Mortality and Glycemic Targets in the Intensive Care Unit: Another Paradigm Shift?

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Within the past year, providers caring for a patient with cardiovascular disease and diabetes have been made to realize that despite the associations of hyperglycemia and cardiovascular complications, the results from the prospective studies evaluating aggressive glycemic intervention did not follow the predicted script! Specifically, the randomized clinical trials that addressed the question of cardiovascular disease and glycemic control (i.e., Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) provided results that suggest we take a closer look at the "one size fits all" glycemic target for A1C that has been suggested in the past (1–3). Is it really surprising that we have a similar situation with hyperglycemia and critically ill patients in the intensive care unit (ICU) setting? For years, it has been recognized that hyperglycemia has been associated with mortality in critically ill patients as observed across many cohorts, and as such, there has been intense interest in evaluating the clinical effect of normalizing glycemia in these critically ill subjects (4–7). However, the recently reported observations from the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial suggest that attempts to normalize glycemia are not the simple answer to the problem (7).

The NICE-SUGAR study was a multicenter, international, and randomized trial that evaluated the effect of intensive versus conventional glucose control on outcomes in hyperglycemic, critically ill subjects. After subjects were identified in the ICU setting, they were randomized either to tight glycemic control, defined as a target blood glucose level of 80–108 mg/dl, or to conventional glycemic control, defined as a blood glucose level in the range of 144–180 mg/dl. Control for each group was achieved by intravenous infusion of insulin. The time-weighted blood glucose level achieved was 115 mg/dl in the intensive group and 144 mg/dl in the conventional group. The primary outcome was death from any cause within 90 days of randomization. The key finding from the study was that the mortality rate at 90 days was 3% higher in the intensive treatment group, essentially representing an ~10% increase from intensive glycemic intervention (7).

The NICE-SUGAR study had many strengths. These strengths included the large number of subjects evaluated (~3,000 in each group) and the uniform insulin infusion protocol that was implemented across all centers participating. The patients enrolled were clearly representative of patients commonly seen in ICU settings and included those admitted for operative procedures or for a wide range of cardiovascular, hepatic, or renal abnormalities. An additional strength was the choice of the primary outcome, i.e., death, given that there would be no question regarding adjudication. Of course, every study can be suggested to have weaknesses, and the NICE-SUGAR study was no different. However, the evaluation of outcomes resulting from a carefully controlled intervention in ICU patients, given the inherent heterogeneity in patient presentation and response, is not a trivial task. The fact that such a study was conducted in a complicated and varied cohort and completed as an international study with a standardized approach is impressive in itself, and the authors should be congratulated.

The results from the NICE-SUGAR trial do raise additional questions and warrants in comparison with and in contrast to those of Van den Berghe et al. (4,5), particularly because the NICE-SUGAR results contradict the findings of the prior studies (4,5,7). In addition, a paradigm shift to institute intensive glycemic control measures in ICU settings appeared to have had its genesis based on the results of the studies of Van den Berghe et al. The apparent differences between the studies may or may not have played a role in the different outcomes. For example, the studies of Van den Berghe et al. reported findings from a single study site, and there may have been unique aspects of treatment and characteristics in that population as opposed to in a multicenter, international study with a cohort with other characteristics. There were also differences in how nutritional therapy was provided, e.g., parenteral versus enteral. Perhaps the most important differences, however, were the levels at which intervention was directed. For example, in the studies of Van den Berghe et al., insulin was initiated in the conventional treatment group only if the blood glucose level exceeded 215 mg/dl, and the infusion was adjusted to maintain the level at a value between 180 and 200 mg/dl. Although the morning blood glucose level was maintained at a mean ± SD value of 153 ± 33 mg/dl, the investigators reported that only 39% of the patients treated with the conventional approach received insulin and that their mean blood glucose level was 173 ± 33 mg/dl compared with 140 ± 25 mg/dl in the patients who did not receive insulin (4). In the NICE-SUGAR trial, 69% of subjects in the conventional treatment group received insulin and, as would be expected, 97% of subjects in the intensive treatment group received insulin (7). Thus, between the two studies, there

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were differences in the percent of subjects receiving insulin. Hypoglycemia for both the NICE-SUGAR trial and the studies of Van den Berghe et al. was much greater in the intensive treatment groups and was defined as a blood glucose level of ≤40 mg/dl. Whereas hypoglycemia occurred in ~5 and 1% of patients in the intensive treatment group versus conventional treatment group in the studies of Van den Berghe et al., hypoglycemia was reported in 6.8 and 0.5% of patients, respectively, in the NICE-SUGAR study (4,7).

The most relevant questions to ask, however, are as follows: What will be the implications of the NICE-SUGAR results for the vast majority of patients with hyperglycemia in the ICU? Are there specific subgroups of patients that perhaps benefited from this intervention? Is there a benefit derived from longer stays in the ICU? What were the mechanisms for the observations? We simply do not know why there was increased mortality in the intensive insulin group, but we could argue that the adverse effect was related to intensive insulin treatment, hypoglycemia, or mechanisms yet undefined. Given the emerging data on the multiple mechanisms by which hypoglycemia can adversely affect cardiovascular disease and knowing the difficulty in detecting neuroglycopenia in the critically ill patient, we need to further evaluate the impact of hypoglycemia in the ICU setting and its effect on outcomes (8,9). An intriguing question yet to be answered is whether intensive glycemic control can be achieved without significant hypoglycemia (e.g., use of continuous monitoring) and whether achieving tight glycemic control without hypoglycemia would have altered outcomes. In regard to intensive insulin therapy, could it have impacted molecular mechanisms that are critical for tissue repair? For example, the term "autophagy" refers to a major catabolic pathway by which cells degrade and recycle macromolecules and organelles, and the process plays a critical role in removing damaged cellular structures to keep the cell healthy (10). Autophagy is inhibited by insulin; thus, theoretically, high insulin concentrations might constrain cellular repair. We also know that critical illnesses, such as those conditions seen in the ICU (i.e., sepsis, trauma, etc.), are accompanied by increased cell death (11). Therefore, is it plausible to postulate that intensive insulin may have impaired tissue remodeling and repair in this critically ill population but perhaps not in clinical situations (e.g., outpatient settings) where this process may be more in balance? This may be a prime example of a situation where an understanding of the molecular biology of apoptosis and of how therapeutic interventions modulate the process in critical illness is direly needed. This information could have great clinical relevance.

Given this data, do we now abandon our attempts at intensive control in the ICU or, for that matter, not worry about glycemic control in hospitalized settings? Should the energy spent by hospitals to develop an infrastructure to allow glucose monitoring and insulin algorithms be considered wasted? Clearly, if this happens, this will be a "knee jerk" reaction. What we do know is that intensive glycemic control to essentially normal levels with insulin infusion in ICU patients did not improve but perhaps worsened mortality compared with more moderate glycemic targets: achieving a range of 144–180 mg/dl and avoiding significant hypoglycemia. This is an important point that does not imply that we now accept glycemic levels of >200 mg/dl and revert back to days of ignoring glycemic levels and relying on sliding-scale regimens. This is clearly not what the findings of the NICE-SUGAR trial suggest. Until we know the answers, we simply need to accept that our glycemic goals in the ICU should be more moderate, e.g., 140–180 mg/dl. To suggest a totally different paradigm now and to revert back to the level of care in the past would simply be an overreaction to this important study.

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