# Blood glucose control in the ICU: how tight?

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Fifteen years after the first randomized controlled trial (RCT) on tight blood glucose control (TGC) in the intensive care unit (ICU), the exact target of blood glucose control remains a matter of debate, especially since subsequent RCTs have found divergent results (1-4). Indeed, whereas the Leuven RCTs found that targeting normal for age fasting blood glucose levels with insulin clearly reduced short-term morbidity and mortality in critically ill adults and children (1-3), with the benefit maintained on the long term (5,6), the largest multicenter RCT (NICE-SUGAR) found excess mortality (4), which was attributed to an increased risk of severe hypoglycemia (7). One crucial difference that may explain this apparent contradiction is the different blood glucose target in the control group (8). Indeed, in the Leuven studies, a tight blood glucose target (80–110 mg/dL for adults, 60–100 mg/dL for children and 50–80 mg/dL for infants) was compared to a liberal approach (only administering insulin when blood glucose exceeded 215 mg/dL and stopping insulin as soon as levels dropped below 180 mg/dL). In contrast, in NICE-SUGAR, the tight target in the intervention group was compared to a lower, intermediate blood glucose target in the control group (<180 mg/dL). Hence, compared to this lower target, further lowering blood glucose appeared to be harmful, which could indeed be explained by a higher incidence of hypoglycemia. Therefore, most current guidelines recommend to target blood glucose levels <180 mg/dL in critically ill patients (9,10). However, no large, adequately powered RCT has investigated whether this intermediate target is indeed superior to more liberal blood glucose control. In addition, although maximal efforts should be performed to prevent hypoglycemia, several observational studies failed to detect a harmful effect of an iatrogenic and short-lasting episode of hypoglycemia (6,11-13).

To provide more evidence with regard to the optimal blood glucose target in intensive care, Yatabe *et al*. performed a network meta-analysis including RCTs that compared two different blood glucose targets in adult critically ill patients (14). In contrast to classic pair-wise meta-analyses, network meta-analyses are able to compare more than two treatments for a given condition (15). In addition, by combining results from direct comparisons and by using a common comparator, it can also indirectly estimate a difference between two treatments for which no—or only limited – head-to-head comparisons exist. Hence, Yatabe *et al*. categorized the study arms from the included RCTs into four different treatment categories, going from tight blood glucose control (<110 mg/dL), over intermediate (110–144 and 144–180 mg/dL) to liberal blood glucose control (>180 mg/dL) (14). In network meta-analysis, there was no significant difference in the risk of hospital mortality or infections between all comparisons. In contrast, the risk of hypoglycemia increased with stricter levels of blood glucose control. For every comparison, the higher target of the two was associated with less hypoglycemia. Only the comparison between the 144–180 and >180 mg/dL target revealed no significant

difference with regard to hypoglycemia. Ranking analysis revealed that the 110–144 and144–180 mg/dL target had the highest probability of being the best treatment with regard to mortality, whereas the >180 mg/dL target had the lowest probability. In addition, the 110–144 mg/dL target had the highest probability of being the best treatment with regard to the risk of infections. In contrast, ranking analysis favored the >180 mg/dL target with regard to the risk of hypoglycemia.

Although Yatabe *et al*. acknowledge a considerable level of uncertainty, they suggest that intermediate blood glucose levels (110–180 mg/dL) may be most optimal for adult critically ill patients, with 144–180 mg/dL probably being the preferred target, based on a lower risk of hypoglycemia than 110–144 mg/dL. The authors performed several sensitivity analyses, which revealed no difference in studied subgroups of patients (different ICU settings, proportion of diabetes patients, severity of illness as judged by the observed mortality). In addition, they found no difference when the analysis was repeated with the actually achieved blood glucose levels instead of the blood glucose target. Recently, a second network meta-analysis with a slightly different methodology found similar results and concluded that intermediate blood glucose levels (140–180 mg/dL) may be preferred (16).

The authors should be commented for performing this important study. However, interpretation of the results is difficult. Indeed, the conclusion that blood glucose levels <180 mg/dL are preferred with regard to mortality risk is only based on ranking analysis, as the individual comparisons were not significant. Alternatively, one could conclude that TGC only increases the risk of hypoglycemia and offers no significant mortality benefit. For a correct interpretation, it is important to understand the methodology and the assumptions involved in network meta-analysis. As in pairwise meta-analysis, one crucial assumption is that there are no other methodological differences between the trials apart from the difference that is studied (15). Yet, apart from differences in blood glucose target, there are several other important methodological differences between the included RCTs that could also explain the divergent results. These differences were not taken into account and include the accuracy of the glucose measurement, the insulin infusion protocol and the feeding strategy. In the pioneer studies on TGC showing benefit, accurate blood gas analyzers were used and blood glucose was measured on arterial blood (1-3), in contrast to several subsequent studies including NICE-SUGAR, in which capillary measurements and inaccurate glucometers were allowed (4,17). Inaccurate blood glucose measurements and an unvalidated insulin infusion protocol may have led to a poor success in reaching the target range in the intervention group of NICE-SUGAR (<50% of measurements within target) and to an increased risk of hypoglycemia, both detected and undetected (8,17). In contrast, in the Leuven studies, ~70% of measurements were within target. On the other hand, unlike in NICE-SUGAR, patients in the Leuven studies received early parenteral feeding as part of standard of care. Recently, two large multicenter RCTs have shown that this feeding strategy, which iatrogenically increases the risk of hyperglycemia, is harmful (18,19). There are no adequately powered RCTs that have investigated the efficacy and safety of TGC, when provided with adequate tools, in a context of withholding early parenteral nutrition. Hence, the above mentioned methodological differences between RCTs—other than the different blood glucose target in the control group—may equally explain the divergent results between the different RCTs. The $I^2$ value, in general between 30–50%, with one value up to 86% actually supports important heterogeneity between the included trials (20).

In summary, the network meta-analysis aimed at identifying an optimal blood glucose target for adult critically ill patients, but failed to reliably identify a target. The main limitation of the current study is the failure to correct for other methodological differences between the included RCTs, including the used glucose monitoring tools, the insulin infusion protocol and the feeding strategy. Although the absence of a clear superiority of one specific target may mean that blood glucose control offers no clinical benefit, it could also mean that other methodological differences are more important in explaining the divergent results between RCTs on blood glucose control. Indeed, the $I^2$ value revealed important heterogeneity. Hence, the optimal blood glucose target remains unclear. The current meta-analysis opens perspectives for future RCTs that investigate the efficacy and safety of tight blood glucose control with the use of adequate monitoring tools and a validated glucose control algorithm in a context of withholding early parenteral nutrition. In the absence of new evidence, preventing severe hyperglycemia (>180 mg/dL) in all critically ill patients is supported by common sense.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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