

GLYCEMIC CONTROL IN THE ICU

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Outline

- Why do patients develop hyperglycemia in the ICU?
- Hyperglycemia in critically ill adult patients...what did the studies show?
- Recommendations & Guidelines
- Hyperglycemia in critically ill pediatric patients...what did the available evidence report?

Why do ICU patients develop hyperglycemia?

- ▣ Hyperglycemia in critically ill patients (stress hyperglycemia or stress diabetes) is common.
- ▣ The incidence of hyperglycemia varies depending on the definition used for hyperglycemia and the patient population.
- ▣ Multiple factors in ICU patients contribute to hyperglycemia:
 - Stress during critical illness increases the levels of counterregulatory hormones and cytokines.
 - Medications (e.g., corticosteroids, epinephrine, norepinephrine), nutrition, and dextrose-containing solutions.
 - Insulin resistance

Hyperglycemia in adult ICU patients...What did the studies show?

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INTENSIVE INSULIN THERAPY IN CRITICALLY ILL PATIENTS

GREET VAN DEN BERGHE, M.D., PH.D., PIETER WOUTERS, M.Sc., FRANK WEEKERS, M.D., CHARLES VERWAEST, M.D.,
FRANS BRUYNINCKX, M.D., MIET SCHETZ, M.D., PH.D., DIRK VLASSELAERS, M.D., PATRICK FERDINANDE, M.D., PH.D.,
PETER LAUWERS, M.D., AND ROGER BOUILLON, M.D., PH.D.

Intensive Insulin Therapy in Critically Ill Surgical Patients

- ▣ Patients in the surgical ICU (n=1543, 60% cardiac surgery)
- ▣ Randomized to Intensive Insulin Therapy (IIT) or conventional therapy (CT)
 - **IIT:** IV insulin was started if blood glucose exceeded 110 mg/dL, goal was to keep glucose 80-110 mg/dL (4.5 – 6 mmol/L)
 - **CT:** Insulin was started if BG>215, goal was to keep glucose 180-200 mg/dL.

Intensive Insulin Therapy in Critically Ill Surgical Patients

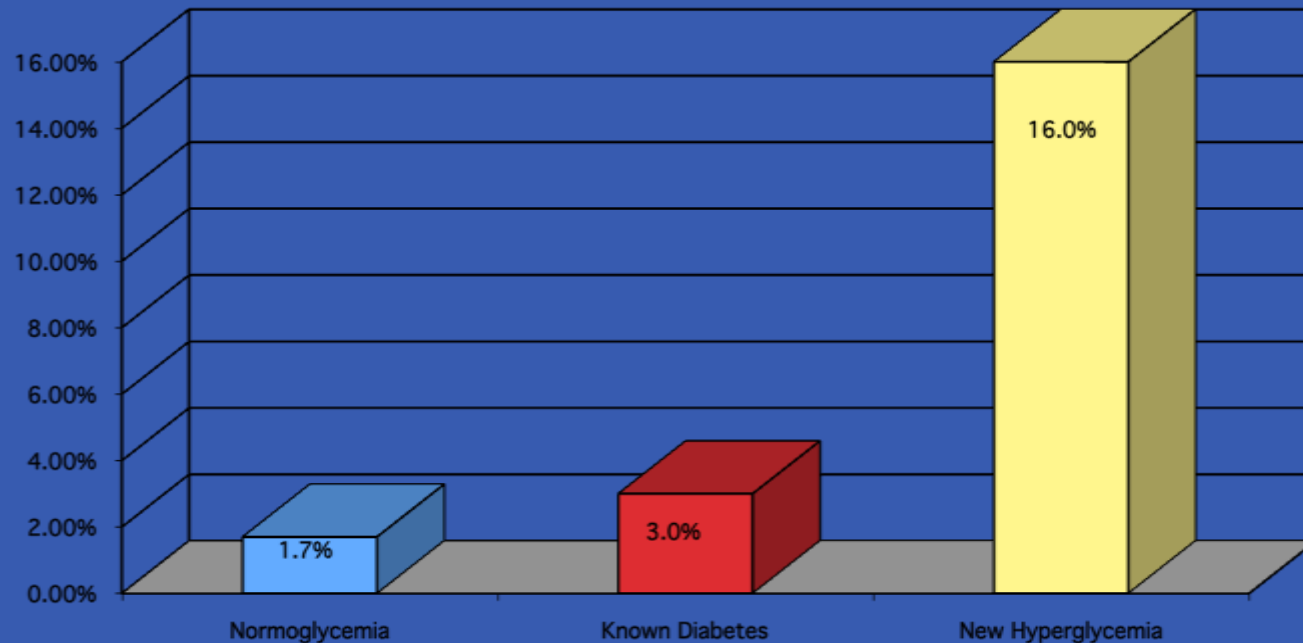
Intensive Insulin Therapy (IIT) was associated with:

- ▣ ICU mortality ↓ 43%
- ▣ ICU mortality for patient staying more than 5 days ↓ 50%
- ▣ Acute renal failure requiring dialysis ↓ 41 %
- ▣ Blood stream infection ↓ 46%
- ▣ Transfusions ↓ 50%
- ▣ Critical illness poly-neuropathy ↓ 44%
- ▣ Hospital mortality ↓ 36%
- ▣ Hospital mortality in patients staying in ICU > 5 days ↓ 35%

Incidence of hypoglycemia was higher in the IIT

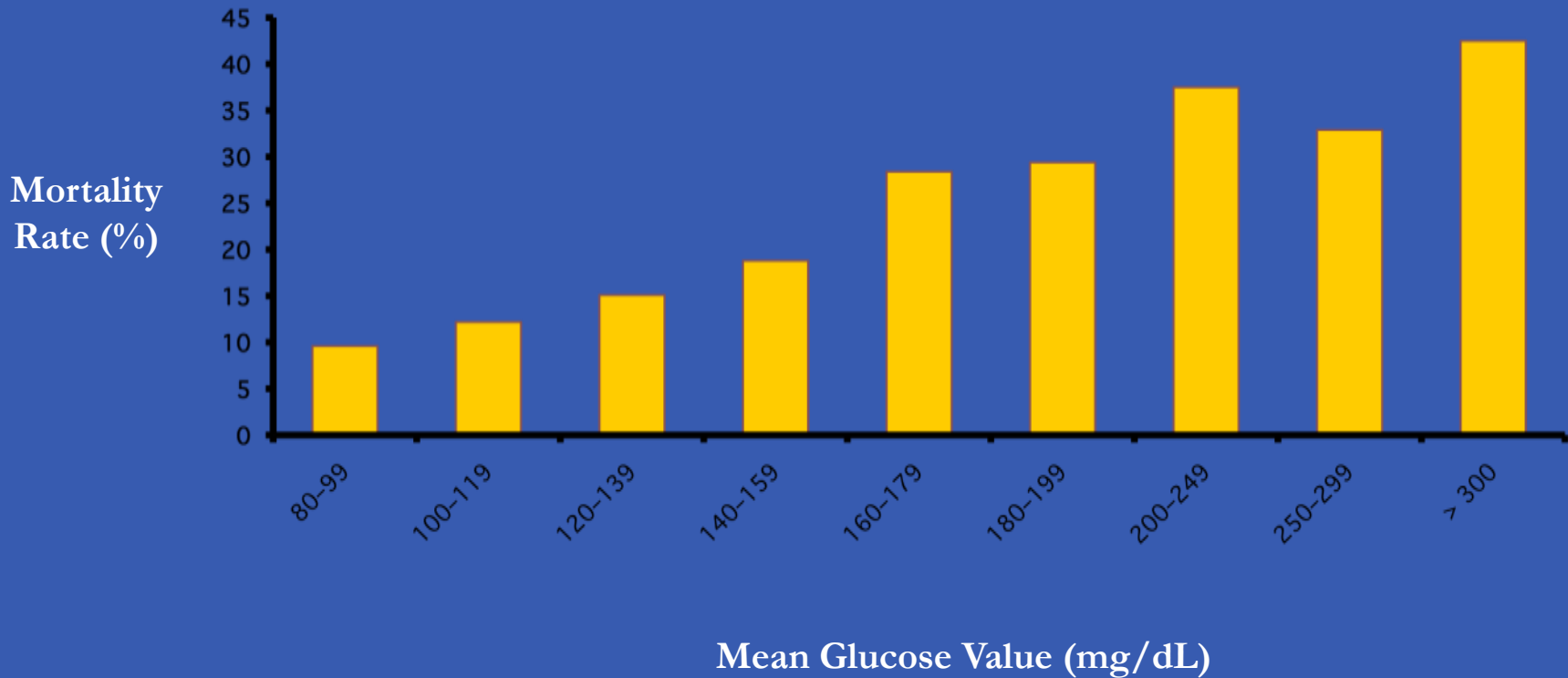
Van der Berghe et al, NEJM 2001;345 1359-1967

Hyperglycemia: an Independent marker of in-hospital mortality



Umpierrez et al.. *J Clin Endocrinol Metab.* 2002;87(3):978-82.

Hyperglycemia is associated with increased mortality in Critically Ill Patients

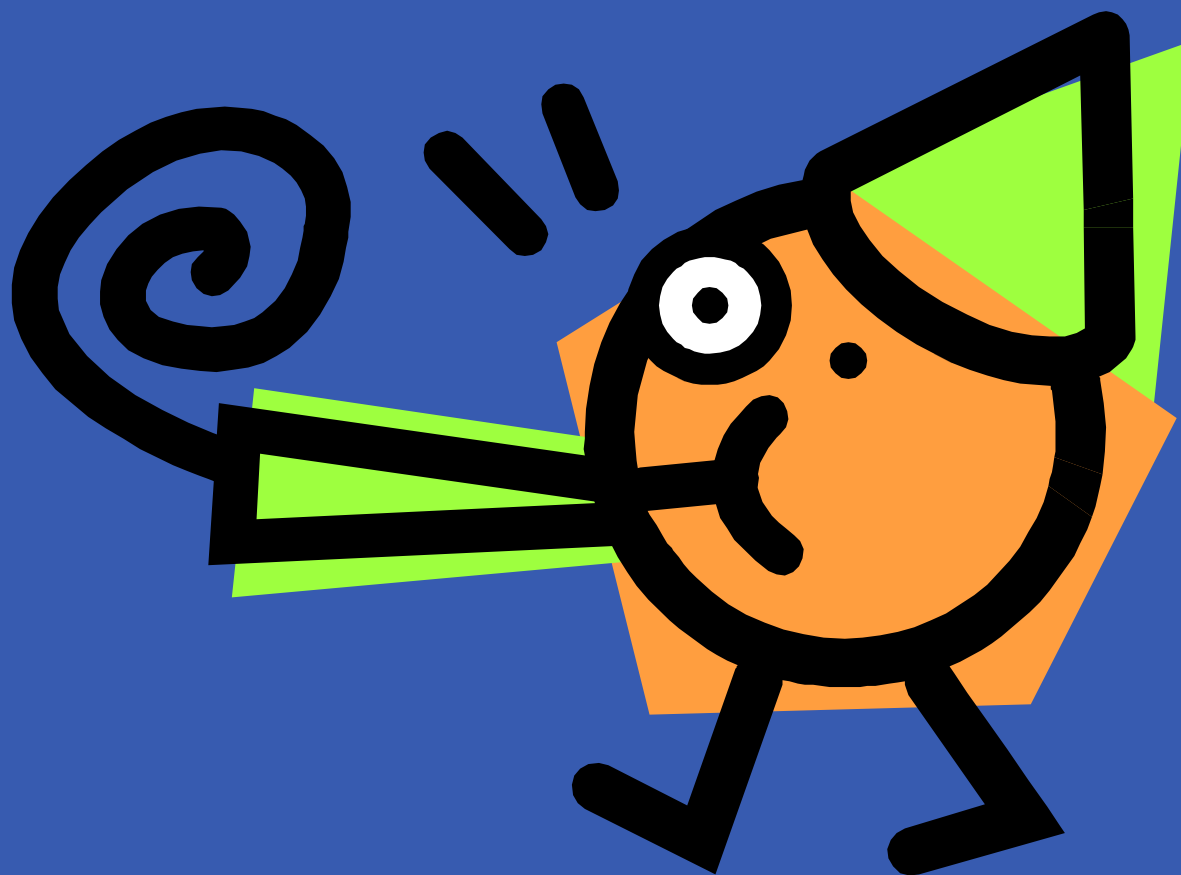


Krinsley JS. Mayo Clin Proc. 2003;78:1471-1478.

Effect of an Intensive Glucose Management Protocol on Mortality in Critically Ill Patients

- ▣ Study of 800 consecutive patients
- ▣ Compared with 800 patients one year prior
- ▣ Groups were well-matched
- ▣ Goal was to get the blood glucose below 140
 - Mean glucose dropped from 152.3 to 130.7 mg/dl
- ▣ Mortality decreased 29% ($p = 0.002$)
- ▣ Decreased LOS in ICU by 10.8%

Wow.....Wow....Wow



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Intensive Insulin Therapy in the Medical ICU

Greet Van den Berghe, M.D., Ph.D., Alexander Wilmer, M.D., Ph.D., Greet Hermans, M.D.,
Wouter Meersseman, M.D., Pieter J. Wouters, M.Sc., Ilse Milants, R.N., Eric Van Wijngaerden, M.D., Ph.D.,
Herman Bobbaers, M.D., Ph.D., and Roger Bouillon, M.D., Ph.D.

Intensive Insulin Therapy in Medical ICU

- ▣ Patients in the medical ICU expected to stay ≥ 3 days (n=1200)
- ▣ Randomized to a target blood glucose:
 - 80-110 mg/dl (Intensive Insulin Therapy - IIT)
 - OR
 - 180-200 mg/dl (Conventional Insulin Therapy - CIT)
- ▣ **Results:**
 - ▣ No difference in ICU and hospital mortality (primary outcome of the study)
 - ▣ Reduced renal injury, accelerated weaning, shorter ICU and hospital discharge.
 - ▣ Beyond the third day of insulin therapy, the in-hospital mortality was reduced (52.5% vs 43%, $p=0.009$)
 - ▣ MORE hypoglycemia in the IIT group.
 - ▣ In patients who stayed < 3 days, mortality was higher in the IIT group (26.8% vs 18.8%), but when adjusted, difference was not statistically significant.

Recommendations - 2006

American College of Clinical Endocrinologists
(ACCE):

Recommends near-normal glucose level in all ICU patients and recommends 110 mg/dL as the upper limit for glycemic targets in the ICU.

NICE-SUGAR

Normoglycemia in Intensive Care Evaluation-
Survival Using Glucose Algorithm Regulation

NICE-SUGAR

Normoglycemia in Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation

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Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

NICE-SUGAR

Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation

- ▣ 6104 ICU patients (medical and surgical) from 42 hospitals in Australia, New Zealand, and North America

- ▣ Patients were randomized to:
 - Insulin given for glucose > 180 mg/dl (10 mmol/L) and stopped for glucose < 144 mg/dl (BG < 8 mmol/L)
 - Glucose Target: 81 – 108 mg/dl (4.5-6 mmol/L)

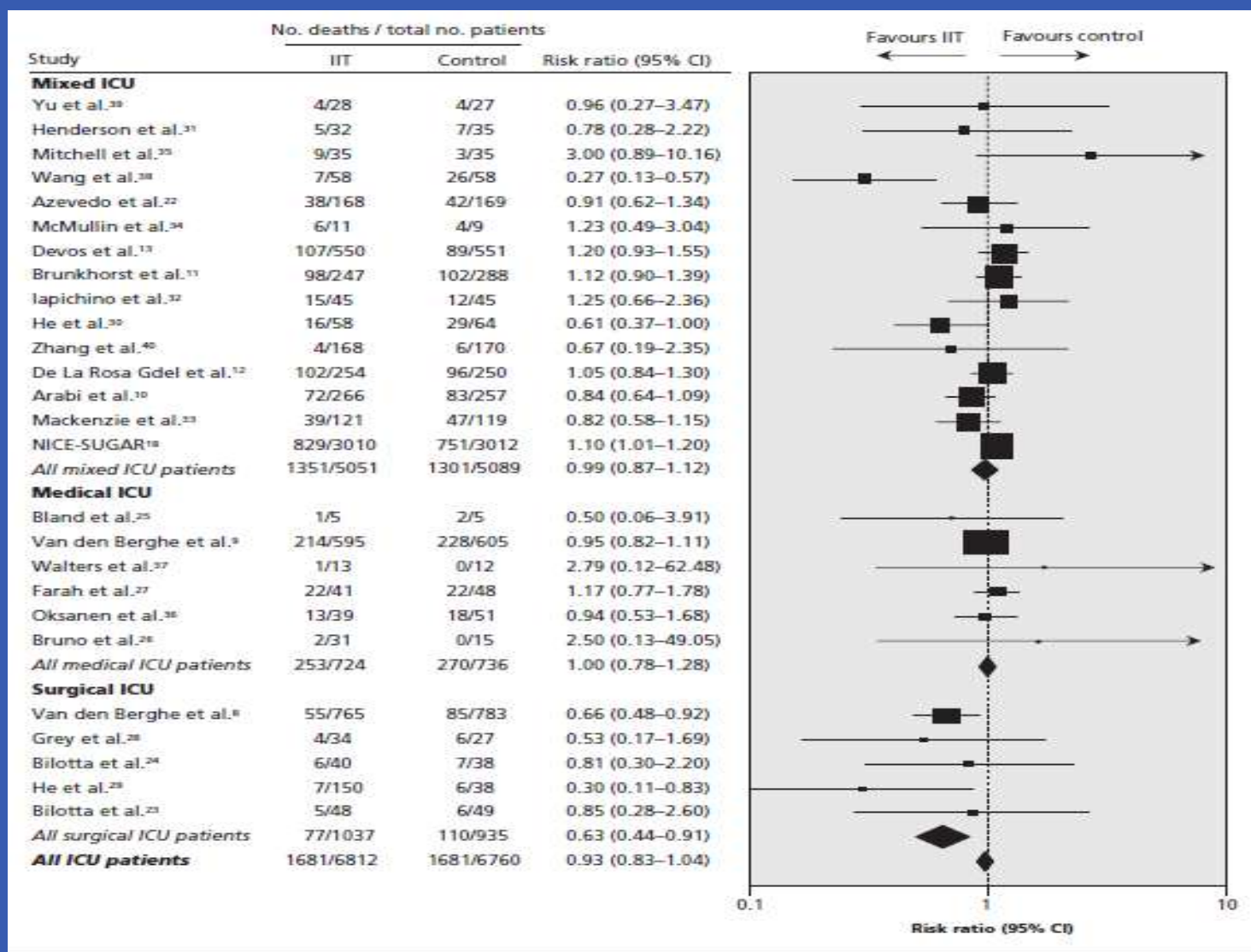
NICE-SUGAR

Results:

- All-cause mortality at 90 days: 27.5% for intensive group vs. 24.9% for conventional group ($p = 0.02$)
- There was no significant difference between the two groups in the median number of days in the ICU or hospital, the median number of days of mechanical ventilation, or renal replacement therapy.
- Severe hypoglycemia: 6.8% vs. 0.5% ($p < 0.001$), respectively

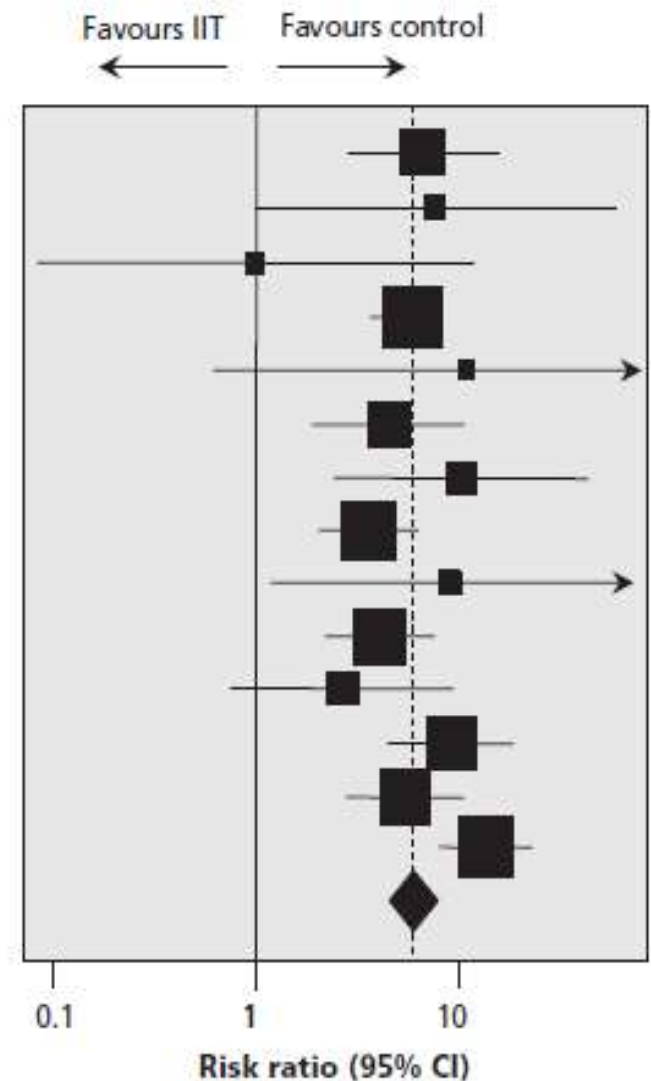
Meta-Analysis including the NICE SUGAR Trial

Donald E.G. Griesdale et al, CMAJ 2009;180(8):821-827



Risk of hypoglycemia with IIT

Study	No. events / total no. patients		Risk ratio (95% CI)
	IIT	Control	
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)
<i>Overall</i>	654/6138	98/6209	5.99 (4.47–8.03)



Standards of Medical Care in Diabetes— 2010 AMERICAN DIABETES ASSOCIATION POSITION STATEMENT



GOALS FOR BLOOD GLUCOSE LEVELS

Critically ill patients:

Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of \geq 180 mg/dL (10 mmol/L).

Once Insulin therapy is started, a glucose range of 140-180 mg/dL is recommended for the majority of critically ill patients. (*Evidence level A*)



Surviving Sepsis Campaign Statement on Glucose Control in Severe Sepsis (June 2009*)

- There is insufficient information from randomized controlled trials to determine the optimal target range of blood glucose in the severely septic patient.
- The NICE-SUGAR trial is the largest most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals, and a more general patient population.
- Based on the results of this trial, we recommend against intravenous insulin therapy titrated to keep blood glucose in the normal range (80-110 mg/dl) in patients with severe sepsis.
- It is clear that attempts to normalize blood glucose with IV insulin during critical illness results in higher rates of hypoglycemia.
- Until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dl as was observed in the beneficial arm of the NICE-SUGAR trial.



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.

There is no evidence to support the use of intensive insulin therapy in general medical-surgical ICU patients who are fed according to current guidelines.

Tight glycemic control is associated with a high incidence of hypoglycemia and an increased risk of death in patients not receiving parenteral nutrition.

Hyperglycemia in Pediatric ICU

- ▣ Hyperglycemia (BG>200 mg/dL) has been reported in up to 35% of critically ill pediatric patients.
- ▣ There is very limited data regarding hyperglycemia in critically ill pediatric patients.
- ▣ A correlation between hyperglycemia and worst clinical outcomes has been reported in a few studies.

Hyperglycemia in Pediatric ICU

- ❑ In a multi-center, international, RCT, intensive insulin therapy did not improve mortality or morbidity, but increased the incidence of hypoglycemia in low birth weight infants. (*Beardsall R, et al. NEJM 2008*)
- ❑ Patients were randomized to continuous infusion of insulin at a dose of 0.05 U per kilogram of body weight per hour with 20% dextrose support or standard care.
- ❑ The study was discontinued early because of concerns about futility with regard to the primary outcome and potential harm.

Hyperglycemia in Pediatric ICU

- ▣ In a RCT involving children and infants, TGC reduced LOS but increased incidence of hypoglycemia (1 vs 25%).
(*Vlasselaers D, et al. Lancet, 2009*)
- ▣ There is high variability in clinical practice.
- ▣ In a recent survey, 84.5% of pediatric ICU physicians considered hypoglycemia more dangerous than hyperglycemia. (*Hirshberg E et al, Chest 2008*)

Summary

- ▣ Hyperglycemia is common in critically ill adult and pediatric patients.
- ▣ Intensive Insulin Therapy (i.e., target 80-110 mg/dL) provided no mortality or morbidity benefit over CIT for mixed medical surgical ICU patients.
- ▣ Intensive insulin therapy *may* still have benefit in surgical (especially cardiac surgery patients)
- ▣ Intensive Insulin therapy is associated with increased hypoglycemia.

Summary

- ▣ Intermediate targets are recommended and may provide mortality benefit over tighter targets with reduction in incidence of hypoglycemia
- ▣ Continuous blood glucose monitoring is required to ensure adequate glucose control and minimal hypoglycemia.
- ▣ More studies are required to determine the safe and effective glycemic control for pediatric patients.

Thank You....