Advantages of Tight Glycemic Control in the Hospital Setting

Richard M. Bergenstal, MD
Executive Director
International Diabetes Center at Park Nicollet
Minneapolis, MN

President, Medicine & Science
American Diabetes Association
Disclosure Statement
Richard M. Bergenstal, MD

I have participated in clinical research and/or served as a consultant for:

- Eli Lilly
- Novo Nordisk
- sanofi-aventis
- MannKind
- Roche
- LifeScan / J&J
- Abbott
- Bayer
- Medtronic
- Intuity
- DexCom / Edwards

RMB receives no personal compensation for any of these activities and all contracts are with the non-profit Park Nicollet Institute for Research and Education

I have inherited Merck stock

I am a volunteer officer of the American Diabetes Association
The previous American Diabetes Association Consensus Statement recommended that the performance goal of all SMBG systems should be to achieve a total error (analytical plus user) of less than 10% at glucose concentrations ranging from 30 to 400 mg/dl. Unfortunately, this goal has not been achieved for most SMBG systems.

1986 ADA recommended 10% not 15% total error?

But by 1993 this goal was not achieved.
Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

DM Kendall. International Diabetes Center
Retinopathy and Hypoglycemia Risk

*Intensive Insulin Therapy for Type 1 Diabetes*

In view of the proven benefits of good metabolic control, it is even more important now than it was in 1986 for SMBG systems to measure glucose accurately. The goal of SMBG device manufacturers should be to make future SMBG systems with an analytic error of +5%.
I believe the American Diabetes Association feels that:

- SMBG is one important component of safely improving glucose control
5. The purpose(s) of performing SMBG and using SMBG data should be agreed between the person with diabetes and the healthcare provider. These agreed-upon purposes/goals and actual review of SMBG data should be documented.
NHS Diabetes publishes
Self-Monitoring of Blood Glucose report
26 February 2010

Self monitoring of blood glucose in non-insulin-treated Type 2 diabetes

A report prepared by an NHS Diabetes Working Group

2. In keeping with the recommendations contained within NICE Clinical Guideline CG87, SMBG should only be provided routinely to people with Type 2 diabetes not treated with insulin or sulphonylureas where there is an agreed purpose or goal to testing.

3. SMBG should be used only within a care package, accompanied by structured education which should include clear instructions as to the place of monitoring and how results can be used to reinforce lifestyle change, adjust therapy or alert healthcare professionals.
Status of Glucose Control in the US
A1C Measures from NHANES

% of Individuals Achieving A1c <7%

1999-2000 2001-2 2003-4

Severe Hypoglycemia Rates in INT & STD Groups

INT

STD

15% vs. 5%
3-fold increase
# Self-reported Antecedents to Hypoglycemia Events

<table>
<thead>
<tr>
<th>Reason</th>
<th>% (n=875 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed/missed meal or ate fewer carbohydrates</td>
<td>58% (510)</td>
</tr>
<tr>
<td>None</td>
<td>17% (148)</td>
</tr>
<tr>
<td>Took incorrect dose of glucose lowering medication</td>
<td>9% (82)</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>8% (70)</td>
</tr>
<tr>
<td>Intercurrent illness</td>
<td>5% (44)</td>
</tr>
<tr>
<td>Ingested alcohol</td>
<td>3% (26)</td>
</tr>
<tr>
<td>Recent weight loss</td>
<td>3% (29)</td>
</tr>
<tr>
<td>Started or increase of other medication</td>
<td>3% (28)</td>
</tr>
</tbody>
</table>
Why Can’t We Improve Glycemic Control & Do it Safely?

Maybe We Rely Too Much on the HbA1c Alone for Clinical Decision Making

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>tells you a change in therapy is needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>if elevated</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SMBG</th>
<th>tells you what change in therapy to make</th>
</tr>
</thead>
<tbody>
<tr>
<td>if displayed to show a pattern</td>
<td></td>
</tr>
</tbody>
</table>
I believe the American Diabetes Association feels that:

- SMBG is one important component of safely improving glucose control
- There is room for improvement in both SMBG accuracy and the clinical use of SMBG data
  - Patients in the hospital setting have the most potential to benefit from improved meter accuracy. In addition, improved accuracy would add some benefit in most outpatient settings
  - Teaching professionals and patients how to effectively use SMBG data needs at least equal emphasis
- The role of CGM (inpatient & outpatient) deserves intense study and continued innovation to define its role in management in both settings.
Special thanks to my colleagues for data and slides

Silvio E. Inzucchi MD
Etie S. Moghissi, MD
Mary Korytkowski MD
Anthony Furnary, MD
Diabetes and Hospitalization
Scope of the Problem

- Prevalence of diabetes is estimated at 12% to 25% of hospitalized patients and may be significantly underestimated.
- 50% of patients admitted to CCU have diabetes or pre-diabetes.
- 29%-50% of all cardiac surgery patients.
- 1-3 days longer hospital stay.

Inpatient Glucose Management

The Past

- Acute hyperglycemia was considered to be benign
- Sliding scale was the norm
- No published standards of care or guidance from medical societies
- Hyperglycemia in the hospital was essentially ignored
Glycemic Control in the Hospital: An Elusive Goal

“Stress hyperglycemia”
D/C outpatient regimens
IV D5/ TPN / PPN
Steroids, pressors
↓ Physical activity
Fear of hypoglycemia

↓ Nutrition
Meal interruptions
Monitored compliance
Insulin ‘stacking’
Δ Mental status

The ‘Portland Protocol’: Glucose Control & Sternal Infections

DSWI = deep sternal wound infection; CII = continuous insulin infusion.

Intensive Insulin Therapy in the Surgical ICU: The Leuven Study

1548 SICU patients

Conventional
IV insulin if BG >215 mg/dl
Target: 180-200 mg/dl

39% insulin
BG=153 mg/dl

Intensive
IV insulin if BG >110 mg/dl
Target: 80-110 mg/dl

99% insulin
BG=103 mg/dl

Primary Outcomes:
ICU Mortality

Intensive Insulin Therapy in the Surgical ICU: The Leuven Study

**A**

![Graph showing survival in the ICU](image1)

- **Intensive treatment**
- **Conventional treatment**

**MORTALITY ↓ 42%**

*P* < 0.04

**B**

![Graph showing in-hospital survival](image2)

- **Intensive treatment**
- **Conventional treatment**

**MORTALITY ↓ 34%**

*P* < 0.01

Hospital Mortality Rate & Glucose Control in a Medical-Surgical ICU

N=1826 ICU patients

Mean Glucose Value During ICU Stay (mg/dL)

Hyperglycemia: A Predictor of Mortality Following CABG in Diabetics

Adjusted for 19 clinical and operation variables

First Postop Glucose >200
- 2x LOS
- 3x Vent duration
- 7x mortality !!!

CABG, coronary artery bypass graft.

Intensive Insulin Therapy in Patients with Severe Sepsis (VISEP Study)

- N = 537
- Multicenter, 2x2 factorial trial
- Intensive group vs conventional group
  - Mean morning blood glucose (112 mg/dL vs 151 mg/dL; P<0.001)
  - Severe hypoglycemia (17.0% vs 4.1%, P<0.001)
  - No difference in mortality

Tight Glucose Control in Critically Ill Patients
A Meta-Analysis


- 29 randomized controlled trials totaling 8432 patients
- Tight glucose control vs usual care: no significant difference in mortality
- Tight glucose control was significantly associated with:
  - Higher risk of hypoglycemia (≤ 40 mg/dL) (13.7% vs 2.5%; RR, 5.13)
Responding to New Evidence

AACE/ADA Inpatient Glycemic task Force

*Etie S. Moghissi, MD, FACP, FACE, AACE Chair*

*Mary T. Korytkowski, MD, ADA Chair*

- Monica DiNardo, MSN, CRNP, CDE
- Daniel Einhorn, MD, FACP, FACE
- Richard Hellman, MD, FACP, FACE
- Irl B. Hirsch, MD
- Silvio E. Inzucchi, MD
- Faramarz Ismail-Beigi, MD, Ph
- M. Sue Kirkman, MD;
- Guillermo E. Umpierrez, MD, FACP, FACE
AACE-ADA Consensus Statement on Inpatient Glycemic Control
May 2009

American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control

Etie S. Moghissi, MD, FACP, FACE; Mary T. Korytkowski, MD; Monica Dinardo, MSN, CRNP, CDE; Daniel Einhorn, MD, FACP, FACE; Richard Hellman, MD, FACP, FACE; Irl B. Hirsch, MD; Silvio E. Inzucchi, MD; Faramarz Ismail-Beigi, MD, PhD; M. Sue Kirkman, MD; Guillermo E. Umpierrez, MD, FACP, FACE

Endocrine Practice 15: 1-17, 2009
Diabetes Care 32: 1119-1131, 2009
NICE-SUGAR Study: Design

- Multi-centre, open label, randomized, controlled trial
- Examining the effects of blood glucose management on 90 day, all cause morbidity and mortality
- 6104 ICU patients
  - 3054 in intensive control group (target: 81 to 108 mg/dL)
  - 3050 in conventional control group (target: ≤180 mg/dL)
- The two groups had similar baseline characteristics
- 40 centers of Australia, New Zealand, and Canada
- Recruitment April 2005 to November 2008
- Last Follow-up November 2008

The NICE-SUGAR Study

Blood Glucose Level, According to Treatment Group

IIT goal: 81 – 108 mg/dL (mean BG 118 mg/dL)
CIT goal: <180 mg/dL (mean BG 145 mg/dL)

Probability of Survival

90 day mortality: IIT: 829 patients (27.5%), CIT: 751 (24.9%)
Absolute mortality difference: 2.6% (95% CI, 0.4 to 4.8); Odds ratio for death with IIT was 1.14 (95% CI, 1.02 to 1.28; P = 0.02).

Nice Sugar, NEJM 360; march 26, 2009
# NICE-SUGAR Study Results: Treatment and Glucose Measures

<table>
<thead>
<tr>
<th>Insulin Rx</th>
<th>Intensive Control Group</th>
<th>Conventional Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients treated with insulin</td>
<td>97.2%</td>
<td>69.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median duration of treatment (IQR)</td>
<td>4.2 days (1.9-8.7)</td>
<td>4.3 days (2.0-9.0)</td>
<td>0.69</td>
</tr>
<tr>
<td>Mean insulin dose, units/day</td>
<td>50.2 ± 38.1</td>
<td>16.9 ± 29.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning BG, mg/dL</td>
<td>118 ± 25</td>
<td>145 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time-weighted BG, mg/dL</td>
<td>115 ± 18</td>
<td>144 ± 23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (BG ≤40 mg/dL), no. of patients/total no. (%)</td>
<td>206/3016 (6.8%)</td>
<td>15/3014 (0.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Intensive Control Group</th>
<th>Conventional Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 Day Mortality</td>
<td>22.3%</td>
<td>20.8%</td>
<td>0.17</td>
</tr>
<tr>
<td>90 Day Mortality</td>
<td><strong>27.5%</strong></td>
<td><strong>24.9%</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Mech. Ventilation</td>
<td>96%</td>
<td>95.3%</td>
<td>0.17</td>
</tr>
<tr>
<td>(Mean days + SD)</td>
<td>(6.6 ± 6.6)</td>
<td>(6.6 ± 6.5)</td>
<td>(0.56)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>15.4%</td>
<td>14.5%</td>
<td>0.34</td>
</tr>
<tr>
<td>Bloodstream infections</td>
<td>12.8%</td>
<td>12.4%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

NICE SUGAR Study: Conclusions

- This large, international, randomized trial, found that intensive glucose control did not offer any benefit in critically ill patients.

- Blood glucose target of ≤ 180 mg/dL with the achieved target of 144 mg/dL resulted in lower (90 day) mortality than did a target of 81-108 mg/dL.

- There was increased hypoglycemia with lower glucose targets.

Mean Glucose & In-Hospital Mortality in Patients with AMI

(Reference: Mean BG 100-110 mg/dl)


N= 16,871
What Should We Take Away from these Trial?

- Good glucose control, as opposed to near-normal control, is likely sufficient to improve clinical outcomes in the ICU setting.
- We need to have a renewed concern about hypoglycemia in critically ill patients.
- Importantly, the NICE-SUGAR results do not endorse a *laissez-faire* attitude toward inpatient hyperglycemia that was prevalent a decade ago.
- It is time to rethink the targets and measurement.
What glycemic targets can be recommended in different patient populations?

**TARGETS: Critically ill**

- Insulin infusion to control hyperglycemia
- Starting threshold no higher than 180 mg/dL
- Maintain BG between 140-180 mg/dL
  - Possibly greater benefit at lower end of range
- Somewhat lower targets may be appropriate in selected patients
- Targets < 110 mg/dL not recommended

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AACE/ADA Target Glucose Levels in Non–ICU Patients

Non–ICU setting:

- Premeal glucose targets <140 mg/dL
- Random BG <180 mg/dL
- To avoid hypoglycemia, reassess insulin regimen if BG levels fall below 100 mg/dL
- Occasional patients may be maintained with a glucose range below and/or above these cut-points

Hypoglycemia = BG <70 mg/dL
Severe hypoglycemia = BG <40 mg/dL

Recommendations for Managing Patients With Diabetes in the Hospital Setting

Antihyperglycemic Therapy

Insulin
Recommended

IV Insulin
Critically ill patients in the ICU

SC Insulin
Non-critically ill patients

OADs
Not Generally Recommended

2. Diabetes Care. 2009;31(suppl 1):S1-S110
IV Insulin Protocols

Multiple published protocols are available that are effective and safe. Some examples include:

- Yale
- Markovitz
- Leuven
- Portland
- Texas Diabetes Council
- DIGAMI
- University of Washington
- Luther Midelfort Mayo Health System
- Rush University Protocol
- Northwestern University

Yale Insulin Infusion Protocol: First 33 Uses

MICU Insulin Infusion Protocol Results

Glucose (mg/dL)

Time (hours)

The Ideal IV Insulin Protocol

- Easily ordered (signature only)
- Effective (gets to goal quickly)
- Maintains BG within a defined target range over several hours
- Includes an algorithm for making temporary corrective increments or decrements of infusion rate
- Safe (minimal risk of hypoglycemia)
- Directions for treatment of hypoglycemia
- Easily implemented
- Can be executed by nursing staff in response to a single physician order
Antihyperglycemic Therapy

Insulin
Recommended

IV Insulin
Critically ill patients
in the ICU

OADs
Not Generally
Recommended

SC Insulin
Non-critically ill patients

1. Diabetes Care. 2009;31(suppl 1):S1-S110
RABBIT 2: Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of patients with type 2 diabetes

Mean blood glucose difference between groups = 27 mg/dL (P<0.01)

*P < 0.01; † P < 0.05
SSI = sliding-scale regular insulin.

"Basal-Bolus" Insulin Therapy

Insulin Level

Hours

Rapid (Lispro, Aspart, Glulisine)

Long (Glargine, Detemir)
Maintaining Physiologic Insulin Delivery in the Hospital --- 3 Part Insulin Order

Breakfast
Lunch
Dinner
Bedtime

Basal insulin

Correction Dose or Supplemental Dose of Insulin

Mealtime insulin (bolus)
Estimating SC Insulin Dose

1. Calculate estimated total daily dose of insulin as follows:
   - T2DM: 0.5 to 0.7 U/kg
   - T1DM or type unknown: 0.3 to 0.5 U/kg

2. Divide total daily dose of insulin into 50% basal as glargine or detemir and 50% prandial as aspart, lispro, or glulisine

3. Divide prandial insulin into 3 equal doses to be given with meals

Premeal Algorithm for Correction-Dose Insulin

To be administered in addition to scheduled insulin to correct premeal hyperglycemia

<table>
<thead>
<tr>
<th>Premeal BG mg/dL</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
<th>Individualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–199</td>
<td>1 unit</td>
<td>1 unit</td>
<td>2 units</td>
<td></td>
</tr>
<tr>
<td>200–249</td>
<td>2 units</td>
<td>3 units</td>
<td>4 units</td>
<td></td>
</tr>
<tr>
<td>250–299</td>
<td>3 units</td>
<td>5 units</td>
<td>7 units</td>
<td></td>
</tr>
<tr>
<td>300–349</td>
<td>4 units</td>
<td>7 units</td>
<td>10 units</td>
<td></td>
</tr>
<tr>
<td>&gt;349</td>
<td>5 units</td>
<td>8 units</td>
<td>12 units</td>
<td></td>
</tr>
</tbody>
</table>
Hypoglycemia Is a Concern

- Areas of risk:
  - Changes in carbohydrate or food intake
  - Changes in clinical status or medications
  - Failure to adjust therapy based on BG patterns
  - Prolonged use of SSI as monotherapy
  - Poor coordination of BG testing with insulin administration and meal delivery
  - Poor communication during patient transfers
  - Errors in order writing and transcription
  - Meter inaccuracy?
Addressing Safety Concerns of Inpatient Management of Hyperglycemia

Hypoglycemia prevention:

- Use Nurse-initiated protocols to treating mild hypoglycemia as a way of avoiding deterioration to a more severe event
- Identify High risk patients: malnutrition, advanced age, severe illness, kidney/liver/heart failure

Frequent bedside glucose monitoring is essential for guiding therapy with important considerations

- Meters can have +/- 20% variation from lab glucose
- Discrepancy between arterial, venous, capillary samples
- Anemia, polycythemia, hypoperfusion, or use of some medications all affect validity of POC bedside glucose measures
What are areas for future research?

- Stress hyperglycemia (mechanisms, targets)
- Severe hypoglycemia (causes, outcomes, risks, costs)
- Comparisons of glycemic targets and outcomes in non-critically ill patient populations
- Effect of glycemic variability on patient outcomes
- Hospital systems and safety
- Monitoring (meter accuracy, CGM)
- Pediatric populations (targets)
Continuous Glucose Monitoring in the Inpatient Setting

- Good control of blood glucose is recommended in the ICU and medical floors.
- If glucose could be accurately measured more frequently (continuously), hypoglycemia may be minimized and even tighter glycemic control may prove beneficial.
- Research is underway by Edwards Lifesciences, DexCom, Inc. and others evaluating the accuracy and utility of frequent IV glucose monitoring in the inpatient setting. Initial results presented at scientific meetings are very encouraging.
How Will We Translate What We Are Learning Into Improved Practice and Outcomes?

- FDA, ISO & CLIA-POC are gathering critical data and writing important standards or guidelines regarding glucose monitoring in the hospital and outpatient settings.

- But where do people with diabetes, clinicians and educators look for guidance on diabetes management?
How Will We Translate What We Are Learning Into Improved Practice Patterns and Outcomes?

- FDA, ISO & CLIA-POC should find a way to Partner with the American Diabetes Association (and others) to translate new science and standards into changes in practice patterns for patients and health care professionals.