Clinical benefits of tight glycaemic control: focus on the intensive care unit

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While stress hyperglycaemia has traditionally been regarded as an adaptive, beneficial response, it is clear that hyperglycaemia and hypoglycaemia are associated with increased risk of death in critically ill intensive care unit (ICU) patients. Recent studies on blood-glucose control failed to fully clarify whether this association is causal. Early proof-of-concept single-centre randomised controlled studies found that maintaining normoglycaemia by intensive insulin therapy, as compared with tolerating hyperglycaemia as an adaptive response, improved patient outcome. However, recent large multicentre studies (VISEP, GLUCONTROL and NICE-SUGAR) could not confirm this survival benefit.

Methodological disparity in the execution of the complex intervention of tight glycaemic control may have contributed significantly to the contradicting results. First, different target ranges for blood glucose were used in the control group of the GLUCONTROL and ‘Normoglycaemia in intensive care evaluation and survival using glucose algorithm’ regulation’ (NICE-SUGAR) studies. Second, problems to steer blood-glucose levels within target range in the intervention group resulted in a significant overlap of the treatment groups. Third, allowing inaccurate blood-glucose measurement devices, in combination with different blood sampling sites and types of infusion pumps, may have led to unnoticed swings in blood-glucose levels. Fourth, the level of expertise of the intensive care nurses with the therapy may have been variable due to low number of study patients per centre. Finally, the studies on tight blood-glucose control were done with vastly different nutritional and end-of-life strategies.
The currently available studies do not allow to confidently recommend one optimal target for glucose in heterogeneous ICU patient groups and settings. Provided that adequate devices for blood-glucose measurement and insulin administration are available, together with an extensive experience of the nursing staff, blood-glucose levels should be controlled as close to normal as possible, without evoking unacceptable fluctuations and hypoglycaemia.

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The concept of tight blood-glucose control by intensive insulin therapy in the ICU

It has been well known for a long time that hyperglycaemia, defined by a blood-glucose level exceeding the normal fasting level of 99 mg/dl$^{-1}$ or 5.5 mmol/l$^{-1}$, is common during critical illness. This stress hyperglycaemia was long deemed a beneficial, adaptive response to provide energy to those organs that predominantly rely on glucose as metabolic substrate, such as the brain and the blood cells.

However, a vast body of evidence now reveals that stress hyperglycaemia is also associated with adverse outcome in varying clinical settings of critical illness, myocardial infarction and cardiac surgery. In fact, the association between blood-glucose levels and mortality risk follows a J-curved relationship with the nadir roughly between 90–140 mg/dl$^{-1}$ (5 and 8 mmol/l$^{-1}$) (Fig. 1). Remarkably, in patients with established diabetes mellitus prior to the stressful insult, the relationship between hyperglycaemia and mortality is significantly blunted and somewhat shifted to the right (Fig. 1).

As this association is derived from observational studies, hyperglycaemia could still either reflect an adaptive, beneficial response (just a marker of severity of illness) or it could induce complications, as in diabetes mellitus, and hereby contribute to adverse outcomes (cause of disease). To show a causal relationship between hyperglycaemia and mortality risk, randomised controlled trials (RCT) that target and achieve different blood-glucose levels are required.

Fig. 1. The association in observational studies between blood-glucose level and risk of death. The statistical association in observational studies between blood-glucose level and risk of death follows a J-shaped curve, with normal, fasting blood levels associated with lowest risk of death.
The Leuven proof-of-concept studies

The first RCT to test this hypothesis was performed in Leuven, Belgium. As one would expect from a seminal study, it had a proof-of-concept design: single centre, a homogeneous patient population (mainly cardiac surgery and high-risk/complicated non-cardiac surgery), standardised arterial blood-glucose measurements and central venous continuous insulin infusion. The study targeted a strictly normal level for fasting blood glucose, that is, 80–110 mg dl\(^{-1}\) (4.4–6.1 mmol l\(^{-1}\)), as compared with the usual care of adult surgical ICU patients in the year 2000.\(^8\) Usual care in Leuven and in most centres worldwide\(^9\) in those days was to tolerate hyperglycaemia as an adaptive response and thus to start insulin only when blood-glucose levels exceeded the renal threshold (215 mg dl\(^{-1}\) or 12 mmol l\(^{-1}\)), because such high levels induce glucosuria, fluid shifts, hypovolaemia and infectious complications. Blood-glucose measurements on whole arterial blood were only done by an accurate blood gas analyser. The intervention itself comprised a reliable continuous infusion of insulin, exclusively through a central venous line, using an accurate syringe pump. The insulin dose adaptations were based on a guideline to stimulate intuitive and anticipating decision making by bedside nurses. Extensive training sessions were organised to optimise the execution of tight glycaemic control. In line with the usual care in Leuven, patients were kept in a non-fasting state at all times. Dextrose 20% was administered on the first day, resulting in a caloric intake of 768 kcal per day. Thereafter, enteral nutrition was started, with the daily amount progressively increased, when tolerated. When enteral nutrition was insufficient, early supplemental parenteral nutrition was given, resulting on average in 1100 non-protein kcal per day.

The intention-to-treat patient population maintaining strict normoglycaemia by intensive insulin therapy lowered ICU mortality from 8.0% to 4.6% (absolute risk reduction (ARR) 3.4%) and in-hospital mortality from 10.9% to 7.2% (ARR 3.7%). It also reduced morbidity by preventing organ failure. This was reflected in a shorter duration of mechanical ventilation, a decreased incidence of acute kidney failure, severe infections and polyneuropathy and fewer blood transfusions.

In a first step to test generalisability, the hypothesis was tested in a different patient population. Therefore, the proof-of-concept design from the Leuven I study was copied to the medical ICU setting.\(^10\) Hence, all other factors, such as blood-glucose measurement, insulin administration and feeding strategy, were kept as constant as possible. In the intention-to-treat analysis of the 1200 included patients, the difference in in-hospital mortality (40.0% in the control group and 37.3% in the intervention group) was not statistically significant. It should be recognised that the Leuven II study was statistically underpowered to detect a mortality difference. Nevertheless, morbidity was significantly reduced by the prevention of newly acquired kidney injury, faster weaning from mechanical ventilation and accelerated discharge from the ICU and the hospital. The impact of tight glycaemic control was not as striking as in the surgical study. This may be explained by a larger fraction of patients in medical ICU who were admitted with established organ damage, which could not be prevented by the intervention.\(^11\)

The subsequent confirmation trials

In the wake of euphoria surrounding the Leuven I and II proof-of-concept studies, several RCTs were designed to confirm their results. The VISEP (Volume substitution and Insulin therapy in severe SEPsis) (\(n = 537\)) multicentre trial was designed as a four-arm study to assess the efficacy of fluid resuscitation (10% pentastarch vs. modified Ringer’s lactate) and of blood-glucose control (intensive-insulin therapy vs. usual care) in patients with severe sepsis and septic shock.\(^12\) In this study, comparable blood-glucose targets, as in the Leuven studies, were set out for the intervention (80–110 mg dl\(^{-1}\) or 4.4–6.1 mmol l\(^{-1}\)) and control (180–200 mg dl\(^{-1}\) or 10–11 mmol l\(^{-1}\)) groups. The insulin administration and blood-glucose measurements had been standardised across the 18 participating intensive care units. Nevertheless, the insulin arm of the study was stopped early after 488 patients had been included, because the incidence of hypoglycaemia (12.1%) in the intensive insulin therapy group was considered unacceptably high. Then, at the first planned interim analysis, the fluid resuscitation arm of the study was also suspended because of increased incidence of renal failure in the 10% pentastarch arm. The 90-day mortality was 39.7% in the intensive versus 35.4% in the conventional treatment arm.
The GLUCONTROL multicentre RCT was larger than the VISEP study \( (n = 1101\) over 21 participating medico-surgical ICUs). However, the blood-glucose target in the control group differed from the 180–200 mg \( \text{dL}^{-1} \) \( (10–11 \text{ mmolL}^{-1}) \) used in the latter and the Leuven studies. In essence, GLUCONTROL investigated whether tight glycaemic control to 80–110 mg \( \text{dL}^{-1} \) \( (4.4–6.1 \text{ mmolL}^{-1}) \) versus an intermediate target of 140–180 mg \( \text{dL}^{-1} \) \( (7.8–10.0 \text{ mmolL}^{-1}) \) improves survival in a mixed population of critically ill patients. The GLUCONTROL did not standardise the blood-glucose measurements and allowed the use of point-of-care glucometers. The study was stopped untimely because the target glycaemic control was not reached and the incidence of hypoglycaemia was 9.8%. Hospital mortality did not differ between the intensive insulin therapy group \( (19.5\%) \) and the control group \( (16.2\%) \).

Two single-centre studies, also in a mixed medical/surgical ICU population, both smaller than the Leuven studies, followed and were unable to reproduce a significant mortality benefit. Both studies used similar blood-glucose targets as the Leuven studies. However, blood-glucose measurements were done by point-of-care glucometers with arterial or capillary blood. Tight glycaemic control in the study by Arabi YM et al. \( (n = 523) \) resulted in mean \( \pm \text{SD} \) blood-glucose levels of 115.2 \( \pm 18 \) mg \( \text{dL}^{-1} \) \( (6.4 \pm 1.0 \text{ mM}) \) versus 171 \( \pm 34.2 \) mg \( \text{dL}^{-1} \) \( (9.5 \pm 1.9 \text{ mM}) \) in the control arm. Hospital mortality of 32.3% in the control group versus 27.1% in the intervention group did not differ. Expectedly, the rate of hypoglycaemia increased in the latter group \( (28.6\% \text{ vs. } 3.1\% \text{ in the control group}) \). The second study by De La Rosa et al. included 504 patients. However, it failed to separate the treatment groups adequately. Median blood-glucose level in the intervention group was 117 mg \( \text{dL}^{-1} \) \( (6.5 \text{ mM}) \), with only 39.4% of the blood-glucose measurements within target range. In the control group, the median glycaemia was 148 mg \( \text{dL}^{-1} \) \( (8.2 \text{ mM}) \) with 17.2% in the preset range. Hospital mortality was similar in the two treatment arms \( (\text{control: } 38.4\%, \text{intervention: } 40\%) \).

The common denominator of all the above-mentioned studies is that they were statistically underpowered to detect a reasonable mortality difference.

**NICE-SUGAR: the definite answer?**

To address the issue of statistical power, the NICE-SUGAR (Normoglycaemia in intensive care evaluation and survival using glucose algorithm regulation) multicentre study included 6100 patients to be able to detect, with a 90% power, an absolute decrease in mortality of 3.8% from a baseline 30%. It was designed to the highest standards of trial medicine, with a reproducible Web-based protocol and a patient follow-up to 90 days post-randomisation. In 42 participating centres, 15% of all patients admitted \( (6104 \text{ of } 40171) \) were considered eligible for inclusion. The study compared a strict blood-glucose target of \(< 108 \text{ mg dL}^{-1} \) \( (< 6.0 \text{ mmolL}^{-1}) \) versus an intermediate target of 140–180 mg \( \text{dL}^{-1} \) \( (8–10 \text{ mmolL}^{-1}) \) in the control group. Contrary to the expectations, NICE-SUGAR revealed that tight blood-glucose control increased 90-day mortality from 24.9% to 27.5% as compared with the control group. Excess deaths were attributed to cardiovascular causes. However, organ failure, assessed by the sequential organ failure assessment (SOFA) score, did not differ between the two study groups. As the NICE-SUGAR study was meant to give the definitive answer, a thorough comparison with the Leuven proof-of-concept studies is crucial (Table 1).

Foremost, as in the GLUCONTROL study, normoglycaemia was compared with distinct control targets \( (140–180 \text{ mg dL}^{-1} \text{ vs. } 180–215 \text{ mg dL}^{-1} \text{ in Leuven}) \). Therefore, the NICE-SUGAR study was executed in the flatter part of the observational glycaemia–mortality risk curve (Fig. 1). The control group in the Leuven studies reflected the assumption of hyperglycaemia as a potentially beneficial adaptation. Hence, blood-glucose levels were left alone unless they exceeded the renal threshold of 215 mg \( \text{dL}^{-1} \) \( (12 \text{ mmolL}^{-1}) \). In the NICE-SUGAR trial, the usual care was already affected by the Leuven studies and, at the time of the study design, tolerating glycaemia up to 215 mg \( \text{dL}^{-1} \) \( (12 \text{ mmolL}^{-1}) \) was deemed unethical. The awareness of the problem of hyperglycaemia during critical illness seemed unstoppable since the publication of the Leuven I study in 2001. In Leuven I, only 39.2% of the patients in the control group received insulin treatment. This almost doubled to 70% in the Leuven II and NICE-SUGAR studies. The lower observed \( (24.9\%) \) than the carefully documented expected mortality \( (30\%) \) in the NICE-SUGAR control group may indeed suggest that there was already such a benefit in the control group. This notion is reflected in the pooled \textit{post hoc} analysis of the Leuven studies. This shows that an intermediate blood-glucose level \( (110–150 \text{ mg dL}^{-1}/6.1–8.3 \text{ mmolL}^{-1}) \) was much better than the high...
target (>150 mg dl\(^{-1}\)/8.3 mmol l\(^{-1}\)), accounting for three-quarters of the mortality benefit with intensive insulin therapy. This analysis also revealed that a further, much smaller reduction in risk of death may be obtained by targeting blood glucose <110 mg dl\(^{-1}\)/6.1 mmol l\(^{-1}\). It should be emphasised that these were post hoc analyses, which can only be confirmed by an RCT comparing the intermediate target level with the high, renal threshold level.

Second, the level of therapy compliance, measured by the degree of success in reaching and maintaining the preset target in the intervention group as well as the degree of overlap with the control group, varied greatly. Mean morning blood-glucose levels in the Leuven studies were 105 ± 24 mg dl\(^{-1}\)/5.8 ± 1.3 mmol l\(^{-1}\) in the intervention group versus 152 ± 32 mg dl\(^{-1}\)/8.4 ± 1.8 mmol l\(^{-1}\) in the control group. In NICE-SUGAR, the mean glycaemias migrated to each other (118 ± 25 mg dl\(^{-1}\)/6.6 ± 1.3 mmol l\(^{-1}\) in the intervention group vs. 145 ± 26 mg dl\(^{-1}\)/8.1 ± 1.4 mmol l\(^{-1}\) in the control group). Also, in the Leuven studies, 70% of the patients in the intervention group were on average in target\(^{18}\), whereas this was less than 50% in NICE-SUGAR. This could be important, as a recent meta-analysis suggested that studies that actually managed to adequately achieve the blood-glucose target, showed a reduced mortality, whereas studies that did not succeed in reaching the target reported no benefit or even an increased mortality.\(^{19,20}\) The methodological aspects of glucose measurement and the level of expertise of the nursing team with blood-glucose control may have played a key role.

Third, safe insulin-dose-adjustment to reach and maintain normoglycaemia needs a standardised, accurate glucose measurement technology. In NICE-SUGAR, a variety of glucometers was allowed and not documented. Most of them have recently shown to be unsuitable in the setting of critical illness.\(^{21}\) Accuracy of certain point-of-care glucometers has shown to be extremely poor in the ICU setting and the wide error goes in the opposite direction for the low and the high glucose ranges, making it impossible to use them for targeting a very narrow glucose range. In addition, varying sampling sites (arterial, venous and capillary) were accepted in the context of routine clinical practice, and these, too, have shown to lead to erroneous results for blood glucose.\(^{22}\) Inaccuracies in glucose measurement may have misguided the insulin titration and thereby induced (undetected) hypoglycaemia and large

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Key differences between the Leuven studies(^{8,10}) and NICE-SUGAR(^{16}).</th>
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<td><strong>Leuven adult studies</strong></td>
<td><strong>NICE-SUGAR</strong></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>2748</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>2 x 1 centre</td>
</tr>
<tr>
<td><strong>Patient sample (% of admissions)</strong></td>
<td>60%(medical), 95%(surgical)</td>
</tr>
<tr>
<td><strong>Methodological aspects</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Comparator group target</strong></td>
<td>10–12 mmol/L (180–215 mg/dL)</td>
</tr>
<tr>
<td><strong>Intervention target</strong></td>
<td>&lt;6.1 mmol/L (&lt;110 mg/dL)</td>
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<tr>
<td><strong>Blood sampling site</strong></td>
<td>Predominantly arterial line</td>
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<tr>
<td><strong>Glucose measurement tool</strong></td>
<td>ABL Radiometer bloodgas analyzer (surgical)</td>
</tr>
<tr>
<td></td>
<td>HemoCue (medical)</td>
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<tr>
<td><strong>Insulin infusion</strong></td>
<td>Continuous only via central line</td>
</tr>
<tr>
<td></td>
<td>Syringe pump</td>
</tr>
<tr>
<td><strong>Nurse instructions</strong></td>
<td>Guideline + Intuitive decision making</td>
</tr>
<tr>
<td><strong>Feeding route first week</strong></td>
<td>Parenteral + Enteral</td>
</tr>
<tr>
<td><strong>Average kcal received during ICU stay</strong></td>
<td>1100 kcal/day</td>
</tr>
<tr>
<td><strong>Therapy compliance</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Blood glucose target reached</strong></td>
<td>70%</td>
</tr>
<tr>
<td><strong>Overlap in blood glucose between two groups</strong></td>
<td>&lt;10%</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
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<tr>
<td><strong>Hypoglycaemia</strong></td>
<td>× 6</td>
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<tr>
<td><strong>Morbidity</strong></td>
<td>Reduced organ failure and infections</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Lowered by absolute 3%</td>
</tr>
<tr>
<td><strong>Therapy withdrawal policy</strong></td>
<td>Late</td>
</tr>
</tbody>
</table>
blood-glucose fluctuations. In addition, repeated large (undetected) fluctuations in blood glucose with hypoglycaemia alternating with hyperglycaemia in ill patients may also be worse than tolerating constant moderate hyperglycaemia.

Fourth, avoiding highly variable blood-glucose levels requires experience and thus has a learning curve. One could argue that overcoming the learning curve is even harder with complex interventions, such as tight blood-glucose control. Taking into account that, in NICE-SUGAR, each individual centre must have recruited only about 145 patients (6100 patients over 42 centres), inevitably, some of them may not ever have come out of their learning curve. It is still unclear if the use of a Web-based protocol was able to offset the liabilities of the inaccurate blood-glucose measurements and the inexperience with the complex intervention of tight glycaemic control.

Fifth, insulin therapy induces a shift of potassium from the extracellular to the intracellular compartment, leading to hypokalaemia. By using an arterial blood gas analyser for glucose monitoring, with each blood-glucose check, potassium levels are also measured and could be corrected when needed. As in NICE-SUGAR bedside glucometers were used, an increased incidence of hypokalaemia may have gone unnoticed. In fact, hypokalemia-induced arrhythmia may have contributed to the excess cardiovascular deaths in NICE SUGAR that were unexplained by organ failure.

Sixth, feeding strategies differed strongly between the studies. In NICE-SUGAR, feeding relied almost exclusively on the enteral route (80 kcal intravenous glucose on the first day; on average, a total of 880 kcal per day), whereas, in Leuven, early parenteral nutrition (about 800 kcal on the first day) supplemented insufficient enteral feeding, resulting in an average of 1100 kcal per day for adult patients. The substantially higher amounts of parenteral nutrition in the Leuven studies, although still, on average, below normal caloric requirements, may have increased the severity of stress-induced hyperglycaemia, and thus, the intervention may have been in part directed to counteract this side effect of parenteral nutrition. Conversely, insulin treatment in a nutritionally deprived state early in the disease course, for example in NICE-SUGAR, may have been deleterious. It may evoke a global substrate deficit through insulin-induced counteracting of proteolysis, lipolysis, glycogenolysis and gluconeogenesis, which could be vital during fasting. Which of the two feeding regimens (the Leuven strategy of early combined parenteral and enteral nutrition, or the NICE-SUGAR protocol resulting in early hypocaloric enteral feeding only) is superior in a context of normoglycaemia, is currently unknown. The EPaNIC-RCT (http://www.clinicaltrials.gov, identifier NCT00512122) will be trying to answer this question and is currently recruiting patients.

Seventh, in a setting where hyperglycaemia is triggered by surgery or trauma, the delay between onset of hyperglycaemia and the start of glycaemic control is short. By contrast, when ICU patients already suffered from chronic illness prior to ICU admission, and hyperglycaemia was present for a longer time, the optimal window of opportunity to prevent hyperglycaemia-induced complications may have been missed. This would be in line with the results of the Leuven II study in medical ICU patients, where tight blood glucose seemed less potent than in surgically critically ill patients. Besides, two-thirds of the NICE-SUGAR patients were medically critically ill patients.

Finally, studies on tight glycaemic control are inherently unblinded and consequently vulnerable to bias. Outspoken enthusiasm in a single-centre, investigator-driven study, or established opinions in a multicentre trial, leading to the discontinuation of the allocated strategy because of physician's request, may have influenced the results. In this context, it should be also be noted that the policy of withdrawal of care was much earlier in NICE-SUGAR (median day 6) as compared with the Leuven studies (median day 14).

Summary

One can state unambiguously that glucose is not just an innocent bystander during critical illness, as altering its circulating levels has shown to result in improved or worsened outcome. Steering blood-glucose levels is a complex intervention requiring serial processes of measurement, anticipation, correction and feedback on performance. The potential serious complications associated with hypoglycaemia make these essential processes gain importance.

Another conclusion to be drawn is that proof-of-concept single-centre studies lack the external validity to enthusiastically implement complex interventions too rapidly. On the other hand,
multicentre trials with, amongst other aspects, large numbers of participants, statistical analyses plans and independent data verification are beyond any doubt superior from a statistical methodology point of view. However, the NICE-SUGAR trialists seem to have overlooked the importance of the basic modalities of the intervention at the bedside. The scientific validity of Web-based protocols and millions of blood-glucose data may become trivial if methods of measurement are not standardised, unspecified, and, most likely, fairly inaccurate. Intensive-care physicians should be aware of those differences in type of evidence.

Finally, to put the debate into perspective, everyone acknowledges that the implementation and evaluation of complex interventions is a stepwise, gradual process that consumes vast amounts of time and resources. More than eight decades after the discovery of insulin and recent major multicentre RCTs, totalling over 23 000 patients, the effect of intensive blood-glucose control on cardiovascular outcome in longstanding type 2 diabetes mellitus is still uncertain. Hence, it would be a missed opportunity for the intensive care community if the debate about and research in blood-glucose control in the ICU would be stopped with many unanswered questions.

Clinical practice points

- Hyperglycaemia during critical illness cannot be neglected, as it is associated with poor outcome.
- A carved in stone blood-glucose target for glycaemic control has not yet been delineated, since randomised clinical trials yielded inconsistent results.
- Heterogeneous patient populations, widely varying practices of blood-glucose and nutritional management and physician’s bias may have played an important role in these discrepancies.
- In light of the detrimental effects in the NICE-SUGAR study, tight glycaemic control <110 mg dl\(^{-1}\) (6.1 mmol l\(^{-1}\)) cannot be generally recommended for all ICUs.
- All intensive-care physicians should take heed of the instrumental modalities of blood-glucose control (measurement device, mode of insulin administration) and markers of a failing strategy (strong blood-glucose fluctuations and high incidence of hypoglycaemia).
- Blood-glucose levels should be controlled as close to normal as possible, without evoking unacceptable glucose fluctuations and hypoglycaemia.

Research agenda

- Post hoc analyses of the NICE-SUGAR study need to be conducted to explore the precise cause of death in the study patients.
- An exploratory individual patient data meta-analysis of randomised clinical trials on tight glycaemic control may help to find possible explanations for the discrepancies between the individual studies.
- Primarily, the focus should shift to studies on the accuracy of blood-glucose measurements, glycaemic management protocols and the validation of markers of quality of glycaemic control.
- Long-term outcome studies need to clarify the impact of hypoglycaemia in the ICU on neurocognitive function.
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Conflict of interest

The authors report to have no conflict of interest

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