Hypoglycémie en réanimation

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JFN Lyon – 14 décembre 2012

Déclaration d'intérêts de Jean-Charles Preiser

- **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

  Edwards, Medtronic,Optiscan

- **Essais cliniques, autres travaux, communications de promotion**

  B Braun, Edwards, Medtronic,Optiscan

- **Intérêts financiers (actions, obligations)**

  Non

- **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

  Non

- **Réception de dons sur une association dont je suis responsable**

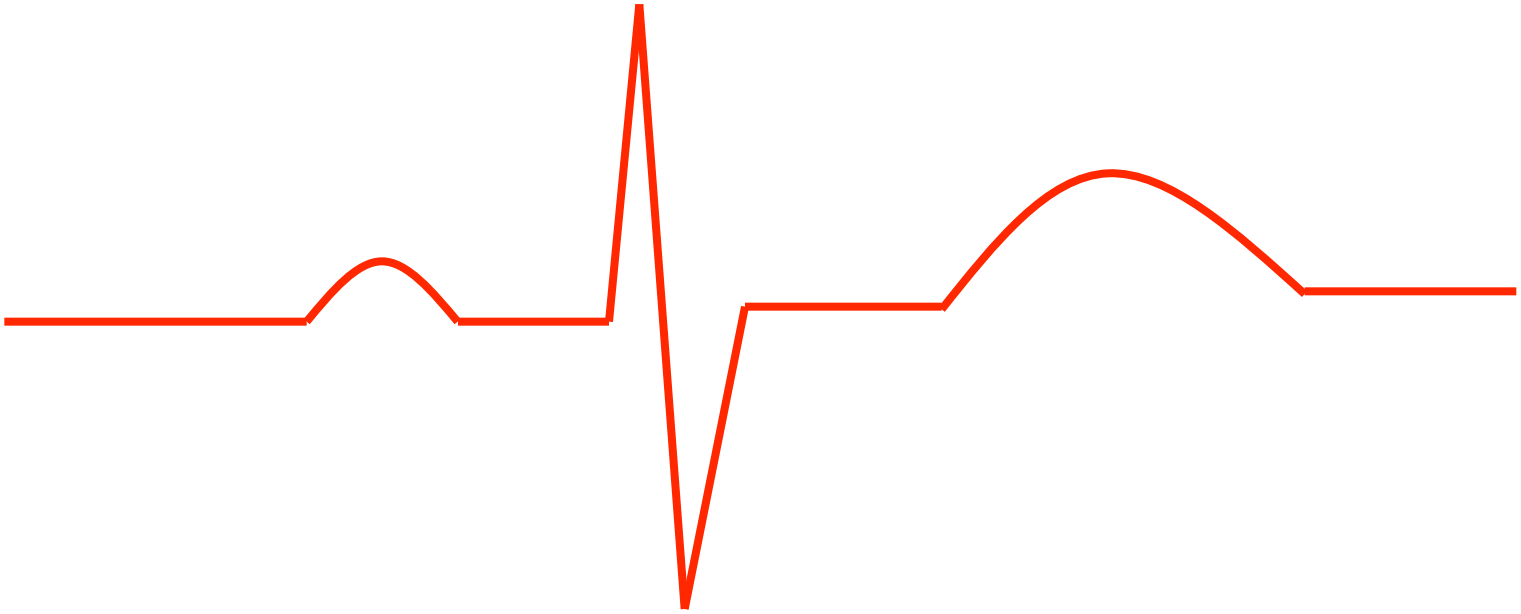
  Non

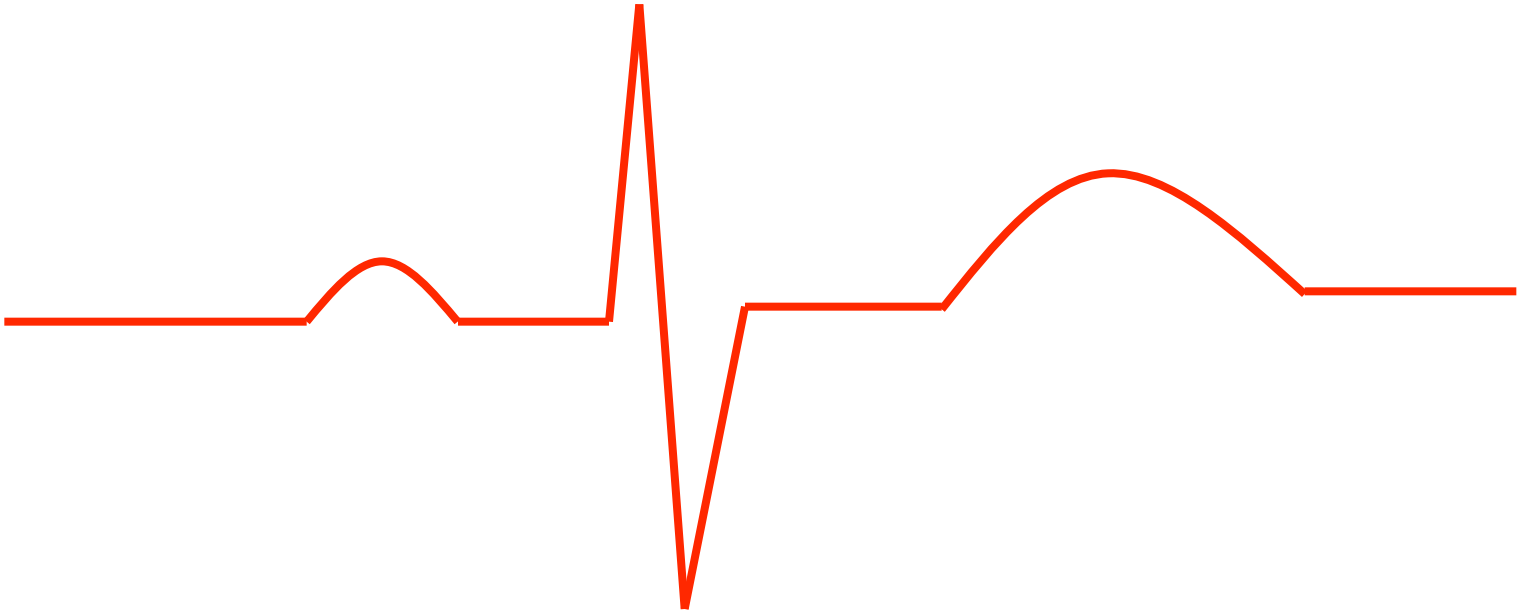
- **Perception de fonds d'une association dont je suis responsable et qui a reçu un don**

  Non

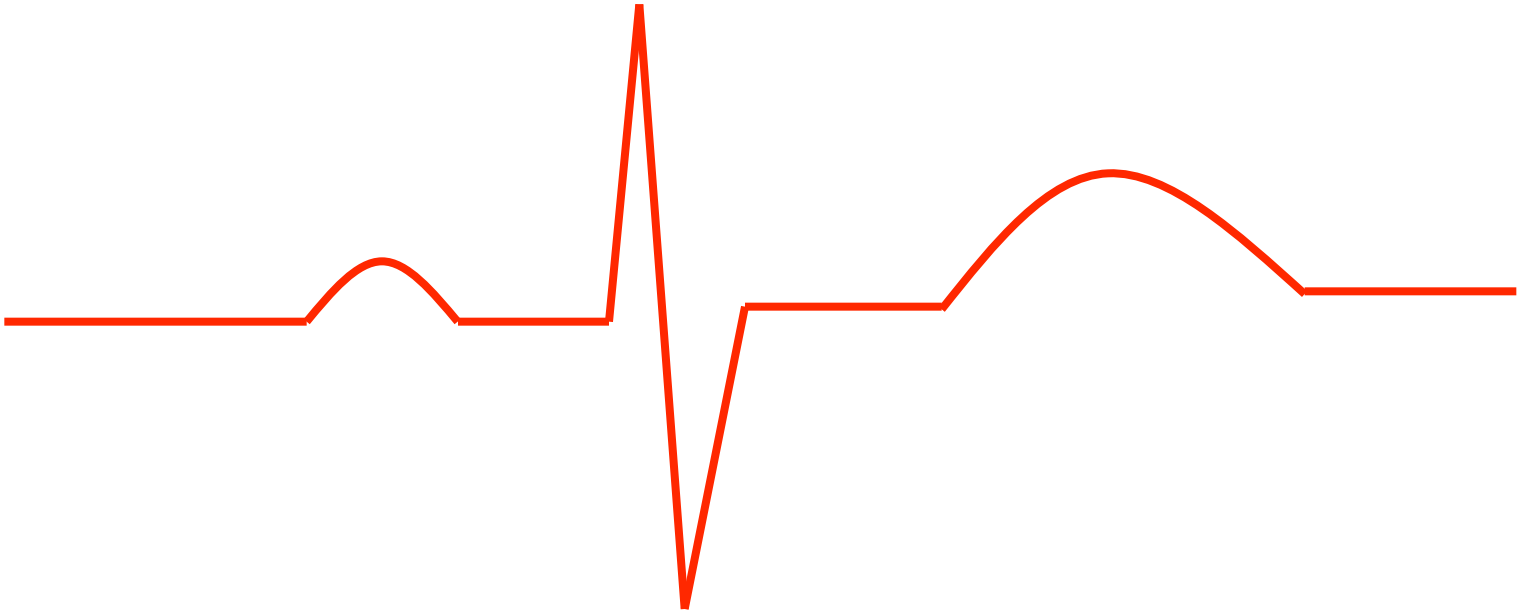
- **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

  Non

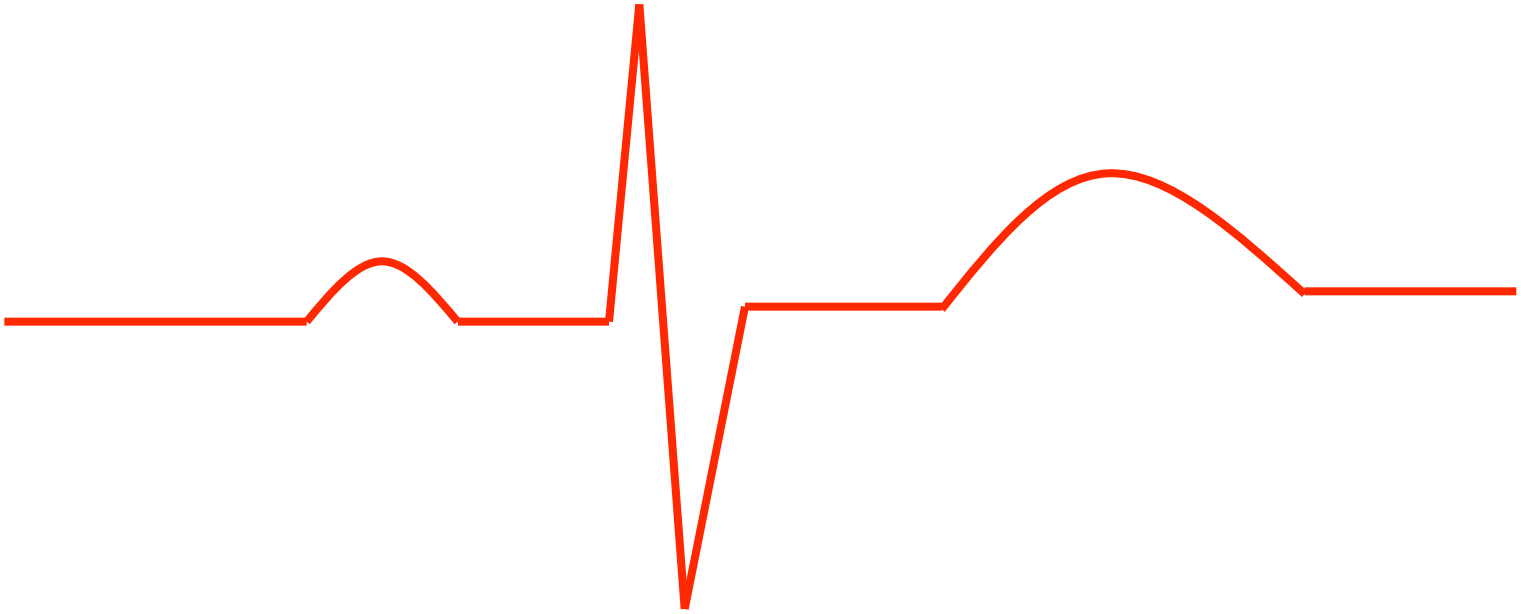




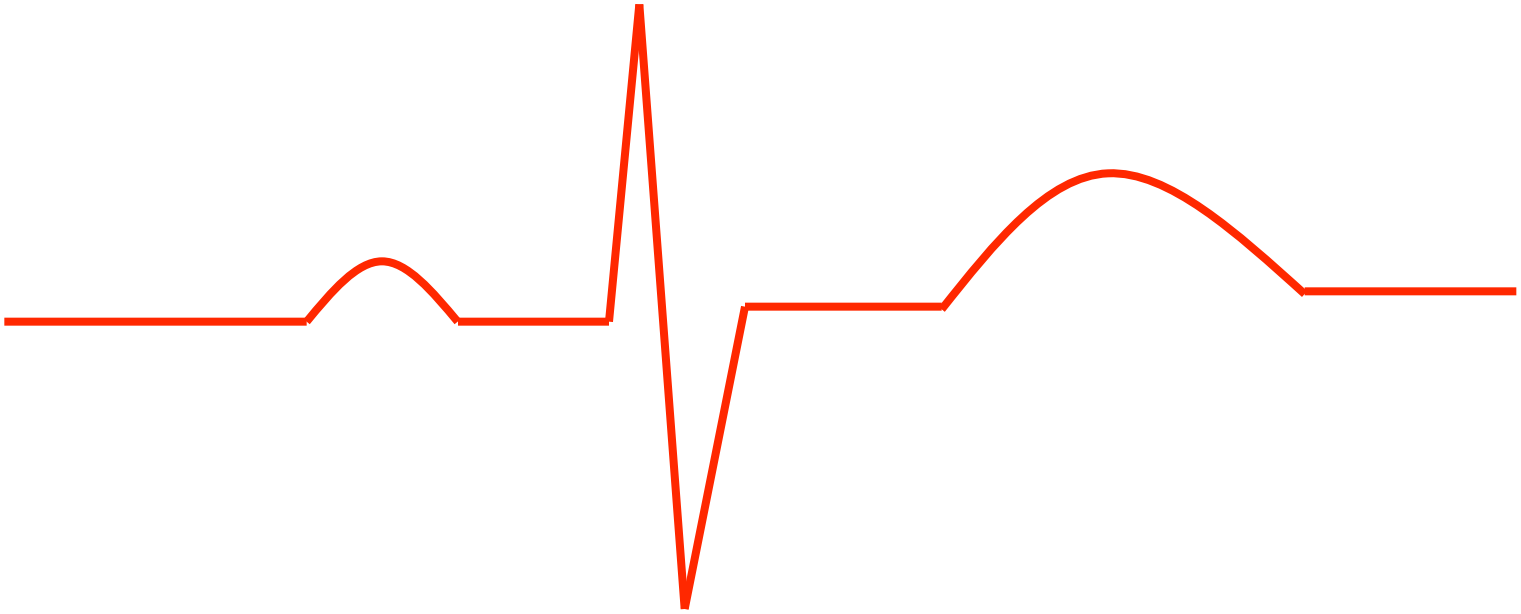
Period 1 : 1970-2000



Period 2
2001

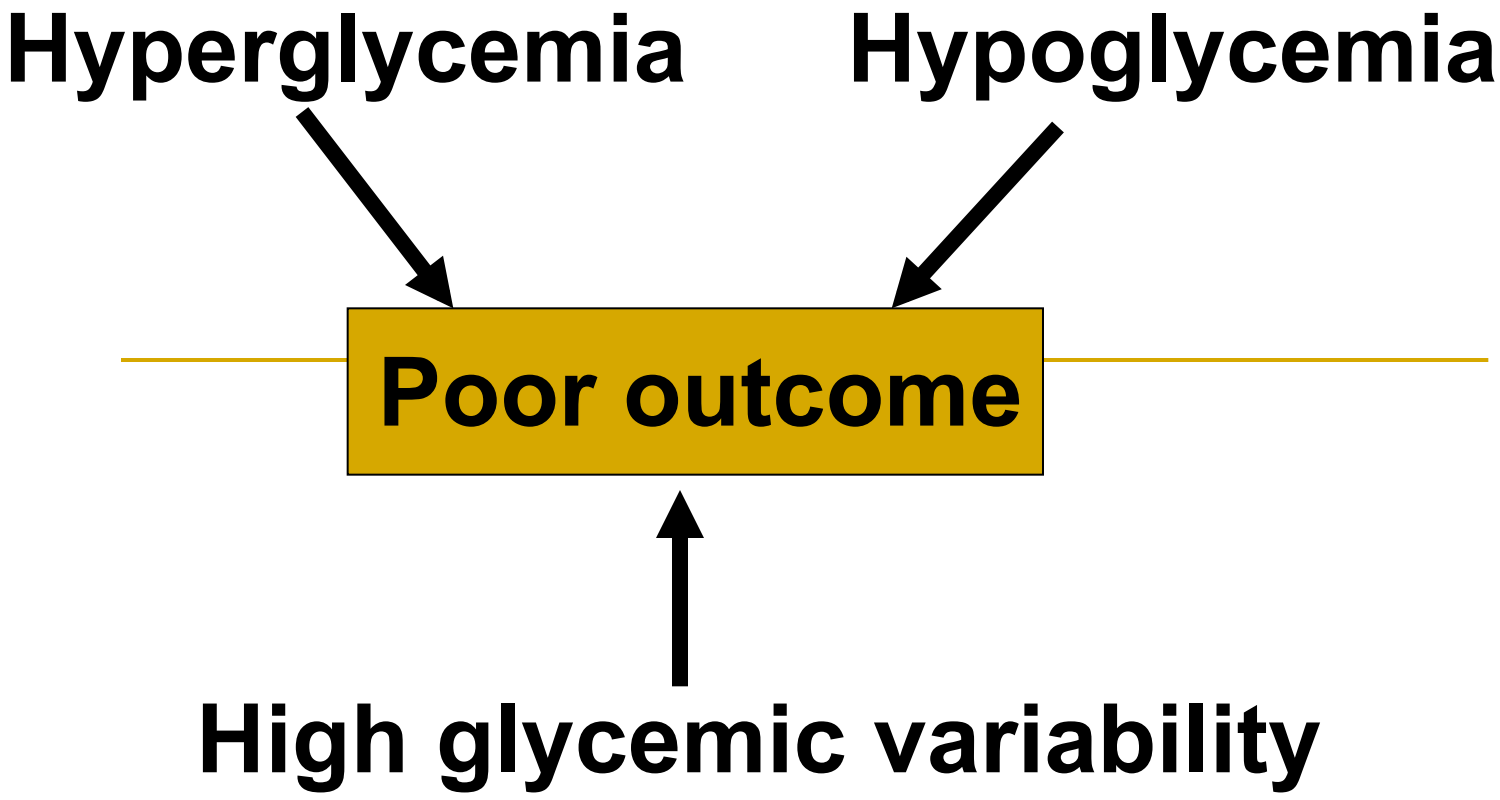


Period 3
2006-2009



Period 4
2009-

In critically ill patients…



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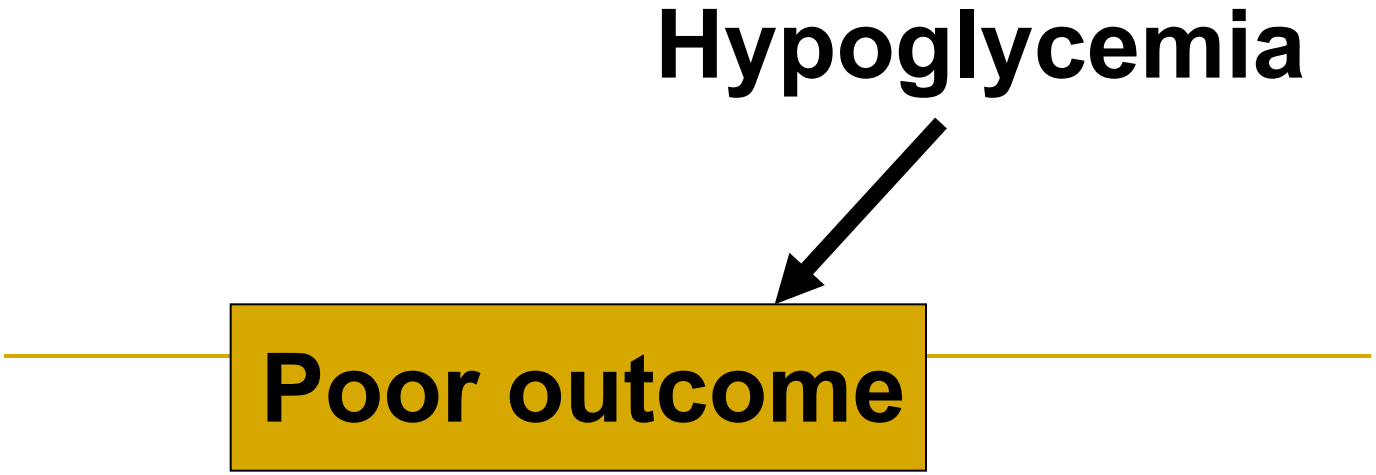


CASE REPORTS

- **Bhatia Anesth Analg 2006;102:549**
  - Cardiac asystole while being given a concentrated glucose solution to treat severe hypoglycemia after administration of insulin. The mechanism appears to be hyperkalemia.
- **Sinha Anaesthesia 2007;62:615**
  - … patient suddenly became irresponsive. BG value 20.8 (400 mg/dl), insulin infusion rate increased. Actually severe hypoglycemia but flushing solution of the arterial cannula was D5%! Patient died 9 days later.

Faster Detection: Both Hypo, Hyper Glycemia

RISK FACTORS FOR HYPOGLYCEMIA

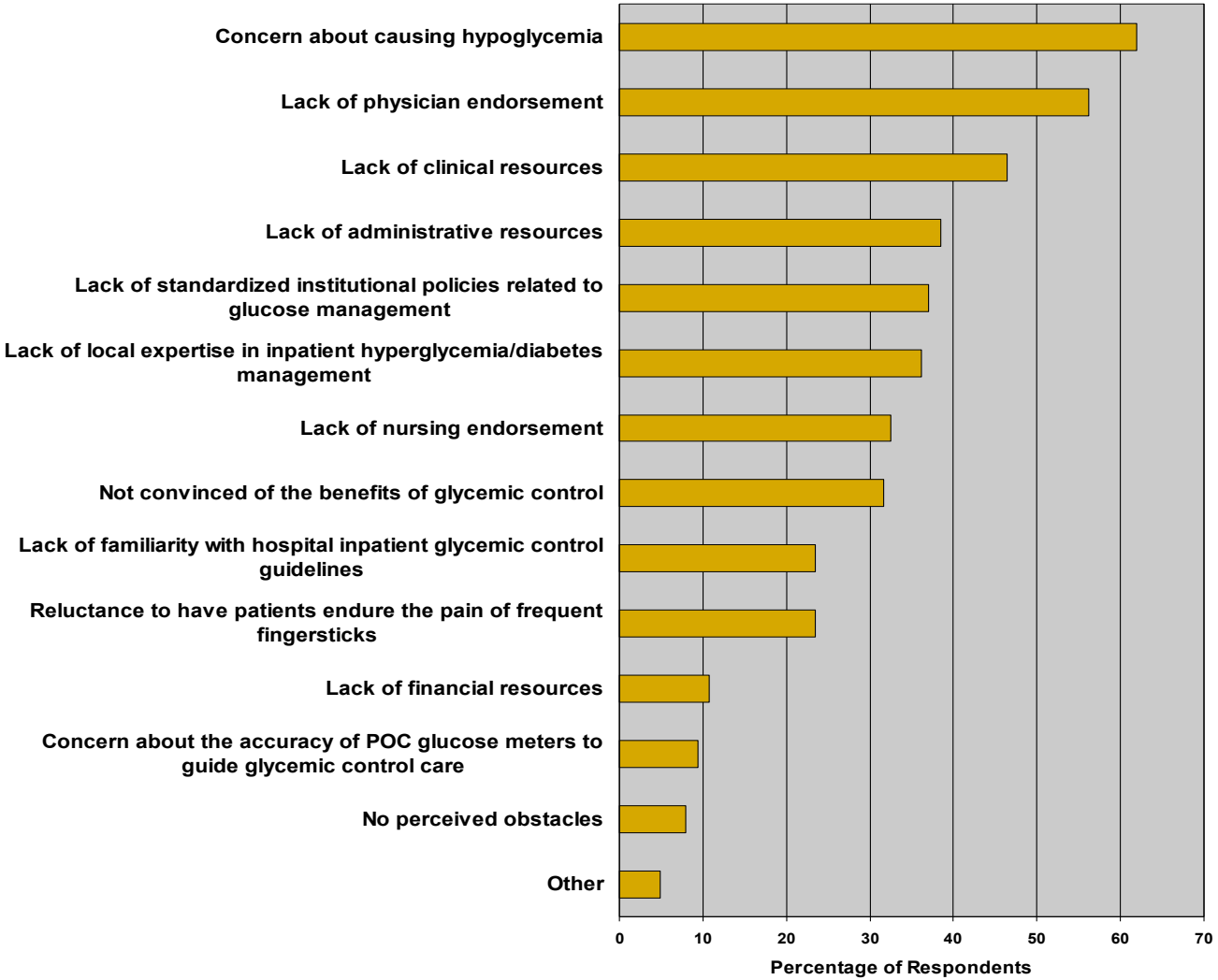
Vriesendorp et al Crit Care Med 2006; 34:96

	Hypo (n = 156)	No hypo (n = 155)
Female	75	52
SOFA shock>1	75	52
Diabetes	47	20
Sepsis	31	14
CVVH	26	8
CVVH bicar	14	1
Lower nutrition	17	2
Insulin	126	83

Retrospective collection ; hypoglycemia < 45 mg/dl

Perceived obstacles to the implementation of TGC US survey

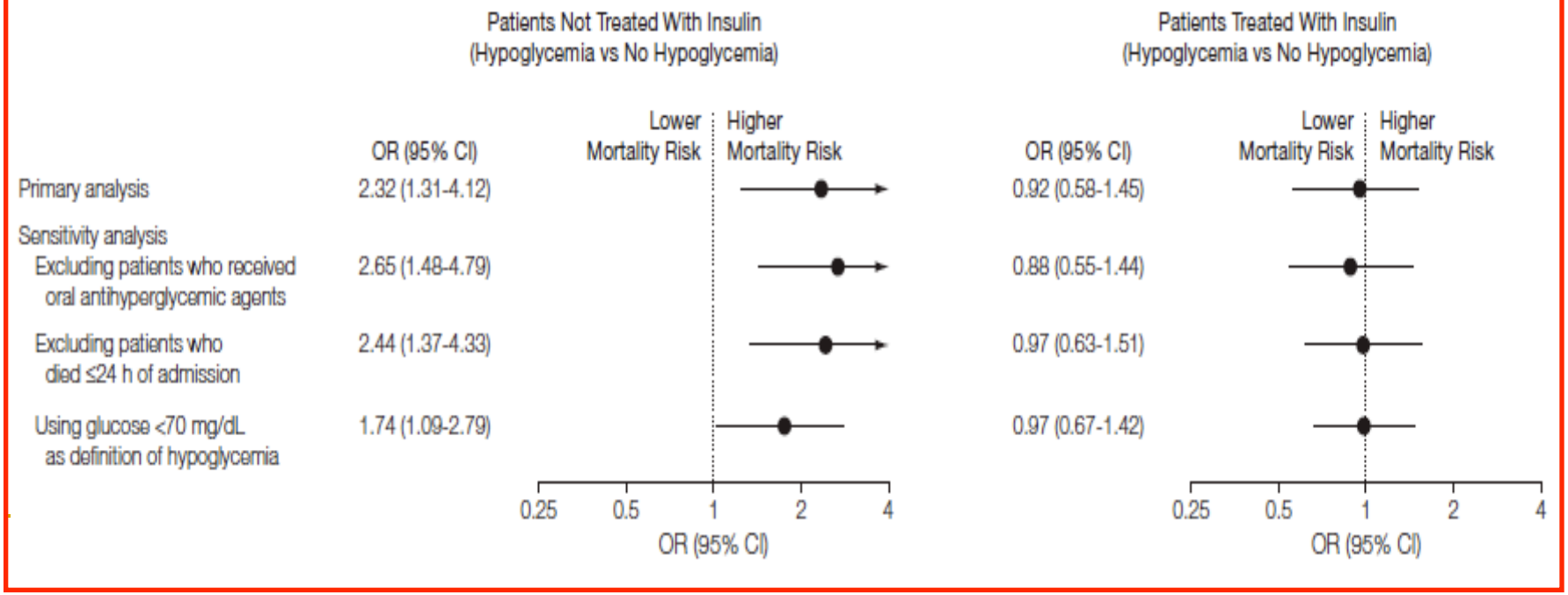
Cook BC et al SCCM congress (poster #282)



L'HYPOGLYCEMIE EN REA

Relationship Between Spontaneous and Iatrogenic Hypoglycemia and Mortality in Patients Hospitalized With Acute Myocardial Infarction

Figure. Association Between Hypoglycemia and Mortality After Multivariable Adjustment



SEVERE HYPOGLYCEMIA : RISK FACTORS AND OUTCOME

Krinsley Grover Crit Care Med 2007;35:2262

- 102 patients with at least one episode of severe hypoglycemia (< 40 mg/dl) matched with 306 control patients from a cohort of 5,365 patients

SEVERE HYPOGLYCEMIA : RISK FACTORS AND OUTCOME

Krinsley Grover Crit Care Med 2007;35:2262

- Mortality 55.9 % in patients with severe hypoglycemia vs 39.5 in non-hypoglycemic patients ($p < .01$)
- Multivariable logistic regression analysis identified hypoglycemia as an independent risk predictor of mortality (OR 2.3[1.4-3.7])

Hypoglycemia and Outcome in Critically Ill Patients

Moritoki Egi, MD; Rinaldo Bellomo, MD; Edward Stachowski, MD; Craig J. French, MD; Graeme K. Hart, MD; Gopal Taori, MD; Colin Hegarty, Bsc; and Michael Bailey, PhD

Mayo Clin Proc. • *March 2010;85(3):217-224*

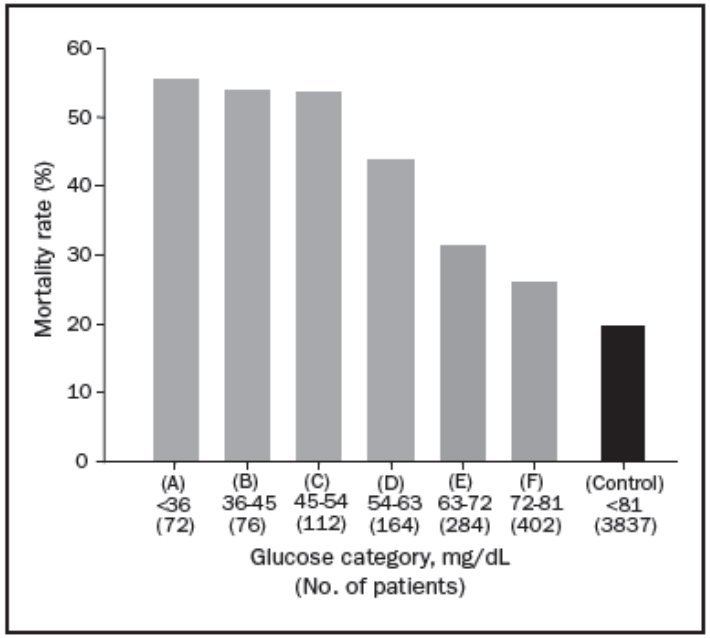


FIGURE. Hospital mortality according to severity of hypoglycemia. Gray bars indicate hospital mortality in each minimum glucose category. Black bar indicates hospital mortality in the nonhypoglycemic cohort (control). Hospital mortality was significantly higher for categories A through D than for categories E and F.

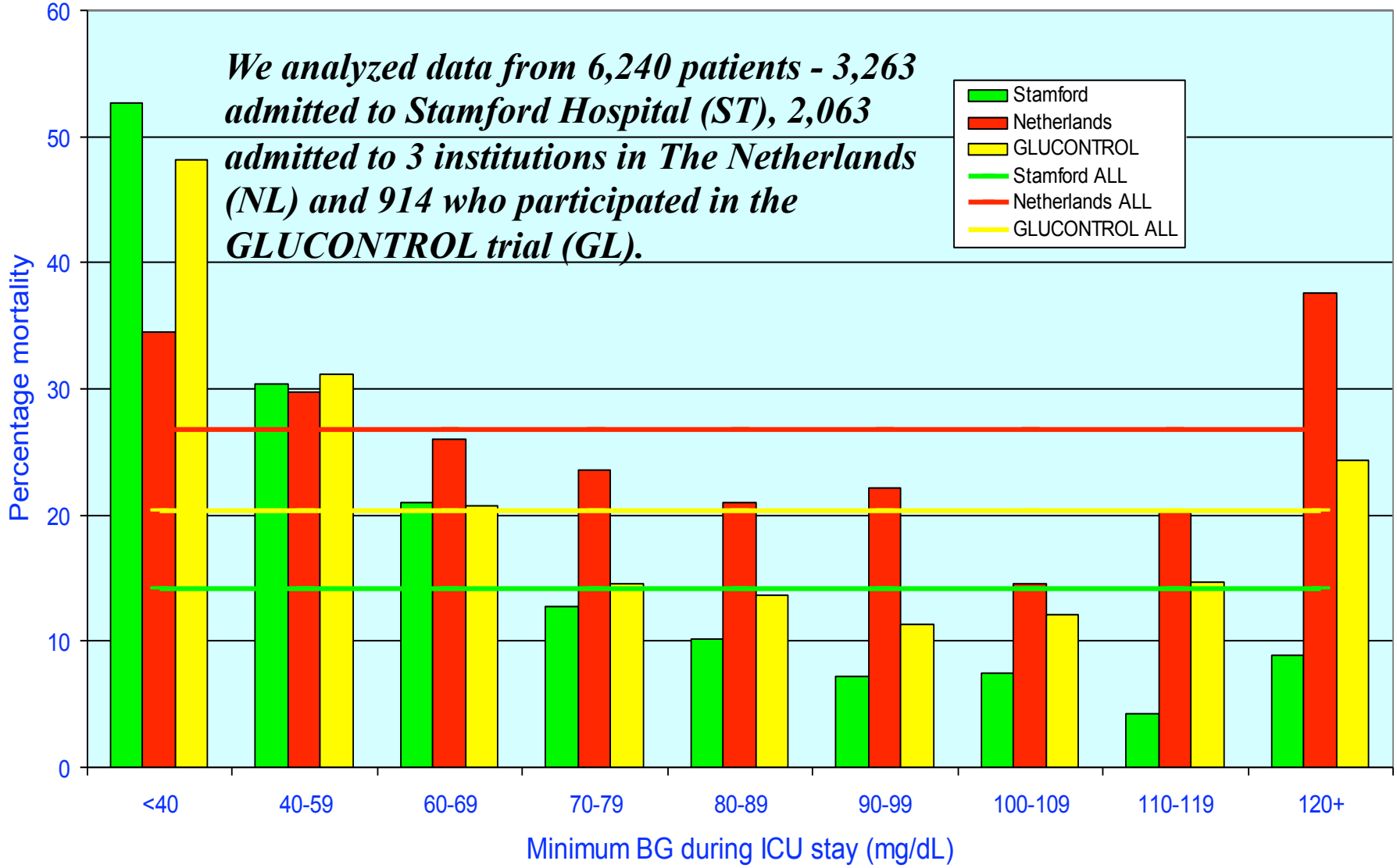
TABLE 2. **Multivariate Analysis of Potential Predictors of Mortality and Infection**[a]

Effect	Hospital mortality, OR (95% CI)	*P* value	ICU mortality, OR (95% CI)	*P* value	Infection, OR (95% CI)	*P* value
APACHE II score	1.13 (1.11-1.15)	<.001	1.15 (1.12-1.18)	<.001	1.09 (1.06-1.12)	<.001
Diabetes	0.70 (0.49-0.99)	.05	0.35 (0.22-0.57)	<.001	0.46 (0.26-0.81)	.007
Date of admission[b]	0.92 (0.86-0.98)	.01	0.87 (0.80-0.95)	.002	0.86 (0.78-0.95)	.003
Length of stay[c]	0.99 (0.99-1.00)	.06	0.97 (0.96-0.98)	<.001	0.99 (0.98-0.99)	.007
Frequency of daily measurement	1.07 (1.02-1.12)	.006	1.12 (1.06-1.19)	<.001	1.02 (0.97-1.07)	.51
Minimum glucose (mg/dL)[d]						
0-36 vs 72-81	2.99 (1.67-5.37)	<.001	4.10 (2.05-8.19)	<.001	3.14 (1.50-6.59)	.002
36-45 vs 72-81	2.14 (1.20-3.81)	.01	2.62 (1.32-5.20)	.006	1.75 (0.80-3.83)	.16
45-54 vs 72-81	2.13 (1.29-3.53)	.003	4.23 (2.29-7.79)	<.001	3.35 (1.76-6.34)	<.001
54-63 vs 72-81	1.93 (1.27-2.95)	.002	2.41 (1.40-4.14)	.002	2.16 (1.17-3.99)	.01
63-72 vs 72-81	1.07 (0.74-1.54)	.74	1.43 (0.88-2.32)	.15	0.93 (0.50-1.72)	.82

[a] APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; ICU = intensive care unit; OR = odds ratio.
[b] ORs represent the risk associated with a 6-month period. Later date of admission was associated with a decreased risk.
[c] ORs represent the risk associated with a 1-day increase in hospital length of stay. All available variables were entered into the model.
[d] SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.

Relationship between mortality and minimum BG during ICU stay

Krinsley, Schulz, Preiser (Crit Care 2011)



Mild hypoglycemia is independently associated with increased mortality in the critically ill

James S Krinsley[1*], Marcus J Schultz[2,3], Peter E Spronk[2,4], Robin E Harmsen[2], Floris van Braam Houckgeest[5], Johannes P van der Sluijs[6], Christian Mélot[7] and Jean Charles Preiser[8]

Crit Care 2011;15:R173

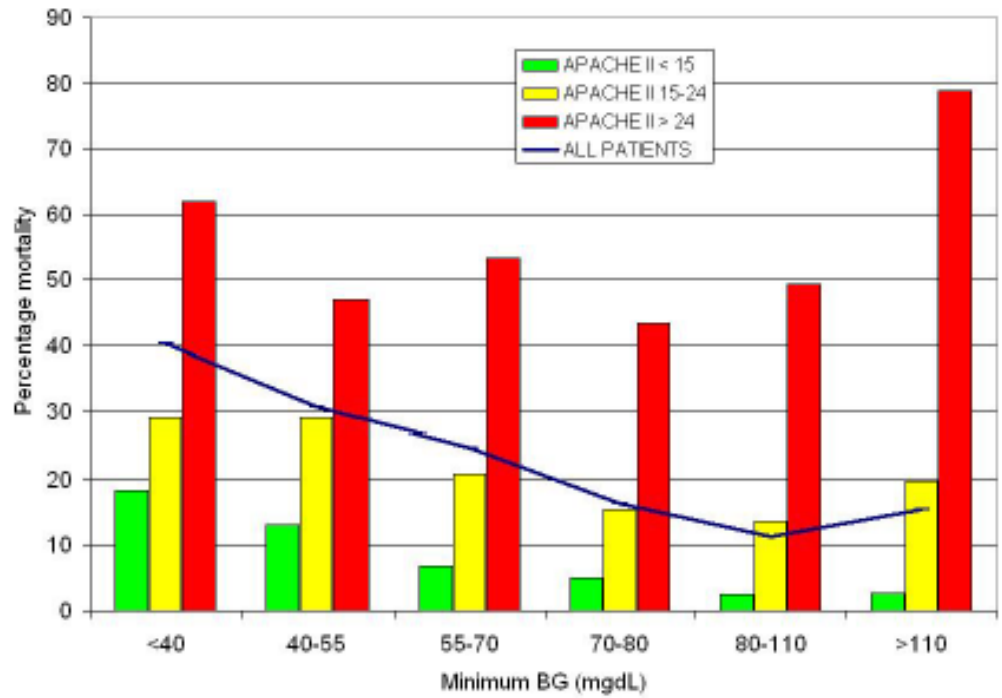
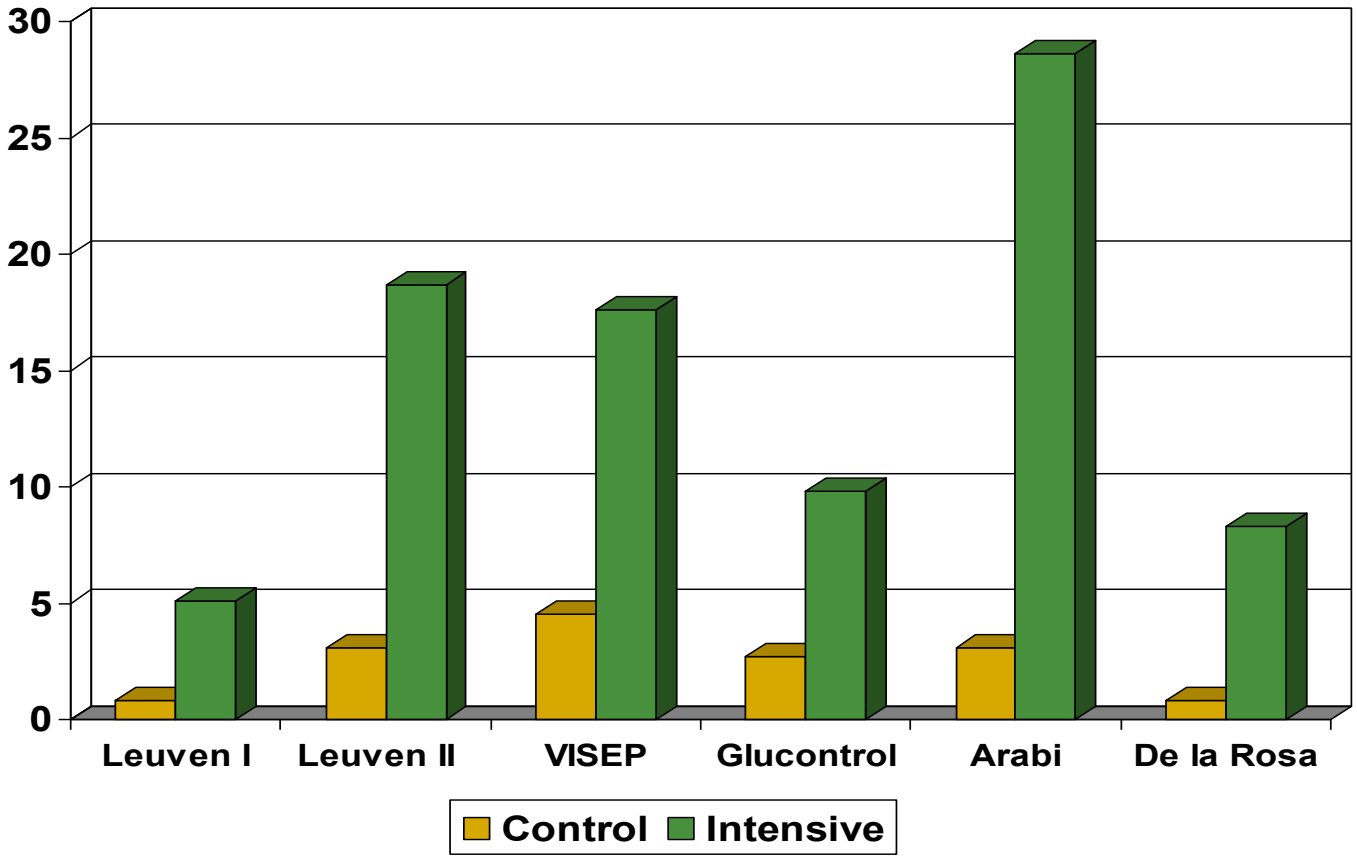


Figure 2 Relationship between minimum BG during ICU stay and mortality, stratified by APACHE II score. APACHE II, Acute Physiology and Chronic Health Evaluation II disease classification system; BG, blood glucose.

Incidence of hypoglycemia during IIT

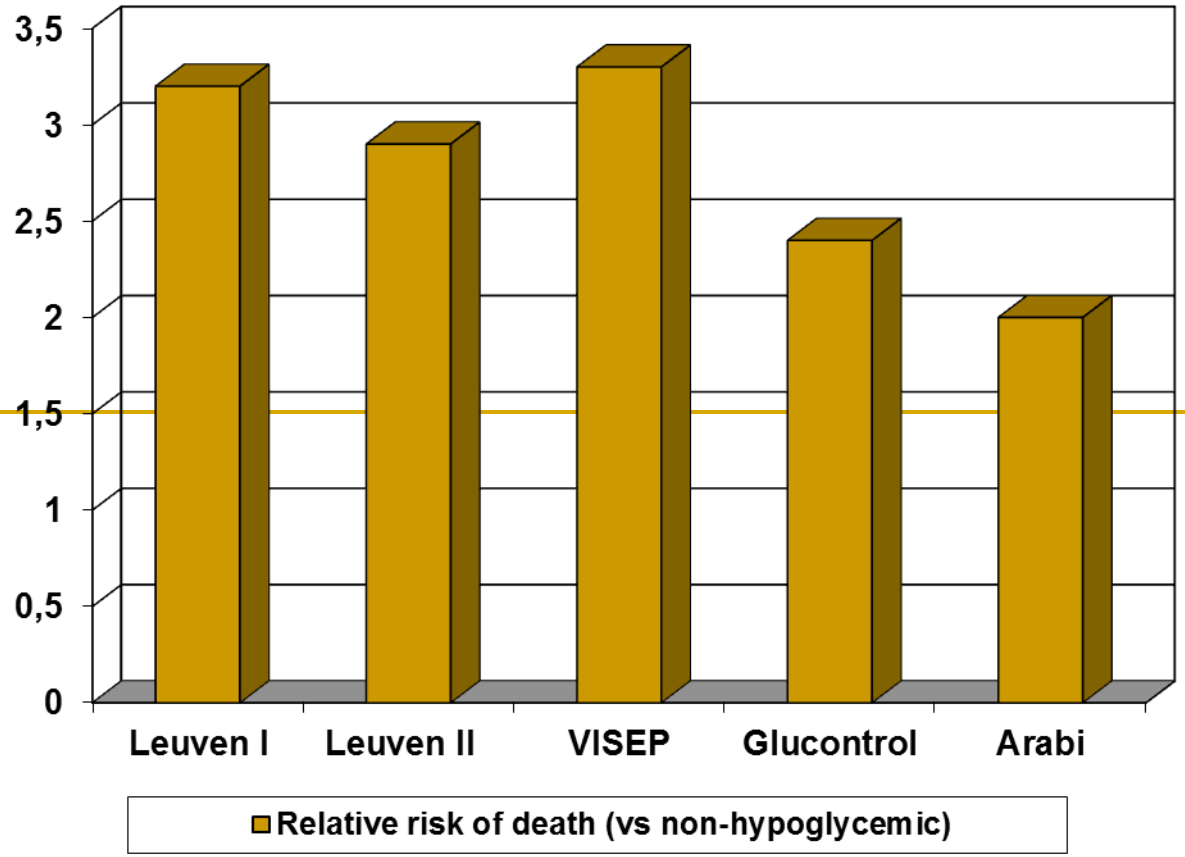
Prospective studies

Increased risk of hypoglycemia (13.7 vs 2.5 (RR 5.13 (4.09-6.43))



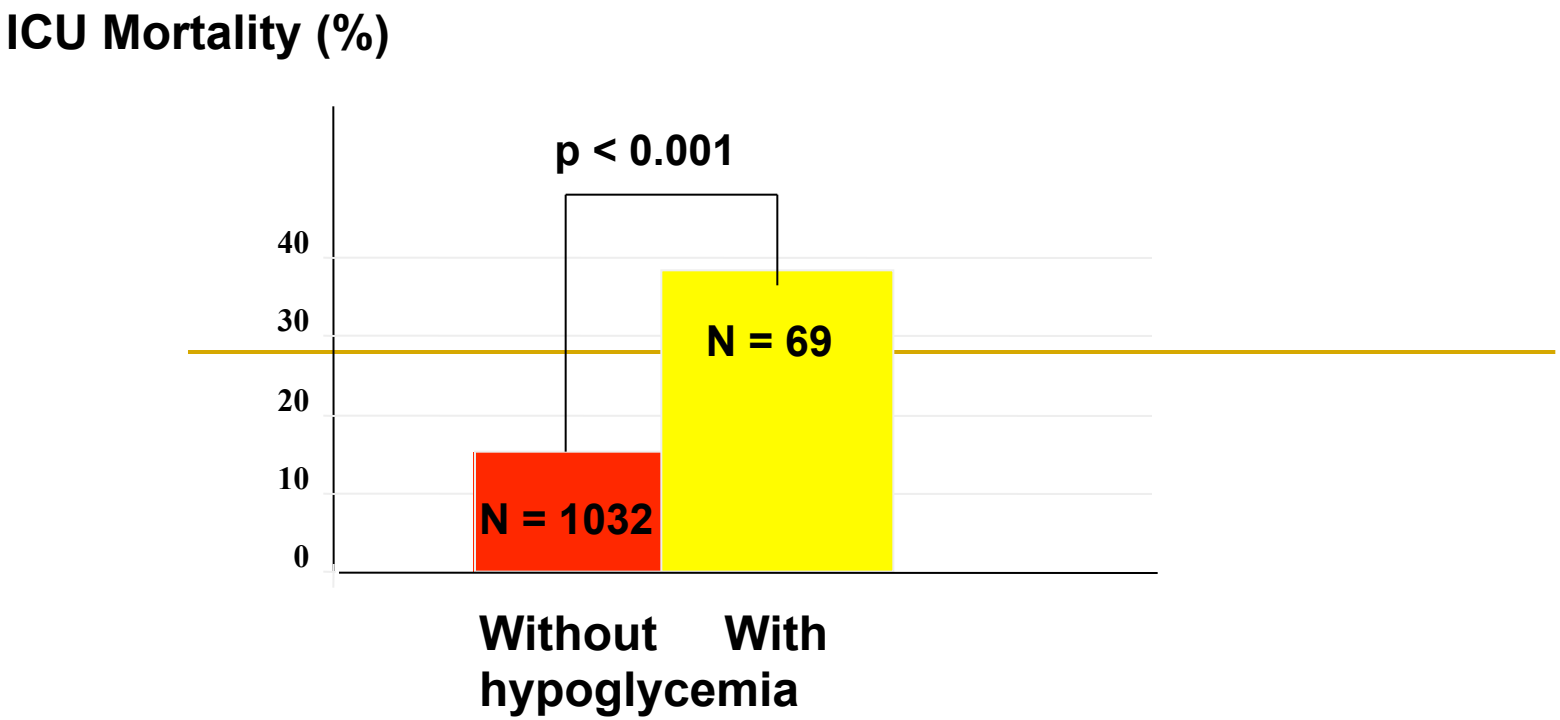
Relative risk of death of patients with hypoglycemia

Prospective studies



Hypoglycemia and ICU mortality

Data from Glucontrol – Preiser et al Intensive Care Med 2009

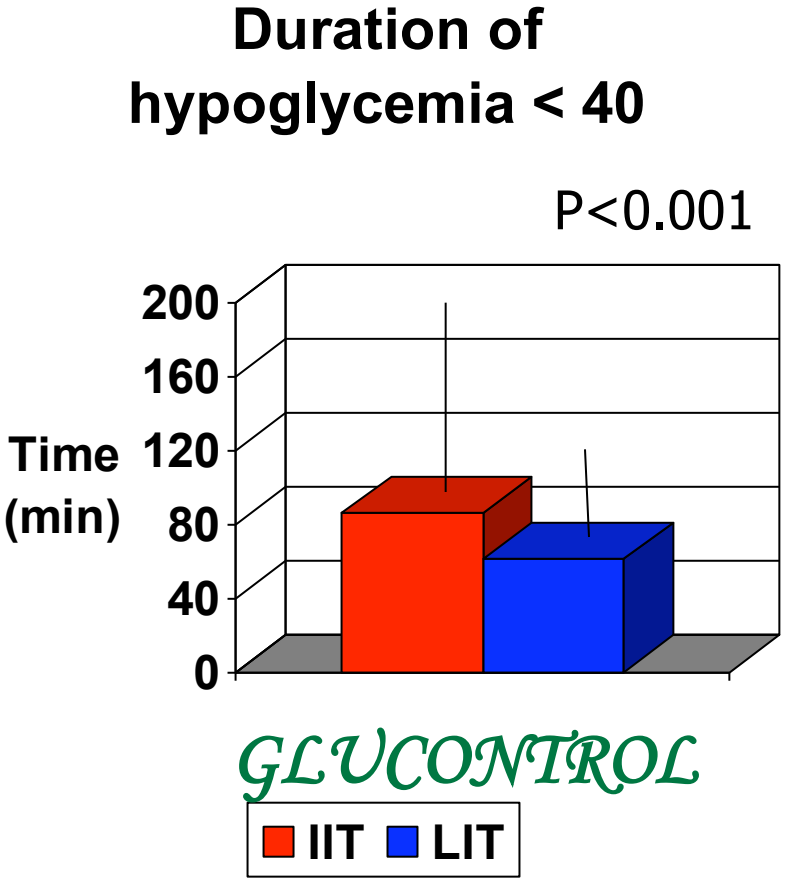


GLUCONTROL

Multivariable analysis: hypoglycemia < 60 mg/dl			
	Adjusted OR	95 % CI	p
Group IIT	7.05	4.72 - 10.53	< 0.0001
Death	2.19	1.38 – 3.48	0.0008
Apache II	1.07	1.04 – 1.10	< 0.0001

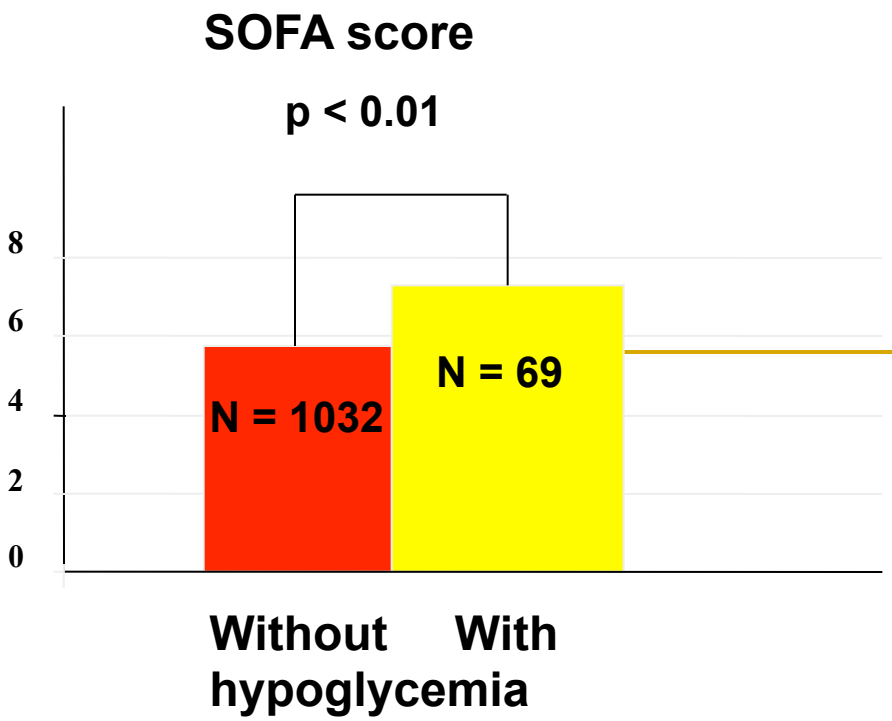
Multivariable analysis: hypoglycemia < 40 mg/dl			
	Adjusted OR	95 % CI	p
Group IIT	4.29	2.10 – 8.76	0.0001
Death	2.26	1.15 – 2.26	0.0177
Apache II	1.07	1.03 – 1.11	0.0008

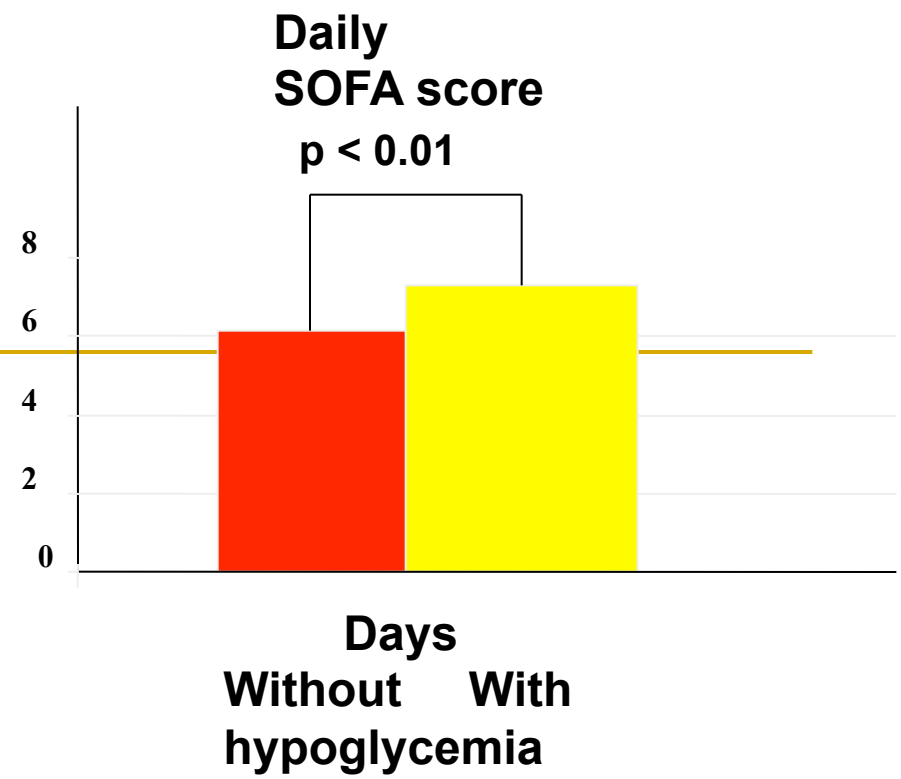
DURATION OF HYPOGLYCEMIA DURING IIT



Brain interstitial glucose Decreased by IIT (Vespa et al Crit Care Med 2006)

Hypoglycemia and organ failures





ORIGINAL ARTICLE

Hypoglycemia and Risk of Death in Critically Ill Patients

N Engl J Med 2012;367:1108-18.

The NICE-SUGAR Study Investigators*

METHODS

We examined the associations between moderate and severe hypoglycemia (blood glucose, 41 to 70 mg per deciliter [2.3 to 3.9 mmol per liter] and ≤40 mg per deciliter [2.2 mmol per liter], respectively) and death among 6026 critically ill patients in intensive care units (ICUs). Patients were randomly assigned to intensive or conventional glucose control. We used Cox regression analysis with adjustment for treatment assignment and for baseline and postrandomization covariates.

Subgroup	Deaths	Population	Median Time from Randomization to Hypoglycemia (IQR)	Median Time from Hypoglycemia to Death (IQR)	Hazard Ratio (95% CI)	P Value
	no.		*days*			
No hypoglycemia	726	3089			1.00	
Moderate hypoglycemia	774	2714	1 (0–2)	7 (2–21)		
Stratified by treatment					1.81 (1.59–2.07)	<0.001
Stratified by treatment and adjusted for baseline characteristics					1.60 (1.39–1.85)	<0.001
Stratified by treatment and adjusted for baseline and postrandomization characteristics					1.41 (1.21–1.62)	<0.001
Severe hypoglycemia	79	223	4 (2–9)	8 (3–15)		
Stratified by treatment					3.21 (2.49–4.15)	<0.001
Stratified by treatment and adjusted for baseline characteristics					2.64 (2.01–3.47)	<0.001
Stratified by treatment and adjusted for baseline and postrandomization characteristics					2.10 (1.59–2.77)	<0.001

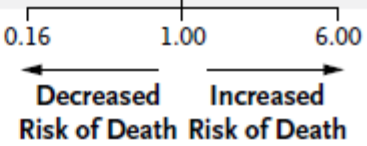


Figure 1. Hazard Ratio for Death According to Occurrence of Moderate or Severe Hypoglycemia.

Moderate hypoglycemia was defined as a blood glucose value of 41 to 70 mg per deciliter (2.3 to 3.9 mmol per liter), and severe hypoglycemia as a blood glucose value of 40 mg per deciliter (2.2 mmol per liter) or less.

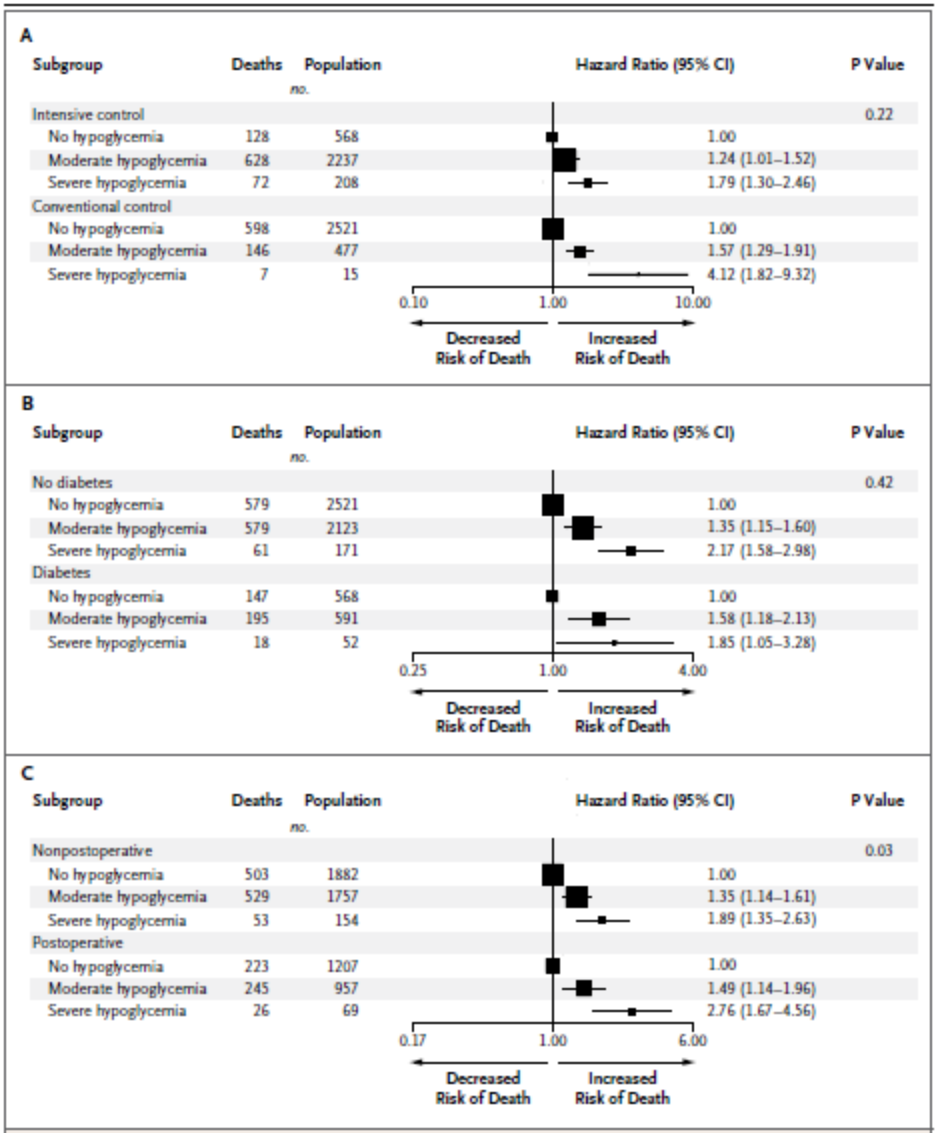


Figure 2. Hazard Ratio for Death According to Treatment Assignment and Status with Respect to Diabetes and Postoperative Status at Baseline.

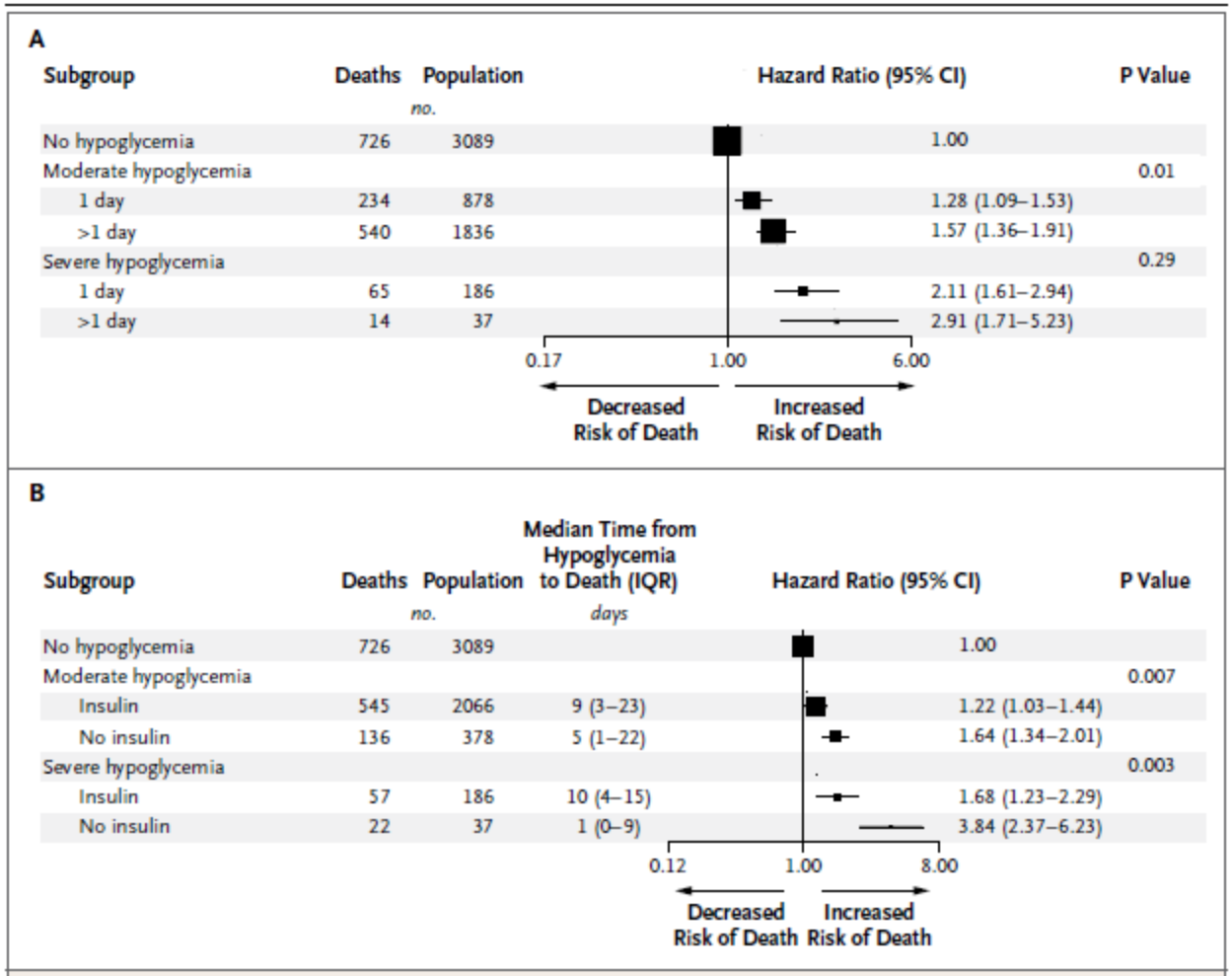


Figure 3. Hazard Ratio for Death According to the Occurrence of Hypoglycemia on 1 Day or More Than 1 Day and Receipt or Nonreceipt of Insulin Therapy at the Time of the First Hypoglycemic Episode.

Physiological response to hypoglycemia

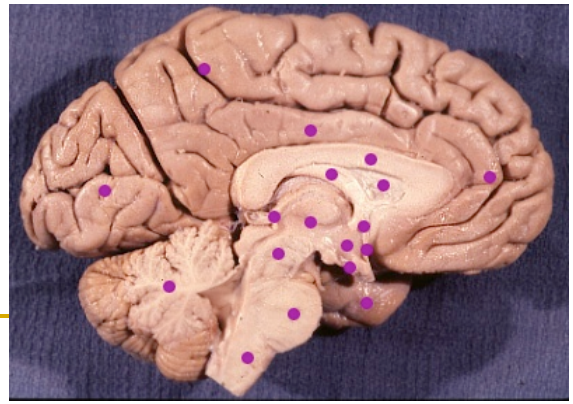
- < 80 mg/dl : **Inhibition of insulin release**
- < 65 mg/dl :
  - **Glucagon** release to increase the release of glucose from liver
  - **Epinephrine** secretion to increase glycogenolysis and the provision of neoglucogenic substrates
  - **Growth Hormone**
- < 55 mg/dl : **Cortisol** release

In case of prolonged hypoglycemia

P. E. Cryer
Division of Endocrinology, Diabetes and Metabolism, Washington University School of Medicine, St. Louis, Missouri, USA

Hypoglycemia and the brain

- Glucose is the obligatory metabolic fuel for the injured brain
- No cerebral stores of glucose
- Glucose diffusion from plasma to neurons and astrocytes (concentration-dependent)
- In case of severe hypoglycemia, fall of ATP and cortical activity (EEG)
- Potential roles of lactate / glycogen released from astrocytes as rescue substrates ?

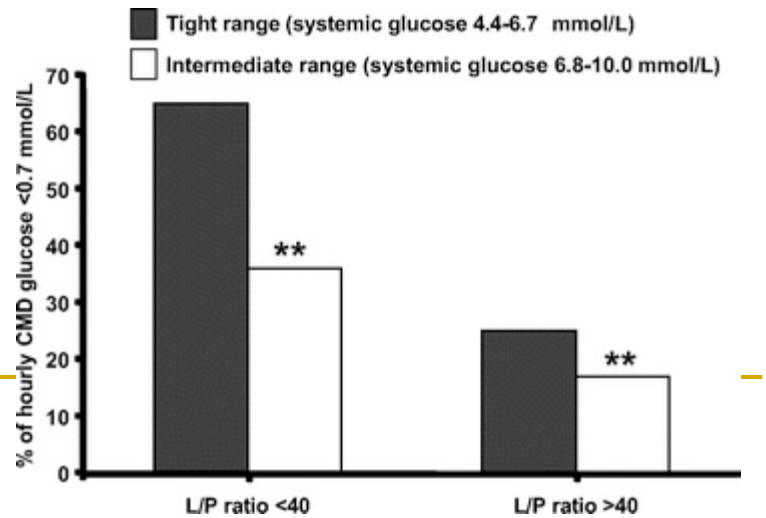


Impact of TGC on cerebral glucose metabolism

Oddo et al Crit Care Med 2008;36:3233

- Twenty patients monitored with microdialysis after severe brain injury
- TGC (target 80-120 mg/dl)
- Cerebral glucose and lactate/pyruvate ratio collected hourly

- ***Outcome variables*** :
  - ranges of BG :
    low (< 80) - tight : (80-120),
    intermediate (120-180) - high (>180)
  - L/P ratio :
    > 25 : abnormal
    > 40 : brain energy failure
    ➢40 + brain glucose < 13 :
    Brain energy crisis



Predictors of brain energy crisis
(multivariate logistic regression adjusted for ICP and CPP) :
Serum glucose and dose of insulin

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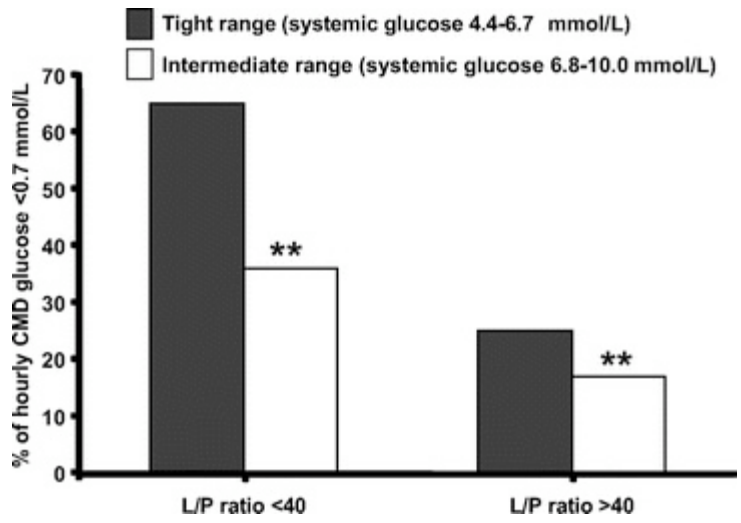

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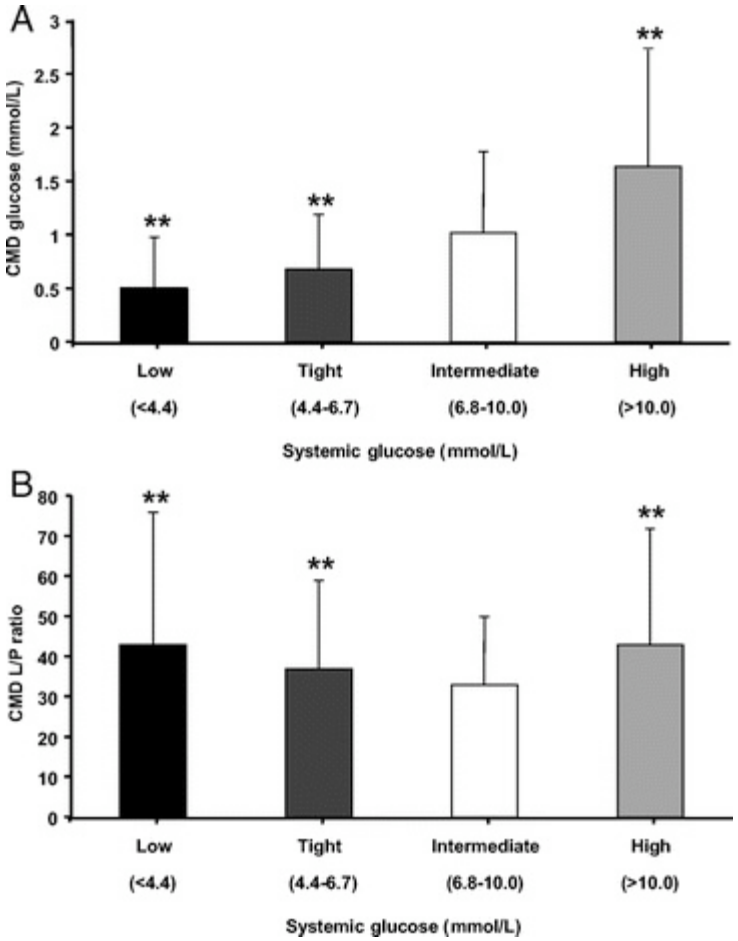

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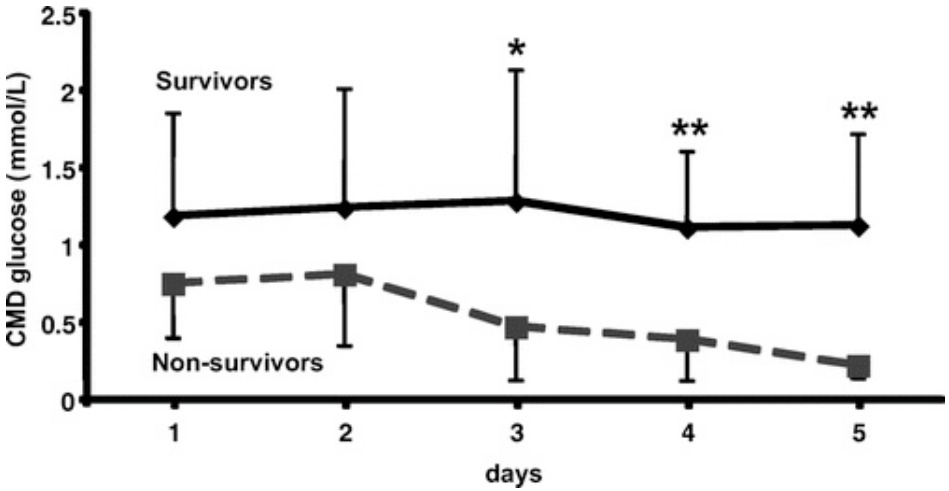

Predictors of hospital mortality (logistic regression)

Brain energy crisis 7.4 (1.4-39.5)*
Glasgow Coma scale 1.1 (.96-1.3)
CPP 1.01 (.97-1.04)
ICP 1 (0.99-1.01)

Hypoglycemia Aggravates Critical Illness–Induced Neurocognitive Dysfunction

Thomas Duning, MD[1]
Ingeborg van den Heuvel, MD[2]
Annabelle Dickmann[2]
Thomas Volkert, MD[2]
Carola Wempe, MD[2]
Julia Reinholz, MD[1]
Hubertus Lohmann, MD[1]
Hendrik Freise, MD[2]
Björn Ellger, MD, PhD[2]

Diabetes Care 33:639–644, 2010

	Hypo group			Control group			
	Score (percentile)	Evaluation	Z scores	Score (percentile)	Evaluation	Z scores	*P*
Dementia screening			0.006			−0.003	0.969
Mini-mental state examination	28.4	Close below average		28.8	Close below average		0.909
Boston Naming Test	13.8	Normal		13.9	Normal		0.871
Attention and working memory			−0.039			−0.045	0.774
Nuernberg Gerontopsychological Inventory							
Digit symbol substitution	30.0 (56.7)	Normal		31.1 (60.7)	Normal		0.770
Color word interference task (reading)	39.8 (10.2)	Far below average		40.0 (12.5)	Far below average		0.861
Color word interference task (color naming)	53.3 (28.4)	Close below average		52.8 (26.6)	Close below average		0.608
Wechsler Memory Scale (revised)							
Digit span forward	11.6 (51.7)	Normal		12.6 (54.4)	Normal		0.156
Digit span backward	10.7 (40.6)	Close below average		11.6 (42.0)	Close below average		0.892
Trail-making test (A)	60.1 (13.9)	Far below average		59.6 (13.0)	Far below average		0.270
Executive function			−0.001			−0.007	0.991
Color word interference task (interference condition)	17.5 (47.9)	Normal		19.5 (51.3)	Normal		0.421
Regensburg Word Fluency Test (letter fluency) (S)	14.2 (28.4)	Close below average		14.2 (28.4)	Close below average		1.000
Trail-making test (B)	117.0 (27.8)	Close below average		110.8 (25.6)	Close below average		0.792
Visuospatial skills			−2.084			−0.145	0.001
Rey Osterrieth Complex Figure Test							
Copy	20.4			24.7			0.007
Delayed recall	9.4 (22.8)	Close below average		14.5 (29.9)	Close below average		0.002
Difference copy (delayed)	−54.3%			−41.9% (4.2)			0.043
Verbal learning and memory			−0.027			−0.064	0.807
Auditory verbal learning test (German)							
Recall trial 1	4.9 (30.2)	Close below average		5.5 (38.4)	Close below average		0.503
Recall trial 5	10.7 (31.1)	Close below average		10.5 (28.8)	Close below average		0.543
Total trials 1–5	38.0 (30.4)	Close below average		38.7 (32.1)	Close below average		0.527
Delayed recall	8.5 (13.8)	Far below average		9.0 (15.0)	Far below average		0.240
Recognition (true positives, false positives)	10.9 (30.5)	Close below average		10.9 (30.5)	Close below average		1.000

The risks of hypoglycemia

- Risk of hypoglycemia increased 4- to 6- fold when applying tight glucose control (BG target 80-110 mg/dl)
- Incidence of hypoglycemia increased in most severely ill patients
- Indirect causal relationships between hypoglycemia and mortality and/or neurological damage are plausible – need to be investigated

Potential toxicity

- Hypoglycemia-associated autonomic failure (HAAF)?
- Neurologic
  - Related to duration?
- Non-neurologic
  - Delayed diagnosis of adrenal / liver failure (falsely attributed to IIT)
  - Others ?
- Workload and stress

TIGHT GLUCOSE CONTROL WITH INTENSIVE INSULIN THERAPY