# *Contrôle glycémique en réanimation*

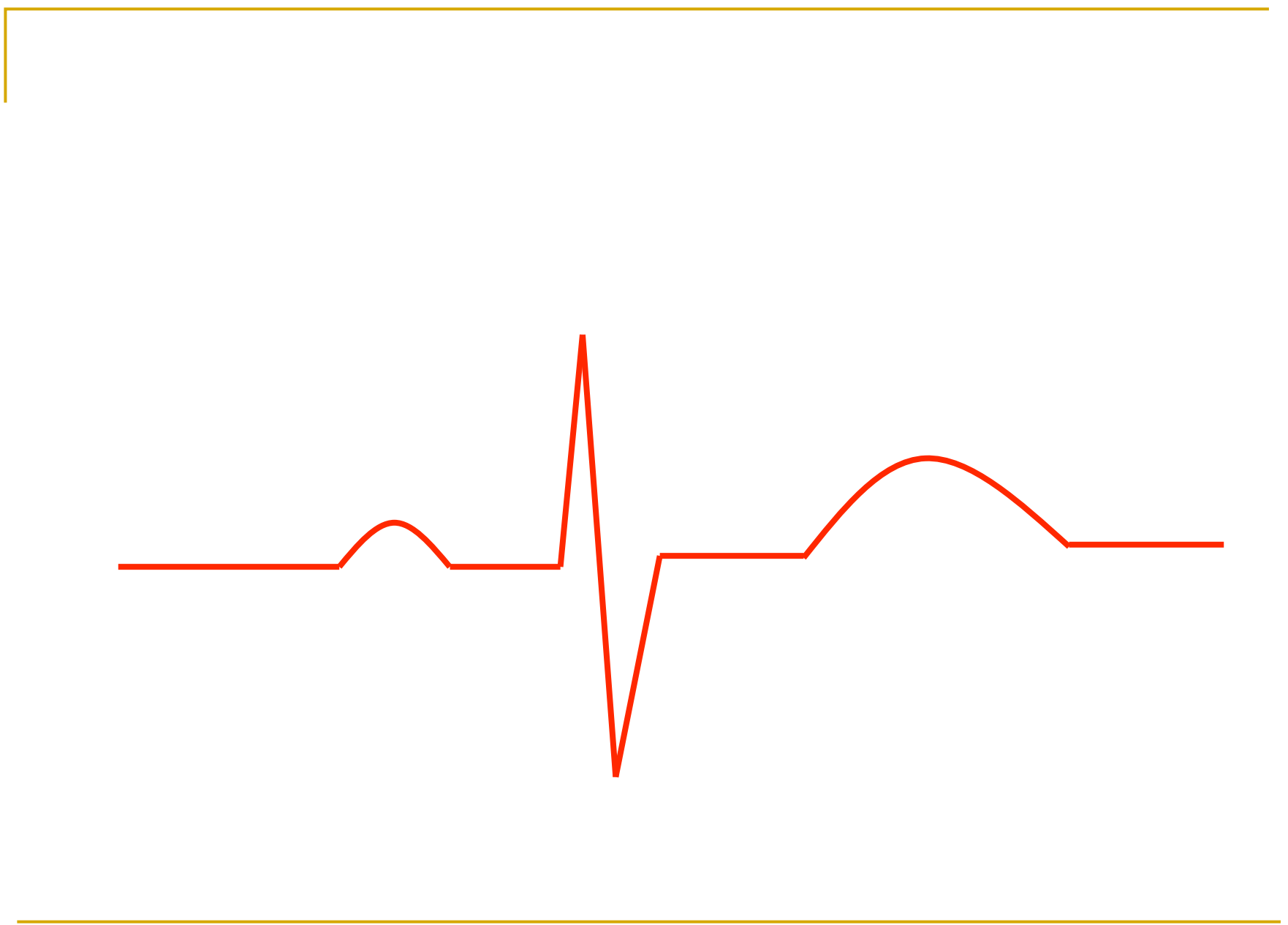
Jean-Charles Preiser – CHU Liège

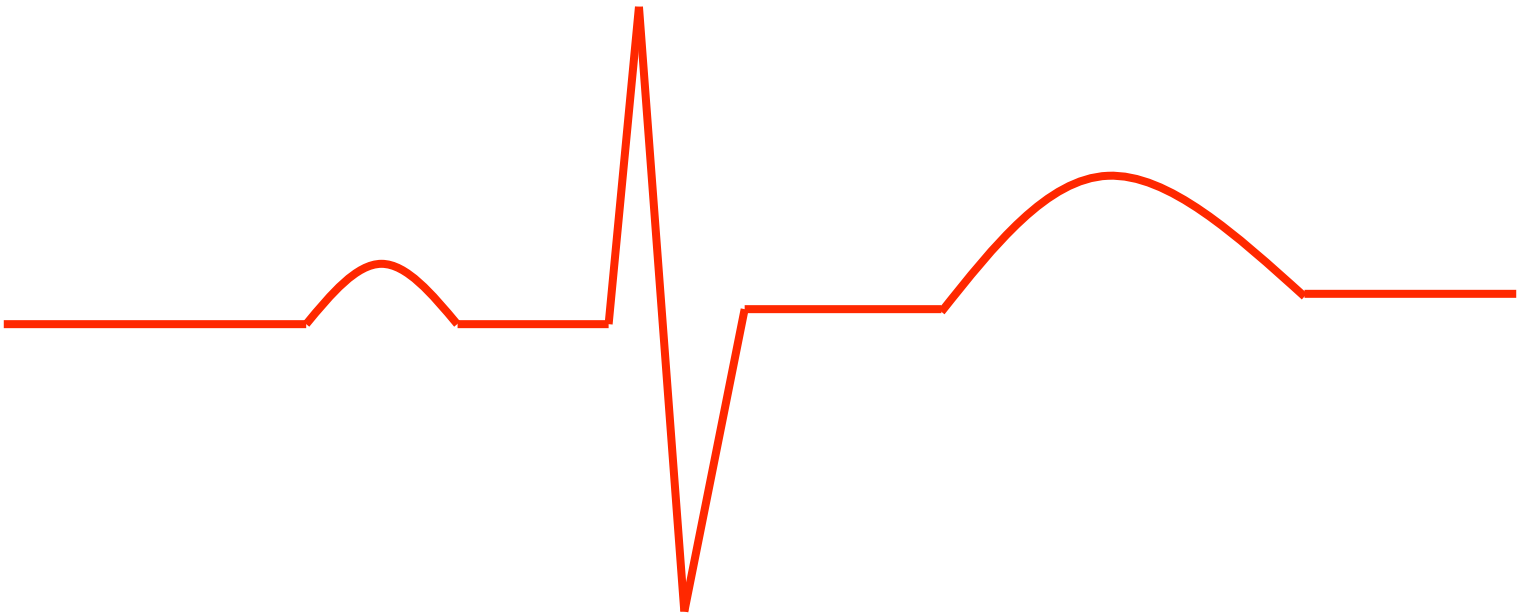
Journées de Printemps de la SFNEP

Strasbourg, 17 juin 2010

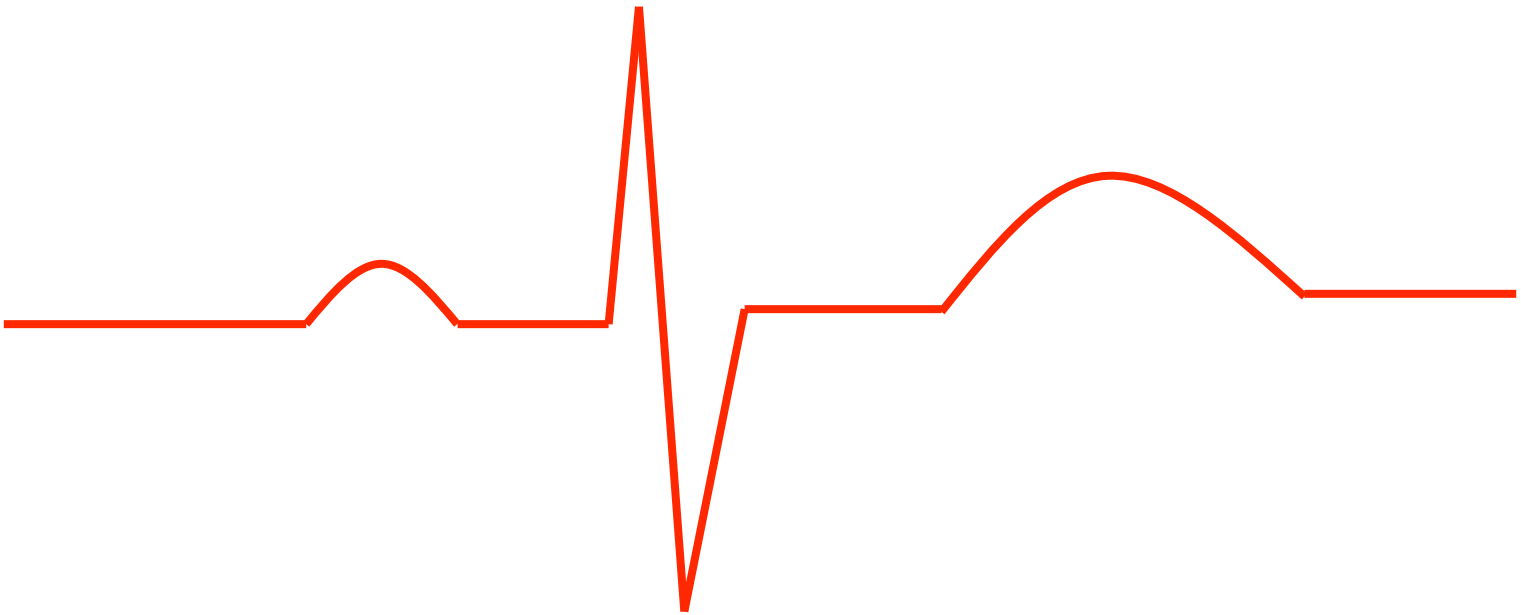
# BELGIUM IS OPEN-MINDED


*The same story can be read and interpreted in different languages*

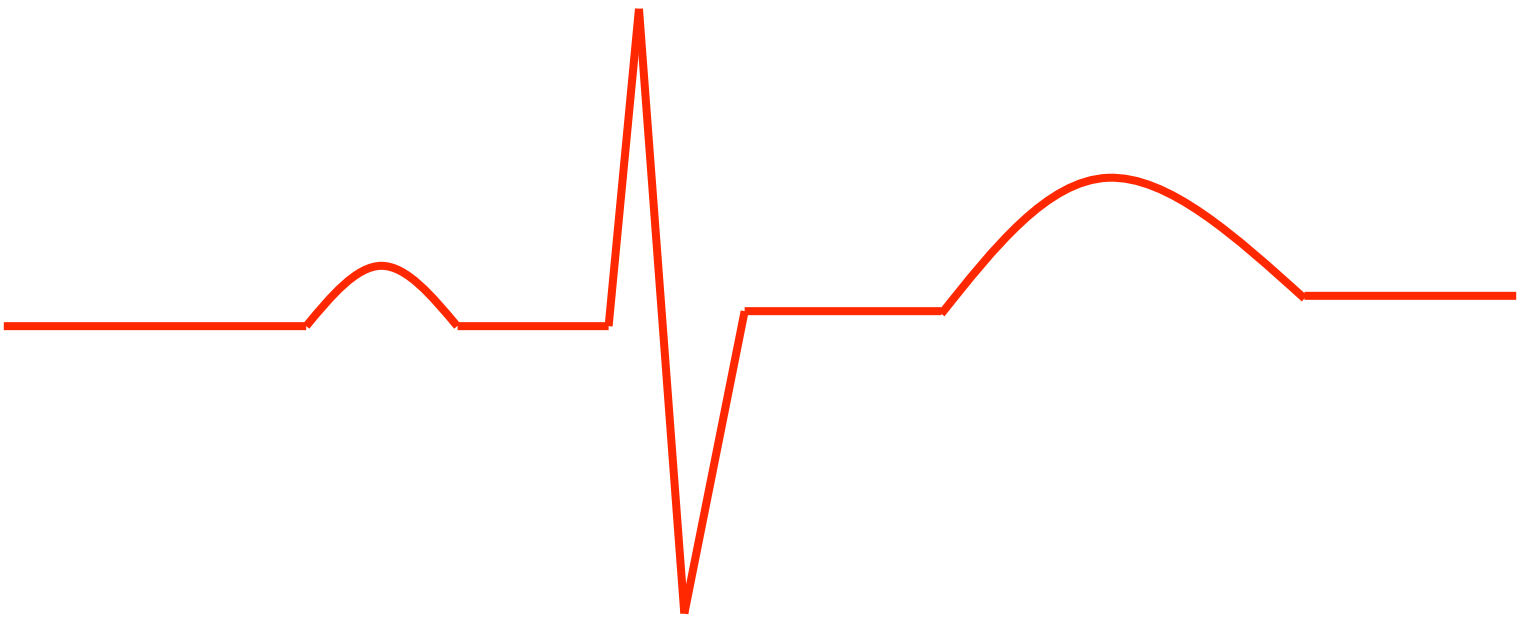




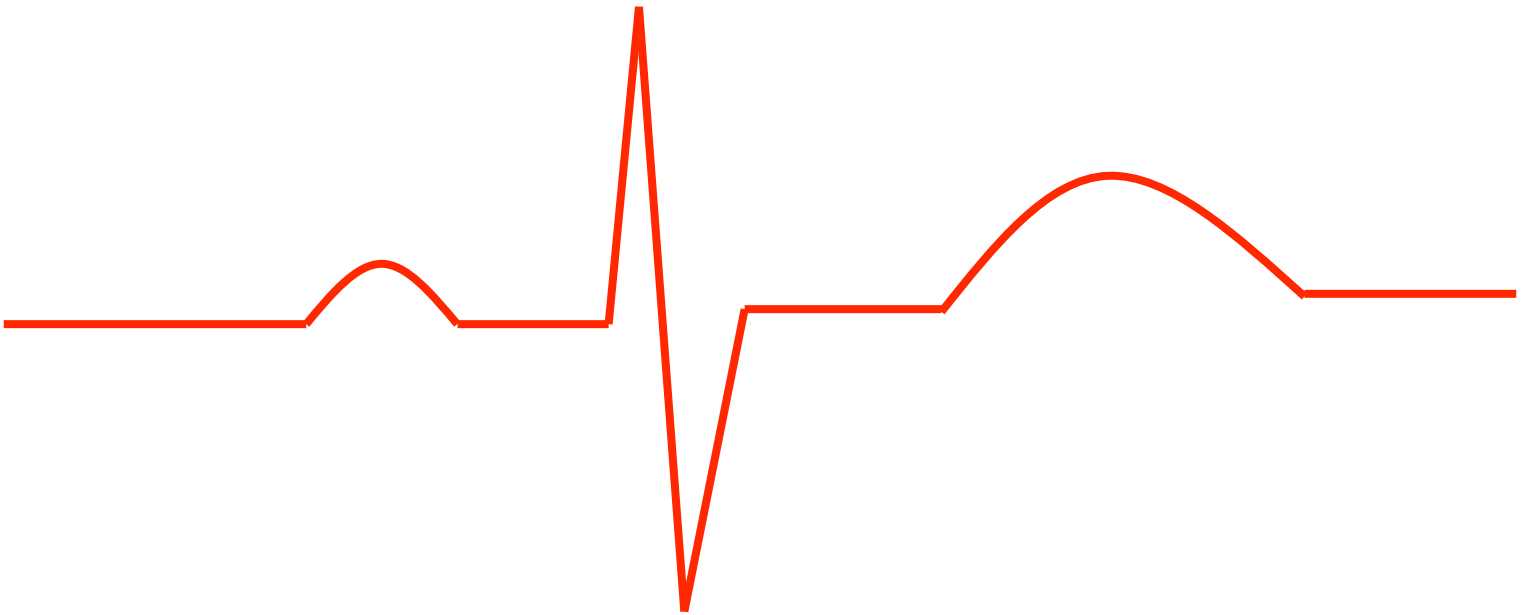
Period 1 : 1970-2000



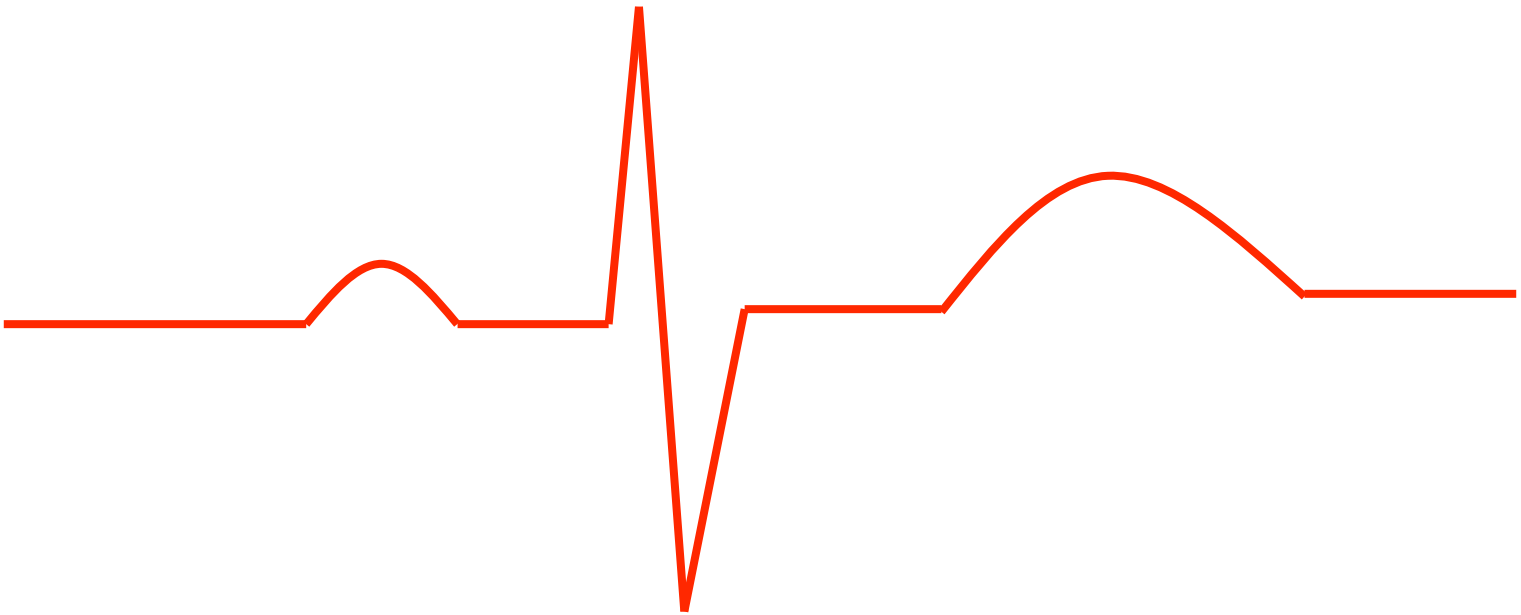
Period 2
2001



Period 3
2006-2009



Period 4
2009-



Period 1 : 1970-2000

# Etiology of stress hyperglycemia

## Dungan K, Braithwaite S, Preiser JC Lancet 2009;373:1798

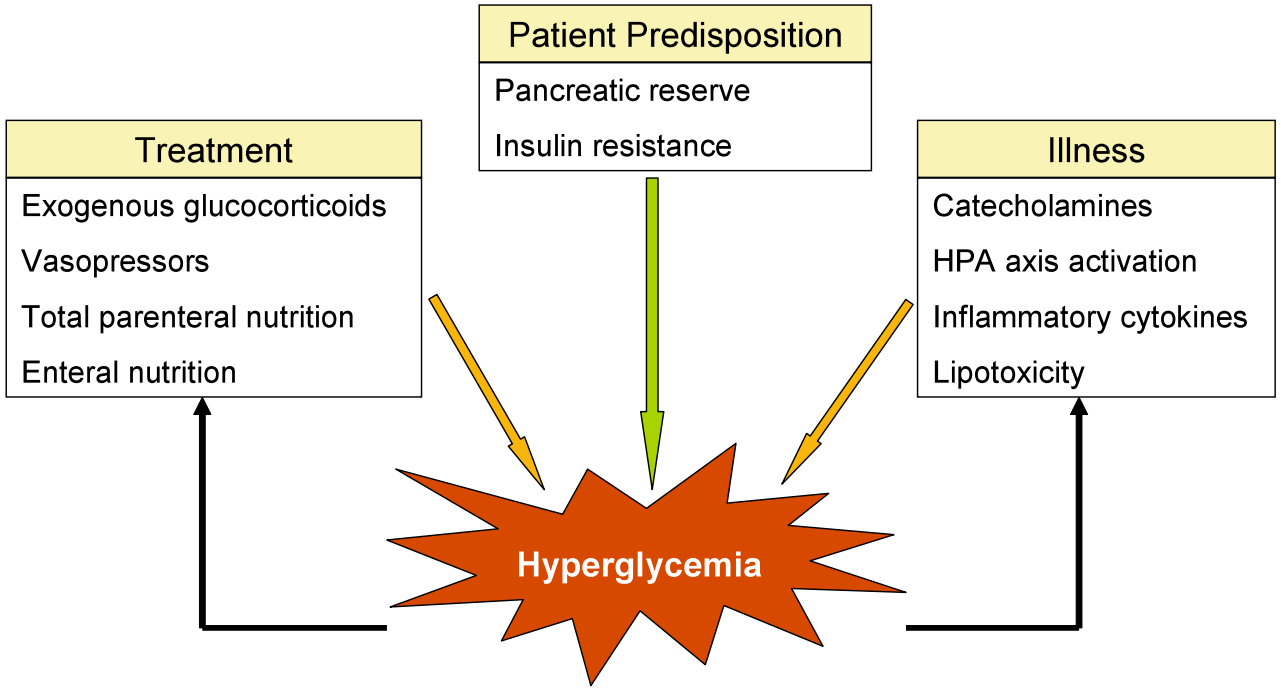



**Figure 1a:** The etiology of hospital-related hyperglycemia is multi-factorial, incorporating patient-specific, illness-specific, and treatment-specific factors. Hyperglycemia may, in turn, exacerbate illness-specific factors and increase the need for treatment-specific factors, thus leading to a vicious cycle by which hyperglycemia begets further hyperglycemia.
HPA=hypothalamic-pituitary-adrenal axis

# Etiology of stress hyperglycemia

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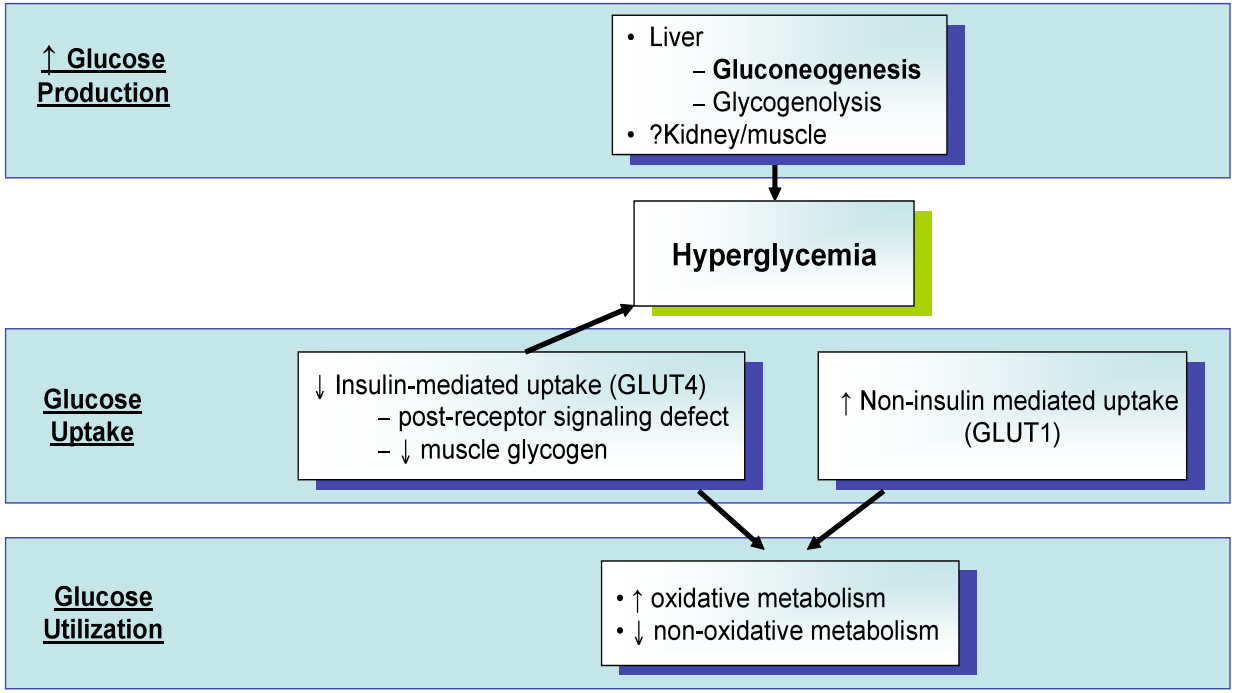
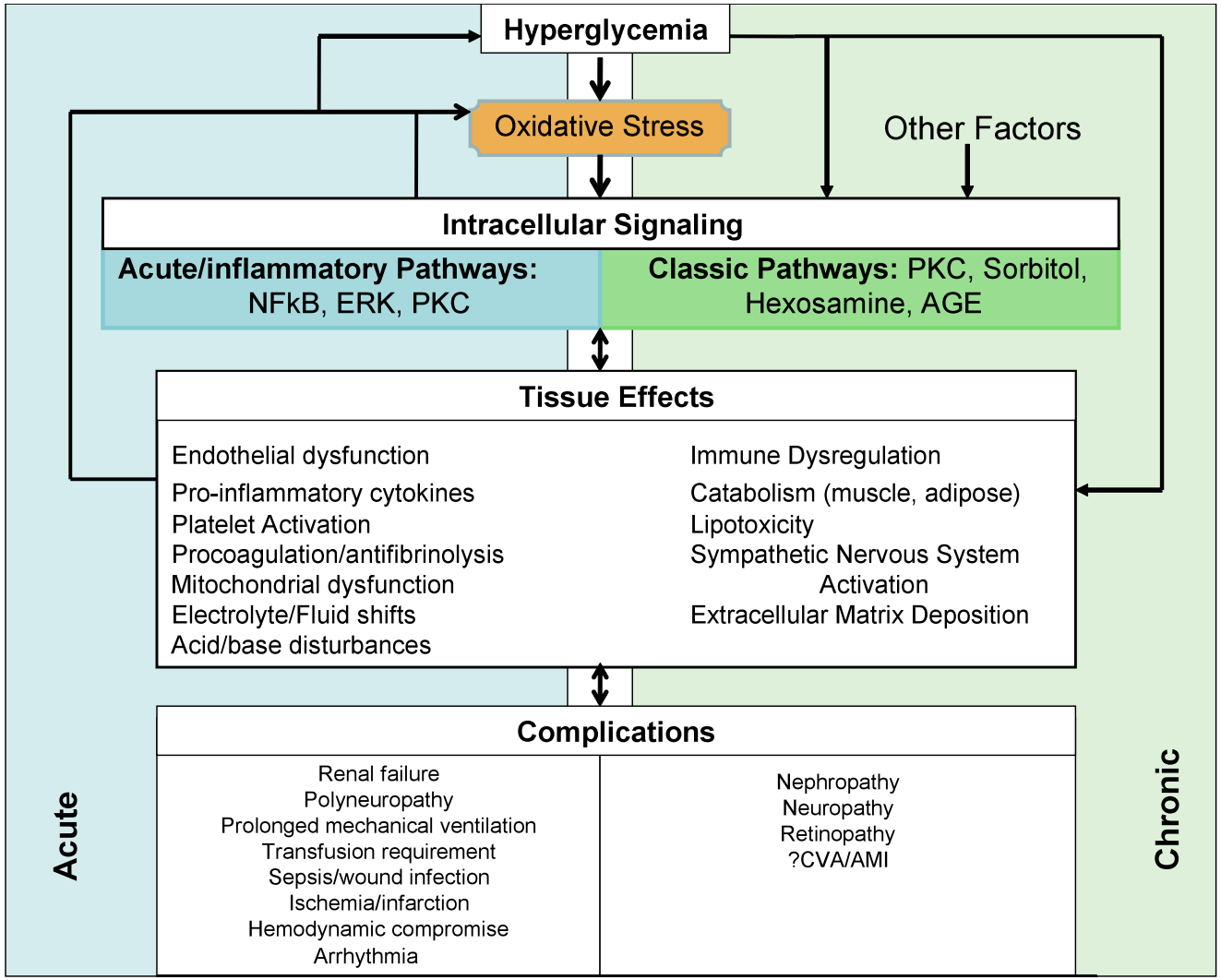


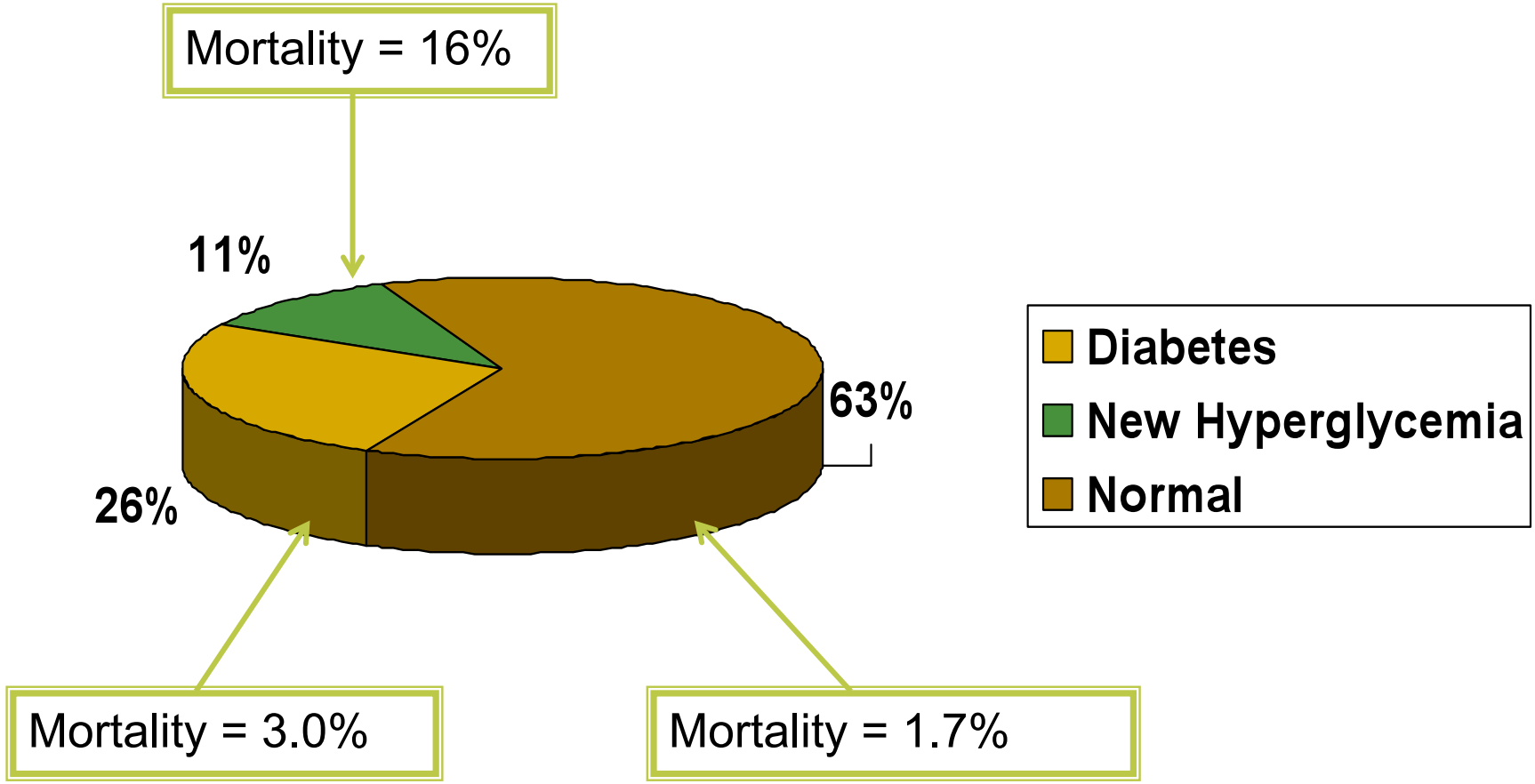

**Figure 1b. Glucose metabolism in stress hyperglycemia.** Stress hyperglycemia is marked by increased whole-body glucose uptake, marked by non-insulin mediated glucose transport via GLUT-1 transporters to body tissues. Insulin-mediated glucose uptake is reduced (insulin resistance), largely due to post-receptor insulin signaling defects that result in reduced GLUT4 mediated glucose transport in insulin sensitive tissues such as liver, muscle, and fat. Muscle glycogen storage is also reduced. Glucose production is generally up-regulated, in large part a result of unregulated hepatic gluconeogenesis. Finally, once inside a target cell, glucose is oxidized readily but non-oxidative metabolism (generally glycogen storage) is impaired.

# Consequences of hyperglycemia

## Dungan K, Braithwaite S, Preiser JC Lancet 2009;373:1798



# Hyperglycemia In The Hospital




*Umpierrez, JCEM 87: 978-982, 2002*

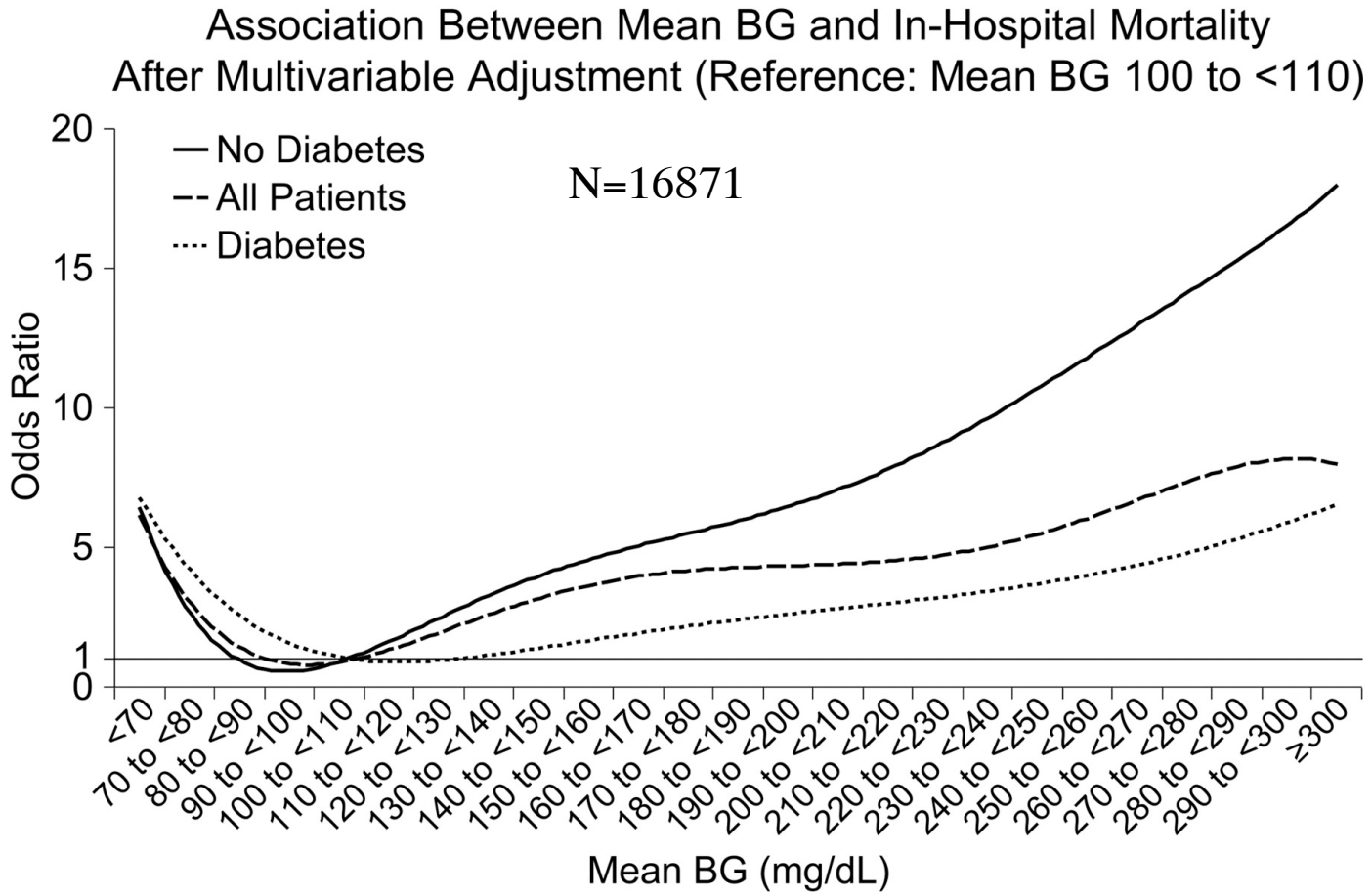
- « Admission glycemia is an independent pronostic factor » : mortality and ventricular dysfunction (180 mg/dl)
- Admission glycemia 144mg/dl = 3.9 more deaths.

- Cardiac surgery : blood glucose is an independent predictive factor for severe infection.

• Admission hyperglycemia is associated with a 2- or 3-fold increase in mortality following focal or global brain ischemia

• After brain trauma, a blood glucose > 200 mg/dl is an independent prognostic factor for poor outcome.

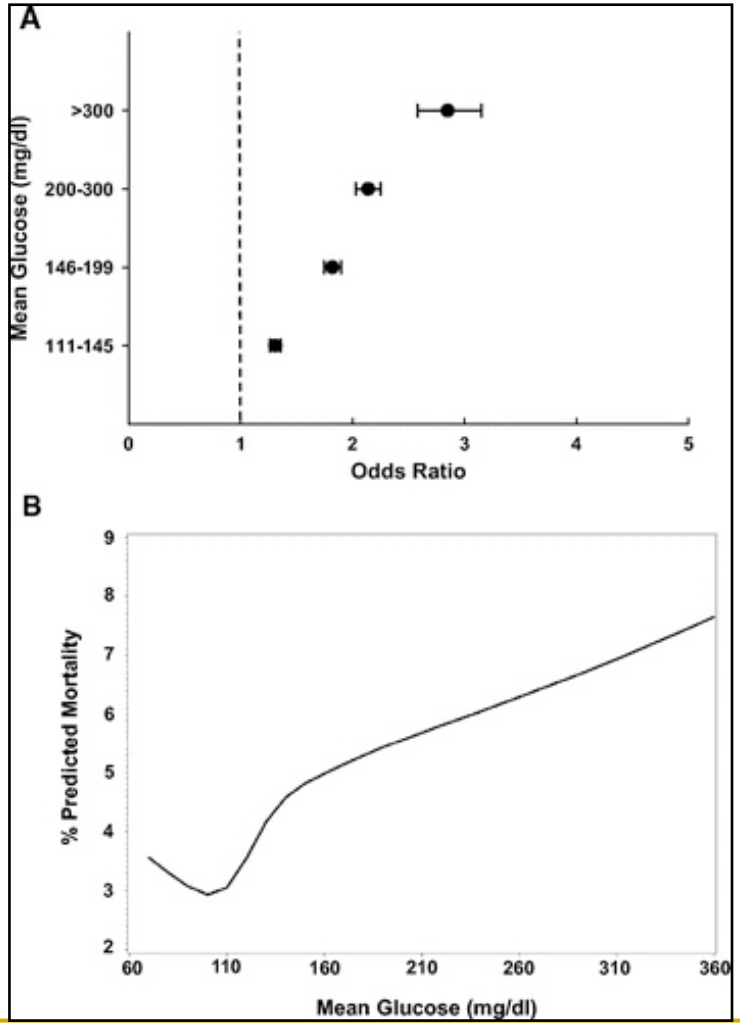
# Nature of the relationship between mean hospitalization glucose and the odds of in-hospital mortality (adjusted analysis)



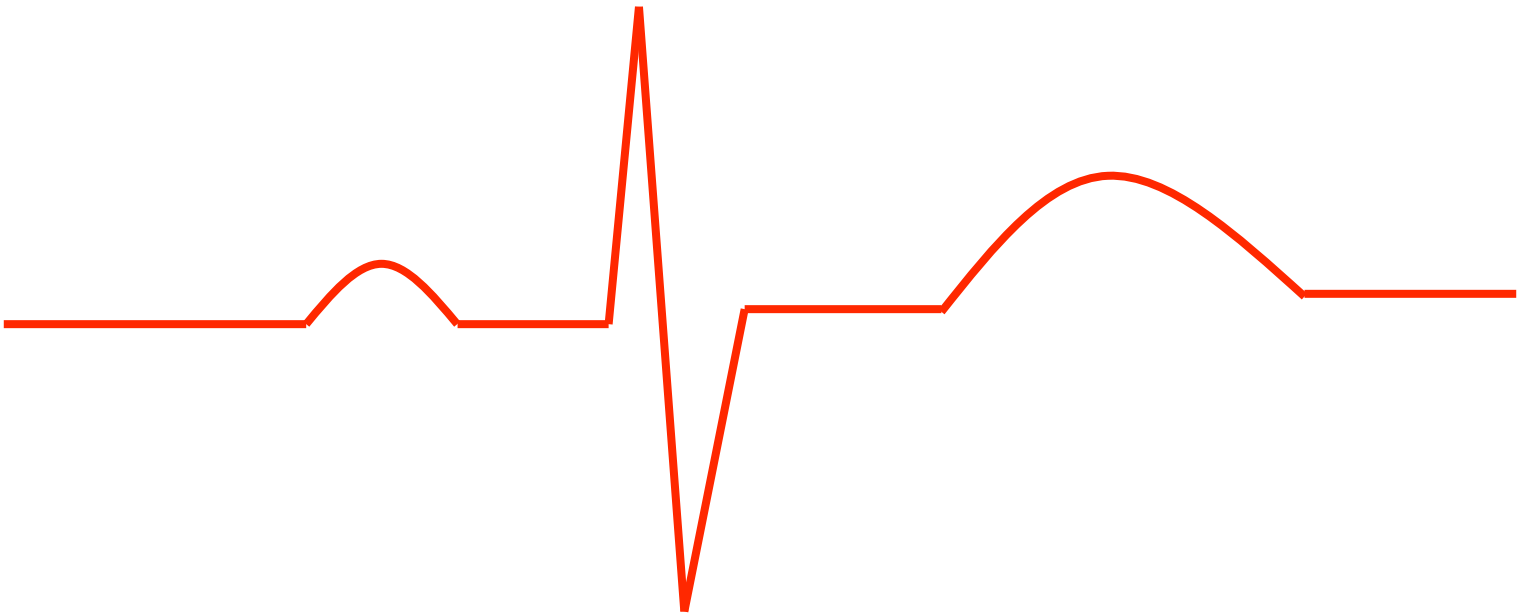

**Kosiborod, M. et al. Circulation 2008;117:1018-1027**

# Hyperglycemia-related mortality in critically ill patients

## Falciglia et al Crit Care Med 2009;37:3001




N = 259,040 ICU admissions (2002-2005)
Unadjusted mortality rate 11.2%
Two-level logistic regression model used to determine a relationship between admission glycemia and predicted mortality



Period 2
2001

# The evidence is clear

- Hyperglycemia is associated with poor outcome
- Treating hyperglycemia is associated with an improvement in outcome (before – after trials)

# RESTORING « NORMOGLYCEMIA » IMPROVES SURVIVAL !

## YES

- Observational findings
  - DIGAMI 1
  - Furnary
  - Reed
  - Krinsley
  - Finney
- Interventional data
  - Leuven 1 study

# Intensive insulin therapy : Mortality

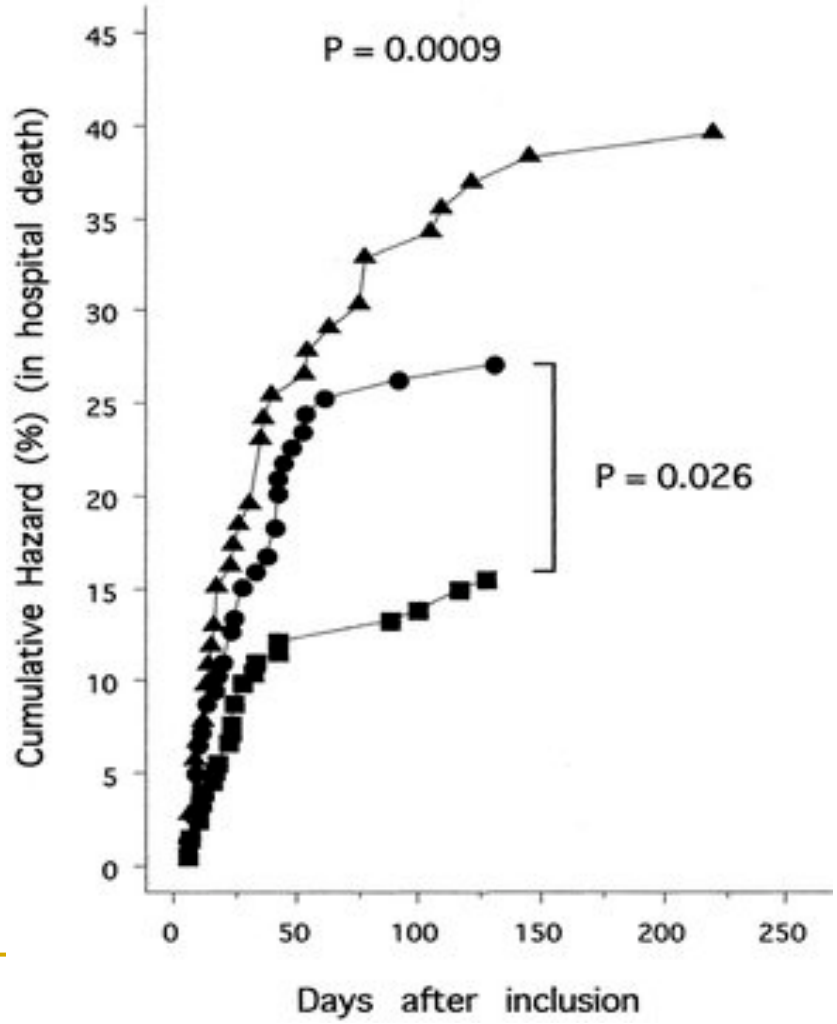
**Intensive treatment → 4.4 – 6.1 mmol/L *versus***
**Conventional treatment → 10.0 – 11.1 mmol/L**

| Result | Control | Intensive | %. | p |
|---|---|---|---|---|
| 1. ICU mortality (%) | 8.04.6- 47% | < 0.004 | | |
| ■ First 5 d. of ICU stay (%) | 1.8 | 1.7 | NS | |
| ■ ICU stay > 5d (%) | 20.210.6- 48% | 0.005 | | |
| ■ Diabetic pat. > 5d (%) | 20.610.7- 48% | 0.005 | | |
| 2. Hospital mortality (%) | 10.97.2- 34% | 0.01 | | |

***N Engl J Med 2001; 345 1359***

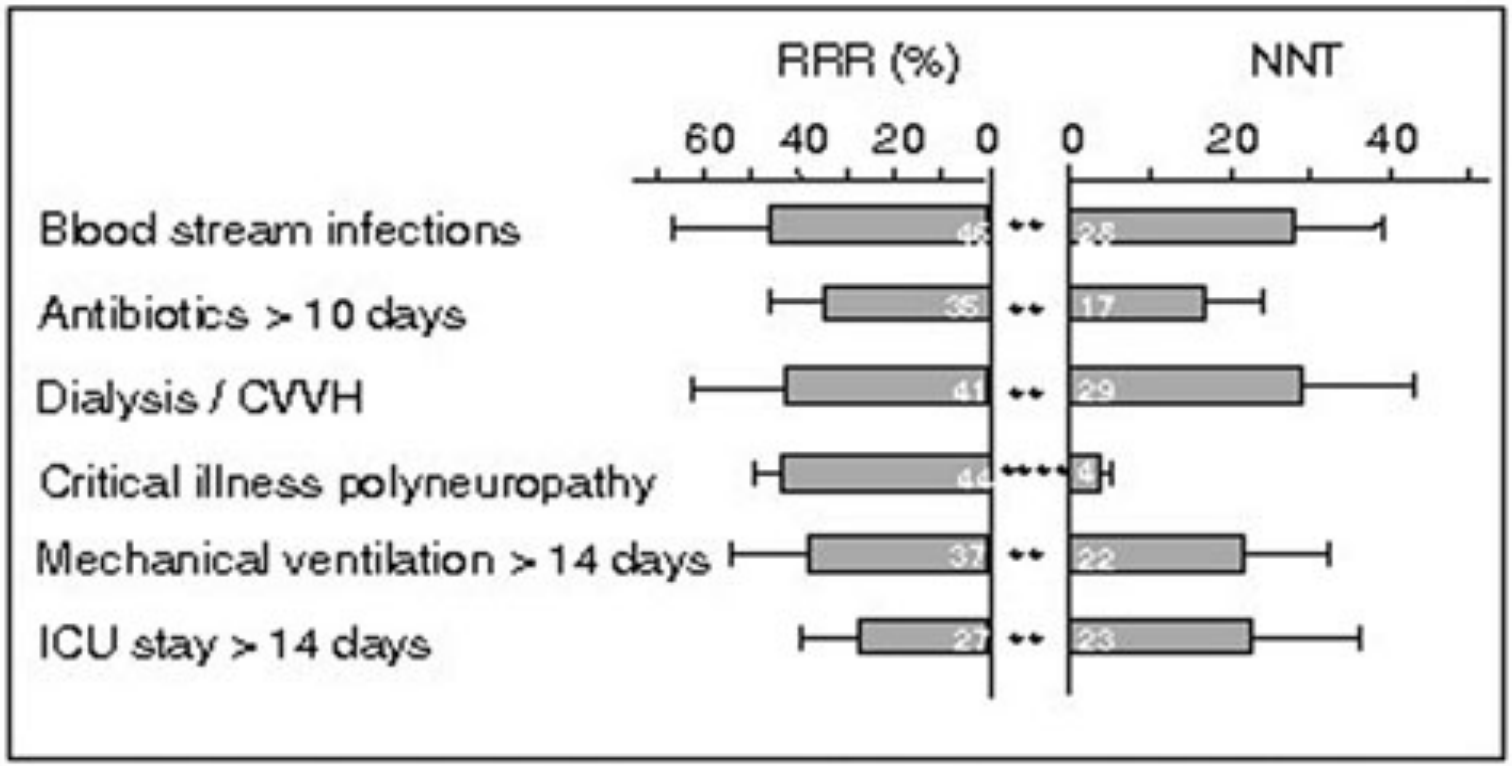
# CUMULATIVE RISK OF DEATH IN ICU PATIENTS

Squares : glycemia < 110 mg/dl
Circles: glycemia 110-150 mg/dl
Triangles: glycemia > 150 mg/dl

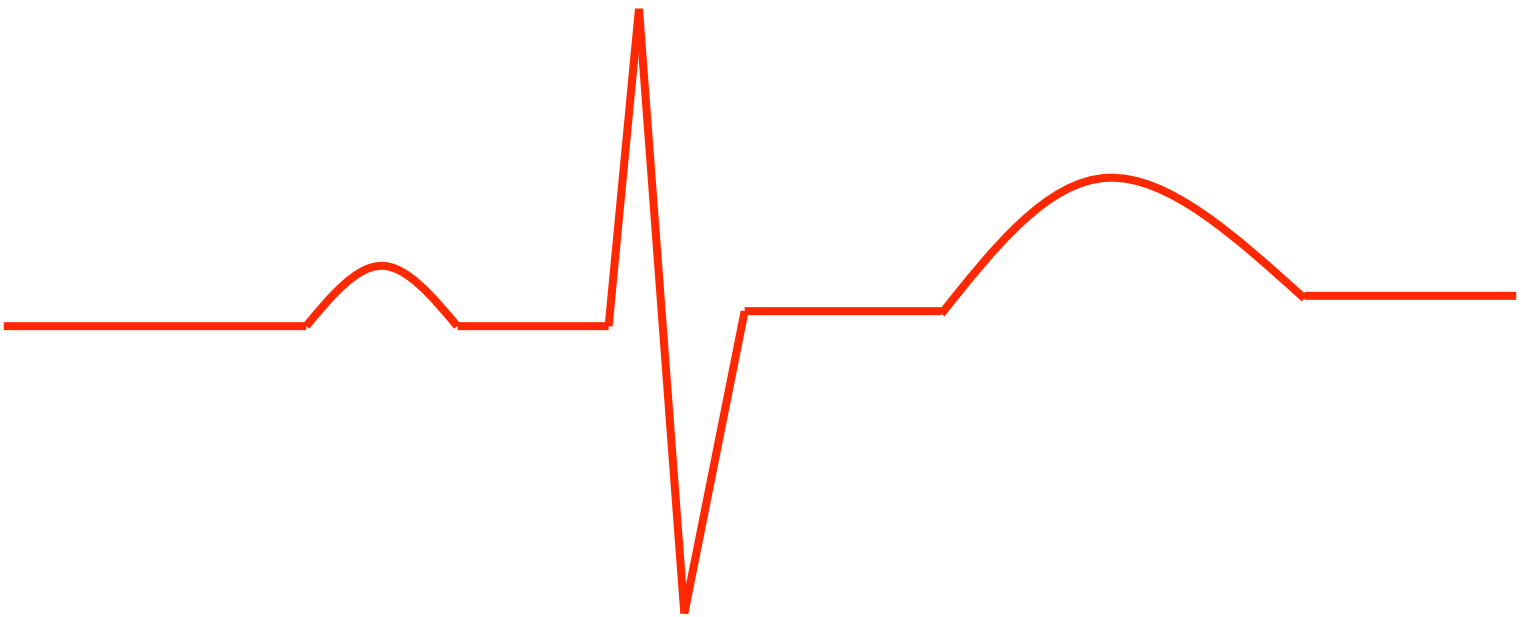



**Van den Berghe Crit Care Med 2003;31:359**

# SECONDARY OUTCOME VARIABLES




RRR = Relative risk reduction
NNT = Number needed to treat



Period 3
2006-2009

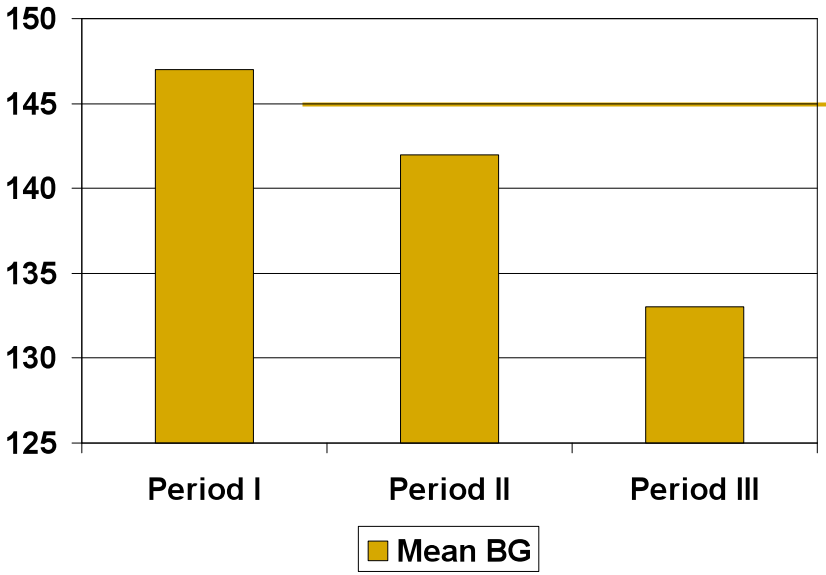
# Intensive insulin therapy and mortality in critically ill patients

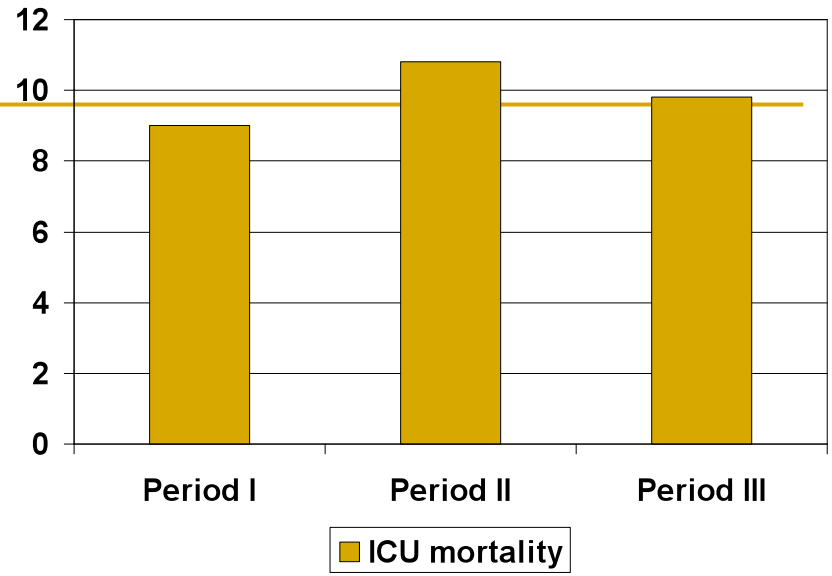
Miriam M Treggiari, Veena Karir, N David Yanez, Noel S Weiss, Stephen Daniel and Steven A Deem

*Critical Care* 2008, **12**:R29 (doi:10.1186/cc6807)

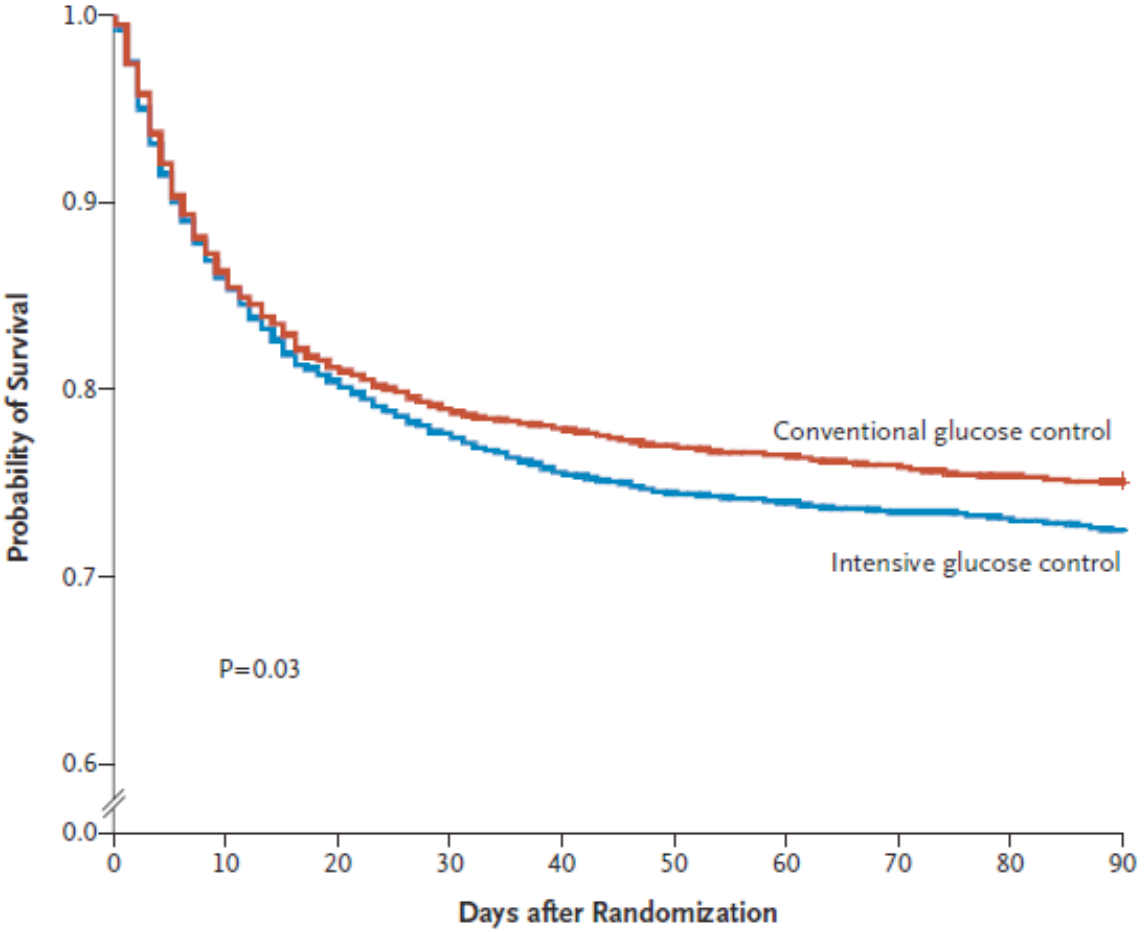
Cohort study comparing three consecutive time periods – total **10,456 patients** :

- period I no protocol (n = 2,366 03/01- 02/02)
- period II target BG 80-130 mg/dl (n= 3,322, 03/02-06/03 ),
- period III target BG 80-110 mg/dl (n= 4,786 , 07/03-02/05)



# NICE-SUGAR trial




| No. at Risk | | | | |
|---|---|---|---|---|
| Conventional control | 3014 | 2379 | 2304 | 2261 |
| Intensive control | 3016 | 2337 | 2227 | 2182 |

# GLUCONTROL

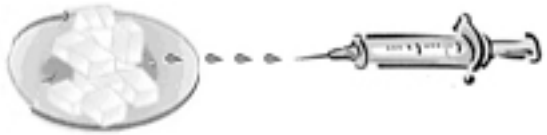
## A Multi-Centre Study Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients

EUROPEAN CRITICAL CARE RESEARCH NETWORK

ECCRN

Endorsed by the ECCRN of the European Society of Intensive Care Medicine

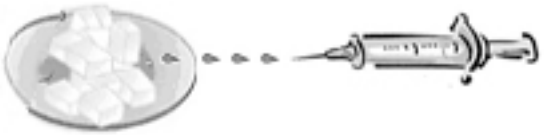
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE



# GLUCONTROL

- 7 countries
- Austria, Belgium, France, Israel, The Netherlands, Slovenia and Spain.
- 21 units in 19 centres

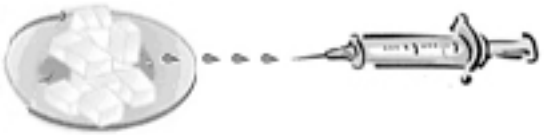
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE



# GLUCONTROL

- Prospective, randomised, controlled, investigator -blinded and multicentric study
- Aimed at comparing the effects of two regimens of insulin therapy, respectively titrated to achieve a blood sugar level
  - between 7.8 and 10.0 mmol/l (140 and 180 mg/dl, respectively) = GROUP 1
  - and between 4.4 and 6.1 mmol/l (80 and 110 mg/dl, respectively) = GROUP 2

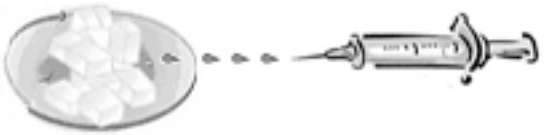
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE



# GLUCONTROL

- **Primary Outcome : absolute intensive care unit (ICU) mortality (target = 4%-decrease).**
- **Secondary outcome variables :**
  - **in-hospital and 28-day mortality,**
  - **lengths of stays in ICU and in the hospital,**
  - **length of ICU stay without life-support therapy, number and clinical signs of episodes of hypoglycaemia,**
  - **rates of infections and organ failures,**
  - **number of red-cells transfusions.**

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

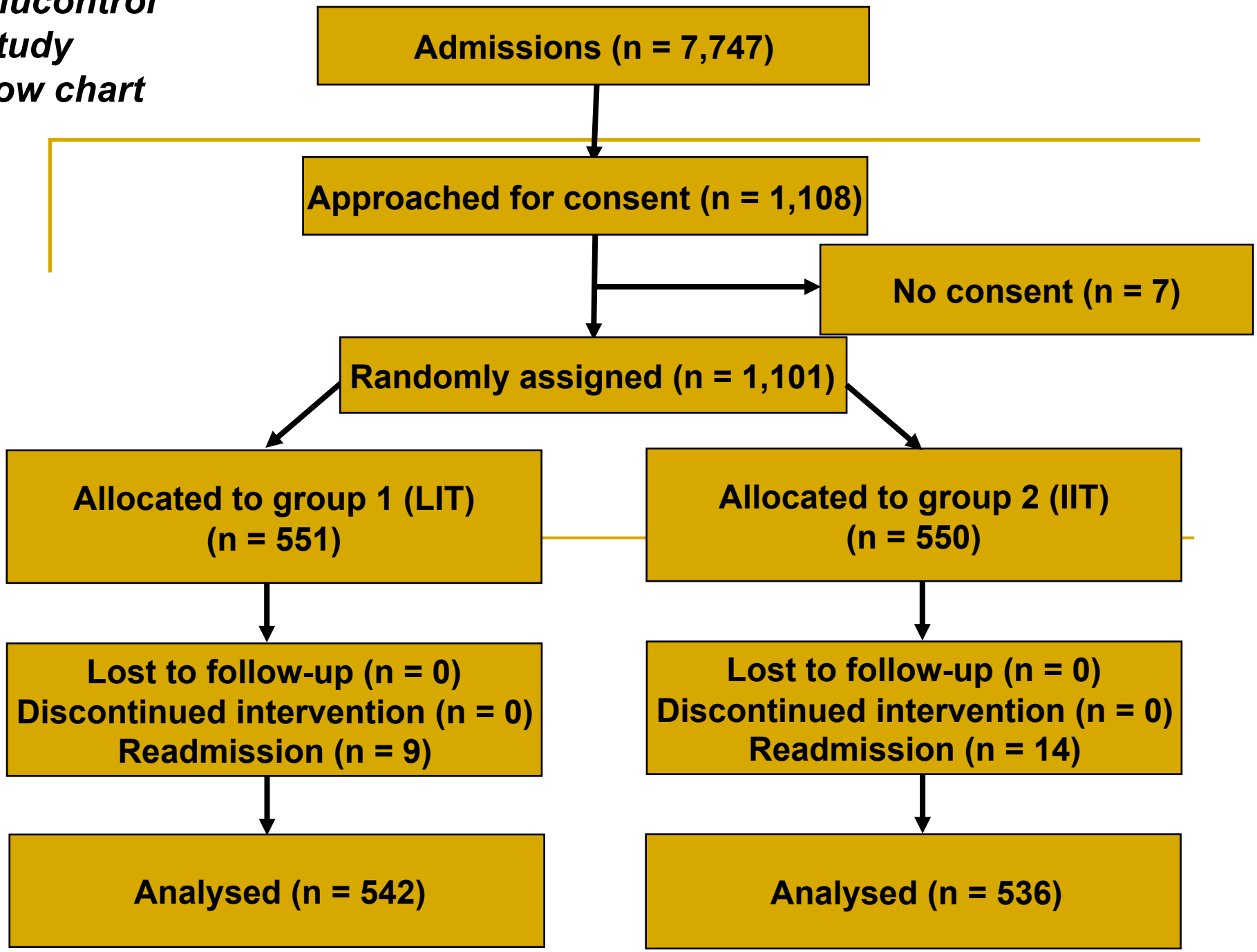


# GLUCONTROL

- **Planning :**
  - **Interim analysis each 100 ICU deaths**
  - **In order to detect a 4% decrease of absolute mortality 3500 patients to be included**
- **STUDY STOPPED ON MAY 29th, 2006**
  - **Safety concern**
  - **High rate of unintended protocol violations**

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

*Glucontrol Study flow chart*



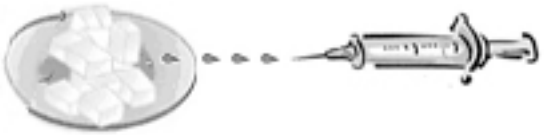
# Characteristics at admission

| | Group 1<br>BG target 7.8-10.0 mmol/L<br>N=542 | Group 2<br>BG target 4.4-6.1 mmol/L<br>N=536 | p value |
|---|---|---|---|
| **Age (median - IQR)** | 64.5 (51.1-74.1) | 64.8 (50.8-74.0) | 0.856 |
| **Male patients (%)** | 333 (61.4) | 345 (64.4) | 0.339 |
| **Type of patients (% of each)** | | | 0.881 |
| - Medical | 219 (40.4) | 226 (42.2) | |
| - Scheduled Surgery | 174 (32.1) | 162 (30.2) | |
| - Emergency Surgery | 96 (17.7) | 89 (16.6) | |
| - Trauma | 43 (7.9) | 41 (7.6) | |

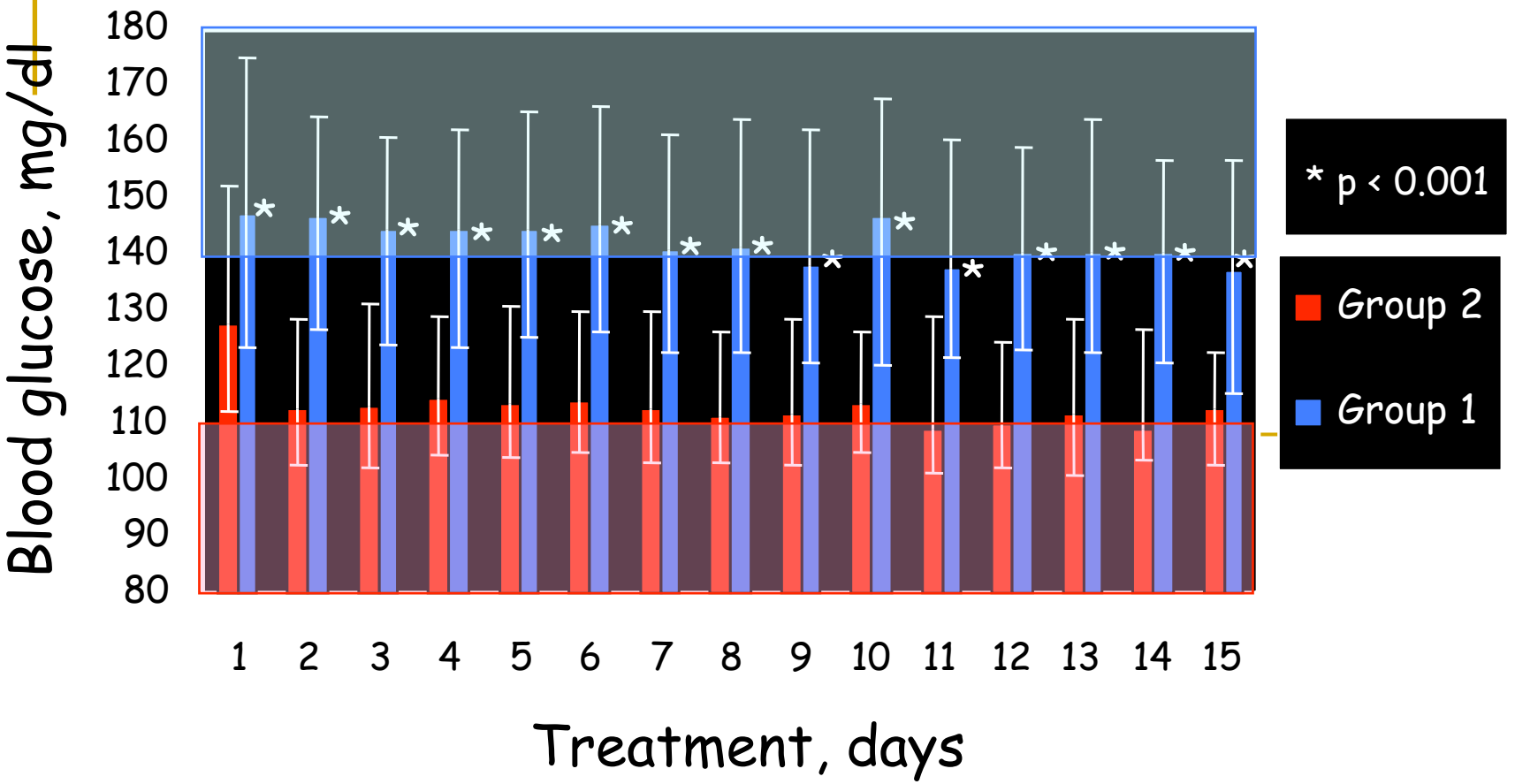
| | | | |
|---|---|---|---|
| **APACHE II score (median - IQR)** | 15 (11-22) | 15 (11-21) | 0.807 |
| **SOFA score (mean ± SD (range))** | 6.7 ± 3.3 (0 - 16) | 6.9 ± 3.1 (0 - 19) | 0.454 |
| **Glasgow Coma Score (median – IQR)** | 15 (9-15) | 15 (8-15) | 0.787 |
| **Respiratory support (% of patients)** | | | 0.444 |
| - Invasive ventilation | 386 (71.2) | 363 (67.7) | |
| - Non invasive ventilation | 28 (5.2) | 33 (6.2) | |
| **Vasopressors/inotropes (% of patients)** | 218 (40.2) | 201 (37.5) | 0.359 |
| **Proportion of patients with T° > 38.5 °C (%)** | 51 (9.4) | 52 (9.7) | 0.741 |
| **Pre-existing diabetes (% of patients)** | 116 (21.4) | 87 (16.2) | 0.029 |

# Insulin therapy

| | | | |
|---|---|---|---|
| **Time from admission to start of insulin drip, hours (median(IQR))** | 0 (0-10) | 0(0-12) | 0.312 |
| **Patients treated with IV insulin, % (n)** | 66.2 (313) | 96.3 (442) | <.0001 |
| **Rate of insulin infusion (IU/h) (median(IQR))** | 0.32 (0-1.27) | 1.30 (0.65-2.3) | <.0001 |
| **Duration of insulin treatment in hours median (IQR)** | 10 (0-43) | 36 (13-96) | <.0001 |
| **Days on insulin (median (IQR) )** | 2(0-5) | 5(2-9) | <.0001 |
| **Insulin-free days (median (IQR))** | 2(0-5) | 0(0-1) | <.0001 |

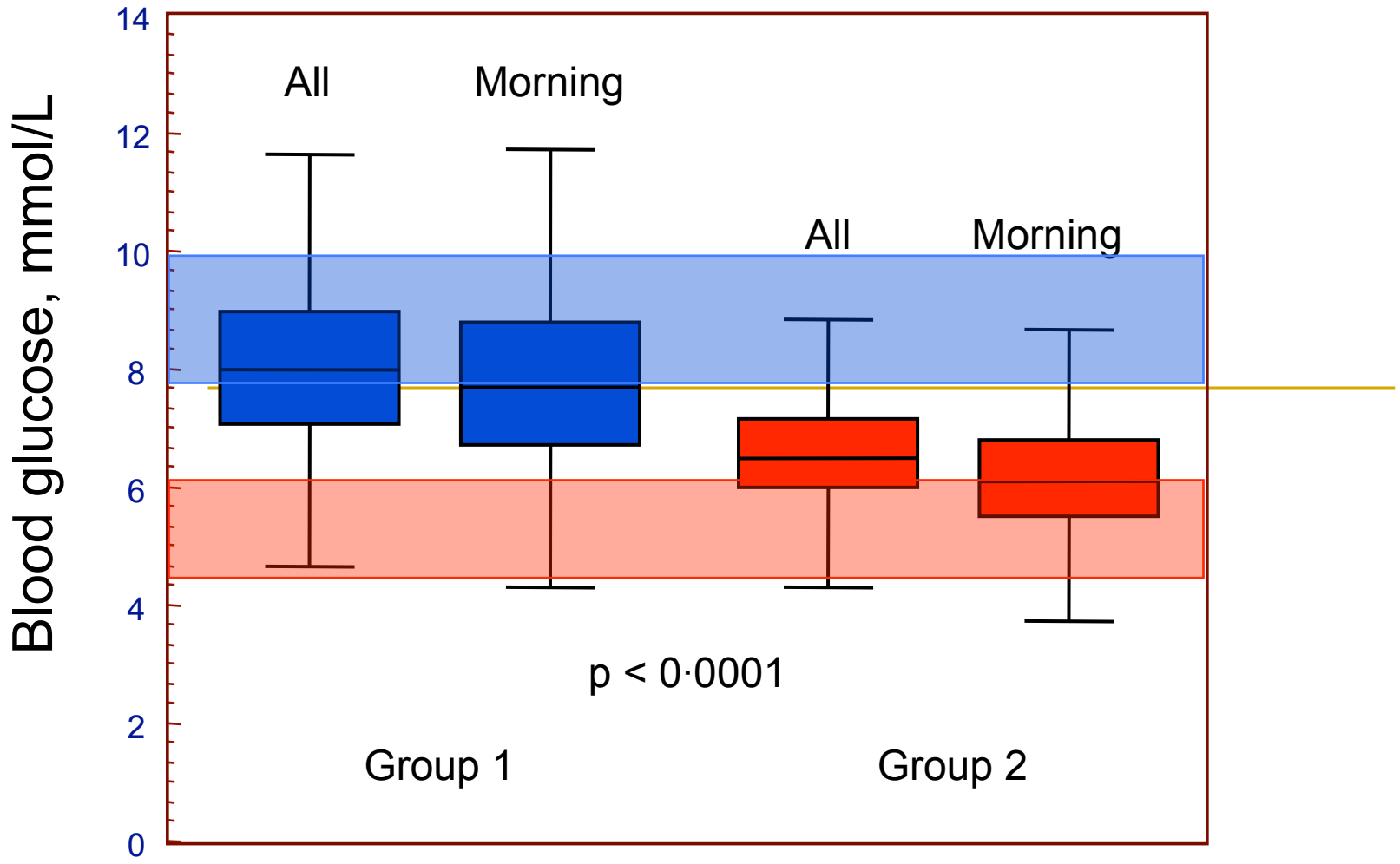


# GLUCONTROL



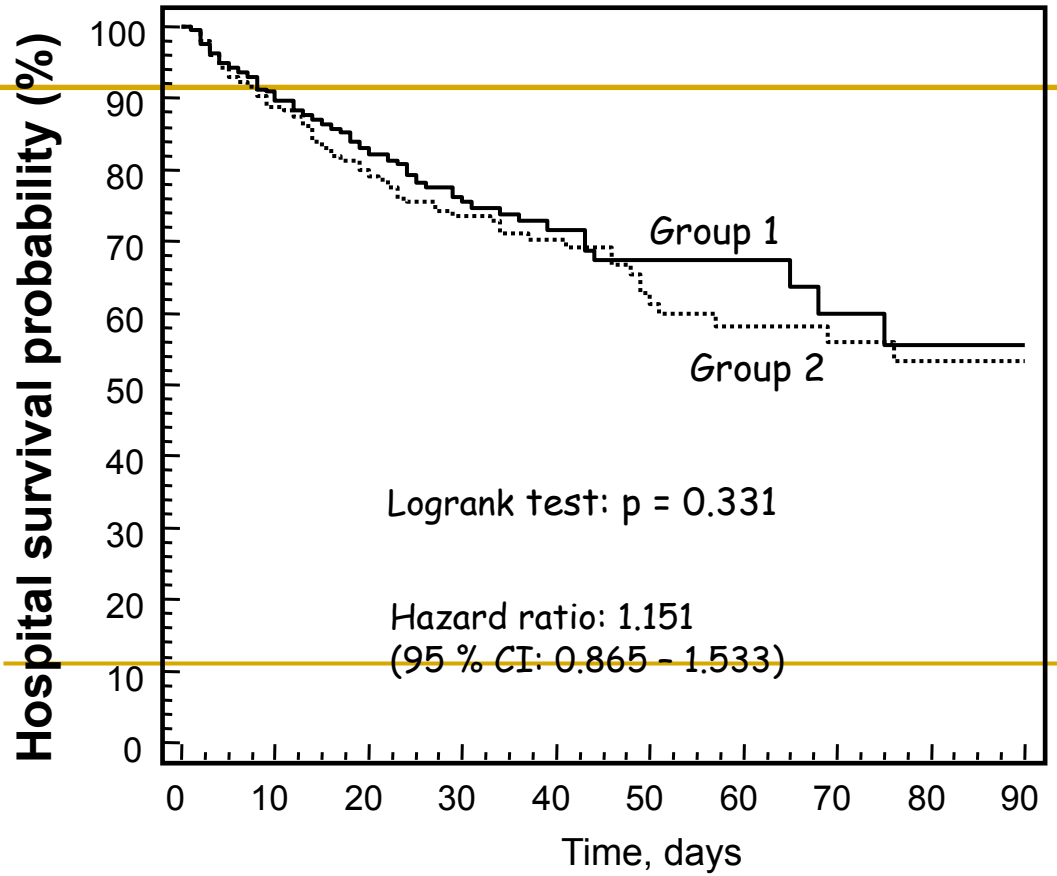

Median with IQR

# Blood glucose values



# Outcome data

| | Group 1<br>BG target<br>7.8-10.0<br>mmol/L<br>N=542 | Group 2<br>BG target<br>4.4-6.1<br>mmol/L<br>N=536 | p value |
|---|---|---|---|
| **Outcome data** | | | |
| **ICU mortality (%)** | 83 (15.3) | 92 (17.2) | 0.410 |
| - Short-stayers (LOS ≤ 3 days) n = 281 | 17/154 (11.0) | 17/127 (13.4) | 0.5483 |
| - Long-stayers (LOS > 3 days) n = 787 | 66/388 (17.0) | 75/399 (18.8) | 0.5135 |
| **28-day mortality (%)**<br>**Patients still in ICU at D28 (n):** | 83 (15.3)<br>33 | 100 (18.7)<br>34 | 0.1438 |
| **Hospital mortality (%)** | 105 (19.4) | 125 (23.3) | 0.1136 |
| **ICU LOS (days) (median (IQR))** | 6 (3-13) | 6 (3-13) | 0.238 |
| **Total ICU stay (LOS)** | 5433 | 5090 | |
| **Hospital LOS (days) (median (IQR))** | 16 (11-29) | 16 (11-29) | 0.708 |

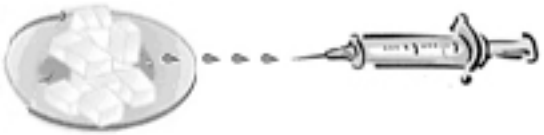



Patient at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group 1: | 542 | 377 | 187 | 109 | 55 | 34 | 24 | 17 | 12 | 9 |
| Group 2: | 536 | 351 | 180 | 104 | 67 | 44 | 33 | 25 | 17 | 11 |

Cumulative deaths

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group 1: | 0 | 46 | 67 | 79 | 83 | 86 | 86 | 88 | 89 | 92 |
| Group 2: | 0 | 48 | 75 | 85 | 89 | 96 | 98 | 99 | 100 | 101 |



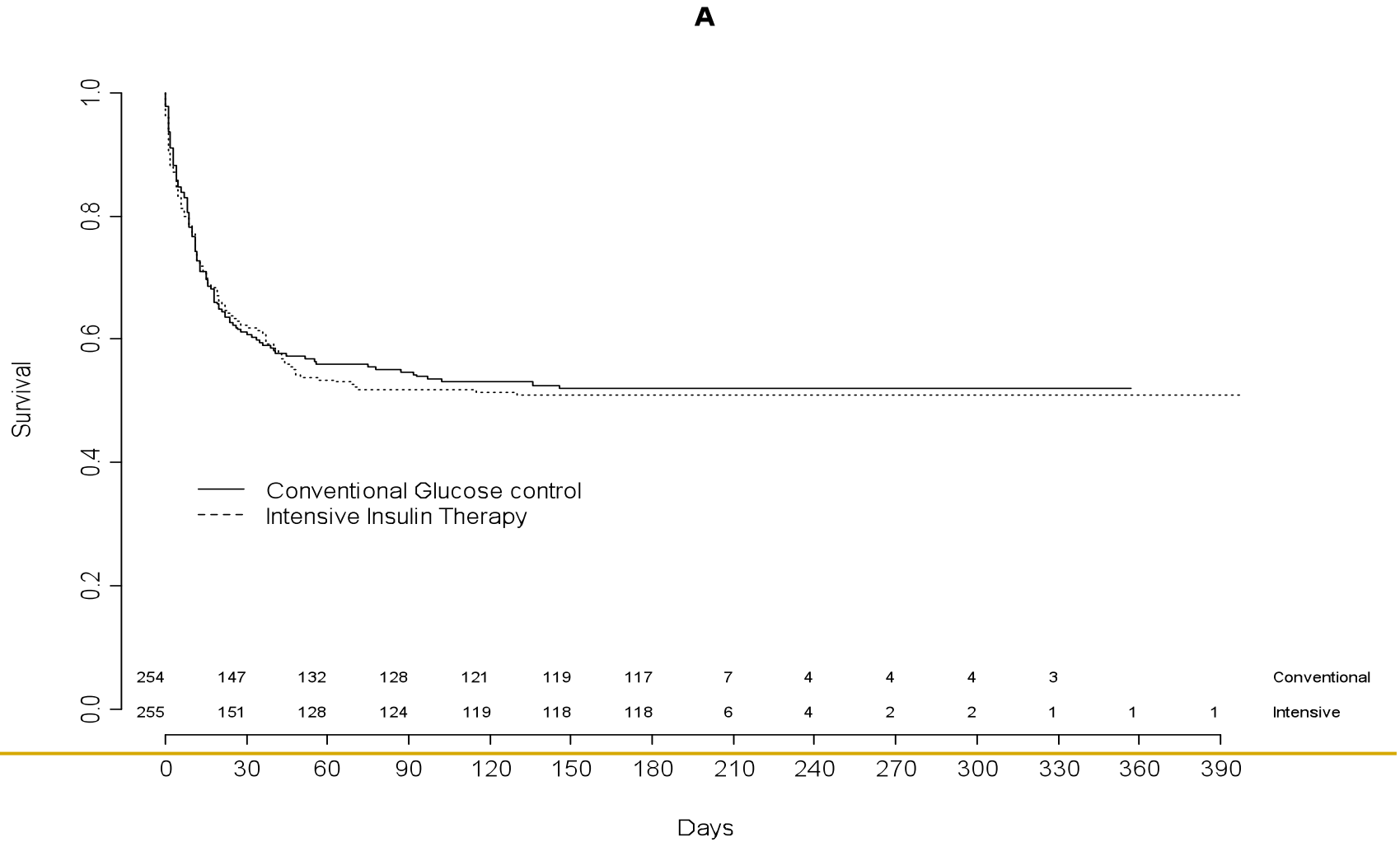
# GLUCONTROL

## RISK OF DEATH

| Univariable analysis | | | |
|---|---|---|---|
| | Crude OR | 95 % CI | p |
| Group 2 | 1.28 | 0.88 - 1.88 | 0.198 |
| **Multivariable analysis** | | | |
| | Adjusted OR | 95 % CI | p |
| Group 2 | 1.31 | 0.88 – 1.95 | 0.178 |
| Gender (male) | 1.78 | 1.15 - 2.75 | 0.0093 |
| Age, yr | 1.02 | 1.01 – 1.04 | 0.0011 |
| Apache II | 1.04 | 1.02 – 1.07 | 0.0003 |
| SOFA | 1.08 | 1.01 – 1.16 | 0.0291 |

# Corticosteroids treatment and intensive insulin therapy for septic shock in Adults

Annane et al JAMA 2010;303:341



CHEST Original Research
CRITICAL CARE MEDICINE

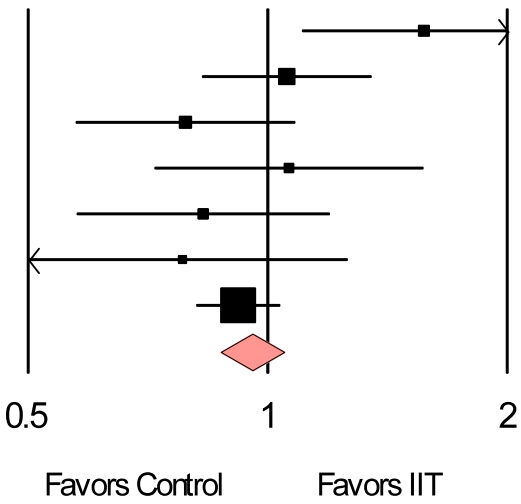
# Toward Understanding Tight Glycemic Control in the ICU

## A Systematic Review and Metaanalysis

*Paul E. Marik, MD, FCCP; and Jean-Charles Preiser, MD*

*CHEST 2010; 137(3):544–551*

| Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|
| Van den Berghe-2001 | 1.572 | 1.102 | 2.242 | 2.498 | 0.012 |
| Van den Berghe-2006 | 1.057 | 0.826 | 1.353 | 0.441 | 0.659 |
| Glucotrol-2006 | 0.788 | 0.573 | 1.085 | -1.460 | 0.144 |
| VISEP-2008 | 1.064 | 0.720 | 1.572 | 0.310 | 0.757 |
| De La Rosa-2008 | 0.830 | 0.574 | 1.199 | -0.994 | 0.320 |
| Arabi-2008 | 0.781 | 0.484 | 1.262 | -1.009 | 0.313 |
| NICE-SUGAR 2009 | 0.918 | 0.812 | 1.038 | -1.361 | 0.173 |
| | 0.954 | 0.871 | 1.046 | -0.995 | 0.320 |



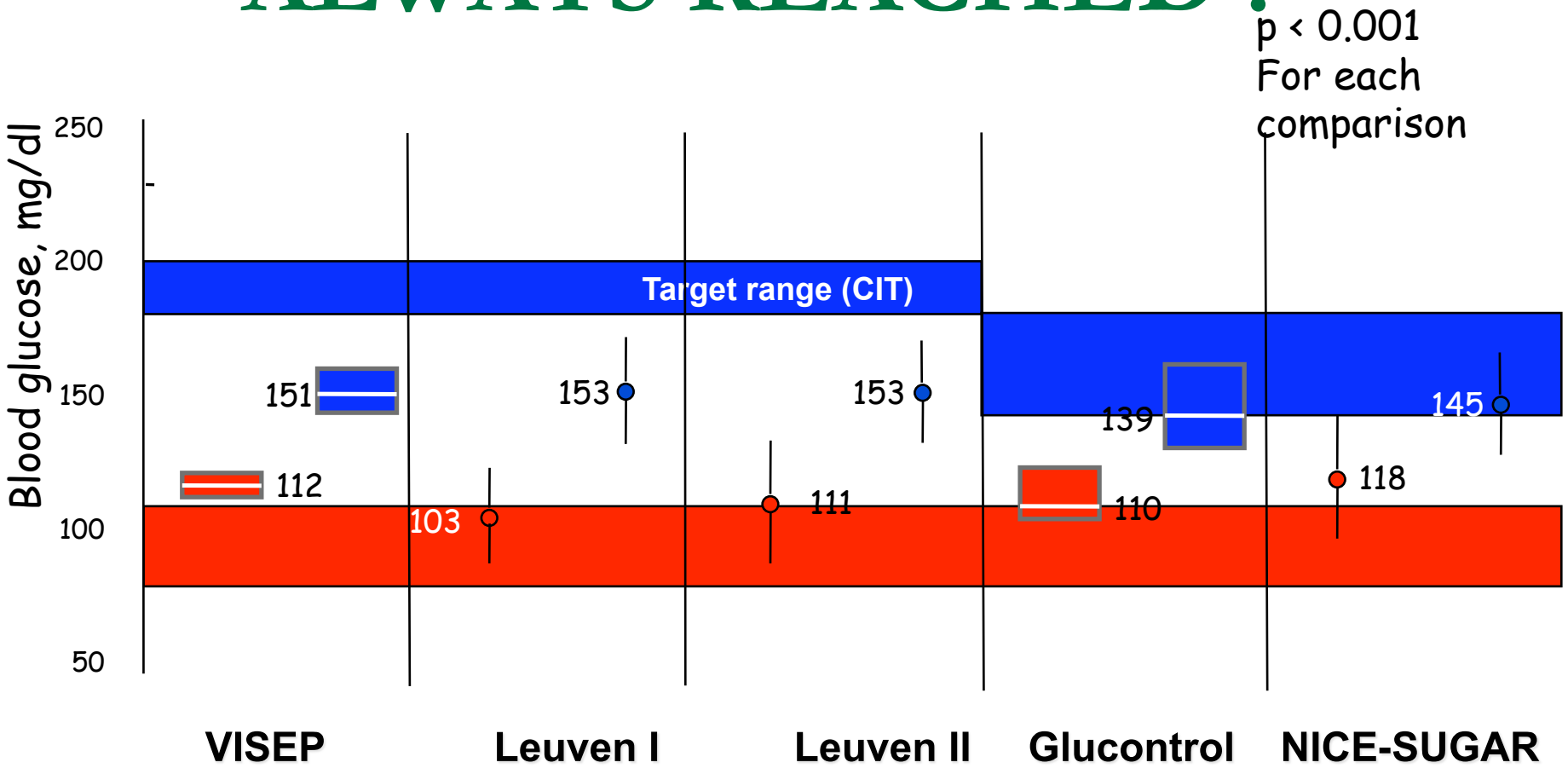

**Meta Analysis**

## Possible reasons for discrepancies between outcome data

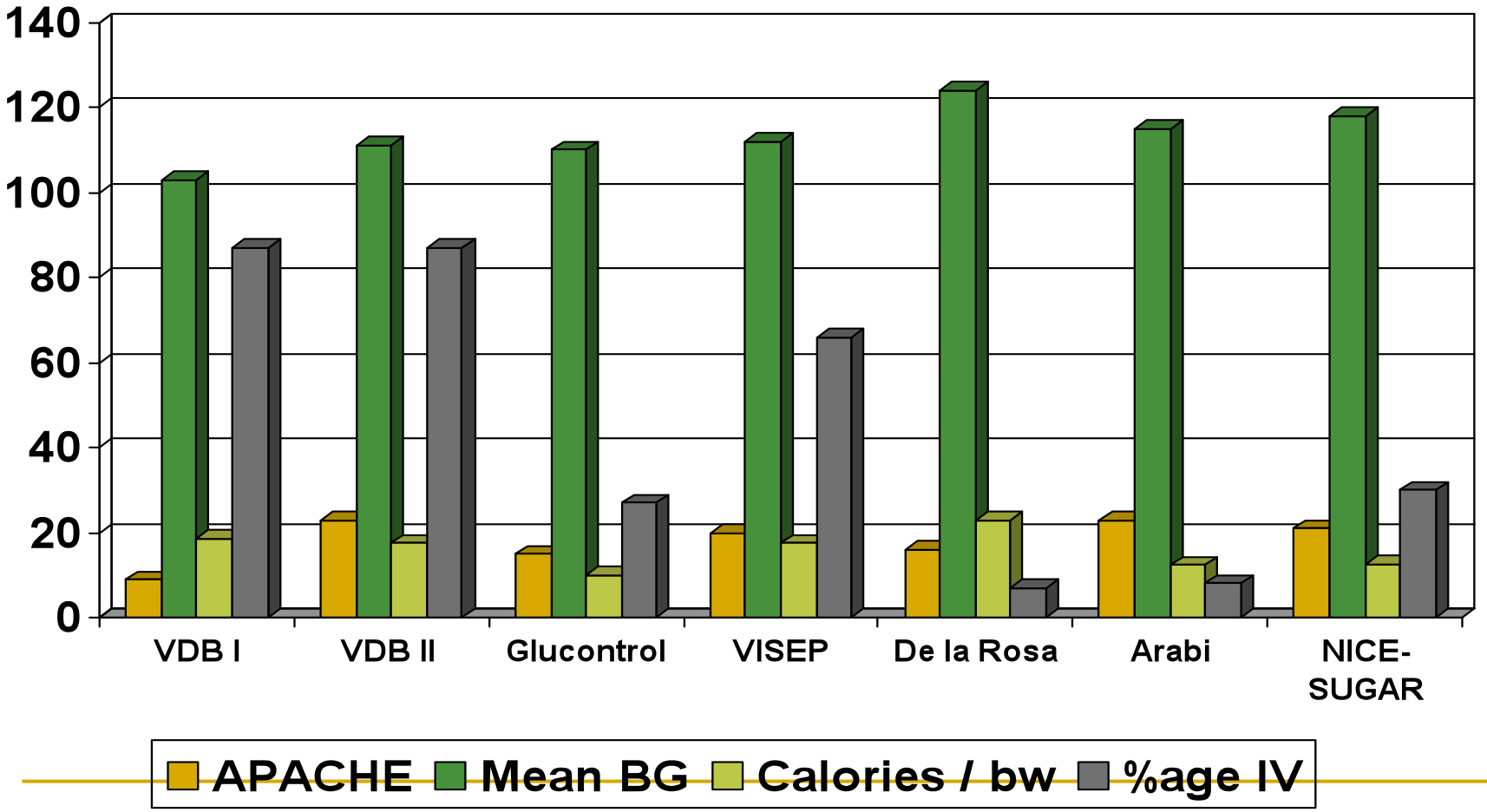
Marik P Preiser JC Chest 2010;137:544

- Severity (APACHE II score)
- Mean BG level
- BG variability (SD)
- Mean daily insulin dose
- Mean daily caloric intake
- Percentage of calories given IV
- Frequency of preexisting diabetes
- Frequency of sepsis

# BG TARGET IS NOT ALWAYS REACHED !



# Some possible reasons for discrepancies between outcome data



CHEST Original Research
CRITICAL CARE MEDICINE

# Toward Understanding Tight Glycemic Control in the ICU

## A Systematic Review and Metaanalysis

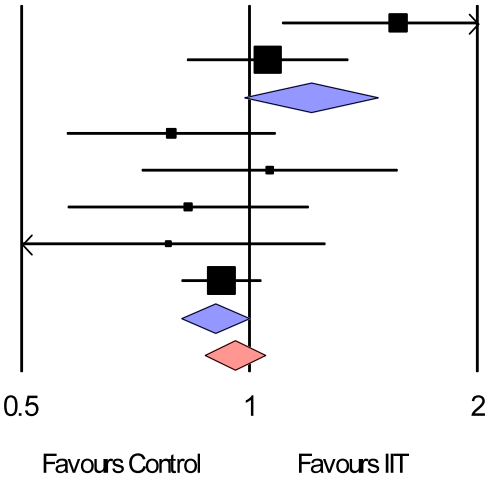
*Paul E. Marik, MD, FCCP; and Jean-Charles Preiser, MD*

*CHEST 2010; 137(3):544–551*

| Group by Nutrition | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| a-TPN | Van den Berghe-2001 | 1.572 | 1.102 | 2.242 | 2.498 | 0.012 |
| a-TPN | Van den Berghe-2006 | 1.057 | 0.826 | 1.353 | 0.441 | 0.659 |
| a-TPN | | 1.203 | 0.982 | 1.474 | 1.789 | 0.074 |
| b-ENT | Glucotrol-2006 | 0.788 | 0.573 | 1.085 | -1.460 | 0.144 |
| b-ENT | VISEP-2008 | 1.064 | 0.720 | 1.572 | 0.310 | 0.757 |
| b-ENT | De La Rosa-2008 | 0.830 | 0.574 | 1.199 | -0.994 | 0.320 |
| b-ENT | Arabi-2008 | 0.781 | 0.484 | 1.262 | -1.009 | 0.313 |
| b-ENT | NICE-SUGAR 2009 | 0.918 | 0.812 | 1.038 | -1.361 | 0.173 |
| b-ENT | | 0.899 | 0.811 | 0.997 | -2.025 | 0.043 |
| Overall | | 0.954 | 0.871 | 1.046 | -0.995 | 0.320 |

Statistics for each study

Odds ratio and 95% CI




**Meta Analysis**

CHEST

Original Research

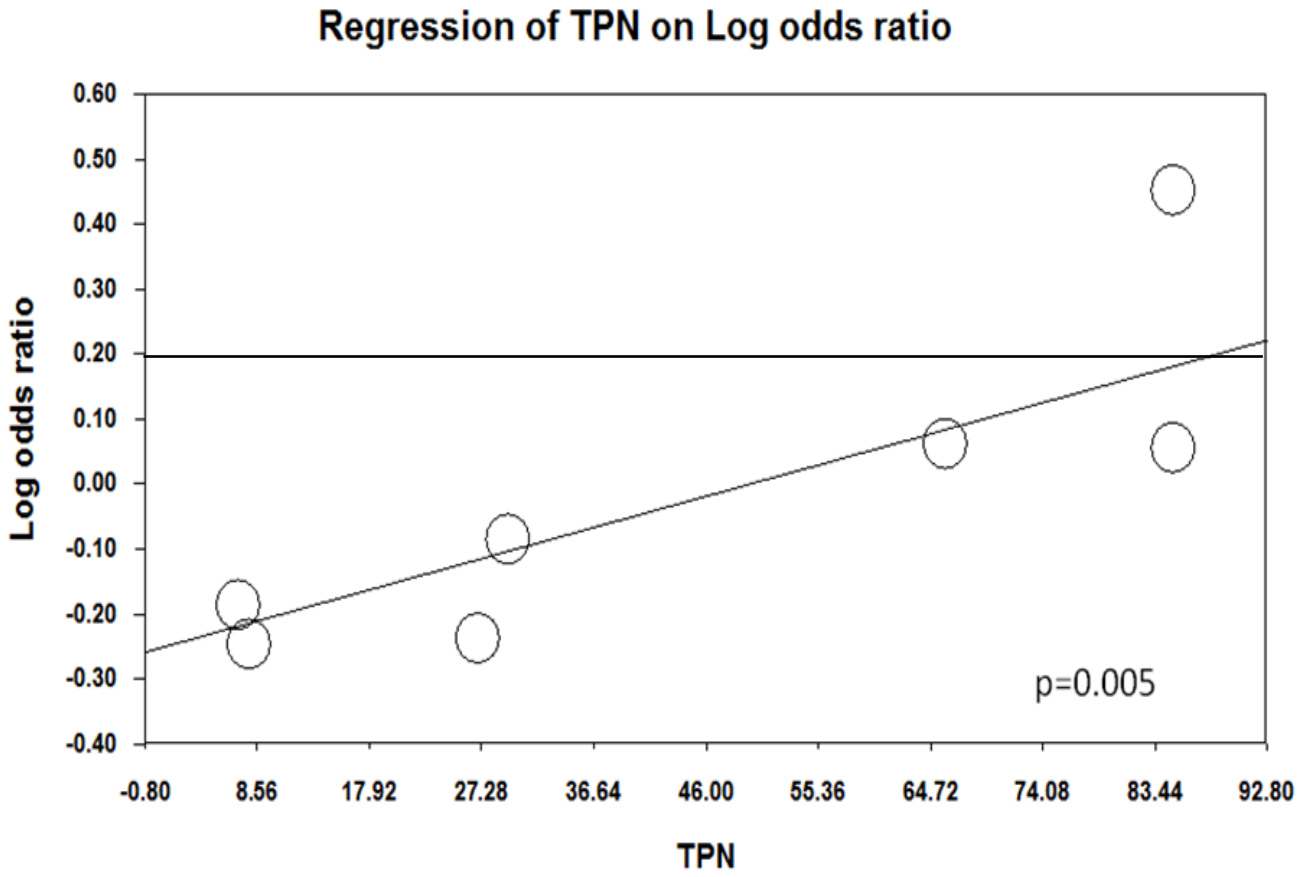
CRITICAL CARE MEDICINE

# Toward Understanding Tight Glycemic Control in the ICU

## A Systematic Review and Metaanalysis

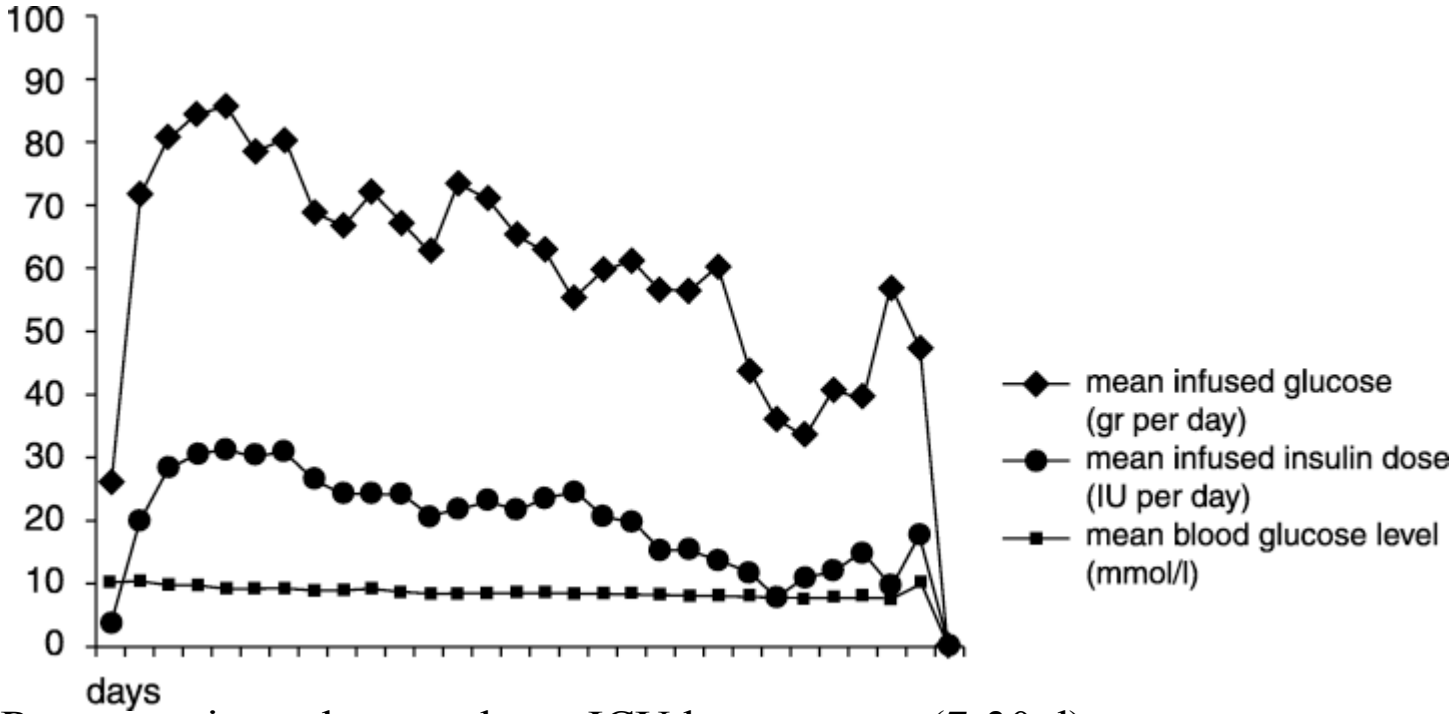
*Paul E. Marik, MD, FCCP; and Jean-Charles Preiser, MD*

*CHEST 2010; 137(3):544–551*



# Intravenous glucose and hospital mortality

Van der voort Clin Endocrinol 2006;64:141



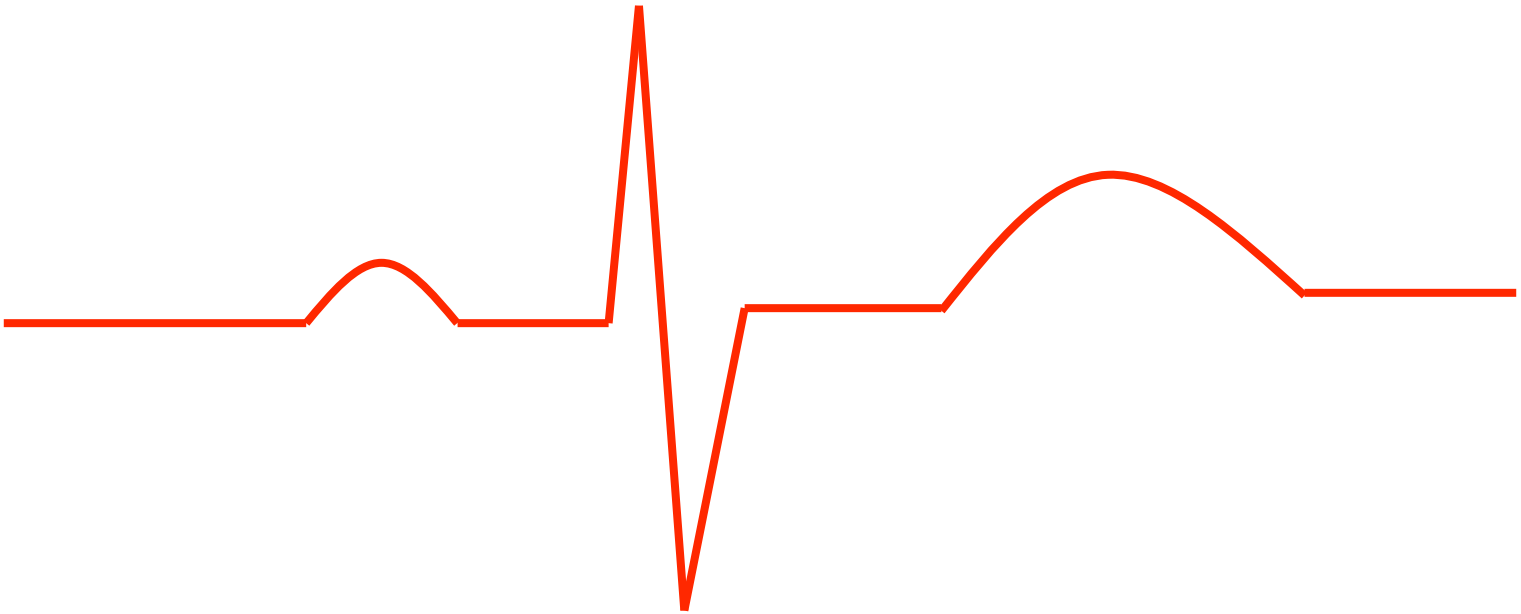

Retrospective cohort study on ICU long-stayers (7-30 d)

N = 273 (/ 2042)

Hospital mortality lower when mean BG < 8 mmol/L

***Logistic multivariate regression analysis : APACHE II and mean daily amount of IV Glucose associated with lower survival (OR 0.94 (0.9-0.98) and 0.65 (0.47-0.89))***

# IT'S TIME TO THINK AND BOUNCE BACK!



Period 4
2009-

# Clinical experience with TGCIIT : pending questions and unsolved issues

Preiser Devos Crit Care Med 2007;35:S503

- Which is the meaning of «normoglycemia » ?
- Non-glycemic effects of insulin ?
- Is hypoglycemia life-threatening?
- Importance of glucose variability?

# WHICH IS THE MEANING OF « NORMOGLYCEMIA » IN THE ICU?

- 80-110 mg/dl

is considered as **Normoglycemia** in fasting conditions

- Stress
- Feeding
- Therapies

Commentary
**Restoring normoglycaemia: not so harmless**
Jean-Charles Preiser
Published: 28 February 2008
***Critical Care* 2008, 12:116** (doi:10.1186/cc6787)

# Clinical experience with TGCIIT : pending questions and unsolved issues

Preiser Devos Crit Care Med 2007;35:S503

- Which is the meaning of «normoglycemia » ?
- **Non-glycemic effects of insulin ?**
- Is hypoglycemia life-threatening?
- Importance of glucose variability?

# How does blood glucose control with insulin save lives in intensive care?

Greet Van den Berghe

Department of Intensive Care Medicine, Catholic University of Leuven, Leuven, Belgium.

**J Clin Invest 2004; 114;1187**

**Metabolic effects**

CHO-related (relief of glucose toxicity)
CHO-independent

**Non-metabolic effects**

# Clinical experience with TGCIIT : pending questions and unsolved issues

Preiser Devos Crit Care Med 2007;35:S503

- Which is the meaning of «normoglycemia » ?
- Non-glycemic effects of insulin ?
- **Is hypoglycemia life-threatening?**
- Importance of glucose variability?

# 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

# 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

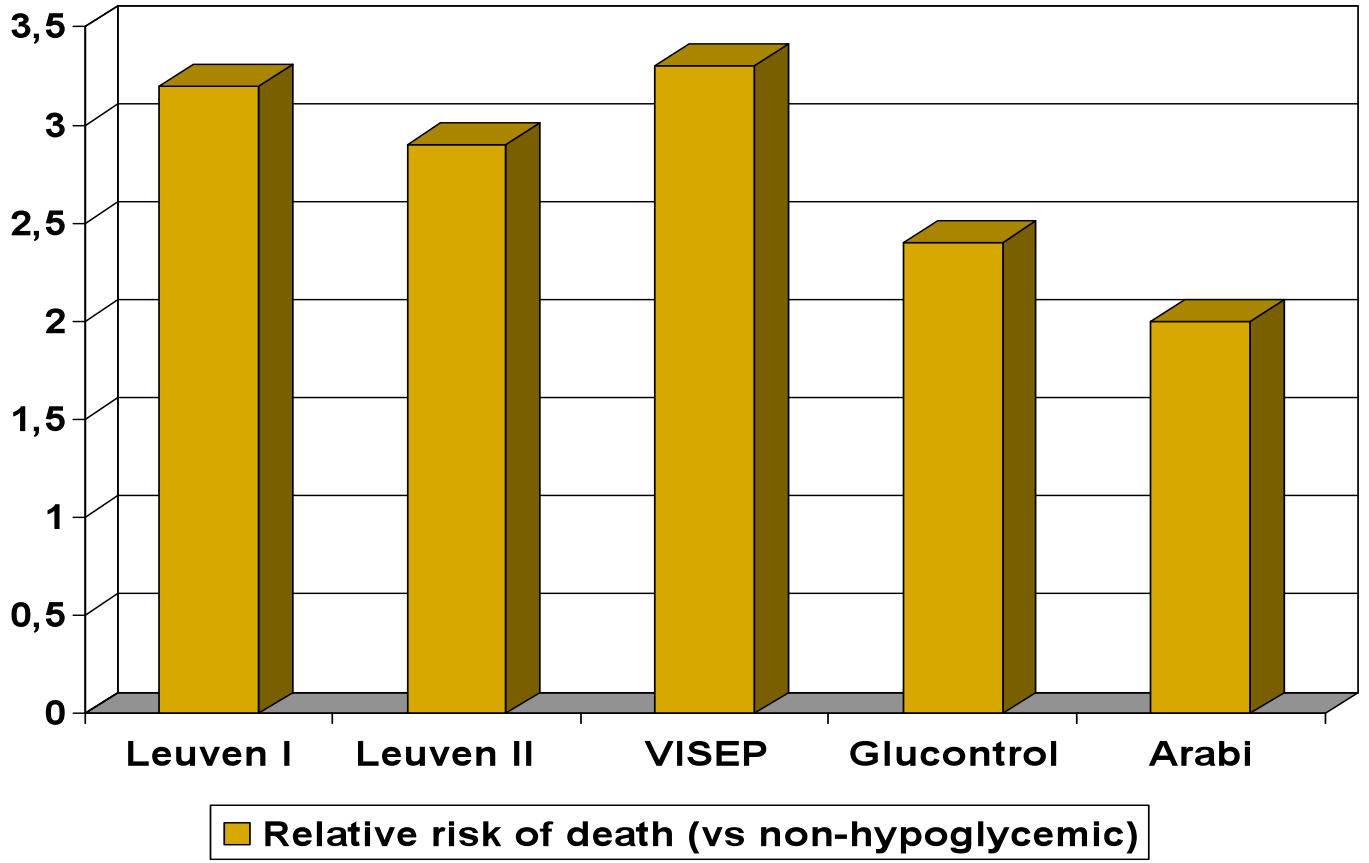
# SEVERE HYPOGLYCEMIA : RISK FACTORS AND OUTCOME

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])

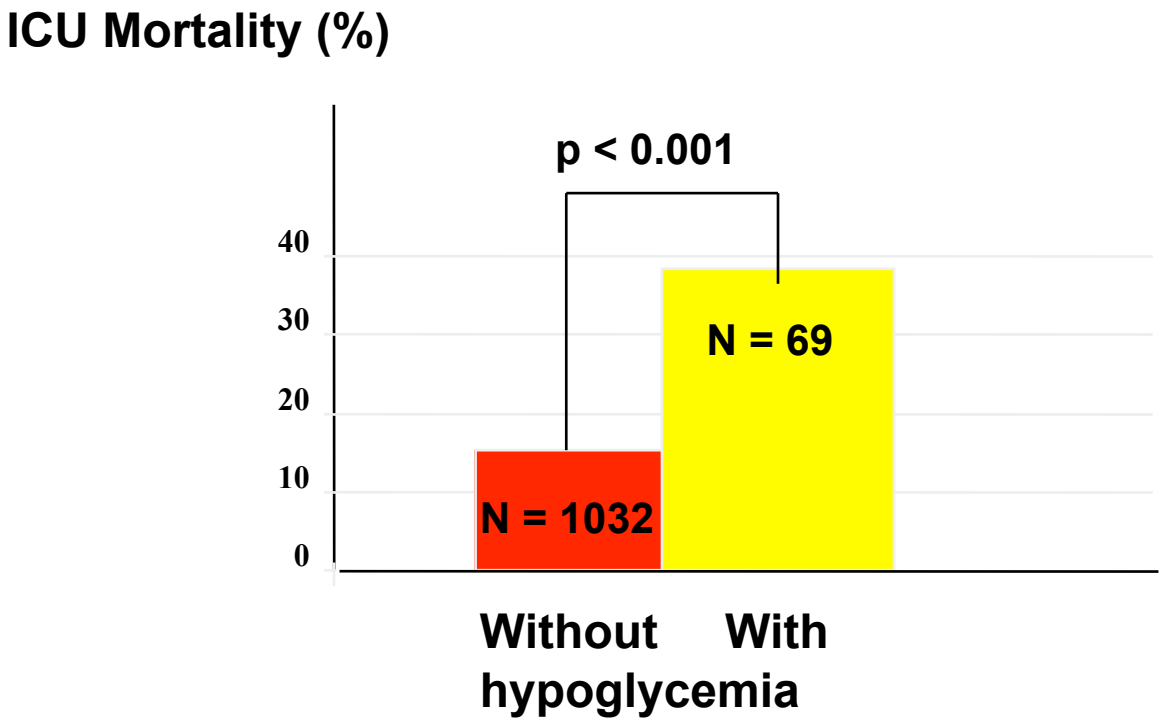
# Relative risk of death of patients with hypoglycemia

## Prospective studies



# Hypoglycemia and ICU mortality

## Data from Glucontrol – Preiser et al Intensive Care Med 2009

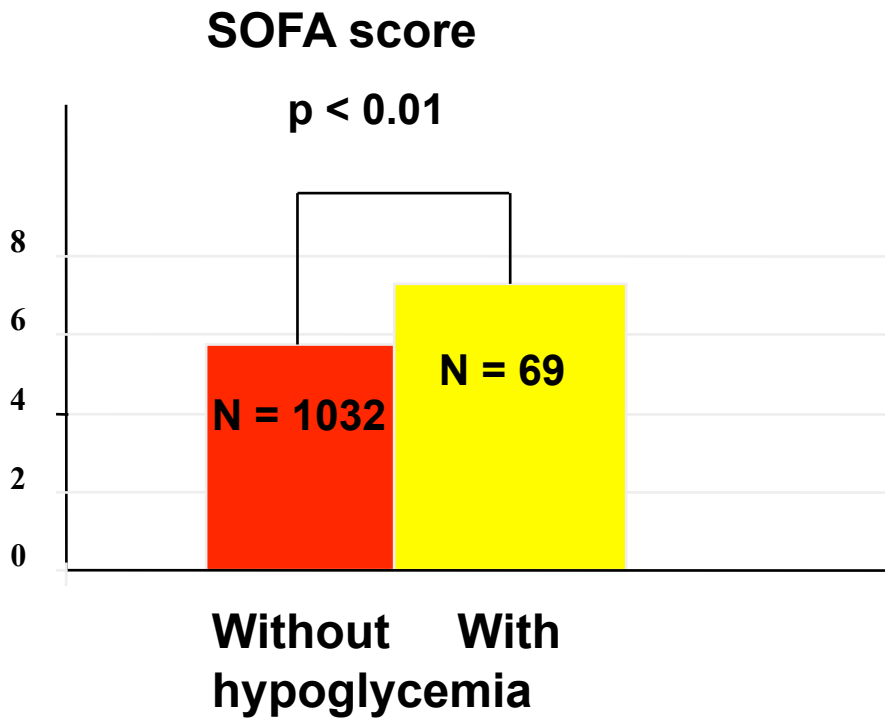


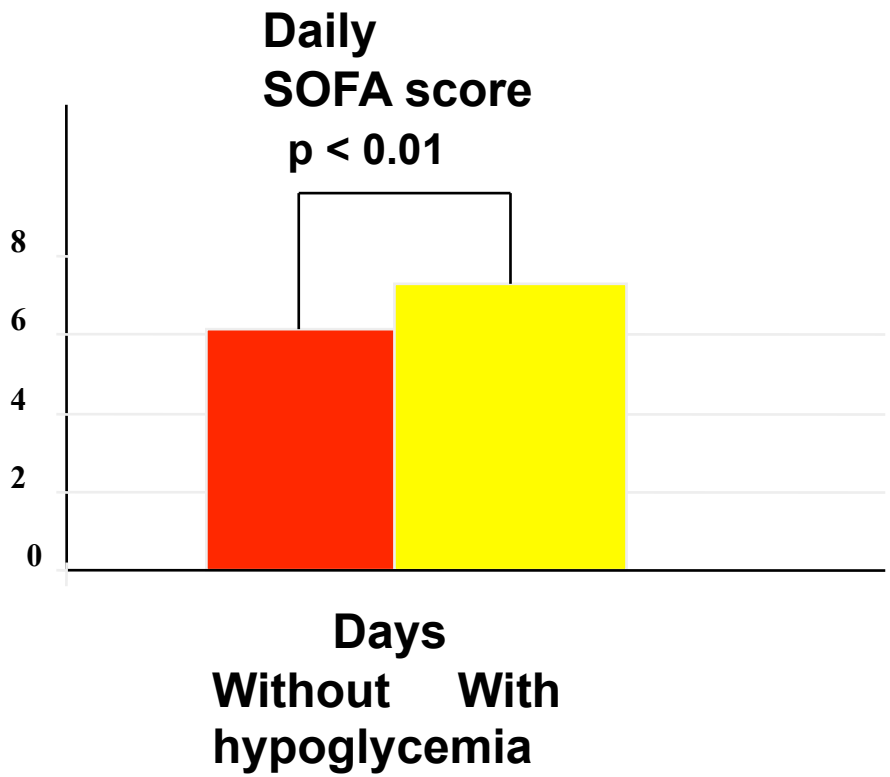
# GLUCONTROL

| 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 |

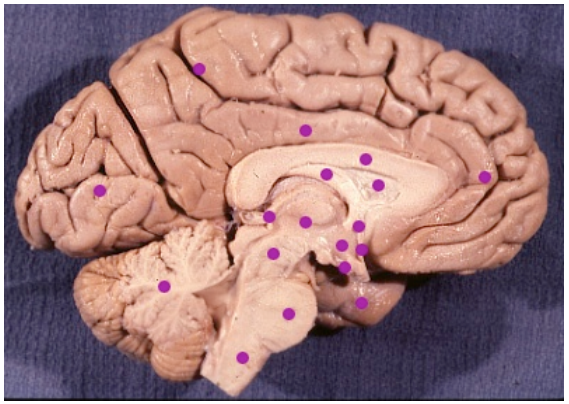
# Hypoglycemia and organ failures



# 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 ?

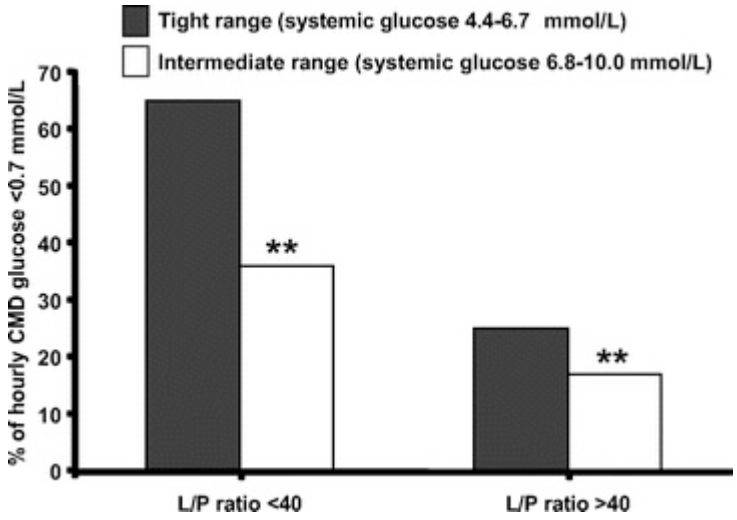


# Impact of TGC on cerebral glucose metabolism

## 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

# Impact of TGC on cerebral glucose metabolism

## Oddo et al Crit Care Med 2008;36:3233

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    > 40 : brain energy failure
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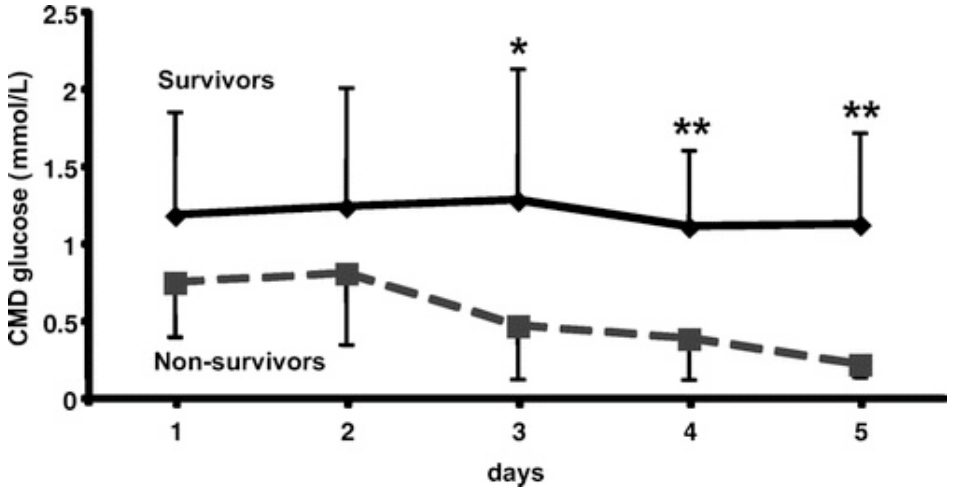
    **Brain energy crisis**




***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)

# Clinical experience with TGCIIT : pending questions and unsolved issues

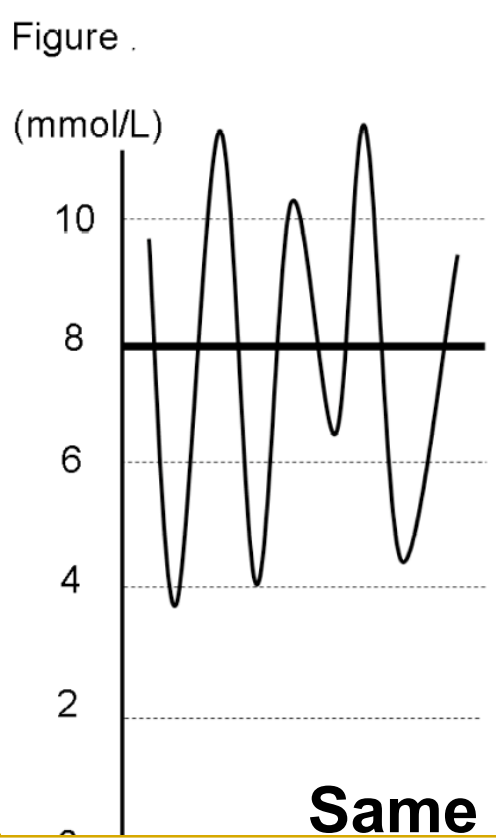
Preiser Devos Crit Care Med 2007;35:S503

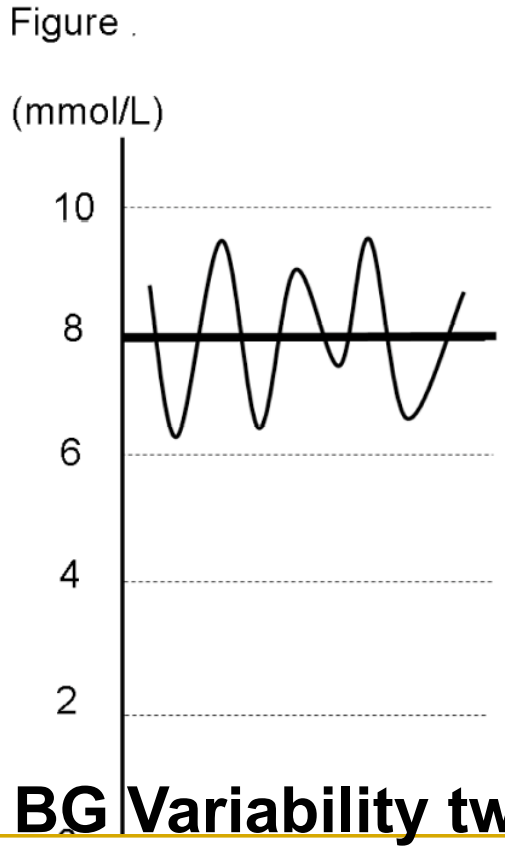
- Which is the meaning of «normoglycemia » ?
- Non-glycemic effects of insulin ?
- Is hypoglycemia life-threatening?
- **Importance of glucose variability?**

# Is reducing variability of blood glucose the real but hidden target of intensive insulin therapy?

M Egi R Bellomo M Reade

Crit Care 2009 (in press)




**Same average BG Variability twice lower**

# IS THE ISSUE OF TGCIIT HOPELESS? SHOULD WE LEAVE THE FIELD? SHOULD WE CLOSE THE CHAPTER?

An unexplored hypothesis is left and appealing !

- Hypothesis : high glucose variability is possibly detrimental for critically ill patients
- Supporting data : retrospective cohort study
- Biological plausibility

Anesthesiology 2006; 105:244–52 

# *Variability of Blood Glucose Concentration and Short-term Mortality in Critically Ill Patients*

*Moritoki Egi, M.D.,* Rinaldo Bellomo, M.D., F.J.F.I.C.M.,† Edward Stachowski, M.D.,‡ Craig J. French, M.D.,§ Graeme Hart, M.D.‖*

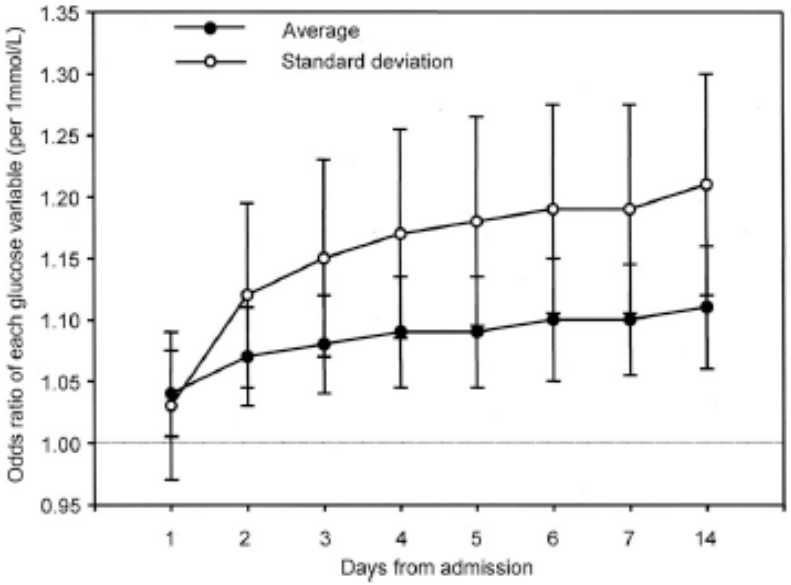



**Fig. 4. Time course of the predictive ability of average and SD of blood glucose. Odds ratios (expressed with 95% confidential intervals) for glucose indexes indicate the risk change of intensive care unit mortality per 1-mmol change in each index. For example, average of blood glucose on 7 days from admission means average of entire glucose measurements during 7 days from admission. As time in intensive care unit increased, so did the ability of glucose control indices to predict outcome.**

## Glucose variability and mortality in patients with sepsis

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD

| Glucose Characteristic | Logistic Regression | | | Comparison of Mortality Discrimination | | |
|---|---|---|---|---|---|---|
| | Mortality Crude Odds Ratio[1] | p-value | 95% CI | Area under the ROC | p-value[2] | 95% CI |
| GLI | 1.25 | < 0.001 | 1.20 – 1.32 | 0.67 | | 0.64 – 0.71 |
| MAGE | 1.12 | < 0.001 | 1.07 – 1.18 | 0.59 | < 0.001 | 0.56 – 0.63 |
| MEAN | 1.17 | < 0.001 | 1.12 – 1.23 | 0.63 | 0.003 | 0.59 – 0.66 |
| Standard Deviation | 1.16 | < 0.001 | 1.11 – 1.21 | 0.62 | < 0.001 | 0.58 – 0.65 |

Ali et al Crit Care Med 2008

# Intermittent high glucose enhances apoptosis in human umbilical vein endothelial cells in culture

A. RISSO,[1] F. MERCURI,[2] L. QUAGLIARO,[2] G. DAMANTE,[1] AND A. CERIELLO[3]
[1]*Department of Science and Biomedical Technology, University of Udine,* [2]*Morpurgo Hofmann Research Laboratory on Aging, and* [3]*Department of Pathology and Experimental and Clinical Medicine, Internal Medicine, University of Udine, 33100 Udine, Italy*

*Am J Physiol Endocrinol Metab*
281: E924–E930, 2001.

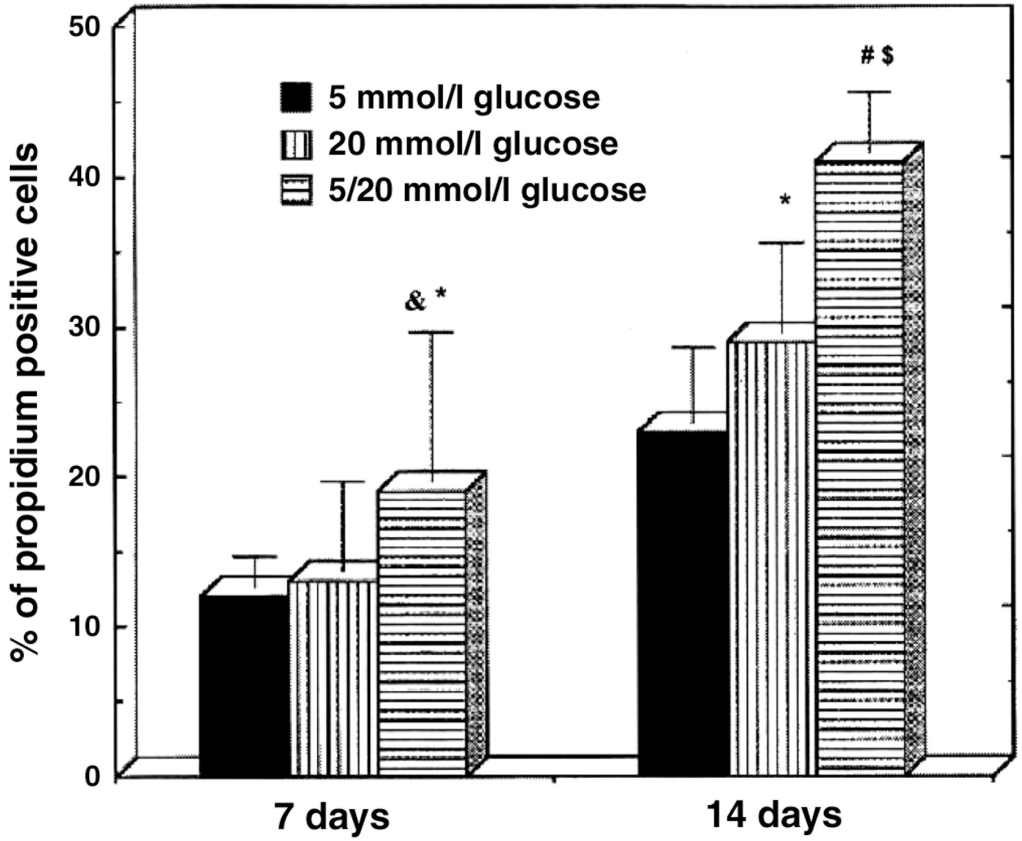



**Fig. 1.** Cell death of human umbilical vein endothelial cells (HUVECs) cultured with different concentrations of glucose. HUVECs were cultured in the presence of normal (5 mmol/l), high (20 mmol/l), or alternating normal/high concentrations, as described in MATERIALS AND METHODS. After 7 and 14 days, they were detached from Petri dishes, stained with 20 μg/ml of propidium iodide, and analyzed with the cytofluorimeter. Data are means ± SD of 6 independent experiments. **P* < 0.05 vs. glucose 5 mmol/l; &*P* < 0.05 vs. glucose 20 mmol/l; #*P* < 0.01 vs. glucose 5 mmol/l; $*P* < 0.01 vs. glucose 20 mmol/l.

DIABETES/METABOLISM RESEARCH AND REVIEWS
*Diabetes Metab Res Rev* 2006; **22**: 198–203.
Published online 2 February 2006 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.613

RESEARCH ARTICLE

# Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction

Ludovica Piconi[1]

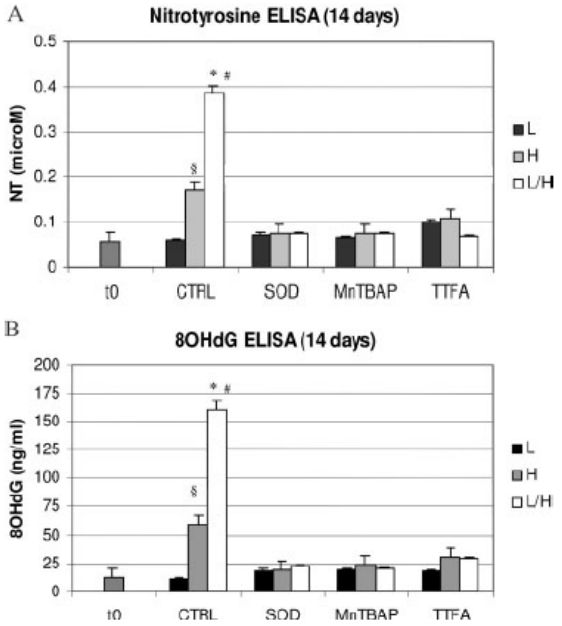



Figure 3. (A) Nitrotyrosine ELISA of HUVEC lysates, $N = 5$ nM glucose; H = 20 nM glucose; H/L = 5/20 nM glucose. (B) 8OHdG content in HUVEC DNA measured with ELISA technique. § = $p < 0.01$ normal *versus* high glucose; # = $p < 0.001$ intermittent *versus* normal glucose; * = $p < 0.01$ intermittent *versus* high glucose. Bars indicate ±SD

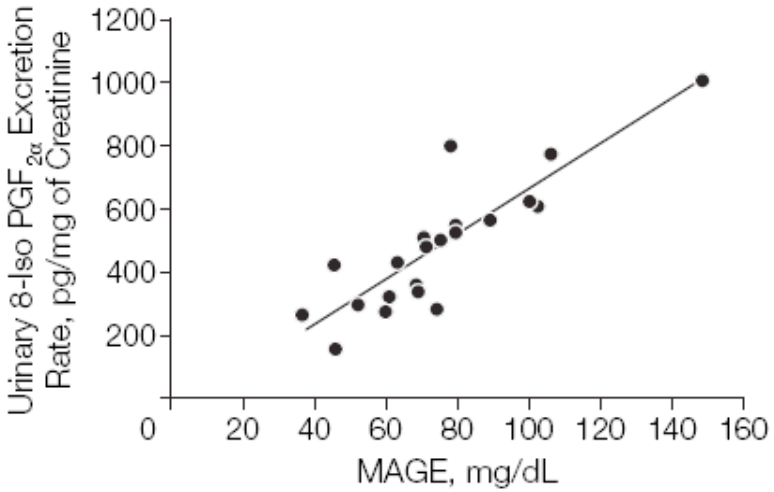
# Activation of Oxidative Stress by Acute Glucose Fluctuations Compared With Sustained Chronic Hyperglycemia in Patients With Type 2 Diabetes

Louis Monnier, MD
Emilie Mas, PhD

**Context** Glycemic disorders, one of the main risk factors for cardiovascular disease, are associated with activation of oxidative stress.

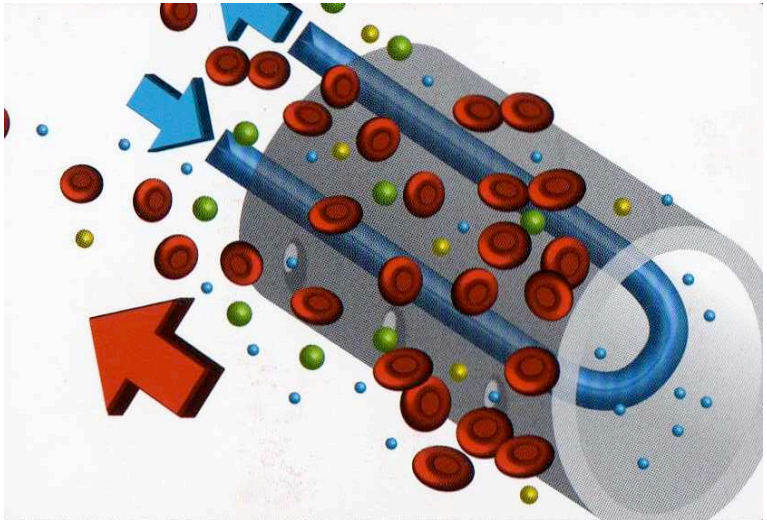
JAMA 2006 ; 295 : 1681

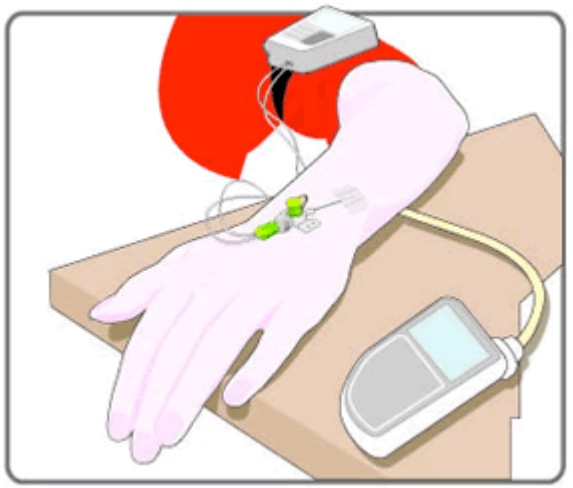
**Figure 2.** Linear Correlation Between 24-Hour Urinary Excretion Rates of 8-Iso Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and Mean Amplitude of Glycemic Excursions (MAGE)




$r$=0.86; $P$<.001.

# The answer : Intravascular continuous blood monitoring?





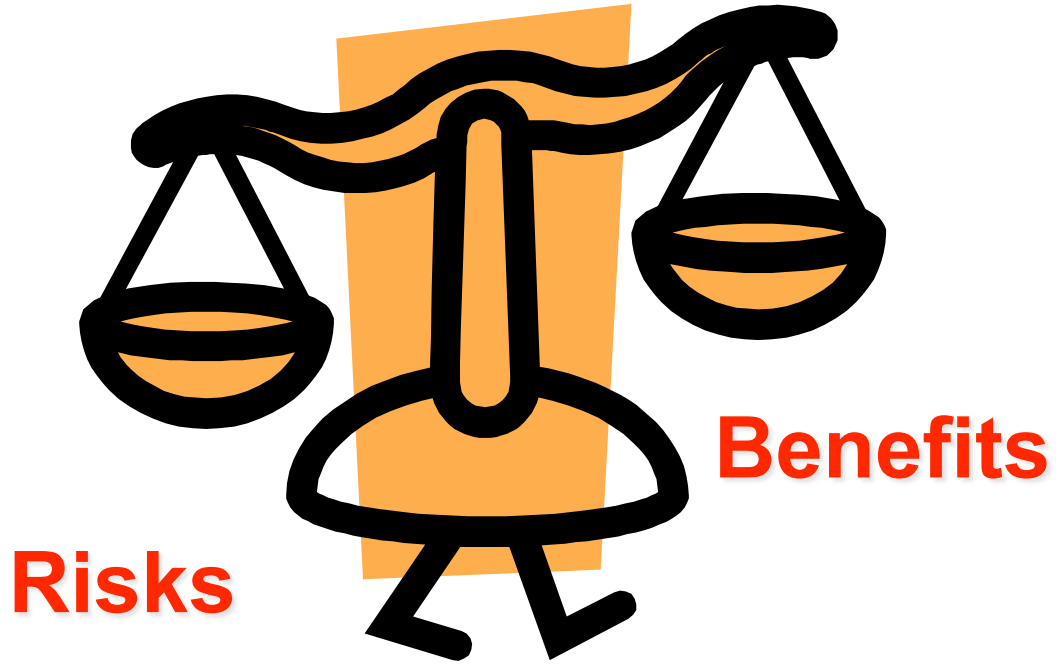
# Meanwhile :

## Moving beyond tight glucose control to safe effective glucose control

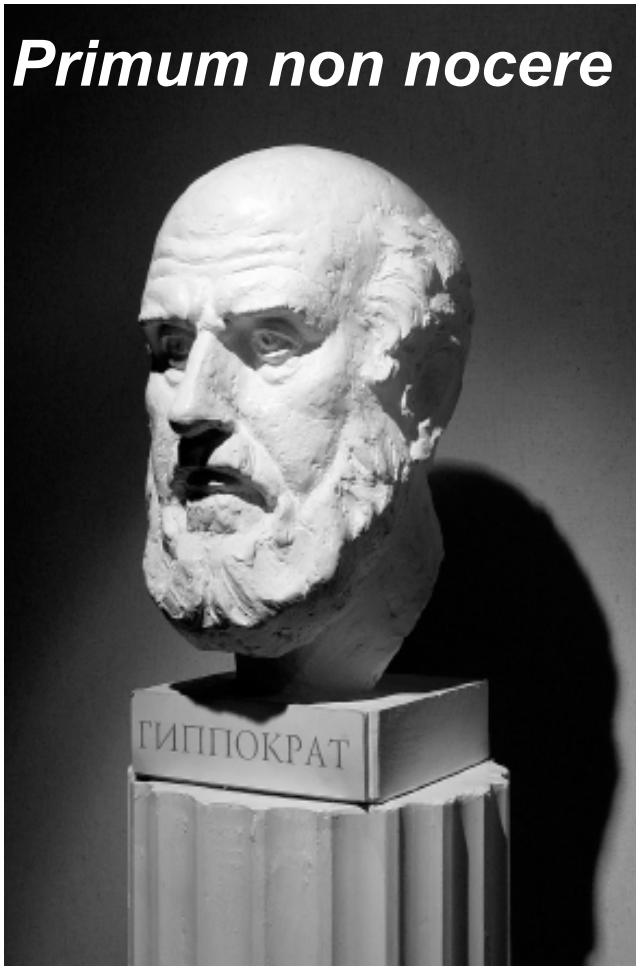
James S Krinsley and Jean-Charles Preiser
*Critical Care* 2008, **12:3:** 149

**Instead of TGC, we propose a stepwise approach defining a new standard – Safe, Effective Glycemic Control (SEGC). SEGC involves, first, adoption of a safe glycemic target appropriate to the skills, experience and available tools of the ICU that does not result in a significant increase in the rate of hypoglycemia. A glycemic target of 80 to 150 mg/dl is not unreasonable for an ICU to choose initially; implementation can subsequently lead to downward revision of the glycemic goal.**

# « TIGHT » GLUCOSE CONTROL BY INTENSIVE INSULIN THERAPY



# FROM MARTIN LUTHER KING BACK TO HIPPOCRATES

# 30th Annual Meeting of the Belgian Society of Intensive Care Medicine December 3, 2010 Palais des Congrès – Liège

## Endocrinology, Metabolism and Nutrition

### *Endocrinology in the ICU*

- Endocrine alterations in the critically ill (G Van den Berghe)
- Adrenal failure in the ICU (D Mesotten)
- Current status of the ACTH test (J Groeneveld Amsterdam)
- Steroid supplementation : for which patients? (D Annane Garches)
- Safe anabolic strategies (J Takala Bern)

### *Metabolic changes of critical illness*

- Use of substrates (M Singer London)
- Insulin resistance (S Weber-Carstens Berlin)
- Promising metabolic substrates : lactate and friends (X Leverve Paris)
- Glucose control in the ICU (JC Preiser)

### *Nutrition in the ICU*

- Permissive underfeeding or early caloric intake adapted to match energy expenditure (R Thibault - Nantes)
- Recent lipid formulations for the critically ill (Y Carpentier Brussels)
- Optimal protein intake (J Wernerman Stockholm)
- Specialised nutrients (R Griffiths Liverpool)
- How to apply guidelines at bedside? (V Fraipont Liege)

SBNC Société Belge de Nutrition Clinique

ESPEN

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

HOCIN VVKVM Vlaamse Vereniging voor Klinische Voeding en Metabolisme

***Meeting secretariat***
*Mrs Christiane Lallemand*
*Department of Intensive Care Medicine*
*C.H.U. Liège – domaine universitaire du Sart-Tilman – 4000 Liege*
*Phone : 04/366.74.95 – Fax : 04/366.88.98 – E-mail : pdamas@chu.ulg.ac.be*