THE ENDOCRINE SOCIETY

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The Endocrine Society Statement to Providers on the Report Published in the *New England Journal of Medicine* on NICE-SUGAR

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The NICE-SUGAR study, published in today's New England Journal of Medicine[1], reports on mortality in 6000 critically ill hyperglycemic patients randomly assigned to either tight control of blood sugar (target blood sugar of 80-108 mg/dl with an achieved mean-weighted glucose of 115 mg/dl) or looser control of blood sugar (target blood sugar of 144-180 mg/dl with an achieved mean-weighted glucose of 144 mg/dl) while they were in the intensive care unit. This multi-center, international study's key conclusion was that the absolute mortality rate at 90 days was actually 3% higher (28% vs. 25%) in the tight control group (829/3010) than in the looser control group (751/3012) which represents a 10% increase in relative mortality in the tight control group. This difference was primarily a result of more cardiovascular deaths in that group.

The Endocrine Society commends the NICE-SUGAR investigators for producing an important and provocative addition to the medical literature and draws the following conclusions and recommendations from their data. First, near-normalization of blood sugar does not clearly improve outcomes in all critically ill hyperglycemic ICU patients, and there is even a suggestion that such an approach may worsen outcomes. Second, looser control of hyperglycemia, i.e., target blood glucose of 144-180 mg/dl, is a reasonable, and perhaps preferable, option in this particular group of very sick patients. Third, it is essential to assess clinically meaningful outcomes, such as mortality, as well as surrogate or intermediate endpoints, such as blood sugar level, in studies of diabetes treatment as the NICE-SUGAR study has done; improvement of blood sugar control may not always translate to better clinical results.

Finally, the rush to deploy difficult and resource-intensive protocols in ICU's may be premature until there is a better understanding of the reasons that the NICE-SUGAR results differ so markedly from those of an earlier study by Van den Berghe et al. [2], which showed that tight control of blood sugar in critically ill hyperglycemic patients seemed to improve outcomes. There are certainly differences in study design and target patient populations between these two studies, and the situation is further clouded by van den Berghe's failure to replicate the results of her original study, which was done in surgical patients, in a subsequent study of critically ill medical patients.[3]

Close analysis of these study differences, including examination of the results in various sub-groups, may give rise to important questions that need to be answered by further studies. For example, are outcomes after tight glucose control the same in those with pre-existing diabetes as in those without it? Does the number or severity of hypoglycemic episodes, or some other aspect of tight glucose control, impair the future counter-regulatory and autonomic nervous system responses to hypoglycemia in this patient

population? What is the temporal relationship of hypoglycemia to death? Would the use of continuous glucose monitoring improve outcomes?

Aggressive outpatient management of hyperglycemia has been the hallmark of diabetes care for almost two decades since the DCCT[4] and UKPDS[5] studies showed reduced microvascular complications with such an approach. Potential benefits of tight glucose control in reducing macrovascular complications and death have been more difficult to demonstrate, with recent studies (ACCORD[6], ADVANCE[7], and VADT[8]) showing that such aggressive management of hyperglycemia can be associated with substantial risks and/or few benefits.

The Endocrine Society believes that we have entered an era of more nuanced and patient-appropriate recommendations as a result of these recent large, well-done outpatient and inpatient studies. We believe physicians should individually tailor their approach to glycemic control in their ICU patients, perhaps targeting glucose values between 144-180 mg/dl, until we better understand the reasons for these somewhat counterintuitive findings.

Founded in 1916, The Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones, and the clinical practice of endocrinology. Today, The Endocrine Society's membership consists of over 14,000 scientists, physicians, educators, nurses and students in more than 80 countries. Together, these members represent all basic, applied, and clinical interests in endocrinology. The Endocrine Society is based in Chevy Chase, Maryland. To learn more about the Society, and the field of endocrinology, visit our web site at www.endo-society.org

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