Endocrine and metabolic considerations in critically ill patients 1

Glucose management in critically ill adults and children

Dieter Mesotten, Jean-Charles Preiser, Mikhail Kosiborod*

Blood glucose management in people with acute myocardial infarction and critical illness has always attracted controversy. Compared with the era before 2001 when no attention was given to blood glucose management, DIGAMI-1 in 1995 and the first Leuven study in 2001 showed improved outcomes with strict control of blood glucose, thereby suggesting a causal association between hyperglycaemia and mortality risk. These landmark trials have set the standard in clinical practice that excessive hyperglycaemia is not acceptable. Multicentre trials contradicted the benefits of tight control of patients' blood glucose and results showed that different standard operating procedures for blood glucose control (eg, blood glucose meters or algorithms), divergent concomitant feeding strategies, and varying patient populations are important confounders. The general consensus now is that excessive hyperglycaemia (>10 mmol/L) and severe hypoglycaemia (<2·2 mmol/L) should be avoided in critically ill adults. If adequate blood glucose meters and clinically validated protocols for insulin-dosing are available, targeting of blood glucose concentrations to less than 8 mmol/L (moderate glycaemic control), while avoiding mild hypoglycaemia (<3·9 mmol/L), is a reasonable strategy in adult patients who are critically ill. This recommendation is not based on findings from randomised controlled trials, but merely represents a very common, pragmatic approach by physicians at the bedside. As a result of the few properly validated technologies for tighter blood glucose control, targeting blood glucose concentrations to less than 6 mmol/L is not recommended, because its risk-to-benefit ratio becomes questionable. Because blood glucose control in the target of adult ranges does not improve patient outcomes for children in the intensive care unit, glucose management in this patient population should be limited to avoid excessive hyperglycaemia (>10 mmol/L).

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This is the first in a Series of four papers about endocrine and metabolic considerations in critically ill patients

KU Leuven—University of Leuven, University Hospitals Leuven, Department of Intensive Care Medicine, Leuven, Belgium (D Mesotten MD)**; Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium** (J-C Preiser MD)**; and Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, MO, USA** (Prof M Kosiborod MD)

Correspondence to: Dr Dieter Mesotten, KU Leuven—University of Leuven, University Hospitals Leuven, Department of Intensive Care Medicine, B-3000 Leuven, Belgium. **dieter.mesotten@med.kuleuven.be**

Introduction

Since the publication of the 2001 landmark study (Leuven I) by Greet Van den Berghe and colleagues[1] on intensive insulin therapy for blood glucose management in patients on the surgical intensive care unit (ICU), glucose management in critically ill adults and children has attracted much attention and controversy. More than 90% of the reports about hyperglycaemia during critical illness have been generated since publication of this randomised controlled trial (RCT).[1] The failure to confirm the results of Leuven I[1]—that intensive insulin therapy reduced mortality and morbidity in critically ill adults—in many other RCTs and the invariably high incidence of hypoglycaemia associated with tight blood glucose control have led to the controversy surrounding blood glucose management in the ICU. Controversy essentially is about the wide gap between findings from well controlled study settings that use a specific tailored management, and daily practice at the patient's bedside in other settings. Fortunately, this controversy also initiated more research to reduce this gap in findings.

Association between blood glucose concentrations and outcome

Hyperglycaemia

More than a century ago, Claude Bernard recognised the acute hyperglycaemic response during acute haemorrhage, called the diabetes of injury.[2] Because the acute hyperglycaemic response was proportional to the extent of injury it was deemed a marker of severity of illness and potentially a beneficial reaction to stress.[3] However, persistent hyperglycaemia was subsequently associated with poor outcome, notably in a case series of patients with head injuries.[4,5] From large epidemiological studies, blood glucose concentrations are now known to often be raised in patients who are severely ill, whether they are admitted to emergency departments,[6,7] ICUs,[8–10] or cardiac care units.[11] These studies also showed a linear correlation between hyperglycaemia and mortality risk (figure).[12,14,15] Consistently and irrespective of the categories of blood glucose concentrations used in the studies, mortality risk begins to increase when blood glucose exceeds 8·0 mmol/L. No clear cutoff value of blood glucose concentration can be defined above which the mortality risk disproportionally or steeply rises. Mortality risk gradually increases in the wide range of severe hyperglycaemia (from 8·0 mmol/L up to 13·9 mmol/L). This association is substantially blunted in patients with established diabetes (figure).[12,13,16,17] Chronic hyperglycaemia—such as with higher HbA_{1c} concentrations—rather than the diagnosis of diabetes itself, is the likely underlying mechanism of this attenuated association.[18–20] Other markers of illness severity, such as blood lactate[21] and cholesterol,[22] might alter this association too.

Hypoglycaemia

Likewise, hypoglycaemia in patients admitted to hospital is also associated with an increased mortality risk (figure).[10,23,24] Before the advent of blood glucose

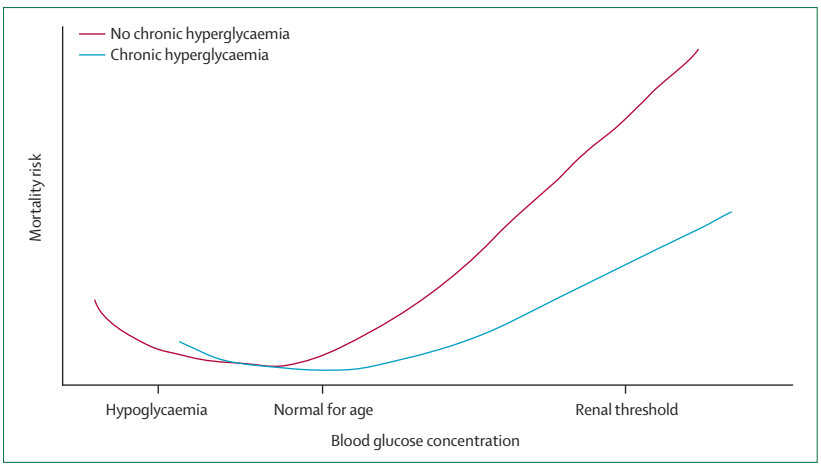

Figure: **J-shaped association curve between blood glucose concentrations and mortality in critically ill patients**
Lowest risk zone for mortality in adults, represented by the red line, is 3·9–8·0 mmol/L. Renal threshold for glucosuria is about 12 mmol/L. Patients with chronic hyperglycaemia, such as in established diabetes, have a blunted association curve represented by the blue line. This figure is based on the results from Falciglia and colleagues,[9] Kosiborod and colleagues,[12] and Egi and colleagues.[13]

management with insulin infusions, hypoglycaemia during critical illness was mainly associated with fulminant hepatic failure or adrenal failure in patients with septic shock and multiple organ failure. Clearly in this context, hypoglycaemia was a sign of imminent death. Since the Leuven I study,[1] research on the association between hypoglycaemia (either spontaneously or insulin-induced) and mortality in critically ill adults and children gained momentum. In critically ill adults, the mortality risk associated with hypoglycaemia increases linearly with progressive increases in severity of hypoglycaemia. Mortality risk in the hypoglycaemic range develops more steeply than in the hyperglycaemic range, leading to a J-shaped curve (figure).[15,16,24,25] If blood glucose concentrations fall below 3·9 mmol/L the mortality risk noticeably increases. This cutoff is in line with the most commonly used threshold to define hypoglycaemia in patients with diabetes.[26] Severe hypoglycaemia in critically ill patients was arbitrarily defined in most studies into blood glucose control as when blood glucose fell below 2·2 mmol/L on at least one occasion. However, this 2·2 mmol/L cutoff is not based on a steep increase in mortality risk in the hypoglycaemic range, which occurs at only extremely low concentrations (<1·2 mmol/L).[27] Since intensive insulin therapy invariably leads to a higher incidence of hypoglycaemia, whether hypoglycaemia is an independent risk factor of mortality in critically ill patients has been much debated. Risk factors such as established diabetes, severe sepsis or septic shock, cardiogenic shock, need for mechanical ventilation or renal replacement therapy, and severity of illness have all been associated with hypoglycaemia.[27–31] Additionally, errors with insulin dosing, notably with decreases in nutrition without adjustment of the insulin infusion rate, often give rise to hypoglycaemia. Findings from multivariable analyses,[15,24,31] correcting for these risk factors, sometimes showed hypoglycaemia to be an independent risk factor for mortality. However, in other studies[27,32] hypoglycaemia was no longer correlated with a mortality risk after adjusting for severity of illness. Furthermore, in patients admitted to hospital after a myocardial infarction, hypoglycaemia (in the context of insulin treatment) was not associated with an increased mortality risk.[33] Generally, patients who are severely ill are thought to have a high risk not only of hypoglycaemia, but also of hyperglycaemia.

Glycaemic variability

The combination of long-term hyperglycaemia and episodic hypoglycaemia, especially in the context of increased blood glucose variability, is associated with the highest mortality risk. Notably, inappropriate treatment of hypoglycaemia with overdosing of the dextrose bolus can lead to rebound hyperglycaemia and increased blood glucose variability. In a meta-analysis,[34] the presence of high blood glucose variability was shown to be an independent risk factor for mortality during critical illness, even after accounting for mean concentrations of blood glucose. However, glycaemic variability is the least validated glycaemic measure, because it is has been studied less than other measures of glycaemia (ie, hyperglycaemia and hypoglycaemia) and is highly affected by the frequency of blood glucose measurements and the measure of variability used.[35–37] Therefore, an increased understanding of the connection between glycaemic variability and patient outcome is needed. Accordingly in 2013, a consensus meeting[38] recommended that blood glucose variability should be reported in studies assessing glucose management (panel 1).

Therefore, analysis of dysglycaemia in critically ill patients should include markers of three domains: hyperglycaemia, hypoglycaemia, and glycaemic variability (panel 1).[38–40] On the basis of these observational studies, hyperglycaemia, hypoglycaemia, and blood glucose variability should all be regarded as independent predictors of adverse outcomes in critically ill patients. However, to establish whether these factors directly cause harm in these patient populations or are merely markers of disease severity, RCTs that address hyperglycaemia, hypoglycaemia, and glycaemic variability, will need to be done.

Mixed findings from RCTs

Effects of intensive glucose control were first assessed in people with acute myocardial infarction as DIGAMI-1[41] was the first large RCT to study and compare intensive with conventional glucose control (table 1). Patients presenting within 24 h of an acute myocardial infarction and diabetes or initial glucose concentrations exceeding 11 mmol/L were randomly assigned to an acute and chronic insulin treatment regimen versus usual care. Individuals randomly assigned to the insulin group

received 24 h or more of intravenous dextrose-insulin infusion titrated to maintain their blood glucose at 7·0–10·0 mmol/L. Their treatment was initiated with intravenous insulin in 5% dextrose in water in the acute phase, followed by subcutaneous insulin injections three times per day for the subsequent 3 months, titrated to standard therapeutic targets for glucose control. This group was compared with individuals given usual care, in which insulin was not given unless it was judged to be clinically needed.[41] This trial enrolled 620 patients, 80% of whom had been diagnosed with diabetes. 24 h after starting treatment, participants randomly assigned to the insulin group achieved significantly lower glucose concentrations than those in the control group; however, average glucose values remained greater than 8 mmol/L in both groups.[41] At hospital discharge, differences between the groups were smaller but significant. Furthermore, HbA_{1c} levels at 3 months were significantly lower in the intervention than the control group (7·0% *vs* 7·5%, p<0·01).[41] Hypoglycaemia (not explicitly defined in the initial study reports) was reported in 15% of patients given insulin infusion compared with 0% in the usual care group. For the primary endpoint of all-cause mortality at 3 months, no significant difference was recorded between the two groups (38 deaths in intervention *vs* 49 deaths in control group). However, subsequent analyses of mortality at both 1 year and 3·5 years of follow-up showed clinically and statistically significant reductions in all-cause mortality in the insulin treated group compared with the control group (at 1 year 18·6% *vs* 26·1%, p=0·027; at 3·5 years 33% *vs* 44%, p=0·011); continuing benefits were reported for people in the intervention group during the 20 year follow-up of the DIGAMI-1 trial.[45] If the validity of the mortality reduction noted in the long-term analyses is accepted, the relative contributions of various aspects of the trial remain uncertain, including the effects of the acute dextrose-insulin infusion, and of multidose insulin injection in the outpatient setting. Therefore, although the DIGAMI-1 study data[45] are the most compelling in this area of targeted glucose control for the treatment of acute coronary syndrome, the relative attribution of improved survival to acute inhospital lowering of glucose is uncertain. This survival benefit could not be reproduced in the DIGAMI-2 trial[42] in which blood glucose concentrations did not differ between the intervention and control groups, because of similar insulin-infusions during the acute phase.[42] In the HI-5 trial,[43] the effect of dextrose-insulin infusion was compared with usual care in patients with myocardial infarction and hyperglycaemia on arrival to hospital. The therapeutic target for the insulin arm was 4·0–10·0 mmol/L and intravenous dextrose was infused with insulin (5% or 10% dextrose in water). The HI-5 trial[43] was terminated early because of slow enrolment and, similar to DIGAMI-2,[42] did not achieve a significant difference in glucose values between the intensive and conventional glucose groups. Accordingly, no significant difference in mortality was recorded between the intervention and control arms at hospital discharge or at 30 days or 6 months follow-up. The latest investigation of glucose control in patients with acute myocardial infarction was the randomised BIOMArCS-2 study,[44] a prospective, single-centre, open-label clinical trial that randomly assigned 294 patients with acute coronary syndrome and glucose concentration between 7·8 mmol/L and 16 mmol/L on admission to hospital to receive either intensive glucose control for 48 h (target glucose of 4·7–6·1 mmol/L) or conventional management (target glucose <16 mmol/L). Primary outcome was high-sensitivity troponin T value 72 h (hsTropT72) after admission, as a marker of infarct size.[44] The extent of myocardial injury was also measured at 6 weeks after participants were randomly assigned by myocardial perfusion scintigraphy. Glucose values were significantly lower in the intensive than in the conventional treatment group at 6 h, 12 h, 24 h, and 36 h, but equalised by 72 h. No significant differences were noted in hsTropT72 between the groups (1197 ng/L *vs* 1354 ng/L, p=0·41). The median extent of myocardial injury measured by myocardial perfusion scintigraphy was similar in the intensive and in the conventional group (2% *vs* 4%, p=0·07). Number of inhospital deaths and recurrent myocardial infarction was only nine events in total, but were more frequently reported in the intensive group than for individuals in the conventional treatment group (eight events *vs* one event, p=0·04). The results of this trial[44] are difficult to interpret because the number of events was very small, it had a single-centre and open-label design, and the findings conflicted with other small clinical trials that showed reduction in infarct size with intensive compared with conventional glucose control.

With the exclusion of people with acute myocardial infarction, the Leuven I study[1] showed that intensive insulin therapy (targeting blood glucose concentrations

***Panel 1*: Key points from the consensus recommendations on reporting of glycaemia in critically ill adults[38]**

Consensus on reporting of hypoglycaemia (number and percentage of patients with at least one episode)

- Mild hypoglycaemia: blood glucose <3·9 mmol/L
- Severe hypoglycaemia: blood glucose ≤2·2 mmol/L
- Separate reporting of iatrogenic and spontaneous hypoglycaemia
- Treatment of severe hypoglycaemia (eg, duration, symptoms, glucose bolus, and rebound hyperglycaemia)
- Standard set of baseline hypoglycaemia risk factors to establish an independent association

Consensus on central tendency of glycaemia

- Median and IQR of individual patient mean blood glucose

Consensus on dispersion of glycaemia (variability)

- Median and IQR of individual patient's SD of blood glucose

	Targeted glucose control	Raised blood glucose on entry	Glucose targets	Blood glucose levels achieved	Clinical endpoints	Results
DIGAMI-1 (1995)[41]	Only intervention group	About 15·6 mmol/L	7·0–10·0 mmol/L *vs* usual care acutely; 5·0–7·0 mmol/L fasting blood glucose *vs* usual care afterwards	9·6 mmol/L *vs* 11·7 mmol/L during first 24 h; difference in HbA_{1c} but not fasting blood glucose afterwards	Yes	Mortality neutral at 3 months (primary endpoint), improved survival in glucose control arm after 1 year
DIGAMI-2 (2005)[42]	Only intervention group	12·7 mmol/L	7·0–10·0 mmol/L inhospital *vs* usual care acutely; 5·0–7·0 mmol/L fasting blood glucose (group one only) *vs* usual care afterwards	9·1 mmol/L *vs* 10·0 mmol/L at 24 h, no difference afterwards	Yes	Mortality neutral between three groups
HI-5 (2006)[43]	Only intervention group	About 11 mmol/L	4·0–10·0 mmol/L *vs* usual care	8·3 mmol/L *vs* 9·0 mmol/L (p=not significant) during first 24 h	Yes	Mortality neutral in hospital, at 3 months and 6 months
BIOMArCS-2 (2013)[44]	Control and intervention group	7·8 mmol/L	4·7–6·1 mmol/L during day, 4·7–7·8 mmol/L at night *vs* <16 mmol/L	6·2 mmol/L *vs* about 7·2 mmol/L	Yes	No difference in infarct size by high-sensitive troponin; composite of inhospital deaths and reinfarction higher in the intensive *vs* standard group (very small number of adverse events)

Table 1: **Overview of studies into blood glucose management in acute myocardial infarction**

between 4·4 mmol/L and 6·1 mmol/L) compared with a policy of tolerating blood glucose up to 12 mmol/L, strongly reduced mortality and morbidity in patients admitted to the surgical ICU (table 2). Additionally, the outcome benefit for those given intensive insulin treatment was maintained after 4 years.[56] This study[1] was subsequently repeated in two other single-centre trials in Leuven, in patients admitted to the medical ICU (Leuven II)[46] and the paediatric ICU (Leuven III).[53] Similar to the Leuven I study,[1] in the usual care groups of these subsequent studies blood glucose concentrations of up to 12 mmol/L were tolerated and in the intervention groups normal fasting concentrations of blood glucose were targeted: 4·4–6·1 mmol/L in adults, 3·9–5·6 mmol/L in children (aged 1–16 years), and 2·8–4·4 mmol/L in infants (aged <1 year). Moreover, strict blood glucose control in the Leuven single-centre setting decreased morbidity in patients in long-stay medical and paediatric patients who were critically ill.[46,53]

Since all the Leuven studies were single-centre trials, with a high level of skill in implementation of the complex intervention for blood glucose control, they had high internal validity. However, results from expert centres, which have low external validity, are often difficult to reproduce in real life settings. Therefore, multicentre studies were set up to test whether tight control of blood glucose could be applied in daily practice in the ICU.

Two large studies, which did not have a factorial design, were done in Europe[51] and in Australia, New Zealand, and Canada.[50] The Glucontrol clinical trial[51] recruited 1078 patients in 21 centres, whereas the NICE-SUGAR trial[50] included 6104 patients in 42 centres. In both studies, tight blood glucose control (maintained within 4·4–6·1 mmol/L) was compared with an intermediate target in the control group (7·8–10·0 mmol/L). Because of the results from the Leuven studies, physicians were already doing some blood glucose control and deemed that the usual care from before 2001 of tolerating hyperglycaemia up to 12 mmol/L was substandard.[57] In the Glucontrol trial[51] the mortality rate did not differ between the randomly assigned groups, but in the NICE-SUGAR study[50] tight blood glucose control increased the 90 day mortality from 24·9% to 27·5%. Excess death was attributed to cardiovascular causes.

Blood glucose control in critically ill children has followed a similar path to that in adult control, from strong effects in the single-centre setting of Leuven III[53] to a neutral effect in multicentre trials.[54,55] As in the adult Leuven studies, usual care in children in Leuven III was to treat hyperglycaemia only when blood glucose concentrations exceeded 12·0 mmol/L.[53] In the intervention group the fasting blood glucose concentrations (2·8–4·4 mmol/L in infants, 3·9–5·6 mmol/L in children) were strictly targeted. As a result, the difference in average blood glucose between patients in the two randomly assigned groups was large (1·7 mmol/L). A simple deduction from the J-shaped association curve can already anticipate a possible strong treatment effect.[53,58] By contrast, the multicentre studies[54,55] had a higher target concentration for blood glucose in the intervention group: 4·0–7·0 mmol/L in the CHiP trial[55] and 4·4–6·1 mmol/L in the SPECS study.[54] In critically ill children, the 4·4–6·1 mmol/L target was thus equal to the Leuven target in adult patients. The higher target range in the intervention group was driven by the fear of patients becoming hypoglycaemic. In the usual care group,

	Number of participants (intervention/ control groups)	Intervention (blood glucose target)	Control (blood glucose target)	Primary outcome variable	Results
Single-centre studies					
Van den Berghe et al,[1] 2001 (Leuven I)	765/783	4·4–6·1 mmol/L	10–12·0 mmol/L	ICU mortality	Better in intervention group than control group
Van den Berghe et al,[46] 2006 (Leuven II)	595/605	4·4–6·1 mmol/L	10–12·0 mmol/L	ICU mortality	Neutral (total population) Better in intervention group (long-term critically ill population)
Arabi et al,[47] 2008	266/257	4·4–6·1 mmol/L	10–11·0 mmol/L	ICU mortality	Neutral
De La Rosa et al,[48] 2008	254/250	4·4–6·1 mmol/L	10–11·0 mmol/L	28 day mortality	Neutral
Multicentre studies					
Brunkhorst et al,[49] 2008 (VISEP)	247/289	4·4–6·1 mmol/L	10–11·0 mmol/L	28 day mortality and SOFA	Neutral
Finfer et al,[50] 2009 (NICE-SUGAR)	3054/3050	4·4–6·1 mmol/L	7·8–10 mmol/L	90 day mortality	Better in control group than intervention group
Preiser et al,[51] 2009 (Glucontrol)	542/536	4·4–6·1 mmol/L	7·8–10 mmol/L	ICU mortality	Neutral
Kalfon et al,[52] 2014	1336/1312	4·4–6·1 mmol/L	<10 mmol/L	90 day mortality	Neutral
Paediatric studies					
Vlasselaers et al,[53] 2009 (Leuven III)	349/351	2·8–4·4 mmol/L for infants, 3·9–5·6 mmol/L for children	10–12·0 mmol/L	Duration of ICU stay	Better in intervention group than control group
Agus et al,[54] 2012 (SPECS)	490/490	4·4–6·1 mmol/L	No target range	Nosocomial infections	Neutral
Macrae et al,[55] 2014 (CHiP)	694/675	4·0–7·0 mmol/L	10–12·0 mmol/L	Number of days alive and free from MV at 30 days	Neutral

ICU=intensive care unit. SOFA=sequential organ failure assessment. MV=mechanical ventilation.

Table 2: **Overview of the main studies on blood glucose management in the intensive care unit**

either no target range was set[54] or, comparable with the Leuven studies, insulin treatment was started only when blood glucose exceeded 12·0 mmol/L.[56] Hence, in Leuven III[53] the target ranges of the treatment groups were set highly apart, whereas in the multicentre trials[54,55] the target ranges were less disparate. No outcome differences were reported because blood glucose concentrations hardly differed between the treatment groups in the multicentre trials. In the Leuven III study,[53] blood glucose concentrations did not overlap and, despite the 25% incidence in hypoglycaemia, tight control of blood glucose in critically ill children had a large treatment effect (ie, fewer nosocomial infections, shortened length of stay in the ICU, and 3% mortality risk reduction). This mortality benefit of strict blood glucose control was maintained for up to 4 years after study inclusion and no adverse effects on neurocognitive development were reported when participants were exposed to tight blood glucose control during their stay in the ICU.[59]

Findings from RCTs into critically ill adults and children strongly suggest that the largest benefit for blood glucose control can be expected if the difference in blood glucose concentrations between the study groups is large and if the study is done in a single-centre setting where the blood glucose management is tailored to the local treatment habits.[60] In a post-hoc analysis[61] of the Leuven adult studies, patients with an average blood glucose concentration less than 8·3 mmol/L already had a survival benefit, compared with patients with average glycaemia (>8·3 mmol/L). Restriction of blood glucose control to less than 6·1 mmol/L not only had a small additional benefit, but also had a much higher risk of hypoglycaemia. In patients with established diabetes, tight blood glucose control did not decrease mortality, which is very much in line with the flattened J-shaped curve. A trend might even be seen towards increased mortality risk in patients with diabetes undergoing tight control of blood glucose to less than 6·1 mmol/L. The fact that findings in a multicentre setting do not accord with the reported benefits of tight blood glucose control in the single centre setting points to the complexity of the treatment and several other factors that clearly interfere with blood glucose control.

Can these trial discrepancies be accounted for?

Apart from the fact that most multicentre studies had lower concentrations of blood glucose in the control arm than in the Leuven studies,[1,46,53] and as a result a smaller difference in average blood glucose between the treatment

groups, several possible explanations were suggested for why the Leuven data have not been replicated.

Blood glucose management in patients with diabetes is perceived to be a daunting task. The exciting results of the well controlled Leuven studies led clinicians to believe that blood glucose control in critically ill patients was a straightforward and cheap treatment that could be easily implemented for any patient in any ICU. However, the results of the NICE-SUGAR study[50] warned that broad implementation of tight management of blood glucose can be harmful.[62] The high variability of essential components of blood glucose control (ie, nutrition, glucose monitoring, and insulin titration protocol) in daily clinical practice might account for the discrepancies between the results from RCTs of blood glucose control in critically ill patients.[62]

Nutritional strategy

The most obvious factor to affect blood glucose concentrations is the enteral and parenteral intake of glucose calories. Decreases in the glucose intake during critical illness do not mitigate stress hyperglycaemia. However, postponing of the administration of parenteral nutrition until the first week of a patient's stay in the ICU significantly lowers the insulin dose needed to keep the blood glucose in a specific target range.[63] Additionally, a meta-regression analysis[64] showed that an increased benefit from tight blood glucose control can be expected when the parenteral nutrition given is increased.[64] Hence, a nutritional strategy in which parenteral nutrition is only started after 5–7 days in the ICU will attenuate stress hyperglycaemia, improve outcome, and reduce health-care costs.[63,65,66] A target range for blood glucose should be independent of the nutritional regimen. Effects of different targets for blood glucose in accordance with the caloric intake should be assessed in prospective RCTs. Of note, blood glucose control in the context of hypocaloric feeding has a high incidence of hypoglycaemia.[63] Furthermore, in patients who have resumed oral food intake—and hence are recovering from critical illness—potential benefits of tight blood glucose control might not outweigh the risk of hypoglycaemia. In these patients, a blood glucose target of less than 10 mmol/L and the interruption of continuous insulin infusion are advised.[67]

Glucose measurement technology

Blood glucose management starts with measurement of blood glucose concentrations. These measurements should be accurate and accessible for health-care workers at the bedside. The gold standard for blood glucose measurement is done in a central hospital laboratory with hexokinase or glucose oxidase enzymatic reactions. Hence, for blood glucose management in the ICU these tests cannot be done and compromises have to be made. In the Leuven studies, blood gas analysers were mainly used, whereas in the NICE-SUGAR study[50] a range of blood glucose meters was allowed. Many authors have questioned the accuracy of these handheld blood glucose meters in critically ill patients.[68,69] This reduced accuracy in such patients is due to anaemia and drugs that interfere with enzymatic reactions of the blood glucose measurement (eg, ascorbic acid, paracetamol [acetaminophen], or icodextrin).[70,71] Use of capillary instead of arterial blood for blood glucose measurements further amplifies the inaccuracy of blood glucose meters. Commonly, these errors result in overestimation of blood glucose concentrations, leading to overtreatment with insulin and finally inducing hypoglycaemia.[70] In 2013, a meta-analysis[72] accorded with these findings that blood glucose measurements in arterial blood on blood gas analysers are more accurate than in capillary blood on blood glucose meters. Some authors even suggested that the use of blood glucose meters might be unsuitable for use in critically ill patients and that variable sites for blood sampling might, at least partly, account for the rise in mortality of patients on tight blood glucose control in the NICE-SUGAR trial.[73] Therefore, consensus meetings have recommended not to use handheld blood glucose meters and capillary blood for blood glucose control in critically ill patients.[38,67] However, in patients who do not need invasive monitoring, such as those with arterial lines, and are admitted to medium-care units, use of handheld blood glucose meters for blood glucose control in wider target ranges to compensate for the inaccuracy, might be acceptable.[74]

Near-continuous monitoring of blood glucose will hopefully replace the frequent intermittent sampling that is necessary for safe and effective blood glucose control with conventional technology (eg, blood gas analyser and blood glucose meters). Several studies[75,76] have already shown that the accuracy of continuous monitoring is in line with the handheld blood glucose meters. Continuity of glucose measurements is then supposed to counterbalance this reduced accuracy of the continuous glucose sensors. Computer simulations have shown that continuous sensors have a lower probability for clinical errors than do intermittent sensors at the same accuracy level.[77,78]

However, more specific quality requirements need to be defined for these continuous blood glucose sensors;[79] also needed are sufficiently powered studies assessing the effectiveness of near-continuous glucose monitoring in improving patients' blood glucose control.[80–82]

Algorithms and protocols for blood glucose management

Methods to calculate the insulin infusion rates, based on at least the blood glucose values, have also been variable. The Leuven studies were done with a loose paper protocol to allow intuitive and anticipative management by nurses at the bedside. Despite the increase in the incidence of hypoglycaemia, this protocol improved patient outcomes.[1,46,53] However, the applicability of such an intuitive

protocol outside the setting of a well controlled, single-centre study is difficult because it heavily relies on the skills of the nursing staff in the management of tight blood glucose control. This factor could explain why the Glucontrol multicentre trial,[51] which used simple paper-based protocols, struggled to separate the treatment groups, and at the same time still saw an increased incidence of participants with hypoglycaemia. Nevertheless, software-guided algorithms for insulin dosing are still unproven to improve blood glucose control in sufficiently powered clinical trials. Conversion of paper-based protocols into a software programme might improve protocol adherence, but it also masks the simplicity of such protocols.[83] If these algorithms are then suddenly tested in a large RCT without previous clinical validation, patient outcomes could be negatively affected.[50] Moreover, simulation modelling has shown that an insulin titration protocol has a greater effect on blood glucose management than the methods of blood glucose measurement.[84] Increasingly complex, dynamic computer algorithms take additional inputs that are necessary for blood glucose control (through present and recent past blood glucose concentration, insulin infusion rate, and caloric intake). Most computer algorithms that are commercially available fall into this category and have been validated in implementation studies or small randomised controlled trials.[85–88] The Yale protocol is also freely available.[85] This protocol showed a good balance between tight regulation of blood glucose control and risk of hypoglycaemia.[84] Software-guided blood glucose control by use of model predictive control algorithms are the most complex because they also take into account patient-related factors such as age, diabetes, and insulin sensitivity. In two small randomised controlled trials,[89,90] model predictive control software improved glycaemic control and decreased incidence of hypoglycaemia compared with nurse-driven blood glucose control. Whether this more safe and effective blood glucose control by computer algorithms can be supported in large multicentre trials is unknown. For example, the CGAO-REA trial[52] could only slightly tighten control of blood glucose and was unable to avoid a strong increase in the incidence of hypoglycaemia. Very much in line with the use of continuous blood glucose sensors, few clinical trial data exist for the effectiveness of software-guided protocols in improvements of blood glucose control, let alone on their effect on patient outcomes. Irrespective of the insulin titration protocol, the following key points should always be taken into account to avoid hypoglycaemia: first, decrease or stop insulin infusion when parenteral or enteral nutrition is discontinued, even for brief periods; second, insulin infusion should be done only by accurate infusion systems, preferably via a separate lumen of the central venous line to avoid fluctuation in flow rate; and finally, do not use bolus to administer insulin in critically ill patients if nutrition is also given continuously.

Trial design for future studies of blood glucose management

At present, the body of evidence for blood glucose management in critically ill adults and children is not available beyond the point of proof of efficacy. Indeed, results of well controlled, single-centre studies[1,46,53] into blood glucose control, comparing minimum (ie, a threshold of 12 mmol/L) versus very strict glycaemic control (to fasting levels), showed improved morbidity and mortality in critically ill patients. Notably, critically ill patients who had an extended stay in the ICU benefited the most, because blood glucose control is a preventive strategy.[91] However, blood glucose management to these narrow levels did not pass the milestones of effectiveness and efficiency, because the multicentre trials could not confirm the results of the single-centre studies.

Contemporary clinical practice suggests that most clinicians do not want to go back to the era before 2001, when blood glucose concentrations were not managed at all. There is a now a broadly supported consensus that repeated blood glucose measurements of more than 10 mmol/L should prompt blood glucose management with an insulin infusion.[38,67] American Diabetes Association's 2015 guidelines[92] recommend that stringent targets, such as 6·1–7·8 mmol/L, might be appropriate for selected patients, as long as this can be achieved without significant hypoglycaemia. Also, many European expert centres now advocate intermediate target ranges, such as 5·6–7·8 mmol/L in the STAR-Liège protocol[93] and 5·0–8·0 mmol/L in most Dutch ICUs.[94] This new perception of hyperglycaemia and its management should be assessed in large surveys and observational studies, and also should lead to consensus definitions of hyperglycaemia and hypoglycaemia (especially for children), which in turn are needed for the choice of target ranges in the control and intervention group of future RCTs. However, if the target ranges of the two randomly

Panel 2: Daily practice targets of patient glucose control in intensive care units

1. We strongly suggest that severe hyperglycaemia (>10 mmol/L) is avoided in adult patients in the intensive care unit, keeping glucose concentrations under moderate control (eg, <8·0 mmol/L), although, a universally acceptable upper limit cannot be specified
2. We suggest avoidance of tight glucose control in an emergency situation because this management does not seem to be reasonable and is potentially dangerous
3. We strongly suggest that severe hypoglycaemia (<2·2 mmol/L) and large variations in glucose concentrations are avoided in critically ill patients
4. We do not recommend the use of any drug other than intravenous insulin for glucose control in intensive care units

Recommendations adapted from Ichai and colleagues,67 by permission of Ichai and colleagues.

assigned group are close, the sample size of the clinical trial will need to be increased. This increase in size is necessary for trials investigating the effect of devices (ie, sensors or algorithms)[83] on patient outcomes.[58]

Conclusions and recommendations for daily practice

As a minimum, guidelines, such as from the Surviving Sepsis Campaign,[95] nowadays recommend to start insulin treatment when two consecutive measurements of blood glucose concentrations exceed 10 mmol/L. The Leuven studies[1,46] showed that strict blood glucose control (maintained at 4·4–6·1 mmol/L) is better than tolerating overt hyperglycaemia (>12 mmol/L). However, the NICE-SUGAR trial[50] reported that the broad implementation of this strict blood glucose control could be dangerous and worsened outcome compared with a target range lower than 10 mmol/L. Poor standardisation in blood glucose measurement and training of nursing staff, inevitable in a large pragmatic multicentre trial, probably contributed to the detrimental effects of tight blood glucose control in a less-controlled setting. To reconcile these findings we believe that patients at risk should be clearly defined, and that they should not be defined by the type of ICU to which they have been admitted (panel 2).[96] Acutely critically ill patients who need invasive support and monitoring will probably benefit more from stricter blood glucose control than both those who are admitted to medium care facilities and those recovering from critical illness. Furthermore, blood glucose management can be done more safely when more invasive monitoring is used. The blunted J-shaped curve already suggests that target concentrations of blood glucose might need to be lower in patients who do not have diabetes than in those with diabetes.

Standardisation in the measurement of blood glucose concentrations is necessary. All present guidelines recommend not to use capillary blood in critically ill patients because it can produce serious errors. Blood glucose measurement with on-site blood gas analysers is the best option of blood glucose management in the ICU. Alternatively, use of one type of handheld blood glucose meter with an acceptable error range could reduce expense, certainly in the population of patients given medium care.

When treatment with insulin is initiated, blood glucose management needs frequent measurements since hypoglycaemia and blood glucose fluctuations need to be swiftly detected. In the immediate phase after admission, blood glucose needs to be checked at least once every hour in critically ill patients until haemodynamic stabilisation. Intervals between blood glucose measurements can be increased (eg, to every 2–4 h) when blood glucose becomes stable. Unavoidably, these frequent but necessary blood glucose measurements increase the workload of nursing staff. In the future, continuous blood glucose monitors might be helpful, but their effect on glucose control and outcomes is yet to be reported.

Thorough training of ICU nurses and doctors in the bedside execution of the complex intervention of blood glucose control is indispensable. Insulin dosing and timing of the blood glucose measurements need to be done through standard protocols and algorithms. Such protocols should be based on evidence from clinical trials, examining its safety and efficacy. Sliding-scales are now deemed insufficient for insulin dosing in critically ill patients. Instead, protocols and algorithms should take into account (besides the present blood glucose concentration) glycaemic trend, carbohydrate intake, and insulin infusion rate. However, evidence from RCTs is insufficient to broadly recommend the use of computerised algorithms for insulin dosing.

Key performance indicators (ie, hyperglycaemia, hypoglycaemia, and glycaemic variability) ought to be followed up in the implementation of any blood glucose management protocol, irrespective of the chosen target range (panel 1).

The general consensus is that excessive hyperglycaemia (>10 mmol/L) and severe hypoglycaemia (<2·2 mmol/L) should be avoided in critically ill adults (panel 2).

Provided that adequate blood glucose meters and clinically validated protocols for insulin-dosing are available, targeting of blood glucose to less than 8 mmol/L (moderate glycaemic control), while avoiding mild hypoglycaemia (<3·9 mmol/L), is a reasonable treatment in adult patients who are critically ill. This moderate glycaemic control is supported by the observation that, if a patient's blood glucose is in the range 3·9–7·8 mmol/L for more than 80% of time, survival is increased in non-diabetic, critically ill adults.[97] Although this pragmatic approach is not based on RCT evidence, the Dutch National Intensive Care Evaluation registry (representing more than 85% of ICUs in the Netherlands) monitors the proportion of glucose measurements outside the range of 2·2–8·0 mmol/L as quality indicators, which provides further support for this moderate approach (panel 2).[96]

Strict control of blood glucose concentrations to less than 6 mmol/L is not yet safe to be generally implemented (panel 2).

Because blood glucose control in critically ill children does not improve outcomes, blood glucose management in this patient group should be limited to avoid excessive hyperglycaemia (>10 mmol/L).

Search strategy and selection criteria

We searched Medline and Embase from inception to Dec 10, 2014, using terms "blood glucose", "blood glucose control", "insulin", or "glycemia" in combination with "critical illness", "intensive care unit", "critical care", "cardiac care unit", or "sepsis". We also hand searched abstracts of conferences and conference proceedings. Non-English articles and articles classified as animal studies were excluded.

Contributors
DM did the literature search. All authors drafted and revised this Series paper for important intellectual content.

Declaration of interests
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