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Sir: Preiser et al. [1] are to be congratulated on their randomized controlled multi-center trial on tight glycemic control (TGC) in critically ill patients. This trial adds to our knowledge of glucose control in intensive care units, but also poses a fascinating dilemma. While we need confirmation of the effects of TGC observed in Leuven, we notice at the same time that the Leuven trials have

already changed the standard of care against which we compare TGC.

First, from this trial we learn that the intensive care community is increasingly practicing (some sort of) glycemic control. Undeniably, all randomized controlled trials focusing on TGC [2–7], including this new trial [1], show a change in standard care: “control” or “conventional therapy” patients are more and more treated with insulin and consequently have lower (mean or median) blood glucose levels (Fig. 1). This at least suggests that the intensive care community is realizing that glucose should not be seen as an innocent bystander during critical illness and that lowering blood glucose levels may have the potential to prevent injury to already threatened vital organs.

This change in standard care, however, forced Preiser et al. and other investigators to face at least one significant problem. The observed diversity in composition of the “control” or “conventional” groups makes the successive randomized controlled trials fundamentally different from the very first trial of TGC [2]. Indeed, these trials were all executed in the

“flattened” part of the observational blood glucose level–mortality risk curve [8]. The hypothesized effect size in the trial by Preiser et al. (4%, absolute mortality reduction, similar to what was observed in the first randomized controlled trial [2]) was therefore far too optimistic: according to the pooled analysis of the original two first randomized controlled trials [9], the absolute reduction in mortality that could have been expected from further lowering blood glucose levels as compared with the “improved” standard care level was much lower. This would mean that tens of thousands of patients are needed to show this effect in a multi-center setting.

While the increased rate of hypoglycemia in the TGC control group was not considered as a safety concern (opposite to information given to the intensive care community on several conference occasions), the lack of difference regarding blood glucose control was a reason to stop the study prematurely. This definitely left us with an underpowered study. Indeed, this study does not help us in making an overall recommendation regarding the optimal target for blood glucose control.

Consequently, any advice regarding the blood glucose control target remains pragmatic: we all should assess whether hypothesized benefits were realistic, whether statistical power was sufficient, whether the targets were reached, and finally whether the levels of glycemic control diverged relevantly in the successive randomized controlled trials. If the above criteria are met, clinicians should determine how their own patients compare to the patients in these trials and decide which is the best target for blood glucose control in their setting.

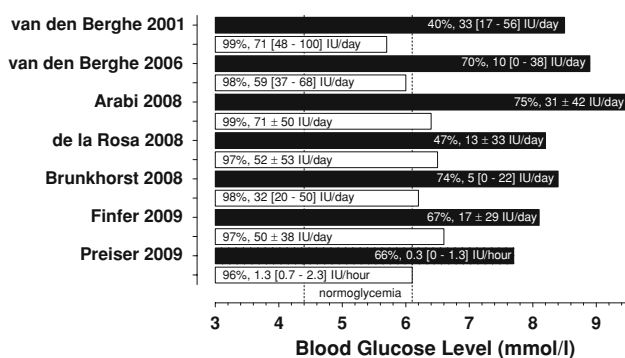


Fig. 1 Blood glucose levels, percentage of patients treated with insulin and insulin dose (mean ± standard deviation or median [interquartile range] in the control or conventional group (filled bars) and tight glycemic control group (open bars) of seven randomized controlled trials

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References

- Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chiolerio R (2009) A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med* 35:1738–1748
- Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359–1367
- Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R (2006) Intensive insulin therapy in the medical ICU. *N Engl J Med* 354:449–461
- Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH (2008) Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med* 36:3190–3197
- De La Rosa GDC, Donado JH, Restrepo AH, Quintero AM, Gonzalez LG, Saldarriaga NE, Bedoya M, Toro JM, Velasquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA (2008) Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial. *Crit Care* 12:R120
- Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 358:125–139
- Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hebert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ (2009) Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 360:1283–1297
- Bagshaw SM, Egi M, George C, Bellomo R (2009) Early blood glucose control and mortality in critically ill patients in Australia. *Crit Care Med* 37:463–470
- Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, Bouillon R, Schetz M (2006) Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 55:3151–3159

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