Glycemic control in critically ill patients

Where do things stand 13 years after PDP-I and 11 years after Leuven-I?

AACC – Prague - October 4, 2012

James Krinsley MD, FCCM
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Stamford Hospital
Clinical Professor of Medicine
Columbia University College of Physicians and Surgeons

Summary of trials

	Year	Rx pts per center	Severe Hypo %	Benefit?
Leuven 1	2001	765	5.3 vs. 0.8	4+
Leuven 2	2006	595	18.7 vs. 3.1	1+
VISEP	2008	15	17.0 vs. 4.1	NO
GLUCONTROL	2009	26	8.7 vs. 2.7	NO
NICE-SUGAR	2009	73	6.8 vs. 0.5	NO

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NICE-SUGAR	2009	73	6.8 vs. 0.5	NO
Stamford	2004	800	1.5 vs. 1.5	3+

The 3 domains of glycemic control

- Hyperglycemia: the focus of the interventional trials

The 3 domains of glycemic control

- Hyperglycemia: the focus of the interventional trials

- Hypoglycemia: the "unifying complication" of the interventional trials

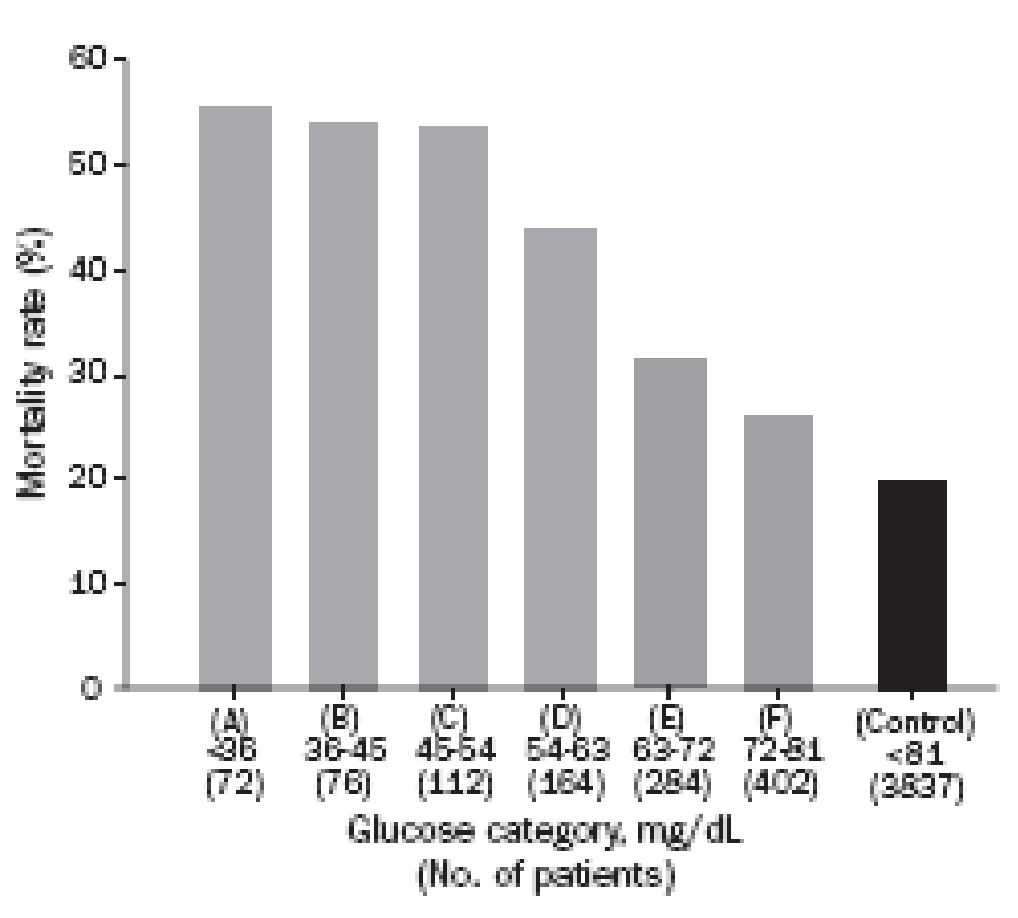
A single episode of severe hypoglycemia (<40 mg/dL) is independently associated with increased risk of mortality

- **OR 2.28 (1.41-2.70)**
  - 5,365 med-surg pts, single center, observational
    - Krinsley and Grover. Crit Care Med. 2007; 35: 2262-2267.
- **OR 2.6 (2.1-3.2)**
  - 66,184 med-surg pts, multi-center, observational
    - Bagshaw S et al. Crit Care Med. 2009; 37: 463-470.
- **OR 3.23 (2.25-4.64)**
  - 2,685 med-surg pts, merged Leuven dataset, prospective
    - Meyfroidt et al. Crit Care Med. 2010; 38: 1021-1029.

Mayo Clinic Proc 2010; 85: 217-224.

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



Even mild hypoglycemia is associated with increased risk of mortality.

Crit Care 2011; 15:R173.

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]

- Academic Medical Center
  - 2,063 patients: 3 centers, observational data
- Stamford Hospital
  - 3,263 patients: single center, observational data
- GLUCONTROL trial
  - 914 patients: 21 centers, RCT data

Crit Care 2011; 15:R173.

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

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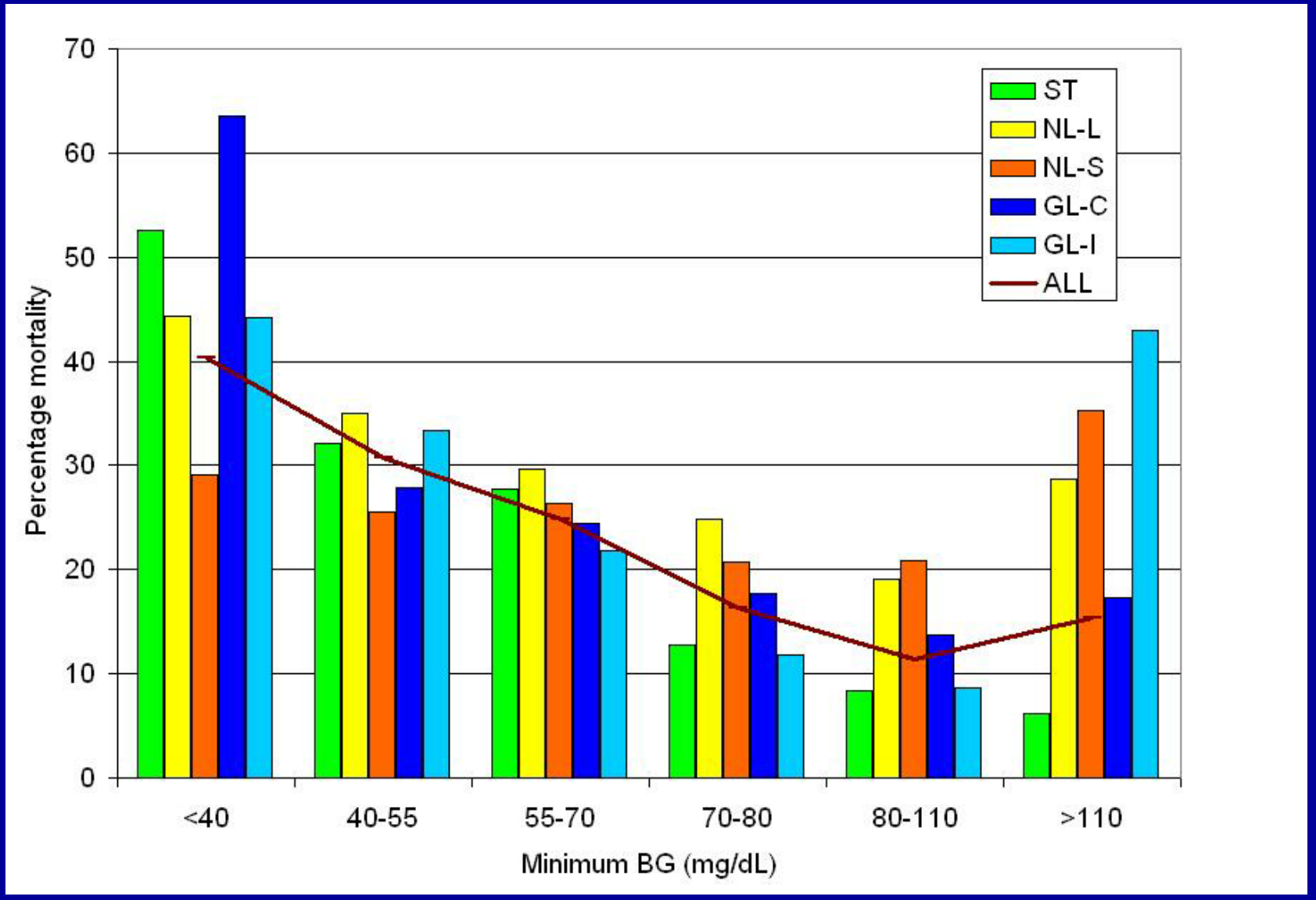


NEJM 2012; 367:1009-1018.

Hypoglycemia and Risk of Death in Critically Ill Patients

The NICE-SUGAR Study Investigators*

***OR 2.10 (1.59-2.77) – BG ≤ 40 mg/dL**

***OR 1.41 (1.21-1.62) – BG 41-70 mg/dL**

6,026 med-surg pts, multi-center, prospective

Glycemic variability

The 3 domains of glycemic control

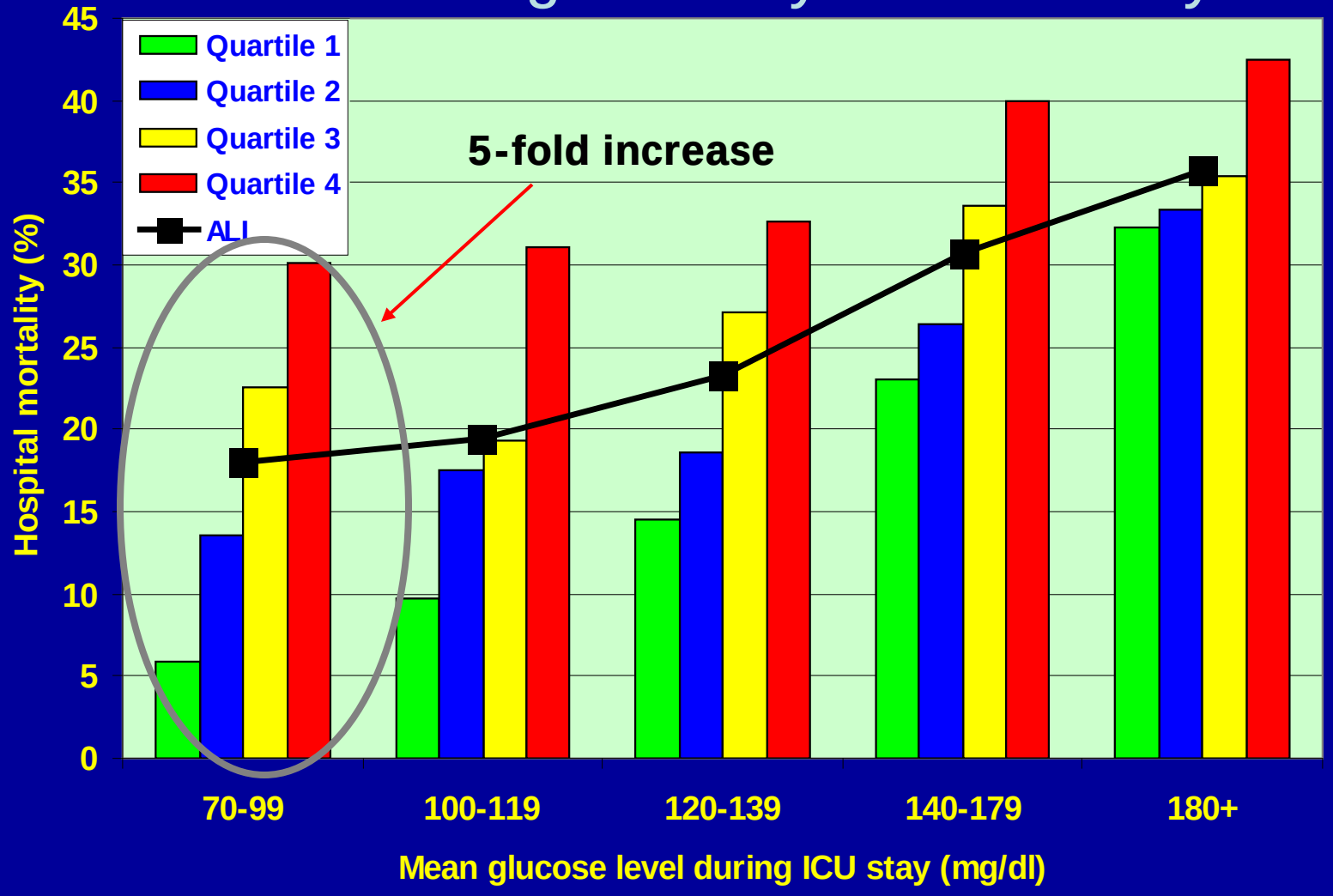
- Hyperglycemia: the focus of the interventional trials
- Hypoglycemia: the “unifying complication” of the interventional trials
- Glycemic variability: the hidden factor impacting the interventional trials

Crit Care Med 2008; 36:3008-3013.

Glycemic variability: A strong independent predictor of mortality in critically ill patients*

James S. Krinsley, MD, FCCM, FCCP

GV during ICU stay and mortality



Crit Care Med 2010; 38:1021-1029.

Dynamic characteristics of blood glucose time series during the course of critical illness: Effects of intensive insulin therapy and relative association with mortality*

Geert Meyfroidt, MD; Daniel M. Keenan, PhD; Xin Wang, PhD; Pieter J. Wouters, MSc; Johannes D. Veldhuis, MD, PhD; Greet Van den Berghe, MD, PhD

Pooled data from Leuven 1 and 2

- The only published data from RCT re: GV

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- Increased GV is independently associated with increased risk of mortality
  - **OR 1.050 (1.003-1.099) p=0.0376**
    - Mean daily delta BG (per mmol/L)

Disturbances in 3 domains of glycemic control: Independent, and cumulative, association with mortality

Int Care Med. 2011; 37:435-443.

Iain M. J. Mackenzie
Tony Whitehouse
Peter G. Nightingale

The metrics of glycaemic control in critical care

Cumulative impact of disturbances in different domains

Risk groups	OR (95% CI)
HYPO	2.5 (2.0-3.1)

- Hypoglycemia has the strongest association with mortality

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- The impact of hyperglycemia is additive. Increasing glycemic targets into the hyperglycemic range may increase mortality.

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HYPO	2.5 (2.0-3.1)
HYPO + HYPER	4.8 (3.4-6.8)
HYPO + HYPER + GV	6.0 (3.9-9.2)

- Hypoglycemia has the strongest association with mortality
- The impact of hyperglycemia is additive. Increasing glycemic targets into the hyperglycemic range may increase mortality.
- GV is associated with additional harm and is an additional therapeutic target.

Does diabetic status matter?

Curr Opin Clin Nutr Metab Care 2012; 15:151-160.

The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients

James S. Krinsley[a], Geert Meyfroidt[b], Greet van den Berghe[b], Mori Egi[c], and Rinaldo Bellomo[d]

- Data from interventional trials suggest that intensive insulin therapy had more benefit among non-DM patients

Curr Opin Clin Nutr Metab Care 2012; 15:151-160.

Table 1. Mortality of diabetic and nondiabetic individuals in the major interventional trials

	Conventional		Interventional		RR, 95% CI, *P* value: mortality IIT	
Author	Nondiabetic individuals	Diabetic individuals	Nondiabetic individuals	Diabetic individuals	Nondiabetic individuals	Diabetic individuals
Leuven 1 [1]	57/680 (8.4%)	6/103 (5.8%)	31/664 (4.7%)	4/101 (4.0%)	0.56 (0.36–0.85)	0.68 (0.20–2.33)
					0.0068	0.5403
Leuven 2 [2]	208/508 (40.9%)	34/97 (35.1%)	180/489 (36.8%)	42/106 (39.6%)	0.90 (0.77–1.05)	1.13 (0.79–1.62)
					0.1815	0.5029
Krinsley 2006[a] [25]	399/2134 (18.7%)	120/532 (22.6%)	287/2121 (13.5%)	111/578 (19.2%)	0.72 (0.63–0.83)	0.85 (0.67–1.07)
					<0.0001	0.1698
Arabi 2008 [5]	19/134 (14.2%)	25/123 (20.3%)	25/181 (13.8%)	11/85 (12.9%)	0.97 (0.56–1.69)	0.64 (0.33–1.22)
					0.9260	0.1754
NICE-SUGAR [6]	586/2416 (24.3%)	165/596 (27.7%)	634/2394 (26.5%)	195/615 (31.7%)	1.09 (0.99–1.20)	1.15 (0.96–1.36)
					0.0760	0.1265

- Mortality of non-DM: conventional vs. interventional Rx

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- RR of mortality for non-DM and DM associated with IIT

Crit Care Med. 2010; 38: 16-24.

Diabetes mellitus does not adversely affect outcomes from a critical illness*

Brian B. Graham, MD; Angela Keniston, Msph; Ognjen Gajic, MD; Cesar A. Trillo Alvarez, MD; Sofia Medvedev, PhD; Ivor S. Douglas, MD

- Two large datasets - heterogeneous
  - UHC: 1.5M pts; 2003-2006
  - Mayo: 36K pts; 1999-2007

Mortality

	DM	NON	OR (95% CI)*	P value
UHC	8.79	9.68	0.75 (0.74-0.76)	<0.001
Mayo	10.31	9.68	0.88 (0.79-0.98)	0.022

*Mulitvariate logistic regression model included age and severity of illness.

Crit Care Med. 2011; 39: 105-111.

The interaction of chronic and acute glycemia with mortality in critically ill patients with diabetes*

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

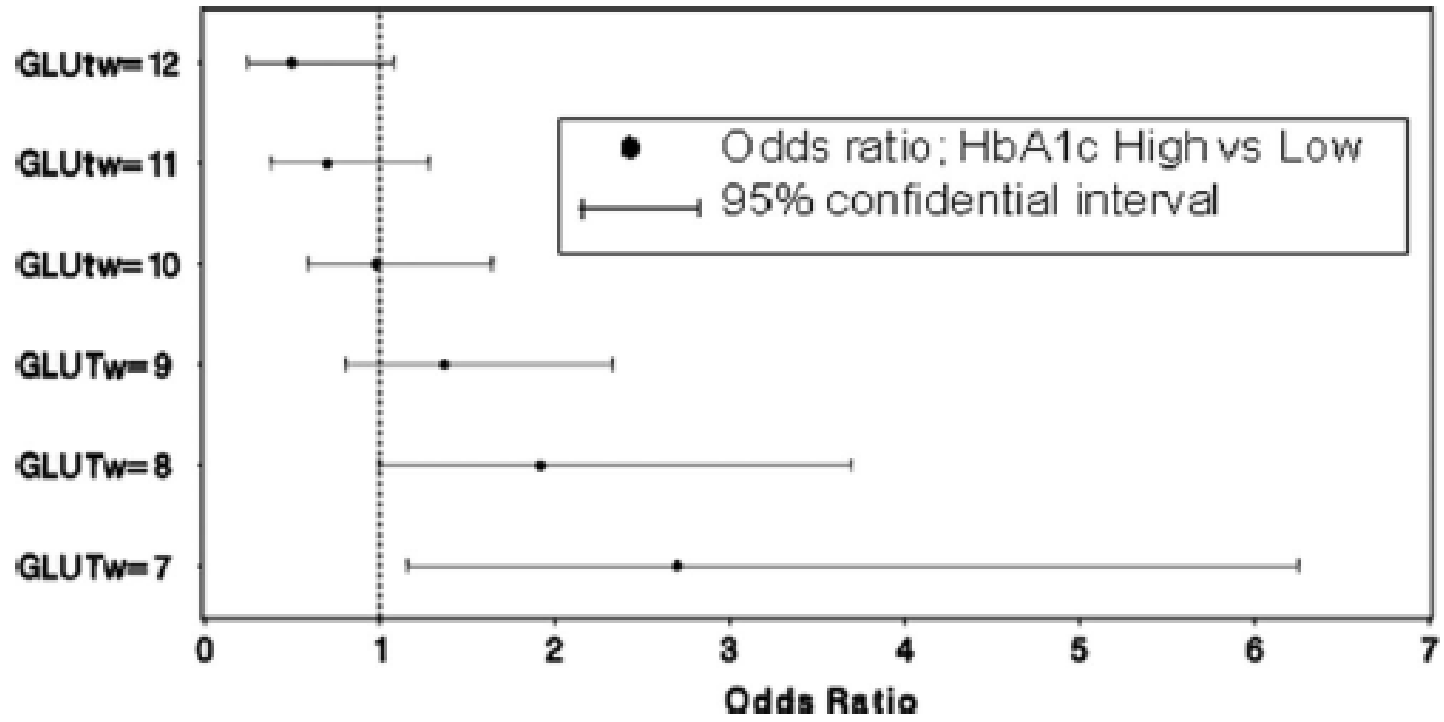

Figure 2. Adjusted odds ratios (*OR*) between lower and higher HbA1c levels for hospital mortality according to the time-weighted average of blood glucose control (Glu_{Tw}). *CI*, confidence interval.

A new 4-continent, 9 center, 23 ICU collaboration

One week from submission

Diabetic status and the relationship of the three domains of glycemic control to mortality in critically ill patients: an international multi-center cohort study

James S Krinsley MD, FCCM, FCCP[1], Moritoki Egi MD[2], Devendra N Amin, MB, FCCM, FCCP[3]; Philipp Schuetz MD[4]; Paula Maurer RN[5]; Marcus J Schultz MD, PhD[6], Roosmarijn TM van Hooijdonk MD[6], Morita Kiyoshi MD, PhD[2], , Iain MJ Mackenzie MD[7], Djillali Annane MD[8], Peter Stow MBBS, FRCA, FCICM[9], Stanley Nasraway MD, FCCM[10], Sharon Holewinski RN[10], Jean-Charles Preiser MD, PhD[11], Jean-Louis Vincent MD, PhD[11], Rinaldo Bellomo MD, FCICM[12]

3 domains international cohort study

- N=44,964
- US – Tufts, Stamford, Baycare
- Europe – Amsterdam Medical Center, Birmingham UK, University of Vienna
- Australia – Geelong, Austin
- Japan - Okayama

3 domains international cohort study

- Change in glycemic control in last decade
  - Mean BG
    - NON: 110-138 mg/dL
    - DM: 135-156 mg/dL

Leuven 1: Mean AM BG in all conventionally treated patients – 153 mg/dL

3 domains international cohort study

- Different glycemic ranges associated with lowest mortality
  - *Compared to mean BG 80-110 mg/dL*
    - NON: 140-180, > 180 **HIGHER** mortality
    - DM: 110-140, 140-180, > 180 **LOWER** mortality

3 domains international cohort study

- Severe (minimum BG < 40) and mild-moderate (minimum BG 40-69) hypoglycemia independently associated with mortality in NON and DM
  - Stronger signal among NON

3 domains international cohort study

- Increased glycemic variability (CV > 40%) strongly associated with increased risk of mortality in NON

- No independent association of glycemic variability with mortality in DM

Clinical implications - I

* Future interventional trials of intensive insulin therapy in critically ill patients – *and best clinical practice* – must manage all three domains of glycemic control: hyperglycemia, hypoglycemia and glycemic variability

Clinical implications - II

* Glycemic targets will be designed based on patient characteristics:

*Diabetic vs. non-diabetic

*Among diabetics, stratification by preadmission glycemic control

*Medical vs. surgical

Clinical implications - III

*Glucometers are not up to the task!

-inadequate accuracy

-too time consuming

-impossible to manage the 3 domains with intermittent monitoring

These principles were endorsed recently in a closed panel roundtable of international opinion leaders and researchers at the International Society of Intensive Care and Emergency Medicine annual congress in Brussels.