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CCL - LISBON - PORTUGAL
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

# CUMULATIVE TIME IN BAND (cTIB): GLYCEMIC LEVEL, VARIABILITY AND PATIENT OUTCOME ALL IN 1

S. Penning[1], M. Signal[2], J.-C. Preiser[3], G.M. Shaw[4], A.J. Le Compte[2], C.G. Pretty[2], T. Desaive[1], J.G. Chase[2]

[1] University of Liege (ULg), GIGA-Cardiovascular Sciences, Liege, Belgium
[2] University of Canterbury, Christchurch, New Zealand
[3] Erasme Hospital, Free University of Brussels, Brussels, Belgium
[4] Christchurch Hospital, Christchurch, New Zealand

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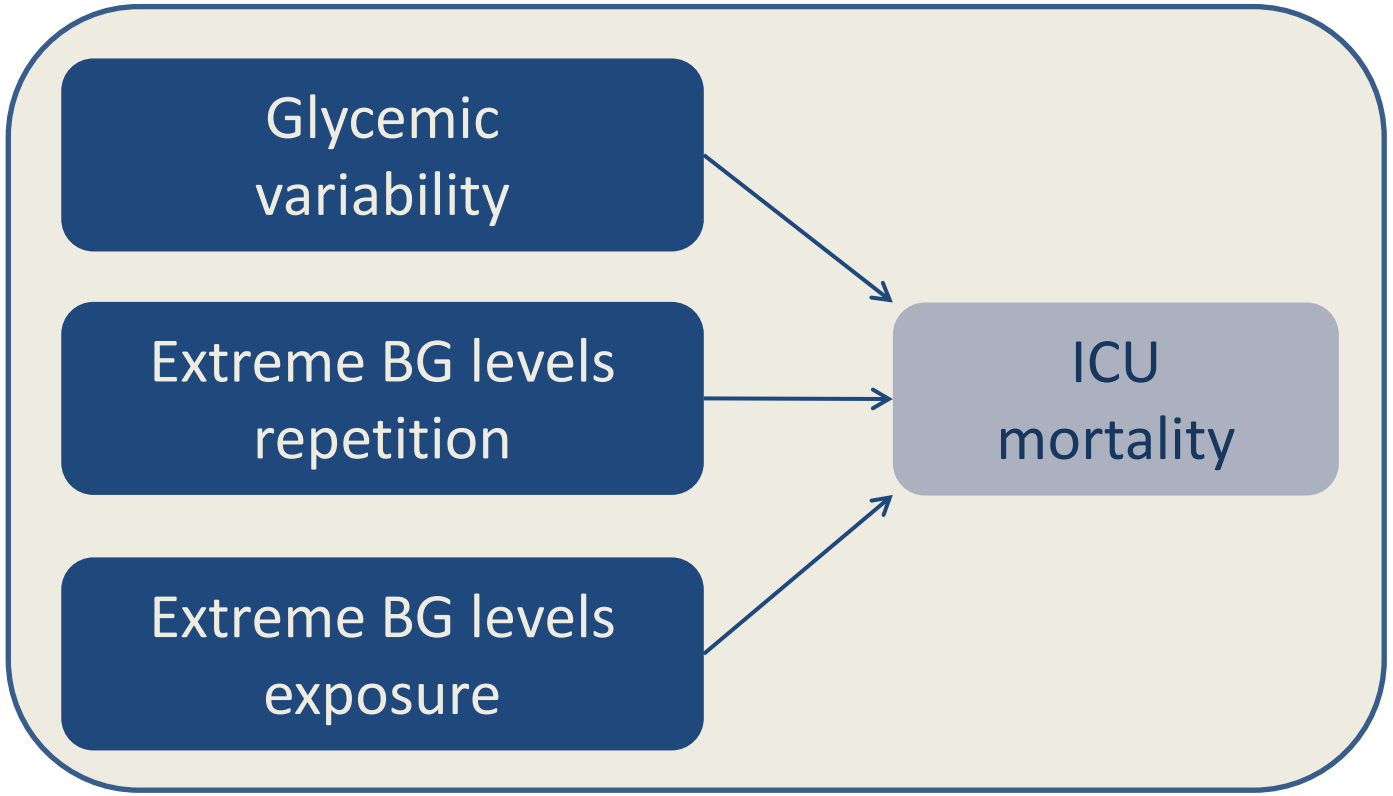
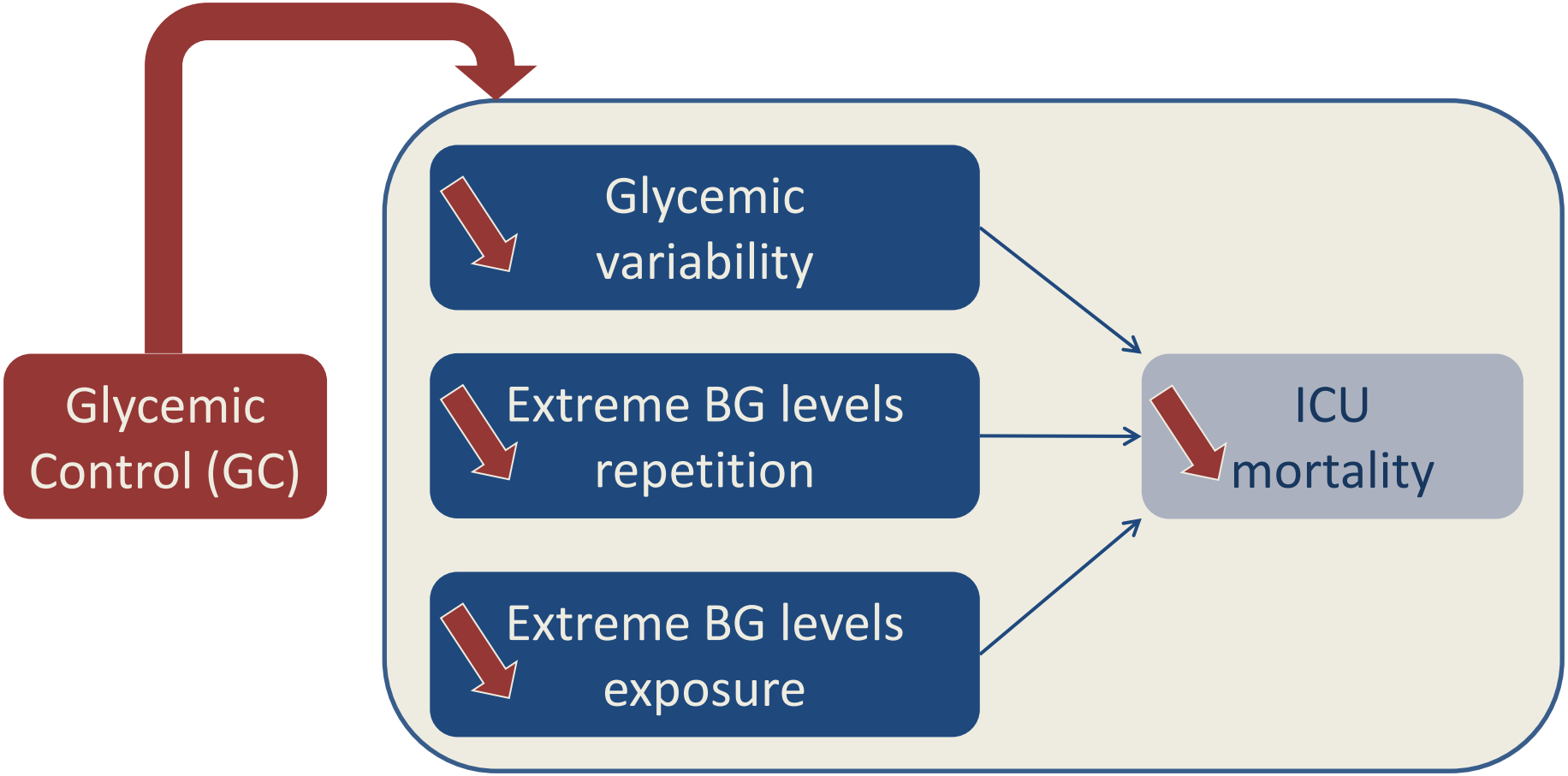
ULB


Glycemic variability
Extreme BG levels repetition
Extreme BG levels exposure
ICU mortality


Glycemic Control (GC)
Glycemic variability
Extreme BG levels repetition
Extreme BG levels exposure
ICU mortality

But…

Does it work?

# But…

## Does it work?

### No

Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S *et al*: **Intensive insulin therapy and pentastarch resuscitation in severe sepsis**. *N Engl J Med* 2008, **358**(2):125-139.

Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR *et al*: **Intensive versus conventional glucose control in critically ill patients**. *N Engl J Med* 2009, **360**(13):1283-1297.

Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P *et al*: **A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study**. *Intensive Care Med* 2009, **35**(10):1738-1748.

### Yes

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients**. *N Engl J Med* 2001, **345**(19):1359-1367.

Krinsley JS: **Effect of an intensive glucose management protocol on the mortality of critically ill adult patients**. *Mayo Clin Proc* 2004, **79**(8):992-1000

Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C: **Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change**. In: *Crit Care.* vol. 12; 2008.

Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S *et al*: **Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data**. *Cmaj* 2009.

# GC implementation difficulties

| | |
|---|---|
| Hypoglycemic risk | Safety |
| Glycemic target band | Efficiency |
| GC performance assessment in real time | Quality |

# Insight on issues that impede GC implementation

1) Can GC positively impact on ICU mortality?

2) Is there a glycemic target band performance metric or level that can be assessed in real time that ensures and discriminates improved patient outcome?

3) When should glycemic control performance be assessed?

## Patient Data

| | SPRINT[1] | Glucontrol[2] | All |
|---|---|---|---|
| Number of patients | 784 | 933 | 1717 |
| Percentage of males | 61.2 | 63.2 | 62.3 |
| Age of patients | 65.0 [52.0 - 74.0] | 65.2 [51.5 - 74.0] | 65.0 [51.8 - 74.0] |
| APACHE 2 score | 18.0 [15.0 - 24.0] | 15.0 [11.0 - 21.0] | 17.0 [13.0 - 23.0] |
| Cohort BG (mmol/L) | 6.2 [5.3 - 7.4] | 6.9 [5.8 - 8.4] | 6.6 [5.6 - 8.1] |
| Per-patient median BG (mmol/L) | 6.3 [5.6 - 7.5] | 6.9 [6.1 - 8.2] | 6.6 [5.8 - 7.9] |
| %BG in 4-7 mmol/L | 66.8 | 49.8 | 56.4 |

Data are in the form of median [inter-quartile range, IQR] where applicable.

[1] Chase JG *et al.*: **Implementation and evaluation of the SPRINT protocol for tight glycemic control in critically ill patients: a clinical practice change**. In: *Crit Care.* vol. 12; 2008.

[2] Preiser JC *et al.*: **A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study**. *Intensive Care Med* 2009, **35**(10):1738-1748.

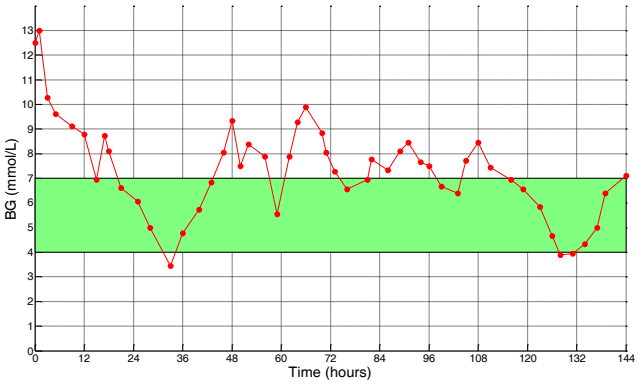
Patient Data → Daily cTIB

Percentage of blood glucose levels within a specific glycemic band from start to the present day

- Calculated per day and per patient
- Accounts for BG levels and variability
- Measures glycemic outcome and control performance

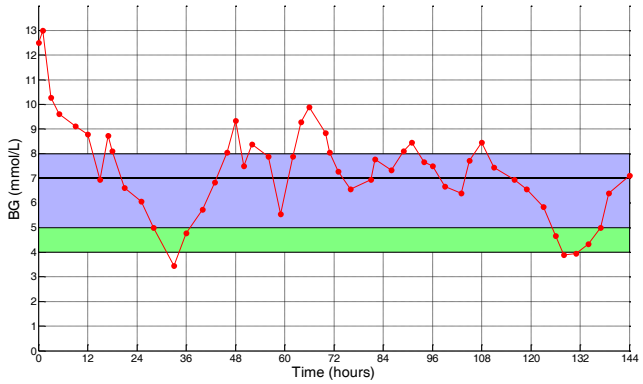
Patient Data → Daily cTIB

4.0-7.0 mmol/L



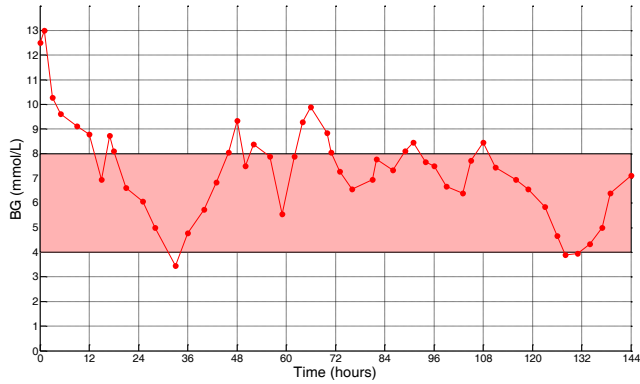

- Intermediate levels
- Δ = 3 mmol/L

5.0-8.0 mmol/L




- Intermediate levels
- Δ = 3 mmol/L

4.0-8.0 mmol/L




- Intermediate levels
- Δ = 4 mmol/L


$cTIB \geq t$

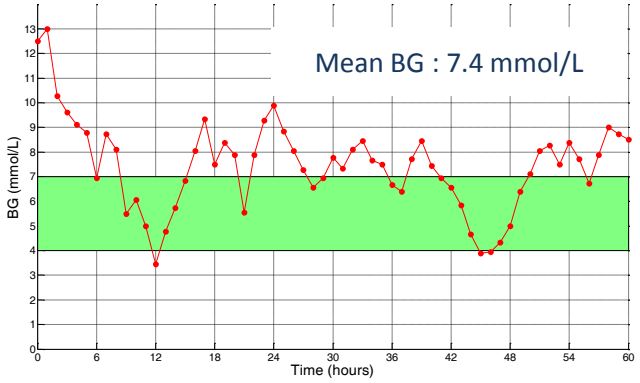
$t = 50\%, 60\%, 70\%, 80\%$

Patient Data → Daily cTIB → cTIB threshold

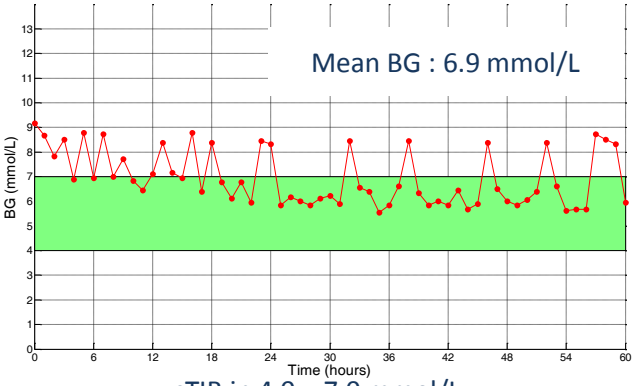
cTIB ≥ t

t = 50%, 60%, 70%, 80%

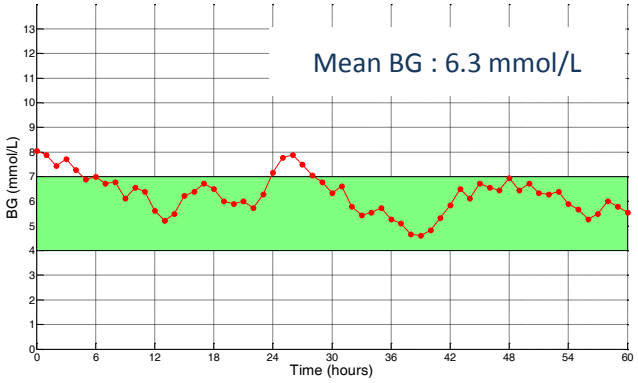
cTIB = 32.8%




cTIB = 65.6%




cTIB = 83.6%



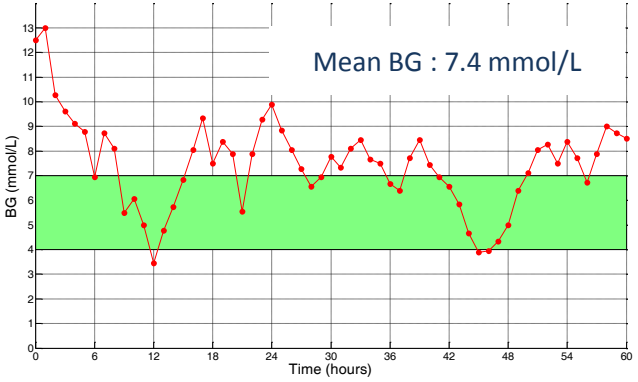

cTIB in 4.0 – 7.0 mmol/L

Patient Data → Daily cTIB → cTIB threshold

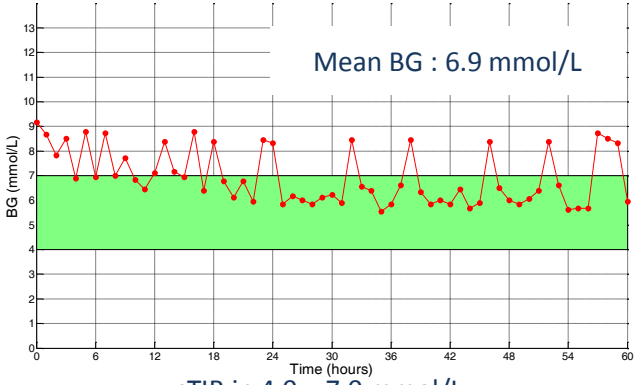
cTIB ≥ t

t = 50%, 60%, 70%, 80%

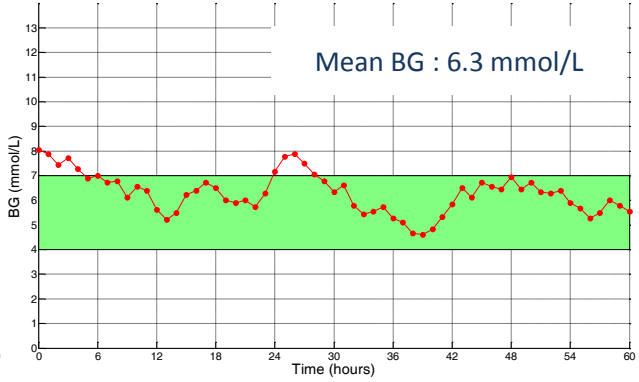
cTIB = 32.8% < 50%




cTIB = 65.6% ≥ 50%




cTIB = 83.6% ≥ 50%



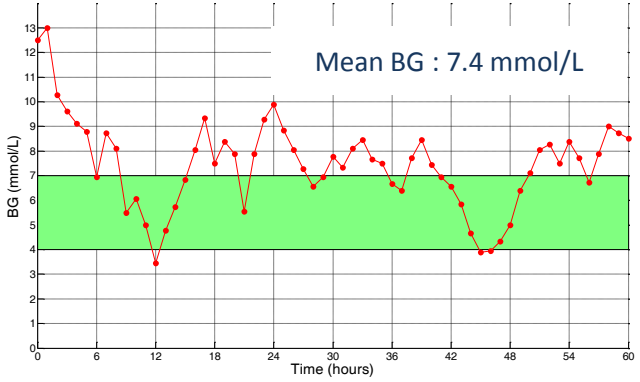

cTIB in 4.0 – 7.0 mmol/L

Patient Data → Daily cTIB → cTIB threshold

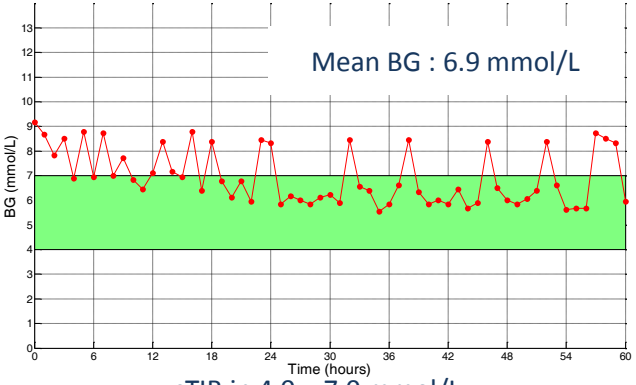
cTIB ≥ t

t = 50%, 60%, 70%, 80%

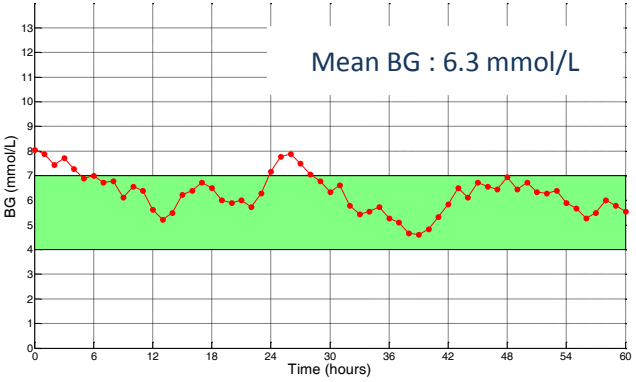
cTIB = 32.8% < 70%




cTIB = 65.6% < 70%




cTIB = 83.6% ≥ 70%



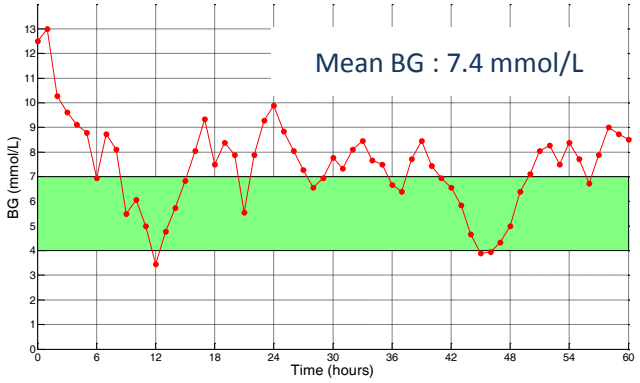

cTIB in 4.0 – 7.0 mmol/L

Patient Data → Daily cTIB → cTIB threshold

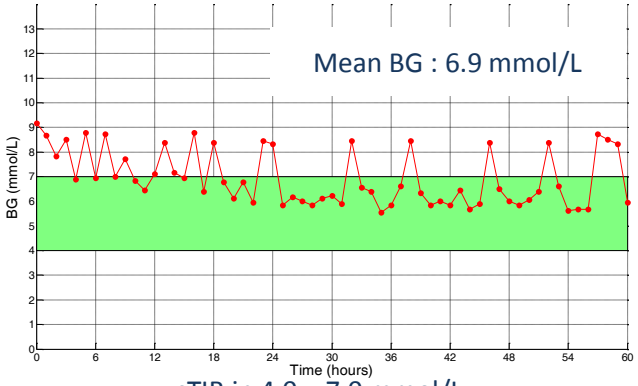
$cTIB \geq t$

t = 50%, 60%, 70%, 80%

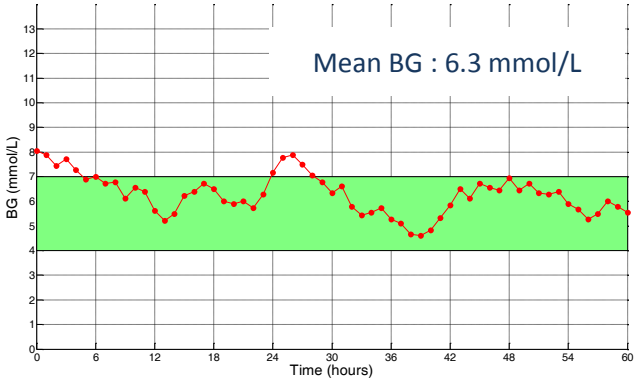
cTIB = 32.8%




cTIB = 65.6%




cTIB = 83.6%




cTIB in 4.0 – 7.0 mmol/L


$cTIB \geq t$

t = 50%, 60%, 70%, 80%

→ different levels of GC performance

→ discrimination of improved outcomes

Patient Data → Daily cTIB → cTIB threshold → OR

Ratio between odds of living given cTIB ≥ t and odds of living given cTIB < t

| *ICU mortality* | Lived | Died |
|---|---|---|
| cTIB ≥ t | $N_1$ | $N_2$ |
| cTIB < t | $N_3$ | $N_4$ |

$$OL_{cTIB \geq t} = N_1 / N_2$$

$$OL_{cTIB < t} = N_3 / N_4$$

$N_i$ : number of patients.

Patient Data → Daily cTIB → cTIB threshold → OR

Ratio between odds of living given cTIB ≥ t and odds of living given cTIB < t

| *ICU mortality* | Lived | Died |
|---|---|---|
| cTIB ≥ t | $N_1$ | $N_2$ |
| cTIB < t | $N_3$ | $N_4$ |

$N_i$ : number of patients.

$$OL_{cTIB \geq t} = N_1/N_2$$
$$OL_{cTIB < t} = N_3/N_4$$

$$OR = \frac{OL_{cTIB \geq t}}{OL_{cTIB < t}} = \frac{N_1 . N_4}{N_2 . N_3}$$

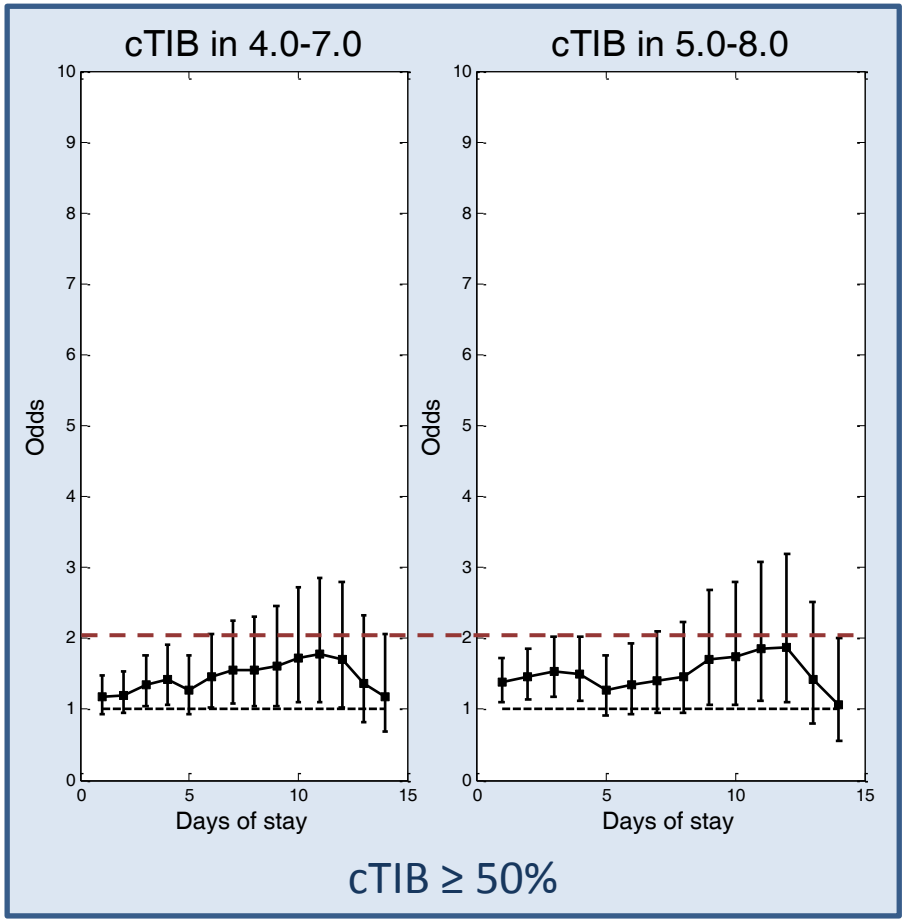
$$CI_{95\%} = \left[ e^{\ln(OR) - 1.96 * \sqrt{\frac{1}{N_1}+\frac{1}{N_2}+\frac{1}{N_3}+\frac{1}{N_4}}};\ e^{\ln(OR) + 1.96 * \sqrt{\frac{1}{N_1}+\frac{1}{N_2}+\frac{1}{N_3}+\frac{1}{N_4}}} \right]$$

Glycemic levels

cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***5.0-8.0 mmol/L***

# Glycemic levels

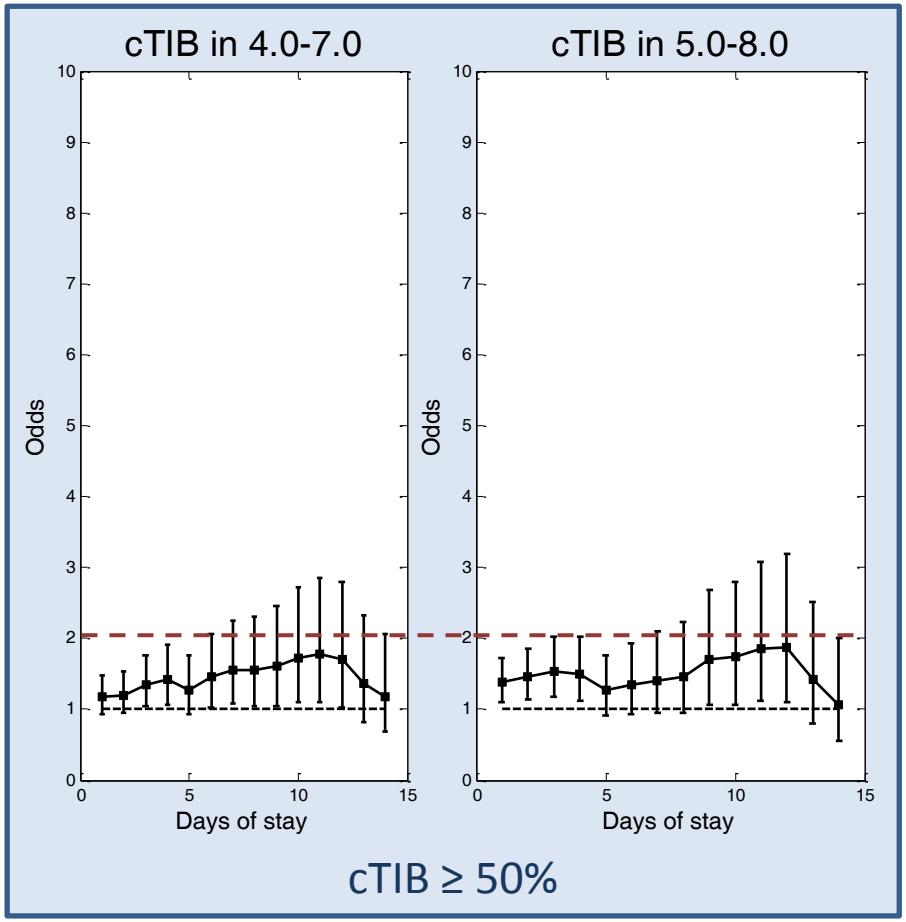
## cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***5.0-8.0 mmol/L***



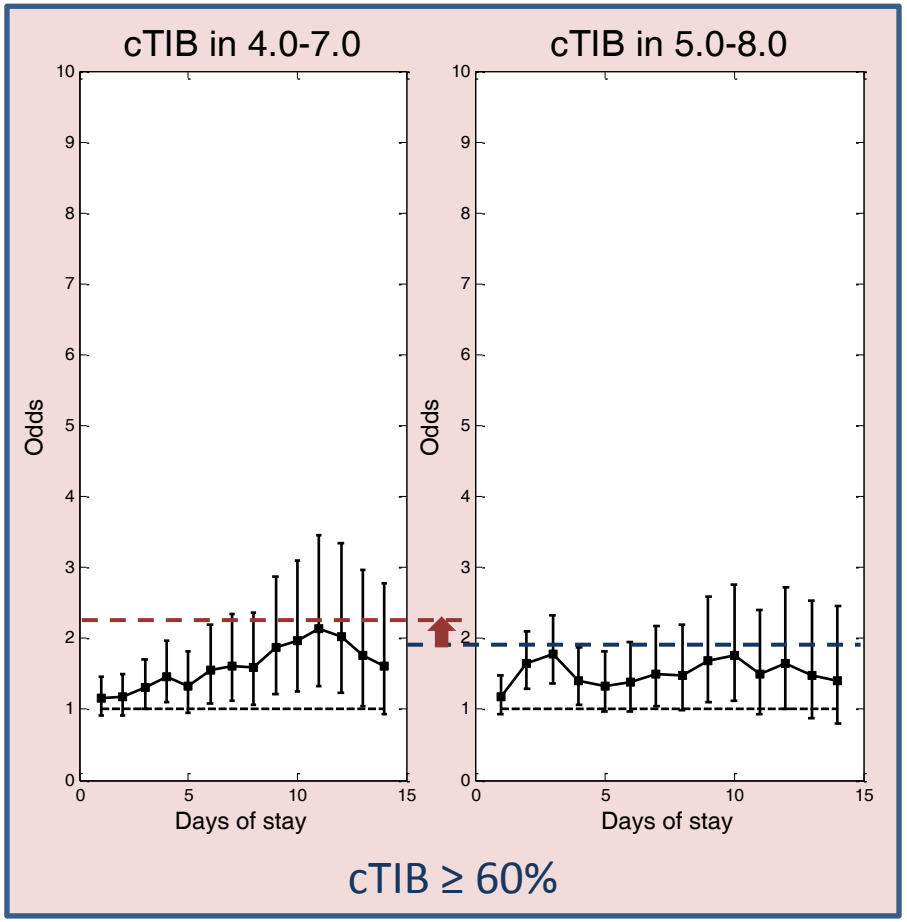

cTIB ≥ 50%

# Glycemic levels

## cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***5.0-8.0 mmol/L***



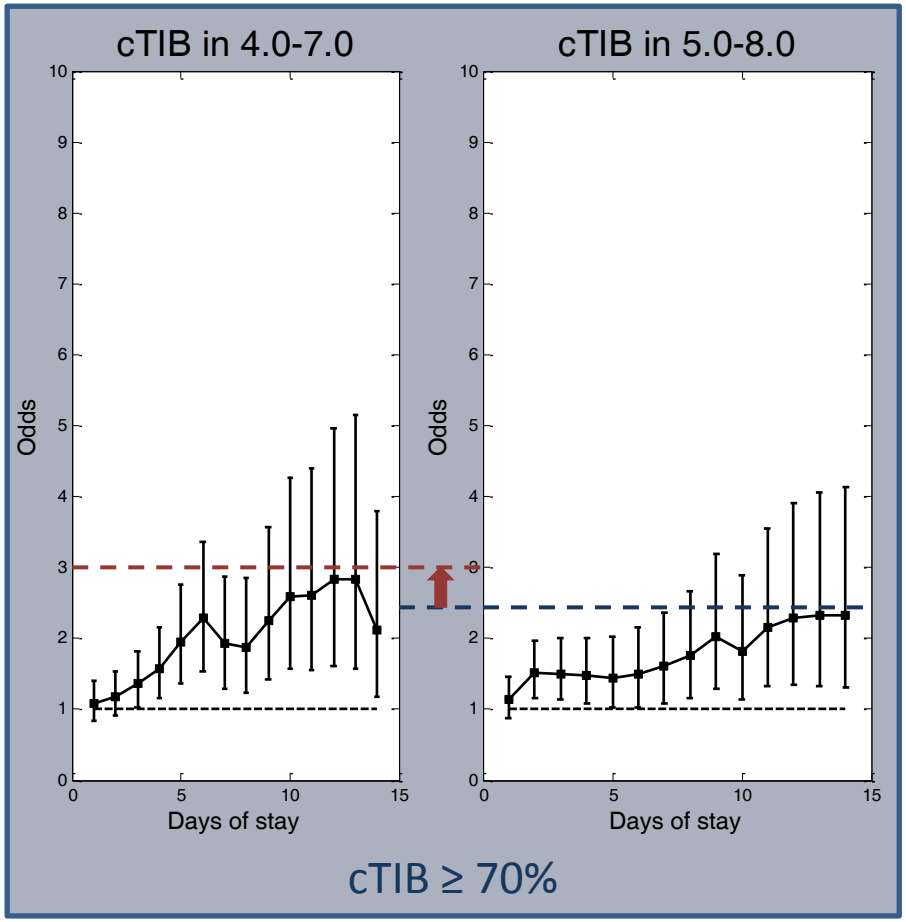

cTIB ≥ 50%

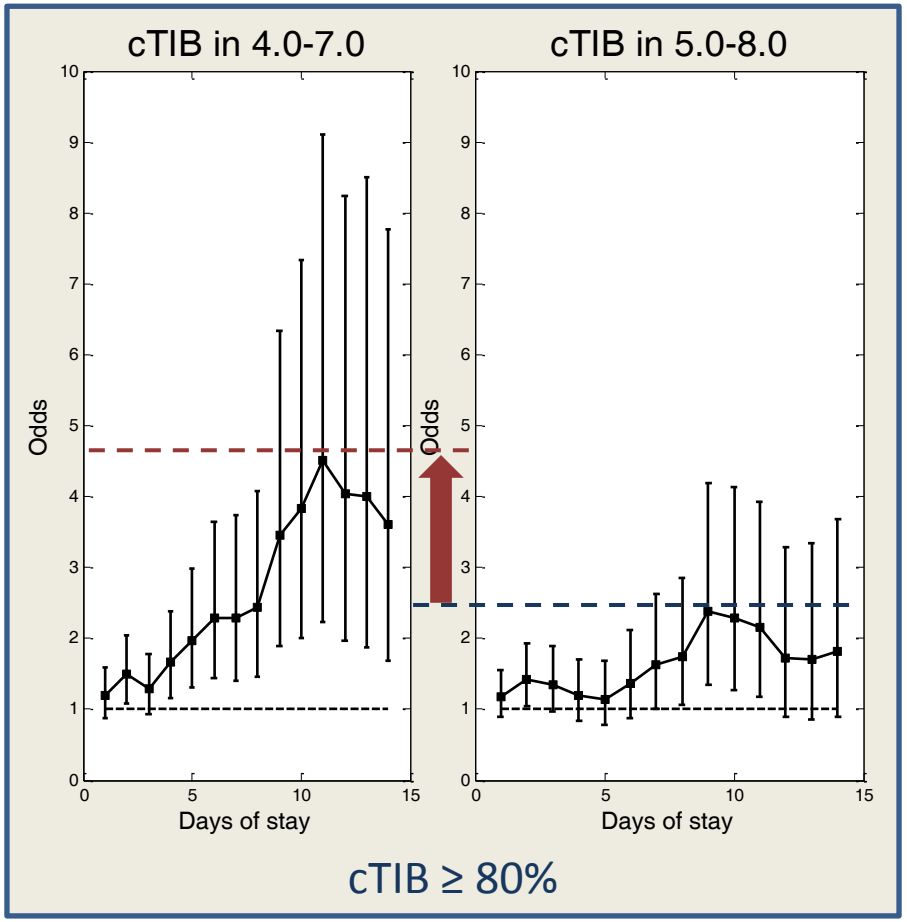



cTIB ≥ 60%

# Glycemic levels

## cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***5.0-8.0 mmol/L***



Glycemic levels

cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***5.0-8.0 mmol/L***

→ 4.0-7.0 mmol/L

Krinsley JS: **Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients**. *Mayo Clin Proc* 2003, **78**(12):1471-1478.

Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC: **Relationship of early hyperglycemia to mortality in trauma patients**. *J Trauma* 2004, **56**(5):1058-1062.

Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML: **Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis**. *Crit Care Med* 2009, **37**(12):3001-3009.

Glycemic variability

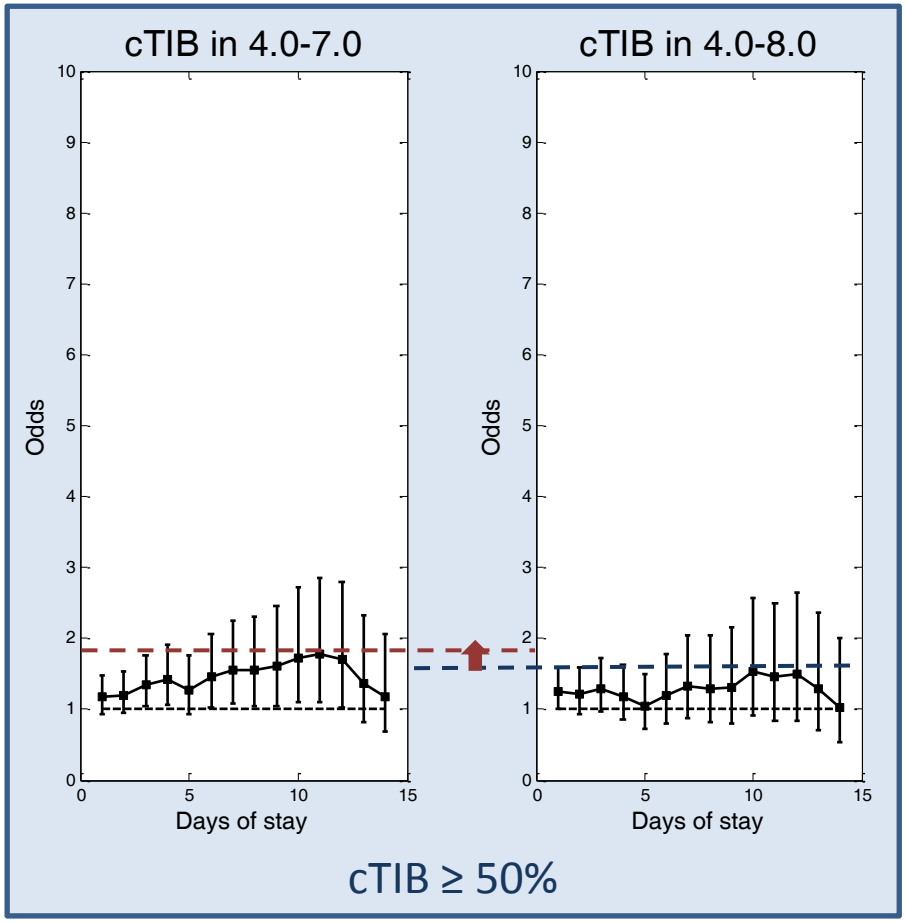
cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***4.0-8.0 mmol/L***

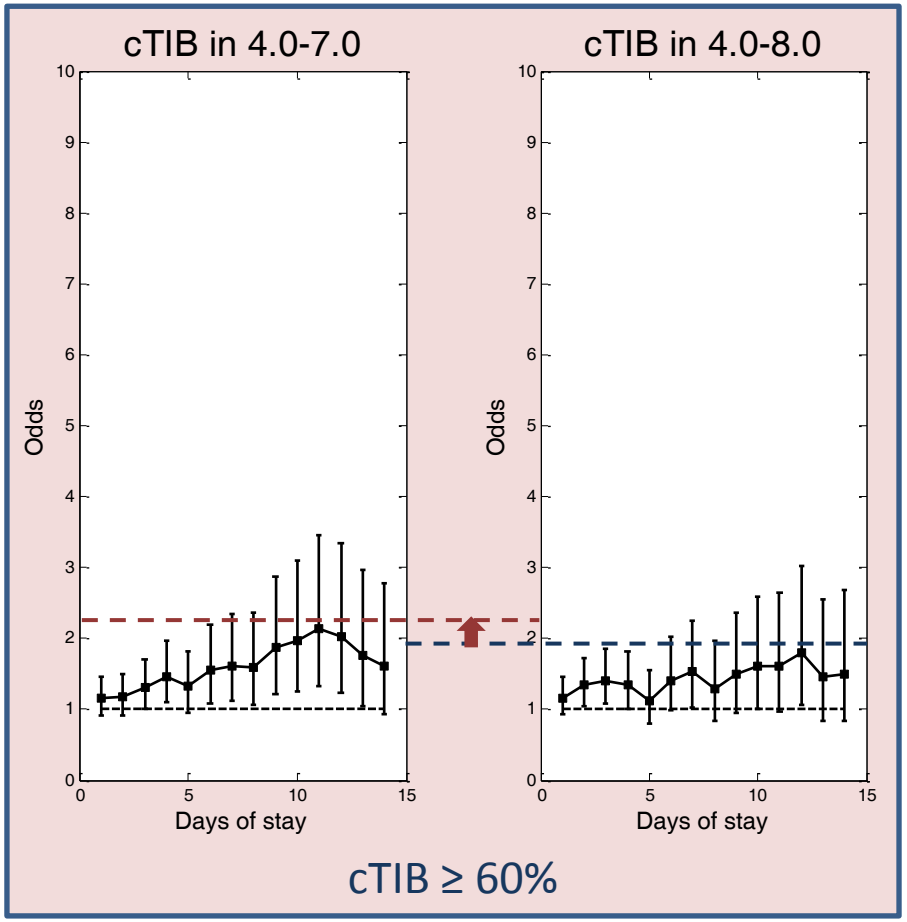
tighter vs. wider glycemic band

# Glycemic variability

## cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***4.0-8.0 mmol/L***

## tighter vs. wider glycemic band

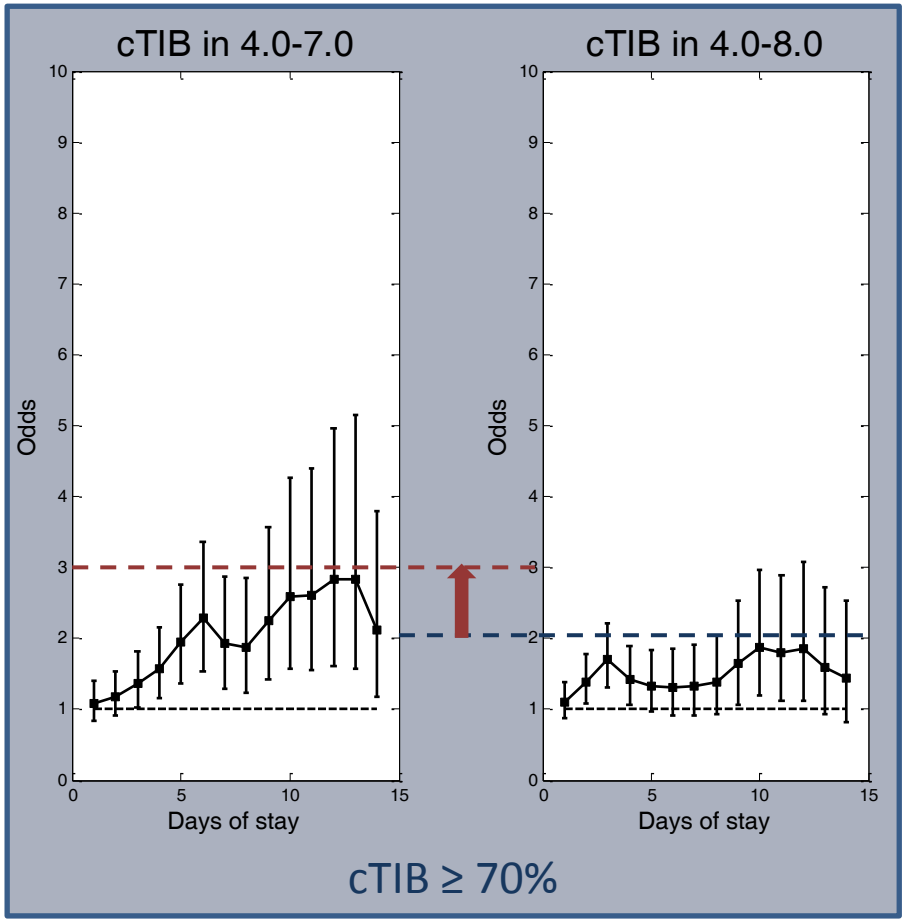


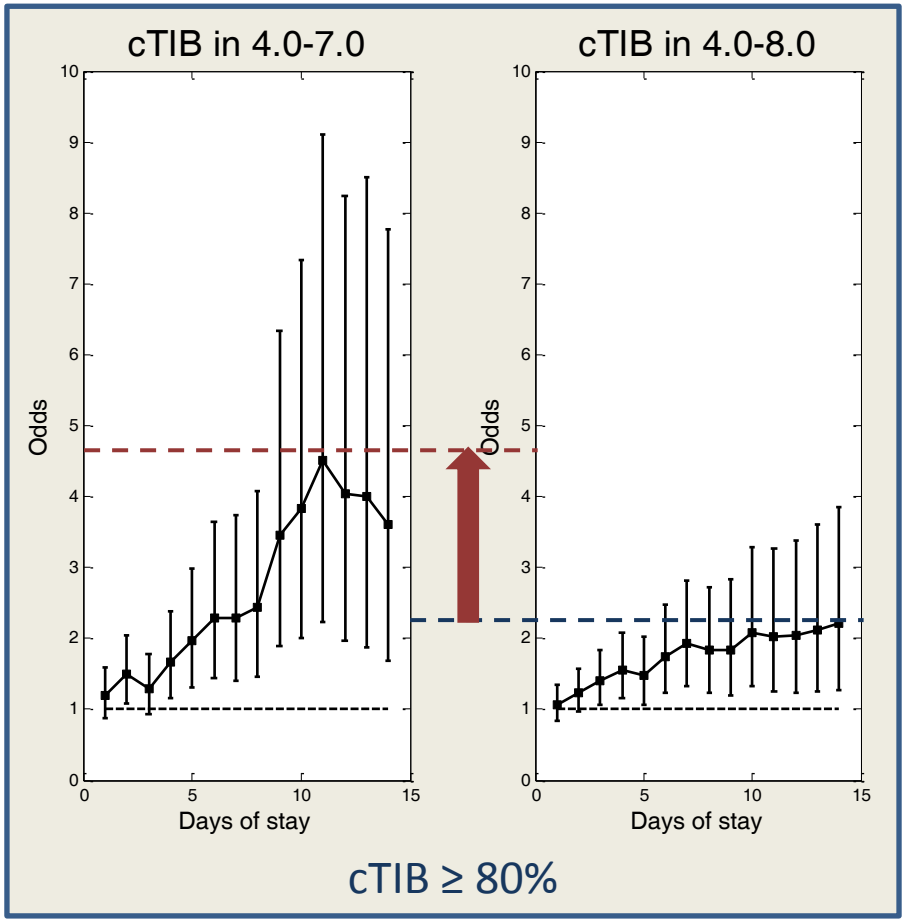
# Glycemic variability

## cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***4.0-8.0 mmol/L***

## tighter vs. wider glycemic band




cTIB ≥ 70%




cTIB ≥ 80%

Glycemic variability

cTIB in ***4.0-7.0 mmol/L*** vs. cTIB in ***4.0-8.0 mmol/L***

tighter vs. wider glycemic band

→ 4.0-7.0 mmol/L

Egi M, Bellomo R, Stachowski E, French CJ, Hart G: **Variability of blood glucose concentration and short-term mortality in critically ill patients**. *Anesthesiology* 2006, **105**(2):244-252.

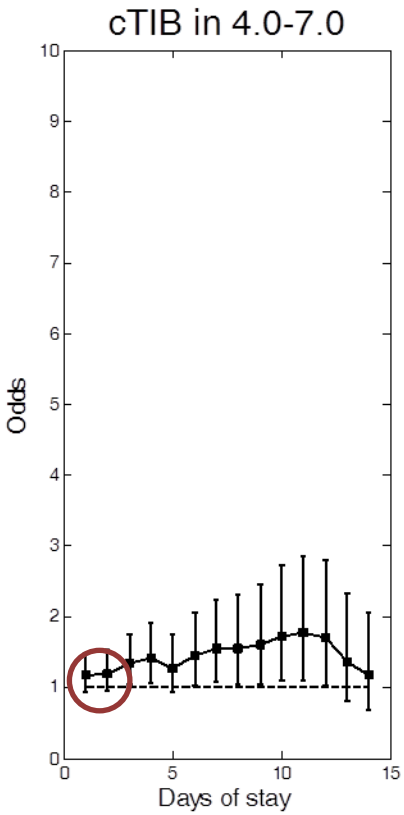
Ali NA, O'Brien JM, Jr., Dungan K, Phillips G, Marsh CB, Lemeshow S, Connors AF, Jr., Preiser JC: **Glucose variability and mortality in patients with sepsis**. *Crit Care Med* 2008, **36**(8):2316-2321.

Krinsley JS: **Glycemic variability: a strong independent predictor of mortality in critically ill patients**. *Crit Care Med* 2008, **36**(11):3008-3013.

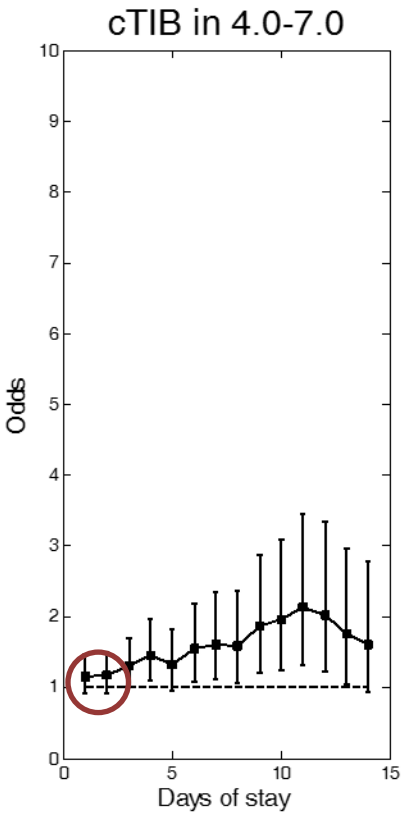
# Glycemic control performance

## When can it be assessed?

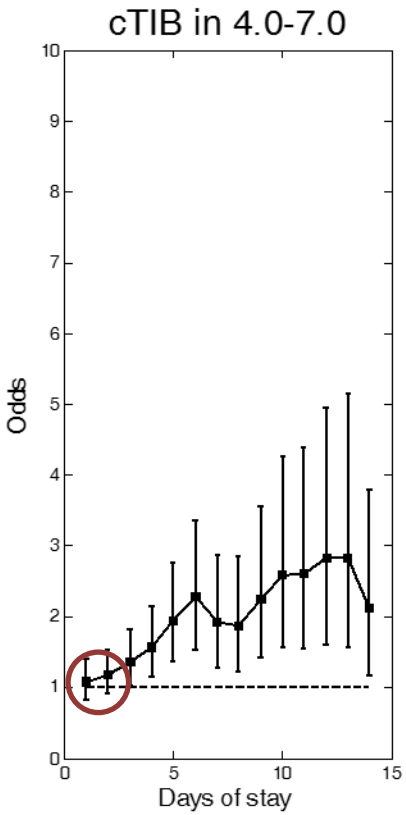
# Glycemic control performance
## When can it be assessed?



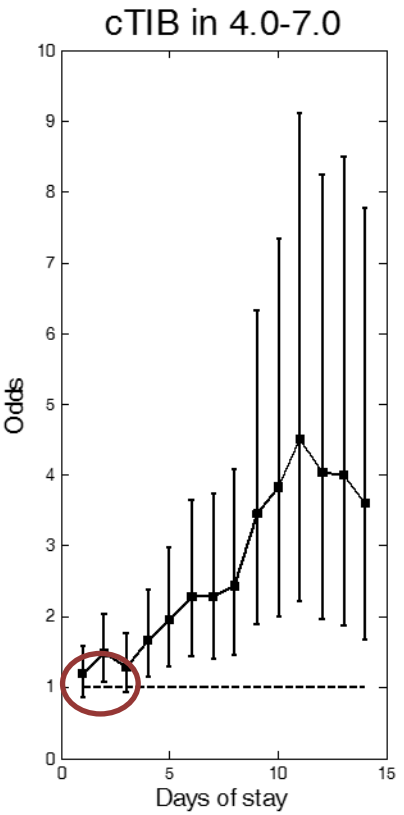

cTIB ≥ 50%




cTIB ≥ 60%




cTIB ≥ 70%




cTIB ≥ 80%

## Glycemic control performance

### When can it be assessed?

→ After 3 days

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients**. *N Engl J Med* 2001, **345**(19):1359-1367.

Krinsley JS: **Effect of an intensive glucose management protocol on the mortality of critically ill adult patients**. *Mayo Clin Proc* 2004, **79**(8):992-1000.

Chase JG, Shaw G, Le Compte A, Lonergan T, Willacy M, Wong XW, Lin J, Lotz T, Lee D, Hann C: **Implementation and evaluation of the SPRINT protocol for tight glycaemic control in critically ill patients: a clinical practice change**. *Crit Care* 2008, **12**(2):R49.

## 1) Can GC positively impact on ICU mortality?

Yes …

(1) Association

max. BG within an intermediate glycemic band

= increased OR = improved patient outcomes

(2) Causation

Previous randomized control trials [1,2]

Physiological reasons [3 + others]

[1] Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients**. *N Engl J Med* 2001, **345**(19):1359-1367.

[2] Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: **Intensive Insulin Therapy in the Medical ICU**. *N Engl J Med* 2006, **354**(5):449-461.

[3] Weekers F, Giulietti AP, Michalaki M, Coopmans W, Van Herck E, Mathieu C, Van den Berghe G: **Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness**. *Endocrinology* 2003, **144**(12):5329-5338.

2) Is there a glycemic target band performance **metric** or level that can be assessed in real time that ensures and discriminates improved patient outcome?

Yes…

cTIB

- 1 metric to assess glycemic levels, glycemic variability and patient outcomes
- 1 metric able to reproduce different previous results about GC assessment
- 1 metric easily calculated in real-time

→ 1 metric to rule them all!

2) Is there a glycemic target band performance metric or **level** that can be assessed in real time that ensures and discriminates improved patient outcome?

Yes…

4.0-7.0 mmol/L = increased OR = improved patient outcome

- BG < 7.0 mmol/L = increased OR
- No hypo (BG < 4.0 mmol/L) = increased OR

## 3) When should glycemic control performance be assessed?

After 3 days…

Lower CI bound < 1.0 for Days 1-3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OF INTENSIVE CARE
MEDICINE

# Thank you for your attention

Questions?

Université de Liège

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Te Whare Wānanga o Waitaha
CHRISTCHURCH NEW ZEALAND

ULB