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Glucose control in the ICU

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Abstract

Purpose of review—Critically ill patients usually develop hyperglycemia, which is associated with adverse outcome. Controversy exists whether the relationship is causal or not. This review summarizes recent evidence regarding glucose control in the intensive care unit.

Recent findings—Despite promising effects of tight glucose control in pioneer randomized controlled trials, the benefit has not been confirmed in subsequent multicenter studies and one trial found potential harm. This discrepancy could be explained by methodological differences between the trials rather than by a different case mix. Strategies to improve the efficacy and safety of tight glucose control have been developed, including the use of computerized treatment algorithms.

Summary—The ideal blood glucose target remains unclear and may depend on the context. As compared to tolerating severe hyperglycemia, tight glucose control is safe and effective in patients receiving early parenteral nutrition when provided with a protocol that includes frequent, accurate glucose measurements and avoids large glucose fluctuations. All patient subgroups potentially benefit, with the possible exception of patients with poorly controlled diabetes, who may need less aggressive glucose control. It remains unclear whether tight glucose control is beneficial or not in the absence of early parenteral nutrition.

Keywords

hyperglycemia; hypoglycemia; insulin; critical illness; intensive care

Introduction

Critically ill patients usually develop hyperglycemia, irrespective of their pre-existing diabetes status. Numerous observational studies have revealed a significant association between blood glucose concentrations upon admission to the intensive care unit (ICU) or in the ICU and outcome [1,2]. The relationship follows a U- or J-shaped pattern, with the lowest risk of mortality associated with blood glucose concentrations in the healthy fasting range, especially in non-diabetic patients. In patients with diabetes mellitus, the curve is

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Conflicts of interest

None.

somewhat flattened and shifted to the right (Figure 1) [1,2]. Evidently, association does not imply causation, which can only be demonstrated by a randomized controlled trial (RCT) interfering with blood glucose control in the ICU. Indeed, a higher mortality risk with blood glucose concentrations outside the normal range could also be explained by a higher illness severity, with more severe insulin resistance in sicker patients and a higher risk of hypoglycemia in patients with preexisting malnutrition and/or established liver failure.

Evidence from randomized controlled trials

In the last 2 decades, several RCTs have investigated whether tight glucose control is beneficial or not in critically ill patients, as compared to more liberal glucose control.

Pioneer randomized controlled trials

In 2001, a pioneer RCT performed in Leuven, Belgium, found clear benefit by treating hyperglycemia, supporting a potential causal relationship between hyperglycemia and outcome. Indeed, in 1548 adult critically ill patients admitted to a predominantly surgical ICU, maintaining blood glucose concentrations in the healthy fasting range (4.4–6.1 mmol/l [80–110 mg/dl]) reduced morbidity and mortality, as compared to tolerating hyperglycemia up to the renal threshold (11.9 mmol/l [215 mg/dl]) [3]. Subsequently, the Leuven research group confirmed clinical benefit in critically ill adults admitted to the medical ICU (n=1200) and in critically ill children (n=700) [4,5]. Importantly, short-term benefit was maintained on the long-term and the intervention was shown to reduce healthcare costs [6–8]. Subsequent mechanistic studies attributed the benefit obtained by tight glucose control to a protection against glucose toxicity and not to glycemia-independent effects of insulin [9–11].

Subsequent studies

After the Leuven RCTs, several implementation studies and single-center RCTs have confirmed morbidity and/or mortality benefit by implementing tight glucose control [12–17]. However, multicenter RCTs in both critically ill adults and children have largely been neutral and the largest RCT, the NICE-SUGAR study (n=6104), even found increased mortality in critically ill adults [18–25]. The increased mortality risk in NICE-SUGAR was subsequently attributed to the increased incidence of hypoglycemia [26]. Hence, at current, tight glucose control remains highly debated, which leads to large variations in clinical practice [27*,28*,29].

How to reconcile the evidence?

Although speculative, a number of methodological differences may potentially explain the discrepant outcome effects seen across RCTs. We here review the –to our opinion– most important differences (Table 1).

Differences in blood glucose target

A first difference is the difference in blood glucose target in both control and intervention groups. In contrast to the Leuven RCTs, in which tight glucose control was compared to tolerating severe hyperglycemia, most subsequent multicenter RCTs used a lower glucose

target in the control group, in general <10 mmol/l (180 mg/dl) [27*]. This is explained by the shift in standard care –the implementation of some degree of glucose control– before the start of the respective multicenter RCTs. However, by comparing to a lower glucose target, the achieved difference in blood glucose concentrations between both groups was smaller, which leaves most studies underpowered to detect a difference. Yet, this does not explain the increased mortality by tight glucose control in NICE-SUGAR, as compared to an intermediate target. Aggregating evidence from Leuven and NICE-SUGAR, one could argue that the intermediate blood glucose target (<10 mmol/l [180 mg/dl]) is the optimum. However, no adequately powered RCT has compared such intermediate target with more liberal control (<11.9 mmol/l [215 mg/dl]), and other differences between Leuven and NICE-SUGAR may explain the different outcome effect [27*]. Moreover, secondary analyses of the Leuven RCTs suggest that strict glucose control is superior to intermediate glucose control [30].

Apart from the blood glucose target in the control group, also the target in the intervention group differed among RCTs, especially in the pediatric RCTs [5,16,23–25]. Indeed, whereas in the Leuven pediatric RCT, the target was age-adjusted (2.8–4.4 mmol/l [50–80 mg/dl] for infants, 3.9–5.6 mmol/l [70–100 mg/dl] for children older than 1 year), subsequent multicenter RCTs did not adjust the target to the age-dependent reference value [5,23–25]. Moreover, since critically ill children also tend to develop less severe hyperglycemia than adults, there was a large overlap in achieved blood glucose concentrations in the pediatric multicenter RCTs, which led to insufficient statistical power [31,32]. Nevertheless, one of these multicenter RCTs suggested a potential benefit of tight glucose control in the high-risk subgroup of non-cardiac surgery patients [23].

Differences in glucose measurement and insulin protocol

A second difference between RCTs on tight glucose control in the ICU is the used protocol to measure and control blood glucose. In the pioneer RCTs showing benefit, blood glucose was measured on arterial blood using an accurate blood gas analyzer, and insulin was only administered through continuous intravenous infusion, without boluses. Insulin was titrated by the nurses, using a standard protocol that allowed intuitive decision-making [33]. This approach led to a relatively high time in target range. Several subsequent studies, including NICE-SUGAR, had a less standardized protocol, allowing a variety of –at that time– inaccurate glucometers. Moreover, venous and capillary blood glucose measurements often were allowed, which can be inaccurate in case of simultaneous intravenous glucose infusion and in patients with shock, respectively. Finally, the insulin protocol of NICE-SUGAR allowed insulin boluses and did not necessarily correct for changes in feeding intake [33]. The combination of potentially inaccurate glucose measurements and an un-validated insulin protocol that allows boluses may substantially increase glucose variability –also associated with poor outcome– and may lead to episodes of undetected and prolonged hypoglycemia [2]. Although speculative, this may explain why NICE-SUGAR found excess mortality by tight glucose control. Hence, if tight glucose control is applied, blood glucose should be measured frequently with an accurate device, preferably on arterial blood, and insulin should probably only be titrated through continuous intravenous infusion using a protocol that corrects for trends in blood glucose and feeding intake [34,35*].

Differences in nutritional management

Third, feeding intake largely differed between the RCTs on tight glucose control, explained by a long-lasting controversy about the optimal feeding regimen for critically ill patients. In the pioneer Leuven RCTs, patients received early parenteral nutrition as part of standard care at that time [3–5]. However, this feeding strategy increases the degree of hyperglycemia and was afterwards shown to be harmful in two large multicenter RCTs, also when iatrogenic hyperglycemia is treated [36,37]. In several other RCTs on tight glucose control, including NICE-SUGAR, parenteral feeding intake was lower in the acute phase [20]. Withholding parenteral nutrition in the acute phase –the current feeding standard for critically ill patients–increases the risk of hypoglycemia when tight glucose control is applied [36,37]. It currently remains unknown whether tight glucose control is protective or not in the absence of early parenteral nutrition, when provided with adequate tools.

Open questions

In view of the divergent results between subsequent RCTs, several open questions remain.

Iatrogenic hypoglycemia: harmful or not?

Tight glucose control inevitably increases the risk of hypoglycemia. Multiple observational studies have associated the occurrence of hypoglycemia with poor outcome [1,2]. The central nervous system has been presumed to be particularly vulnerable. Evidently, long-lasting hypoglycemia is known to be harmful. It remains unclear, however, whether a short-lasting iatrogenic episode of hypoglycemia is by itself harmful or not [30]. Indeed, the association between hypoglycemia and outcome is confounded by severity of illness, with sicker patients being more prone to hypoglycemia. Several lines of evidence suggest that a short-lasting episode of iatrogenic hypoglycemia may be innocent. Indeed, several nested case-control studies could not identify harm by an iatrogenic episode of hypoglycemia when corrected for baseline risk factors and duration of ICU stay [7,38,39]. In addition, a long-term follow-up study of the pediatric Leuven RCT found an improved neurocognitive outcome of critically ill children 4 years after randomization to tight glucose control, despite a high incidence of hypoglycemia, suggesting that hyperglycemia is more deleterious to the brain than hypoglycemia [7]. In this regard, an animal study found that not profound hypoglycemia, but rebound hyperglycemia during glucose reperfusion induced neuronal death [40]. Also in NICE-SUGAR, long-term follow-up of the subgroup of patients with traumatic brain injury did not find long-term harm by tight glucose control, despite a significant increase in severe hypoglycemia [41]. However, proof of innocence of short-lasting iatrogenic hypoglycemia would require a RCT, which is obviously not justifiable. Moreover, NICE-SUGAR statistically attributed harm by tight glucose control in the total study population to the increased incidence of hypoglycemia [26]. Therefore, it seems prudent to prevent hypoglycemia as much as possible by frequent and accurate glucose measurements and by use of a validated insulin protocol.

Which patient subgroups benefit more or less from tight glucose control?

Observational studies and experts have suggested that certain patient subgroups may respond differently to the impact of tight glucose control, including patients after cardiac surgery,

patients in the neuro-ICU and patients with pre-existing diabetes [1,42**]. Subgroup analyses of RCTs largely refute this, however. Indeed, subgroup analyses from Leuven and NICE-SUGAR did not find a different effect among subgroups, with the potential exception of patients with pre-admission diabetes [20,30]. Indeed, in a secondary analysis of the Leuven studies, benefit of tight glucose control was present in all studied subgroups, except in the patients with pre-existing diabetes [30].

An individualized blood glucose target?

The potentially different effect of tight glucose control in patients with pre-existing diabetes may point to adaptations to chronic hyperglycemia, whereby acute lowering of blood glucose may be unwanted. In this regard, the degree of chronic hyperglycemia may play a role. Observational studies in diabetes patients have found a flattening and rightward displacement of the U-shaped association between blood glucose concentrations and short-term mortality, especially in patients with poorly controlled diabetes [1,43,44]. Patients with poorly controlled diabetes, as expressed by a high HbA1c level upon ICU admission, also appear more vulnerable to hypoglycemia [45]. However, whether the optimal blood glucose target depends on the pre-existing level of blood glucose control, remains unclear. A multicenter RCT aiming to compare individualized –based on the upon admission HbA1c level– versus standard glucose control was recently terminated by the data safety monitoring board (<https://clinicaltrials.gov/ct2/show/NCT02244073>). The results of this RCT haven't been published yet.

Impact of tight glucose control in the absence of early parenteral nutrition

As mentioned above, the nutritional standard differed between RCTs. A meta-analysis suggested that the benefit of tight glucose control related to the amount of parenteral calories administered. Benefit was only present in RCTs in which a high amount of (early) parenteral feeding was administered, however, without adjustment for confounders [46]. In contrast, a secondary analysis of the Leuven RCTs suggested that the benefit of tight glucose control was also present in patients receiving the lowest amount of parenteral glucose [30]. In the absence of an adequately powered RCT, the impact of tight glucose control in the absence of early parenteral nutrition, when provided with adequate tools, remains unknown. This is currently being investigated by a multicenter RCT (<https://www.clinicaltrials.gov/ct2/show/NCT03665207>).

Strategies to improve the quality and safety of blood glucose control

In view of the open questions, the ideal blood glucose target remains unclear and may depend on the context. Nevertheless, the divergent effect between RCTs illustrates that tight glucose control is a complex intervention, which requires frequent and accurate monitoring of blood glucose and a reliable algorithm, especially when strict glucose control is aimed for. Several strategies may further improve the quality and safety of blood glucose control, including the use of validated computerized algorithms, (near-)continuous glucose monitoring and closed-loop glucose control [35*,42**]. Several software algorithms have been developed, with high performance confirmed outside expert centers [35*,47,48*]. Use of these validated algorithms may decrease the incidence of hypoglycemia and prevent large

glucose fluctuations [47,48*]. Theoretically, (near-)continuous glucose monitoring (CGM) and closed-loop blood glucose control could virtually prevent episodes of severe hypoglycemia, which may further improve the quality and safety of tight glucose control. Several CGM devices have been developed, either with an intravascular or interstitial sensor. However, accuracy of several devices does not meet the strict standards for CGM put forward by experts [42**,49]. Hence, a substantial number of CGM devices currently have no regulatory approval for use in critically ill patients [42**]. In addition, the discussion about the ideal blood glucose target for critically ill patients, the substantial cost and limited durability of a CGM device, as well as the absence of studies demonstrating cost-effectiveness preclude widespread use, and have withheld companies to invest in CGM [42**,50]. Nevertheless, some CGM devices have shown improved blood glucose control as add-on to standard monitoring [51,52]. Likewise, closed-loop glycemic control has the potential to significantly improve the quality and safety of the intervention [17,53,54]. However, largely the same limitations as for CGM devices preclude its widespread use at current.

Conclusion

The optimal blood glucose target for critically ill patients remains unclear. Tight glucose control is safe and effective in patients receiving early parenteral nutrition when provided with accurate monitoring and a reliable insulin protocol. The efficacy and safety of the treatment in the absence of early parenteral nutrition remains unclear. In the absence of new evidence, it seems prudent to at least prevent severe hyperglycemia, hypoglycemia and large glucose fluctuations in all ICU patients. There is no evidence for a different response across patient subgroups, with the possible exception of patients with diabetes, who may benefit from a higher glucose target.

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References and recommended reading

Papers of particular interest have been highlighted as

* of special interest

** of outstanding interest

1. Falciglia M, Freyberg RW, Almenoff PL, et al. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med.* 2009; 37:3001–3009. [PubMed: 19661802]

2. Krinsley JS, Egi M, Kiss A, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care*. 2013; 17:R37. [PubMed: 23452622]
3. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001; 345:1359–1367. [PubMed: 11794168]
4. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. 2006; 354:449–461. [PubMed: 16452557]
5. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet*. 2009; 373:547–556. [PubMed: 19176240]
6. Ingels C, Debaveye Y, Milants I, et al. Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care, and quality-of-life. *Eur Heart J*. 2006; 27:2716–2724. [PubMed: 16608860]
7. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. *JAMA*. 2012; 308:1641–1650. [PubMed: 23101118]
8. Van den Berghe G, Wouters PJ, Kesteloot K, Hilleman DE. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. *Crit Care Med*. 2006; 34:612–616. [PubMed: 16521256]
9. Ellger B, Debaveye Y, Vanhorebeek I, et al. Survival benefits of intensive insulin therapy in critical illness - Impact of maintaining normoglycemia versus glycemia-independent actions of insulin. *Diabetes*. 2006; 55:1096–1105. [PubMed: 16567534]
10. Vanhorebeek I, Gunst J, Ellger B, et al. Hyperglycemic kidney damage in an animal model of prolonged critical illness. *Kidney Int*. 2009; 76:512–520. [PubMed: 19536085]
11. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Crit Care Med*. 2003; 31:359–366. [PubMed: 12576937]
12. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Semin Thorac Cardiovasc Surg*. 2006; 18:317–325. [PubMed: 17395028]
13. Lecomte P, Van Vlem B, Coddens J, et al. Tight perioperative glucose control is associated with a reduction in renal impairment and renal failure in non-diabetic cardiac surgical patients. *Crit Care*. 2008; 12:R154. [PubMed: 19055829]
14. Bilotta F, Spinelli A, Giovannini F, et al. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. *J Neurosurg Anesthesiol*. 2007; 19:156–160. [PubMed: 17592345]
15. Bilotta F, Caramia R, Paoloni FP, et al. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology*. 2009; 110:611–619. [PubMed: 19237874]
16. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. *Am J Respir Crit Care Med*. 2010; 182:351–359. [PubMed: 20395554]
17. Okabayashi T, Shima Y, Sumiyoshi T, et al. Intensive versus intermediate glucose control in surgical intensive care unit patients. *Diabetes Care*. 2014; 37:1516–1524. [PubMed: 24623024]
18. Preiser JC, Devos P, Ruiz-Santana S, et al. 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*. 2009; 35:1738–1748. [PubMed: 19636533]
19. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008; 358:125–139. [PubMed: 18184958]
20. Finfer S, Blair D, Bellomo R, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009; 360:1283–1297. [PubMed: 19318384]

21. Kalfon P, Giraudeau B, Ichai C, et al. Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial. *Intensive Care Med.* 2014; 40:171–181. [PubMed: 24420499]
22. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA.* 2010; 303:341–348. [PubMed: 20103758]
23. Macrae D, Grieve R, Allen E, et al. A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med.* 2014; 370:107–118. [PubMed: 24401049]
24. Agus MS, Steil GM, Wypij D, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. *N Engl J Med.* 2012; 367:1208–1219. [PubMed: 22957521]
25. Agus MS, Wypij D, Hirshberg EL, et al. Tight glycemic control in critically ill children. *N Engl J Med.* 2017; 376:729–741. [PubMed: 28118549]
26. Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med.* 2012; 367:1108–1118. [PubMed: 22992074]
27. Gunst J, Van den Berghe G. Blood glucose control in the ICU: don't throw out the baby with the bathwater! *Intensive Care Med.* 2016; 42:1478–1481. [PubMed: 27161085] [* This review article highlights current evidence regarding blood glucose control in current ICU practice and summarizes the potential mechanisms underlying organ protection, with reference to the mechanistic studies.]
28. Marik PE. Tight glycemic control in acutely ill patients: low evidence of benefit, high evidence of harm! *Intensive Care Med.* 2016; 42:1475–1477. [PubMed: 27161084] [* This viewpoint argues that tight blood glucose control is unsafe under all circumstances.]
29. Preiser JC, Straaten HM. Glycemic control: please agree to disagree. *Intensive Care Med.* 2016; 42:1482–1484. [PubMed: 27161083]
30. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units - Benefit versus harm. *Diabetes.* 2006; 55:3151–3159. [PubMed: 17065355]
31. Agus MSD, Wypij D, Nadkarni VM. Tight glycemic control in critically ill children. *N Engl J Med.* 2017; 376:e48.
32. Gunst J, Van den Berghe G. Tight glycemic control in critically ill children. *N Engl J Med.* 2017; 376:e48.
33. Gunst J, Van den Berghe G. Blood glucose control in the intensive care unit: benefits and risks. *Semin Dial.* 2010; 23:157–162. [PubMed: 20525106]
34. Ichai C, Preiser JC, Société française d'anesthésie-réanimation. et al. International recommendations for glucose control in adult non diabetic critically ill patients. *Crit Care.* 2010; 14:R166. [PubMed: 20840773]
35. Chase JG, Desai T, Bohe J, et al. Improving glycemic control in critically ill patients: personalized care to mimic the endocrine pancreas. *Crit Care.* 2018; 22:182. [PubMed: 30071851] [* Report of a consensus meeting by experts. Strategies to improve the quality of glucose control are discussed, with a focus on computerized treatment algorithms.]
36. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* 2011; 365:506–517. [PubMed: 21714640]
37. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med.* 2016; 374:1111–1122. [PubMed: 26975590]
38. Vanhorebeek I, Gielen M, Boussemaere M, et al. Glucose dysregulation and neurological injury biomarkers in critically ill children. *J Clin Endocrinol Metab.* 2010; 95:4669–4679. [PubMed: 20668035]
39. Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med.* 2006; 34:2714–2718. [PubMed: 16943734]
40. Suh SW, Gum ET, Hamby AM, et al. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. *J Clin Invest.* 2007; 117:910–918. [PubMed: 17404617]
41. Finfer S, Chittock D, Li Y, et al. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. *Intensive Care Med.* 2015; 41:1037–1047. [PubMed: 26088909]

42. Krinsley JS, Chase JG, Gunst J, et al. Continuous glucose monitoring in the ICU: clinical considerations and consensus. *Crit Care*. 2017; 21:197. [PubMed: 28756769] [*** Report of a consensus meeting by experts. The potentially added value of using continuous glucose monitoring is discussed, as well as the limitations of current systems. Also, the potentially divergent effect of glucose control in patient subgroups is reviewed.]
43. Egi M, Bellomo R, Stachowski E, et al. The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes. *Crit Care Med*. 2011; 39:105–111. [PubMed: 20975552]
44. Plummer MP, Bellomo R, Cousins CE, et al. Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. *Intensive Care Med*. 2014; 40:973–980. [PubMed: 24760120]
45. Egi M, Krinsley JS, Maurer P, et al. Pre-morbid glycemic control modifies the interaction between acute hypoglycemia and mortality. *Intensive Care Med*. 2016; 42:562–571. [PubMed: 26846519]
46. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest*. 2010; 137:544–551. [PubMed: 20018803]
47. Stewart KW, Pretty CG, Tomlinson H, et al. Safety, efficacy and clinical generalization of the STAR protocol: a retrospective analysis. *Ann Intensive Care*. 2016; 6:24. [PubMed: 27025951]
48. Dubois J, Van Herpe T, van Hooijdonk RT, et al. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. *Crit Care*. 2017; 21:212. [PubMed: 28806982] [* Randomized controlled trial that shows external generalizability of a software algorithm for tight glucose control, with safe and effective glucose control in all centers.]
49. Finfer S, Wernerman J, Preiser JC, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. *Crit Care*. 2013; 17:229. [PubMed: 23767816]
50. Preiser JC, Chase JG, Hovorka R, et al. Glucose control in the ICU: a continuing story. *J Diabetes Sci Technol*. 2016; 10:1372–1381. [PubMed: 27170632]
51. Preiser JC, Lheureux O, Thooft A, et al. Near-continuous glucose monitoring makes glycemic control safer in ICU patients. *Crit Care Med*. 2018; 46:1224–1229. [PubMed: 29677007]
52. Holzinger U, Warszawska J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. *Diabetes Care*. 2010; 33:467–472. [PubMed: 20007948]
53. Yatabe T, Yamazaki R, Kitagawa H, et al. The evaluation of the ability of closed-loop glycemic control device to maintain the blood glucose concentration in intensive care unit patients. *Crit Care Med*. 2011; 39:575–578. [PubMed: 21178768]
54. Leelarathna L, English SW, Thabit H, et al. Feasibility of fully automated closed-loop glucose control using continuous subcutaneous glucose measurements in critical illness: a randomized controlled trial. *Crit Care*. 2013; 17:R159. [PubMed: 23883613]

Key points

1. Numerous observational studies have indicated a J-shaped relationship between blood glucose concentrations and outcome of critically ill patients, with the lowest risk of mortality associated with blood glucose concentrations in the normal fasting range.
2. Although the optimal blood glucose target for critically ill patients remains unclear, it seems prudent to prevent at least severe hyperglycemia, hypoglycemia and large glucose fluctuations.
3. Safe glucose control requires regular monitoring with accurate devices and a reliable insulin treatment protocol that prevents severe hyperglycemia, hypoglycemia and large glucose fluctuations.
4. When provided with frequent, accurate glucose monitoring and a reliable insulin treatment protocol, tight glucose control is beneficial in critically ill patients receiving early parenteral nutrition.
5. The efficacy and safety of tight blood glucose control in the absence of early parenteral nutrition, when provided with validated tools, is unclear.

Figure 1. Association of blood glucose with outcome

In critically ill patients, upon-admission and mean blood glucose concentrations reveal a U-shaped relationship with the risk of subsequent mortality. In patients without a history of diabetes mellitus, the lowest risk is associated with healthy, age-adjusted fasting blood glucose concentrations. In patients with established diabetes, the curve is flattened, with the nadir somewhat shifted to the right.

Source: original

Table 1
Key differences between the pioneer RCTs and subsequent multicenter RCTs on tight glucose control in the ICU

	Pioneer Leuven RCTs	Multicenter RCTs
Glucose control		
Target control group	<11.9 mmol/l	In general <10 mmol/l
Target intervention group	Age-adjusted: 4.4-6.1 mmol/l for adults 3.9-5.6 mmol/l for children older than 1 year 2.8-4.4 mmol/l for infants	Not age-adjusted 4.4-6.1 mmol/l or higher
Overlap in blood glucose	<10%	In general >50%
Glucose measurement		
Sampling site	Predominantly arterial	Venous and capillary measurements allowed in some RCTs
Measurement device	Predominantly blood gas analyzer	Blood gas analyzer or glucometer
Insulin protocol		
Insulin administration	Continuous	Bolus administration allowed in some RCTs
Nutritional management		
Feeding route first week in ICU	Enteral + parenteral	Predominantly enteral in adult RCTs Mixed in pediatric RCTs

Abbreviations:

ICU: intensive care unit; RCT: randomized controlled trial To convert blood glucose in mmol/l to mg/dl, multiply by 18

Source: original