The Optimal Glycemic Control in Patients with Diabetes in the ICU
Where Is the Sweet Spot?

The NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trial is one of the largest randomized controlled trials (RCTs) to determine the optimal target of acute glycemic control and showed that targeting a glucose concentration between 8 and 10 mmol/l (145–180 mg/dl) in critically ill patients reduced 90-day mortality, as compared with 4.5–6.0 mmol/l (81–109 mg/dl) (1). Thereafter, guidelines for acute setting suggested to maintain a blood glucose concentration below 10 mmol/L (180 mg/dl) (2, 3). In the NICE-SUGAR trial, the treatment effect did not significantly differ for patients with and without diabetes ($P = 0.60$) (1). In a combined Leuven trials analysis, patients with diabetes were the only subgroup not to benefit from intensive glucose lowering (4). However, a recent network analysis concluded that there is a lack of sufficient evidence to determine the optimal target of glucose concentrations in critically ill patients with diabetes (5).

Patients with premorbid hyperglycemia have a higher risk of hypoglycemia in the ICU and a stronger association between the occurrence of hypoglycemia during ICU stay and subsequent mortality (6). In addition, among acutely ill patients with premorbid hyperglycemia, higher mean glucose concentrations during ICU stay were associated with decreased hospital mortality compared with those within conventional range (7). This may generate the hypothesis that liberal glycemic control (i.e., higher glucose range than the conventional range of <180 mg/dl) might be optimal in patients with diabetes, especially those with premorbid hyperglycemia (8).

On the other hand, such a liberal glycemic control might have the potential to be harmful (9). One of the concerns of liberal glycemic control is the potential of increased risk of infection (10). Furthermore, there is a risk of glycosuria accompanied with liberal glycemic control, which may hinder optimizing intravenous blood volume. Finally, pooled datasets from two RCTs from the Leuven ICUs reported a nonsignificant trend of lowering the risk of critical illness-induced polyneuropathy in patients with diabetes (odds ratio, 0.62; $P = 0.25$) (4).

The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) multicenter RCT, conducted in patients with acute myocardial infarction and premorbid hyperglycemia (11), showed that liberal glycemic control (glucose 24 hours after randomization, 11.7 mmol/l [212 mg/dl]) increased 1-year mortality as compared with 9.6 mmol/l (174 mg/dl).

Considering the inconclusive and scarce evidence so far and an approximated diabetes incidence in the ICU of 25%, the issue of optimal glycemic control in patients with diabetes is relevant for daily clinical practice (8). Accordingly, the Surviving Sepsis Campaign points out the necessity of further research to determine the optimal glycemic control for different patient populations, including diabetes patients (3).

In this issue of the *Journal*, Poole and colleagues (pp. 874–882) report the results of the LUCID (Liberal Glucose Control in Critically Ill Patients with Preexisting Type 2 Diabetes) trial (12), a multicenter RCT to assess the effect of a liberal approach to glucose control, randomizing 434 critically ill patients with type 2 diabetes (DM2). In the LUCID trial, a liberal approach (target range; 10–14 mmol/l (180–252 mg/dL)) reduced the 28-day incidence of hypoglycemia (glucose <4 mmol/L (72 mg/dL)) from 18% to 5% when compared with a conventional target range of <10 mmol/L (180 mg/dL) (incidence rate ratio, 0.21; 95% confidence interval, 0.09 to 0.49; $P < 0.001$). There was no difference in other clinical outcomes, but 90-day mortality differed nonsignificantly with 29.5% in the liberal group versus 24.9% in the conventional group (4.6%; 95% confidence interval, −3.9% to 13.2%). Unfortunately, there was an HbA1c result available for only 75% of the patients, and a subgroup analysis of patients with an HbA1c of more than 7% did not provide additional insight, and patients were not stratified according to their HbA1c result. Furthermore, every center used their own protocol, an understandable pragmatic approach, but without a specific protocol in place for patients with DM2. The authors did perform an analysis into the heterogeneity between study sites and concluded that protocol-driven differences in blood glucose control between sites were highly unlikely.

The LUCID trial is the first to study this liberal approach in DM2 in a RCT in the ICU setting. The recent CONTROLING (Controle Individualisé de la Glycémie) trial (13) did compare a glycemic target based on admission HbA1c (individualized group) with a control group targeting <10 mmol/L (180 mg/dl). They included a little more over 30% of patients with DM2, and time-weighted average glucose was 8.8 mmol/L (158 mg/dl) ($n = 306$) in the individualized group versus 9.4 mmol/L (169 mg/dl) ($n = 296$) in the conventional group with DM2. There was no between-group difference in mortality. For comparison, the median glucose in the LUCID trial was 11.8 mmol/L (212 mg/dl) in the liberal group versus 9.3 mmol/L (167 mg/dl) in the group targeting <10 mmol/L (180 mg/dl). One could hypothesize that a liberal approach for a patient with DM2 and an HbA1c between 6% and 7% is potentially harmful when comparing this with a patient with admission HbA1c of 8%. In addition, perhaps mortality in patients with diabetes does not follow the well-known U-shaped curve (14), but there may be a more "stretched" curve as proposed by van den Berghe (15).

Hence, we are left with a well-performed study, clearly showing a reduction in hypoglycemia in patients with DM2 when using a liberal glucose target, but with a nonsignificant 90-day mortality increase in the liberal group of 4.6 percentage points. Although the LUCID study was not powered to detect any mortality differences, it is the first study specifically addressing patients with diabetes mellitus and with an unexpected higher mortality in the liberal group. It is difficult to

Supported by a Grant-in-Aid for Scientific Research (22K09093 to M.E.).

Originally Published in Press as DOI: 10.1164/rccm.202206-1045ED on June 6, 2022

ignore these results for future treatment targets. Considering this, we believe that it is too premature to implement the LUCID strategy in daily clinical practice. However, a subsequent trail studying the effect of a liberal approach on mortality in patients with DM2 patients is justified, taking admission HbA1c into consideration when choosing the glucose target and designing the trial. Probably there is not a one-size-fits-all approach, and a personalized approach may be the way forward also in patients with DM2. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Jeroen Hermanides, M.D., Ph.D.
Amsterdam University Medical Centers
Location AMC
Amsterdam, the Netherlands

Moritoki Egi, M.D., Ph.D.
Department of Intensive Care and Anaesthesiology
Kyoto University Hospital
Kyoto, Japan

References

1. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, *et al.*; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–1297.
2. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, *et al.* The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). *J Intensive Care* 2021;9:53.
3. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021;49: e1063–e1143.
4. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bruyninckx F, *et al.* Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes* 2006;55:3151–3159.
5. Yatabe T, Inoue S, Sakaguchi M, Egi M. The optimal target for acute glycemic control in critically ill patients: a network meta-analysis. *Intensive Care Med* 2017;43:16–28.
6. Egi M, Krinsley JS, Maurer P, Amin DN, Kanazawa T, Ghandi S, *et al.* Pre-morbid glycemic control modifies the interaction between acute hypoglycemia and mortality. *Intensive Care Med* 2016;42: 562–571.
7. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Taori G, *et al.* The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med* 2011;39:105–111.
8. Bellomo R. Acute glycemic control in diabetics. How sweet is oprimal? Pro: sweeter is better in diabetes. *J Intensive Care* 2018;6:71.
9. Egi M. Acute glycemic control in diabetics. How sweet is oprimal? Con: just as sweet as in nondiabetic is better. *J Intensive Care* 2018;6:70.
10. Rayfield EJ, Ault MJ, Keusch GT, Brothers MJ, Nechemias C, Smith H. Infection and diabetes: the case for glucose control. *Am J Med* 1982; 72:439–450.
11. Malmberg K, Rydén L, Efendic S, Herlitz J, Nicol P, Waldenström A, *et al.* Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. *J Am Coll Cardiol* 1995; 26:57–65.
12. Poole AP, Finnis ME, Anstey J, Bellomo R, Bihari S, Birardar V, *et al.*; LUCID Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG). The effect of a liberal approach to glucose control in critically ill patients with type 2 diabetes: a multicenter, parallel-group, open-label, randomized clinical trial. *Am J Respir Crit Care Med* 2022;206:874–882.
13. Bohé J, Abidi H, Brunot V, Klich A, Klouche K, Sedillot N, *et al.*; CONTROLe INdividualisé de la Glycémie (CONTROLING) Study Group. Individualised versus conventional glucose control in critically-ill patients: the CONTROLING study-a randomized clinical trial. *Intensive Care Med* 2021;47:1271–1283.
14. Siegelaar SE, Hermanides J, Oudemans-van Straaten HM, van der Voort PH, Bosman RJ, Zandstra DF, *et al.* Mean glucose during ICU admission is related to mortality by a U-shaped curve in surgical and medical patients: a retrospective cohort study. *Crit Care* 2010;14:R224.
15. Gunst J, De Bruyn A, Van den Berghe G. Glucose control in the ICU. *Curr Opin Anaesthesiol* 2019;32:156–162.

Deep Learning–based Classification of Fibrotic Lung Disease: Can Computer Vision See the Future?

Despite existing diagnostic criteria and guidelines for identifying and classifying fibrotic lung disease such as idiopathic pulmonary fibrosis (IPF) (1, 2), their diagnosis can be challenging. Current guidelines emphasize the role of high-resolution computed tomography (HRCT), and place particular importance on identifying the presence of underling usual interstitial pneumonia (UIP), which suggests a diagnosis of IPF (1). However, this approach is binary: it requires patients be classified based on the predominant pattern on HRCT, while in practice patients may have some evidence of UIP features but a different predominant disease pattern (1, 2). Clinically, current UIP diagnosis also relies on subjective readings of the HRCT that may vary from radiologist to radiologist (3). These issues are of particular concern because of the importance of UIP in identifying patients likely to have faster disease progression and worse prognosis (4–7). Thus, missed or inaccurate diagnosis has the potential to have significant clinical impact, and there has been great interest in

Supported by the NIH (T32HL007633) (B.C.) and the NIH (K08HL145118) (S.Y.A.).

Originally Published in Press as DOI: 10.1164/rccm.202206-1036ED on June 15, 2022