Tight versus liberal blood-glucose control in the intensive care unit: special considerations for patients with diabetes

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Stress hyperglycaemia, hypoglycaemia, and diabetes are common in critically ill patients and related to clinical endpoints. To avoid complications related to hypoglycaemia and hyperglycaemia, it is recommended to start insulin therapy for the majority of critically ill patients with persistent blood glucose concentrations higher than 10·0 mmol/L (>180 mg/dL), targeting a range of 7·8–10·0 mmol/L (140–180 mg/dL). However, management and evidence-based targets for blood glucose control are under debate, particularly for patients with diabetes. Recent randomised controlled clinical trials now challenge current recommendations. In this Personal View, we aim to highlight these developments and the important differences between critically ill patients with and without diabetes, taking into account the considerable heterogeneity in this patient group. We critically discuss evidence from prospective randomised controlled trials and observational studies on the safety and efficacy of glycaemic control, specifically in the context of patients with diabetes in intensive care units.

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Introduction

Diabetes, inpatient hyperglycaemia, and hypoglycaemia are common in hospital care and are associated with increased complications and mortality.[1] An ongoing debate addresses their management in the intensive care unit (ICU) setting.[1,2] Inpatient hyperglycaemia is defined by blood glucose concentrations exceeding 7·8 mmol/L (>140 mg/dL), whereas the definition of hypoglycaemia is more complex.[3] Additionally, the role of prehospital glycaemic control for inpatient management still needs to be defined.[2] Interest in controlling inpatient hyperglycaemia through intensive insulin therapy (IIT) increased after the 2001 publication of the LEUVEN randomised controlled trial (RCT) that mainly included critically ill cardiac surgery patients, reporting significantly reduced mortality.[4] However, subsequent single-centre and multicentre RCTs were less conclusive, with the majority unable to substantiate the previous findings, or (in the case of the VISEP trial[5]) even being prematurely terminated due to safety concerns. The main reason discussed for the observed discrepancies was the high incidence of hypoglycaemic episodes with IIT, whereas other proposed explanations included, for instance, differences in early parenteral nutrition. The multicentre, international RCT NICE-SUGAR[6] finally related IIT to increased 90-day mortality, ultimately leading to adapted guidelines.[2] Accordingly, to avoid both complications related to hyperglycaemia and hypoglycaemia, it is currently recommended to initiate insulin therapy for ICU patients with persistent blood glucose concentrations over 10·0 mmol/L (>180 mg/dL), targeting a range of 7·8–10·0 mmol/L (140–180 mg/dL) for the majority of critically ill patients.[3] However, the largest RCT on inpatient hyperglycaemia management in the ICU setting to date, the Tight Glucose Control (TGC)-FAST trial,[7] was published in 2023, challenging these recommendations.

In this Personal View, we discuss evidence from (mainly prospective) RCTs on the safety and efficacy of glycaemic control specifically from the perspective of ICU patients with diabetes (table). We further highlight important differences in risk assessment and management options between critically ill patients with versus without diabetes, and also highlight that patients with diabetes show great heterogeneity in their risk profiles (ie, due to pre-admission glycaemia or other factors, such as COVID-19).[13] In an era of precision medicine and rapid technological advances in diagnosis and glycaemic monitoring, these are areas that deserve greater attention in the future. Here, we define tight glucose control as targeting a range of approximately 4·4–6·1 mmol/L (80–110 mg/dL) compared with standard treatment that targets approximately 7·8–11·1 mmol/L (140–200 mg/dL), whereas liberal control was defined by exceeding standard conditions (ie, >11·1 mmol/L [200 mg/dL]).

Glycaemic targets and the risk of complications in RCTs

Early on, doubts arose about whether patients in ICUs with diabetes should be treated the same way as those without diabetes. This concern was due to a combined analysis of the LEUVEN trials that showed that patients with diabetes did not have the same benefit when treated with IIT and still had the same risk of complications.[4,8,9] This finding was later substantiated by various single-centre and multicentre RCTs that included important numbers of patients with diabetes (table). Since then, reasonable evidence has been provided for patients with (mainly) type 2 diabetes in the ICU to not exceed blood glucose concentrations of 14 mmol/L (252 mg/dL), which is also endorsed by 2022 standards of care.[3] Conversely, exceeding these blood glucose concentrations could be acceptable in terminally ill patients when hypoglycaemia cannot be avoided.[3] Otherwise, a target blood glucose range of 10–14 mmol/L (180–252 mg/dL) appears to be preventive for incident hypoglycaemia.[12,14] However, in the LUCID trial,[12] the secondary endpoint of 90-day mortality was higher in the liberal intervention (treatment started when blood glucose >14 mmol/L [252 mg/dL]) than in standard conditions (treatment started when

	Patient numbers per group, intervention *vs* control	Blood glucose target for intervention group	Blood glucose target for control group	Primary outcome	Results, n (%)	Subgroup of patients with diabetes	Results in the subgroup of patients with diabetes and other relevant results
Single-centre trials							
van den Berghe et al (2001), LEUVEN I[4]	765 *vs* 783	Start insulin infusion at >6·1 mmol/L (110 mg/dL); target range 4·4–6·1 mmol/L (80–110 mg/dL)	Start insulin >12 mmol/L (215 mg/dL); target range 10–11·1 mmol/L (180–200 mg/dL)	ICU mortality	ICU mortality: 63 (8·0%) under control *vs* 35 (4·6%) under IIT conditions, p=0·04	..	..
van den Berghe et al (2006), LEUVEN II[8]	595 *vs* 605	Start insulin infusion at >6·1 mmol/L (110 mg/dL); target range 4·4–6·1 mmol/L (80–110 mg/dL)	Start insulin >12 mmol/L (215 mg/dL); target range 10–11·1 mmol/L (180–200 mg/dL)	ICU mortality	ICU mortality: total study group: 162 (26·8%) under control *vs* 144 (24·2%) under IIT conditions, p=0·31;subgroup (ICU stay >3 days): 145 (38·1%) under control *vs* 121 (31·3%) under IIT conditions, p=0·05	..	..
van den Berghe et al (2006), LEUVEN I and LEUVEN II[9]*	..	..	..	..	..	407 patients with diabetes; 188 on insulin treatment; 219 on oral antidiabetics or diet; no reported differentiation of type 1 *vs* type 2 diabetes	No benefit of IIT; hypoglycaemia incidence similar to other subgroups; risk of death in patients with diabetes was the highest, with blood glucose <6·1 mmol/L (<110 mg/dL) and ICU-stay of at least 3 days, although not significant (p=0·2)
Multicentre trials							
Brunkhorst et al (2008), VISEP[5]	247 *vs* 290	Start insulin infusion at >6·1 mmol/L (110 mg/dL); target range 4·4–6·1 mmol/L (80–110 mg/dL)	Start insulin infusion at >11·1 mmol/L (200 mg/dL); target range 10·0–11·1 mmol/L (180–200 mg/dL)	28-day mortality	First safety analysis: study was suspended by the data and safety monitoring board, and the second stage was aborted; safety endpoints: severe hypoglycaemic episodes†—12 (4·1%) under control *vs* 42 (17·0%) under IIT, p<0·001; life-threatening hypoglycaemia—6 (2·1%) under control *vs* 13 (12·1%) under IIT conditions, p=0·05; 28-day mortality: 75 (26·0%) under control *vs* 61 (24·7%) under IIT conditions, p=0·74; 90-day mortality: 102 (35·4%) under control *vs* 98 (39·7%) under IIT conditions, p=0·31	163 patients with diabetes (n=73 with type 1 diabetes, n=90 with type 2 diabetes)	Outcomes similar to total study; hypoglycemia of ≤2·2 mmol/L (≤40 mg/dL) was defined as safety endpoint: ≥1 episode in 17·0% (IIT) *vs* 4·1% (control), p<0·001; IIT not verified as an independent risk factor for death (hazard ratio 0·95; 95% CI 0·70–1·28; p=0·72), but hypoglycaemic episodes were more often classified as life-threatening in IIT *vs* control (5·3% *vs* 2·1%; p=0·05), requiring long hospital stay (2·4% IIT *vs* 0·3% control, p=0·05)
Finfer et al (2009), NICE-SUGAR[6]	3016 *vs* 3014	Start insulin infusion at >6·1 mmol/L (110 mg/dL); target range 4·5–6·0 mmol/L (81–108 mg/dL)	Start insulin >10 mmol/L (180 mg/dL); target range 8·0–10 mmol/L (144–180 mg/dL)	90-day mortality	90-day mortality: 751 (24·9%) under control *vs* 829 (27·5%) under IIT conditions, p=0·02; 28-day mortality: 627 (20·8%) under control *vs* 670 (22·3%) under IIT conditions, p=0·17	1211 patients with diabetes in a predefined subgroup (92 with type 1 diabetes; 1119 with type 2 diabetes)	Outcomes and hypoglycaemia risk similar to total study group; severe hypoglycaemia (≤2·2 mmol/L [≤40 mg/dL]): 6·8% (IIT) *vs* 0·5% (conventional group), p<0·001; deaths from cardiovascular causes 41·6% (IIT) *vs* 35·8% (control), p=0·02

(Table continues on next page)

	Patient numbers per group, intervention *vs* control	Blood glucose target for intervention group	Blood glucose target for control group	Primary outcome	Results, n (%)	Subgroup of patients with diabetes	Results in the subgroup of patients with diabetes and other relevant results
(Continued from previous page)							
Kalfon et al (2014), CGAO–REA[10]	1336 *vs* 1312	Computerised glucose control; target range 4·4–6·1 mmol/L (79–110 mg/dL)	Non-computerised glucose control; target range <10 mmol/L (180 mg/dL)	90-day mortality	90-day mortality: 447 (34·1%) under control *vs* 431 (32·3%) under IIT conditions, p=0·32; 28-day mortality: 328 (25·0%) under control *vs* 326 (24·4%) under IIT conditions, p=0·72; ICU mortality: 310 (23·6%) control *vs* 302 (22·6%) under IIT conditions, p=0·53	536 patients with diabetes (85 with type 1 diabetes; 451 with type 2 diabetes)	Outcomes and hypoglycaemia risk similar to total collective; severe hypoglycemia (≤2·2 mmol/l [≤40 mg/dl]): 13·2% (IIT) *vs* 6·2% (conventional group), p<0·001
Bohé et al (2021), CONTROLING[11]	942 *vs* 975	Individual glucose management targeting pre-admission glycaemia, delineated through HbA_{1c} at ICU admission	Start insulin at >10 mmol/L (180 mg/dL), target range <10 mmol/L (180 mg/dL)	90-day mortality	90-day mortality: 2958 (30·5%) under control conditions *vs* 308 (32·8%) under individual glucose management, p=0·23	636 patients with diabetes (154 on insulin treatment; 250 on oral antidiabetics or diet; no reported differentiation of type 1 *vs* type 2 diabetes)	No benefit of individual therapy and hypoglycaemia risk similar to total study; total study frequency of hypoglycaemia at <2·2 mmol/L (<40 mg/dL): 3·9% (individual glucose management) *vs* 2·5% (control), p=0·09; total frequency of hypoglycaemia at <4 mmol/L (<72 mg/dL) 31·2% (individual glucose management) *vs* 15·8% (control), p<0·0001
Poole et al (2022), LUCID[12]	210 *vs* 209	Start insulin at >14 mmol/L (252 mg/dL), target range 10–14 mmol/L (180–252 mg/dL)	Start insulin at >10 mmol/L (180 mg/dL), target range 6–10 mmol/L (108–180 mg/dL)	Incident hypoglycaemia of <4 mmol/L (<72 mg/dL)	≥1 episode of hypoglycaemia: 38 (18%) under control *vs* 10 (5%) under intervention conditions, p<0·001; 90-day mortality: 52 (24·9%) under control *vs* 62 (29·5%) under intervention conditions, p=0·29	Exclusive inclusion of critically ill patients with type 2 diabetes	..
Gunst et al (2023), TGC-Fast[7]	4608 *vs* 4622	Computer algorithm-based intervention, target range 4·4–6·1 mmol/L (80–110 mg/dL)	Start insulin at >11·9 mmol/L (215 mg/dL), target range 10–11·9 mmol/L (180–215 mg/dL)	ICU length of stay; severe acute kidney injury; 90-day mortality	ICU length of stay: mean 6 days (SD 12 days) for IIT *vs* 7 days (13 days) for liberal glucose control, p=0·94; severe acute kidney injury: 326 (7·2%) under IIT conditions *vs* 387 (8·6%) under liberal glucose control, p=0·97; 90-day mortality: 486 (10·5%) under IIT conditions *vs* 468 (10·1%) under liberal glucose control, p=0·51	1888 patients with diabetes in a prespecified subgroup (no reported differentiation of type 1 *vs* type 2 diabetes)	Outcome measures similar to total study group; odds ratio for the 90-day mortality with IIT for patients with diabetes was 1·19 (95% CI 0·90–1·58) *vs* 1·01 (0·86–1·17) for patients without diabetes, p>0·05; hypoglycaemia risk for patients with diabetes was similar to the total study group (total study: 0·7 [liberal glucose control] *vs* 1% [IIT], p>0·05)

ICU=intensive care unit. IIT=intensive insulin therapy. *Evaluation of combined LEUVEN I and LEUVEN II trials. †Severe hypoglycaemia episodes were <2·2 mmol/L (<40 mg/dL).

Table: **Randomised controlled trials comparing IIT, conventional blood glucose control, and liberal glucose control in critically ill patients with a focus on patients with diabetes**

>10 mmol/L [180 mg/dL]), although the trial was not sufficiently powered for this endpoint.

Thus, an evidence-based blood glucose target range, which balances both the risks of stress hyperglycaemia and of hypoglycaemic events, remains to be determined for critically ill patients with diabetes. Recently, Gunst and colleagues have published the large TGC-Fast trial[7] on liberal versus tight glycaemic control in more than 9200 medical and surgical ICU patients, comprising a predefined subgroup of over 1800 patients with diabetes. Their results suggest that in critically ill patients, targeting concentrations of 4·4–6·1 mmol/L (80–110 mg/dL) versus concentrations below 11·9 mmol/L (<215 mg/dL) had no effect on the length of time that ICU care was needed or mortality. The risk of severe hypoglycaemia of less than 2·2 mmol/L (<40 mg/dL) was similar between liberal and tight blood glucose control, despite a slightly higher incidence under IIT (table). By contrast, the NICE-SUGAR trial[6] had a significantly higher 90-day mortality with IIT (blood glucose target 4·5–6·0 mmol/L [81–108 mg/dL]) than with standard treatment (blood glucose target 8·0–10·0 mmol/L [144–180 mg/dL]). The trial's findings included a 10–15-times greater risk of hypoglycaemia in the IIT group, which could have contributed (among other reasons) to the observed adverse events.[3] In this trial, patients with diabetes did not differ from the rest of the patients in terms of hypoglycaemia risk and mortality. Safety concerns associated with tight blood glucose control, as shown by the NICE-SUGAR trial,[6] were supported by later research that suggested increased mortality and hypoglycaemia risk with IIT compared with standard glycaemic targets.[3,15–18] Whether cardiovascular events in particular contribute to adverse outcomes under conditions of IIT, as discussed by Finfer and colleagues,[6] and whether hypoglycaemia is the driver of such events, is currently under debate.[19,20] It is possible that increased cardiovascular risk, mortality, and risk of hypoglycaemia coincide in a susceptible patient population as a result of the same condition, rather than causally linked.[21–24] It is important to note that in the TGC-Fast trial,[7] glycaemic control followed a strict protocol, which differentiates this trial from others. In accordance with a computer algorithm, blood glucose concentrations were taken every 1–4 hours through rapidly available blood gas analysis, while under continuous intravenous insulin treatment. This multifactorial procedure was helpful for minimising hypoglycaemic episodes under IIT. However, the CGAO–REA RCT[10] also shows that use of only a computerised algorithm for targeting blood glucose concentrations might not be sufficient for avoiding severe hypoglycaemia (table). Instead, implementing a group of measures (ie, a so-called bundle) into routine clinical practice (ie, rapidly available blood gas analysis monitoring in line with appropriate measurement intervals and continuous insulin application, established via a computerised algorithm) appears to increase patient safety.[7] Therefore, protocol differences regarding the management of blood glucose concentrations could partly explain the significantly different incidence of clinically relevant hypoglycaemic events under IIT in the discussed trials. At the same time, the TGC-Fast trial provides reliable evidence that through the use of an antihypoglycaemia bundle, stricter blood glucose concentration targets can be safely reached in ICU patients who are critically ill without clinically significantly elevating the risk of hypoglycaemia, even in absence of early parenteral nutrition; yet, it is still not more effective in reducing serious endpoints, including mortality.

Notably, in the TGC-Fast trial,[7] the large subgroup of patients with diabetes did not show significant deleterious effects with IIT, but they also did not show significant harm when tolerating a liberal strategy, with blood glucose concentrations of up to 11·9 mmol/L (<215 mg/dL). In the control arm of the NICE-SUGAR trial[6] similar results were observed under standard treatment conditions, with a substantially reduced hypoglycaemia risk of 0·5%, which is similar to the control arm of TGC-Fast.[7] Thus, on the basis of current evidence from multicentre RCTs, including the to-date largest subgroups of critically ill patients with diabetes, it appears practicable and safe to support a blood glucose target range of 8·0–11·9 mmol/L (144–215 mg/dL) to avoid hypoglycaemia in ICU patients with diabetes. In terms of clinical practice, such liberal blood glucose targets could further help clinicians to keep critically ill patients with diabetes successfully within the target range, which can be particularly challenging under conditions of a concomitant enteral or parenteral nutrition therapy. Moreover, regarding the risk for severe hypoglycaemia specifically, these more liberal blood glucose targets are supported by a meta-analysis published in 2017.[25] In line with this notion, predictors of the general risk of hypoglycaemia are related to poor glucose control with large glucose variability rather than near to normal glucose concentrations,[21,26] in addition to duration of diabetes, prevalent microvascular disease, and previous hypoglycaemia.

The role of preadmission glycaemic control and the risk of relative hypoglycaemia

Previous hypoglycaemia is of particular importance for the risk of relative hypoglycaemia, predominantly in severely ill ICU patients with diabetes and potentially delayed neurohormonal defence mechanisms. In critically ill patients, relative hypoglycemia is defined as either an at least 30% decrease from preadmission glycaemic status or any drop into the blood glucose range of 3·9–6·1 mmol/L (70–110 mg/dL) for patients with preadmission HbA_{1c} of at least 8·0%.[27] Although relative hypoglycaemia remains to be fully defined,[28,29] it is broadly accepted that the condition consists of situations where the threshold for the perception and response to low blood glucose concentrations is elevated compared with absolute hypoglycaemia. The physiological perception threshold for low blood glucose concentrations typically ranges at a level between

2·8–3·4 mmol/L (50–60 mg/dL), but can be much higher for people with diabetes, potentially exposing critically ill patients to a serious risk of harm.[27] Relative hypoglycaemia has not yet been studied in large multicentre RCTs, and has not even been considered by most observational studies on blood glucose management in critically ill patients. Relative hypoglycaemia is therefore an often-overlooked complication of diabetes, which can result in cardiovascular stress or neurological symptoms in people with diabetes at blood glucose concentrations that would be considered typical for people without diabetes.[27] The use of modern continuous glucose monitoring technologies, together with pattern-recognition algorithms powered by artificial intelligence, in ICUs[30] will potentially lead to a deeper understanding and improved treatment of relative hypoglycaemia in the future.

Research from the past decade has developed the hypothesis that the quality of prehospital glycaemic control could be one of the major determinants of relative hypoglycaemia risk. According to a retrospective observational study in critically ill patients with diabetes with elevated preadmission HbA_{1c} (>7%; >53 mmol/mol), higher (>10 mmol/L [>180 mg/dL]) time-weighted acute glucose concentration during ICU stay was associated with lower hospital mortality.[31] Similarly, another retrospective observational study reported increased mortality associated with rising glycaemia among patients with admission HbA_{1c} lower than 6·5% (<47·5 mmol/mol), whereas the opposite was observed in patients with HbA_{1c} of at least 8% (≥63·9 mmol/mol).[32] This result could suggest that critically ill patients with poor preadmission glycaemic control (ie, HbA_{1c} ≥8% [≥63·9 mmol/mol]) are exposed to a greater risk of harm due to relative hypoglycaemia.[27] This hypothesis led to the introduction of the stress-hyperglycaemia ratio[33] and is corroborated by a retrospective observational study showing an association between prehospital glycaemic control (assessed through admission HbA_{1c} concentrations) and the time under relative hypoglycaemia during ICU stay and mortality.[34] These data suggest that determining a single blood glucose target range for all critically ill patients with diabetes is not appropriate[35] and highlights the considerable heterogeneity of this group of patients.

The CONTROLING trial[11] was the first multicentre, double-blind, parallel group RCT on individualised blood glucose targets, in which preadmission glucose control was taken into account through algorithms that used HbA_{1c} concentrations obtained at ICU admission. Although the approach of this ambitious trial can be regarded as an important step forward in precision medicine, it had several limitations—namely, that randomisation occurred in at least 25% of patients after at least 2·1 days in the ICU, with delays occurring due to screening and awaiting HbA_{1c} measurement.[36] Accordingly, patients in the interventional arm were exposed to standard glucose control (<10 mmol/L [<180 mg/dL]) for a median of 26% of their time in the ICU, which was further reflected by small timespans within the individualised target range (median 51%). The small amount of time patients were in their target range suggests that the study did not achieve adequate glycaemic separation between intervention groups. Furthermore, a higher rate of hypoglycaemic episodes was observed in the intervention arm than the control arm, and the intervention was stopped prematurely by the data safety monitoring board due to a low likelihood of benefit and the potential harm associated with hypoglycaemia.[36] Due to these limitations, data from the only RCT on individualised blood glucose concentrations control are therefore not helpful in clinical routine. However, the trial's substantiation of the association between hypoglycaemia and mortality could be interpreted as a reason to accept liberal blood glucose targets of 10–14 mmol/L (180–252 mg/dL) in the majority of critically ill patients with diabetes. Such a strategy would not only be helpful in reducing the risk of absolute hypoglycaemia, but likely also the risk of relative hypoglycaemia in clinically vulnerable people.[14]

Could subgroups of critically ill patients with diabetes benefit from stricter blood glucose control?

As indicated by the LUCID trial,[12] the safety of liberal blood glucose targets of up to 14 mmol/L (252 mg/dL) for critically ill patients with diabetes is yet to be evaluated by sufficiently powered RCT. Moreover, some groups of ICU patients with diabetes could benefit from stricter blood glucose targets. For instance, a meta-analysis showed that blood glucose targets of less than 8·3 mmol/L (<150 mg/dL) could have preventive effects for surgical site infections,[37] which is of substantial relevance in surgical ICU patients, and specifically in cardiac surgery.[18,38,39] Additionally, the subgroup of patients with neurological or neurosurgical diagnoses tended to show reduced 90-day mortality with IIT in the TGC-Fast trial. Even severe acute kidney injury and cholestatic liver dysfunction were less prevalent with strict blood glucose targets,[7] which could be important due to the well known risk of stroke, diabetic nephropathy, and complications in metabolic-associated fatty liver disease in non-critically ill patients with diabetes. However, specific subgroup analyses on this matter have not been published yet. It should be otherwise recognised that, similar to the first LEUVEN trial,[4] overall mortality in TGC-Fast was lower than the majority of RCTs on stress hyperglycaemia control (table). This difference could reflect the inclusion of a large proportion of patients in the ICU who have lower-stage critical illness and therefore with varying risk profiles, even in terms of blood glucose tolerance. Additionally, no stratification by pre-admission glycaemia was done in the TGC-FAST trial and, accordingly, the relationship between glucose variability and metrics related to mortality was not reported. Thus, the results could have been biased by

Search strategy and selection criteria

All publications and trials of relevance were identified through a selective literature search from database inception until Nov 1, 2023, on PubMed and Google Scholar, with emphasis on the following (variously combined) terms: "Diabetes", "Critical Care", "Blood Glucose", "Glucose Control", Glucose Monitoring", "Glucose Management", "Intensive Care Unit", "ICU", "Relative Hypoglycaemia/Hypoglycemia", "Hypoglycaemia/Hypoglycemia" and "Outcome". For the table, primary research articles published between January, 2001 and October, 2023 were included. Studies including less than 100 patients with diabetes per group were excluded, as were trials with a significantly unequal distribution of patients with diabetes between the intervention and comparator group.

heterogeneity of treatment effect. Therefore, whether (and how) positive findings on strict versus liberal or very liberal blood glucose targets can be applied to specific subgroups of ICU patients with diabetes remains to be elucidated. Such research could result in more precise or even individualised therapy regimens in critically ill patients with diabetes, depending on their respective preadmission glycaemia and risk profiles.

Future directions

The need for research on individualised therapy regimens in critically ill patients with diabetes is supported by findings in patients in the ICU with diabetes and COVID-19 with poor prehospital glycaemic control. These patients had higher COVID-19-related mortality than patients with better chronic pre-admission glycaemia. Older age, male gender, previous stroke, renal impairment, non-White ethnicity, socioeconomic deprivation, and heart failure were additional covariates associated with increased COVID-19-related mortality in patients with type 1 and type 2 diabetes.[13] However, it remains unknown whether targeting strict versus liberal blood glucose concentrations is superior for such groups of patients in ICUs. The 2024 recommendations of the American Diabetes Association principally support the view that more stringent glycaemic goals could be appropriate for specific patient groups with diabetes, as long as these goals can be achieved without exposing them to significant risk of hypoglycaemia.[3] However, as long as subgroups of critically ill patients with diabetes who evidently benefit from stricter blood glucose goals, remain to be defined, avoiding relative hypoglycaemia and absolute hypoglycaemia represents the main therapeutic goal of blood glucose concentrations management in the ICU. Evaluation of admission HbA_{1c} could be helpful in clinical routine to at least roughly identify individuals who will be at an increased risk of relative hypoglycaemia and related harms. Consequently, future research needs to identify the subgroups of critically ill patients with diabetes who will benefit from stricter blood glucose target ranges for specific clinical endpoints. For such groups, it will be of interest to determine if and how blood glucose management strategies guided by a computer algorithm are effective and practicable to prevent absolute hypoglycaemia and relative hypoglycaemia, and related complications. It will also be important to evaluate if novel technologies, such as continuous glucose monitoring, could be helpful to maintain patients over appropriate timespans within their individualised target range.[40] More detailed data is needed on whether there should be sex differences in blood glucose target ranges in critically ill ICU patients with and without diabetes. In particular, if and how the female menstrual cycle affects blood glucose targets, as mean daily glucose levels rise and fall in a biphasic pattern during the luteal and late follicular phases, should be explored more thoroughly.[41–43] Similarly, there is still very little knowledge on whether the same blood glucose targets are applicable to people of different ethnic backgrounds and whether and how socioeconomic factors need to be integrated.[44,45] Collecting such comparative data is an urgent clinical need for the future and needs to involve all stakeholders.

Conclusion

In summary, prevention of absolute hypoglycaemia in all critically ill patients, and of relative hypoglycaemia in those with diabetes, remains the primary goal of blood glucose management in the ICU. For the majority of ICU patients without diabetes, it is suggested to start insulin treatment at a threshold of more than 10·0 mmol/L (>180 mg/dL), targeting a range of 7·8–10·0 mmol/L (140–180 mg/dL). In ICU patients with diabetes, pre-admission HbA_{1c} of at least 8% (≥63·9 mmol/mol) can be considered as a surrogate of poor prehospital glycaemic control and increased risk of relative hypoglycaemia. According to subgroup analyses from a prospective RCT that included a large number of patients with diabetes, liberal blood glucose targets of 8·0–11·9 mmol/L (144–215 mg/dL) were estimated to be safe and could hypothetically be preventive for relative hypoglycaemia in susceptible groups, such as patients with previous hypoglycaemia, multimorbidity, frailty, or long standing diabetes.[27] Whether acceptance of liberal blood glucose targets of up to 14 mmol/L (252 mg/dL) is safe, particularly in severely ill ICU patients with poor prehospital glycaemic control, substantial comorbidities, and high risk of surgical site infections, needs to be clarified by sufficiently powered RCTs in the future. Data from observational studies otherwise point to increased mortality with liberal glucose control among patients with admission HbA_{1c} of less than 6·5% (<47·5 mmol/mol),[27,32] suggesting the existence of subgroups of patients with diabetes that could benefit from stricter blood glucose targets. Current recommendations support more stringent glycaemic targets of 6·1–7·8 mmol/L (110–140 mg/dL) as appropriate for specific patient groups, as long as this can be achieved without hypoglycaemia. A recent RCT

indicates that use of a so-called antihypoglycaemia bundle of tools, including appropriate measurement intervals and computerised algorithms for insulin therapy, is effective in achieving stricter blood glucose concentrations in critically ill ICU patients without necessarily elevating the risk of hypoglycaemia.[7] Whether or not such an approach is cost-effective and will reduce clinical endpoints (eg, length of hospital stay, cardiovascular events, and mortality) needs to be determined. Finally, blood glucose concentrations exceeding 13·9 mmol/L (250 mg/dL) could be acceptable in some patients with short life expectancy if hypoglycaemia cannot otherwise be prevented.[3]

In an era of technological, bioinformatic, and therapeutic advances and the increasing importance of precision strategies, it is important to test new approaches to offer improved treatment options for all ICU patients, who are at a critical stage of their illness and life. All stakeholders need to work together to achieve this important goal.

Contributors
CvL and ALB contributed equally to the manuscript.

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