Blood glucose control in the ICU:

“How did I get involved…?”

Greet Van den Berghe M.D., Ph.D.
Department of Intensive Care Medicine
University Hospital Gasthuisberg
Catholic University of LEUVEN
B-3000 BELGIUM

G.V.d.B., K.U.Leuven
Disclosure: current (last 2 years) funding

- Flemish Government (Methusalem program)
- Fund for Scientific Research Flanders Belgium
- Leuven University (GOA grant)
- Baxter Healthcare: <30% funding of EPaNIC trial
Overview

• We started it, by doing the first RCT …

• What did “repeat” studies say?

• Why the ongoing controversy?

• Can we reconcile the evidence into “customized guideline”

• What’s required for > 2012?
Association hyperglycemia and death

![Graph showing the relationship between blood glucose levels and mortality. The x-axis represents blood glucose levels with three labeled points: hypo, normal for age, and "renal threshold". The y-axis represents mortality. The graph shows a decrease in mortality from hypo to normal for age, and an increase beyond the "renal threshold".](image-url)
Association hyperglycemia and death

No history of diabetes

History of diabetes

BLOOD GLUCOSE

MORTALITY

hypo normal for age “renal threshold”

G.V.d.B., K.U.Leuven
Association hyperglycemia and death

BLOOD GLUCOSE

MORTALITY

- hypo
- normal for age
- "renal threshold"

No history of diabetes

History of diabetes

adaptive?
contributing to adverse outcome?
Causality? RCT!

The Leuven comparison

"Don’t touch"

Intervention group

Control group

G.V.d.B., K.U.Leuven
Blood glucose control

S-ICU

M-ICU

The New England Journal of Medicine


Medians
Boxes = IQR
Whiskers = P10-P90
How did we do this?

- **Arterial blood** for blood glucose monitoring
- ABL *blood gas analyzer SICU/PICU* (HemoCue MICU)
- *Frequent* blood glucose *sampling* (0.5h-4h)
- *Continuous IV* insulin (regular) infusion
- *Syringe pump* for insulin infusion
- *Central venous* line for insulin infusion
  
  *(connection of infusion as close as possible to patient; dedicated lumen)*

- *Nurse driven* guideline; *most patients included*
With careful K+ correction by the nurses!

Nursing standing order to:
measure $K^+$ with each blood glucose check on ABL
maintain $K^+ > 4$ meq/l by IV potassium supplements

TGC: 55% more potassium given as supplements than in the usual care group (p < 0.01)

Van den Berghe G et al. J Clin Endocrinol Metab 2009
Mixed M-ICU / S-ICU population (N=2748)

Cumulative risk for in-hospital mortality

Intention-to-treat (N = 2748)
- Hosp mort 24% -> 20%
- p = 0.02
- † - 4%

In ICU at least 3 days (N = 1389)
- Hosp mort 38% -> 30%
- p = 0.006
- † - 8%

Van den Berghe G et al. DIABETES 2006, 55: 3151-3159

G.V.d.B., K.U.Leuven
Intensive insulin therapy for patients in pediatric intensive care: A prospective randomized controlled study


Lancet 2009; 373: 547-556
Age-adjusted glucose control in PICU study

Vlasselaers et al. Lancet 2009

Infants (aged < 1 y)

Children (aged >= 1 y)
Age-adjusted glucose control in PICU study

Infants (aged < 1 y)

6.4 mmol/l --> 4.8 mmol/l
115 mg/dl --> 86 mg/dl

Children (aged >= 1 y)

8.2 mmol/l --> 5.3 mmol/l
148 mg/dl --> 95 mg/dl

Vlasselaers et al. Lancet 2009
Age-adjusted glucose control in PICU study

Infants (aged < 1 y)
- 6.4 mmol/l --> 4.8 mmol/l
- 115 mg/dl --> 86 mg/dl

Children (aged >= 1 y)
- 8.2 mmol/l --> 5.3 mmol/l
- 148 mg/dl --> 95 mg/dl

ADULT TGC
(80-110 mg/dl)

Vlasselaers et al. Lancet 2009
Age-adjusted glucose control in PICU study

**Infants (aged < 1 y)**
- Blood glucose: 6.4 mmol/l --> 4.8 mmol/l
- 115 mg/dl --> 86 mg/dl

**Children (aged >= 1 y)**
- Blood glucose: 8.2 mmol/l --> 5.3 mmol/l
- 148 mg/dl --> 95 mg/dl

*Vlasselaers et al. Lancet 2009*
Age-adjusted glucose control in PICU: reduced mortality

Cumulative incidence of PICU death (%)

- Usual care: 5.7% (p = 0.038)
- TGC: 2.6%

N = 700

Vlasselaers et al. Lancet 2009
How low a blood glucose is enough to do the job?

Don’t know, no RCTs …
Post-hoc comparison in M-ICU / S-ICU population (N=2748)

Cumulative risk in-hospital mortality

% new kidney injury

first EMG positive for CIPNP Cum hazard

Van den Berghe G et al. DIABETES 2006, 55: 3151-3159
Patients with diabetes vs. without diabetes

Van den Berghe G et al. Diabetes 2006
Overview

• We started it, by doing the first RCT…

• What did “repeat” studies say ?

• Why the ongoing controversy ?

• Can we reconcile the evidence into “customized guideline”

• What’s required for > 2012 ?
Implementation studies

BLOOD GLUCOSE

MORTALITY

The Leuven comparison

Furnary, Krinsley; Reed etc...

"Don’t touch"

hypo normal for age "renal threshold"

G.V.d.B., K.U.Leuven
Implementation studies: confirmed benefit

• Implementation studies in CABG patients with diabetes by Furnary et al.: better outcome!

• Implementation study in (predominantly non-diabetic) mixed MICU/SICU by Krinsley et al.: better outcome!
  – Chest 2006; 129: 644-650 (cost-saving)

• A recent implementation study in non-diabetic trauma patients in ICU by Reed et al.: better outcome!
Targeting an intermediate level was a good idea!

Van den Berghe G et al. DIABETES 2006, 55: 3151-3159

Cumulative risk
in-hospital mortality

Intention-to-treat
(N = 2748)

mean BG > 150 mg/dl
mean BG 110-150 mg/dl
mean BG <110 mg/dl

3/4 of the effect is due to avoiding excessive hyperglycemia

mean BG <110 mg/dl

mean BG 110-150 mg/dl

mean BG > 150 mg/dl

p = 0.0005

G.V.d.B., K.U.Leuven
NICE-SUGAR study

The NICE-SUGAR comparison

The Leuven comparison

MORTALITY vs BLOOD GLUCOSE

hypo, normal for age, "renal threshold"

"Don’t touch"

Targeting normoglycemia vs. intermediate level: what to expect?

Van den Berghe G et al. DIABETES 2006, 55: 3151-3159

Cumulative risk
in-hospital mortality

Intention-to-treat
(N = 2748)

mean BG > 150 mg/dl
mean BG 110-150 mg/dl
mean BG <110 mg/dl

1.0 % ARR
Power 80%
Type 1 error < 0.05
70,000 patients needed
Outcome of NICE-SUGAR (N=6100)

- no difference in organ function
- more cardiovascular deaths
- hypoglycemia x 13

Overview

- We started it, by doing the first RCT …
- What did “repeat” studies say?
- Why the ongoing controversy?
- Can we reconcile the evidence into “customized guideline”
- What’s required for > 2012?
NICE-SUGAR:
Evidence against glucose control?
NICE-SUGAR was not a "repeat study"

The Leuven comparison

The NICE-SUGAR comparison

"Don’t touch"

MORTALITY

hypogenormal for age

"renal threshold"

BLOOD GLUCOSE


G.V.d.B., K.U.Leuven
## Differences between 3 Leuven studies and NICE-SUGAR

<table>
<thead>
<tr>
<th></th>
<th>Leuven</th>
<th>NICE-SUGAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>3448</td>
<td>6100</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>3x1 center</td>
<td>41 centers</td>
</tr>
<tr>
<td><strong>Sample (% of admissions)</strong></td>
<td>68-95%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Comparator group target</strong></td>
<td>180-215 mg/dl</td>
<td>140-180 mg/dl</td>
</tr>
<tr>
<td></td>
<td>(10 - 12 mmol/l)</td>
<td>(7.8 - 10 mmol/l)</td>
</tr>
<tr>
<td><strong>Intervention target</strong></td>
<td>“normal for age”</td>
<td>“normal for age”</td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td>reduced organ failure</td>
<td>negative</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>reduced by 3% (late)</td>
<td>increased by 3% (early)</td>
</tr>
</tbody>
</table>
## Differences between 3 Leuven studies and NICE-SUGAR

<table>
<thead>
<tr>
<th></th>
<th>Leuven</th>
<th>NICE-SUGAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>3448</td>
<td>6100</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>3x1 center</td>
<td>41 centers</td>
</tr>
<tr>
<td><strong>Sample (% of admissions)</strong></td>
<td>68-95%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Comparator group target</strong></td>
<td>180-215 mg/dl (10 - 12 mmol/l)</td>
<td>140-180 mg/dl (7.8 - 10 mmol/l)</td>
</tr>
<tr>
<td><strong>Intervention target</strong></td>
<td>“normal for age”</td>
<td>“normal for age”</td>
</tr>
<tr>
<td><strong>Feeding status first week</strong></td>
<td>fed (parenteral+ enteral)</td>
<td>hypocaloric (enteral only)</td>
</tr>
<tr>
<td><strong>Insulin infusion</strong></td>
<td>only continuous</td>
<td>continuous + bolus</td>
</tr>
<tr>
<td><strong>Glucose monitoring tool</strong></td>
<td>ABL Radiometer (HemoCue)</td>
<td>all glucometers</td>
</tr>
<tr>
<td><strong>Blood sampling site</strong></td>
<td>arterial</td>
<td>arterial/venous/cap.</td>
</tr>
<tr>
<td><strong>Nurse instructions</strong></td>
<td>guideline + intuitive decision</td>
<td>‘if-then’ algorithm</td>
</tr>
<tr>
<td><strong>Target BG reached</strong></td>
<td>70%</td>
<td>&lt;50%</td>
</tr>
<tr>
<td><strong>Overlap BG</strong></td>
<td>&lt;10%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td><strong>Morbidity</strong></td>
<td>reduced organ failure</td>
<td>negative</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>reduced by 3%</td>
<td>increased by 3%</td>
</tr>
<tr>
<td>(therapy withdrawal)</td>
<td>(late)</td>
<td>(early)</td>
</tr>
</tbody>
</table>

G.V.d.B., K.U.Leuven
Used inaccurate glucose meters.

“Glucose meters were designed for the monitoring of blood glucose levels in diabetics in a home environment and are not accurate enough to keep BG levels within the narrow range of TGC”
Bland-Altman (ABL blood gas analyzer) (Bias)

TGC target range = 30 mg/dL

95% CI = 40.5 mg/dL

95% CI = 37.1 mg/dL

Did this problem occur in NICE-SUGAR? Yes!

“... the NICE-SUGAR study should be repeated with more attention paid to the accuracy of the glucose measuring device”

(reportled by a Nice-Sugar participating center, Alberta Canada)

<table>
<thead>
<tr>
<th>Variability of true glucose</th>
<th>TE 8% (Leuven studies)</th>
<th>TE &gt;20% (NICE-SUGAR, etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Little change from</td>
<td>Chaotic pattern</td>
</tr>
<tr>
<td></td>
<td>perfect assay</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Errors in insulin dose of 2 or more categories</th>
<th>TE 8% (Leuven studies)</th>
<th>TE &gt;20% (NICE-SUGAR, etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2%</td>
<td>&gt;6%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severe missed hypoglycemia (Measured &gt; 50 mg/dL at true &lt;30 mg/dL)</th>
<th>TE 8% (Leuven studies)</th>
<th>TE &gt;20% (NICE-SUGAR, etc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6%</td>
<td>&gt;16%</td>
<td></td>
</tr>
</tbody>
</table>

Bruns D., presented at ISICEM Brussels, March 2011
NICE-SUGAR study

The Leuven comparison

The NICE-SUGAR comparison

“Don’t touch”

Mortality

Blood Glucose

Hypo normal for age “renal threshold”


G.V.d.B., K.U.Leuven
Achieved in NICE-SUGAR?

Mortality vs Blood Glucose:
- Hypo: Low glucose levels
- Normal for age: Average glucose levels
- "Renal threshold": High glucose levels

G.V.d.B., K.U.Leuven
Achieved in NICE-SUGAR?

MORTALITY

hypo normal for age “renal threshold”

BLOOD GLUCOSE

G.V.d.B., K.U.Leuven
Achieved in NICE-SUGAR?

MORTALITY

hypo  normal for age  “renal threshold”

BLOOD GLUCOSE

G.V.d.B., K.U.Leuven
Achieved in NICE-SUGAR?

Trade-off: HYPOGLYCEMIA

hypo normal for age “renal threshold”

BLOOD GLUCOSE

MORTALITY

G.V.d.B., K.U.Leuven
Achieved in NICE-SUGAR?

**Trade-off Leuven:**

- Severe hyperglycemia

*MORTALITY*

- hypo
- normal for age
- “renal threshold”

**BLOOD GLUCOSE**

G.V.d.B., K.U.Leuven
Where does this leave the bedside clinician?

Blood glucose target?
Clinical practice? Leuven or NICE-SUGAR target?

Simple reasoning:

Targeting “age normal” levels better than “don’t touch” (3 Leuven studies)

Targeting intermediate levels safer than “age normal” (NICE-SUGAR)

---

intermediate level (+/- 140 mg/dl or 7-8 mmol/l) is preferable
“age normal” if you work in “Leuven settings”

- **Arterial blood** for blood glucose monitoring
- **ABL** blood gas analyzer SICU/PICU *(HemoCue MICU)*
- **Frequent** blood glucose *sampling* (0.5h-4h)
- **Continuous IV** insulin (regular) infusion
- **Syringe pump** for insulin infusion
- **Central venous** line for insulin infusion
  
  (connection of infusion as close as possible to patient; dedicated lumen)

- **Nurse driven** guideline; *most patients included*
Essential logistics to perform BGC safely:

- **One meter** (check for accuracy) and measure frequently
- **No capillary** blood
- **Syringe pump, hard** infusion line, **continuous** infusion only
- “Educated” **ICU nurses are the experts!”
Overview

• We started it, by doing the first RCT…

• What did “repeat” studies say?

• Why the ongoing controversy?

• Can we reconcile the evidence into “customized guideline”

• What’s required for > 2012?
What’s required for > 2012?

• **accurate sensor for glucose** in the blood

• **frequent readouts** (continuous ?)

• scientifically sound, trained, **validated algorithm**

• (semi ?) **closed loop**

• **Tested for efficacy and safety in ICU patients**
Thank You

Laboratory and Department of Intensive Care Medicine