Tight Glycemic Control in Critically Ill Patients Reply

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Tight Glycemic Control in Critically Ill Patients

To the Editor: Recently published trials[1,2] of tight glycemic control in critically ill patients have documented lack of treatment benefit and frequent severe hypoglycemia. The NICE-SUGAR trial raised the question of potential treatment-related harm and also documented significant hypoglycemia.[3] The COIITSS Study[4] evaluated intensive insulin therapy in critically ill patients with sepsis who were treated with glucocorticoids and reported a high incidence of hypoglycemia (16.4% vs 7.8% in the conventional treatment group) without apparent benefit. These large complex multicenter trials that evaluated insulin therapy during critical illness consistently demonstrated high rates of hypoglycemia with tight insulin therapy. However, they did not investigate the possibility of identifying patient subpopulations at increased risk for treatment-related hypoglycemia.

Control of hyperglycemia during critical illness has become a standard of care. Although optimal glucose targets and protocols continue to be examined, hypoglycemia is a recurrent complication reported in all key clinical trials. Identifying which patients are at increased risk for hypoglycemia may improve patient safety. A factor that may influence the risk and benefit of insulin therapy is prehospital glycemic status. The COIITSS study and previous trials tended to treat critically ill patients with hyperglycemia as a single cohort, yet these patients are a heterogeneous population of individuals with known diabetes, with prediabetes, and with no prior history of a disorder of glucose metabolism. Multicenter randomized trials have not considered prehospital glycemic status as an important variable that may affect hypoglycemia risk during treatment. Defining patient characteristics better may reduce complications of treatment and maximize benefit.

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In Reply: Since the 2001 study by van den Berghe et al,[1] practices in the intensive care unit have been altered toward avoiding persistent hyperglycemia. Since then, our study and others[2] have provided additional evidence suggesting that normalization of blood glucose levels should not be a target, at least with tools available at the bedside. As pointed out by Dr Castellanos and colleagues, hypoglycemia may be the price of blood glucose control. In the COIITSS trial, a total of 62 patients experienced a total of 108 episodes of hypoglycemia, ranging from 1 to 10 per patient. Of these patients, 51 were hypoglycemic on a single day, 10 had hypoglycemic episodes on 2 distinct days, and 1 patient had this complication occurring over 4 days. These findings suggest that hypoglycemia may be predominantly a complication of the initiation of intensive insulin therapy. In the COIITSS trial, this complication was not associated with an increased risk of death.

At day 7, the cumulative incidence of first hypoglycemia was 12.3%, with a 7-day cumulative incidence of death free of hypoglycemia of 15.0%. Unfortunately, glycosylated hemoglobin levels were not recorded in the COIITSS trial, precluding an accurate assessment of the role of underlying diabetes mellitus in the risk of occurrence of hypoglycemia.

We assessed factors predictive of the cumulative incidence of first hypoglycemia, taking into account death prior to such an event as a competing risk. Univariable analyses used the Gray test based on the cumulative incidence approach, while multivariable analysis used the Fine and Gray model for subdistribution hazards.[3] All analyses were performed at the 5% significance level from the cmprsk package in R version 2.10.1 (http://www.r-project.org). Among baseline variables, randomization to the tight glucose control group and blood glucose levels at or above 190 mg/dL (to convert to mmol/L, multiply by 0.0555) were the only variables independently associated with an increased cumulative incidence of hypoglycemia, whereas a

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Simplified Acute Physiology Score (SAPS) II of 60 or more had a protective association (TABLE). However, only the SAPS II was independently associated with a higher cumulative incidence of death prior to hypoglycemia, with an estimated subdistribution hazard ratio of 1.82 (95% confidence interval, 1.14-2.90). This suggests that the sickest patients died before hypoglycemia could occur, which would explain the decreased incidence of such an event in these patients.

Table. Predictive Factors for the Cumulative Incidence of First Hypoglycemia

Variable	Subdistribution Hazard Ratio (95% CI)	
	Univariable Analysis	Multivariable Analysis[a]
Age, y		
<65	1 [Reference]	
≥65	0.70 (0.43-1.16)	
Sex		
Male	1 [Reference]	
Female	1.10 (0.66-1.83)	
Time in hospital prior to ICU admission, d		
0	1 [Reference]	
>0	0.75 (0.45-1.28)	
Time in ICU prior to randomization, d		
≤1	1 [Reference]	
>1	0.74 (0.39-1.41)	
Physiology scores		
SAPS II		
<60	1 [Reference]	1 [Reference]
≥60	0.52 (0.31-0.87)	0.53 (0.32-0.88)
SOFA		
<11	1 [Reference]	
≥11	0.90 (0.55-1.46)	
Type of infection		
Community acquired	1 [Reference]	
Hospital acquired	1.04 (0.63-1.71)	
Blood glucose levels, mg/dL		
<10.5	1 [Reference]	1 [Reference]
≥10.5	2.16 (1.27-3.65)	2.20 (1.30-3.71)
Cumulative insulin dose on day 1, IU/d		
<51	1 [Reference]	
≥51	0.72 (0.42-1.22)	
Lactate levels, mg/dL		
<2.8	1 [Reference]	
≥2.8	1.06 (0.64-1.75)	
Mechanical ventilation on day 1		
No	1 [Reference]	
Yes	1.03 (0.49-2.17)	
Renal replacement therapy		
No	1 [Reference]	
Yes	0.73 (0.36-1.46)	
Randomization group		
Conventional glucose control	1 [Reference]	1 [Reference]
Intensive insulin therapy	2.19 (1.29-3.70)	2.06 (1.23-3.47)

Abbreviations: CI, confidence interval; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.
SI conversion factors: To convert glucose to mmol/L, multiply by 0.0555; to convert lactate to mmol/L, multiply by 0.111.
[a] Only variables with statistically significant associations in the univariable analyses were included in the multivariable model.

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Trends in Obesity and Extreme Obesity Among US Adults

To the Editor: Using data from the National Health and Nutrition Examination Survey (NHANES), Dr Flegal and colleagues[1] documented that, based on body mass index (BMI), the prevalence of overweight (BMI, 25-<30) and obesity (BMI ≥30) among adults in the United States in 2007-2008 was 68%. Additionally, a recent article[2] suggested that another 10% of the US population may have normal weight obesity, defined as a high percentage of body fat despite a normal BMI (<25).

Almost 80% of US adults may be carrying excess body fat, which may predispose them to chronic health problems. As the authors noted, extreme obesity is particularly important, given the association with increased mortality that is largely attributable to cardiovascular disease, diabetes mellitus, and malignancy. Therefore, we are particularly interested in the prevalence of grade 2 (BMI, 35-<40) and grade 3 (BMI ≥40) obesity (8.5% and 5.7%, respectively). It would be helpful to have information about changes in grade 2 and grade 3 obesity prevalence since 1999. It is possible that, even as overall obesity rates have plateaued, severe obesity rates have continued to increase.

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In Reply: In response to Dr Main and colleagues, we provide a TABLE that shows the age-standardized prevalence of grade 2 obesity (BMI of 35-<40), grade 3 obesity (BMI of