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Tight Blood Glucose Control With Insulin in the ICU*

Facts and Controversies

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Recently, the concept that stress hyperglycemia in critically ill patients is an adaptive, beneficial response has been challenged. Two large randomized studies demonstrated that maintenance of normoglycemia with intensive insulin therapy substantially prevents morbidity and reduces mortality in these patients. Since then, questions have been raised about the efficacy in general and in specific subgroups, and about the safety of this therapy with regard to potential harm of brief hypoglycemic episodes and of high-dose insulin administration. These issues are systematically addressed in relation to the available evidence. Intensive insulin therapy during intensive care is effective in reducing the mortality and morbidity of critical illness. The available randomized studies show that an absolute reduction in risk of hospital death of 3 to 4% is to be expected from this therapy in an intention-to-treat analysis. In order to confirm this survival benefit and assign it as statistically significant, future studies should be adequately powered, and hence sample size should be at least 5,000. The absolute reduction in the risk of death increases to approximately 8% when patients are treated with intensive insulin for at least 3 days. Data available thus far indicate that blood glucose control to strict normoglycemia is required to obtain the most clinical benefit. The risk of hypoglycemia increases with this therapy, but it remains unclear whether this is truly harmful in the setting of critical care.

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Key words: critical illness; hyperglycemia; insulin; morbidity; mortality

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CREATE-ECLA = Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Cardiologicas Latin America; DIGAMI = Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction; GIK = glucose together with insulin and potassium; OR = odds ratio; VISEP = Volume Substitution and Insulin Therapy in Severe Sepsis

Glucose homeostasis is dysregulated in critically ill patients, resulting in hyperglycemia, irrespective of previously diagnosed diabetes. Peripheral insulin resistance, characterized by hyperinsulinemia, increased gluconeogenesis, and impaired peripheral insulin-mediated glucose uptake, plays a central role.[1] This condition has been labeled *stress diabetes* or *diabetes of injury*.[2,3]

Whereas stress hyperglycemia had long been considered an adaptive and beneficial response, it has become clear that it may have possible detrimental effects. Two large randomized, controlled clinical trials[4,5] demonstrated that maintenance of normoglycemia with intensive insulin therapy can reduce morbidity and mortality in critically ill patients.

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Several issues have been raised with regard to efficacy and safety of this intervention. These critiques

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are systematically addressed in this review and discussed with the available evidence.

Hyperglycemia Is Associated With Adverse Outcome From Critical Illness

Several studies clearly associated hyperglycemia with a higher risk for mortality and morbidity of critical illness, some of which are listed here. A metaanalysis[6] revealed a strong and consistent association between stress hyperglycemia after myocardial infarction, and increased risk of in-hospital mortality, congestive heart failure, and cardiogenic shock. In patients undergoing cardiac surgery, hyperglycemia has been associated with a substantial mortality risk[7] and delayed extubation.[8] Also, intraoperative hyperglycemia appeared to be an independent risk factor for adverse outcome after cardiac surgery.[9] Elevated blood glucose levels predicted mortality and length of ICU and hospital stay of trauma patients, and were associated with infectious morbidity and prolonged need of mechanical ventilation.[10–13] Apart from the predictive value of hyperglycemia for mortality of patients with severe brain injury, a significant relationship was found between high blood glucose levels and worse neurologic status, impaired pupil reactivity, intracranial hypertension, and longer hospital length of stay.[14,15] Similarly, hyperglycemia predicted a higher risk of death after stroke and a poor functional recovery in those patients who survived.[16] In addition, a strong link has been described between increased blood glucose levels and the risk of critical illness polyneuropathy in sepsis and the systemic inflammatory response syndrome.[17] Also, in critically ill children, hyperglycemia develops and is associated with worse outcome.[18] Particularly in severely burned children, mortality, incidence of bacteremia and fungemia, and number of skin grafting procedures were higher in hyperglycemic patients.[19] A retrospective analysis[20] of a heterogeneous population of critically ill patients revealed that even a modest degree of hyperglycemia was associated with a substantially increased hospital mortality. In addition, variability in glucose levels during critical illness has been related to mortality.[21]

Impact of Strict Blood Glucose Control With Intensive Insulin Therapy During Critical Illness: Available Data

Establishing a causal relationship between hyperglycemia and adverse outcome, vs hyperglycemia as a marker of more severe illness, requires randomized controlled trials assessing the impact of a treatment that prevents hyperglycemia. An overview of studies on this topic is presented in Table 1. The first study,[4] performed in Leuven, was published in 2001 and included adult patients receiving mechanical ventilation admitted to the ICU predominantly after extensive, complicated surgery or trauma, or after medical complications of major surgical procedures. Nursing staff in this research setting was unaltered compared to before the onset of the study, with one nurse taking care of two patients. In the intervention group, glucose levels were targeted with insulin to 80 to 110 mg/dL, resulting in mean blood glucose levels of 103 mg/dL (normoglycemia), vs 153 mg/dL in the patients treated according to the conventional approach (hyperglycemia). Arbitrarily, based on another study[22] with a similar target population, patients needing intensive care for at least 5 days were assumed to be the target population for this intervention. Since no data were available with regard to the size of the expected benefit, interim analysis was performed for safety reasons. The study was stopped after inclusion of 1,548 patients. In the intention-to-treat population, tight blood glucose control with insulin 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%; Table 2). The benefit was much larger in the target population of patients who required intensive care for at least 5 days, with a reduction of ICU mortality from 20.2 to 10.6% (ARR of 9.6%) and of in-hospital mortality from 26.3 to 16.8% (ARR, 9.5%). In retrospect, it appeared indeed that the impact of the intervention increased with the duration of its application and that a substantial benefit was present with at least 3 days of intensive insulin therapy (Table 2). Besides saving lives, intensive insulin therapy substantially prevented several critical illness-associated complications, including the development of critical illness polyneuropathy, blood stream infections, anemia, acute renal failure, and hyperbilirubinemia. In addition, patients were less dependent on prolonged mechanical ventilation and intensive care. Intensive insulin therapy protected the central and peripheral nervous system from secondary insults and improved long-term rehabilitation of patients with isolated brain injury.[23] The therapy was also associated with substantial cost saving.[24] A 4-year follow-up of the cardiac surgery patients, comprising 63% of the study population, showed that intensive insulin therapy also improved long-term outcome with maintenance of the survival benefit without inducing more need for medical care.[25]

Subsequently, a small (n = 61) prospective, randomized, controlled study[26] was performed in a predominantly

Table 1—*Available Publications of Intensive Insulin Therapy in the ICU and Their Limitations*

Study	Patients, No.	Patient Type	Glycemia, mg/dL	Positive Effects	Possible Harm	Limitations
Van den Berghe et al[4]	1,548	Surgical	153 decreased to 103; 73% < 110 in intensive insulin group	Mortality intention to treat decreased; mortality target group 5-d ICU decreased; critical illness polyneuropathy decreased; protection nervous system[23]; bloodstream infection decreased; anemia decreased; acute renal failure decreased; hyperbilirubinemia decreased; duration of mechanical ventilation decreased; ICU stay decreased; improved long-term outcome[23,25]; costs decreased[24]	Increased risk of hypoglycemia; high insulin dose is statistical positive risk factor for mortality	Single-center study; surgical patients only
Grey and Perdrizet[26]	61	Surgical	179 decreased to 125	Nosocomial infections decreased		Small study; surgical patients only
Krinsley[27]	1,600	Medical/ surgical	152 decreased to 131	Mortality decreased; anemia decreased; acute renal failure decreased; ICU stay decreased; costs decreased[28]		Not randomized
VISEP[29,30]	488	Sepsis/ septic shock	Not reported in abstract	90-d mortality decreased (not significant)	Increased risk of hypoglycemia	Only published as abstract; four-arm study with two interventions tested concomitantly; lacking statistical power to document the hypothesized difference in mortality
Glucontrol[31]	855	Medical/ surgical	147 (127–163) decreased/118 (109–131)*			Increased risk of hypoglycemia; only presented at international symposium,[55] no formal publication; lacking statistical power to document the hypothesized difference in mortality
Van den Berghe et al[5]	1,200	Medical	160 decreased to 105; 64% < 110 in intensive insulin group	Mortality intention to treat decreased (not significant); mortality target group 3-d ICU decreased; critical illness polyneuropathy/myopathy decreased[32]; myopathy decreased[32]; new kidney injury decreased; hyperbilirubinemia decreased; duration of mechanical ventilation decreased; ICU and hospital stay decreased	Increased risk of hypoglycemia	Single-center study; medical patients only; appropriately powered for target population, but not intention-to-treat population
Van den Berghe et al[33]	2,748	Medical/ surgical	152 decreased to 105; 70% < 110 in intensive insulin group	Mortality intention to treat decreased; mortality target group 3-d ICU decreased; critical illness polyneuropathy decreased; new kidney injury decreased; efficacy present in all large subgroups (cardiovascular disease/surgery, respiratory disease or thoracic noncardiac surgery, abdominal disease/surgery, patients with sepsis)	Increased risk of hypoglycemia, but no detectable clinical consequences; harm by brief treatment excluded	Metaanalysis of the two Belgian studies[4,5]

*Median (interquartile range) from the mean morning blood glucose levels.

general surgical patient population. It targeted glucose levels between 80 mg/dL and 120 mg/dL with intensive insulin therapy, which resulted in mean daily glucose levels of 125 mg/mL vs 179 mg/dL in the standard glycemic control group, and found that the incidence of total nosocomial infections was decreased.

Thereafter, in a heterogeneous medical/surgical patient population (n = 1,600), an observational study[27] evaluated the impact of implementing a tight glucose management protocol in "real-life" intensive care. IV insulin was administered only if glucose levels were > 200 mg/dL on two successive measurements and aimed to lower glycemia < 140 mg/dL. Mean glucose levels of 131 mg/dL were reached in the protocol period, compared to 152 mg/dL in the baseline period. In comparison with the historical control group, hospital mortality decreased from 20.9 to 14.8% (ARR, 6.1%). Length of ICU stay, incidence of newly developed renal injury, and number of patients needing RBC transfusion were also lower. Implementation of this protocol also substantially saved money.[28]

In Germany, a prospective, randomized, multicenter trial[29] was subsequently designed as a four-arm study to assess the impact of two types of fluid resuscitation and the efficacy and safety of intensive insulin therapy in patients with severe sepsis and septic shock (Volume Substitution and Insulin Ther-

Table 2—*Mortality Benefit of Intensive Insulin Therapy in Surgical and Medical ICU Patients in Relation to Duration of Application

Variables	Surgical ICU				Medical ICU			
	Conventional Insulin Therapy	Intensive Insulin Therapy	p Value	Absolute Mortality Reduction, %	Conventional Insulin Therapy	Intensive Insulin Therapy	p Value	Absolute Mortality Reduction, %
All patients	85/783 (10.9)	55/765 (7.2)	0.01	3.7	242/605 (40.0)	222/595 (37.3)	0.3	2.7
ICU stay > 2 d	70/432 (16.2)	48/419 (11.5)	0.05	4.7	218/450 (48.4)	184/455 (40.4)	0.01	8.0
ICU stay > 3 d	66/321 (20.6)	41/301 (13.6)	0.02	7.0	200/381 (52.5)	166/386 (43.0)	0.008	9.5
ICU stay > 4 d	64/272 (23.5)	36/246 (14.6)	0.01	8.9	174/323 (53.9)	152/335 (45.4)	0.03	8.5
ICU stay > 5 d	64/243 (26.3)	35/208 (16.8)	0.02	9.5	157/286 (54.9)	133/290 (45.9)	0.03	9.0

*Data are presented as No./total (%) unless otherwise indicated.

apy in Severe Sepsis [VISEP]). The insulin arm of the study was stopped prematurely because the rate of hypoglycemia in the intensive treatment group (12.1%) was considered unacceptably high. At this point (n = 488), 90-day mortality was 29.5% in the intensive vs 32.8% in the conventional insulin treatment arm (ARR of 3.3%, not significant).[30]

"Glucontrol" was the next prospective, randomized, controlled, multicenter trial[31] designed to investigate whether tight glycemic control to 80 to 110 mg/dL with insulin improves survival in a mixed population of critically ill patients. The steering and safety committee of this trial decided to stop enrollment after a first interim analysis because the targeted glycemic control was not reached and the risk of hypoglycemia was considered high.

In Leuven, after the first surgical study, a second large randomized, controlled trial[5] was started in medical ICU patients, a study that used the same insulin-titration protocol as in the previous surgical study. Based on the outcome results of the surgical study, which had indicated that the impact of intensive insulin therapy was dependent on the duration of its application (Table 2),[4] the medical study was powered to demonstrate or exclude an absolute reduction of 7% in the risk of death of long-stay patients needing at least a third day of intensive care. Long-stay patients cannot be identified on ICU admission; thus, in order to obtain the required 700 long-stay patients, inclusion of 1,200 patients was necessary. Blood glucose was controlled to mean levels of 105 mg/dL in the intensive insulin therapy group, as compared with 160 mg/dL in the conventional glucose management. In-hospital mortality of the intention-to-treat population of 1,200 patients was reduced from 40.0 to 37.3% (ARR, 2.7%; not significant). The lack of statistical significance was not surprising because the study was not statistically powered for this end point. In the target group of long-stay patients, tight glycemic control with insulin significantly reduced in-hospital mortality from 52.5 to 43.0% (ARR, 9.5%; Table 2). Morbidity was significantly reduced in the intention-to-treat group of patients receiving intensive insulin therapy, with less kidney injury, less hyperbilirubinemia, earlier weaning from mechanical ventilation, and earlier ICU and hospital discharge. The reduction in morbidity was even more striking in the target group. These long-stay patients were discharged from the hospital alive on average 10 days earlier than those who received conventional insulin therapy. There was no difference in bacteremia or prolonged antibiotic therapy requirement, but the number of long-stay patients with hyperinflammation was also reduced. Among long-stay patients, intensive insulin therapy also reduced the incidence of critical illness polyneuropathy and/or myopathy.[32]

In the pooled data set of the two Leuven studies[4,5] (mixed medical/surgical patient population, n = 2,748), hospital mortality was reduced from 23.6 to 20.4% (ARR, 3.2%; p = 0.04) for all patients, and from 37.9 to 30.1% (ARR, 7.8%; p = 0.002) for the patients who remained in the ICU for at least 3 days.[33] Kidney injury developing during ICU stay and critical illness polyneuropathy were reduced to almost half.

Issues Raised Regarding Efficacy and Safety of Intensive Insulin Therapy

In the literature, concerns have been raised regarding consistency of the available data on efficacy, identifiable subgroups of patients who would or would not benefit, the role of parenteral nutrition, the optimal level of blood glucose control, and potential harm of intensive insulin therapy in criti-

cally ill patients. These issues are systematically addressed and discussed in the light of the available evidence.

Are the Available Data Consistent?

Comparing the available randomized studies[4,5,29,30,33] reporting mortality data, it is striking to find a uniform 3 to 4% lower risk of death in the intention-to-treat patient populations receiving intensive insulin therapy as compared with patients receiving conventional blood glucose management. Also, the nonrandomized Stamford study[27] showed an ARR of 6%. This consistency in the absolute rather than relative risk reduction is in line with intensive insulin therapy preventing a certain number of avoidable deaths because it prevents additional pathology during intensive care, rather than it is being a cure for a disease. Furthermore, the two Leuven studies have clearly shown that the impact of such a preventive intervention depends on the duration of its application (Table 2).

Whether or not the 3 to 4% ARR was statistically significant in the available studies, of course, depends on the statistical power and thus on the size of the trial. Indeed, the size of a study required to assign a certain ARR as statistically significant depends on the baseline risk of death and the size of the ARR that is anticipated. The higher the baseline risk and the smaller the anticipated ARR, the larger the sample size required. Small studies, with only a few hundred patients, are unable to detect a 3 to 4% ARR in mortality of ICU patients. For example, the second Leuven study, performed in the medical ICU, was statistically powered for the larger 7% ARR in mortality that was expected in the target population of patients treated at least 3 days, and not for the 3 to 4% ARR in the intention-to-treat group. To prove or exclude the latter effect with enough statistical power in the studied high-risk intention-to-treat population would require a sample size of at least 5,000 patients. When correcting for well-known on-admission risk factors (malignancy, diabetes, kidney failure, on-admission APACHE [acute physiology and chronic health evaluation] II, TISS-28 [simplified therapeutic intervention scoring system], C-reactive protein, creatinine, and alanine aminotransferase), the benefit of intensive insulin therapy in the intention-to-treat medical ICU population did, however, reach statistical significance (odds ratio [OR] for intensive insulin, 0.77; 95% confidence interval [CI], 0.60 to 0.99; $p = 0.04$).

The impact of intensive insulin therapy increases with time of application. The parallelism between the surgical and the medical Leuven studies of this increasing mortality benefit with time is striking (Table 2; Fig 1). Indeed, a more pronounced benefit is present among long-stay patients (7 to 9% ARR) than in the intention-to-treat population (3 to 4% ARR) because the effect among long-stay patients gets diluted by the lack of mortality benefit when applied only briefly. Pooling of the datasets from the surgical and the medical Leuven studies created the statistical power to show the morbidity and mortality benefits of intensive insulin therapy in the intention-to-treat mixed medical/surgical patient population, with a larger benefit for those who were treated at least 3 days.[33] Other studies[34–36] are in agreement with 3 days of intensive insulin therapy being minimally required to obtain a sizable outcome benefit. Furthermore, from Figure 1 it is also clear that a surrogate end point, such as 30-day mortality, is inappropriate for a preventive strategy such as intensive insulin therapy because clear separation of the survival curves occurs only after this time point.

The VISEP study,[29] which was stopped early for risk of hypoglycemia after inclusion of only 488 patients, was clearly underpowered to assign the expected and documented 3 to 4% difference in mortality as statistically significant. Furthermore, VISEP was a four-treatment arm study (two fluid-resuscitation strategies, and two levels of blood glucose control), and 17 centers participated, which may have caused confounders.[29] For the Glucontrol trial,[31] also stopped early for inadequate blood glucose control (unintended protocol violations) and risk of hypoglycemia, no published data are available regarding mortality, but it is clear that this study was also underpowered to exclude a 3 to 4% mortality benefit on only 855 patients from a total of 19 centers. These observations underline the importance of adequate power and thus large-enough sample size for future studies in order for them to generate conclusive results on reproducibility and consistency of the impact of intensive insulin therapy. Appropriate statistical tools are easily accessible,[37] and thus investigators should use them correctly.

Are There Identifiable Subgroups of Patients Who Would Not Benefit From Intensive Insulin Therapy?

Since a novel intervention can only be advocated for patients who are likely to benefit from the therapy, it is important to address this question. The pooled database of the two Leuven studies[4,5,33,38] generated the possibility to look into this issue. In all large diagnostic subgroups of mixed medical/surgical patients, including patients with cardiovascular, respiratory, GI/hepatic disease or surgery, patients with active malignancy, and those with sepsis on ICU admission, intensive insulin

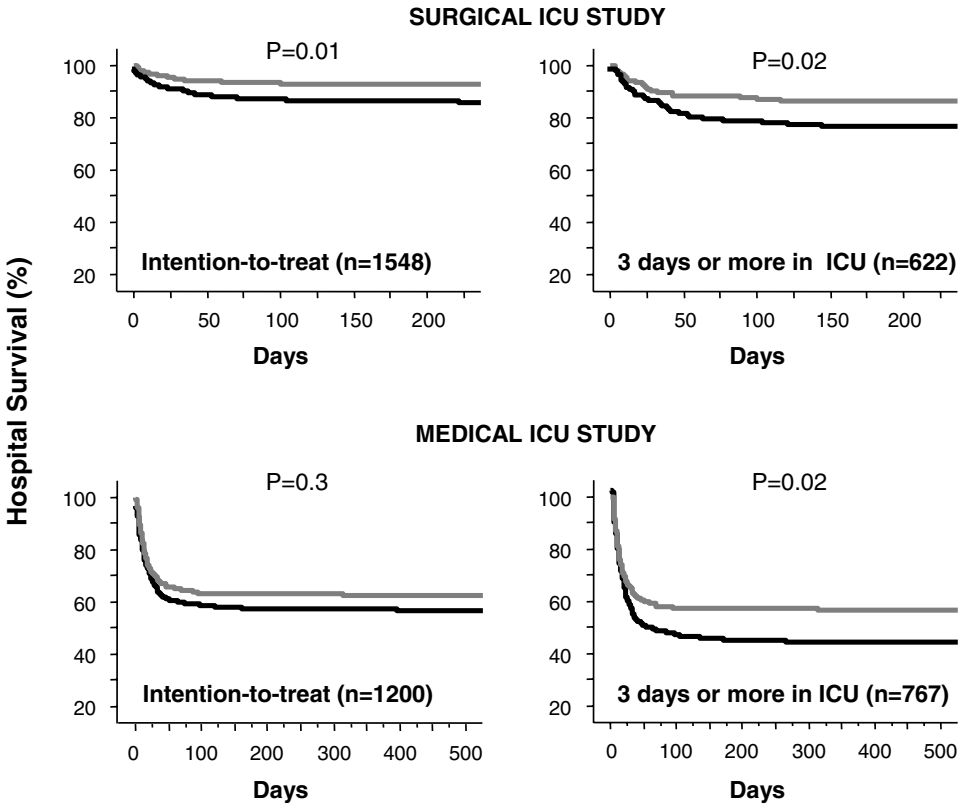

FIGURE 1. Kaplan-Meier curves for in-hospital survival of surgical and medical ICU patients. The effect of intensive insulin treatment on the time from admission to the ICU until death is shown for surgical (*upper panel*) and medical (*lower panel*) ICU patients. *Left panel*: Analysis for the intention-to-treat patient population. *Right panel*: Subgroup of patients staying in the ICU for ≥ 3 days. Black lines represent the conventional group, and the gray lines the intensive insulin therapy group. Patients discharged alive from the hospital were considered survivors. The indicated p values were calculated by proportional-hazards regression analysis.

therapy reduced mortality and morbidity (Table 3).[33,38] The absolute reduction in the risk of death was quite comparable in all these subgroups. Only in the group of patients with a history of diabetes was no survival benefit observed, but morbidity also tended to be reduced in these patients. In multivariate logistic regression analysis, correcting for other on admission risk factors such as severity of illness and cancer, and for intensive insulin therapy in ICU (OR, 0.78; 95% CI, 0.63 to 0.96; p = 0.02), patients with diabetes who had previously been treated with medication other than insulin had a lower risk of death (OR, 0.61; 95% CI, 0.40 top 0.93; p = 0.02), whereas those who were receiving insulin treatment prior to critical illness had a tendency for an increased risk of death (OR, 1.39; 95% CI, 0.96 to 2.01; p = 0.08). The exact reason for this statistical association remains to be investigated.

Is There Evidence Against Implementation of Intensive Insulin Therapy in the ICU?

Skeptics have labeled Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)-2, Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation-Estudios Cardiologicas Latin America (CREATE-ECLA), and Glucose Insulin in Stroke Trial as studies in the literature that provide "evidence against" intensive insulin therapy in ICU patients. Several decades ago, the infusion of glucose together with insulin and potassium (GIK) emerged as a metabolic cocktail to reduce early mortality and morbidity of patients with acute myocardial infarction and yielded promising results. The DIGAMI study[39–41] was the largest and also covered the longest follow-up period, showing that for patients with diabetes and an acute myocardial infarction, 24-h infusion of GIK followed by blood glucose control at approximately 145 to 155 mg/dL improved survival. This study could not differentiate between an acute effect of GIK vs that of blood glucose control with insulin during the months following the infarction. This question was addressed in the second DIGAMI study.[42] This study had three arms: one

Table 3—*Outcome Benefit and Rate of Hypoglycemia in Subgroups of Critically Ill Patients

Insulin Treatment	Conventional	Intensive	ARR, %
Cardiovascular disease or surgery	n = 549	n = 533	
Hospital mortality	48 (8.7)	34 (6.4)	2.3
New kidney injury	35 (6.4)	17 (3.2)	3.2
Critical illness polyneuropathy†	41 (40.6)	17 (23.3)	17.3
Hypoglycemia	3 (0.5)	21 (3.9)	
Respiratory/thoracic disease or surgery	n = 317	n = 317	
Hospital mortality	128 (40.4)	103 (32.5)	7.9
New kidney injury	36 (11.4)	20 (6.3)	5.1
Critical illness polyneuropathy†	71 (52.9)	48 (35.0)	17.9
Hypoglycemia	6 (1.9)	58 (18.3)	
GI/hepatic disease or surgery	n = 549	n = 533	
Hospital mortality	60 (28.6)	50 (25.1)	3.5
New kidney injury	11 (5.2)	7 (3.5)	1.7
Critical illness polyneuropathy†	38 (51.4)	18 (32.7)	18.7
Hypoglycemia	6 (2.9)	22 (11.0)	
Active malignancy	n = 247	n = 256	
Hospital mortality	105 (42.5)	95 (37.1)	5.4
New kidney injury	23 (9.3)	16 (6.3)	3.0
Critical illness polyneuropathy†	54 (54.5)	31 (30.7)	23.8
Hypoglycemia	3 (1.2)	39 (15.2)	
Sepsis	n = 471	n = 479	
Hospital mortality	172 (36.5)	160 (33.4)	3.1
New kidney injury	49 (10.4)	34 (7.0)	3.4
Critical illness polyneuropathy†	114 (53.3)	69 (31.9)	21.4
Hypoglycemia	14 (2.9)	94 (19.6)	
History of diabetes	n = 200	n = 207	
Hospital mortality	44 (22.0)	48 (23.2)	
New kidney injury	14 (7.0)	11 (5.3)	1.7
Critical illness polyneuropathy†	25 (43.9)	14 (32.6)	11.3
Hypoglycemia	8 (4.0)	29 (14.0)	

*Data are presented as No. (%). Data are derived from Van den Berghe et al.[33] Patients can fit into more than one subgroup, but if they are included in one of the first three categories, they cannot belong to either one of the other two of those three categories.
†Percentage of screened patients.

with GIK, one with GIK followed by strict blood glucose control, and one control arm. No significant difference in mortality, and morbidity, the latter evaluated by the occurrence of nonfatal reinfarctions and strokes, was observed among the three arms. Importantly, however, the three study arms resulted in identical blood glucose levels after the first 24 h due to unintended protocol violation. Hence, the study only excluded an acute effect of GIK when administered in the absence of strict blood glucose control, but no conclusion on the impact of tight blood glucose control could be drawn. The large CREATE-ECLA study[43] on GIK therapy after acute myocardial infarction also excluded a benefit on mortality and morbidity with GIK. Also in this study, no glucose control was advised, and GIK therapy resulted in increased rather than decreased blood glucose levels as compared with the usual care. Similarly, GIK infusion for 24 h after stroke failed to realize a significant reduction in blood glucose levels or mortality, as examined in the Glucose Insulin in Stroke Trial.[44] These studies are often promoted to argue against the efficacy of tight blood glucose control with intensive insulin therapy. Clearly, this is unjustified. What the studies show is that short-term GIK therapy without sustained blood glucose control does not work, but they do not provide evidence against tight blood glucose control because this was not studied. However, both the DIGAMI-2 and CREATE-ECLA trials showed an association between higher glucose levels and increased risk of death.[42,43]

Potential Harm of Intensive Insulin Therapy

Intensive Insulin Therapy and the Risk of Hypoglycemia: Harmful? Severe or prolonged hypoglycemia can cause convulsions, coma, and irreversible brain damage as well as cardiac arrhythmias. The risk of hypoglycemia is a concern when intensive insulin therapy is administered to critically ill patients because early hypoglycemic symptoms are not easily recognized in ICU patients.[45]

The risk of hypoglycemia (glucose $\leq$ 40 mg/dL) with intensive insulin therapy increased from 0.8 to 5.1% in the surgical ICU study[4] and from 3.1 to 18.7% in the medical ICU study.[5] The patients in the medical ICU study represented a sicker patient population than in the surgical study, with a higher incidence of liver and kidney failure, making the patients more susceptible to the development of hypoglycemia. In particular, patients with sepsis appeared to be at risk, with an overall incidence of 11.4% (2.9% for conventional, and 19.6% for intensive insulin therapy) vs 3.9% for patients without sepsis (1.2% for conventional, and 6.8% for intensive insulin therapy) [Table 3].[38] Importantly, these brief episodes of biochemical hypoglycemia were not associated with obvious clinical problems. Indeed, hypoglycemia did not cause early deaths, only minor immediate and transient morbidity was seen in a minority of patients, and no late neurologic sequellae occurred among hospital survivors.[33] Nevertheless, as the risk of hypoglycemia coincided with a higher risk of death (OR, 3.2 in the surgical ICU study[4]; and OR, 2.9 in the medical ICU study[5] when corrected for randomization, APACHE II score, history of diabetes, history of malignancy and common diagnostic subgroups) equally in both conventional and intensive insulin groups, it cannot be completely excluded that hypoglycemia counteracted some of the survival benefit of intensive insulin therapy. Interestingly, however, a higher mortality was observed with spontaneous hypoglycemia than with hypoglycemic events during insulin infusion. More-

over, in a recent, nested-case control study,[46] no causal link was found between hypoglycemia in the ICU and death when case and control subjects were matched for baseline risk factors and time in the ICU before the hypoglycemic event. These observations support the previous suggestion that hypoglycemia in ICU patients who receive intensive insulin therapy may merely identify patients at high risk of dying rather then representing a risk on its own.[47] The future development of accurate, continuous blood glucose monitoring devices, and preferably closed-loop systems for computer-assisted blood glucose control in the ICU, will likely help to avoid hypoglycemia.

Intensive Insulin Therapy for < 3 Days: Dangerous? In the Leuven medical ICU study,[5] among patients treated in ICU for < 3 days, a higher number of deaths were present among intensive insulin-treated patients (56 of 209 patients, 26.8%) than in the conventional group (42 of 224 patients, 18.8%). If these numbers would reflect a true causal association, a harmful effect of intensive insulin therapy administered briefly would be suggested, whereas beyond 3 days it becomes beneficial. This generated concern among the practicing clinicians because it is virtually impossible to predict which patient will require > 3 days of intensive care. However, a *post hoc* exploratory mortality analysis revealed that this observation was likely explained by selection bias. Indeed, for 36 short-stay patients, intensive care had been limited or withdrawn within 72 h after ICU admission for reasons of futility, imbalanced among the conventional (n = 10) and intensive (n = 26) insulin therapy groups. Importantly, when correcting for the well-known on-admission risk factors that are the major reasons for therapy restriction, the apparent difference in mortality disappeared. Furthermore, detailed analysis of the pooled data sets from the surgical and the medical ICU study showed, with enough statistical power, that brief insulin treatment for < 3 days did not cause harm.[33]

High-Dose Insulin Administration to Critically Ill Patients: Harmful? Apart from the risk of hypoglycemia, multivariate logistic regression analysis had identified the dose of insulin as a positive risk factor for mortality.[4,33,48,49] Such an association between high insulin dose and mortality can be explained by more severe insulin resistance in the sicker patients, who have a high risk of death or, alternatively, by a true deleterious effect of hyperinsulinemia. However, it was recently shown that circulating insulin levels with intensive insulin therapy are only transiently higher than in conventionally treated patients, and that intensive insulin therapy actually reduces or prevents insulin resistance in the critically ill, possibly via its effect on blood glucose and lipids.[50–52] More study is needed to address this important question.

Does Intensive Insulin Therapy Merely Antagonize Deleterious Effects of Parenteral Nutrition?

Guidelines were followed with regard to feeding of the patients in the Leuven studies.[4,5,53] Enteral feeding was attempted as soon as possible when the patients were hemodynamically stable; but when the caloric target could not be reached, parenteral feeding was administered early to compensate for the deficit. Criticism has been raised that with this regimen patients were at risk for overfeeding, and that this regimen did not represent the approach adopted in many centers. It was suggested that intensive insulin therapy merely serves to offset the risk associated with "excessive" parenteral glucose. This important question was addressed in the analysis of the pooled data set of the two Leuven studies, and the data argue against such criticism. Indeed, the benefit of intensive insulin therapy was independent of parenteral glucose load because mortality was lowered both in the lowest and the highest tertile of parenteral glucose load in the intention-to-treat population, and in all tertiles of parenteral feeding for patients treated in intensive care for at least 3 days. In fact, the most pronounced benefit was present for patients who received the smallest amount of parenteral feeding.[33]

The Importance of Achieving the Normoglycemic Target

In clinical studies on intensive insulin therapy, it is impossible to completely separate impact of insulin infusion vs that of blood glucose control because both are done concomitantly. However, in a rabbit model of prolonged critical illness, a four-arm study[54] design (two normoglycemic groups and two hyperglycemic groups, each with either normal or elevated insulin levels) recently revealed that glycemic control mediated the survival benefit of intensive insulin therapy, independent of insulin. The mortality rate was 41.4% in hyperglycemic vs 11.1% in normoglycemic rabbits, whereas insulin levels did not contribute to the survival benefit.

The clinical data are in line with this experimental observation. Indeed, in the critically ill patients of the surgical study, the risk of death appeared to be linearly correlated with the degree of hyperglycemia, with no clear cutoff level below which there was no further benefit.[48] The highest risk of death was observed for the conventionally treated patients who

had severe hyperglycemia (150 to 200 mg/dL), intermediate risk for patients who received conventional insulin therapy and who had only moderate hyperglycemia (110 to 150 mg/dL), whereas the lowest risk was present in the patients whose blood glucose levels were controlled at < 110 mg/dL with intensive insulin therapy. This pattern of risk of death in relation to stratification of glycemia was confirmed in the mixed medical/surgical patient population, with most benefit gained when glycemia was controlled at < 110 mg/dL.[33] In patients with diabetes, however, risk of death for the three strata of glucose control appeared to mirror this pattern, although no significant differences were noted among these three levels.

Glycemic control also accounted for most effects on morbidity of critical illness.[4,33,48] As for mortality, tight glycemic control < 110 mg/dL appeared to be of crucial importance for the prevention of critical illness polyneuropathy, bacteremia, anemia and acute renal failure.[33,48] This underscores the importance of achieving tight glucose control within the normoglycemic target range to obtain the clinical benefits. In the Leuven studies,[4,5,33] 70% of the patients allocated to intensive insulin therapy actually achieved a mean daily blood glucose level < 110 mg/dL. In contrast, at the time of interim analysis of the Glucontrol study, median levels of glucose were 147 mg/dL (interquartile range, 127 to 163 mg/dL) in the conventional arm, and 118 mg/dL (interquartile range, 109 to 131 mg/dL) in the intensive insulin arm.[55] This means that tight glycemic control was achieved in only approximately 25% of the patients receiving intensive insulin therapy, whereas the incidence of hypoglycemia was comparable (10%) to the Leuven studies (11%). If optimal level of blood glucose control (*ie*, normoglycemia) is not achieved and hypoglycemia is frequent, the therapy is not likely to bring about benefit and thus only exposes patients to risks.

Prevention of hyperglycemia appears the most important mechanism mediating the clinical benefits of intensive insulin therapy. Hyperglycemia could affect several cell types that take up glucose passively, independent of insulin, including hepatocytes,[56] alveolar cells, endothelial cells,[54,57] neurons,[23] and immune cells.[58] Prevention of glucose toxicity to the mitochondrial compartment appears very important.[56] However, insulin may also exert direct effects when hyperglycemia is avoided. Such insulin effects include partial correction of dyslipidemia,[52] prevention of excessive inflammation,[58,59] and attenuation of the cortisol response to critical illness.[60] A detailed description of mechanistical studies is beyond the scope of this review and can be found in other overviews.[1,61]

Obstacles for Implementation

Applying tight blood glucose control in the routine clinical setting of certain ICUs may prove to be a challenge. As for other new interventions, success of implementation relies on a strong leader in the team who drives the change in practice, and a clear guideline for and adequate education of the nursing staff, who should be the ones to titrate the insulin infusions. The study by Krinsley[27] clearly shows that when these conditions are fulfilled, successful implementation is feasible. The absence of an arterial line may make tight blood glucose control very difficult because capillary blood glucose values, obtained by finger stick[62] or measurements in fluid obtained from subcutaneous sites,[63] do not appear to be reliable in the ICU setting. Again, the development of an accurate and reliable continuous blood sensor is likely to facilitate implementation of tight blood glucose control in ICU and to reduce the nursing workload.

Conclusions

Available data, largely derived from the two randomized single-center Leuven studies, suggest that intensive insulin therapy achieving sustained blood glucose control < 110 mg/dL and avoiding prolonged hypoglycemia reduces mortality and morbidity of critical illness. A reduction of mortality by an absolute 3 to 4% is to be expected with this therapy. The survival benefit appears to increase to approximately 8% absolute reduction in the risk of death when intensive insulin therapy is continued at least 3 days, irrespective of the cause of illness. In order to confirm these clinical benefits, appropriately designed, adequately powered studies in a multicenter setting are needed but are not yet available. Confirmation of the 3 to 4% mortality reduction in an intention-to-treat analysis requires a sample size of at least 5,000 to 6,000 patients. The only clinical trial that is currently ongoing and that has sufficient statistical power to address this question in a mixed medical/surgical population is the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (or NICE-SUGAR) multicenter trial.[64] Provided the target of normoglycemia is reached in a large-enough fraction of patients allocated to intensive insulin therapy and overlap of blood glucose control with the control group is avoided and provided excessive hypoglycemia is prevented, this study will generate the answers to the remaining questions. We anxiously await the completion of patient enrollment and the results of this study. After acceptance of the manuscript, another observational study [65] was published showing that

implementation of an intensive insulin protocol in a surgical trauma ICU resulted in improved blood glucose control and was associated with reduced mortality, fewer intraabdominal abscesses, and reduced dependency on prolonged mechanical ventilation.

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