CORRESPONDENCE

Glucose Control in Critically Ill Patients

TO THE EDITOR: In the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study (ClinicalTrials.gov number, NCT00220987), reported by Finfer et al. (March 26 issue),[1] intensive glucose control increased mortality. These findings are clearly at variance with the decreased mortality that we reported from our center in Leuven, Belgium.[2-4] Finfer et al. do not address several possible explanations for this discrepancy.

First, normoglycemia (blood glucose level, <110 mg per deciliter [6.1 mmol per liter]) was compared with distinct blood glucose control with target ranges of 140 to 180 mg per deciliter (7.8 to 10.0 mmol per liter) in the NICE-SUGAR study and 180 to 215 mg per deciliter (10.0 to 11.9 mmol per liter) in the Leuven studies, making the studies fundamentally different.

Second, safe adjustment of the insulin dose to target normoglycemia requires standardized and accurate techniques for glucose measurement and monitoring of the potassium level. Otherwise, the degree of treatment compliance (the targets reached and acceptable fluctuations in glucose levels) is enigmatic. In the NICE-SUGAR study, it is surprising that a variety of glucometers, most of which were unsuitable for this purpose,[5] were allowed; thus, undetected hypoglycemia, large fluctuations in glucose levels, and possibly hypokalemia were tolerated or even induced. Such errors may have contributed to excess "cardiovascular" deaths, in the absence of differences in organ failure.

Third, in the NICE-SUGAR study, patients received enteral nutrition exclusively, whereas in the Leuven studies, parenteral nutrition supplemented insufficient enteral feeding. The administration of insulin during hypocaloric feeding in the NICE-SUGAR study may have been deleterious.

Finally, an unexplained policy of early withdrawal of care in the NICE-SUGAR study (after a median duration of study treatment of 6 days), which was not balanced between the two treatment groups of this nonblinded study, may have introduced a bias that could explain the excess mortality.

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TO THE EDITOR: The NICE-SUGAR study investigators randomly assigned patients not to target blood glucose values but rather to alternative

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strategies for the administration of insulin. The difference in mortality between the study groups should not be attributed to the stated targets but rather to treatment, which was shown to be less safe in the intensively treated group. Among critically ill patients treated under a policy of strict control, it is difficult to prove the consequences of severe hypoglycemic episodes. Potentially harmful effects of counterregulation may occur even when severe hypoglycemic episodes are not documented. In the Leuven study, involving patients in a surgical intensive care unit (ICU), hypoglycemia might have had unproven adverse consequences that were outweighed in the statistical analysis by benefits of strict control.[1] Carefully engineered insulin-treatment algorithms can reduce severe hypoglycemia.[2] Variability in glucose levels must be managed and reported, potentially with the use of different rules according to whether the blood glucose level is above or below the true target. The NICE-SUGAR results should prompt renewed enthusiasm for the development of techniques that will reduce the confounding factor of iatrogenic hypoglycemia and thus enable future investigators to determine optimal blood glucose targets in given populations.

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1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.
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TO THE EDITOR: In their article about the optimal target range for blood glucose in critically ill patients, Finfer and colleagues state that "intensive glucose control increased mortality among adults in the ICU." However, the authors do not call attention to some important details. As shown in Table 3 of their article, there was no significant difference between the two study groups in the rate of death at 28 days, but there was a significant difference at 90 days. The former category included the time of insulin therapy and patients were mainly in the ICU, but the trial intervention was discontinued once the patients were discharged from the ICU. Whether these patients received intensive insulin outside the ICU is not clear, so the focus on insulin as the primary cause of death at 90 days among patients who were not in the ICU is not justified. There is no explanation about why more patients in the intensive-control group than in the conventional-control group were treated with corticosteroids.

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TO THE EDITOR: The NICE-SUGAR trial was highly anticipated by endocrinologists and intensivists alike, and it contributes new data on the subject of "tight" glycemic control in the ICU. Unlike the Leuven investigators,[1,2] the NICE-SUGAR investigators did not find a mortality benefit with intensive glucose control.

The differences between the studies were thoughtfully reviewed in the accompanying editorial.[3] However, one difference that is worth noting is that the patients were fed differently in the studies. Indeed, in the Leuven studies, patients received up to 30 kcal per kilogram of body weight, which would be at or above the basal energy expenditure (according to the Harris–Benedict equation), whereas in the NICE-SUGAR trial, patients received significantly fewer kilocalories. Patients who weighed 80 kg received 2400 kcal in the former studies, whereas in the latter study, such patients received about half that amount. Therefore, caloric intake itself may partially explain some of the discrepancies in the results, independently of actual glycemic status. Indeed, many investigators have long wondered whether the benefit of aggressive insulin use in the Leuven studies was directly related to the glycemic control or whether this approach merely counteracted the effects of higher caloric intake.

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TO THE EDITOR: In the NICE-SUGAR trial, the intensive-control group differed from the con-

ventional-control group not only with respect to blood glucose levels but also in terms of corticosteroid therapy. It is plausible that the patients who were treated with corticosteroids were severely ill or had more corticosteroid-related adverse effects. The use of corticosteroids was probably not associated with randomization to intensive glucose control, since the median time from randomization to commencement of corticosteroid treatment was 0 days (interquartile range, 0 to 1) in both groups (P=0.34). Furthermore, the safety of corticosteroids in patients admitted to an ICU is uncertain. In the randomized, controlled Medical Research Council CRASH (Corticosteroid Randomization after Significant Head Injury) trial (Current Controlled Trials number, ISRCTN74459797),[1] the risk of death was higher in the corticosteroid group than in the placebo group. In the present study, were the excess deaths due to a need for corticosteroid treatment or to the adverse effects of this therapy, or were they truly due to adverse effects of the intensive glucose-control intervention?

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1. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury — outcomes at 6 months. Lancet 2005;365:1957-9.

TO THE EDITOR: Insulin can modify the hemodynamic effects of beta-blockade.[1] Could this modification explain the discrepancies between the results reported by Finfer et al. and those reported by Van den Berghe et al.?[2] A majority of the patients in the study by Van den Berghe et al. had undergone cardiac surgery, and it is likely that they received beta-blockers preoperatively, postoperatively, or both. Finfer et al., in contrast, studied a mixed group of ICU patients, and only some of them would be expected to have received beta-blockers.

Thus, the beta-blockade would have been modified by insulin in only a minority of the patients in the intensive-control group, and the discrepancies in the results of the studies might not be related to glucose levels at all but rather to the insulin dose in patients who received beta-blockade. This issue should be clarified by performing a subgroup analysis according to the use or nonuse of beta-blockers.

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THE AUTHORS REPLY: Van den Berghe et al., Pei and Yi, Khoo and Olsen, Mohammedi et al., and Hallas speculate on the possible causes of the increased mortality among patients assigned to intensive glucose control in the NICE-SUGAR study. They variously suggest that the increased mortality could be due to treatment with corticosteroids, an interaction with beta-adrenergic blockers, inaccurate blood glucose measurement, large fluctuations in blood glucose levels, hypocaloric feeding, undetected hypoglycemia, hypokalemia, or an imbalance between the two groups of the study with regard to withdrawal of active treatment. Unfortunately, defining the mechanism by which intensive glucose control might affect mortality was beyond the scope of our large, pragmatic effectiveness study.

The increased use of corticosteroids in patients assigned to intensive glucose control is intriguing and is being investigated further. The most common stated indication for corticosteroid treatment was "septic shock," and the doses administered were far smaller than those used in the CRASH trial.[1] Current evidence does not convince us that low-dose corticosteroid therapy is harmful in critically ill patients. We disagree with the suggestion by Van den Berghe et al. that withdrawal of care was early and unbalanced: the study treatment was discontinued because of the institution of palliative care in 3.8% of patients in both groups of our study. We do agree that more accurate systems for blood glucose measurement are required. The questions of whether more accurate blood glucose measurement can make intensive glucose control safe and beneficial should be addressed in another large trial. To be credible, such a trial should be conducted in multiple centers and in patients receiving nutrition by both the enteral and parenteral routes. Braithwaite suggests that the NICE-SUGAR study

should renew enthusiasm for techniques that will minimize the risk of iatrogenic hypoglycemia; we suggest that such techniques, if affordable, would be welcome regardless of the results of our trial.

Van den Berghe and colleagues describe the feeding practices of the 42 ICUs in our study in which there was a clear preference for enteral nutrition as being "hypocaloric." However, other commentators, including Khoo and Olsen, suggest that the patients in the Leuven studies were overfed,[2] raising the possibility that the benefit of intensive glucose control that was apparent in the Leuven studies accrues by counteracting the adverse effects of overfeeding. In truth, the optimal quantum of nutrition for critically ill patients is unknown, and rather than address these issues by stating and restating entrenched opinions that are unsupported by high-quality data, we should conduct large, methodologically sound multicenter trials so that we can provide the best and most appropriate nutrition for our patients.

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Racial Differences in Heart Failure

TO THE EDITOR: It is not known whether concentric hypertrophy is a common precursor to systolic dysfunction in human hypertensive heart disease.[1-3] Bibbins-Domingo et al. (March 19 issue)[4] report that increased left ventricular mass was associated with incident heart failure in young adults (18 to 30 years of age at baseline) in bivariate models. However, they do not report whether the increased left ventricular mass was secondary to left ventricular dilation or wall thickening and whether patients with hypertrophy in whom heart failure developed had a preserved or a reduced ejection fraction. In an elderly cohort, eccentric but not concentric hypertrophy was associated with the development of a reduced left ventricular ejection fraction.[5] Therefore, it would be informative if the authors could report what fraction of patients with hypertrophy (overall and separately for concentric and eccentric hypertrophy) had systolic heart failure (with a reduced left ventricular ejection fraction or dilated cardiomyopathy at autopsy), as well as the hazard ratios associated with concentric hypertrophy and with eccentric hypertrophy for incident heart failure (overall and for systolic heart failure) in bivariate and multivariate models.

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THE AUTHORS REPLY: In our study, we found that most black patients with left ventricular hypertrophy in whom heart failure subsequently developed had eccentric, not concentric, hypertrophy, consistent with what Drazner and his colleagues have observed in older cohorts. The limited number of end points in our analysis precluded more detailed exploration of this association in the published manuscript. Analyses of the sort Drazner proposes are currently under way with the expanded number of patients with heart failure in our study.

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