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Glycemic Variability and Glycemic Control in the Acutely Ill Cardiac Patient

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SCOPE OF THE PROBLEM

For the estimated 25.6 million Americans more than the age of 20 years who have diabetes, the risk of having a myocardial infarction or congestive heart failure is about twice as great as those without diabetes.[1,2] In addition, it is estimated that 20% to 30% of patients admitted to the hospital with acute coronary syndrome, and 20% to 40% of those admitted with congestive heart failure exacerbation, have diabetes.[3-5] Diabetes is believed to be an independent risk factor for heart failure.[6-8] However, the association between acute and chronic hyperglycemia and outcomes after acute cardiovascular events is less clear.

Published studies have used different diagnostic criteria for identification of diabetes and inpatient (or stress-induced) hyperglycemia.[9-11] Current estimates suggest that 37% of persons with diabetes are unaware of their diagnosis.[12] Within this context, studies have shown that 10% to 34% of patients with myocardial infarction who had hyperglycemia on admission (defined differently) with no known history of diabetes were subsequently diagnosed with diabetes within 1 week of discharge.[13-15] The remainder are assumed to have stress-induced hyperglycemia.

In addition, cardiovascular disease (and possibly inpatient outcomes) in patients with diabetes or prediabetes represents a complex interplay of disease processes that may not be adequately modeled by the current diagnostic criteria, which are based on the correlation of laboratory values with the onset and progression of microvascular disease processes over many years of exposure.[9,10,16,17] Cardiac risk increases before a patient becomes hyperglycemic by the traditional definition. Furthermore, as discussed later, short-term hyperglycemia or glycemic fluctuations may also have an important effect on outcomes in acutely ill patients, although this is less well established. This situation should be considered when evaluating studies that dichotomously categorize populations as either having or not having diabetes or hyperglycemia.

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MECHANISMS FOR HYPERGLYCEMIA IN HOSPITALIZED PATIENTS

In the acutely ill cardiac patient, many reasons coexist for the development of hyperglycemia, whether or not a patient has known diabetes. Certain therapeutic interventions, such as vasopressor agents, glucocorticoids, and parenteral nutrition can worsen or precipitate hyperglycemia.[18] Patient-specific factors also probably contribute, including a patient's underlying insulin resistance and β-cell function. However, hyperglycemia may be exacerbated by the severity of illness itself, which is marked by a proportionate increase in counterregulatory hormones and cytokines that have an adverse effect on insulin sensitivity. For example, in patients without known diabetes who were admitted to the hospital with acute myocardial infarction, cortisol, epinephrine, and norepinephrine (not hemoglobin A1c [HbA1c] or infarct size) were reported to be the primary determinants of glucose levels.[19] In patients presenting with chest pain, plasma cortisol, catecholamines, glucose, and insulin were increased across the spectrum from noncardiac chest pain to unstable angina to myocardial infarction.[20] Cortisol was associated with glucose levels. Such neurohormonal abnormalities have been known for decades.[21,22]

Neurohormonal derangements lead to excessive hepatic glucose production and insulin resistance during critical illness.[23,24] Although hepatic glucose production seems to be the major player,[25,26] peripheral insulin-mediated glucose uptake and nonoxidative glucose disposal are also reduced, at least in sepsis, which parallels the hormonal response observed after myocardial infarction in some ways.[27,28] Acute illness is generally associated with a catabolic metabolism that is marked by hyperglycemia as well as lipolysis. Hyperglycemia, lipolysis, and hyperinsulinemia are known to interact in complex ways, contributing to exaggerated inflammatory and counterregulatory hormone responses.[29,30] Resolution of hyperglycemia is associated with normalization of the inflammatory response.[31]

In heart failure, metabolic abnormalities also reflect the severity of symptoms.[32,33] Low cardiac output leads to compensatory increases in hormones that are counterregulatory to insulin in patients with heart failure.[34,35] Moreover, inflammatory cytokines such as tumor necrosis factor α (TNF-α) are increased and have been shown to directly inhibit insulin signaling.[36,37] These changes mirror those observed in acute illness in general, but it is unclear whether harmful effects would be additive to abnormalities already present during heart failure. The question is whether hyperglycemia induced by such neurohormonal changes is harmful or whether it is simply a marker of severe illness.

MECHANISMS OF ACUTE HYPERGLYCEMIA-MEDIATED HARM

Diabetes

The presence of diabetes is believed to increase the risk of death for patients who are admitted with the diagnosis of myocardial infarction.[38-40] This risk is related both to the direct, short-term sequelae of the infarction itself as well as to the heart failure that may subsequently result from it. Microvascular perfusion abnormalities and impaired myocardial energy production are suspected to affect patients with diabetes more prominently than those without diabetes.[17] In part, these factors are suspected of predisposing patients with diabetes to larger infarct sizes, as measured by serologic biomarkers and magnetic resonance imaging, as well as rates of postinfarction heart failure that are 2 times greater than for those without diabetes.[8,39,41] In the case of heart failure, the correlates of chronic metabolic and neurohormonal derangements are already a feature, including activation of the sympathetic nervous system and renin-angiotensin system,[42,43] increased oxidative stress,[44-46] endothelial dysfunction,[47,48] inefficient myocardial substrate use, and catabolic metabolism.[34] Thus, it is less clear whether exacerbation worsens outcomes. The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment In Hospitalized

Patients With Heart Failure) trial found no correlation between in-hospital, 30-day, and 60-day postdischarge mortality for patients who were admitted with both heart failure and diabetes, but this study did not examine the role of glycemic control.[5]

Hospital Hyperglycemia

The typical chronic complications of diabetes require several years to develop. Outside the hospital, cardiovascular benefits from glycemic control emerge only after long-term follow-up, and any mortality benefit from tight glycemic control seems be limited to patients with recently diagnosed diabetes.[49,50] However, it is unclear if these observations can be extended to acute hyperglycemia associated with acute illness. Limited evidence suggests preferential downregulation of glucose transporters under conditions of chronic hyperglycemia as opposed to intermittent hyperglycemia and acute illness, potentially allowing glucose to enter cells unchecked by normal downregulatory responses.[51,52] This situation provides a rationale for differential outcomes associated with stress hyperglycemia compared with chronic hyperglycemia. Stress hyperglycemia can also be considered to contribute to glycemic variability (Fig. 1). Outside the inpatient setting, intermittent glycemic excursions are associated with more profound endothelial toxicity than increases in tonic glucose level in vitro,[53-55] and glycemic variability is independently associated with higher levels of oxidative stress in patients with type 2 diabetes.[56] A study using a euinsulinemic, hyperglycemic clamp in patients with or without type 2 diabetes reported that oscillating glucose levels between 90 and 270 mg/dL resulted in increased endothelial dysfunction and oxidative stress that exceeded the effects of sustained hyperglycemia at 270 mg/dL in both groups.[57] This finding was confirmed in another study.[58]

Cardiovascular Harm

In the cardiac patient, other lines of evidence exist for a role of glycemic fluctuations in disease onset or modification. In patients admitted with chest pain, glycemic variability was an independent predictor of the severity of coronary artery disease on angiography and was superior to HbA1c.[59] Glycemic variability was associated with coronary artery calcium scores in men but not women with type 1 diabetes.[60] In a mouse model of diabetes, induced glycemic variability impaired ischemia-induced angiogenesis, independently of mean glucose level, through alteration of the vascular endothelial growth factor pathway.[61] A prospective study of patients with type 2 diabetes and ischemic heart disease found that ischemic electrocardiographic changes were more common during rapid glucose changes (>100 mg/dL/h) than during normoglycemia or sustained hyperglycemia.[62] Glycemic variability was associated with sympathovagal balance, endothelial function, and left ventricular mass index in patients with type 2 diabetes.[63] Thus, it makes sense to consider short-term and long-term glycemic control separately in the hospitalized cardiac patient.

DIABETES, HYPERGLYCEMIA, AND OUTCOMES IN CARDIAC PATIENTS

Chronic Hyperglycemia

The lower limit at which chronic glycemic control (determined by HbA1c) becomes insignificant in acute cardiovascular disease is unknown.[10] For example, a recent observational study of patients hospitalized for myocardial infarction found that stepwise increases in HbA1c, even if they were less than 6.5%, were associated with higher 1-year and 3-year mortality.[64] On the other hand, a study of 827 patients with diabetes and average HbA1c levels near 8.0% who were admitted with a diagnosis of myocardial infarction found that HbA1c was not associated with in-hospital mortality.[65] Therefore, chronic hyperglycemia may be more reflective of long-term outcomes. In heart failure, HbA1c was a progressive risk factor for mortality and hospitalization for heart failure in patients with or

without diabetes[66] but a U-shaped relationship may exist.[67] Heart failure readmission has been associated with increasing HbA1c.[68]

Acute Hyperglycemia

Increasing admission blood glucose levels have also been shown to have an inverse relationship with in-hospital and long-term postmyocardial infarction survival, independent of a diagnosis of diabetes.[64,65,69-71] More specifically, larger deviations of admission glucose level from a patient's preillness glycemic control, defined by HbA1c (suggesting the presence of stress hyperglycemia), are correlated with 30-day and 1-year mortality.[65,72-74] Thus, acute hyperglycemia seems to be a better predictor of mortality than chronic hyperglycemia for myocardial infarction. It is also sometimes difficult to know whether outcomes are observed with improved glycemic control per se or because of secondary effects of insulin itself. In 1 study of 141,680 patients admitted with an acute myocardial infarction,[65] three-quarters of the patients with diabetes and admission glucose levels greater than 240 mg/dL received insulin therapy, compared with only 22% of those without diabetes. Thirty-day and 1-year mortality were greater in the patients without diabetes. By comparison, 1 study found no correlation between admission glucose levels and 30-day and 1-year mortality in patients admitted with heart failure.[75]

Most retrospective studies rely heavily on admission glucose level for analysis, which provides only a snapshot of glycemic control. A recent study of approximately 17,000 patients admitted with myocardial infarction showed that increasing in-hospital mean glucose level was associated with increasing inpatient mortality.[76] The effect was observed in patients with and without diabetes, although a higher threshold for harm was identified in those with diabetes. Furthermore, mean hospital glucose level was a better predictor of mortality than admission glucose level. The importance of acute hyperglycemia, relative to chronic hyperglycemia, may be further supported by a study that showed that among intensive care unit (ICU) patients with diabetes who had poor chronic glycemic control (determined by HbA1c), rapid achievement of normoglycemia in the ICU was associated with higher mortality.[77] Thus, the unique role of stress hyperglycemia deserves further attention in prospective studies.

Glycemic Variability

One factor that is receiving increasing attention both in the inpatient and outpatient setting is glycemic variability. A large review of more than 7000 medical and surgical ICU patients found that the standard deviation of glucose level was a better predictor of mortality than mean glucose level.[78] This finding has been observed in other critical care settings,[79,80] but has not been well studied in myocardial infarction. In patients admitted with heart failure exacerbation, glycemic variability, but not mean hospital glucose level, was associated with inpatient mortality.[81] There are currently no prospective studies specifically examining outcomes through the pharmacologic manipulation of glycemic variability in the hospital. Moreover, such a study would be technically difficult to perform.

Clinical Trials Data

Over the past decade, awareness has increased about the need to find appropriate management strategies for treating hyperglycemia in hospitalized patients. Recent reports in the medical and surgical ICU have tempered any enthusiasm for strict glycemic control (target of 80–110 mg/dL), because of what has been considered an unacceptable risk of hypoglycemia and possible increase in mortality.[82-85] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial added another layer of complexity when it was ended early because of higher all-cause and cardiovascular mortality in the intensive therapy group compared with the standard therapy group.[50] However, in both settings, tight glycemic

control was compared with what many consider acceptable glycemic control, not poor control. Therefore, it does not follow that glycemic control should be abandoned in the hospital. For example, in a smaller multicenter randomized controlled trial of 211 surgical patients,[86] basal bolus insulin resulted in lower mean glucose level compared with sliding scale insulin (147 vs 172 mg/dL, $P < .01$), and there was a reduction in the composite outcome of wound infection, pneumonia, bacteremia, and respiratory and acute renal failure (odds ratio [OR] 3.4, 95% confidence interval [CI] 1.5–7.7). In addition, a meta-analysis of clinical trials aiming for at least less than 180 mg/dL also showed benefits in multiple outcomes after cardiac surgery.[87]

Studies evaluating the management of hyperglycemia in patients with acute nonsurgical cardiovascular disease have been difficult to interpret. DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) 1 and DIGAMI 2 trials attempted to determine if improved inpatient glucose control would decrease mortality after acute myocardial infarction. DIGAMI 1 evaluated the effectiveness of immediate intravenous (IV) insulin therapy followed by insulin-based long-term therapy for patients with diabetes who were admitted with an acute myocardial infarction. Whereas 1-year mortality was reduced, in-hospital and 3-month mortality were not significantly reduced in the group treated with IV insulin.[88] DIGAMI 2 was designed to determine whether the mortality benefit was caused by acute IV insulin or long-term subcutaneous insulin.[89] Low enrollment and a failure to reach statistically significant differences in plasma glucose and HbA1c levels amongst the 3 groups hampered the study and no difference in short-term and long-term mortality was observed.

GIPS 1 (Glucose-Insulin-Potassium Study-1), GIPS 2 (Glucose-Insulin-Potassium Study-2), and CREATE-ECLA (The Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Clinicos Latino America) are examples of trials that attempted to determine whether insulin itself had a beneficial impact on mortality in patients suffering from acute myocardial infarction.[90-92] The impetus for conducting these trials was held in the theory that high-dose glucose-insulin-potassium (GIK) infusion after a myocardial infarction would increase glucose use by myocytes and decrease use of free fatty acids. This situation would result in a decreased production of free oxygen radicals, which may cause further injury to ischemic myocytes. These trials failed to show a consistent benefit, and results were confounded by hyperglycemia in the intervention arms, which exceeded that of control arms. However, post hoc analyses did show that hyperglycemia, defined by a glucose level more than 140 mg/dL at 6 or 24 hours, was associated with increased mortality in patients without known diabetes and in patients who did not receive GIK.[93] This finding suggests that a different threshold of harm may exist for patients with or without diabetes, and possibly that GIK may still mitigate the harm. Post-admission hypoglycemia (<70 mg/dL) was not associated with mortality.

Given the limitations of data to guide clinicians in the management of hyperglycemia in acute cardiovascular disease, it is not surprising that from 1997 to 2006, there was no improvement in mortality related to glycemic control in patients hospitalized with acute myocardial infarction.[94]

MANAGEMENT

Targets

The current American Diabetes Association (ADA)/American Association of Clinical Endocrinology hospital guidelines recommend a target glucose level of 140 to 180 mg/dL based on the control arm of the NICE-SUGAR ICU study in both ICU and non-ICU settings until further data are available (Fig. 2).[95] However, NICE-SUGAR did not address whether

glycemic control targeting a more modest glucose range (110–140 mg/dL) is better. In particular, hypoglycemia is less common when a more modest target (100–150 mg/dL) is attempted (frequency of blood glucose of <60 mg/dL was 5% in both medical and cardiac care units).[96] As a result, an intermediate target glucose range between 110 and 140 mg/dL may be reasonable in certain populations (for example, after cardiac surgery) and institutions and patients in whom it can be performed safely. By comparison, the Endocrine Society recommends meal-specific targets, including a fasting glucose level less than 140 mg/dL and postprandial target of less than 180 mg/dL in noncritical care settings.[97] Regardless, a target glucose range attempting to achieve normoglycemia (80–110 mg/dL) is not recommended because of the unacceptable risk of hypoglycemia. Furthermore, this tight glucose range is probably not technically feasible in most circumstances because of limitations of IV infusion algorithms and glucose monitoring.[98] Improvements in technology, such as more precise methods of glucose monitoring and computerized (or even closed loop) IV infusion algorithms, are needed to determine whether achievement of normoglycemia is beneficial.[99] Until more data are available, separate targets for acute and chronic hyperglycemia are not advocated.

General Approach

Current hospital and outpatient guidelines as well as large clinical studies focus mainly on the achievement of specific mean glucose targets and not necessarily on how those targets are achieved. The tendency for preoccupation with average glucose level neglects details in overall glucose control that may be linked to outcomes. One cannot just extrapolate successful approaches from the outpatient arena to the inpatient arena, because the dynamic nature of acute illness and the effects of other variables such as nutritional status and renal function necessitate constant vigilance and a flexible management plan. For these reasons, it is of interest to determine whether management of hyperglycemia is better viewed through the lens of minimizing glycemic variability rather than mean glucose level.

It is unknown whether measures that specifically minimize illness-induced glycemic excursions improve outcomes. In addition, some evidence suggests that glycemic variability is a function of patient-specific factors that are difficult to manipulate. Patients with glycemic lability may have long-standing diabetes with both β cell and counterregulatory hormone failure.[100] In hospitalized patients, glycemic variability has been associated with age, diabetes, and total insulin requirements.[101] However, measures that minimize fluctuations are more likely to achieve overall glycemic control without increasing the risk of hypoglycemia.[102,103] Studies in the outpatient setting suggest that physiologic insulin regimens reduce both mean glucose level and glycemic fluctuations.[104-106] Physiologic regimens, particularly when used in lieu of traditional sliding scale insulin, could also reduce glycemic variability in the hospital. Dozens of studies have investigated the efficacy of various IV insulin protocols.[107,108] However, efficacy is usually not defined in terms of glycemic variability. Computerized IV insulin protocols show reductions in hypoglycemia and hyperglycemia, indicating that they may also reduce glycemic variability.[109-111] More studies are needed to recommend for or against specific measures to reduce glycemic variability outside the traditional framework for tight glycemic control in the hospital. The remainder of this section focuses on strategies to provide physiologic glycemic control in hospitalized patients, with particular attention to the needs of the cardiac patient.

Insulin

The current ADA guidelines recommend insulin as the primary modality of therapy in most hospitalized patients with hyperglycemia.[96,98] In general, a physiologic regimen containing basal, prandial, and supplemental (correction) insulin components is advised to obtain glycemic control (Table 1).[96,98]

IV insulin—IV insulin is advised in patients with severe hyperglycemia and in patients who are critically ill, particularly those with hypotension or who are undergoing major surgery. Issues unique to the acutely ill cardiac patient, such as poor perfusion and edema, may render IV insulin a safer, more effective choice because of slower absorption of subcutaneous insulin and the potential for insulin stacking and delayed hypoglycemia (Table 2).[112] IV insulin is often necessary for treatment of hyperglycemia associated with high-dose steroids and total parenteral nutrition. Multiple algorithms have been published,[108,109] but few randomized trials comparing algorithms are available.[113] In general, a validated protocol should be used, keeping in mind the ease of implementation and use as well as its efficacy and safety.[114]

Another issue of importance is the patient who is eating while receiving an insulin infusion. Even the most sophisticated insulin infusion algorithms are perturbed in patients who are eating,[115,116] likely representing the inability of standardized algorithms to adapt to the rapid glucose level changes induced by eating. In such patients, subcutaneous rapid-acting insulin may be provided to cover meals.[117] An alternative is to use an infusion algorithm that provides a programmable temporary step-up in infusion rate after a meal.[111,118]

Moving patients from IV to subcutaneous insulin should be deferred ideally until a patient is hemodynamically stable, off pressors, extubated, and eating.[119] Among patients undergoing postcardiac surgery, those with good glycemic control on stable or minimal insulin requirements meeting the aforementioned criteria are more successful with the transition. In surgical patients, an initial basal insulin dose of 50% to 65% of the daily IV insulin requirements (calculated from the average infusion rate during fasting or adequate subcutaneous prandial insulin coverage) is adequate for many patients 48 hours after surgery.[118,120] Inadequate prandial insulin coverage during an infusion may also lead to an overestimation of basal insulin necessary for transitioning a patient off an insulin infusion.[118] On the other hand, patients with more chronic hyperglycemia, marked insulin resistance, or shorter duration of infusion after the initial event may require a higher conversion factor or weight-based dosing.[121,122] The dosing regimen should be compared with the patient's home insulin requirements, HbA1c level, and weight (see later discussion).

Subcutaneous insulin

Initiation of insulin: Subcutaneous insulin is the mainstay of treatment of hospitalized patients with diabetes. However, the initiation of insulin can be a challenging proposition for patients who are acutely ill, because a variety of factors, including altered eating habits and a rapidly changing clinical course, may significantly affect insulin requirements over time. It may be helpful to stratify the approach by preadmission glycemic control and therapy (Fig. 3).

Insulin-naive patients

- Poor baseline control: in patients with severe hyperglycemia (>300 mg/dL) refractory to intervention or who have other indications, IV insulin is an efficient means of calculating total insulin requirements, as noted earlier. In patients with moderate hyperglycemia or stable patients with more advanced hyperglycemia, a weight-based algorithm has been used for the initiation of subcutaneous insulin. The total daily dose is calculated as 0.4 to 0.5 units/kg and 50% is administered as basal insulin and 50% as prandial insulin, divided evenly over 3 meals. A lower dose (0.2–0.3 unit/kg) should be considered in patients at risk for hypoglycemia, such as elderly patients or those with renal or liver impairment.[98]

- Mild to moderate baseline control: there are few studies supporting approaches to insulin therapy in insulin-naive patients with more mild to moderate (<200 mg/dL) or intermittent hyperglycemia. These patients may be best treated with a stepwise approach. Outside the hospital, basal insulin is typically initiated before prandial insulin, but in the hospital, prandial insulin may be the preferred first-line therapy in patients who periodically must receive nothing by mouth for tests. If the fasting glucose level remains increased, a low dose of basal insulin can be implemented at 0.1 to 0.2 unit/kg.

Noninsulin-naive patients: In noninsulin-naive patients, continuation of the home insulin regimen requires special consideration. First, it must be emphasized that patients with type 1 diabetes require basal insulin without exception at all times. Otherwise, one must inquire about the patient's level of adherence, the frequency of glucose self-monitoring, and patterns of hypoglycemia. In all cases, basal insulin is administered at no more than 50% of the total home daily dose (basal plus prandial) and the rest of the total daily requirements are spread out over meals.[87,123] In particular, nonphysiologic insulin regimens (particularly in cases in which basal insulin accounts for a large proportion of the total daily dose) need adjustment because patients must often receive nothing by mouth or otherwise may not be eating in the same way with hospital food. In such cases, basal insulin may require reduction in favor of more prandial insulin.

- Poor baseline control: the total daily dose may be increased 10% to 20% in patients who are adherent and uncontrolled.
- Good baseline control: the total daily dose may be continued without adjustment provided that hypoglycemia is not a significant problem and that a physiologic regimen is used.

Special considerations for prandial and correction insulin: In general, a patient who is eating reasonably well should receive no more than 50% of the total daily insulin dose as basal insulin (Table 3).[87,123] Ideally, the prandial insulin dose is tailored to carbohydrate intake (flexible insulin dosing or carbohydrate counting starting at 1 unit per 10 or 15 g of carbohydrates). If fixed meal dosing is used, a consistent carbohydrate diet is necessary. Special precautions should accompany the order (cut dose in half if patient eats 50% of the tray or if glucose level is 70–90 mg/dL, hold dose if <50% of the tray is eaten, and so forth). Correction (supplemental) insulin should also be adjusted based on the patient's total daily insulin requirements. Coverage for enteral and parenteral feeding requires additional consideration, which is beyond the scope of this article.

Adjustment of therapy: Daily adjustment of therapy should be directed at hypoglycemia first. Targeted reduction in insulin doses should be commensurate with the degree and frequency of hypoglycemia and risk of adverse consequences. In patients whose illness is marked by significant stress hyperglycemia (such as after cardiac surgery or large myocardial infarction), one must also allow for continued reduction in insulin requirements as the stress of the illness dissipates.[118,122] Continued preemptive dose reduction (10%–20% per day) may be required in patients who are tightly controlled (glucose level consistently <100 mg/dL) with severe illness.[98] Patients with chronic hyperglycemia or less acute illness may require less aggressive dose reduction.[123] Home insulin requirements may be a helpful guide. In patients with persistent hyperglycemia, randomized controlled trials have indicated that daily dose adjustment of 10% to 20% per day is reasonable in patients receiving basal bolus insulin analogues.[87,124]

Periprocedural care—The cardiac patient is particularly prone to changes in oral intake because of the need for frequent procedures. In general, it is not necessary to withhold basal insulin entirely. Although limited prospective data are available, 1 retrospective review reported that among patients who were told to take 50% of their home dose of basal insulin before surgery, hypoglycemia was uncommon (2% among patients with a preoperative glucose level <200 mg/dL; 0% among those with preoperative hyperglycemia).[124] However, postoperative hyperglycemia was persistent in most patients with preoperative hyperglycemia. By comparison, patients who are undergoing procedures such as cardiac stress testing or catheterization may have a smaller stress response, and a reduction of 50% may still be reasonable. However, the necessity for dose reduction may be negligible and omissions may be minimized by prophylactically adjusting the home regimen to a more physiologic distribution at the time of admission, as discussed earlier. In patients with type 1 diabetes, minimal reductions (<20%), are necessary, and generally only in patients with tight glycemic control.[125]

Noninsulin Therapy

Oral agents—As stated earlier, for a variety of reasons guidelines advise discontinuation of oral agents in most hospitalized patients with diabetes (Table 4). Oral sulfonylureas may result in prolonged hypoglycemia in patients with even modest renal dysfunction, a common comorbidity in the cardiac patient, or nil-by-mouth status.[126,127] Metformin is associated with lactic acidosis in a variety of conditions, such as renal insufficiency (which is especially relevant in patients receiving IV contrast), decompensated heart failure, or hypoxia.[128-131] Although the risk is low, the estimated mortality is still high.[129,130,132] Thiazolidinediones are well known to be associated with congestive heart failure.[132,133] Furthermore, they have a slow onset of action and thus have limited use in the inpatient setting.

GLP-1 based therapy—Glucagonlike peptide 1 (GLP-1)-based therapies have garnered increasing interest for the treatment of diabetes or hyperglycemia in patients with diabetes. These agents do not generally cause hypoglycemia in the absence of other therapies that cause hypoglycemia.[134,135] There are GLP-1 receptors in the myocardium, and preclinical and early clinical studies raise the possibility that there may be beneficial cardiac effects, such as reduction of ischemic preconditioning and improved left ventricular function.[136] Furthermore, these therapies counteract the effects of inappropriate glucagon release, a pathologic feature of diabetes and stress hyperglycemia alike.[72] There are 2 main approaches to augmenting GLP-1 to treat hyperglycemia: (1) GLP-1 receptor agonists or mimetics and (2) inhibition of dipeptidyl peptidase IV (DPP-IV), the enzyme that degrades GLP-1.

- GLP-1 receptor agonists are generally more potent and have the advantage of promoting weight loss long-term.[137,138] These agents have been studied intravenously in small studies of hospitalized cardiac patients, but nausea is a major potential side effect and it is too early too tell if cardiac benefits are present.[139-143]
- DPP-IV inhibitors are generally well tolerated but have more limited efficacy.[136] However, in some patients with mild hyperglycemia, they may be considered. Meta-analyses from randomized controlled trials suggest cardiovascular benefits from these agents versus active comparators, although most studies were short-term.[144,145]

The long-term safety of these agents is unknown and the safety and efficacy of GLP-1–based therapies have not been extensively tested in hospitalized patients. Further study therefore is warranted.

Other approaches—Many other noninsulin therapies are under investigation for the treatment of diabetes in the outpatient setting.[146] There has been little interest in developing targeted therapies for inpatient use, possibly because of the complexity of the patients and the lack of randomized controlled trials that establish an appropriate glucose target. Noninsulin agents that lower glucose level without causing hypoglycemia are candidates for inpatient therapy. Agents that target major components of stress-induced hyperglycemia, such as hepatic glucose output or insulin resistance in general, are needed. These agents must be safe, effective, and ideally compatible with other IV medications. Until such therapies become available, insulin remains the mainstay of therapy.

Discharge

Sustained glycemic control after discharge may be facilitated with proper planning that begins at the time of hospital admission. Patients should be screened for medication adherence and discharge needs with appropriate social work input early. Diabetes education should be considered early in the hospital course when needed, because education is best received when there is time for continued follow-up and reinforcement.[147,148] Likewise, diabetes physician consultation should be considered early in the course when necessary, because the attainment of glycemic control typically requires several days to achieve.[87,124] The HbA1c may be used to guide hospital discharge regimens such that those who are well controlled before admission may resume their preadmission therapy, provided there are no contraindications and oral intake has resumed to normal (Table 5). In other patients, 1-step or 2-step intensification of therapy is necessary based on the severity of hyperglycemia, comorbidities, and contraindications.[149] Written communication of changes in the diabetes regimen is crucial for patients at the time of discharge, and outpatient follow-up should be ensured.

SUMMARY

More studies are needed to recommend for or against specific measures to reduce glycemic excursions outside the traditional framework for tight glycemic control. However, measures to stabilize glucose through physiologic insulin regimens may have the potential to preserve or enhance the benefits of glycemic control and reduce the risks of hypoglycemia in the hospital. Such efforts also serve to build a united front with outpatient providers in reinforcing the importance of glycemic control for reducing the long-term risk of microvascular complications.

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KEY POINTS

- Acute hyperglycemia is associated with worse outcomes in hospitalized cardiac patients.
- Hospitalized cardiac patients are at particular risk for developing hyperglycemia and hypoglycemia for a variety of reasons.
- Flexible physiologic insulin regimens are appropriate for most hospitalized patients.
- Hospitalization provides an opportunity for reinforcement of good diabetes-related self-care behaviors to prevent long-term complications.
- Well-designed studies addressing glycemic control in the hospitalized cardiac population are needed.

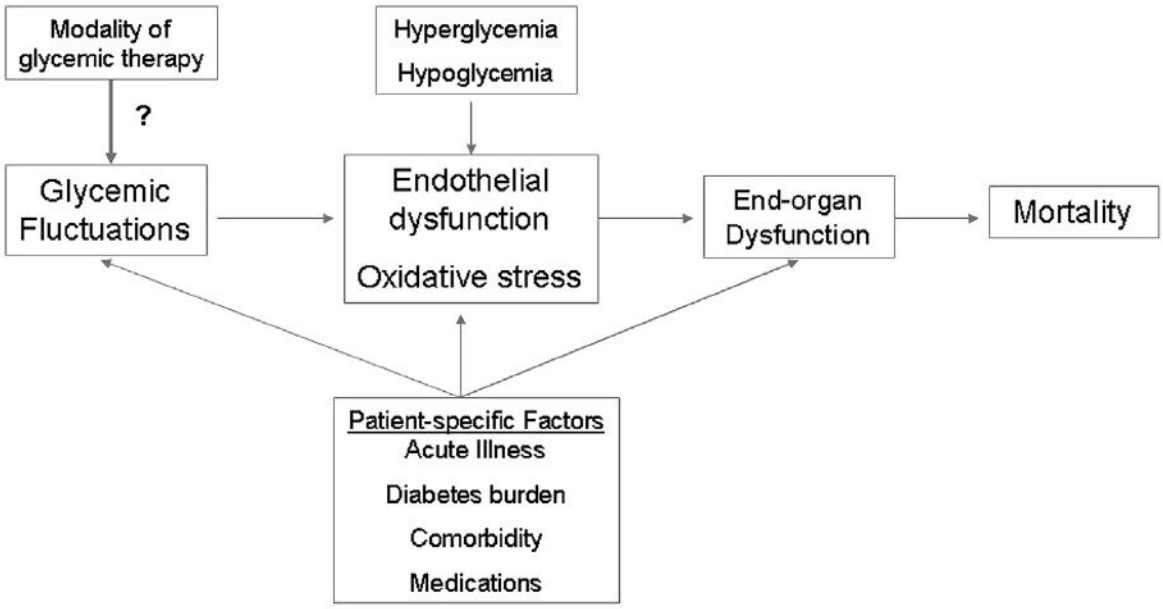

Fig. 1.

Conceptual framework for a theoretic role of glycemic variability in the acutely ill patient. Glycemic variability may be influenced by patient-specific factors such as acute illness, duration of diabetes, presence of comorbidities, and other medications. Sustained hyperglycemia, hypoglycemia, and glycemic variability may lead to endothelial dysfunction and oxidative stress, which in turn contribute to end-organ dysfunction and death.

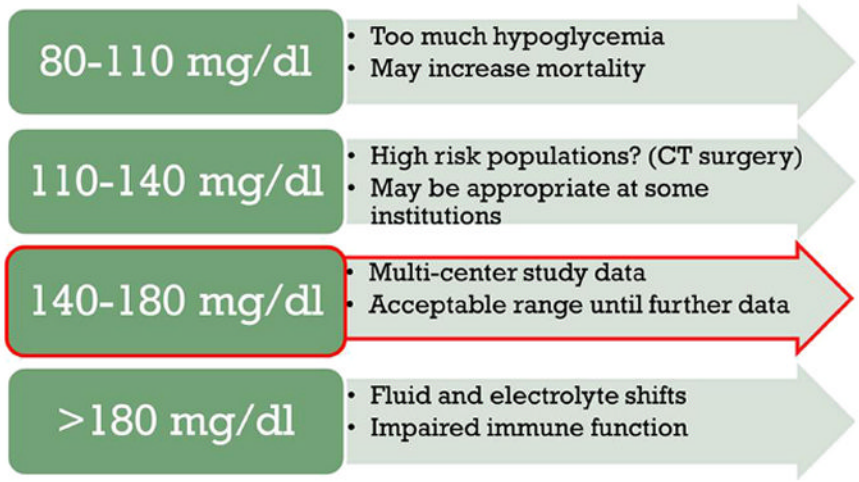

Fig. 2.
Rationale for current glycemic targets in the hospital.

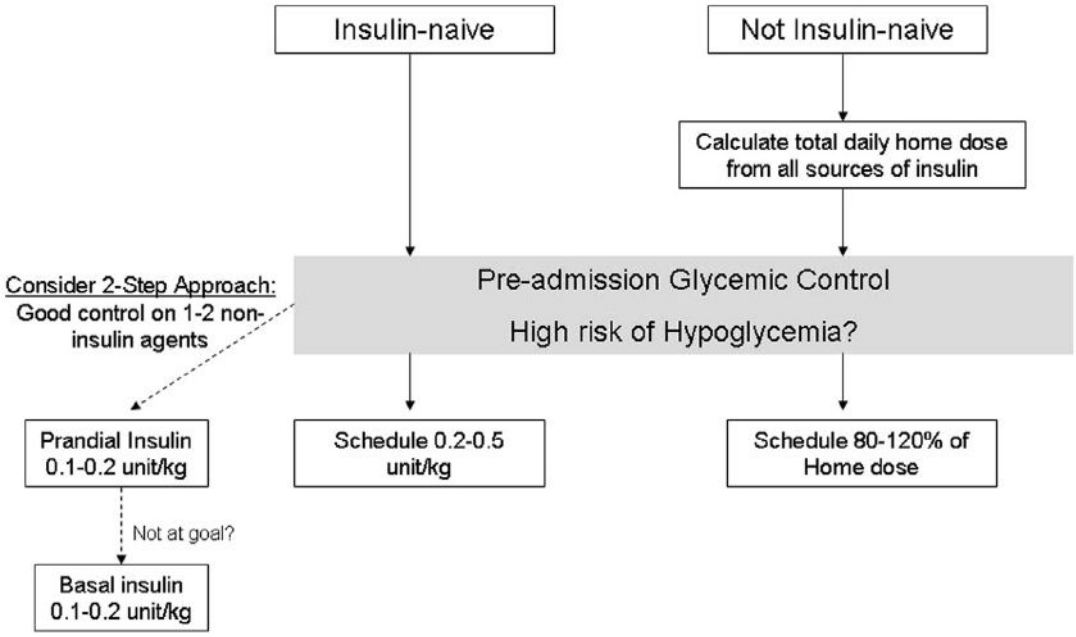

Fig. 3.
Calculation of the initial total daily dose of insulin in the hospital.

Table 1

Approaches to physiologic insulin use in the hospital

	% of Total Daily Insulin[a]	Examples
Basal	<50% (if eating)	Long-acting insulin analogue Neutral protamine Hagedorn Continuous subcutaneous insulin (pump) IV insulin infusion
Prandial	≥50% divided evenly over meals (if eating)	Rapid-acting insulin analogue Regular insulin (tube feeds)
Correction	Varies	See prandial insulin IV insulin infusion

[a]Total estimate insulin per day from all sources. If patient is not eating, then basal insulin may account for most insulin requirements.

Table 2

Comparison of IV and SQ insulin in the hospital

	IV	SQ
Frequency of titration	Hourly	Daily
Time to target glucose	~12 h	~3 d
Adaptability to clinical status	+++	++
Absorption issues	No	Yes
Duration of hypoglycemia	<1 h	Hours
Labor	+++	++

Table 3

Distribution of insulin dosing in hospitalized patients with normal oral intake[a] based on the total estimated daily dose

Total Daily Dose[b] (Units)	Basal Insulin Dose	Fixed Meal Dose[c] (Per Meal)	Insulin: Carbohydrate (Units: g)	Correction Factor (1 Unit per __ mg/dL More Than 150 mg/dL)
<20	≤10	2–3	1:20	100
20–40	10–20	4–5	1:15	50 (standard dose)
41–50	20–25	6–8	1:10 (standard dose)	50 (standard dose)
51–80	25–40	9–13	1:8	25
>80	40+	14+	1:5	25

[a] Assumes patient is eating a typical (carbohydrate-controlled) diet.

[b] Total estimated insulin per day from all sources.

[c] Accompany with appropriate hold parameters (eg, hold if patient eats less than half of tray or if glucose level <80 mg/dL).

Table 4

Comparison of insulin and noninsulin hypoglycemic agents in the hospital

	Noninsulin Agents	Insulin[a]
Frequency of titration	Days to weeks	Daily
Adaptability to changes in nutritional status	+	+++
Duration of hypoglycemia	None (M, T, G) Days (S)	Hours
Other cautions	Renal dysfunction (M, S) Liver disease (M, S, T) Lactic acidosis[b] (M) Nausea/vomiting/pancreatitis (G) Heart failure (T, M) Elderly (M, S)	Rare

DPP-4 inhibitors are generally safe but have limited efficacy and there are limited data for use in the hospital.

Abbreviations: G, GLP-1 (exenatide, liraglutide, pramlintide); M, metformin; S, sulfonylureas; T, thiazolidinediones.

[a] Using a physiologic regimen.

[b] Metformin-associated lactic acidosis is increased in patients with renal dysfunction (and IV contrast administration), acidosis, respiratory failure, acute heart failure, and hemodynamic compromise.

Table 5

Home-going strategy based on HbA1c[a]

HbA1c (%)	Suggested Regimen
>9	Basal + oral or basal + bolus insulin
7–9	1-step to 2-step increase in therapy: oral → 2 oral → oral + basal insulin → basal bolus
<7	Resume home regimen

[a]Strategy assumes that patient is resuming a normal diet and that there are no contraindications.