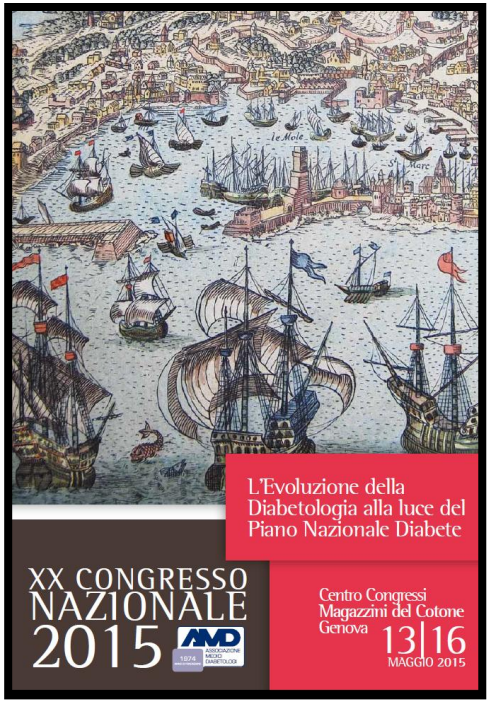


Iperglicemia e ipoglicemia in corso di nutrizione artificiale

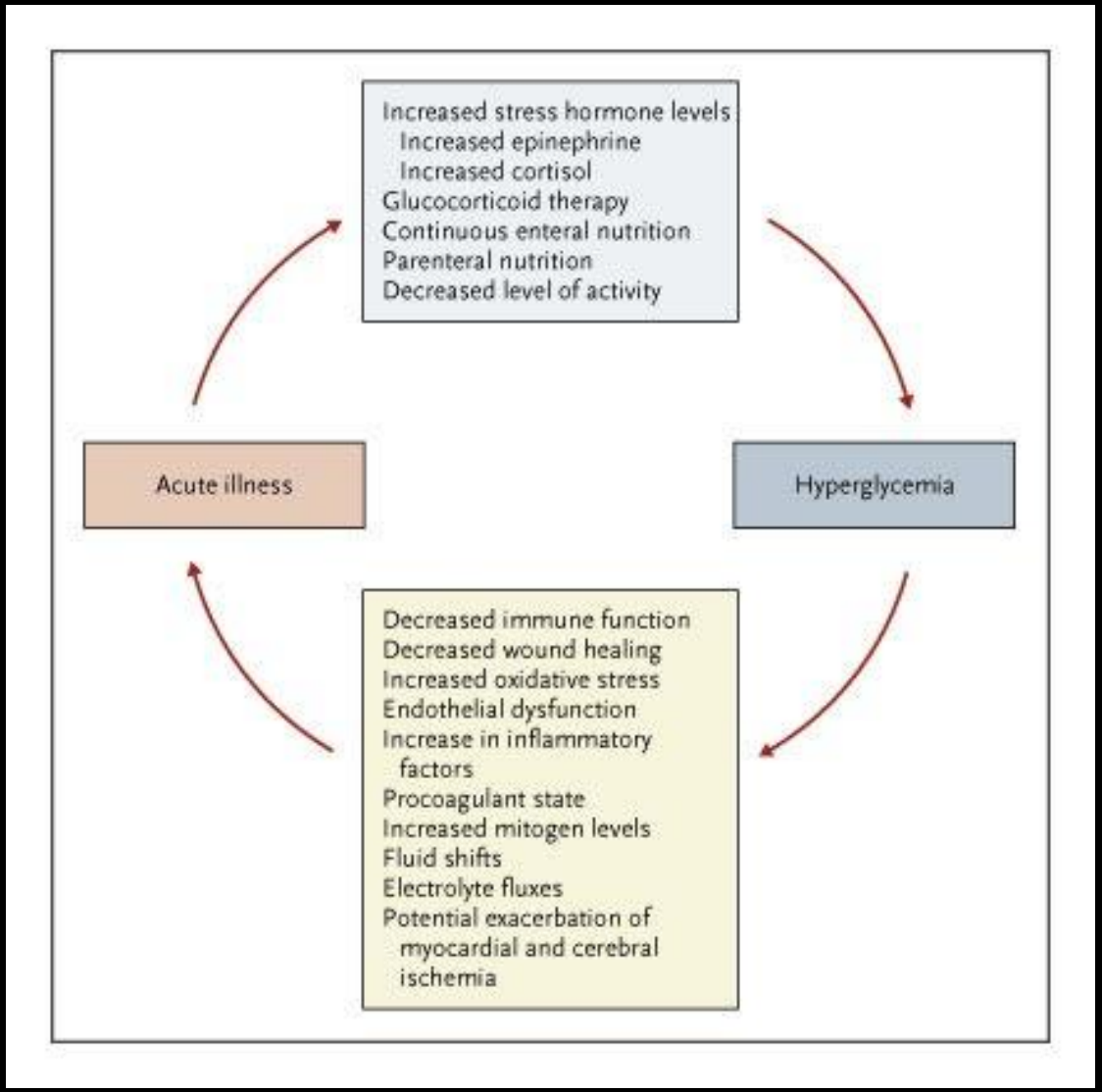
Giuseppe Fatati

Strutura Complessa di Diabetologia, Dietologia e Nutrizione Clinica

Azienda Ospedale S.Maria Terni

Paradoxically, the patients who need nutritional support are underfed for fear of hyperglycemia and receive an unsatisfactory insulin treatment for fear of hypoglycemia.

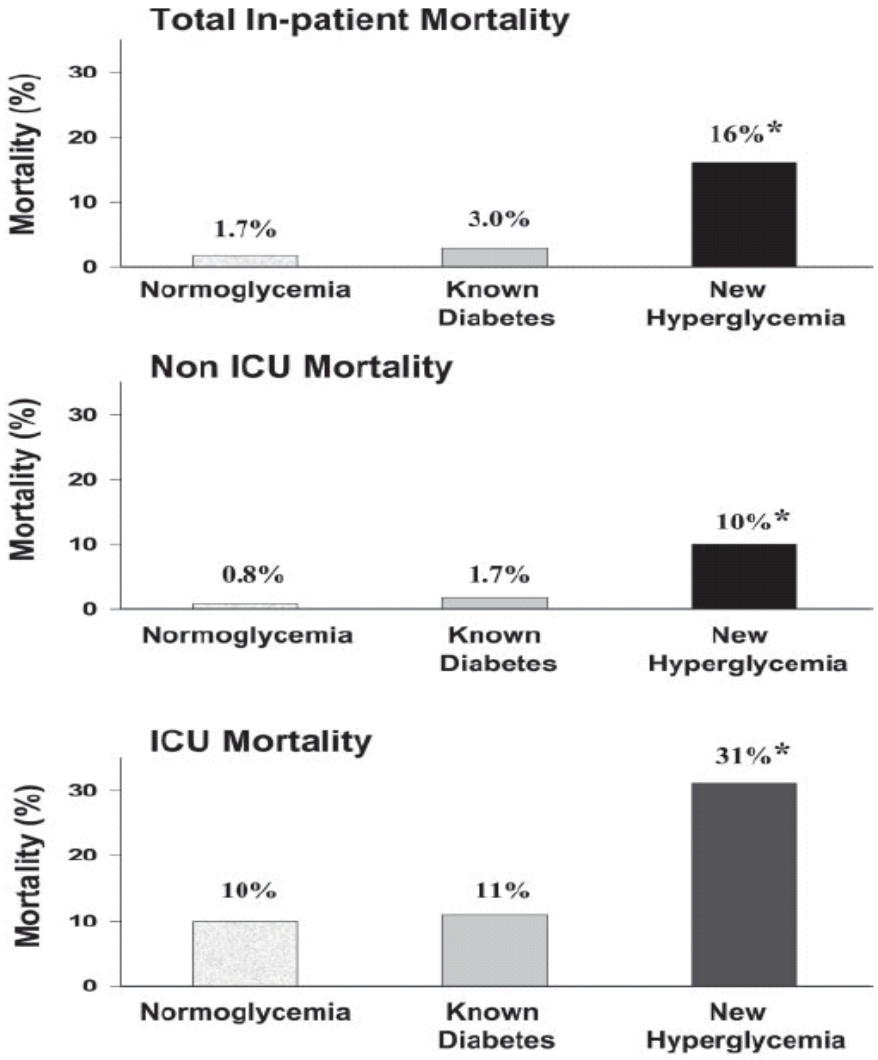
(Fatati 2005)



G Inzucchi S: The Relationship between Acute Illness and Hyperglycemia. N Engl J Med 2006; 355: 1903-11

Grau T: Caloric intake and liver dysfunction in critically ill patients. Curr Opin Clin Nutr Metab Care. 2009;12(2):175-9.

Conclusion: The pathogenesis of artificial nutrition associated with liver dysfunction is related to overfeeding and sepsis with a **pathophysiology, similar to metabolic syndrome and type 2 diabetes.** Changing nutritional strategies and adding new drugs will prevent, in part, liver dysfunction in these patients.



* $P < 0.01$

FIG. 1. In-hospital mortality n patients with normoglycimia, known diabetes, and newly discovered hyperglycemia.

UMPIERREZ GE: Hyperglycemia: An Independent Marker of In-Hospital Mortality in Patients with Undiagnosed Diabetes The Journal of Clinical Endocrinology & Metabolism March 2002, 87(3):978

La gestione dell'ipoglicemia in ambiente ospedaliero

- **Se non esistesse il rischio di ipoglicemia la terapia del diabete sarebbe molto semplificata**

- L'ipoglicemia è l'evento acuto più frequente e più temibile cui il diabetico possa andare incontro

- La soglia glicemica al di sotto della quale cominciano a comparire i primi sintomi è piuttosto variabile da soggetto a soggetto ed è compresa tra 40 e 70 mg%

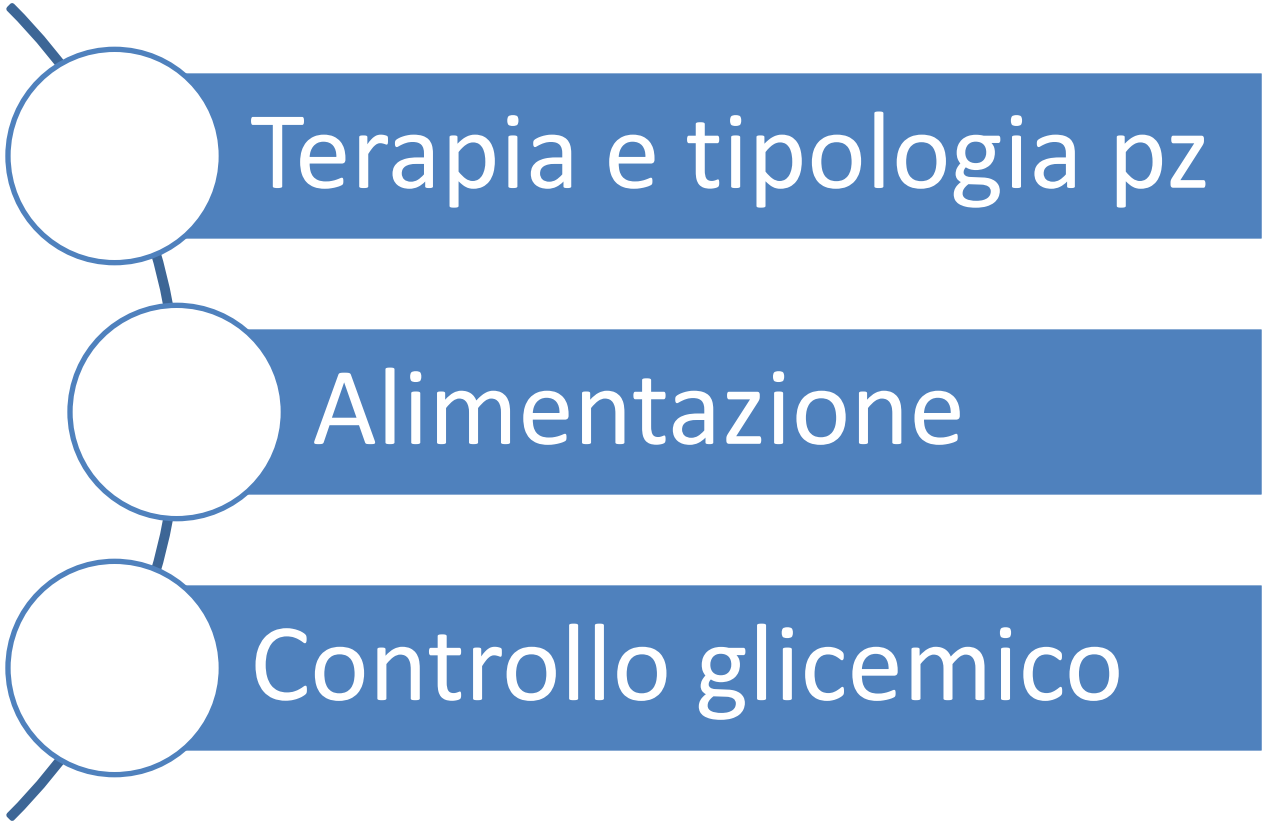
General causes of hypoglycaemia

- **Inadequate, delayed or missed meal**
- Exercise
- **Too much insulin** or oral antidiabetic medications
- Drug/alcohol consumption
- Increased insulin sensitivity
- Reduced insulin clearance

Risk factors for severe hypoglycaemia

- Age/duration of insulin treatment
- **Strict glycaemic control**
- **variety of glucometers**
- Impaired awareness of hypoglycaemia
- Sleep
- History of previous severe hypoglycaemia
- Renal failure

IPOGLICEMIA: FATTORI DI RISCHIO



Gli obiettivi glicemici durante un ricovero ospedaliero possono essere differenziati in funzione delle diverse situazioni cliniche:

• Pazienti in **situazione critica**, ricoverati in Terapia Intensiva, medica o chirurgica:
valori glicemici 140-180 mg/dl, in funzione del rischio stimato di ipoglicemia.
(Livello della prova II, Forza della raccomandazione B)

• Pazienti in **situazione non critica**: valori glicemici preprandiali <140 mg/dl, postprandiali <180 mg/dl o valori random <180 mg, se ottenibili senza rischi elevati di ipoglicemia. Target più stringenti possono essere perseguiti in soggetti clinicamente stabili e in precedente controllo glicemico ottimale. Target meno stringenti possono essere accettati in presenza di severe comorbilità.
(Livello della prova VI, Forza della raccomandazione B)

In alcune situazioni cliniche a elevato rischio di ipoglicemia è opportuno un innalzamento degli obiettivi glicemici.
(Livello della prova VI, Forza della raccomandazione B)

GLI OBIETTIVI DEL CONTROLLO GLICOMETABOLICO IN CORSO DI NUTRIZIONE ARTIFICIALE ED I RISCHI DI IPOGLICEMIA

R: La normalizzazione dei livelli glicemici utilizzando protocolli intensivi di infusione insulinica (IIP) migliora gli esiti clinici nelle persone in condizioni critiche. Livello di Prova II, Forza B

R: Il raggiungimento di targets glicemici "prossimi alla normalità" deve essere graduale: anche nelle terapie intensive deve realizzarsi in 6-24 ore, per non aumentare il rischio di ipoglicemia. Livello di Prova VI, Forza B

R. Valori glicemici ≤ 140 mg/dl sono indicati nelle persone in condizioni critiche in terapia intensiva medica e chirurgica. Livello di Prova II, Forza B

R: Nelle persone ospedalizzate in condizioni non critiche i valori auspicabili sono <126 mg/dl a digiuno e <180 mg/dl postprandiale o random.
Livello di Prova VI, Forza B

R: Valori glicemici ≤140 mg/dl sono sufficienti nelle persone ricoverate in Unità Coronarica indipendentemente dalla presenza o meno di diabete in anamnesi. Livello di Prova VI, Forza B

R: Nelle persone con coronaropatia ricoverate in degenze non intensive è raccomandato un target <180 mg/dl. Livello di Prova VI, Forza C

GLI OBIETTIVI DEL CONTROLLO GLICOMETABOLICO IN CORSO DI NUTRIZIONE ARTIFICIALE ED I RISCHI DI IPOGLICEMIA

K: L'iperglicemia è un importante fattore prognostico sfavorevole, sia nelle persone con diabete, sia in quelle non diabetiche.

K: Le persone con iperglicemia da stress devono essere studiate dopo l'evento acuto per verificare il livello di compromissione metabolica con glicemia a digiuno, HbA1c ed eventualmente OGTT.

K: Le persone in NA ricoverate nelle degenze ordinarie o seguite in RSA o a domicilio, in condizioni cliniche stabilizzate, possono essere trattate con gli stessi standard di quelle in condizioni non critiche.

K: La variabilità glicemica, è un importante fattore prognostico nelle persone in condizioni critiche.

GLI OBIETTIVI DEL CONTROLLO GLICOMETABOLICO IN CORSO DI NUTRIZIONE ARTIFICIALE ED I RISCHI DI IPOGLICEMIA

- È verosimile che i target debbano essere differenziati fra diabetici e non diabetici che esprimono un iperglicemia da stress, dato l'adattamento tessutale all'iperglicemia nei primi e la diversa soglia di risposta iperglicemica allo stress.

- Il monitoraggio della glicemia nelle persone in condizioni critiche deve essere effettuato con glucometri validati nelle ICU, onde evitare errori soprattutto sul versante dell'ipoglicemia.

13. Diabetes Care in the Hospital, NursingHome, and Skilled Nursing Facility Diabetes Care 2015;38(Suppl. 1):S80–S85 | DOI: 10.2337/dc15-S016 (American Diabetes Association)

- Critically Ill Patients

- Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, **a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. A**
- More stringent goals, such as 110–140 mg/dL (6.1–7.8 mmol/L), may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia. C
- Critically ill patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia. E

Executive Summery – Standards of Medical Care in Diabetes – 2010. Diabetes Care January 2010 33:S4S10; 10.2337/dc10-S004

- **Critically ill patients: Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dl (10 mmol/l). Once insulin therapy is started, a glucose range of 140–180 mg/dl (7.8 to 10 mmol/l) is recommended for the majority of critically ill patients. These patients require an intravenous insulin protocol that has demonstrated efficacy and safety in achieving the desired glucose range without increasing risk for severe hypoglycemia.**
- **The largest study to date, NICE-SUGAR, a multicenter, multinational RCT, tested the effect of tight glycemic control (target 81–108 mg/dl) on outcomes among 6,104 critically ill participants, the majority of whom (>95%) required mechanical ventilation. Ninety-day mortality was significantly higher in the intensive versus the conventional group (target 144–180 mg/dl) (78 more deaths; 27.5 vs. 24.9%, P = 0.02) in both surgical and medical patients. Mortality from cardiovascular causes was more common in the intensive group (76 more deaths; 41.6 vs. 35.8%; P = 0.02). Severe hypoglycemia was also more common in the intensively treated group (6.8 vs. 0.5%; P < 0.001).**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2009 VOL. 360 NO. 13

Intensive versus Conventional Glucose Control in Critically Ill Patients

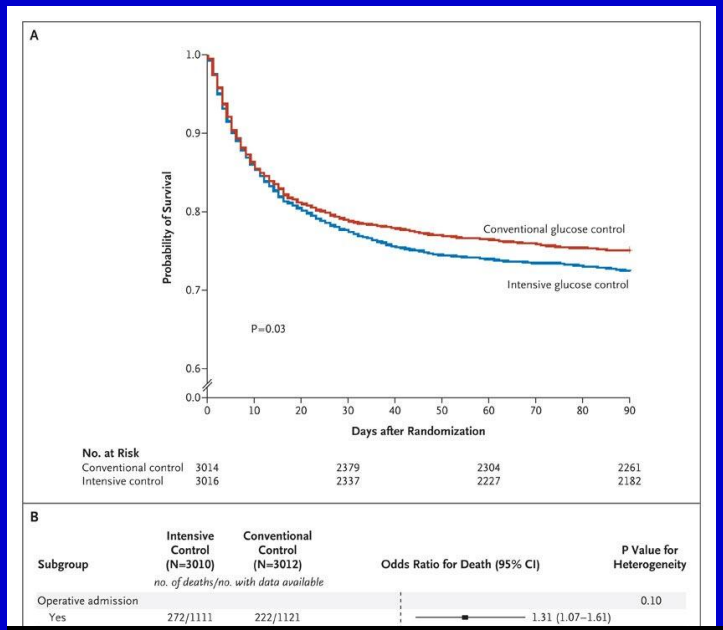
The NICE-SUGAR Study Investigators*

- Study participants were randomly assigned to glucose control with one of two target ranges: the intensive (i.e., tight) control target of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), based on that used in previous studies or a conventional-
- Control target of 180 mg or less per deciliter (10.0 mmol or less per liter), based on practice surveys in **Australia, New Zealand, and Canada.** Randomization was stratified according to type of admission (operative or nonoperative) and region (Australia and New Zealand or North America).

The NICE-SUGAR Study Investigators. N Engl J Med 2009;360:1283-1297

Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. **The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died** (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P = 0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P = 0.10). **Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001).**

Probability of Survival and Odds Ratios for Death, According to Treatment Group



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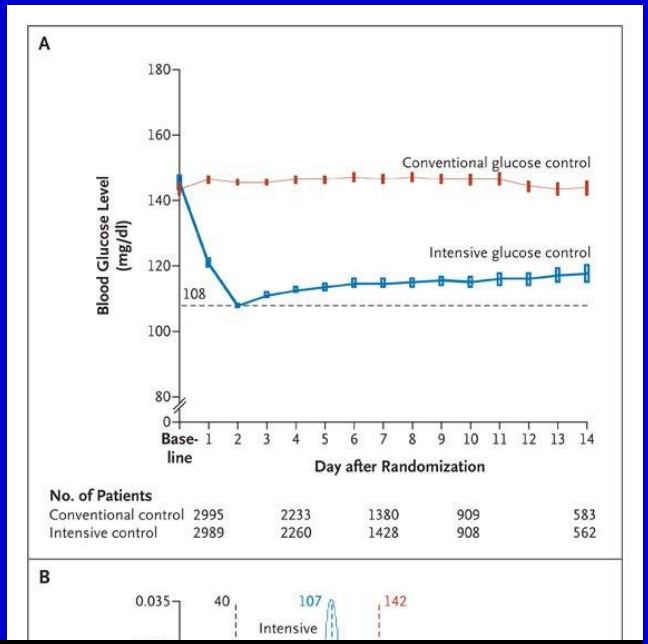
Data on Blood Glucose Level, According to Treatment Group



Insulin Administration and Treatment Effects

Patients undergoing intensive glucose control were more likely than those undergoing conventional control to have received insulin (2931 of 3014 patients [97.2%] vs. 2080 of 3014 [69.0%], P<0.001), and they received a larger mean insulin dose (50.2±38.1 units per day, vs. 16.9±29.0 with conventional control; P<0.001). The mean time-weighted blood glucose level was significantly lower in the intensive-control group than in the conventional-control group (115±18 vs. 144±23 mg per deciliter [6.4±1.0 vs. 8.0±1.3 mmol per liter], P<0.001).

The NICE-SUGAR Study Investigators.
N Engl J Med 2009;360:1283-1297

The NEW ENGLAND JOURNAL of MEDICINE

IPOGLICEMIA: FATTORI DI RISCHIO

The trial intervention was discontinued once the patient was eating or was discharged from the ICU but was resumed if the patient was readmitted to the ICU within 90 days. It was discontinued permanently at the time of death or 90 days after randomization, whichever occurred first.

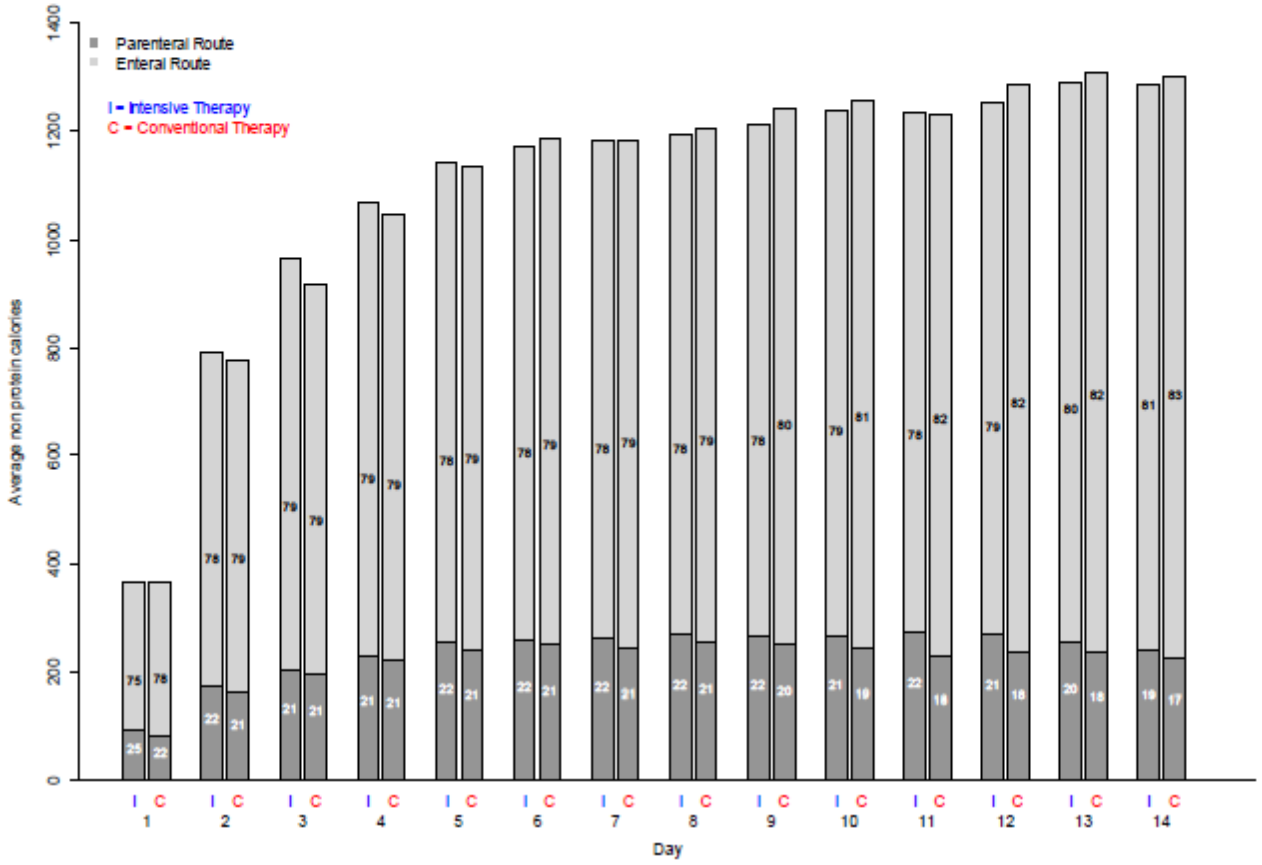
The NICE-SUGAR Study Investigators. N Engl J Med 2009;360:1283-1297

Total non protein calories averaged over day 1-14 for each Patient
(P = Student's or Welch's t test as appropriate)

	Intensive Control Mean (SD)	Conventional control Mean (SD)	Difference (95%CI)	P value
Non protein nutrition via all routes	891 (490)	872 (500)	19 (-6,44)	0.1
Non protein nutrition via IV route	93 (89)	87 994)	6 (2,11)	0.008
Non protein nutrition via enteral route	624 (496)	623 (496)	2 (-24,27)	0.9
Non protein nutrition via parenteral route	173 (359)	162 (345)	11 (-7,29)	0.2

The NICE-SUGAR Study Investigators. N Engl J Med 2009;360:1283-1297

Appendix B - Median non protein calories per patient administered by enteral and parenteral routes – days 1 – 14; Day 1 is the day of randomization from randomization to end of ICU day, day 2 is first full day after randomization. Numbers within bars represent percentage of total calories given by enteral or parenteral route.



IPOGLICEMIA: FATTORI DI RISCHIO

The NICE-SUGAR Study Investigators. N Engl J Med 2009;360:1283-1297

Blood samples for glucose measurement were obtained by means of arterial catheters whenever possible; the use of capillary samples was discouraged.

IPOGLICEMIA: FATTORI DI RISCHIO

To the Editor:

These findings are clearly at variance with the decreased mortality that we reported from our center in Leuven, Belgium.

First, normoglycemia (blood glucose level, <110 mg per deciliter) was compared with distinct blood glucose control with target ranges of 140 to 180 mg per deciliter in the NICE-SUGAR study and 180 to 215 mg per deciliter in the Leuven studies, making the studies fundamentally different.

Second, in the NICE-SUGAR study, **it is surprising that a variety of glucometers,** most of which were unsuitable for this purpose, were allowed; thus, undetected hypoglycemia, large fluctuations in glucose levels, and **possibly hypokalemia were tolerated or even induced**. Such errors may have contributed to excess "cardiovascular" deaths, in the absence of differences in organ failure.

Third, in the NICE-SUGAR study, patients received enteral nutrition exclusively, whereas in the Leuven studies, parenteral nutrition supplemented insufficient enteral feeding. **The administration of insulin during hypocaloric feeding may have been deleterious.**

Finally, an unexplained policy of early withdrawal of care in the NICE-SUGAR study (after a median duration of study treatment of 6 days),…, may have introduced a bias that could explain the excess mortality.

Greet Van den Berghe, M.D., Ph.D.

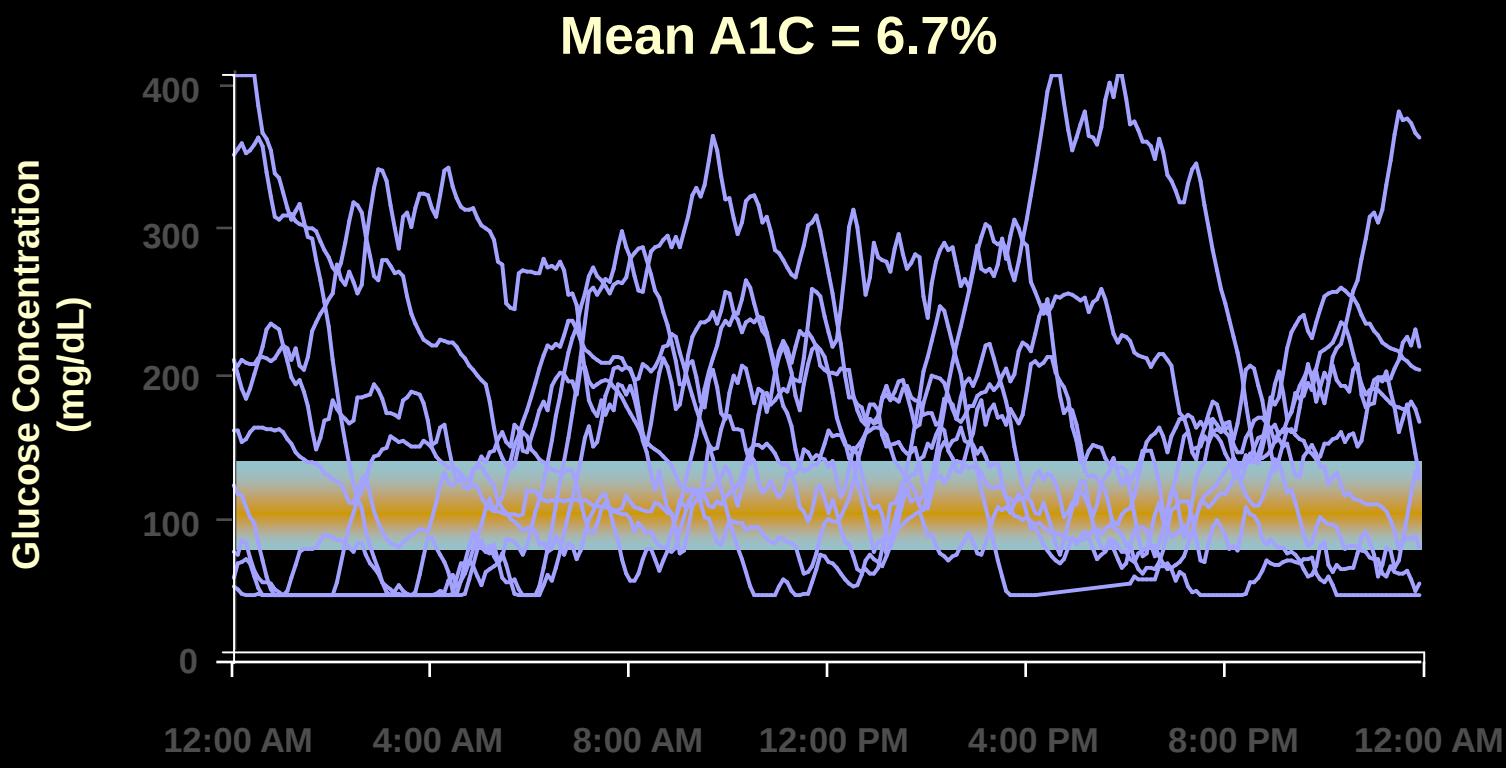
James S. Krinsley, Mark T. Keegan: **Hypoglycemia in the Critically Ill: How Low Is Too Low? Mayo Clin Proc. March 2010 85(3):217- 224**

It is biologically plausible that hypoglycemia contributes to mortality. Neurons are obligate users of glucose, and a large body of evidence suggests that hypoglycemia, especially if severe or prolonged, can cause irreversible neuronal damage by a variety of mechanisms. Furthermore, hypoglycemia-induced sympathetic stimulation may lead to cardiac arrhythmias and/or myocardial compromise. However, the specific mechanisms of any hypoglycemia-related increases in mortality seen in recent trials in critically ill patients, if they exist, remain to be elucidated.

Glycemic variability has recently been shown to be an independent predictor of mortality among various populations of critically ill patients. Oxidative stress induced by glycemic variability may be an important contributor to the risk of mortality among vulnerable patients, such as those with vascular disease. Although the authors do not address this question directly, there is a suggestion that the impact of hypoglycemia is independent of the potential effect of glycemic variability in this cohort; among patients with hypoglycemia, survivors and nonsurvivors had similar mean and maximum glucose values

Mayo Clinic Proceedings

Excessive Glucose Fluctuations With Same A_{1C} Values



24-h CGMS glucose sensor data in 9 subjects with type 1 diabetes

Type 1 diabetes (N = 9)

Glucose variability predicts future risk of hypoglycaemia

James S. Krinsley, Mark T. Keegan: **Hypoglycemia in the Critically Ill: How Low Is Too Low? Mayo Clin Proc. March 2010 85(3):217- 224**

The investigation by Egi et al underlines the important role that hypoglycemia played in determining the negative result of this large randomized trial**. It is highly likely that there will not be another large multicenter randomized trial of insulin therapy in critically ill patients until there is a fundamental change in the manner by which we monitor and control glucose values in the ICU. Specifically, we await the development and clinical implementation of continuous or near-continuous glucose monitoring devices and "closed-loop" glycemic control systems.** With the use of these new technologies, coupled with algorithm-driven treatment protocols, the rate of hypoglycemia should plummet... Until then, we think that the study by Egi et al confirms the deleterious effect of hypoglycemia, especially severe hypoglycemia, in critically ill patients; highlights the complexity of this clinical problem; **and reinforces the principle that clinicians practicing glycemic control must do so safely.**

Mayo Clinic Proceedings

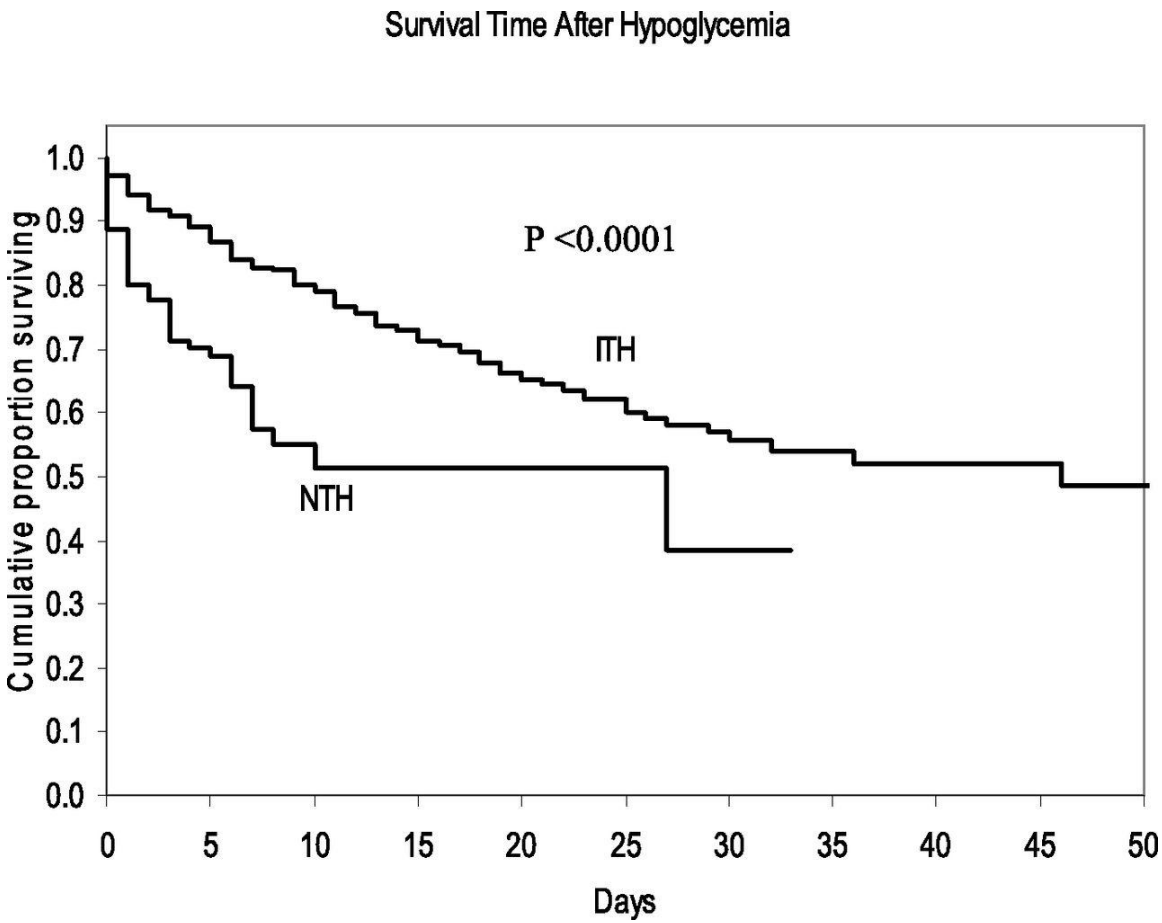
Glucose Control in the ICU — How Tight Is Too Tight?

Silvio E. Inzucchi, M.D., and Mark D. Siegel, M.D.

However, we would caution against any overreaction to the NICE-SUGAR findings. The NICE-SUGAR study simply tells us that in cohorts of patients such as those studied, there is no additional benefit from the lowering of blood glucose levels below the range of approximately 140 to 180 mg per deciliter; indeed, for unclear reasons, there may be some risk that remains to be elucidated. Notwithstanding, it would be a disservice to our critically ill patients to infer from the NICE-SUGAR data that neglectful glycemic control involving haphazard therapeutic approaches (e.g., use of insulin "sliding scales") — all too common a decade ago — is again acceptable practice in our ICUs…

… how might we explain the surprising finding of a possible risk of death from intensive insulin therapy? Could insulin itself have direct deleterious effects (sym-pathetic activation, sodium retention, or mitogenicactions)? Was the increased mortality simply related to hypoglycemia and resultant neuroglycopenia, which is difficult to detect in patients who are intubated and sedated? Did the well-recognized complexities of intensive management of glucose distract from other, ostensibly more important management practices in the ICU? Is stress hyperglycemia the body's proper response to illness, an attempt to shunt energy from temporarily unessential skeletal muscle to critical organs? Do all measured biologic perturbations due to illness require medical correction? …

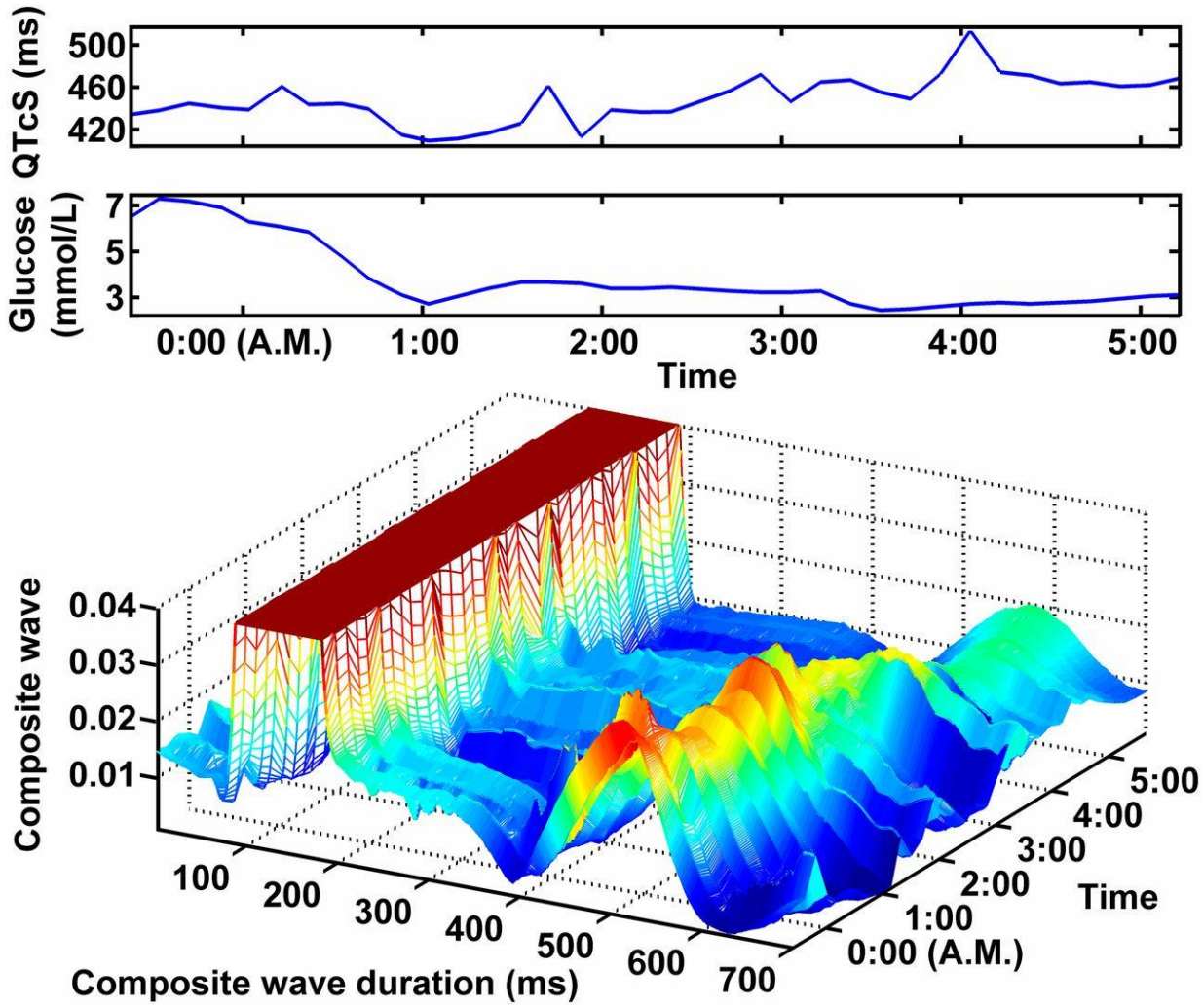
Plot of survival after the first episode of hypoglycemia for the ITH group versus the NTH group.



Insulin-associated and spontaneous hypoglycemia are associated with increased mortality among hospitalized patient
Garg R et al. Dia Care 2013;36:1107-1110

American Diabetes Association.

Abnormal QT prolongation and T-wave morphology during hypoglycemia in a single patient.



Chow E et al. Diabetes 2014;63:1738-1747

Gill GV, Woodward A, Casson IF, Weston PJ: Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes: the 'dead in bed' syndrome revisited. Diabetologia. 2009 Jan;52(1):42-5.

Hanefeld *et al. Cardiovascular Diabetology* 2013, **12**:135
http://www.cardiab.com/content/12/1/135

CARDIO VASCULAR DIABETOLOGY

REVIEW **Open Access**

Cardiac implications of hypoglycaemia in patients with diabetes – a systematic review

Markolf Hanefeld[1*], Eva Duetting[2] and Peter Bramlage[3]

Results: Six recent comprehensive clinical trials have reinforced the critical importance of understanding the link between hypoglycaemia and the CV system. In addition, 88 studies have indicated that **hypoglycaemia mechanistically contributes to CV risk by increasing thrombotic tendency, causing abnormal cardiac repolarization, inducing inflammation, and contributing to the development of atherosclerosis.** These hypoglycaemia-associated risk factors are conducive to events such as unstable angina, non-fatal and fatal myocardial infarction, sudden death, and stroke in patients with diabetes.

Conclusions: Emerging data suggest that there is an impact of hypoglycaemia on CV function and mechanistic link is multifactorial. Further research will be needed to ascertain the full impact of hypoglycaemia on the CV system and its complications.

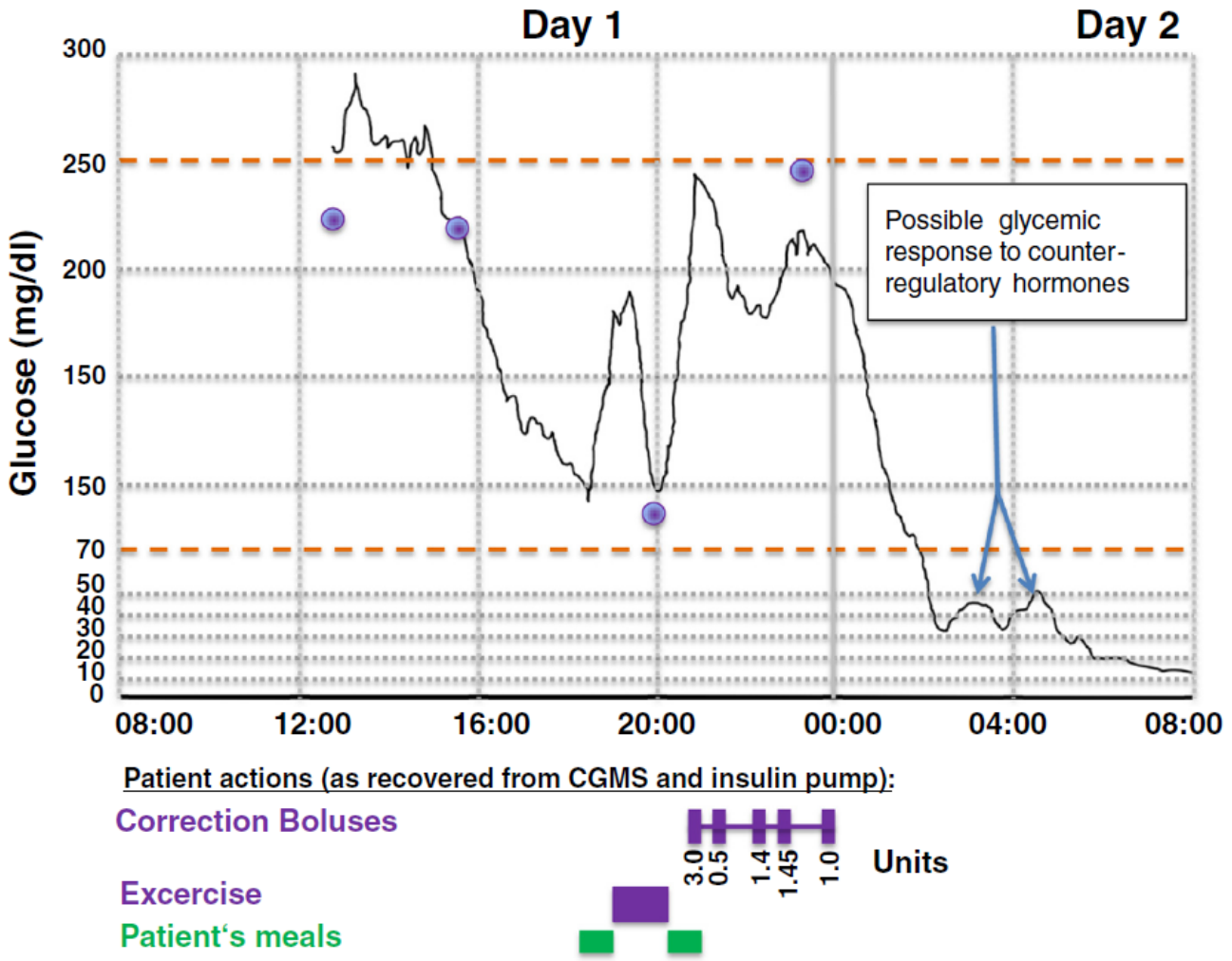


Figure 3 "Dead in bed" syndrome (adapted from Tanenberg et al. [17]). Glucose levels captured by the retrospective continuous subcutaneous glucose monitoring system (CGMS) for the evening before and the morning of the patient's death. The calibrations measured and entered by the patient are represented by the 4 circles. The timing of the patient's meals, exercise, and correction insulin boluses are represented by the bars along the bottom of the graph. The precipitous decrease in glucose level after the correction doses can be observed to start just after midnight, and possible counterregulatory efforts are noted once the glucose level declined to below 30 mg/dL shortly after 2 am.

Conclusioni

Nutrition FYI

Do We Know What Our Patients With Diabetes Are Eating in the Hospital?

Mary Beth Modic, MSN, RN, CNS, CDE, Andrea Kozak, RD, LD, CNSC, Sandra L. Siedlecki, PhD, RN, CNS, Diane Nowak, RD, LD, Desiree Parella, MS, RD, LD, Mary Pat Morris, RD, LD, Leslie Braun, RD, Sharon Schwam, and Sade Binion

Diabetes Spectrum 2011; Volume 24, n 2.

Table 2. Comparison of Caloric Needs and Caloric Intake by Day*

	Caloric needs			Caloric intake				
	n	Mean	SD	Mean	SD	*t*	df	*P*
Day 2	223	2,090	482	775	574	28.942	222	< 0.001
Day 3	162	2,136	467	828	548	27.129	161	< 0.001
Day 4	131	2,095	455	812	542	24.887	130	< 0.001

**Calories reported as kilocalories. df, degrees of freedom*

Reasons for inadequate meal consumption were divided into four categories: patient-related issues (42.2%), treatment issues (32.6%), illness-related issues (15.1%), and nursing-food service issues (1.9%)

Published in final edited form as:
JPEN J Parenter Enteral Nutr. 2011 November ; 35(6): 686–694. doi:10.1177/0148607111413904.

Provision of Balanced Nutrition Protects Against Hypoglycemia in the Critically Ill Surgical Patient

Rondi M. Kauffmann, MD, MPH[*], **Rachel M. Hayes, BSN, PhD**[**], **Judith M. Jenkins, MSN**[*], **Patrick R. Norris, PhD**[*], **Jose J. Diaz, MD, CNS, FACS, FCCM**[*], **Addison K. May, MD, FACS, FCCM**[*], and **Bryan R. Collier, DO, CNSP, FACS**[*]

[*]Division of Trauma and Surgical Critical Care, Department of Surgery, Vanderbilt University Medical Center, Nashville, TN

[**]Informatics Center, Information Integration Technology, Vanderbilt University Medical Center, Nashville, TN

Conclusioni

Krinsley *et al. Critical Care* 2013, **17**:R37
http://ccforum.com/content/17/2/R37

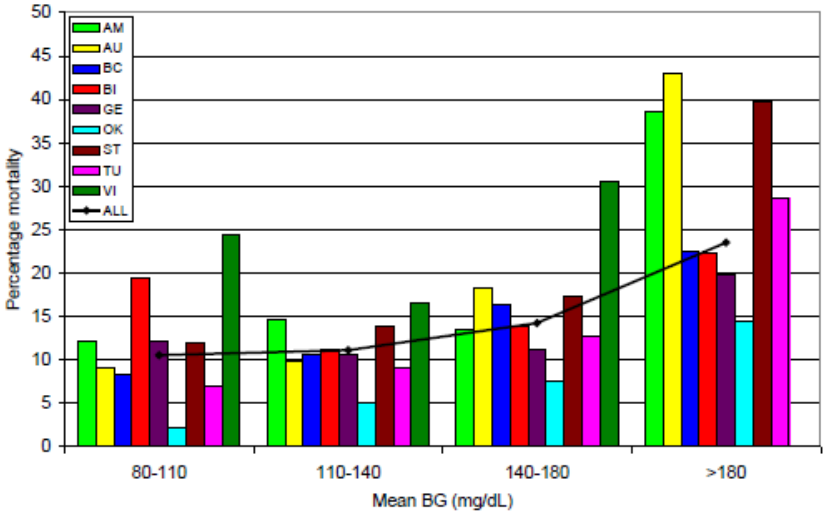
CRITICAL CARE

RESEARCH Open Access

Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study

James S Krinsley[1*], Moritoki Egi[2], Alex Kiss[3], Amin N Devendra[4], Philipp Schuetz[5], Paula M Maurer[6], Marcus J Schultz[7], Roosmarijn TM van Hooijdonk[7], Morita Kiyoshi[2], Iain MJ Mackenzie[8], Djillali Annane[9], Peter Stow[10], Stanley A Nasraway[11], Sharon Holewinski[11], Ulrike Holzinger[12], Jean-Charles Preiser[13], Jean-Louis Vincent[13] and Rinaldo Bellomo[14]

A. Non-diabetics



B. Diabetics

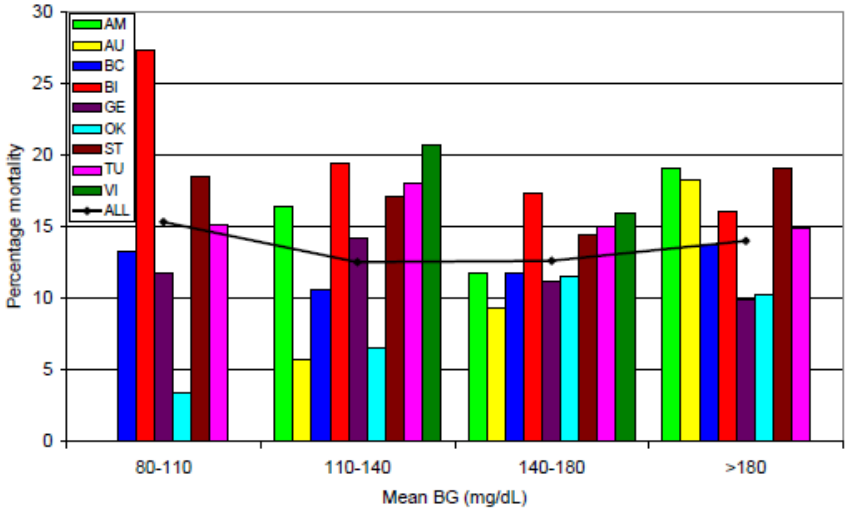
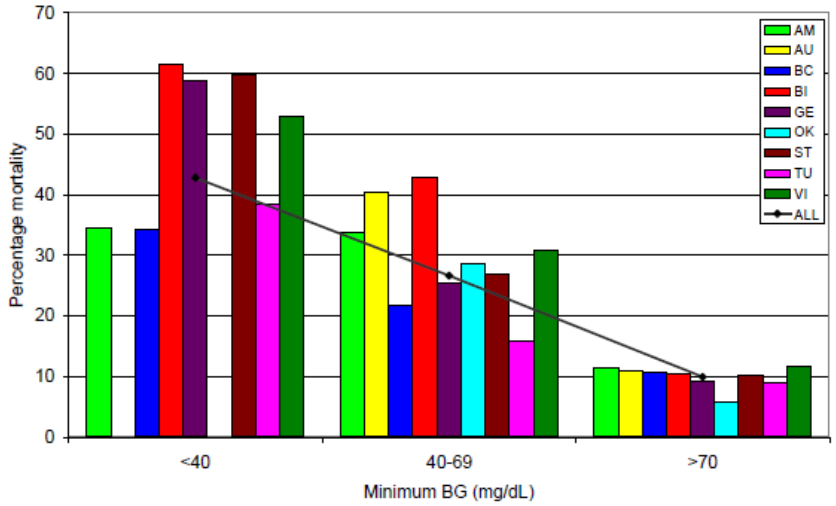
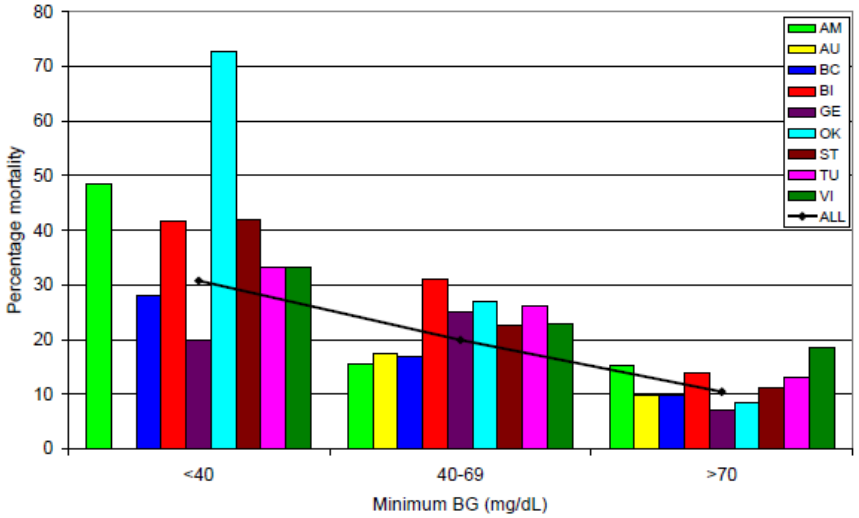


Figure 1 Mean blood glucose (BG) and mortality. The relation of mean BG (milligrams per deciliter) during ICU stay to mortality in those without **(A)** and those with diabetes **(B)**, for each of the nine cohorts as well as the entire population.

A. Non-diabetics



B. Diabetics



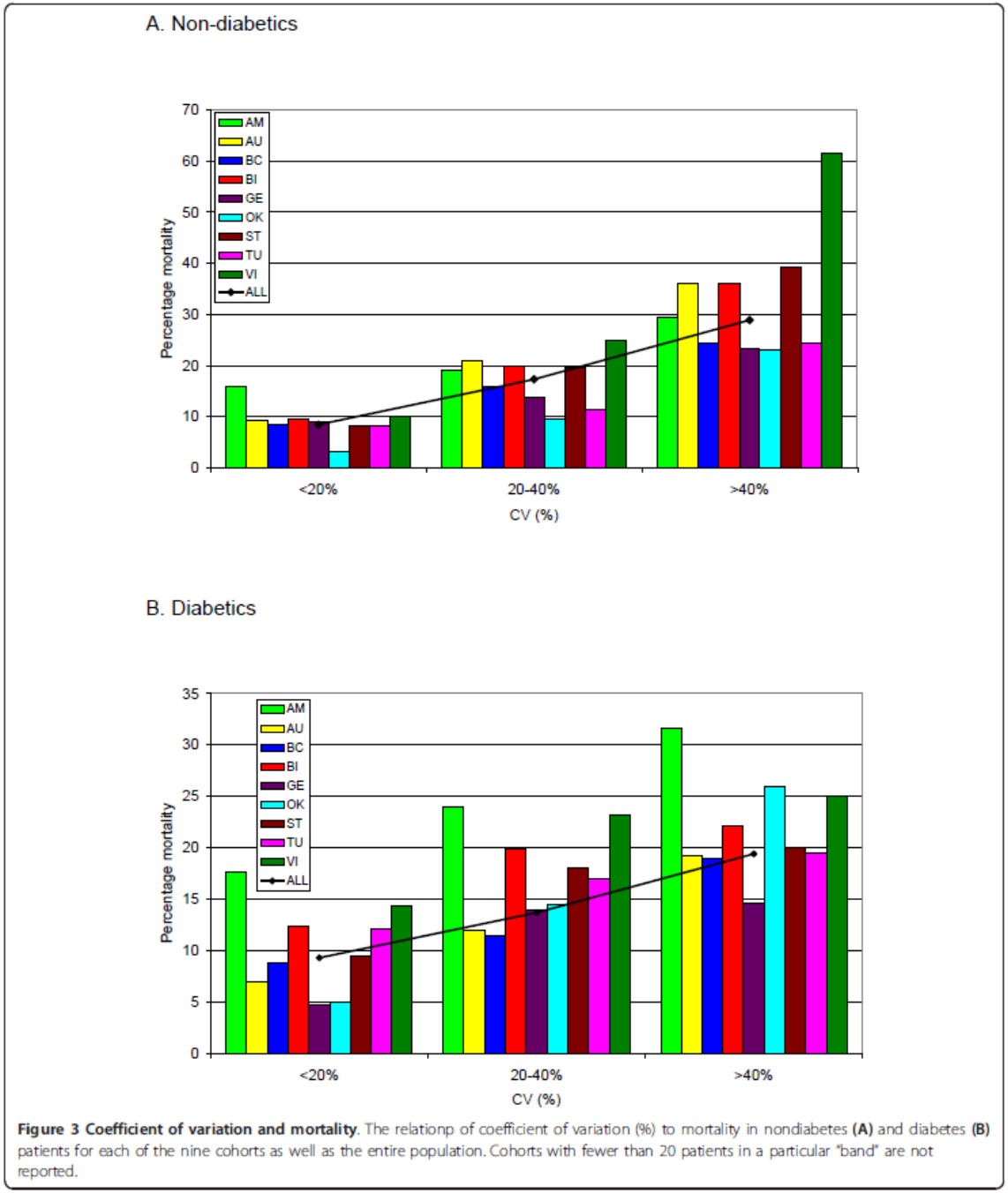


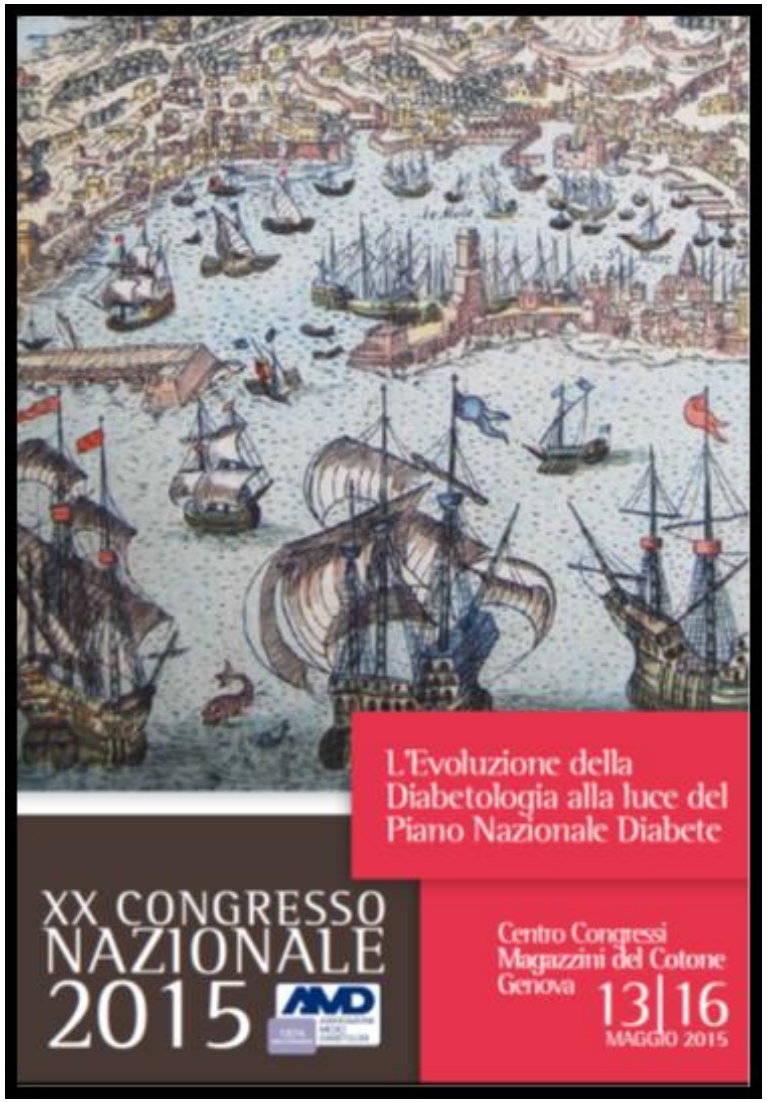
Figure 3 Coefficient of variation and mortality. The relationp of coefficient of variation (%) to mortality in nondiabetes **(A)** and diabetes **(B)** patients for each of the nine cohorts as well as the entire population. Cohorts with fewer than 20 patients in a particular "band" are not reported.

James S Krinsley1: Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study Critical Care 2013, 17:R37

- This is a retrospective analysis of prospectively collected data involving 44,964 patients admitted to 23 intensive care units (ICUs) from nine countries, between February 2001 and May 2012. We analyzed mean blood glucose concentration (BG), coefficient of variation (CV), and minimal BG and created multivariable models to analyze their independent association with mortality. Patients were stratified according to the diagnosis of diabetes.
- Although hyperglycemia, hypoglycemia, and increased glycemic variability is each independently associated with mortality in critically ill patients, diabetic status modulates these relations in clinically important ways. **Our findings suggest that patients with diabetes may benefit from higher glucose target ranges than will those without diabetes.** Additionally, hypoglycemia is independently associated with increased risk of mortality regardless of the patient's diabetic status, and increased glycemic variability is independently associated with increased risk of mortality among patients without diabetes.

Conclusioni

IPOGLICEMIA: SI PUO' E SI DEVE EVITARE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