucose level of 151 to 200 mg/dL. Their outcomes were compared to those from a historical control group who were mainly managed conventionally with subcutaneous regular human insulin (every 4 hours on a sliding scale with a target of ~200 mg/dL). Deep sternal wound infections occurred in 0.8% of the study group and in 2.0% of the controls (relative risk [RR] reduction, 66%; $P = 0.01$). Impressively, the annual rates of deep sternal wound infections in diabetic patients at the end of the study had reached the rates similar to those in nondiabetic individuals. The nonrandomized nature of this study, however, limited the conclusiveness of its findings.

The DIGAMI (Diabetes Insulin-Glucose Infusion in Acute Myocardial Infarction) study[6] examined the short- and long-term effects of intensive insulin treatment in patients with diabetes during and soon after AMI. A total of 360 patients were randomly assigned within 24 hours of admission to receive an intravenous infusion of insulin (and glucose) for 48 hours, with a target blood glucose level of 126 to 196 mg/dL, followed by multidose subcutaneous insulin injections for 3 months. A total of 314 patients in the control group received conventional diabetes care. An 11% absolute and a 28% relative mortality risk reduction was dem-



Slide 3. Kaplan–Meier survival curves from the Leuven SICU study. More intensive glucose control with IV insulin resulted in lower ICU and in-hospital mortality among the 1548 patients studied. From N Engl J Med, van den Berghe G, Wouters P, Weekers R, et al, Intensive insulin therapy in critically ill patients, 3459, 1359–1367. Copyright © 2001 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[10]



3054 received IIT goal: 81–108 mg/dL
(time weighted BG = **118 mg/dL**)

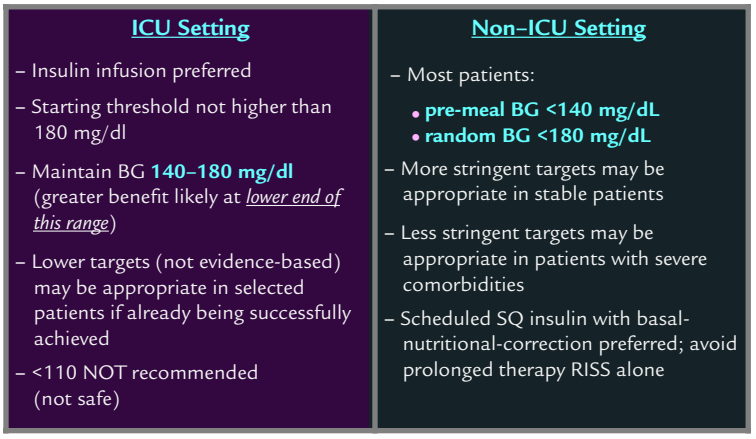
3050 received CIT goal: <180 mg/dL
(time-weighted BG = **145 mg/dL**)

90-day mortality: IIT: 829 patients (**27.5%**), CIT: 751 (**24.9%**)

Absolute mortality difference: **2.6%**
(95% CI, 0.4–4.8)

Odds ratio for death with IIT:
1.14 (95% CI, 1.02–1.28; *P* = 0.02)

Slide 4. Glycemic control and Kaplan–Meier survival curve from the NICE-SUGAR study. Despite lower glucose levels in the intensive group, mortality was increased. The explanation for this finding has remained elusive. From N Engl J Med, Finfer S, Chittock DR, Su SY, et al, for the NICE-SUGAR Study Investigators, Intensive versus conventional glucose control in critically ill patients, 3603, 1283–1297. Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[12]



AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; SQ, subcutaneous; RISS, regular insulin sliding scale.

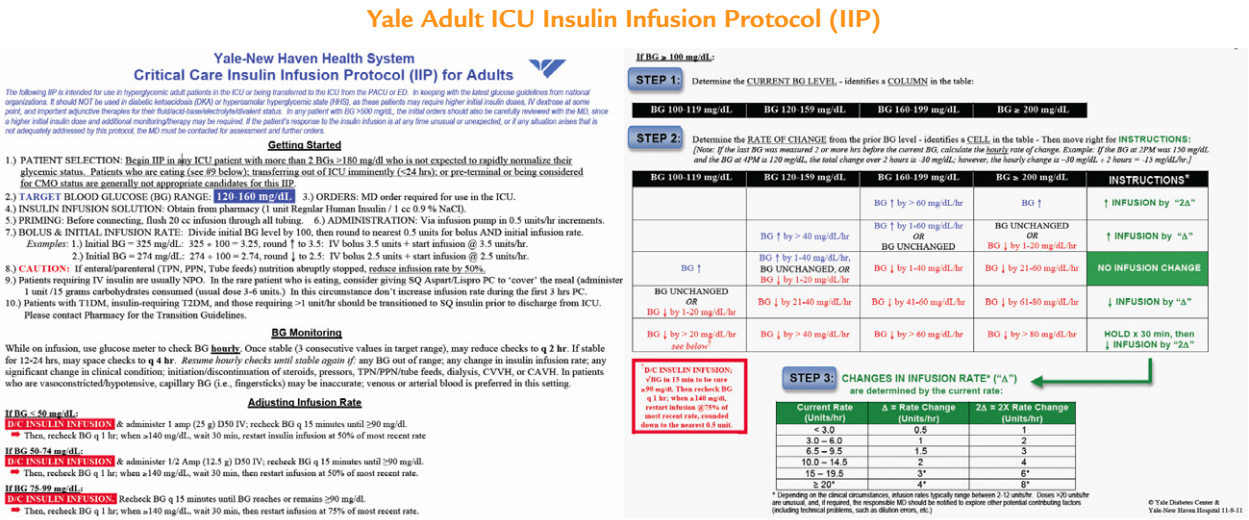
Slide 5. Major recommendations from the AACE-ADA Consensus Statement on inpatient glycemic control. Moghissi ES, Korytkowski MT, Di-Nardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care*. 2009; 32:1119–1131.[15] and Moghissi ES, Korytkowski MT, Di-Nardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocr Pract*. 2009;15:353–369.[26]

lin therapy was statistically indistinguishable compared to that with conventional approaches (0.93 [0.83–1.04]). The RR, however, varied according to the type of unit, with intensive insulin showing apparent benefit in the surgical ICU setting (0.63 [0.44–0.91]) but not in mixed ICUs (0.99 [0.87–1.12]) or medical ICUs (1.00 [0.78–1.28]). Fourteen of those trials reported hypoglycemia, and not surprisingly the RR for severe hypoglycemia in the intensive insulin therapy group was 6.0 (4.5–8.0). Although earlier trials have linked hypoglycemia to increased mortality, its cause-and-effect relationship is not clear. Kosiborod et al[14] reported that hypoglycemia is more likely to be a predictor of the severity of illness than a direct cause of mortality. In his study involving hyperglycemic patients during AMI, hypoglycemia was associated with higher mortality only in those patients not treated with insulin (odds ratio [OR] = 2.32 [95% CI, 1.31–4.12]). Those who developed hypoglycemia and were being treated with insulin had mortality similar to those who experienced no hypoglycemia (OR = 0.92 [0.58–1.45]).

These often-conflicting sets of data led the American Association of Clinical Endocrinology (AACE) and the American Diabetes Association (ADA) to develop consensus recommendations concerning the management of hyperglycemia in the hospital[15] (Slide 5). According to this AACE-ADA statement, which was more moderate in tone than were prior guidelines, intensive glucose control with insulin infusion should be undertaken in those ICU patients (regardless of prior diabetes history) with blood glucose >180 mg/dL, and maintained between 140 and 180 mg/dL, with greater benefit believed to be likely at the lower end of this range. The consensus panel went on to note that somewhat lower targets (110–140 mg/dL) might be appropriate in select patients but that blood glucose targets <110 mg/dL could no longer recommended.

Insulin Infusions

A successful intravenous insulin protocol consistently reaches and maintains blood glucose successfully within a specified target range while minimizing hypoglycemia (and providing specific directions for the treatment of hypoglycemia if it does occur). The protocol should have a clear, nurse-driven algorithm for making temporary corrective changes in the insulin rate as a patient's glucose levels and degree of insulin sensitivity change. The most successful protocols incorporate not



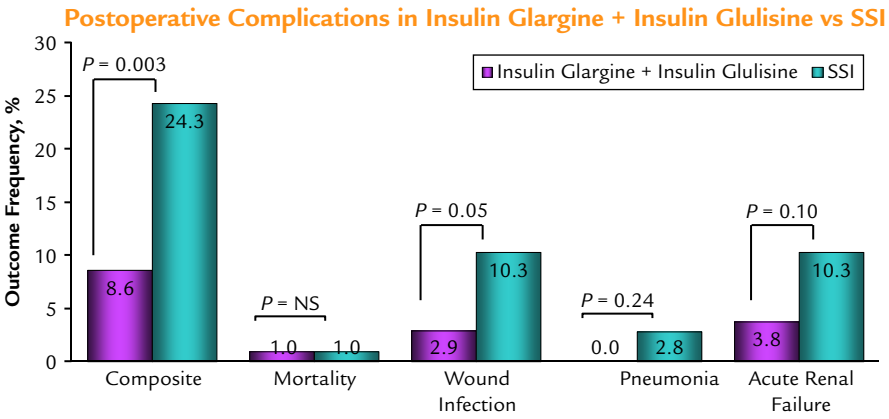
Slide 6. The Yale Insulin Infusion Protocol. Reprinted with permission from Shetty S, Inzucchi SE, Goldberg PA, et al. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale insulin infusion protocol. *Endocr Pract*. 2012;18:363–370.[17]

only the absolute blood glucose level but also its rate of change from prior values, as well as the current insulin infusion rate. Ideally, the delineation of specific measures for the transition to subcutaneous insulin that will ultimately be required in most patients should be incorporated. These instructions would necessarily include the initial doses and types and timing of insulin injections.

Wilson et al[16] compared 12 published protocols in a sample patient and reported great variability in target ranges, thresholds for insulin infusion initiation, initial infusion rates, and the frequency and intensity of adjustments, with markedly different glycemic outcomes predicted. The insulin-infusion protocol in use at our institution (Slide 6).[17] in adult ICU patients recommends starting the insulin infusion when 2 consecutive blood glucose readings exceed 180 mg/dL (the target range is 120–160 mg/dL). This target was chosen to be slightly lower than the AACE-ADA target because experience with older versions of our protocol resulted in mean blood glucose levels in the upper end of the target ranges. We therefore believed that mean blood glucose closer to 140 to 150 mg/dL (as intimated by the guidelines) was more desirable than one closer to 170 to 180 mg/dL. The infusion is adjusted in increments of 0.5 U/h. The initial infusion rate is preceded by a bolus, with both calculated by dividing the baseline glucose level by 100, rounded to the nearest 0.5 U. The blood glucose is then checked every hour; the subsequent frequency of monitoring can be decreased if 3 consecutive findings are within target. In our published initial cohort of 90 patients, the protocol achieved a median blood glucose of 150 mg/dL (range, 127–180 mg/dL), with a low rate of severe hypoglycemia (0.01% of glucose measurements and 1.7% of patients). Notably, these results compare favorably with those in the standard-therapy groups in the largest randomized trials of intensive insulin therapy (mean of 2.1% from references 10–12 and 18–20).

Glucose Control on General Medical-Surgical Wards

Much less is known about the impact of acute glycemic control in the non–critical care setting—which encompasses the majority of all hospitalized patients. As in the ICU, many observational studies have linked hyperglycemia to adverse clinical outcomes,[21,22] but the same concerns regarding glucose being a marker as opposed to a mediator of complications remain. For example, Baker et al[21] studied 433 patients with acute exacerbations of chronic obstructive pulmonary disease and found that the absolute risk for adverse outcomes (death or prolonged stay) was increased by 15% per 18-mg/dL increase in glucose level. In the perioperative setting, Pomposelli et al[22]



Slide 7. Results of the RABBIT 2-Surgery study. Overall decrease in post-operative complications was associated with more intensive glucose control using a scheduled basal-bolus-correction insulin strategy. Reprinted with permission from Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basalbolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 Surgery). *Diabetes Care*. 2011;34:256–261.[25]

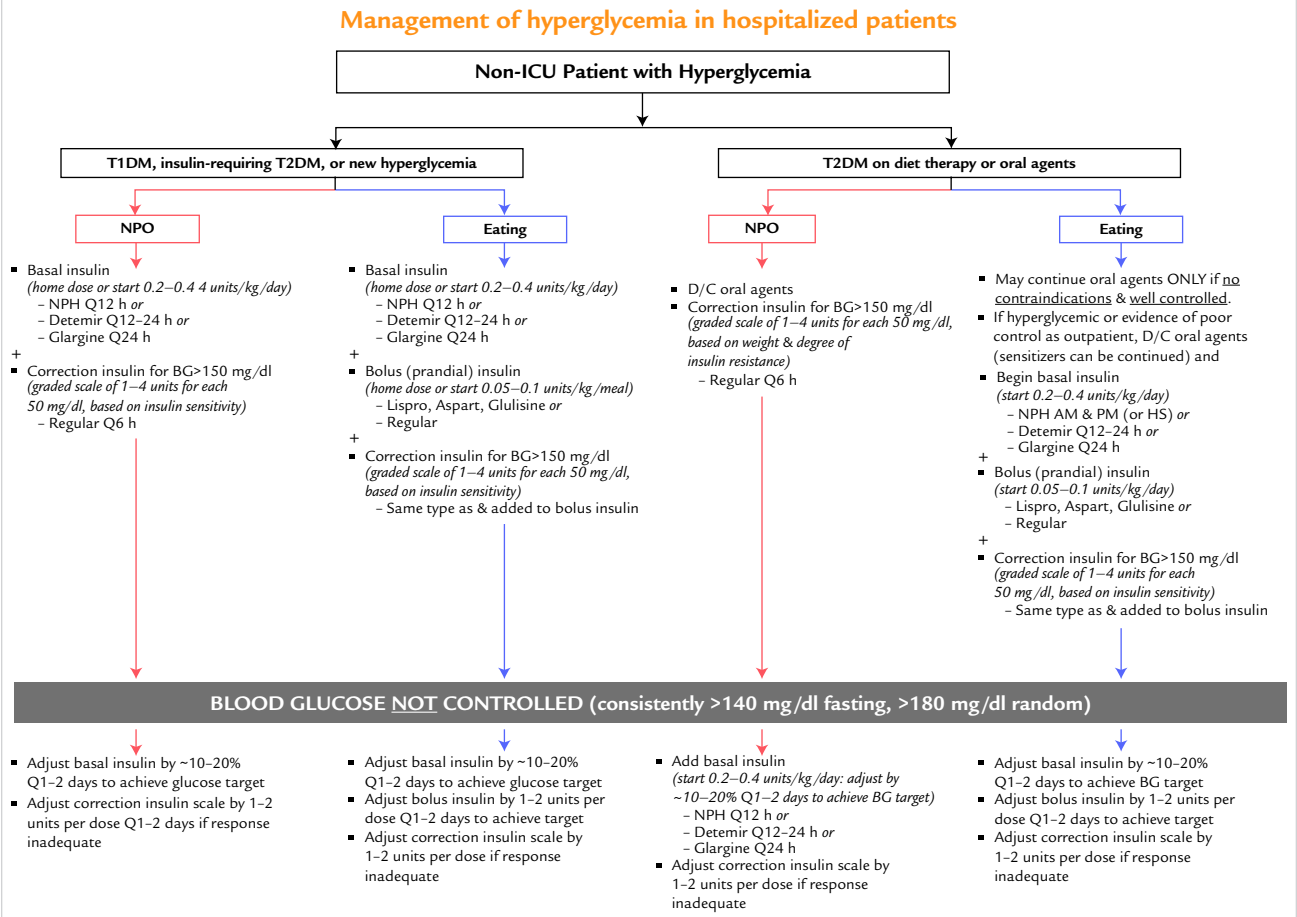
reported that in postoperative diabetic patients whose glucose levels were >220 mg/dL, the infection rate was 2.7-fold increased (exclusive of urinary tract infections), with the risk for more serious infections increased by 5.7-fold.

The only randomized studies in this area come from Umpierrez's group.[23] The RABBIT 2 study explored the glycemic effects of scheduled long-acting and premeal rapid-acting insulin ("basal-bolus") versus conventional sliding scales. In 130 insulin-naive patients with a mean (SD) blood glucose level of 229 (6) mg/dL, basal-bolus therapy (using the insulin analogues glargine and glulisine) was more effective than was the sliding-scale regimen.[23] About two thirds of the patients treated with glargine-glulisine achieved the blood glucose target (<140 mg/dL) versus about one third of patients in the sliding-scale group. More insulin, however, was ultimately used in the former (40 vs 15 total daily units) The rate of hypoglycemia (defined as a blood glucose level <60 mg/dL) was similar between groups, and no blood glucose levels <40 mg/dL were reported.

In the DEAN (Insulin Detemir Versus NPH Insulin In Hospitalized Patients With Diabetes) study,[24] the insulin analogues detemir (basal) and aspart (prandial) were compared with the more conventional human insulins, neutral protamine Hagedorn (NPH) and regular human insulin. Here, the overall blood glucose target was achieved in 45% of the analogue-treated patients and 48% of the human insulin–treated patients ($P = 0.86$). The difference in the rate of hypoglycemic episodes was not significantly different (33% vs 25%; $P = 0.34$). Taken together, these studies suggest that tighter glycemic control can be achieved in hospitalized patients with scheduled insulin approaches as opposed to sliding scales but that the types of insulin used may not be crucial.

Finally, in RABBIT 2-Surgery (Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients with Type 2 Diabetes Undergoing General Surgery),[25] the basal-bolus program, again using glargine and glulisine, was compared to regular insulin sliding scale in 211 patients undergoing general surgery. There was an overall mean blood glucose advantage of −27 mg/dL in the basal-bolus group. A variety of postoperative complications were tracked, including wound infections, pneumonia, respiratory failure, acute renal failure, and bacteremia. The presence of wound infections was significantly lower with basal-bolus (2.9% of patients) than with sliding scale (10.3%) ($P = 0.05$), whereas differences in other complications between the 2 groups did not reach statistical significance. However, when all of the complications were assembled into a composite, a clear advantage to the more intensive strategy was reported (8.6% vs 24.3% of patients) (Slide 7).

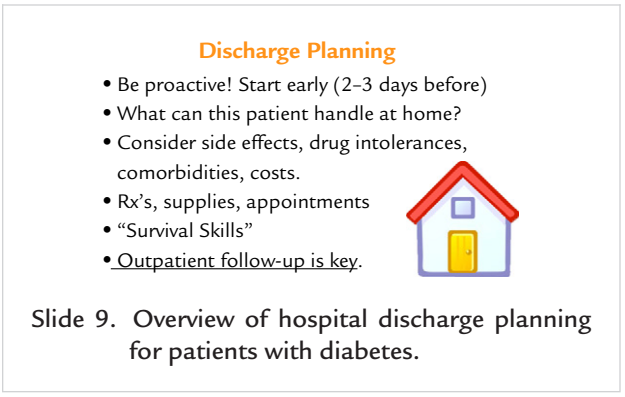
The AACE-ADA[15,26] inpatient consensus statement also addressed the management of hyperglycemia outside of the ICU setting (Slide 5). The panel advised



Slide 8. Proposed strategy for managing hyperglycemia in non-critically ill hospitalized patients. Adapted with permission from Inzucchi SE. Clinical practice. Management of hyperglycemia in the hospital setting. *N Engl J Med*. 2006;355:1903–1911.

trying to maintain all glucose levels <180 mg/dL and premeal glucose <140 mg/dL. The preferred approach was that employing scheduled basal-nutritional ("bolus")-correction insulin instead of the still widely used regular insulin sliding scales. At our institution, we encourage the routine use of such a strategy in those patients who appear to require insulin therapy for >1–2 days. In contrast, in short-term patients, the temporary use of correction insulin only is reasonable, especially if for those with NPO status or if nutritional intake is tenuous.

We tend to avoid the use of oral antihyperglycemic agents. Sulfonylureas may lead to hypoglycemia if nutrition is interrupted. There is no inherent reason that metformin could not be used, but given its risk for lactic acidosis and the frequent complicating features of hospitalized patients that might increase this risk (renal failure, dehydration, severe heart failure, acidosis), it would appear best to avoid this medication. Thiazolidinediones can be continued if there are no concerns of heart failure, although an interruption in therapy of a few days should not appreciably alter glucose levels. Incretin-based therapies (DPP-4 inhibitors and GLP-1 receptor agonists) are ideally used in patients who are eating because they target mainly postprandial glucose and so should probably be avoided when nutritional intake is forbidden or tentative. GLP-1 receptor agonists may also result in nausea so are best avoided in this setting. Some experts have proposed that, because these drug classes are not associated with hypoglycemia and because their activity appears to be in part related to the degree of hyperglycemia, they may have a role in acutely ill pa-



Slide 9. Overview of hospital discharge planning for patients with diabetes.

tients. Adequately powered, randomized clinical trials will be needed.

See (Slide 8). for our general approach to managing glucose in hospitalized but not non-critically ill diabetic patients.

Transitioning to Outpatient Care

Discharge planning is an important part of in-hospital diabetes management, especially in newly diagnosed patients or in those whose antihyperglycemic regimen has been altered during the admission. Ideally, this planning should begin several days before the anticipated discharge and should carefully take into account whether the patient can successfully implement the prescribed regimen and any accompanying comorbidities, prevalent contraindications, and anticipated side effects. If the diagnosis of diabetes has already been established, the level of control should be assessed with adjustment of therapy, if necessary. If the disease was newly identified during the hospitalization, the diagnosis should be confirmed. Here, the hospitalization becomes an opportunity to educate and implement an initial therapeutic plan. Finally, if stress hyperglycemia resolves in-hospital or soon after discharge, then no further action would be required other than routine follow-up. Good communication with the patient's primary care clinician or endocrinologist is key to ensure a smooth transition postdischarge (Slide 9).

CONCLUSIONS

Hyperglycemia occurs frequently in the hospital, both in patients with and without diabetes; its implications may be more serious in the former. Inpatient hyperglycemia is a predictor of adverse outcomes including mortality and is associated with increased length of stay and costs. Intensive glucose management in the ICU setting has led to improved outcomes in some single-center studies, not all of which were randomized. Yet other trials have questioned this benefit, and one even suggested a mortality risk associated with intensive insulin therapy. A rational synthesis of these data would suggest that good (mid-100 mg/dL range) but not necessarily stringent (<110 mg/dL) glucose control is the preferred approach in the ICU setting and is most easily achieved through a validated intravenous insulin-infusion protocol. On medical-surgical wards, a premeal blood glucose target of <140 mg/dL is reasonable and achievable in most patients. Physiologic, proactive insulin-replacement therapy (ie, the basal-bolus correction approach) to prevent hyperglycemia is preferred to more conventional, retroactive approaches, such as regular insulin sliding scales. Lastly, the discharge planning should always ensure a smooth transition to outpatient care.

ACKNOWLEDGMENTS

Dr. Bogun drafted the manuscript, collected and interpreted the data. Dr. Inzucchi was responsible for the critical review of the manuscript, collected and interpreted data and created the slides.

CONFLICTS OF INTEREST

Dr. Bogun has no conflicts of interest with regard to the content of this article. Dr. Inzucchi has served as a consultant/advisor to Merck, Boehringer Ingelheim, Bristol Myers Squibb, and Novo Nordisk.

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Address correspondence to: Silvio Inzucchi, MD, Section of Endocrinology, Yale Diabetes Center, Yale University School of Medicine, PO Box 208020, 333 Cedar Street, New Haven, CT 06520-8056. E-mail: xxxx