

to tease out what, if any, benefit accrued from strict glucose control as opposed to other changes in ICU management over time.

In contrast, recent studies have demonstrated no mortality benefit and more adverse outcomes with strict glucose control (6,7). One multicenter, randomized controlled trial conducted in 18 centers using treatment protocols based on the trial by Van den Berghe (2) was stopped early, because there was no significant mortality difference and the intensive-therapy group experienced higher rates of severe hypoglycemia than the conventional-therapy group (17.0% vs. 4.1%, $p < 0.001$), higher rates of serious adverse events (10.9% vs. 5.2%, $p = 0.01$), and a trend to longer ICU stays (6). Another multicenter, randomized controlled study conducted in 7 countries and in 21 ICUs was halted prematurely, because of safety concerns and an increased rate of hypoglycemia and a trend toward higher mortality in the intensive-therapy group (7). In another cohort study of 10,456 ICU patients, there was also a trend toward higher mortality with strict glucose control (8). Finally, a meta-analysis of 29 randomized controlled trials of 8,432 ICU patients demonstrated no hospital mortality benefit of strict glucose control and no significant difference in mortality when stratified by glucose goal, but there was a 5-fold increased risk of hypoglycemia, leading the authors to conclude, "tight glucose control is not associated with significantly reduced hospital mortality but is associated with an increased risk of hypoglycemia" (3). Taken together, one is left to question the purported "beneficial" effects of strict glucose control in the ICU setting over the potential for significant harm incurred by hypoglycemia.

***John R. Kapoor, MD, PhD**
Roger Kapoor, MD, MBA

*Division of Cardiology
Stanford University
300 Pasteur Drive
Stanford, California 94305
E-mail: jkapoor@stanford.edu

doi:10.1016/j.jacc.2009.03.059

REFERENCES

- Ceriello A, Zarich SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. *J Am Coll Cardiol* 2009;53 Suppl:S9-13.
- Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;345:1359-67.
- Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008;300:933-44.
- Kreymann KG, Berger MM, Deutz NE, et al. ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr* 2006;25:210-23.
- Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004;79:992-1000.
- Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.
- Devos P, Preiser J, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the glucontrol study. *Intensive Care Med* 2007;33 Suppl 2:S189.
- Treggiari MM, Karir V, Yanez ND, Weiss NS, Daniel S, Deem SA. Intensive insulin therapy and mortality in critically ill patients. *Crit Care* 2008;12:R29.

Reply

I thank Drs. Kapoor and Kapoor for their letter concerning our recent paper (1). They question the evidence that a strict glycemic control might be beneficial in cardiac intensive care unit.

First of all, I would like to underline that the available evidence has been considered strong enough to induce the American Heart Association to suggest controlling hyperglycemia during acute coronary syndrome (2).

Furthermore, certainly the letter has been written before the publication from Kosiborod et al. (3), who definitively show—following 7,820 patients—that glucose normalization after admission is associated with better survival in hyperglycemic patients hospitalized with acute myocardial infarction whether or not they receive insulin therapy.

My worry is that we are still debating about the usefulness of lowering glucose, although evidence is forthcoming suggesting that this might not be enough, because the "variability of glucose" is also probably involved in worsening the prognosis of patients in the critical care setting (4,5).

The hypothesis that maintaining the level of glycemia under very strict control would be relevant in any clinical setting is, in my opinion, stressed by the recent evidence that in normal people glycemia is always maintained in a very narrow range of 70 to 140 mg/dl (6). One can argue that, if the human body spends so much energy to maintain the blood glucose level under so strict a range, it is because otherwise it could be deleterious. So, in my opinion—while waiting for more detailed, ad hoc designed studies, particularly intervention studies—it is already the time for a step ahead and to raise attention to this new therapeutic challenge not only for diabetes but also for a number of critical conditions.

***Antonio Ceriello, MD**

*Warwick Medical School
Clinical Science Research Institute
Clinical Science Building
University Hospital
Walsgrave Campus
Clifford Bridge Road
Coventry CV2 2DX
United Kingdom
E-mail: antonio.ceriello@warwick.ac.uk

doi:10.1016/j.jacc.2009.03.058

REFERENCES

- Ceriello A, Zarich SW, Testa R. Lowering glucose to prevent adverse cardiovascular outcomes in a critical care setting. *J Am Coll Cardiol* 2009;53 Suppl:S9-13.
- Deedwania P, Kosiborod M, Barrett E, et al., American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008;117:1610-9.
- Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucose normalization and outcomes in patients with acute myocardial infarction. *Arch Intern Med* 2009;169:438-46.
- Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006;105:244-52.
- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008;36:3008-13.
- Mazze RS, Strock E, Wesley D, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technol Ther* 2008;10:149-59.