Advancing Glycemic Control in an Inpatient Setting
Background
Diabetes Statistics

The Americas
2000: 33 million
2030: 67 million

Europe
2000: 33 million
2030: 48 million

Africa and Middle East
2000: 22 million
2030: 61 million

Asia and Australia
2000: 83 million
2030: 190 million

World
2000: 171 million
2030: 366 million

<2%  2%-5%  5%-8%  8%-11%  11%-14%

Nationwide Diabetes Prevalence Categories

CDC Nat’l Diabetes Fact Sheet, 2014
Prevalence of Obesity & Diabetes
(U.S. Adults Aged > 18 Years)

**Obesity (BMI ≥30 kg/m²)**

- 1994
- 2000
- 2010

**Diabetes**

- 1994
- 2000
- 2010

Number and Percentage of U.S. Population with Diabetes, 1958-2009

Significance

• The Center for Disease Control reports **29.1 million** people (9.3% of the U.S. population) have diabetes

• Diabetes is 7th leading cause of death

• **20-50% of inpatients** have diabetes or hyperglycemia

• **1 in 4 patients admitted to hospitals** have a known diabetes diagnosis

• **30% of patients** with diabetes have 2 or more hospital admissions per year.

1: Umpierrez et al J Clin Endocrinol Metab 2002; 87: 978-82.
2. CDC Nat’l Diabetes Fact Sheet, 2014
Why Does this Matter?

- Significant impact on morbidity and mortality
  - New hyperglycemia, higher in hospital death rate
  - Missed diabetic diagnosis, readmit 30.6% (vs 9.4%)
  - (Noncardiac) perioperative risk of death increased with an OR of 1.19 for every 1mmol/L increase in BG

Crit Care Med 2009; 37:3001-3009
Why does this matter?

• Regulatory Interest

  – Emerging Metrics for CMS

  • NQF2362, Hyperglycemia (2 values >200)

  • NQF2363, Hypoglycemia (any value <40)
Number of US Hospital Discharges with Diabetes as Any-Listed Diagnosis

Hyperglycemia and Mortality in the Medical Intensive Care Unit

N=1826 ICU patients.

Mortality Increases With Increases in Average BG Levels Post-CABG

CABG, coronary artery bypass graft. *Average Postoperative Glucose (mg/dL)*

Mortality Risk is Greater in Hyperglycemic Patients Without History of Diabetes

No History Diabetes, N=152,910

<table>
<thead>
<tr>
<th>Mean BG (mg/dL)</th>
<th>Odds Ratio</th>
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<tbody>
<tr>
<td>&gt;300</td>
<td></td>
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<tr>
<td>200-300</td>
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<tr>
<td>146-199</td>
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<td>111-145</td>
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History Diabetes, N= 62,868

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Hyperglycemia is Linked to Mortality Regardless of Diabetes Status
180-day Mortality in Patients Admitted for MI (%)

Mortality in Inpatients with “New Hyperglycemia”

Admission Hyperglycemia Is Also Associated With Adverse Outcomes in Non-ICU Settings


Non-ICU patients with community-acquired pneumonia

N = 2471

$P = .03; \dagger P = .01.$

‡ Complications include all in-hospital complications except for abnormalities of glucose.
Outcomes Associated With Glycemic Control in the Hospital
## Benefits of Tight Glycemic Control: Observational Studies and Early Intervention Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furnary, 1999</td>
<td>ICU</td>
<td>DM undergoing open heart surgery</td>
<td>65% ↓ infection</td>
</tr>
<tr>
<td>Furnary, 2003</td>
<td>ICU</td>
<td>DM undergoing CABG</td>
<td>57% ↓ mortality</td>
</tr>
<tr>
<td>Krinsley, 2004</td>
<td>Medical/surgical ICU</td>
<td>Mixed, no Cardiac</td>
<td>29% ↓ mortality</td>
</tr>
<tr>
<td>Malmberg, 1995</td>
<td>CCU</td>
<td>Mixed</td>
<td>28% ↓ mortality After 1 year</td>
</tr>
<tr>
<td>Van den Berghe, 2001*</td>
<td>Surgical ICU</td>
<td>Mixed, with CABG</td>
<td>42% ↓ mortality</td>
</tr>
<tr>
<td>Lazar, 2004</td>
<td>OR and ICU</td>
<td>CABG and DM</td>
<td>60% ↓ A Fib post op survival 2 yr</td>
</tr>
</tbody>
</table>

*RCT, randomized clinical trial.

Intensive Insulin Management in Medical-Surgical ICU

$P < 0.001$

Mean BG Levels (mg/dL)
- Baseline group (n = 800)
  - 152
- Glucose management group (n = 800)
  - 130

$P < 0.002$

Hospital Mortality (%)
- Baseline group (n = 800)
  - 29.3% Reduction

Intensive Insulin Therapy in Critically Ill Patients: SICU

Relative Risk Reduction (%)

- Mortality
- Bacteremia
- Prolonged (>10 d) antibiotics
- Prolonged (>14 d) ventilation
- Dialysis
- Prolonged (>14 d) ICU stay

*P < 0.01

Severe Hypoglycemia in the Medical ICU - 2\textsuperscript{nd} Leuven Study

<table>
<thead>
<tr>
<th></th>
<th>Conventional (605)</th>
<th>Intensive (595)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia events # (%)</td>
<td>19 (3.1)</td>
<td>111 (18.7)</td>
</tr>
<tr>
<td>Two or more episodes</td>
<td>5 (0.8)</td>
<td>23 (3.9)</td>
</tr>
<tr>
<td>Glucose level (mg/dL)</td>
<td>31 ± 8</td>
<td>32 ± 5</td>
</tr>
</tbody>
</table>

Identified hypoglycemia as an “\textit{independent} risk factor for death.”

## NICE-SUGAR Study Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Intensive Group</th>
<th>Conventional Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning BG (mg/dL)</td>
<td>118 + 25</td>
<td>145 + 26</td>
</tr>
<tr>
<td>Hypoglycemia (≤ 40mg/dL)</td>
<td>206/3016 (6.8%)</td>
<td>15/3014 (0.5%)</td>
</tr>
<tr>
<td>28 Day Mortality (p=0.17)</td>
<td>22.3%</td>
<td>20.8%</td>
</tr>
<tr>
<td>90 Day Mortality (p=0.02)</td>
<td>27.5%</td>
<td>24.9%</td>
</tr>
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</table>

NICE-SUGAR: Intensive vs Conventional Glucose Control in Critically Ill Patients

Kaplan–Meier Estimates For The Probability Of Survival

% HR = 1.11
95 confidence interval: (1.01-1.23)

Summary of the Clinical Trials

• Hyperglycemia is associated with poor clinical outcomes across many disease states in the hospital setting.
• Despite the inconsistencies in the clinical trial results, good glucose management remains important in hospitalized patients.
• It is likely that benefits on outcomes can be derived from somewhat higher glucose targets than previously proposed.
• More conservative glucose targets would be predicted to result in lower rates of hypoglycemia.
Landmark Trials: Why basal bolus?

- **RABBIT2: Diabetes Care 2007**
  - Patients with Type 2 diabetes not on insulin admitted for medical diagnoses had better glycemic control without significant adverse events on a combined basal-bolus insulin regimen

- **RABBIT2 Surgery: Diabetes 2011**
  - Patients with Type 2 diabetes undergoing surgery had better glycemic control on a combined basal bolus regimen
What Should We Take Away from These Trials?

- Moderate glucose control, as opposed to near-normal control (tight), is likely sufficient to improve clinical outcomes in the ICU setting.
- Hyperglycemia and hypoglycemia are markers of poor outcomes in critically and non-critically ill patients.
- Importantly, the recent studies do not endorse a *laissez-faire* attitude toward inpatient hyperglycemia that was prevalent a decade ago.
Background - The Evidence

CCU
VanDenBerghe et al. NEJM 2001
Tight Control
NICESUGAR NEJM 2009
Moderate Control

SQ
Sliding Scale Monotherapy
RABBIT2 Diabetes Care 2007
RABBIT2 Surgery Diabetes 2011
Basal Bolus Therapy
Current Recommendations
## ADA/SCC Target Glucose Levels in Critical Care/ICU Patients

### American Diabetes Association
- Starting threshold of >180 mg/dL
- Once IV insulin is started, the glucose level should be maintained between 140 and 180 mg/dL
- Lower glucose targets (110-140 mg/dL) may be appropriate in selected patients
- Targets <110 mg/dL or >180 mg/dL are not recommended

### Society of Critical Care Medicine
- Starting threshold of >150 mg/dL and absolutely at 180 mg/dL
- Use protocol to achieve low rate of hypoglycemia <70 mg/dL
- Minimal excursions of <100 mg/dL

<table>
<thead>
<tr>
<th>Not recommended</th>
<th>Acceptable</th>
<th>Recommended</th>
<th>Not recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100-110</td>
<td>110-150</td>
<td>140-180</td>
<td>&gt;180</td>
</tr>
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</table>

ADA/Endocrine Society Target Glucose Levels in Non–Critical Care Patients

• Endocrine Society
  – Premel glucose targets <100-140 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

• American Diabetes Association
  – Target 140 – 180 mg/dL
  – Certain groups <140 mg/dL
  – Certain groups with higher targets (terminally ill or comorbidities)

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

Thank you