PEC GLYCÉMIQUE EN RÉA

JDP 2015
Journées de Printemps de Nutrition Clinique de la SFNEP
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Université Nice Sophia Antipolis

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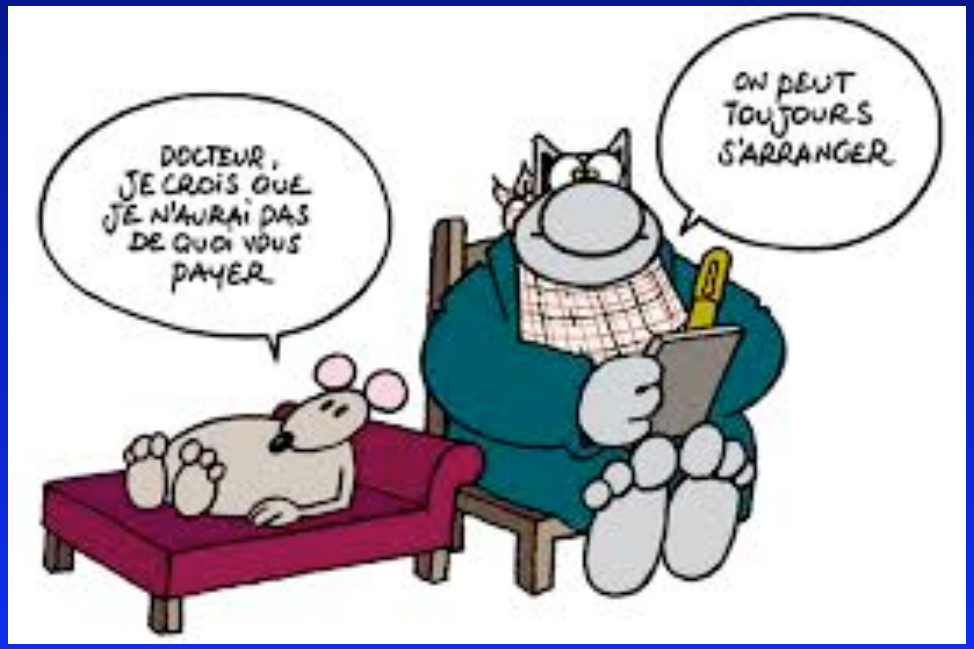
Service de Réanimation

CNRS UMR 7284 - INSERM U 1081 - UNS

PEC GLYCÉMIQUE EN RÉA

Partenariat scientifique avec :

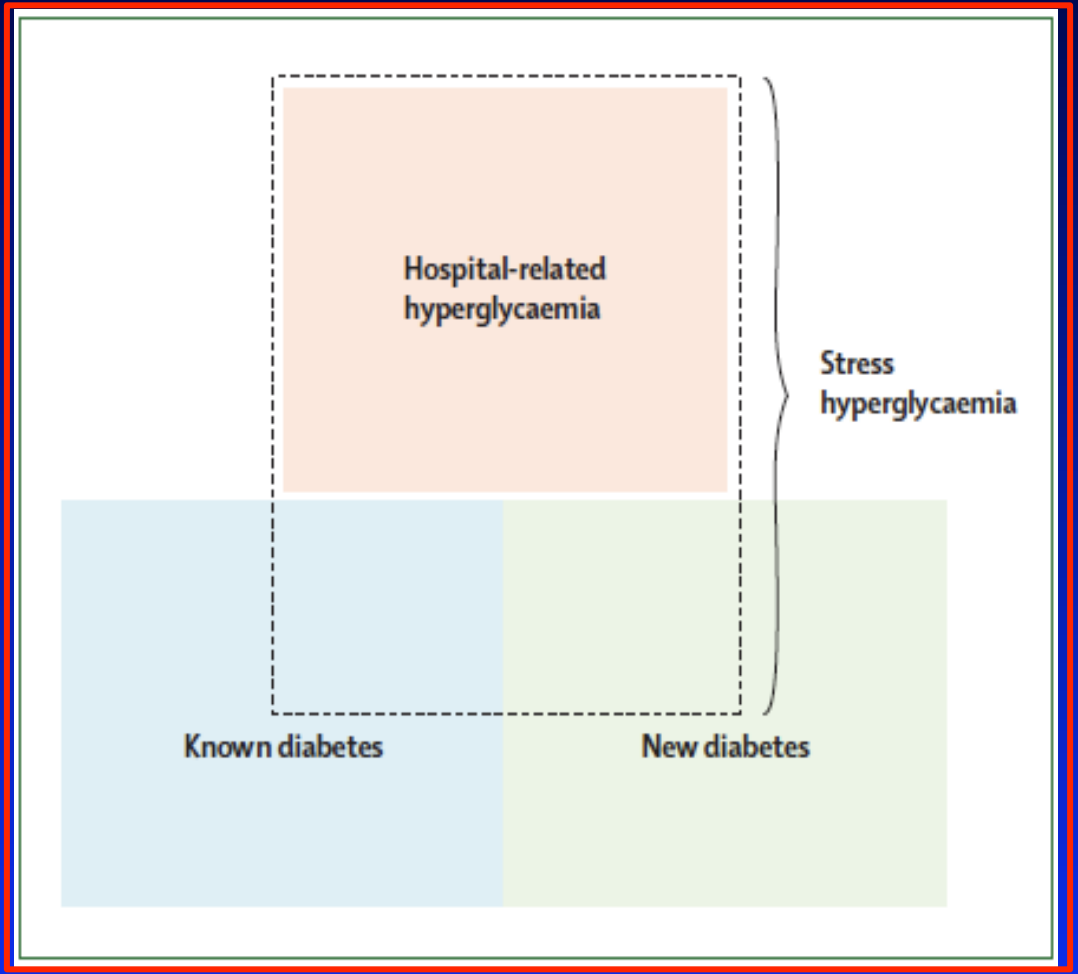
- Gambro-Hospal
- Fresenius Medical Care
- Fresenius Kabi
- BBraun
- Edwards
- Baxter
- Astute Inc



HYPERGLYCEMIE EN RÉANIMATION

Stress hyperglycaemia

Kathleen M Dungan, Susan S Braithwaite, Jean-Charles Preiser



Panel: Classification of hyperglycaemia in hospital[9]

Known diabetes
Diabetes diagnosed and treated before admission

Newly diagnosed diabetes
Fasting glucose more than 6·9 mmol/L or random glucose higher than 11·1 mmol/L during hospital stay and confirmed after discharge

Hospital-related hyperglycaemia
Fasting glucose more than 6·9 mmol/L or random glucose higher than 11·1 mmol/L during hospital stay that reverts to normal range after discharge

Lancet 2009; 373: 1798-807

HYPERGLYCEMIE EN RÉANIMATION

Stress hyperglycaemia

Kathleen M Dungan, Susan S Braithwaite, Jean-Charles Preiser

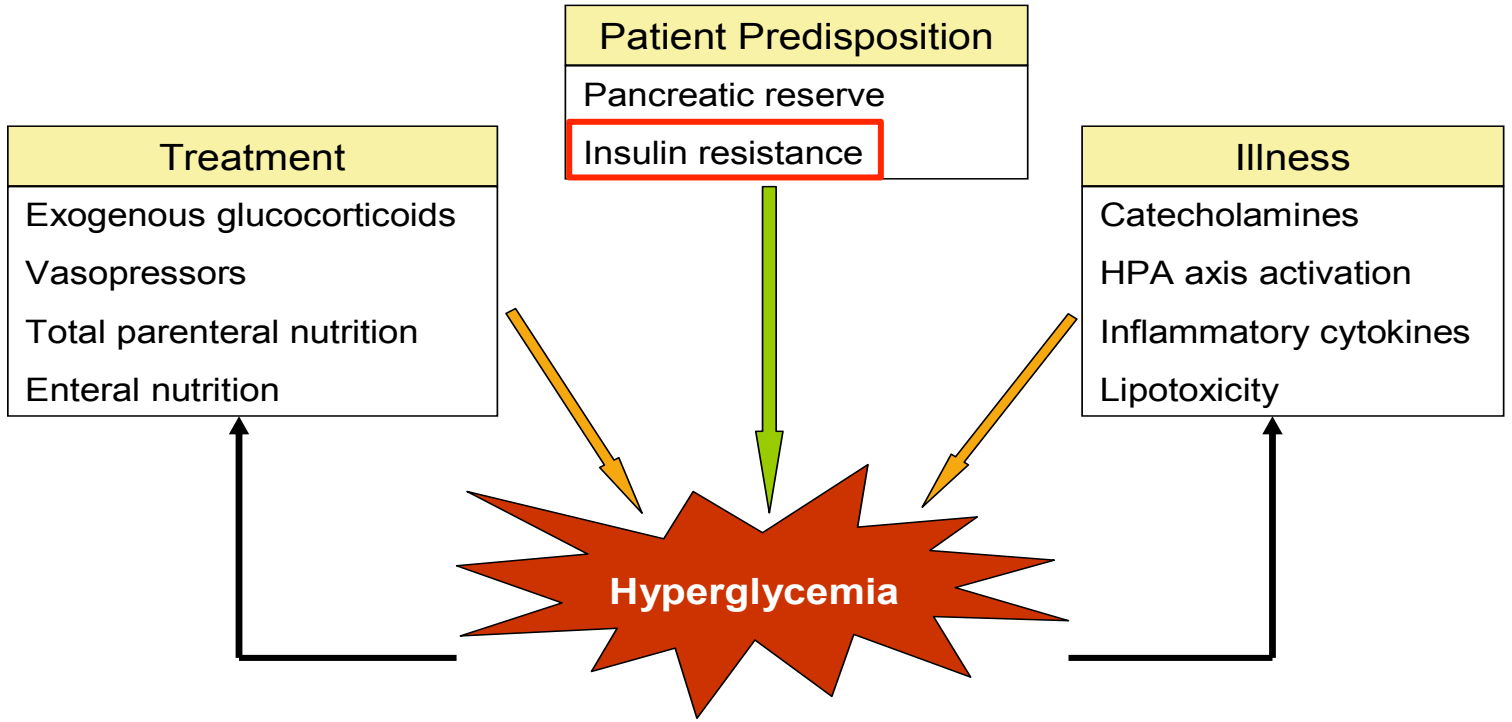


Figure 1a: The etiology of hospital-related hyperglycemia is multi-factorial, incorporating patient-specific, illness-specific, and treatment-specific factors. Hyperglycemia may, in turn, exacerbate illness-specific factors and increase the need for treatment-specific factors, thus leading to a vicious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

Lancet 2009; 373: 1798-807

CONTRÔLE GLYCÉMIQUE EN RÉA

. **Années 2000-2005** (Van Den Berghe G *et al*, New Engl J Med 2001; 345 : 1359-67)

L'enthousiasme : **il faut faire du contrôle glycémique strict chez les patients de réa**

. **Années 2006-2009**

(Brunkhorst F et al, N Eng J Med 2008;358:125-39, Van Den Berghe G et al, New Engl J Med 2006;354:449-61, Preiser JC et al Intensive Care Med 2009;35:1738-48)

La controverse : **faut-il faire du contrôle glycémique (strict) chez les patients de réa**

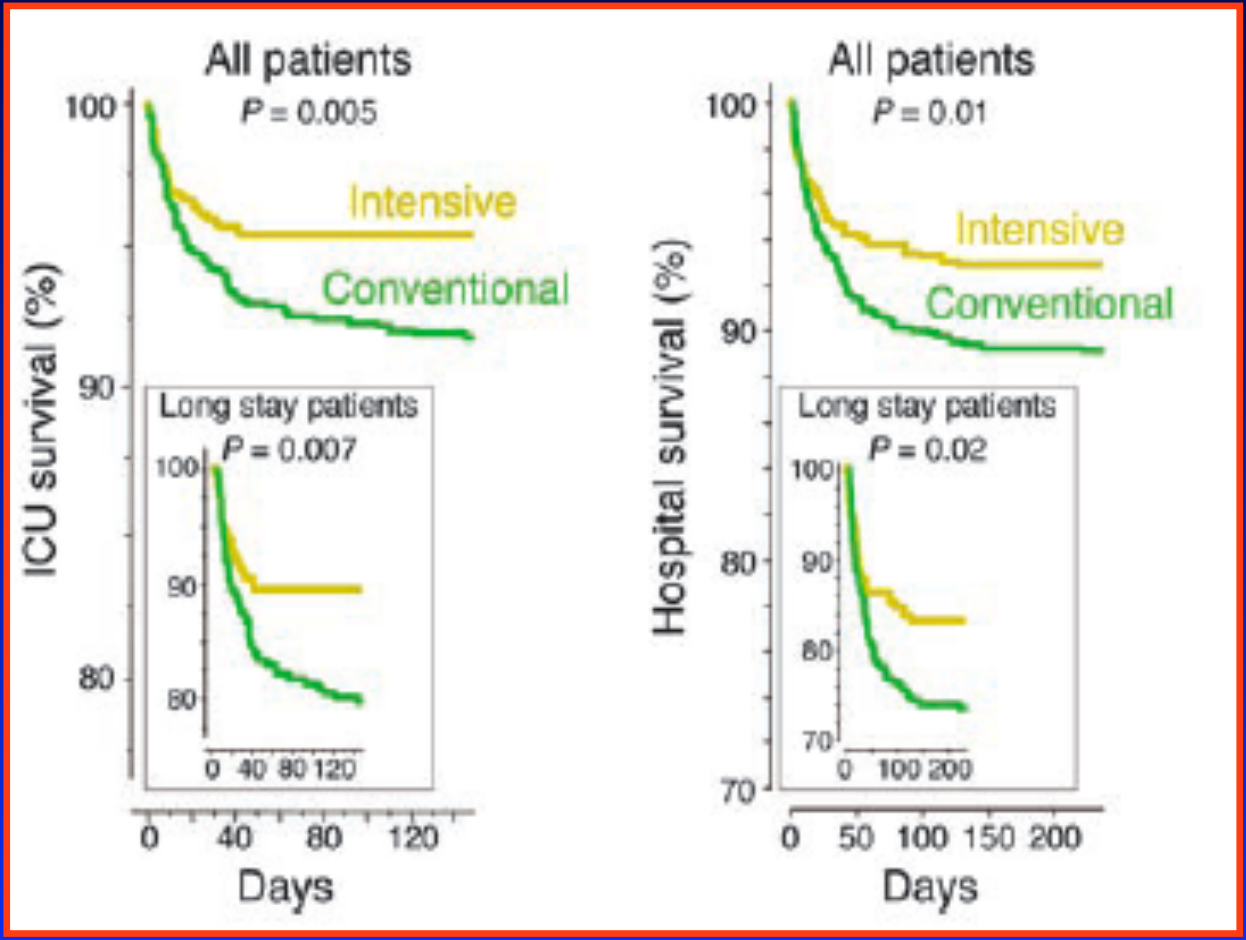
. **Année 2009** Finfer S et al N Engl J Med 2009;360:1283-97

Le retour du balancier: **il ne faut pas faire du contrôle glycémique chez les patients de réa**

CONTRÔLE GLYCÉMIQUE EN RÉA

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

Le début et l'enthousiasme



Patients chirurgicaux

Baisse de mortalité

4,6 vs 8,4%

(Van Den Berghe G *et al*, New Engl J Med 2001; 345 : 1359-67)

CONTRÔLE GLYCÉMIQUE EN RÉA

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

La controverse

Intensive Insulin Therapy in the Medical ICU

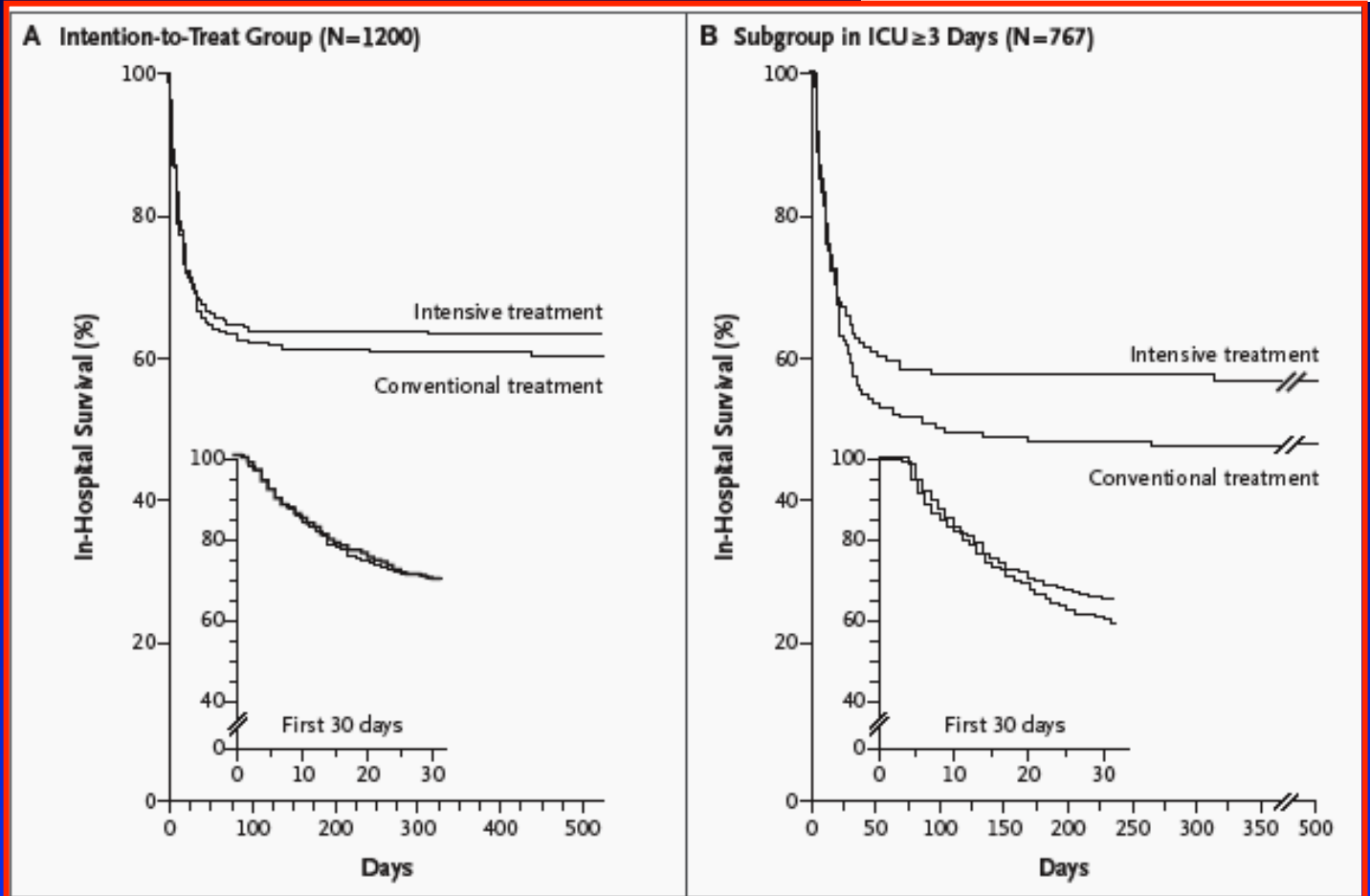


Figure 4. Kaplan–Meier Curves for In-Hospital Survival.

Patients médicaux

Pas de ≠ de mortalité

7,2 vs 10,9%

Van Den Berghe G *et al*, New Engl J Med 2006; 354 : 449-61

CONTRÔLE GLYCÉMIQUE EN RÉA

La controverse

Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

N Engl J Med 2008;358:125-39.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

Pas de ≠ de mortalité

39,7 vs 35,4%

Patients en sepsis sévère

Table 2. Primary and Secondary Outcomes.*

Variable	Insulin Therapy			
	All Patients (N=537)	Conventional (N=290)	Intensive (N=247)	P Value†
Death				
At 28 days§				0.74
No./total no.	136/536	75/289	61/247	
Percent (95% CI)	25.4 (21.7–29.1)	26.0 (20.9–31.0)	24.7 (19.3–30.1)	
At 90 days				0.31
No./total no.	200/535	102/288	98/247	
Percent (95% CI)	37.4 (33.3–41.5)	35.4 (29.9–40.9)	39.7 (33.6–45.8)	

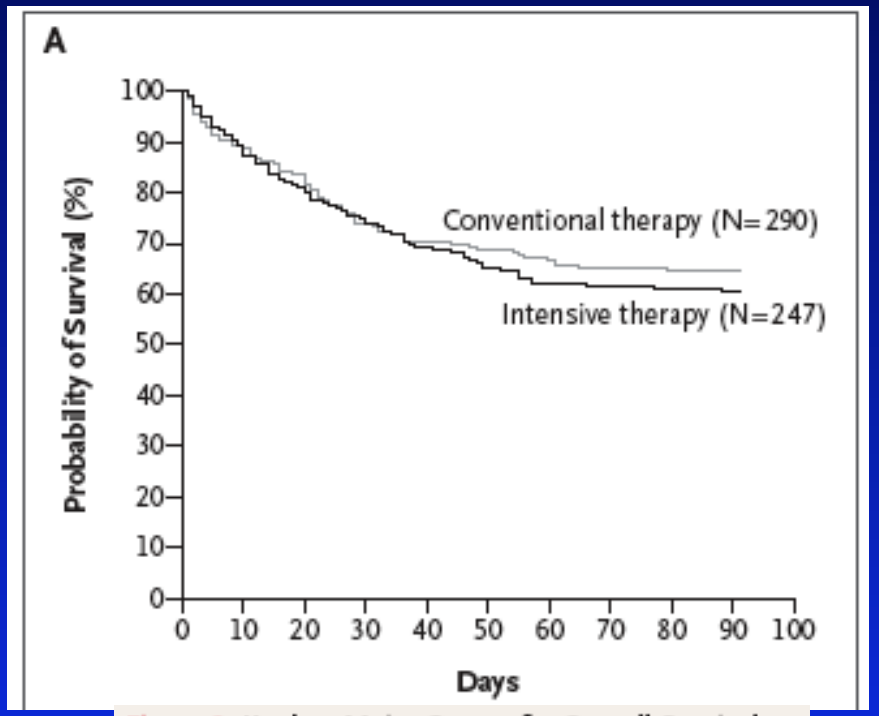


Figure 2. Kaplan–Meier Curves for Overall Survival.
Panel A shows the comparison of overall survival between patients receiving intensive insulin therapy and those receiving conventional insulin therapy (P=0.36

Brunkhorst F *et al*

CONTRÔLE GLYCÉMIQUE EN RÉA

La controverse

EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

GLUCONTROL

Preiser JC *et al* Intensive Care Med 2009;35:1738-48

Etude randomisée, multicentrique, investigateur aveugle
2 régimes d'insulinothérapie :

4.4 - 6.1 mmol/l (80 and 110 mg/dl) = Groupe A

7.8 - 10.0 mmol/l (140 and 180 mg/dl) = Groupe B

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 (%)	83 (15.3)	100 (18.7)	0.1438
Patients still in ICU at D28 (n):	33	34	
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)	5,433	5,090	
Hospital LOS (days) [median (IQR)]	16 (11–29)	16 (11–29)	0.708
Number of febrile days (patient days)	384	392	0.980
Mean SOFA score (during ICU stay) (mean ± SD)	5.9 ± 3.1	6.0 ± 2.9	0.583

CONTRÔLE GLYCÉMIQUE EN RÉA

Le retour du balancier

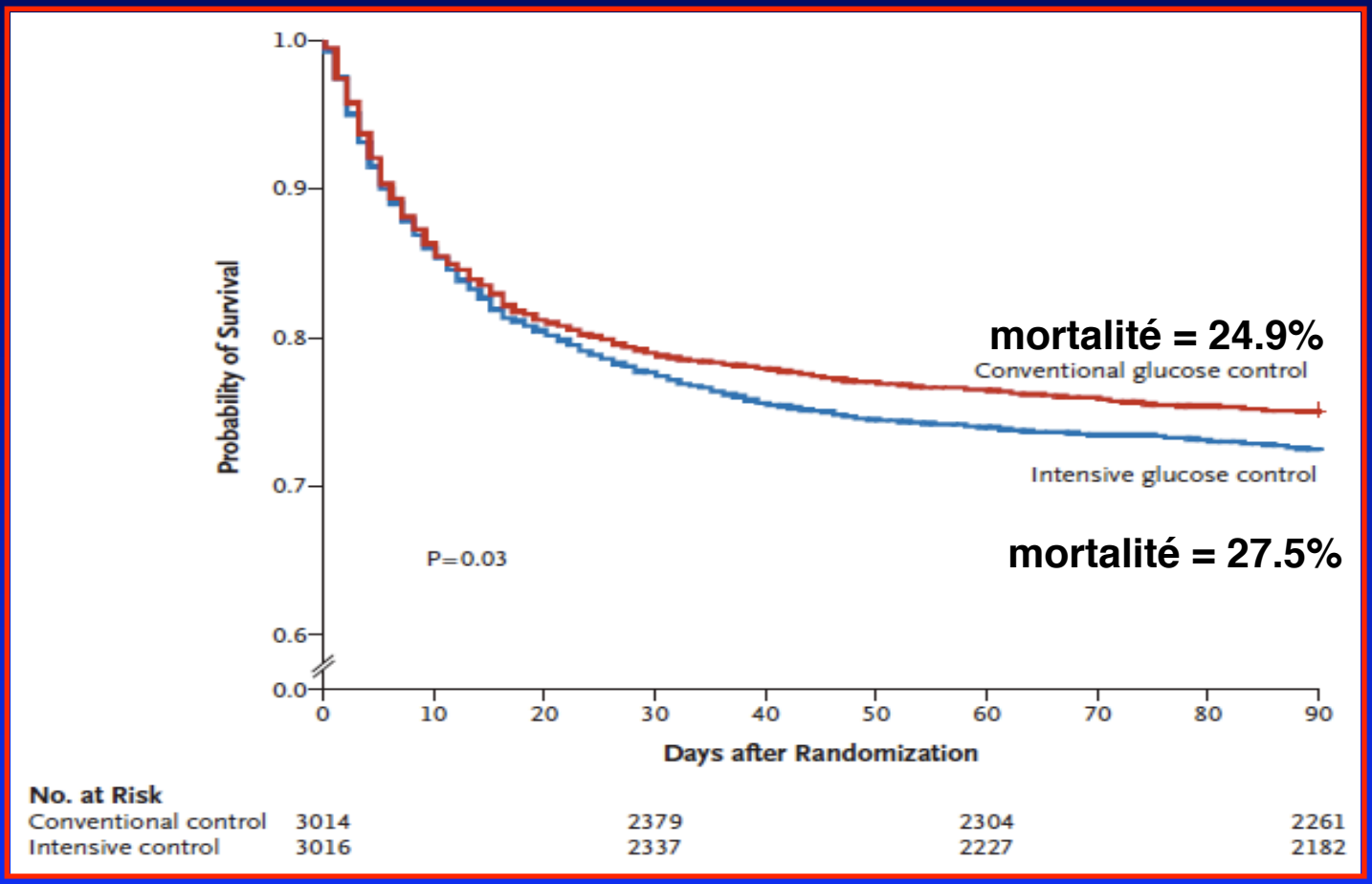
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED 1812 • ISSN 0028-4793 • WWW.NEJM.ORG

Finfer S *et al*, NICE-SUGAR

N Engl J Med 2009;360:1283-97



Patients mixtes

Surmortalité 27,5 vs 24,9%

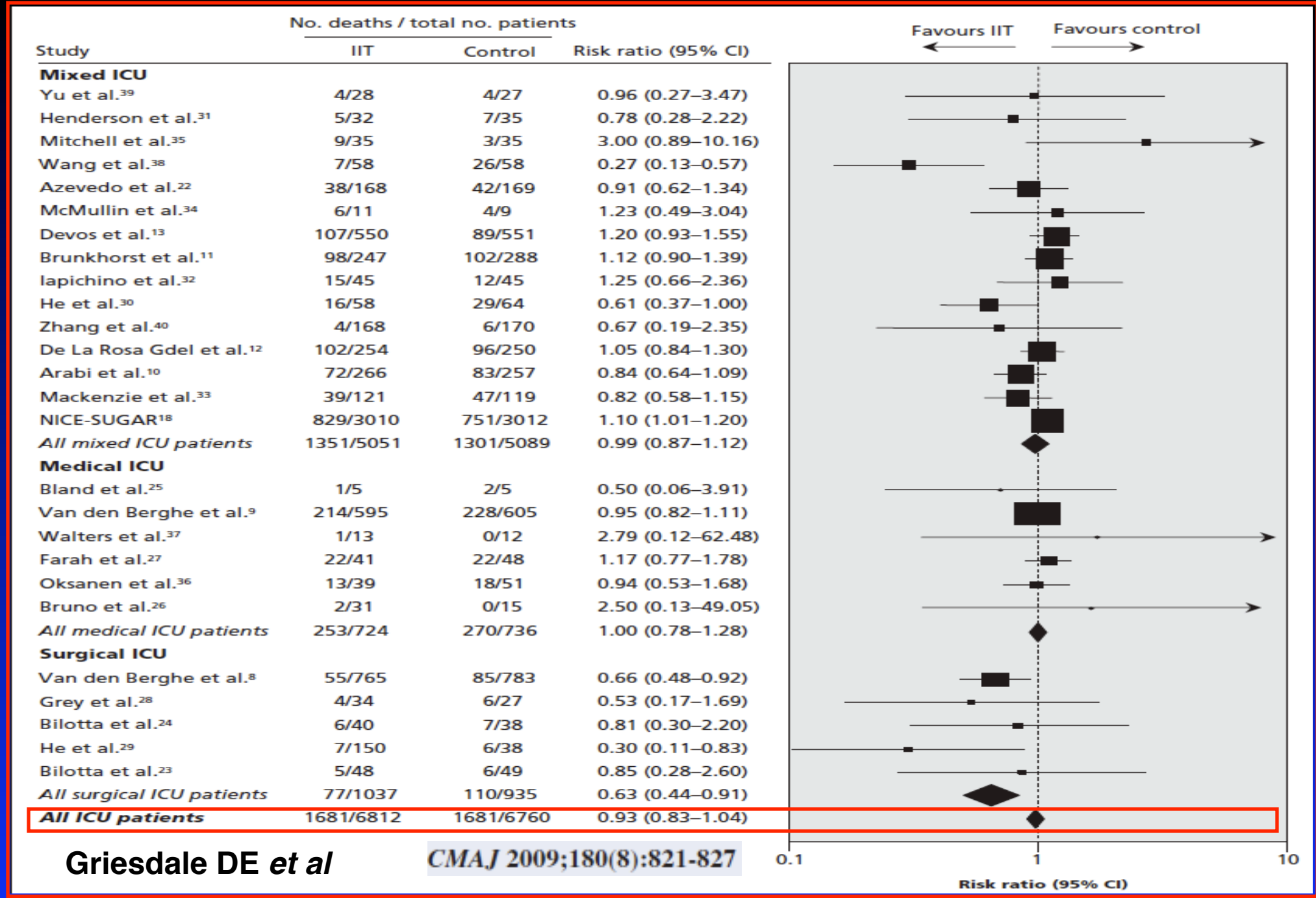
Pas de ≠ de morbidité

CONTRÔLE GLYCÉMIQUE EN RÉA

Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data

Griesdale DE *et al* *CMAJ* 2009;180(8):821-827

- 25 RCT (13567 patients)
- Objectif = mortalité à 90 j, puis 28 j puis en réa
- Hypoglycémie = < 2.2 mmol/l
- Inclut NICE-SUGAR



Griesdale DE *et al*

CMAJ 2009;180(8):821-827

CONTRÔLE GLYCÉMIQUE EN RÉA

International recommendations for glucose control in adult non diabetic critically ill patients

Critical Care 2010, **14**:R166 doi:10.1186/cc9258

Carole Ichai (ichai@unice.fr)
Jean-Charles Preiser (Jean-Charles.Preiser@erasme.ulb.ac.be)

Recommendations	Strength of agreement
Glucose target in ICUs	
. We **strongly suggest** to avoid severe hyperglycemia (> 10 mmol/L - 180 mg/dL) in adult ICU patients. We **suggest** to keep glucose levels under control although a universally acceptable upper limit cannot be specified.	Strong agreement
. We **suggest** to avoid tight glucose control in an emergency situation as this management seems to be not reasonable and potentially dangerous.	Strong agreement
. We **strongly suggest** to avoid large variations in glucose levels in ICUs.	Strong agreement
. We **do not recommend** to use any drug other than intravenous insulin for glucose control in ICUs.	Weak agreement

SFAR

Société de Réanimation de Langue Française

CONTRÔLE GLYCÉMIQUE EN RÉA

Facile : une cible glycémique universelle

Depuis 2009

Difficile et complexe

. Les objectifs = 3 domaines du contrôle (cible, hypoglyc, variab)

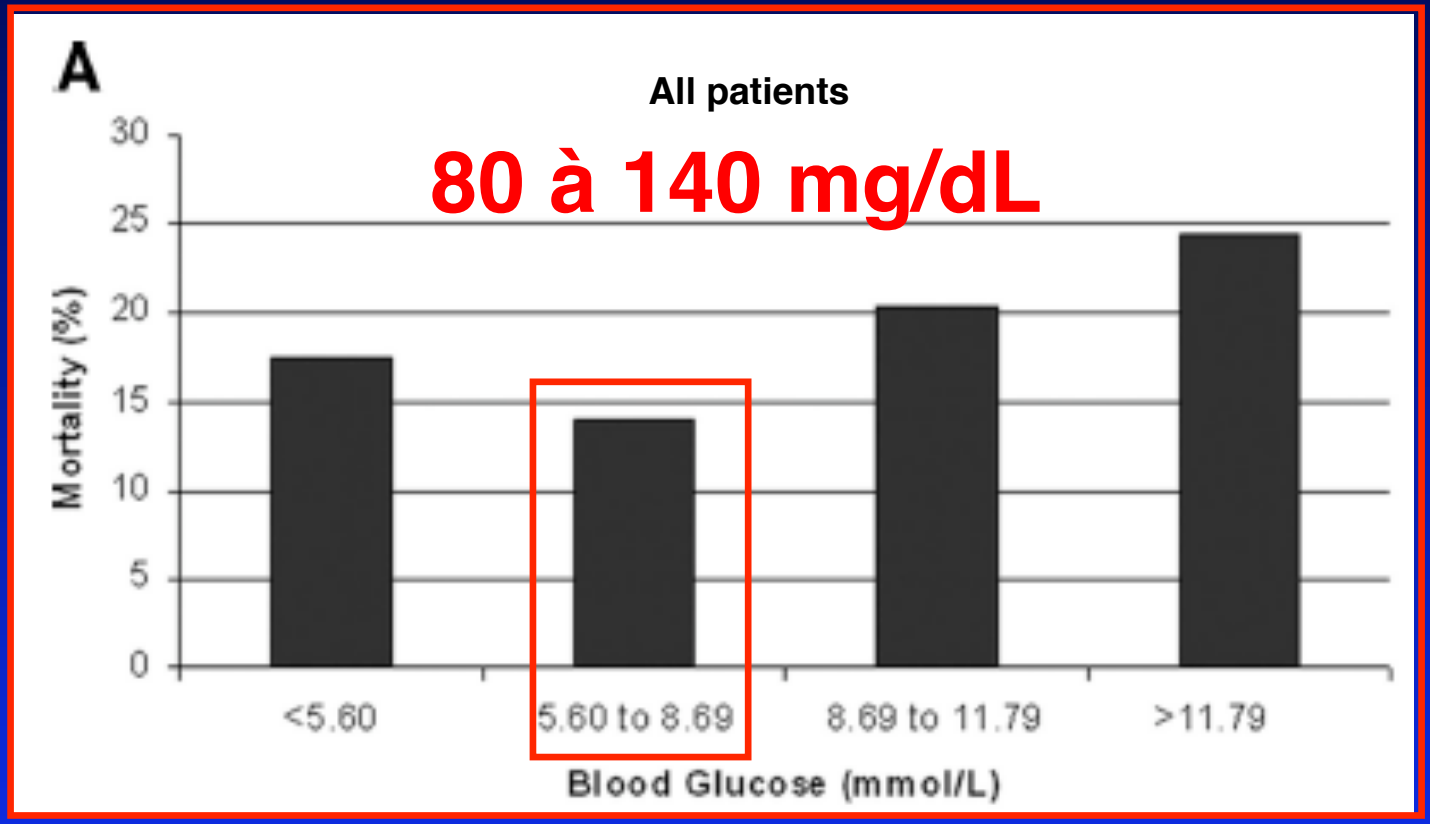
. Les patients : hyperglyc ß (diabète) vs hyperglyc de stress, le cérébrolésé, sepsis

. Les mesures : technique, délai, fiabilité

LA CIBLE

Early blood glucose control and mortality in critically ill patients in Australia*

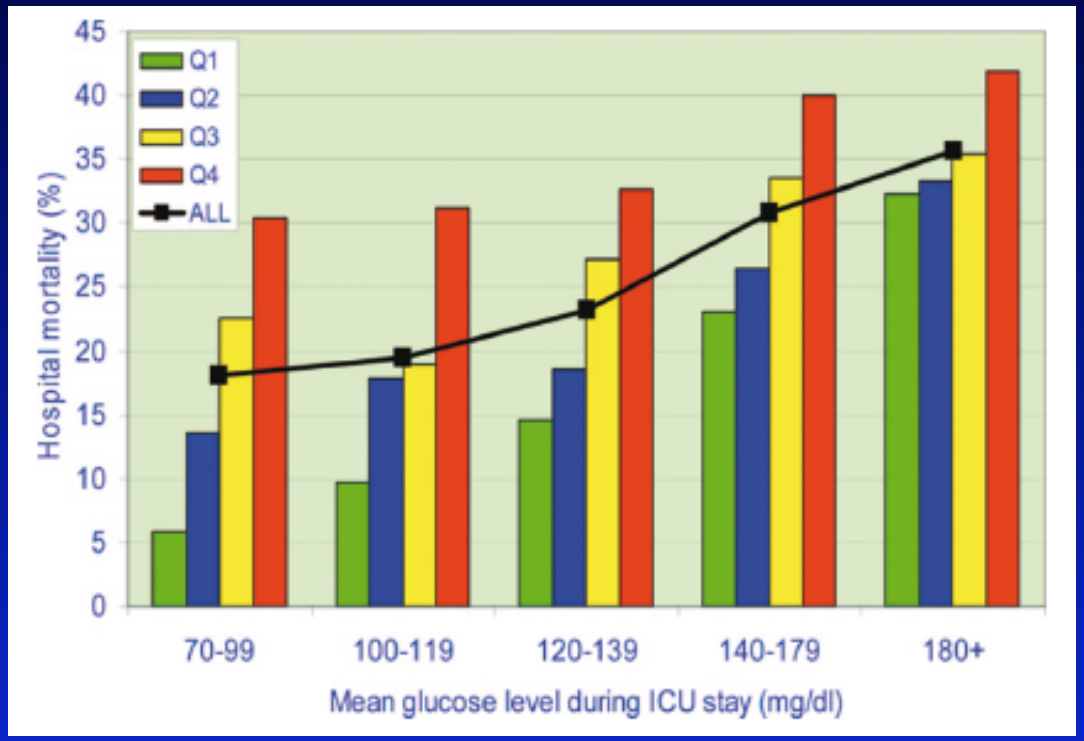
Retrospective , 66 184 patients (2000-2005)



Bagshaw SR et al, Crit Care Med 2009;37:463-73

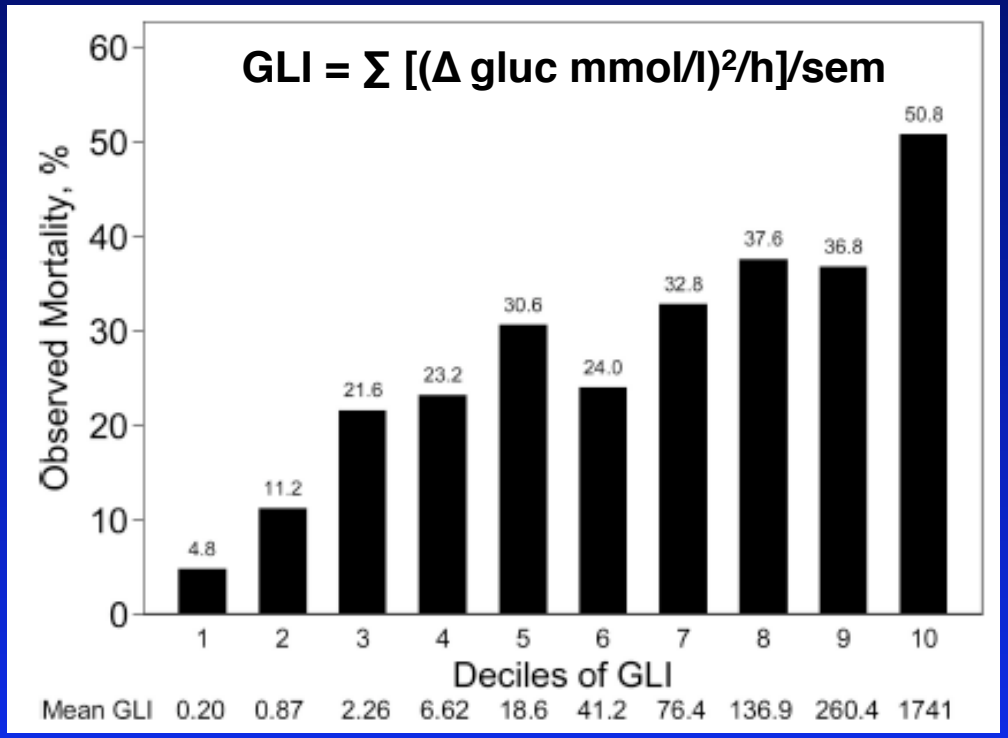
LA VARIABILITÉ GLYCÉMIQUE

Krinsley JS *et al* Crit Care Med 2008; 36:3008-13



3252 patients (69% médicaux)

1246 patients en sepsis



Ali NA *et al* Crit Care Med 2008; 36:2316-21

LA VARIABILITÉ GLYCÉMIQUE

Glucose variability is associated with intensive care unit mortality*

Jeroen Hermanides, MD; Titia M. Vriesendorp, MD, PhD; Robert J. Bosman, MD, PhD; Durk F. Zandstra, MD, PhD; Joost B. Hoekstra, MD, PhD; J. Hans DeVries, MD, PhD

Crit Care Med 2010 Vol. 38, No. 3

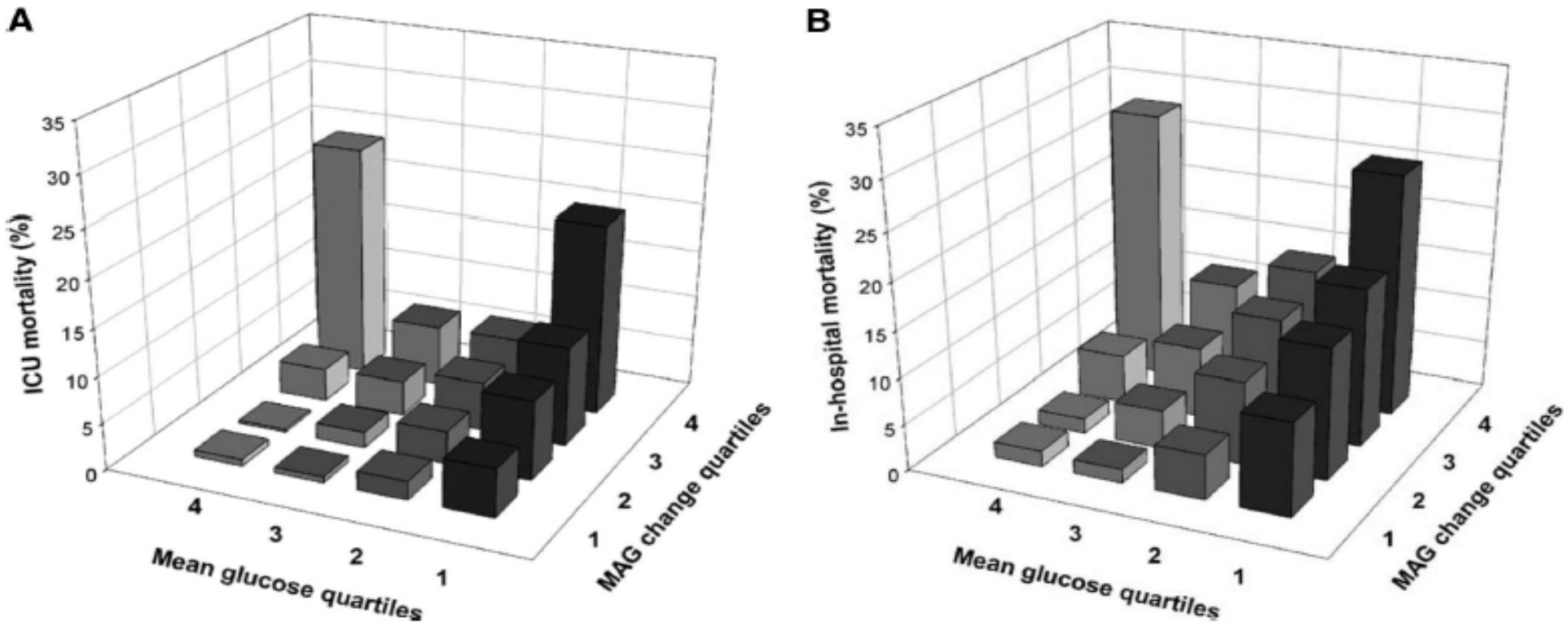


Figure 2. *A*, Intensive care unit mortality (%). *B*, In-hospital mortality (%). All mortality rates were calculated per quartiles of mean absolute glucose change (*MAG*) divided by quartiles of mean glucose.

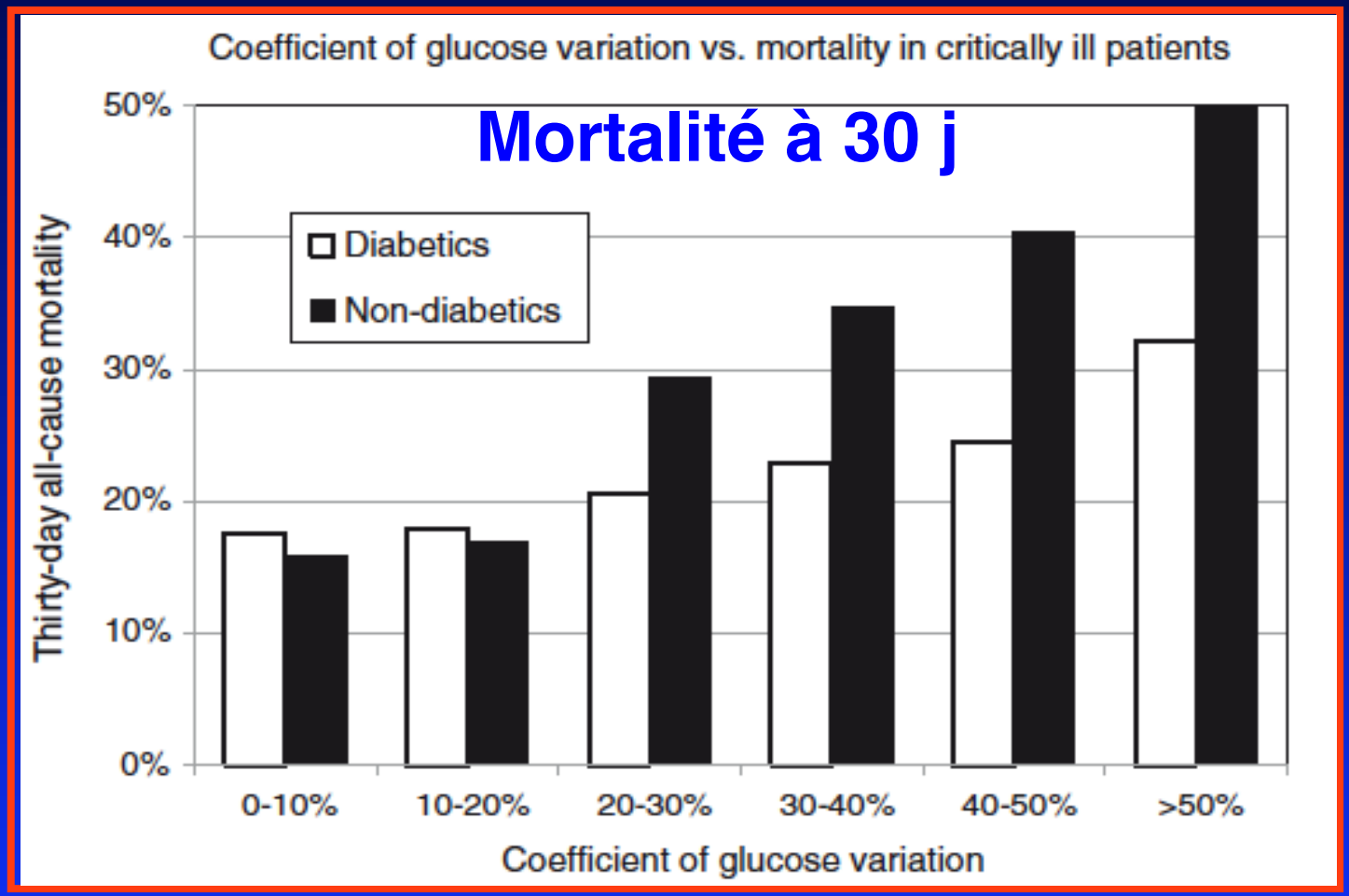
LA VARIABILITÉ GLYCÉMIQUE

Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin

Lanspa MJ et al Crit Care 2014;18:R86

6101 patients

CV associée à une mortalité + importante chez les non diabétiques surtout avec ajustement sur gravité, âge, hypogly…



LA VARIABILITÉ GLYCÉMIQUE

Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin

Lanspa MJ et al Crit Care 2014;18:R86

	Odds ratio (95% CI) (model 1)	*P*-value (model 1)	Odds ratio (95% CI) (model 2)	value (model 2)
Diabetic patients (n = 2,847)				
Age (decade)	1.29 (1.19, 1.40)	<0.001		0.001
Charlson score	1.25 (1.14, 1.37)			001
Acute physiology score	1.12 (1.09			<0.001
Hypoglycemia			, 1.61)	0.020
Interaction of Charlson and acute physiolo			0.99 (0.99, 1.00)	0.018
Coefficient of variation (10%)			1.15 (1.06, 1.24)	0.001
Non-diabetic pati				
Age (d	(1.08, 1.21)	<0.001	1.13 (1.07, 1.20)	<0.001
Charlsc	1.31 (1.20, 1.43)	<0.001	1.30 (1.18, 1.42)	<0.001
Acute pl	1.09 (1.07, 1.11)	<0.001	1.08 (1.06, 1.10)	<0.001
Hypoglyce	1.65 (1.36, 2.01)	<0.001	1.35 (1.10, 1.66)	0.004
Interaction of Charlson and acute physiology scores	0.99 (0.99, 1.00)	0.001	0.99 (0.99, 1.00)	0.003
Coefficient of variation (10%)			1.37 (1.25, 1.50)	<0.001

CV associée à une mortalité + importante chez les non diabétiques surtout avec ajustement sur gravité, âge, hypoglycémie…

LES PATIENTS : LE DIABÉTIQUE

Blood glucose concentration and outcome of critical illness: The impact of diabetes*

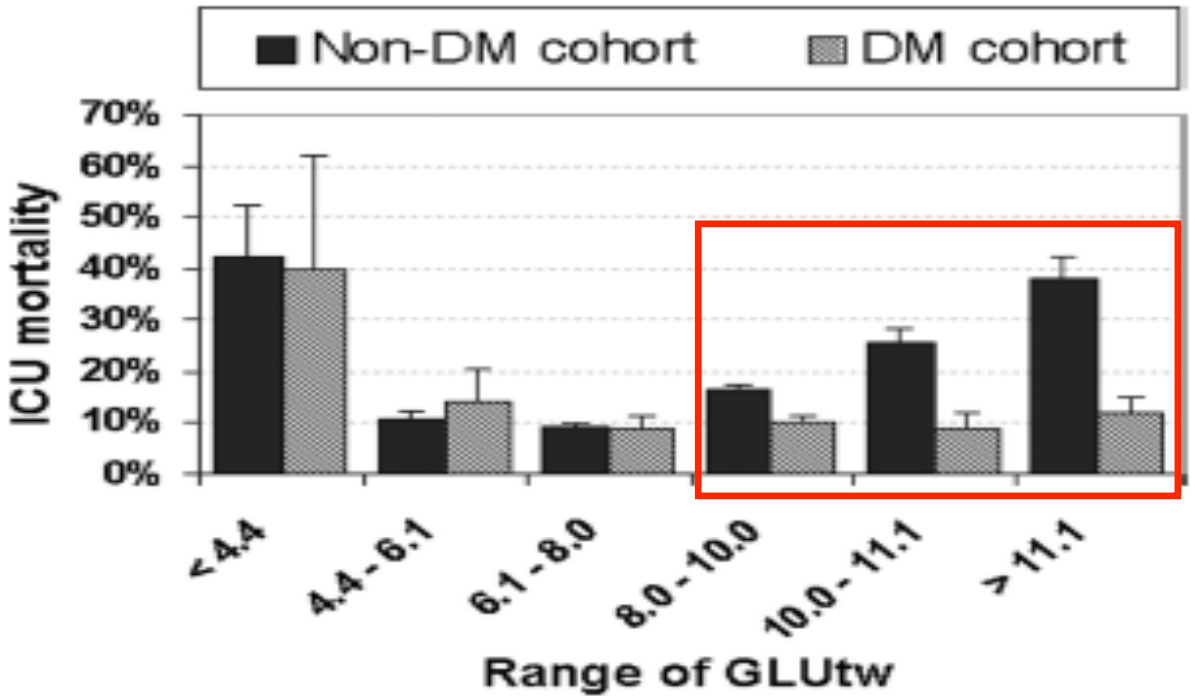


Figure 4. Intensive care unit mortality according to glucose categories. The bars indicate the intensive care unit mortality of different glucose categories based on time-weighted blood glucose levels. *DM*, diabetes mellitus; Glu_{Tw}, time-weighted glucose measurements.

Egi M et al Crit Care Med 2008;36:2249-55

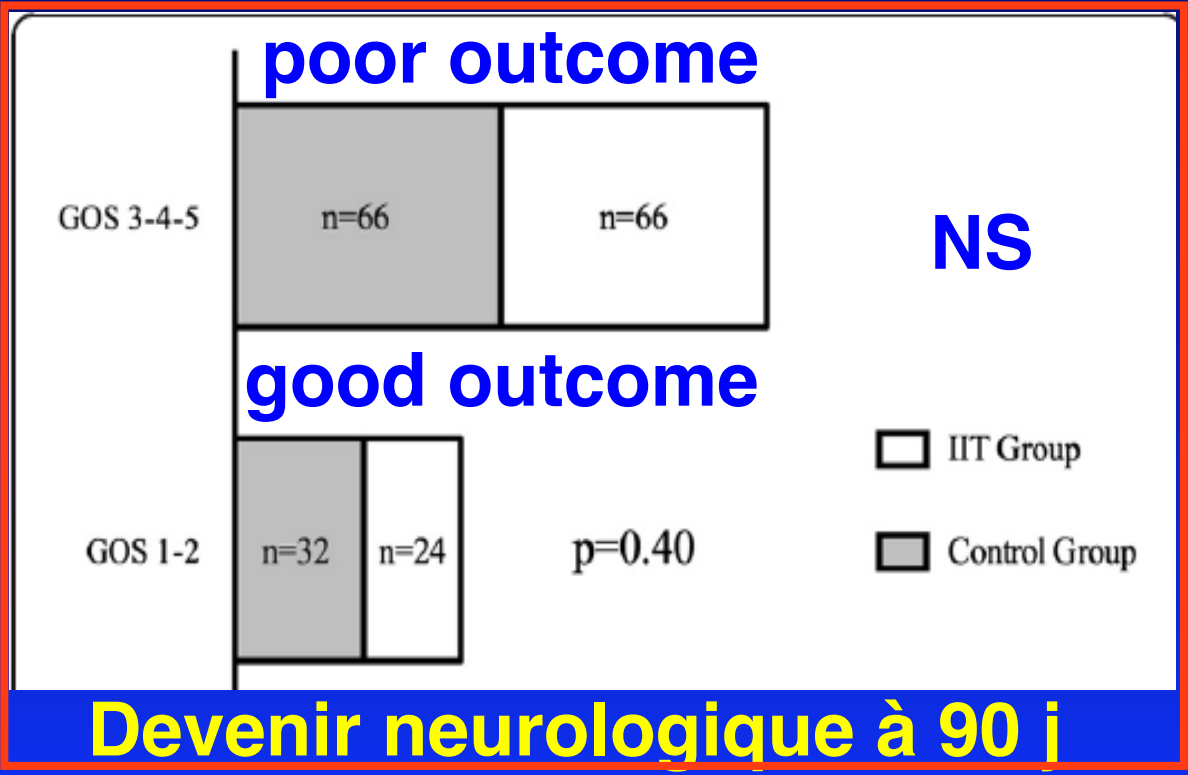
LES PATIENTS : LE CÉRÉBROLÉSÉ

Effects of tight computerized glucose control on neurological outcome in severely brain injured patients: a multicenter sub-group analysis of the randomized-controlled open-label CGAO-REA study

Cinotti *et al. Critical Care* 2014, **18**:498

Etude randomisée CGAO

188 pts cérébrolésés



Devenir neurologique à 90 j

Figure 1 Day 90 neurological outcome following ICU admission. The figure represents the day-90 neurological outcome after ICU admission in severely brain-injured patients in the control group (blood glucose range between 5.5 and 9 mmol.L^{-1}) and the intensive insulin therapy (IIT) group (blood glucose range between 4.4 and 6 mmol.L^{-1}). Good neurological outcome is classified as a Glasgow outcome scale (GOS) score of 1 to 2 (good recovery, moderate disability). Poor neurological outcome is classified as a GOS score of 3, 4 or 5 (severe disability, vegetative state, death). χ^2 test.

IIT = 4.4-6 mmol/L

Contrôle = 5.5-9 mmol/L

LES PATIENTS : LE CÉRÉBROLÉSÉ

Cinotti *et al. Critical Care* 2014, **18**:498

Effects of tight computerized glucose control on neurological outcome in severely brain injured patients: a multicenter sub-group analysis of the randomized-controlled open-label CGAO-REA study

Table 2 In-ICU blood glucose events

	Control group Number = 98	IIT group Number = 90	*P* value
Median of the first five days morning laboratory blood glucose ($mmol.l^{-1}$)	6.5 (5.6 to 7.2)	5.9 (5.1 to 6.7)	< 0.001[a]
Episodes of moderate hypoglycemia **<3.3 mmol/L**	19 (19.3)	46 (51.1)	< 0.001[b]
Episodes of severe hypoglycemia **<2.2 mmol/L**	4 (4)	6 (6.6)	0.50
Patients treated with insulin	81 (82.6)	87 (96.6)	0.002[b]
Total of insulin dose (IU) in the first five days	74 (13 to 165)	130 (68 to 251	0.01[a]

Etude randomisée CGAO

188 pts cérébrolésés

Table 3 Outcome of severely brain-injured patients

	Control group Number = 98	IIT group Number = 90	*P* value
Ventilation-free days	8.5 (0 to 22)	9 (0 to 20)	0.40
ICU-free days	8.5 (0 to 20)	8 (0 to 20)	0.50
Day-28 mortality	28 (28.6)	26 (28.9)	0.90
Day-28 good neurologic outcome	31 (31.6)	24 (26.6)	0.40

LES PATIENTS : LE CÉRÉBROLÉSÉ

Optimal glycemic control in neurocritical care patients: a systematic review and meta-analysis

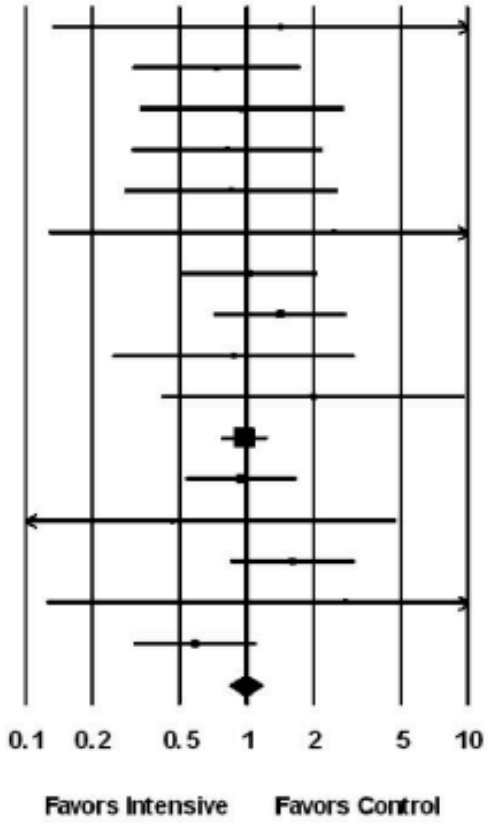
16 RCT, 1248 pts cérébrolésés

pas de ≠ de mortalité en réa

Kramer AH et al Crit Care 2012;16:R203

Mortalité en réa

Study name	Events / Total		Risk ratio	p-Value
	Intensive	Control		
Arabi 2008	2 / 55	1 / 39	1.42	0.77
Azevedo 2007	8 / 31	6 / 17	0.73	0.48
Azevedo 2009	4 / 14	6 / 20	0.95	0.93
Bilotta 2007	6 / 40	7 / 38	0.81	0.69
Bilotta 2008	5 / 48	6 / 49	0.85	0.78
Bruno 2008	2 / 31	0 / 15	2.50	0.55
Coester 2010	11 / 39	11 / 40	1.03	0.94
Green 2010	16 / 45	9 / 36	1.42	0.32
Johnston 2009	3 / 24	7 / 49	0.88	0.84
Kreisel 2009	4 / 20	2 / 20	2.00	0.39
Meng 2009	61 / 117	62 / 116	0.98	0.84
Oksanen 2007	13 / 39	18 / 51	0.94	0.85
Staszewski 2011	1 / 26	2 / 24	0.46	0.52
van den Bergh 2005	16 / 33	9 / 30	1.62	0.15
Walters 2006	1 / 13	0 / 12	2.79	0.52
Yang 2009	15 / 75	12 / 35	0.58	0.10
	168 / 650	158 / 591	0.99	0.89



RR 0.99 [0.83-1.17, p = 0.89]

Tests for heterogeneity: I^2 = 0%; Q=8.7, p=0.89

LES PATIENTS : LE CÉRÉBROLÉSÉ

Optimal glycemic control in neurocritical care patients: a systematic review and meta-analysis

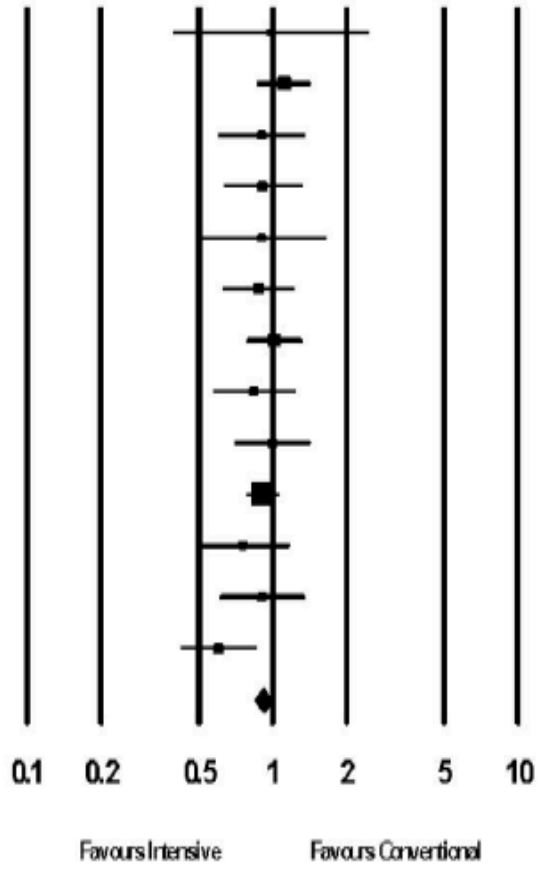
Kramer AH et al Crit Care 2012;16:R203

16 RCT, 1248 pts cérébrolésés

Moins de mauvais devenir neurologique, mais si comparaison avec glyc > 2 g/L

Mauvais devenir neurol

Study name	Events / Total		Risk ratio	p-Value
	Intensive	Control		
Azevedo 2007	9 / 31	5 / 17	0.99	0.98
Azevedo 2009	13 / 14	15 / 18	1.11	0.40
Bilotta 2007	21 / 40	22 / 38	0.91	0.63
Bilotta 2008	25 / 48	28 / 49	0.91	0.62
Bruno 2008	15 / 31	8 / 15	0.91	0.75
Coester 2010	23 / 39	27 / 40	0.87	0.43
Green 2010	32 / 42	24 / 32	1.02	0.91
Johnston 2009	14 / 24	34 / 49	0.84	0.38
Kreisel 2009	15 / 20	15 / 20	1.00	1.00
Meng 2009	83 / 117	90 / 116	0.91	0.25
Staszewski 2011	14 / 26	17 / 24	0.76	0.22
van den Bergh 2005	19 / 33	19 / 30	0.91	0.64
Yang 2009	31 / 75	24 / 35	0.60	0.00
	314 / 540	328 / 483	0.91	0.04



RR 0.91 [0.84-1.00, p = 0.04]

LES PATIENTS : LE CÉRÉBROLÉSÉ

Optimal glycemic control in neurocritical care patients

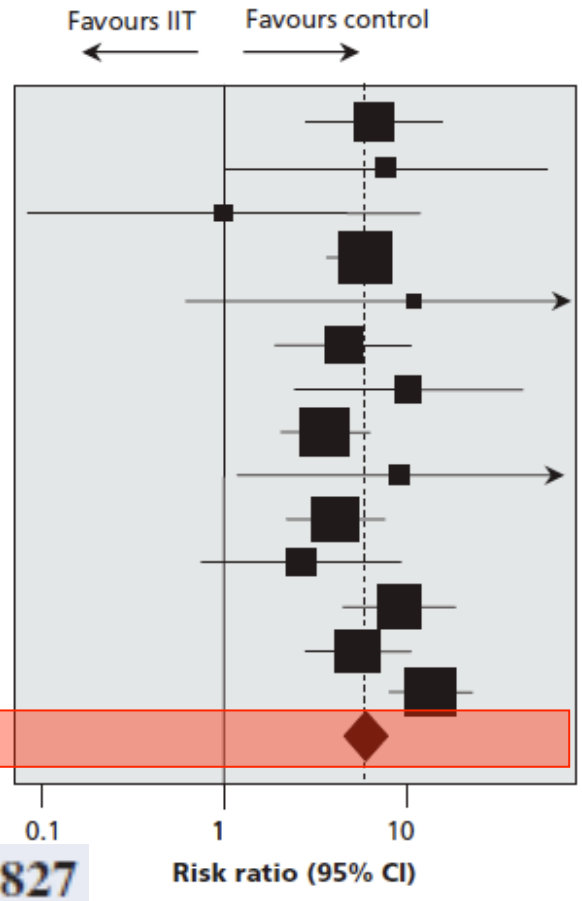
Billota F et al Crit Care 2012;16:163

In accordance with the conclusions of Kramer and colleagues, we recommend that insulin infusion for glucose control in NCC patients be aimed at a 'moderate' target range (110 to 180 mg/dL). In addition, we would recommend an adequate nutrition support of NCC patients before and during insulin infusion, the avoidance of insulin boluses, and the use of continuous insulin infusions initially at low dose, titrated to individual sensitivity with the application of a standardized and easily applied glycemic monitoring protocol.

LES HYPOGLYCÉMIES

Le contrôle glycémique ↗ les hypoglycémies

Study	No. events / total no. patients: IIT	Control	Risk ratio (95% CI)
Van den Berghe et al.[8]	39/765	6/783	6.65 (2.83–15.62)
Henderson et al.[31]	7/32	1/35	7.66 (1.00–58.86)
Bland et al.[25]	1/5	1/5	1.00 (0.08–11.93)
Van den Berghe et al[9]	111/595	19/605	5.94 (3.70–9.54)
Mitchell et al.[35]	5/35	0/35	11.00 (0.63–191.69)
Azevedo et al.[22]	27/168	6/169	4.53 (1.92–10.68)
De La Rosa Gdel et al.[12]	21/254	2/250	10.33 (2.45–43.61)
Devos et al.[13]	54/550	15/551	3.61 (2.06–6.31)
Oksanen et al.[36]	7/39	1/51	9.15 (1.17–71.35)
Brunkhorst et al.[11]	42/247	12/290	4.11 (2.21–7.63)
Iapichino et al.[32]	8/45	3/45	2.67 (0.76–9.41)
Arabi et al.[10]	76/266	8/257	9.18 (4.52–18.63)
Mackenzie et al.[33]	50/121	9/119	5.46 (2.82–10.60)
NICE-SUGAR[18]	206/3016	15/3014	13.72 (8.15–23.12)
Overall	654/6138	98/6209	5.99 (4.47–8.03)



Griesdale DE et al *CMAJ 2009;180(8):821-827*

Figure 3: Risk ratios of hypoglycemic events in clinical trials comparing intensive insulin therapy (IIT) to conventional glycemic control. The dashed vertical line represents the pooled estimate. There was significant heterogeneity between trials (Q statistic = 20.71, p = 0.08, I^2 statistic = 37.0%. Note: CI = confidence interval.

LES HYPOGLYCÉMIES

Fréquence

Facteurs de risque de survenue d'hypoglycémie

Hypoglycemia with intensive insulin therapy in critically ill patients: Predisposing factors and association with mortality*

Arabi YM *et al* Crit Care Med 2009; 37: 2536-44

Table 3. Independent predictors of hypoglycemia

Predictors	Adjusted Odds Ratio	95% Confidence Interval	*p*
Intensive insulin therapy	50.65	17.36, 147.78	<.0001
Female gender	2.04	1.02, 4.07	.04
Diabetes	4.41	2.28, 8.50	<.0001
BMI (for each 1-point increase)	0.94	0.89, 0.98	.004
APACHE II score (for each 1-point increase)	1.05	1.01, 1.10	.01
Mechanical ventilation	3.17	1.10, 9.13	.03
Received CVV	2.77	1.18, 6.46	.02
Received HD	0.39	0.13, 1.19	.10
ICU LOS (for each 1-day increase)	1.09	1.06, 1.12	<.0001

Sujet âgé
Arrêt de la nutrition
Insuffisance rénale
Insuffisance hépatique
Beta-bloquants

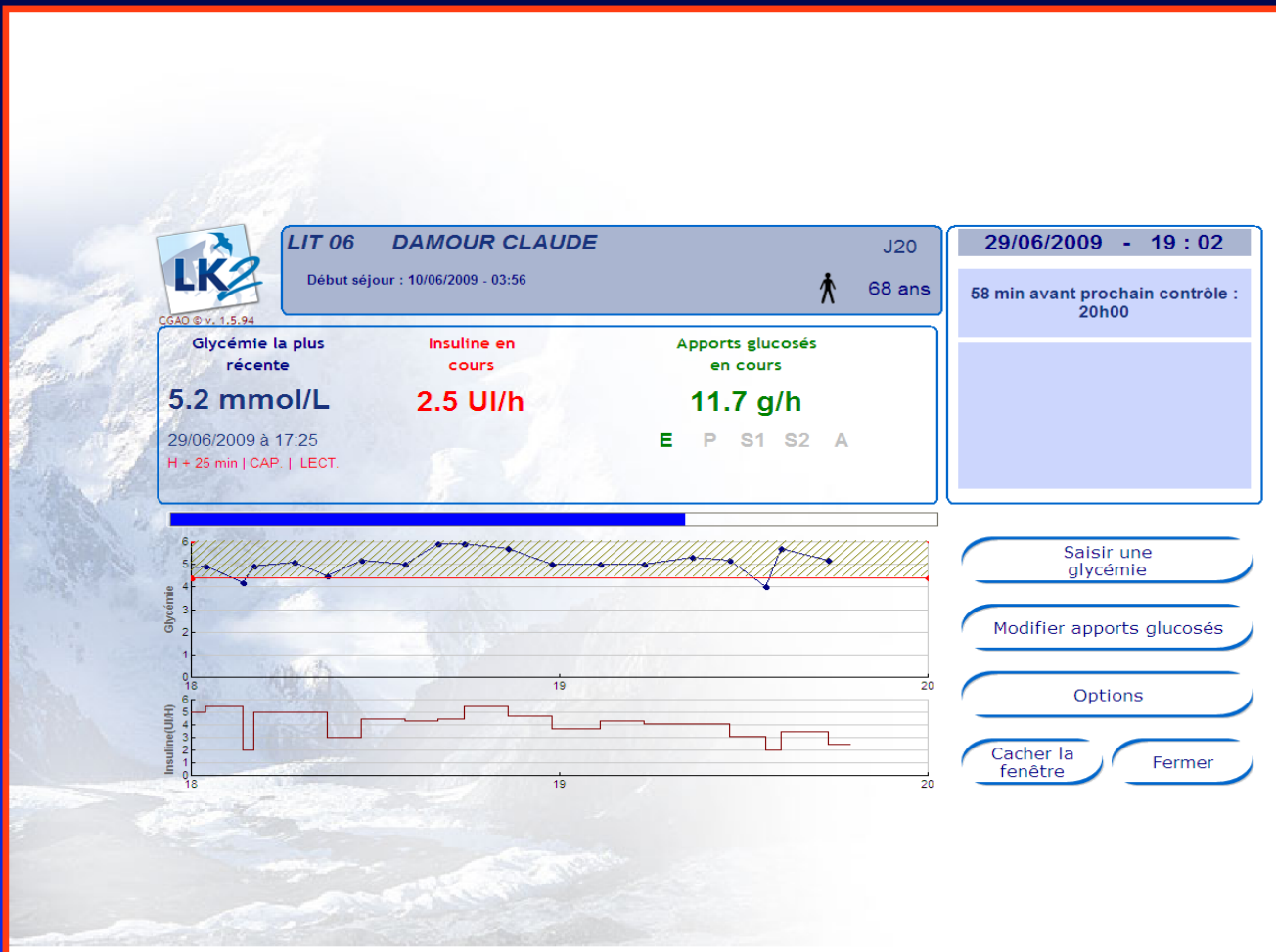
Vriesendorp TM et al Crit Care Med 2006; 34:96-104

LES HYPOGLYCÉMIES

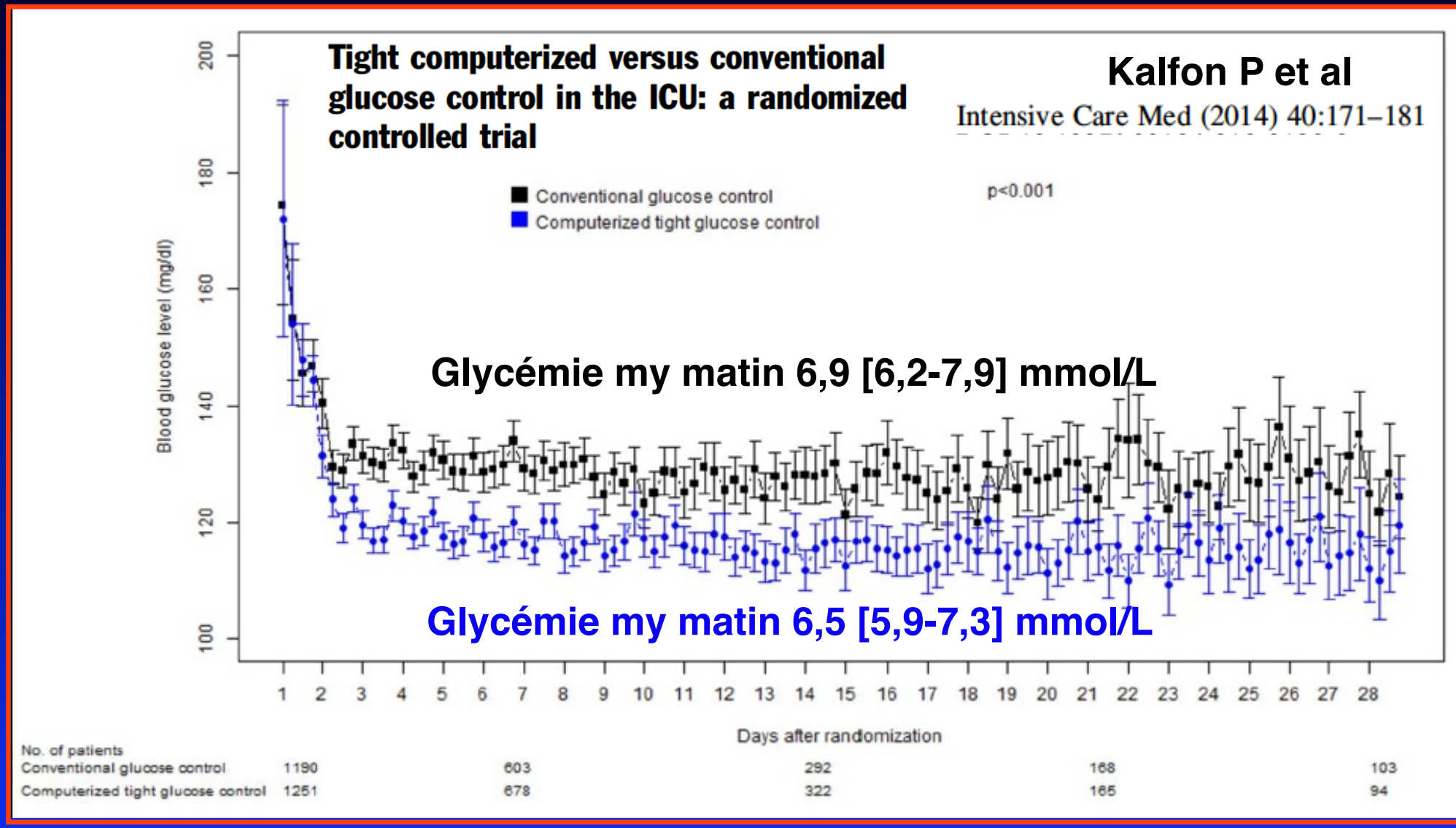
Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial

Kalfon P et al Intensive Care Med (2014) 40:171–181

RCT 2684 pts avec DDS > 3 j en réa randomisés : computerized decision-support system (CGAO) = contrôle strict glycémique vs contrôle habituel



LES HYPOGLYCÉMIES



LES HYPOGLYCÉMIES

Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial

Kalfon P et al

Intensive Care Med (2014) 40:171–181

Management strategy	TGC (n = 1,336)	CGC (n = 1,312)	p
Patients with BG data, n (%)	1,317 (98.6)	1,284 (97.9)	
Morning laboratory BG, mmol/L; median (IQR)	6.5 (5.9; 7.3)	6.9 (6.2; 7.9)	<0.001
Mean bedside BG, mmol/L; median (IQR)	6.4 (6.0; 7.1)	7.0 (6.3; 7.9)	<0.001
Standard deviation of bedside BG, mmol/L; median (IQR)	1.6 (1.2; 2.3)	1.6 (1.2; 2.2)	0.17
Minimal BG, mmol/L; median (IQR)	3.2 (2.6; 3.9)	3.9 (3.2; 4.8)	<0.001
Interval between 2 measures, min; median (IQR)	139 (120; 161)	175 (141; 210)	<0.001
Severe hypoglycemia, n (%)[a]	174/1,317 (13.2)	79/1,284 (6.2)	<0.001
Moderate hypoglycemia, n (%)[a]	743/1,317 (56.4)	384/1,284 (29.9)	<0.001
Treated with insulin, n (%)[b]	1,239/1,314 (94.3)	1,052/1,290 (81.6)	<0.001
Daily insulin dose, IU[c]; median (IQR)	43.1 (24.5; 70.0)	34.1 (17.9; 58.3)	<0.001

Table 2 Blood glucose management, according to treatment group

LES HYPOGLYCÉMIES

Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial

	TGC (n = 1,336)	CGC (n = 1,312)	p value
Death: no. of patients/total no. (%)			
At day 90	431/1,336 (32.3 %)	447/1,312 (34.1 %)	0.32
At day 28	326/1,336 (24.4 %)	328/1,312 (25.0 %)	0.72
In ICU	302/1,336 (22.6 %)	310/1,312 (23.6 %)	0.53
In hospital	376/1,336 (28.1 %)	393/1,312 (30.0 %)	0.30
SOFA[a]			0.048
Day 1: median (IQR)	8 (5–11) (n = 1,287)	8 (5–11) (n = 1,264)	
Day 3: median (IQR)	7 (3–10) (n = 1,210)	6 (3–10) (n = 1,164)	
Day 7: median (IQR)	5 (3–8) (n = 826)	5 (2–9) (n = 751)	
Day 14: median (IQR)	4 (2–7) (n = 448)	4 (2–7) (n = 420)	
28-day-ICU-free days: median (IQR)	14 (0–22)	13 (0–23)	0.98
28-day-hospital-free days: median (IQR)	0 (0–11.5)	0 (0–11)	0.41
28-day-ventilator-free days: median (IQR)	18 (0–25)	18 (0–25)	0.82
28-day-free-of-catecholamines days: median (IQR)	24 (0–28)	24 (0–28)	0.48
28-day life-support-free-days: median (IQR)	16 (0–24)	17 (0–24)	0.86
Days with antibiotics in ICU: median (IQR)	3 (3–11)	6 (2–11)	0.22
Bacteremia: no. of patients/total no. (%)	183/1,335 (13.7 %)	172/1,311 (13.1 %)	0.66
Tracheotomy: no. of patients/total no. (%)	144/1,335 (10.8 %)	135/1,311 (10.3 %)	0.68
Transfusion of red cells: no. of patients/total no. (%)	440/1,272 (34.6 %)	452/1,234 (36.6 %)	0.29
Units of packed red cells: median (IQR)	4 (2–6)	4 (2–8)	0.19

Kalfon P et al

Intensive Care Med (2014) 40:171–181

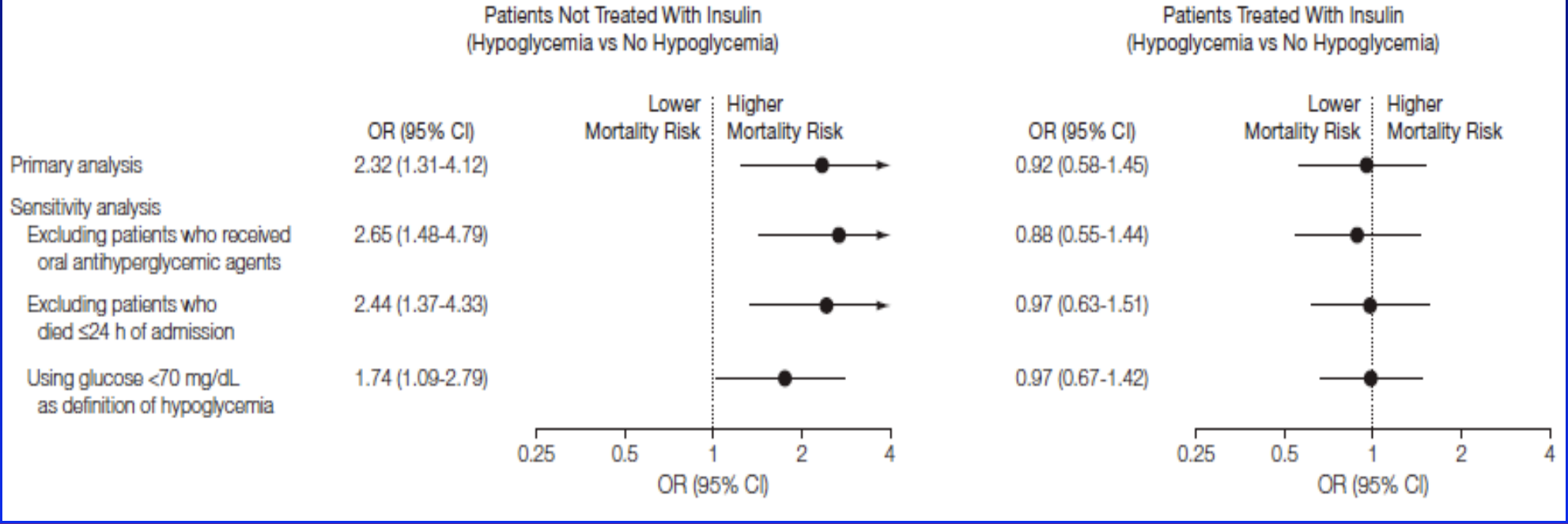
LES HYPOGLYCÉMIES

Quel danger de l'hypoglycémie en réa?

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

Kosiborod M *et al* JAMA 2009; 301: 1556-64

Figure. Association Between Hypoglycemia and Mortality After Multivariable Adjustment



LES HYPOGLYCÉMIES

Impact des hypoglycémies?

. Chez le diabétique conscient

Atteintes neurologiques
non létales sauf si hypo
profonde et prolongée…..

. En réa ????

- Profondeur : seuil biologique arbitraire
- Durée, nombre, iatrogénie…

Association avec surmortalité mais
pas de preuve du lien de causalité

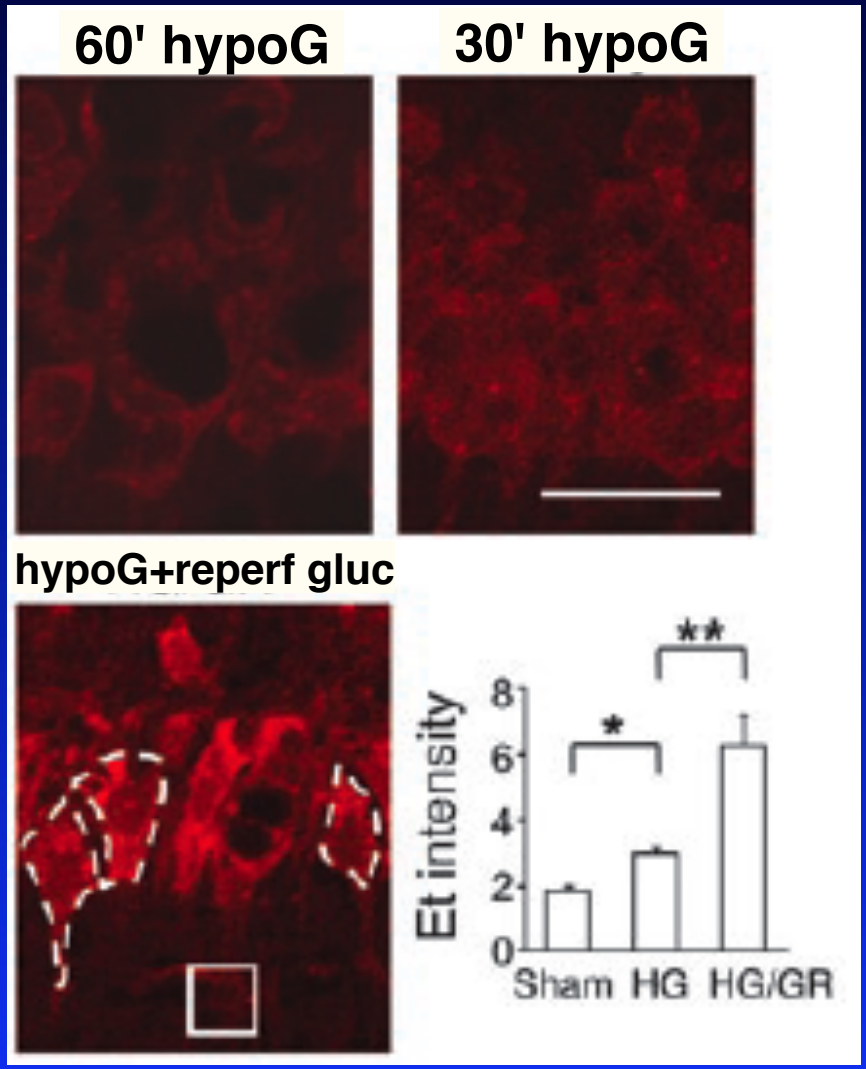
LES HYPOGLYCÉMIES

Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase

Suh SW *et al,* J Clin Invest 2007;17:910-8

Coupes hippocampales de rats : 60' d'hypoG sévère (EEG plat) vs 30' d'hypoG sévère (EEG) puis 30' de reperfusion avec du glucose

Et intensity = ethidium fluorescence = production de ROS



CONTRÔLE GLYC = 3 DOMAINES

Available online http://ccforum.com/content/12/6/R139

Research

Open Access

A systematic review on quality indicators for tight glycaemic control in critically ill patients: need for an unambiguous indicator reference subset

Saeid Eslami[1], Nicolette F de Keizer[1], Evert de Jonge[2], Marcus J Schultz[2] and Ameen Abu-Hanna[1]

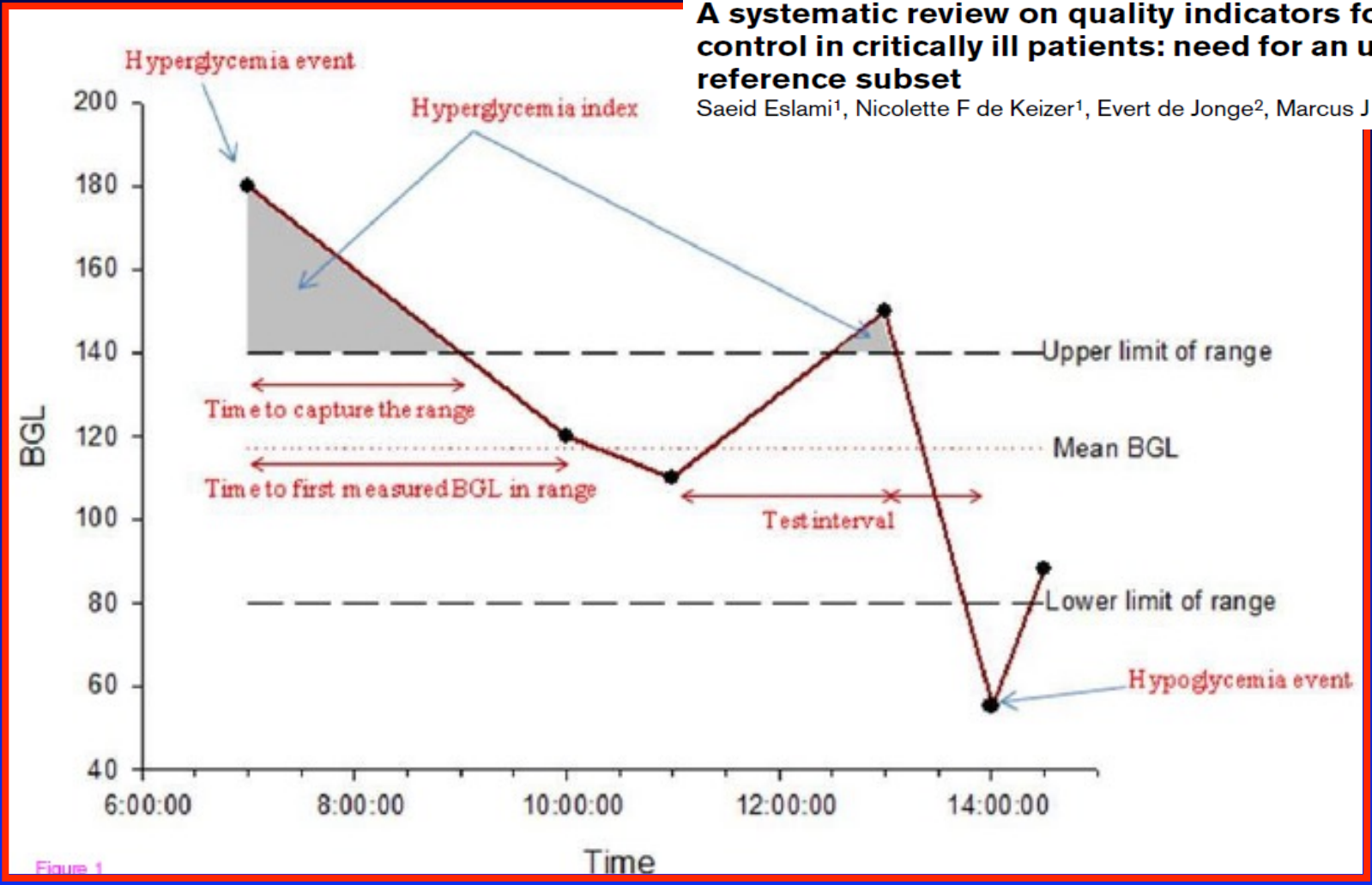


Figure 1

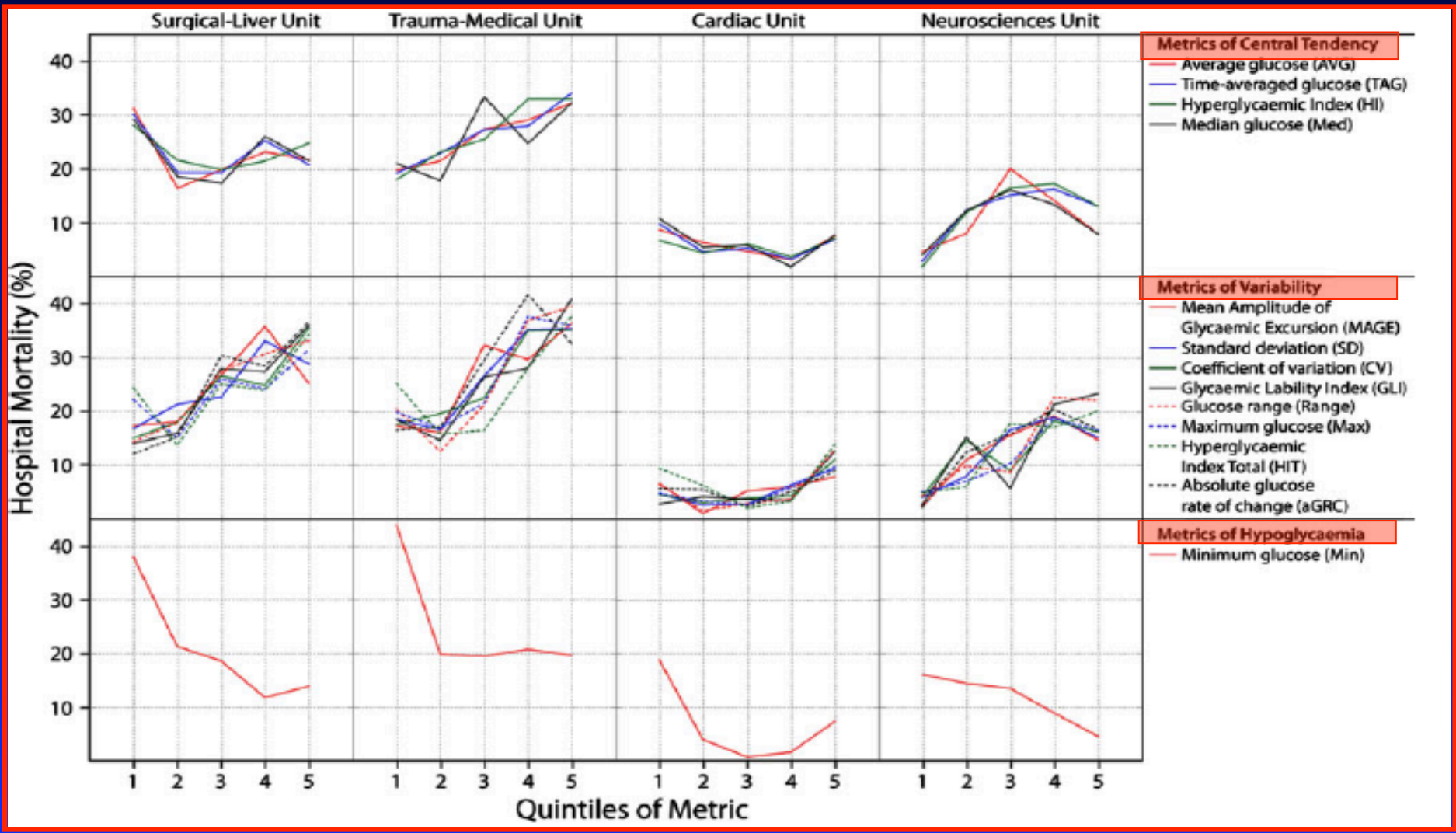
"Les metrics"

CONTRÔLE GLYC = 3 DOMAINES

The metrics of glycaemic control in critical care

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

Intensive Care Med
2011;37:435-43



CONTRÔLE GLYC = 3 DOMAINES

Moderate Glucose Control Is Associated With Increased Mortality Compared With Tight Glucose Control in Critically Ill Patients Without Diabetes

Diabétique vs non diabétique

Table 1—*Patient Demographics, Glucose Metrics, and Unadjusted Mortality*

Measure	80-110 mg/dL (n = 1,526)	90-140 mg/dL (n = 2,003)	*P* Value
Age, y	65 (54-75)	64 (53-74)	.09
Female, %	38.6	42.7	.02
Diabetic, %	38.7	40.1	.43
APACHE II score	23 (18-29)	25 (19-31)	< .01
Charlson comorbidity score	2 (1-5)	2 (1-5)	.67
Patient mean blood glucose, mg/dL	118 (109-131)	131 (123-143)	< .01
Patients with diabetes	124 (113-139)	138 (127-151)	< .01
Patients without diabetes	115 (107-126)	128 (121-137)	< .01
Patient SD of glucose, mg/dL	25 (33-46)	24 (33-45)	.78
Patients with diabetes	42 (31-59)	39 (30-53)	< .01
Patients without diabetes	31 (24-40)	28 (22-38)	< .01
Incidence of hypoglycemia			
< 60 mg/dL, %	30.3	14.3	< .01
< 40 mg/dL, %	3.6	2.0	< .01
30-d mortality, %	9.7	11.1	.20
Patients with diabetes, %	12.3	9.8	.12
Patients without diabetes, %	8.1	11.9	< .01
Patients with hypoglycemia < 60 mg/dL, %	14.4	17.4	.33
Patients with hypoglycemia < 40 mg/dL, %	14.5	20.0	.58

Lanspa MJ et al Chest 2013;143:1226-34

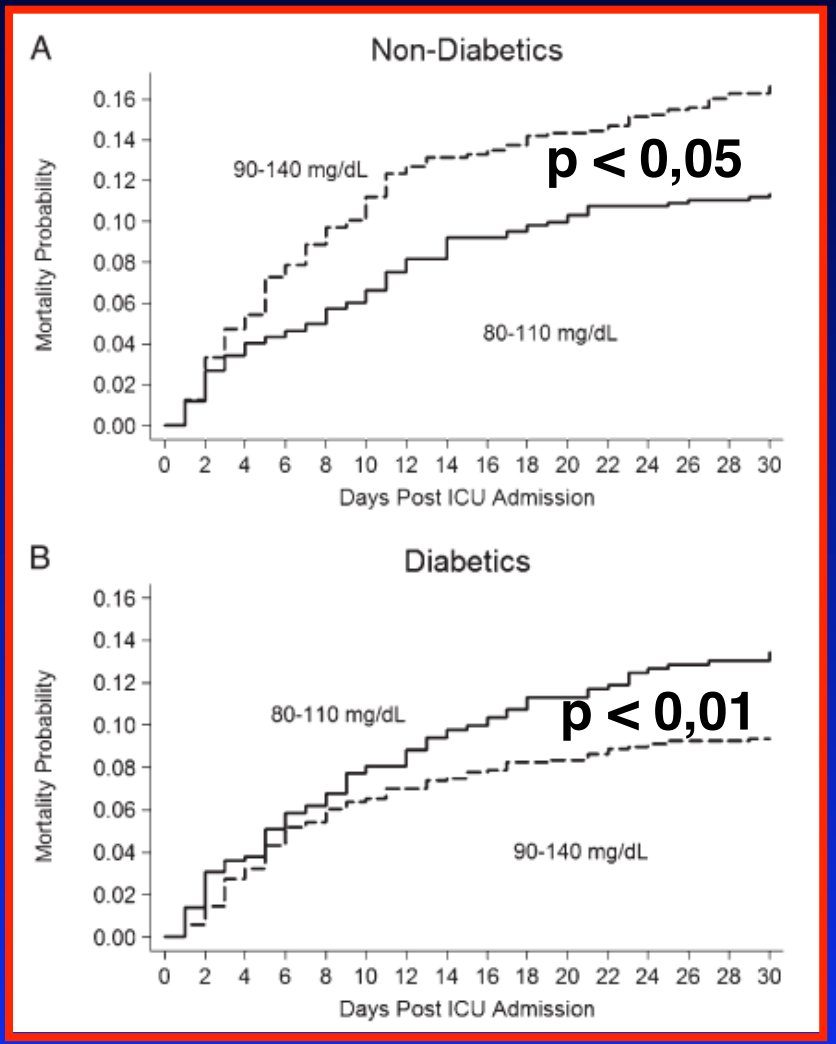
CONTRÔLE GLYC = 3 DOMAINES

Moderate Glucose Control Is Associated With Increased Mortality Compared With Tight Glucose Control in Critically Ill Patients Without Diabetes

Diabétique vs non diabétique

Table 2—Logistic Regression for 30-d Mortality, Comparing 90 to 140 mg/dL Glucose Target to the 80 to 110 mg/dL Target

Predictor	OR	95% CI	*P* Value
Patients without diabetes (n = 2,143)			
90-140 mg/dL	1.36	1.01-1.84	.05
Modified APACHE II score[a]	1.09	1.07-1.11	< .01
Charlson comorbidity score	1.06	1.01-1.13	.01
Age, y	1.02	1.01-1.03	< .01
Patients with diabetes (n = 1,386)			
90-140 mg/dL	0.65	0.45-0.93	.02
Modified APACHE II score[a]	1.07	1.05-1.10	< .01
Charlson comorbidity score	1.05	1.00-1.10	.06
Age, y	1.04	1.02-1.06	< .01



Lanspa MJ et al Chest 2013;143:1226-34

CONTRÔLE GLYC = 3 DOMAINES

Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults

Krinsley JS et al Crit Care 2015;19:179

cible : 70-140 mg/dL

Relation entre temps passé dans la cible et survie stratifié diabétique/non diabétique

	NON	DM	*P*-value
Number	2,550	747	
Age (yr)	67 (52 to 81)	70 (60 to 80)	0.0009
Median ICU LOS (IQR)	2.3 (1.5 to 5.0)	2.4 (1.6 to 5.0)	0.3004
Mean ICU LOS (SD)	4.5 (5.8)	4.6 (5.6)	N/A
Mechanical ventilation (%)	48.20	51.94	0.0790
APS	51 (37 to 70)	60 (44 to 79)	<0.0001
APACHE IV PM (%)	19.6 (23.5)[b]	25.4 (25.6)[c]	<0.0001
Mortality (%)	12.12	15.26	0.0282
TIR	80.6 (61.4 to 94.0)	55.0 (35.3 to 71.1)	<0.0001
Median number of BG tests (IQR)	17 (9 to 36)	22 (12 to 48)	<0.0001
Mean number of tests (SD)	33.6 (45.8)	43.7 (59.1)	N/A
BG tests per 24 hr	7.47	9.50	
Mean BG	121.4 (111.5 to 132.6)	140.3 (127.6 to 154.9)	<0.0001
CV (%)	17.6 (13.6 to 22.9)	27.3 (20.8 to 36.3)	<0.0001
Hypo <70 (% of patients)	18.04	31.46	<0.0001
Hypo <40 (% of patients)	1.37	2.81	0.0118

CONTRÔLE GLYC = 3 DOMAINES

Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults

Krinsley JS et al Crit Care 2015;19:179

cible : 70-140 mg/dL

Glucose metrics	TIR-hi	TIR-lo	*P*-value
diabétiques			
TIR (%)	71.1 (63.4 to 82.0)	35.4 (24.1 to 47.3)	<0.0001
Median number of BG tests (IQR)	24 (13 to 62)	20 (12 to 36)	0.0023
Mean number of tests (SD)	52.0 (68.7)	35.4 (46.3)	N/A
BG tests per 24 hr	9.3	9.8	
Mean BG (SD)	129.6 (119.9 to 138.8)	151.7 (142.1 to 166.7)	<0.0001
CV (%)	25.2 (19.3 to 33.8)	29.5 (22.2 to 37.7)	<0.0001
Hypo <70 (% of patients)	38.07	24.87	0.0001
Hypo <40 (% of patients)	2.95	2.67	0.9919
Mortality (%)	16.09	14.44	0.5994
non diabétiques			
TIR (%)	94.0 (87.8 to 100.0)	61.4 (46.5 to 71.4)	<0.0001
Median number of BG tests (IQR)	15 (9 to 35)	18 (10 to 39)	0.0001
Mean number of tests (SD)	30.7 (40.5)	36.6 (50.4)	N/A
BG tests per 24 hr	7.0	8.0	
Mean BG (SD)	113.4 (105.3 to 119.4)	131.9 (123.7 to 140.7)	<0.0001
CV (%)	15.0 (11.6 to 19.2)	20.8 (16.3 to 25.8)	<0.0001
Hypo <70 (% of patients)	16.63	19.45	0.0718
Hypo <40 (% of patients)	1.10	1.65	0.3066
Mortality (%)	8.47	15.76	<0.0001

CONTRÔLE GLYC = 3 DOMAINES

Time in blood glucose range 70 to 140 mg/dl >80% is strongly associated with increased survival in non-diabetic critically ill adults

Krinsley JS et al Crit Care 2015;19:179

cible : 70-140 mg/dL

Relation entre temps passé dans la cible et survie stratifié diabétique/non diabétique

Table 4 Multivariable analysis: association with mortality[a]

Variable		Coefficient	Standard error	OR (95% CI)	*P* value
NON group					
	Age	0.0213	0.0049	1.02 (1.02 to 1.03)	<0.0001
	APS	0.0499	0.0031	1.05 (1.04 to 1.06)	<0.0001
	Mechanical ventilation	0.7025	0.1794	2.02 (1.42 to 2.87)	0.0001
	TIR-lo	0.4744	0.1531	1.61 (1.19 to 2.17)	0.0019
DM group					
	Age	0.0364	0.0102	1.04 (1.02 to 1.06)	0.0004
	APS	0.0532	0.0054	1.05 (1.04 to 1.07)	<0.0001
	Mechanical ventilation	0.6886	0.3177	1.99 (1.07 to 3.71)	0.0302
	TIR-lo	0.0780	0.2610	1.08 (0.65 to 1.80)	0.7649

[a]Age, OR per 1 year. APS, OR per 1 point. APS, Acute Physiology Score component of the Acute Physiology and Chronic Health Evaluation IV predicted mortality severity scoring system; CI, Confidence interval; DM, Diabetes mellitus group; NON, Non-diabetic group; OR, Odds ratio; TIR-hi, Time in targeted blood glucose range above median value for non-diabetic and diabetes mellitus groups; TIR-lo, Time in targeted blood glucose range below median value for non-diabetic and diabetes mellitus groups.

CONTRÔLE GLYC ET HbA1C

Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality

Plummer MP et al Intensive Care Med 2014;40:973-80

1000 pts de réa et mesure de HbA1c à l'adm

. Hyperglyc + HbA1c < 6,5% = hyperglyc de stress = 48,8%

. Hyperglyc + HbA1c > 6,5% = diabète = 22% connus & 5,5% méconnus

Table 2 Patient characteristics and outcomes according to category of premorbid chronic glycaemia (HbA_{1c})

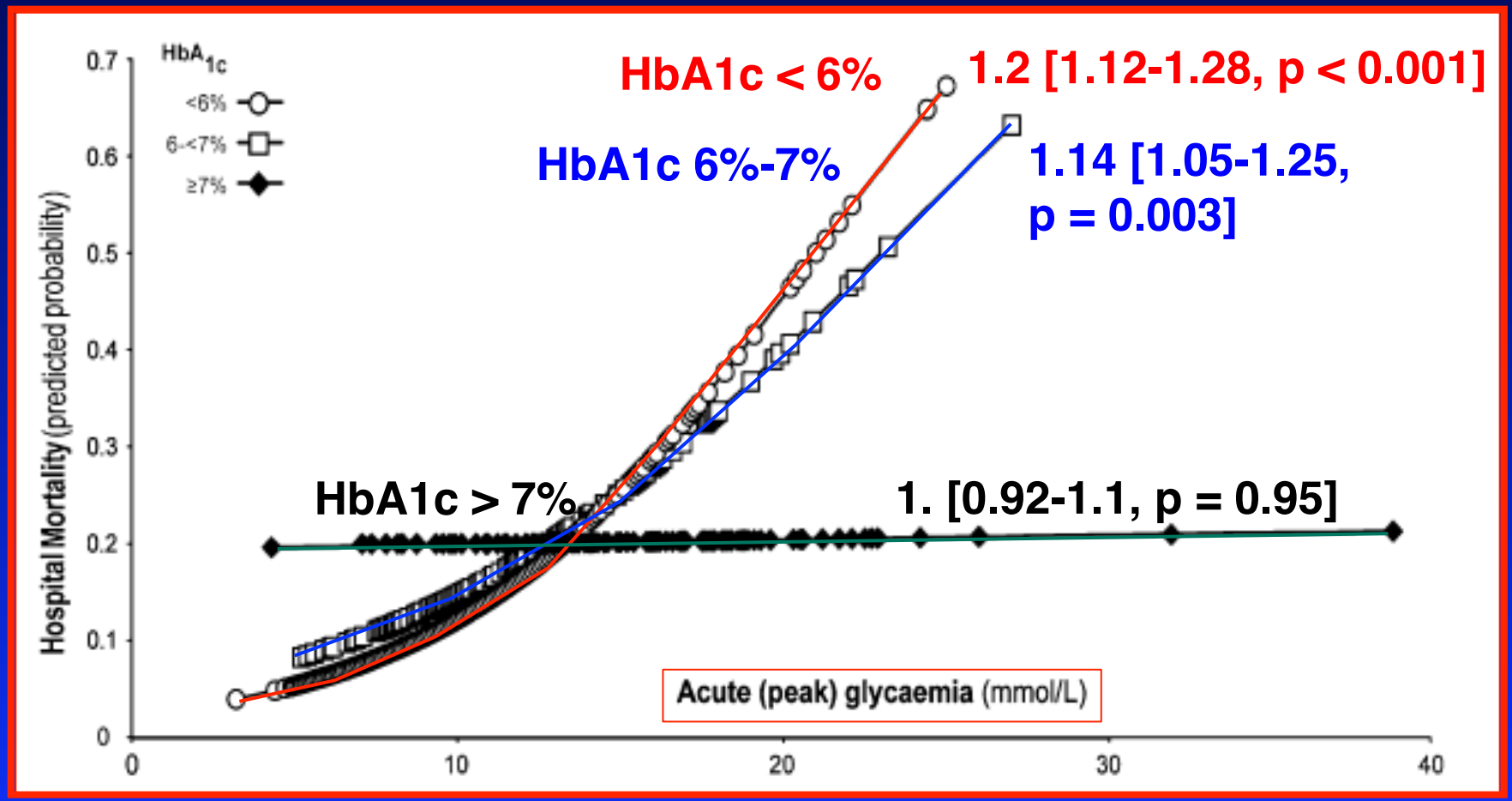
	$HbA_{1c} < 6\ \%$	$6\ \% \leq HbA_{1c} < 7\ \%$	$HbA_{1c} \geq 7\ \%$	*P* value
Number of patients	672	197	129	–
HbA_{1c} (%) [mean (SE)]	5.4 (0.01)	6.3 (0.02)	8.6 (0.14)	–
Known diabetes	55	57	108	–
Age (years) [mean (SE)]	51.7 (0.7)[b,c]	63.4 (1.0)[a]	62.6 (1.3)[a]	<0.001
BMI (kg/m^2) [mean (SE)]	26.3 (0.2)[b,c]	29.0 (0.5)[a]	30.9 (1.0)[a]	<0.001
APACHE II max during first 24 h of ICU admission [mean (SE)]	17.0 (0.3)[b,c]	20.1 (0.5)[a]	19.5 (0.7)[a]	<0.001
Medical admission [*n* (%)]	583 (87 %)	174 (89 %)	103 (80 %)	0.056
Peak blood glucose (mmol/l) [mean (SE)]	9.4 (0.1)[b,c]	11.5 (0.3)[a,c]	15.1 (0.4)[a,b]	<0.001
Catecholamine use [*n* (%)]	259 (39 %)	94 (48 %)	57 (44 %)	0.053
Steroid use [*n* (%)]	95 (14 %)[c]	38 (19 %)	29 (23 %)[a]	0.027
ICU mortality [*n* (%)]	77 (12 %)[b]	39 (20 %)[a]	23 (18 %)	0.005
Hospital mortality [*n* (%)]	87 (13 %)[b]	42 (21 %)[a]	26 (20 %)	0.005
ICU length of stay (days) [median (IQR)]	2.8 (1.6–6.2)	2.9 (1.8–6.1)	2.9 (1.7–6.9)	0.809
Hospital length of stay (days) [median (IQR)]	15.0 (7.6–29.6)	13.3 (8.2–29.8)	13.5 (8.6–24.6)	0.748

CONTRÔLE GLYC ET HbA1C

Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality

Plummer MP et al Intensive Care Med 2014;40:973-80

1000 pts de réa et mesure de HbA1c à l'adm



CONTRÔLE GLYC : LE DIABÉTIQUE

Treatment thresholds for hyperglycemia in critically ill patients with and without diabetes

Table 1 Suggested blood glucose targets in diabetic and non-diabetic ICU patients

Patient group	Therapeutic blood glucose target, mg/dl (mmol/l)
Non-diabetic	140–200 (7.7–11.1)
Diabetic HbA1C <7 %	140–200 (7.7–11.1)
Diabetic HbA1C ≥7 %	160–220 (8.8–12.2)
Cardiac surgery, non-diabetic	140–180 (7.7–10.0)
Cardiac surgery, diabetic HBA1C <7 %	140–180 (7.7–10.0)
Cardiac surgery, diabetic HbA1C ≥7 %	160–200 (8.8–11.1)

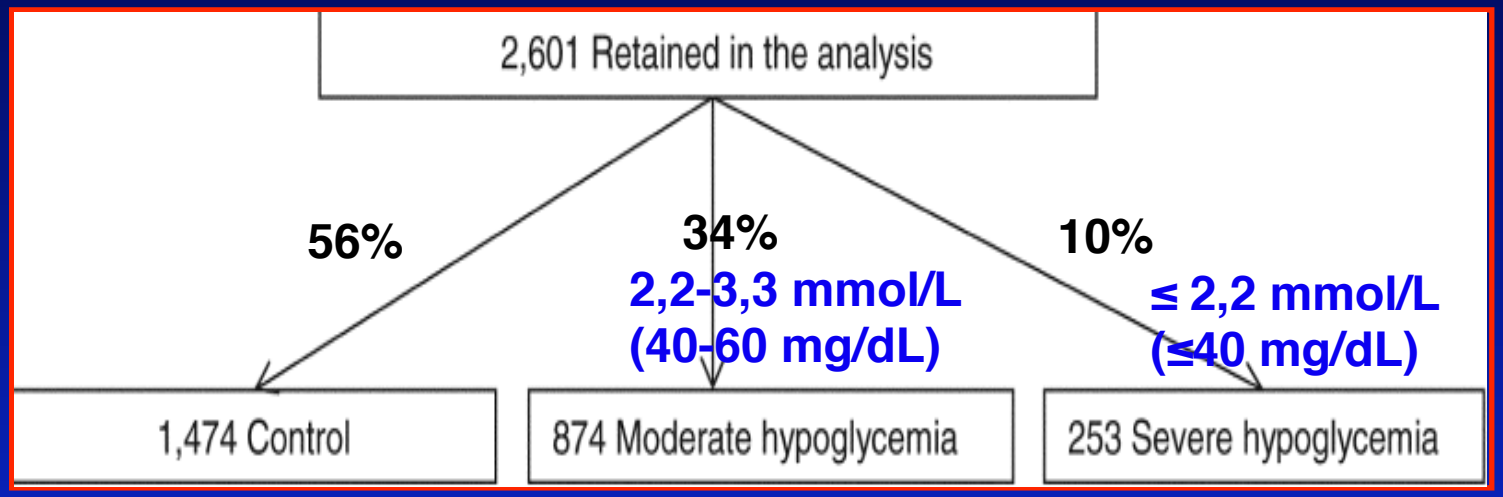
Marik PE et al Intensive Care Med 2014;40:1049-51

HYPOGLYCÉMIES ET METRICS

Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients

Etude ancillaire de CGAO

- hypoglyc multiples = > 3 épisodes



	hypoglyc isolées		hypoglyc multiples
Fréquence	81%		19%
Mortalité J90	29%	p < 0,001	51%

Kalfon P et al Crit Care 2015;19:153

HYPOGLYCÉMIES ET METRICS

Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients

Etude ancillaire de CGAO

Table 3 Multivariable analysis of variables associated with 90-day mortality (n = 2,312)

Variables	Odds ratio [95% IC]	P value
Age (per 1 year)	1.024 [1.017-1.031]	<0.001
Body mass index (per 1 $kg.m^{-2}$)	0.979 [0.963-0.995]	0.008
SAPS II score (per 1 point)	1.019 [1.012-1.025]	<0.001
SOFA score (per 1 point)	1.086 [1.053-1.120]	<0.001
McCabe score (per 1 point)	1.587 [1.357-1.885]	<0.001
Type of patient		
Medical	1	-
Scheduled surgical	0.663 [0.532-0.827]	<0.001
Emergency surgical	0.460 [0.321- 0.657]	<0.001
Moderate hypoglycemia	1.114 [0.865-1.436]	0.40
Severe hypoglycemia	1.571 [1.055-2.339]	0.03
Number of hypoglycemic events ≥3	1.834 [1.361-2.471]	<0.001
Mean blood glucose (per 1 $mmol.L^{-1}$)	1.086 [1.010-1.168]	0.03
Blood glucose CV <0.20	1	-
Blood glucose CV 0.20-0.39	1.155 [0.906-1.472]	0.24
Blood glucose CV ≥0.40	1.041 [0.698-1.552]	0.84
Computerized blood glucose control	0.786 [0.639-0.958]	0.02

Kalfon P et al Crit Care 2015;19:153

HYPOGLYCÉMIES ET METRICS

Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients

Etude ancillaire de CGAO

	Matching for severe hypoglycemia			
	P value	No hypoglycemia (n = 366)	Severe hypoglycemia (n = 199)	P value
Probability of death	0.66	0.32 (0.19)	0.35 (0.19)	0.12
Outcome				
RRT free days	0.06	28 [0–28]	24 [0–28]	<0.001
Catecholamines free days	<0.001	24 [0–26]	18 [0–25]	<0.001
Mechanical ventilation free days	<0.001	17 [0–24]	18 [0–25]	<0.001
ICU free days	<0.001	17 [0–24]	0 [0–28]	<0.001
Mortality 28 days	0.38	102 (28%)	75 (38%)	0.017
Mortality 90 days	0.029	131 (35%)	106 (53%)	<0.001
Blood glucose metrics				
Mean blood glucose	<0.001	7.3 (1.6)	6.8 (1.5)	<0.001
Blood glucose CV	<0.001	0.22 (0.09)	0.33 (0.12)	<0.001
Insulin dose ($IU.day^{-1}$)	<0.001	23 [7–41]	35 [19–56]	<0.001

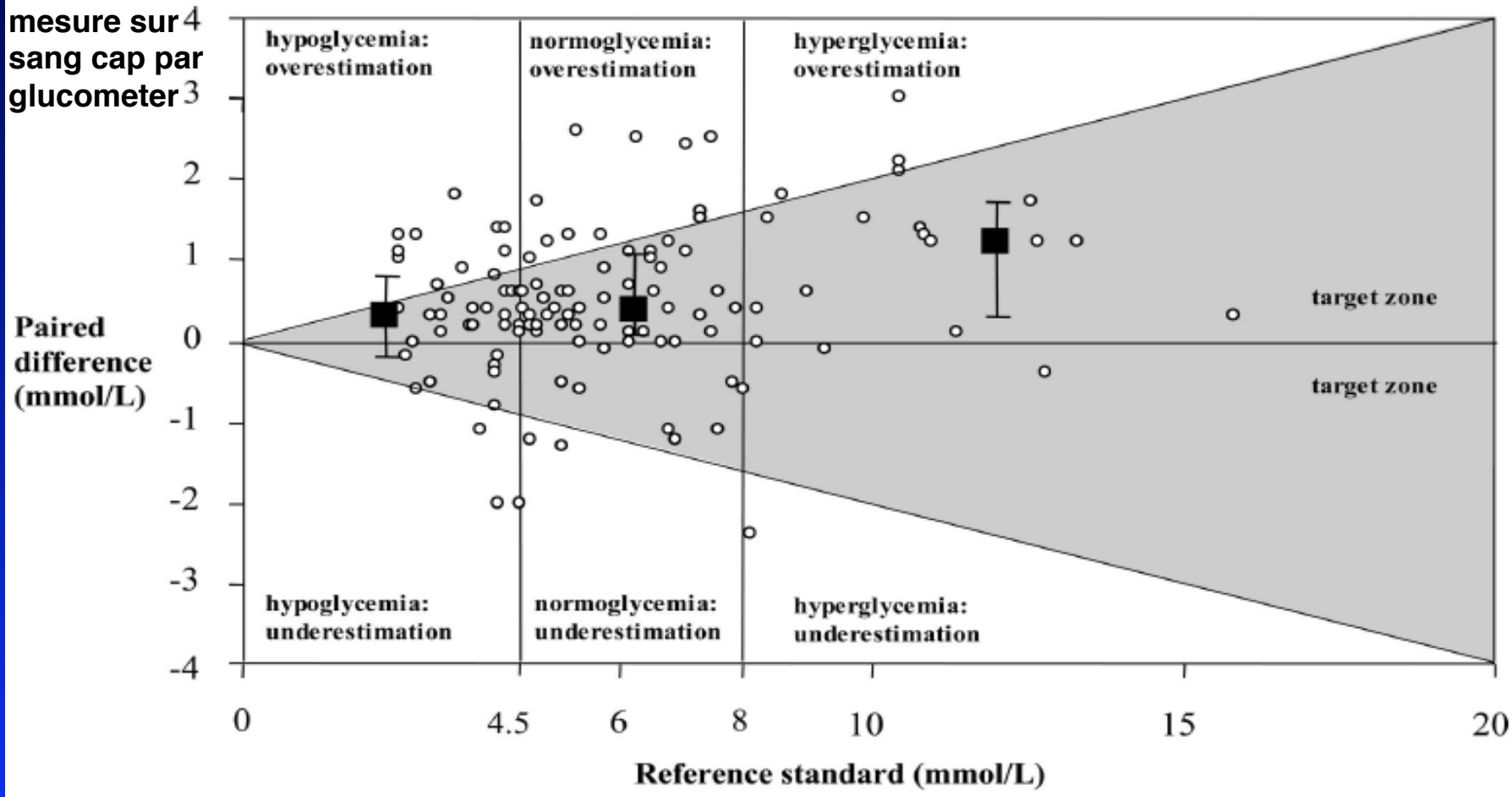
Matching for multiple hypoglycemic events			
	No hypoglycemia (n = 445)	Multiple hypoglycemic (n = 234)	P value
RRT free days	28 [0–28]	28 [0–28]	0.06
Catecholamines free days	24 [0–26]	19 [0–25]	0.001
Mechanical ventilation free days	18 [0–24]	5 [0–18]	<0.001
ICU free days	17 [0–24]	1 [0–17]	<0.001
Mortality 28 days	115 (26%)	64 (27%)	0.71
Mortality 90 days	141 (32%)	108 (46%)	<0.001
Blood glucose metrics			
Mean blood glucose	7.0 (1.5)	6.7 (1.0)	<0.001
Blood glucose CV	0.24 (0.10)	0.31 (0.09)	<0.001
Insuline dose ($IU.day^{-1}$)	26 [8–49]	41 [22–63]	<0.001

Kalfon P et al Crit Care 2015;19:153

MÉTHODES DE MESURES

Reliability of point-of-care testing for glucose measurement in critically ill adults*

(Crit Care Med 2005; 33:2778–2785) Kanji S *et al*



MÉTHODES DE MESURES

TABLE 2. **Differences in Selected Parameters Between Concordant and Conflicting Values of Capillary Blood Glucose Levels Obtained Using Test Strips at the Bedside**[a]

Variables	Concordant values (n=232 [85%])	Conflicting values (n=41 [15%])	*P* value
Diabetes	44 (19.0)	5 (12.2)	.38
Perfusion index	2.3±2.6	1.5±1.5	.04
Heart rate (beats/min)	95.4±24.7	98.5±23.6	.35
Mean arterial pressure (mm Hg)	78.8±16.3	76.3±15.2	.41
Acrocyanosis of the sampled finger	18 (7.8)	6 (14.6)	.23
Generalized mottling	21 (9.1)	2 (4.9)	.55
Shock	78 (33.6)	8 (19.5)	.10
Hematocrit (%) (N=163)	32.9±7.0 (n=137)	33.1±8.6 (n=26)	.98
Total SOFA score[14]	4.3±3.7	3.8±3.8	.40

Surtout si valeurs extrêmes, choc, oedèmes, vasopresseurs

Desachy A *et al,* Mayo Clin Proc 2008;83:40-5

MÉTHODES DE MESURES

International recommendations for glucose control in adult non diabetic critically ill patients

Critical Care 2010, **14**:R166 doi:10.1186/cc9258

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Glucose monitoring

. We **recommend** to perform glucose measurements in the laboratory which remains the current gold standard technique	Strong agreement
. We **recommend** to perform glucose measurements in the following preferential order of sampling: arterial, venous, capillary.	Strong agreement
. As total blood and plasma glucose measurements differ, we **recommend** to know the specifications of the device used (not all devices apply an automatic correction factor).	Strong agreement
. Owing to endogenous and exogenous physicochemical interference, we **recommend** to be aware of the precise specifications of the device and paper-strips that are used.	Strong agreement

MÉTHODES DE MESURES

Arterial line blood sampling: preventing hypoglycaemic brain injury 2014 The Association of Anaesthetists of Great Britain and Ireland

Anaesthesia 2014

. Prélèvements sur cathéter artériel

. Solutés pour rincer = NaCl 0,9%

. Privilégier les systèmes clos; si système ouvert évacuer "l'espace mort" avant prélèvement

. Si possible monitorage des tendances de glycémie, FC et Freq Resp

MESURES DE GLYCEMIE

Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults

Finfer S et al Crit Care 2013;17:229

1. Patients whose severity of illness justifies invasive vascular monitoring
   a. All blood samples should be drawn from an arterial line
   b. If an arterial line is temporarily or permanently unavailable, sample from a venous line
   c. Capillary (needle stick) samples are inaccurate and should not be used
2. Patients whose severity of illness *does not* justify invasive vascular monitoring
   a. Capillary (needle stick) samples may be used
3. Clinical research papers should report the number and percentage of blood samples obtained from arterial catheters, central and peripheral venous catheters and capillary (needle stick) samples

Choice of blood glucose analyzer in clinical research in critical care units

a. Samples taken from arterial or central venous catheters should be analyzed in a central laboratory or blood gas analyzer; a blood gas analyzer should be the default analyzer
b. Only when capillary samples are taken from patients without invasive vascular monitoring is analysis using a glucose meter acceptable
c. Clinical research papers should report the number and percentage of samples analyzed using central laboratory or blood gas analyzers or glucose meters. In all cases, the make and model of the analyzer used should be reported along with routine calibration and quality assurance measures

Reporting glycemic control – trials or observational studies should report

1. Central tendency – for blood glucose concentration measurements from a population of patients, the median and interquartile range of individual patient means should be reported
2. Dispersion – calculate the standard deviation of blood glucose concentration for each patient then report the median and interquartile range of standard deviations for the population
3. Hypoglycemia – as a minimum, investigators should report the number and percentage of patients experiencing at least one episode of severe and moderate hypoglycemia (blood glucose concentration ≤2.2 (≤40 mg/dl) and 2.3 to 3.9 mmol/l (41 to 70 mg/dl) respectively). Report separately the number and percentage of patients experiencing hypoglycemia related to insulin treatment (iatrogenic) and unrelated to insulin treatment (spontaneous)

For severe hypoglycemia, report duration of hypoglycemia, associated symptoms, amount of glucose administered, and next blood glucose concentration

CONCLUSION

1 protocole universel pour tous et partout

Un contrôle glycémique efficace, sûre, individualisé

Cibles appropriées
Outils adaptés
Informatisation

CONCLUSION

Bcp de paramètres à intégrer et à maîtriser : marge thérapeutique, efficacité et sécurité

Cibles de glycémie : 1,1-1,8 g/l

De la certitude et la simplicité au doute et la complexité

"Ce n'est pas le doute mais la certitude qui rend fou"