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CORRESPONDENCE

# Unsettled issues regarding intensive insulin therapy in the intensive care unit

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With interest we read the editorial by Preiser [1] outlining the future of blood glucose control in critically-ill patients following publication of the NICE-SUGAR trial [2]. We would like to raise several issues that intensivists should consider first before they change their approach to blood glucose control.

First, while NICE-SUGAR was planned to compare a strategy aiming for normoglycaemia (blood glucose level of 4.5-6.0 mmol/L) with standard care (blood glucose levels of < 10 mmol/L) as did the two original randomized controlled trials from Leuven [3,4], instead NICE-SUGAR compared something else. In the NICE-SUGAR control group, blood glucose control was far better than in the two original trials. Obviously, standard care has changed over the past decade. This difference may in part explain the fact that in the NICE-SUGAR control group the mortality that was observed (25%) was lower than expected (30%); patients were probably already benefiting from some sort of blood glucose control. But more importantly, this diversity makes NICE-SUGAR fundamentally different from the two original trials. Indeed, NICE-SUGAR was executed in the "flattened" part of the observational blood glucose level-mortality risk curve [5], and the hypothesized effect size in NICE-SUGAR (3-4% absolute reduction in risk of death) was therefore far too optimistic. The absolute reduction in mortality that could have been expected from further lowering blood glucose levels compared with the standard care level, was only roughly 1% [6].

Second, in the NICE-SUGAR intervention group, mean blood glucose levels reached normoglycaemia only two days after admission. The reason for this lack of blood glucose control in the first days remains to be elucidated. But when time to target is so long, the time window for prevention of toxicity of hyperglycaemia may have passed and irreversible damage may already have occurred [7]. This phenomenon has also been suggested by the pooled analyses [6] of the two original trials from Leuven [3,4].

Third, while hospital mortality in NICE-SUGAR was not affected by blood glucose control, mortality rate diverged after hospital discharge. It is difficult to appreciate that this truly resulted from differences in blood glucose control, which to the best of our understanding, was only performed in the intensive care unit. We are puzzled about the late mortality in NICE-SUGAR study group. We suggest the following issue is a potentially harmful factor in the intervention algorithm of NICE-SUGAR. This algorithm dictated administration of 5 or 10 grams of intravenous dextrose at blood glucose levels < 3.4 or < 2.5 mmol/L, respectively. This must certainly often have resulted in overcorrection, although not reported by the NICE-SUGAR investigators. When following the Leuven algorithm, insulin was to be stopped and adequate nutritional intake was to be checked when blood glucose levels were between 2.2-3.3 mmol/L. Only when blood glucose levels dropped < 2.2 mmol/L the Leuven algorithm dictated administration of 10 grams of intravenous dextrose [3]. Why do we consider this so important? Preclinical studies suggest that neuronal tissue does not suffer from oxidative stress during severe hypoglycaemia itself, but during so-called glucose reperfusion. When various doses of glucose were administered to hypoglycaemic rats, a dose-dependent level of oxidative stress and neuronal death was observed [8]. This "glucose reperfusion" phenomenon may be analogous with ischaemia-reperfusion damage. We suggest that it is the too-rapid and high rise of blood glucose levels from hypoglycaemia that may be harmful, and not hypoglycaemia itself.

Finally, we consider it surprising that Preiser concludes with the recommendation to aim for an "intermediate blood glucose level since it is safe and effective", when he is in fact referring to blood glucose levels reached in the NICE–SUGAR study group. If we are to believe the results from NICE–SUGAR - which we do not - such blood glucose levels surely cannot be considered safe?

May we suggest an alternative view on the future of blood glucose control? The currently available evidence from six consecutive trials on blood glucose control in critically ill patients [2-4,9-11], does not allow overall recommendations to be confidently made. Indeed, the question of one optimal target for blood glucose control in critically-ill patients remains unanswered. We advise the assessment of how realistic the hypothesized benefit in the trials is, the assessment of the adequacy of the statistical power of the trials, the assessment of the level of evidence of the trials, the assessment of whether the pre-set targets were reached, and finally the assessment of the relevant divergence of the levels of glycaemic control If the above criteria are all met satisfactorily, clinicians should determine how comparable the patients in the different trials are to their own, and decide on what is their best target for blood glucose control.

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