Clinical Need for Tighter Performance Requirements

David B. Sacks
FDA/CDRH Public Meeting: Blood Glucose Meters
Washington DC
16th March, 2010
Overview

1. Need for near-normoglycemia

2. Clinical use of meters:
   
   A. Self-monitoring of blood glucose (SMBG)
   
   B. Tight glycemic control (in ICUs)
Millions of Cases of Diabetes (in 2000 and projections for 2030)
The Major Complications of Diabetes

- Eyes (retinopathy)
- Brain and cerebral circulation (cerebrovascular disease)
- Heart and coronary circulation (coronary heart disease)
- Kidney (nephropathy)
- Peripheral nervous system (neuropathy)
- Lower limbs (peripheral vascular disease)
- Diabetic foot (ulceration and amputation)
Diabetes Control and Complications Trial (DCCT)

1. 1441 patients with type 1 diabetes

2. Intensive vs. conventional insulin therapy

3. Goals of intensive therapy evaluated by:
   A. SMBG 4x/day
   B. HbA1c monthly

4. Patients followed for 6.5 years

NEJM 1993;329:977
Measurement of Glucose in DCCT
Development of Complications - DCCT

NEJM 1993; 329:977
Portable Meter Use

1. By patients at home, work, school (SMBG)

2. Acute and chronic care facilities (including ICUs), physician offices
Self-monitoring of blood glucose (SMBG)
SMBG Recommended

1. Determine insulin doses at meals (at least 3X daily if multiple insulin injections; glycemic control worsens with less)

2. Determine insulin dose in gestational diabetes

3. Achievement of glycemic goals

4. Detection and avoidance of hypoglycemia

Diabetes Care 2010;33:S11
Does meter performance meet clinical needs?
Hypoglycemia

1. Risk increases with therapy directed at near-normoglycemia
2. Near-normoglycemia reduces risks of chronic complications; improves pregnancy outcomes
3. Many with type 1 or long-standing type 2 diabetes have hypoglycemia unawareness
4. SMBG is only defense when symptoms lost
5. Severe hypoglycemia associated with mortality, dementia, harm to self or others (e.g., driving)
THE RECIPE TO CONQUERING HYPOGLYCEMIA

BY NOEL GLASS

Recognize the symptoms before it's too late and more serious diseases take their toll.
Can Meters Reliably Detect Hypoglycemia?

1. Using current ISO/CLSI criteria
2. True glucose 50 mg/dL (2.8 mmol/L)
3. Acceptable results 35-65 mg/dL (1.9-3.6 mmol/L)
4. 5% of values may be <35 or >65 mg/dL
5. Patient not know which values are wrong
6. These results cannot reliably detect hypoglycemia
Severe Hypoglycemia

- Confused
- Pale
- Sweating
- Shaking
- Feels Hungry
- Feels Weak
- Unconscious

CALL 911
Meter Use in Practice

1. Accuracy criteria exclusively for analytical performance
2. Do not consider pre- or post-analytical error
3. Evaluation usually performed by highly-trained technologist under optimal conditions
4. ISO/CLSI specifications do not inform clinician of how meters perform in patient’s hands
1. Current meters have performance superior to prior generations

2. Technological advances decrease operator error

3. Performance by patients inferior to medical technologists

(CVs: patients 7-20%; techs 2.5-5.9% for 5 meter types)
Technologists Perform Better Than Patients

Patients failed to meet ISO criteria

\[ y = -1.9(0.6)x + 20(6) \]

\[ y = -0.7(0.1)x + 11(1) \]
How Accurate Does Glucose Measurement Need to Be?

1. Several criteria proposed for analytical goals
   - expert opinion (consensus conference)
   - opinion of clinicians
   - “state of the art”
   - regulation
   - biological variation

2. No consensus
What Do Patients Think?

1. 201 patients with type 1 diabetes
2. SMBG x10 y
3. Completed questionnaire
4. Patients react to critical difference (CD, difference between 2 consecutive results) of 22-30%

Clin Chem 2001; 47:67
Patient-derived SMBG Criteria

Analytical CV 6.4-9.7% needed
For hypoglycemia, CV 3.1%
CV ≤5% and bias ≤5% are required to meet expectations of 75% of patients (excluding hypoglycemia)

Fig. 2. Relationship between allowable imprecision and bias when the CD is 22% (reflecting optimum quality) or 30% (reflecting desirable quality).
Analytical Goals for Glucose Meters

1. 1987: ADA recommended total error (user plus analytical) of <10% for 100% of results

2. 1996: ADA recommendation modified in response to DCCT: total analytical error < 5%
### Analytical Goals for Glucose Meters

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCLS/CLSI 1994</td>
<td></td>
<td>&gt;100 mg/dL ± 20% for 95% of results ≤100 mg/dL ± 15 mg/dL</td>
</tr>
<tr>
<td>ISO/TC212 2003</td>
<td></td>
<td>≥75 mg/dL ± 20% for 95% of results ≤ 75 mg/dL ± 15 mg/dL</td>
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</tbody>
</table>
Addendum to Meter Performance Criteria

1. 5% of results excluded from accuracy criteria
2. Values can be essentially anything
3. If patient does SMBG 4x/d, expect 1 result outside analytical limit every 5 days
4. Need to define criteria that include these values
Tight glycemic control
Does meter performance meet clinical needs in TGC?
## Association of Tight Glucose Control vs Usual Care

<table>
<thead>
<tr>
<th>Source</th>
<th>Hospital Mortality, No./Total No. of Patients</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tight Control</td>
<td>Usual Care</td>
<td></td>
<td>Tight Control</td>
</tr>
<tr>
<td>Surgical ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very tight control (glucose goal ≤ 110 mg/dL)</td>
<td>55/765</td>
<td>85/783</td>
<td>0.66 (0.48-0.92)</td>
<td></td>
</tr>
</tbody>
</table>
| Van den Bergh et al,
 | 2001 | | | | | |
| Stecher et al,
 | 2006 | | | | | |
| Moderately tight control (glucose goal < 150 mg/dL) | 19/132 | 11/133 | 1.74 (0.86-3.51) |        |        |
| Kia et al,
 | 2005 | | | | | |
| Grey and Perel,
 | 2004 | | | | | |
| Blotta et al,
 | 2007 | | | | | |
| Blotta et al,
 | 2008 | | | | | |
| Chan et al,
 | 2008 | | | | | |
| All surgical ICU patients | 99/1123 | 123/1141 | 0.88 (0.63-1.22) |        |        |
| Medical ICU |                           |                                        |        |        |
| Very tight control (glucose goal ≤ 110 mg/dL) | 222/595 | 242/605 | 0.93 (0.81-1.08) |        |        |
| Van den Bergh et al,
 | 2006 | | | | | |
| Fernandez et al,
 | 2005 | | | | | |
| Bland et al,
 | 2005 | | | | | |
| Okesan et al,
 | 2007 | | | | | |
| Moderately tight control (glucose goal < 150 mg/dL) | 6/35 | 6/34 | 0.97 (0.35-2.72) |        |        |
| Davies et al,
 | 1991 | | | | | |
| Waiters et al,
 | 2006 | | | | | |
| Gray/GIST-UK et al,
 | 2007 | | | | | |
| Brum/CIN et al,
 | 2008 | | | | | |
| All medical ICU patients | 321/1193 | 356/1200 | 0.92 (0.82-1.04) |        |        |
| Medical-surgical ICU |                           |                                        |        |        |
| Very tight control (glucose goal ≤ 110 mg/dL) | 61/247 | 75/289 | 0.95 (0.71-1.27) |        |        |
| Brunkhorst/VESE et al,
 | 2008 | | | | | |
| Devos/GLUCONTROL et al,
 | 2007 | | | | | |
| Mackenzie/GiyCOGENIC et al,
 | 2005 | | | | | |
| Araba et al,
 | 2006 | | | | | |
| Wang et al,
 | 2006 | | | | | |
| Yu et al,
 | 2005 | | | | | |
| Mitchell et al,
 | 2006 | | | | | |
| De La Rosa et al,
 | 2006 | | | | | |
| Moderately tight control (glucose goal < 150 mg/dL) | 22/41 | 22/48 | 1.17 (0.77-1.78) |        |        |
| Farah et al,
 | 2007 | | | | | |
| McMullin/LOGIC et al,
 | 2007 | | | | | |
| Henderson/SUGAR et al,
 | 2005 | | | | | |
| Azevedo et al,
 | 2008 | | | | | |
| All medical-surgical ICU patients | 472/1811 | 498/1847 | 0.95 (0.80-1.13) |        |        |
| All critically ill patients | 892/4127 | 977/4188 | 0.93 (0.85-1.03) |        |        |

JAMA 2008;300:933
1. Multinational study to test hypothesis that intensive glucose control reduces 90 d mortality

2. Study population: 6,104 adults admitted to medical or surgical ICU at one of 42 hospitals in Australia, New Zealand or Canada

3. Within 24 h of admission, patients requiring ≥3 days of critical care were randomized to intensive or conventional glucose control

4. Target glucose ranges:
   - intensive: 81-108 mg/dL (4.5-6 mol/L)
   - conventional: ≤180 mg/dL (10 mmol/L)

NEJM 2009; 360:1283
## NICE-SUGAR Results

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time-weighted</td>
<td><strong>115 ± 18 mg/dL</strong> (6.4 ± 1.0 mmol/L)</td>
<td><strong>144 ± 23 mg/dL</strong> (8 ± 1.3 mmol/L)</td>
</tr>
<tr>
<td>glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>27.5%</td>
<td>24.9%</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>6.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>≤40 mg/dL (2.2 mmol/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NEJM 2009; 360:1283*
NICE-SUGAR Glucose Measurement

1. Impossible to obtain details concerning glucose analysis

2. Glucose measurements were performed on arterial blood “whenever possible” using “point-of-care or arterial blood gas analyzers or laboratory analyzers in routine use at each center”
Potential Problem With Glucose Results in NICE-SUGAR

Different glucose values produced by diverse methods and samples will lead to different insulin doses and potentially wide variations in true glucose concentrations.
NICE-SUGAR Analysis

1. CAP proficiency testing data for 17 meters show CVs 12-15% and bias up to 41%

2. If true glucose is 144 mg/dL (9.0 mmol/L), bias of 41% = 59 mg/dL (3.3 mmol/L)

3. Difference in mean glucose between intensive and conventional groups in NICE-SUGAR was 29 mg/dL (1.6 mmol/L)

4. Therefore, bias can be twice the difference in mean glucose between intensive and conventional groups
If meter has high bias, results will be higher than patient’s actual glucose and patient will receive too much insulin, producing hypoglycemia (which might not be detected)
1. Patient has true glucose of 95 mg/dL (5.3 mmol/L)

2. Acceptable range for meter is 76-114 mg/dL (4.2-6.4 mmol/L)
   [ 5% of values could be outside this range]

3. These values exceed the range for intensive control target of 81-108 mg/dL (4.5-6.0 mmol/L)
Summary

1. Measurement of blood glucose concentrations plays a very important role in patient management.

2. Accurate identification of hypoglycemia is essential.

3. Current performance criteria for glucose meters are inadequate for clinical needs.

4. Recommended accuracy criteria for meters:
   - Minimum: ± 15%
   - Desirable: ± 10%
   - Optimum: ± 5%
Potential New Problem With Meters

“Sorry. It’s just my glucose monitor.”
“One must always keep scientists away from committees – they are apt to change their minds in response to the evidence”
Analytical Goals for Glucose Meters

1. 1987: ADA recommended total error (user plus analytical) of <10% for 100% of results

2. 1996: ADA recommendation modified in response to DCCT: total analytical error < 5%

3. More recently, ADA has publicly supported total analytic error < 10%
1. Meter performance criteria: ±20% of the ‘true’ glucose value at ≥75 mg/dL (4.2 mmol/L)
2. Patient has true glucose of 95 mg/dL (5.3 mmol/L)
3. Acceptable range for meter is 76-114 mg/dL (4.2-6.4 mmol/L) [note 5% of values could be outside this range]
4. These values exceed the range for intensive control target of 81-108 mg/dL (4.5-6.0 mmol/L)
NICE-SUGAR Analysis

1. CAP proficiency testing data for 17 meters show CVs 12-15% and bias up to 41%.

2. If true glucose is 144 mg/dL (9.0 mmol/L), bias of 41% = 59 mg/dL (3.3 mmol/L).

3. Difference in mean glucose between intensive and conventional groups in NICE-SUGAR was 29 mg/dL (1.6 mmol/L).

4. Therefore, bias can be **twice** the difference in mean glucose between intensive and conventional groups.

5. If meter has high bias, results will be higher than patient’s actual glucose and patient will receive too much insulin, producing hypoglycemia (which might not be detected).
Recommended Accuracy Criteria (based on biological variation)

1. **At minimum:** 95% of results +/-15% of reference at glucose $\geq 100$ mg/dL (5.1 mmol/L) and +/- 15 mg/dL (0.83 mmol/L) at glucose <100 mg/dL (5.1 mmol/L)

2. **Desirable:** +/- 10%

3. **Optimal:** +/- 5%
Measurement of HbA1c in DCCT

![Graph showing glycosylated hemoglobin changes over the years of study for both conventional and intensive treatment groups.](image)

**Conventional**

**Intensive**

**Year of Study**

**Glycosylated Hemoglobin (%)**

NEJM 1993; 329:977
1. Mean time-weighted glucose:
   intensive - 115 ± 18 mg/dL (6.4 ± 1.0 mmol/L)
   conventional - 144 ± 23 mg/dL (8 ± 1.3 mmol/L)

2. Mortality:
   intensive - 27.5%
   conventional - 24.9%

2. Severe hypoglycemia ≤40 mg/dL (2.2 mmol/L):
   intensive - 6.8%
   conventional - 0.5%

NEJM 2009; 360:1283
Limitations of POC Glucometers

1. Less accurate than laboratory instruments
2. Variation among meters (even same manufacturer)
3. Glucose concentration varies among blood specimens (arterial, venous and capillary)
4. Plasma glucose higher than WBG (11% at Hct of 43%)
Limitations of POC Glucometers (ctd)

5. Capillary glucose altered if reduced peripheral blood circulation, e.g. hypotension, shock, dehydration, hyperosmolar states

6. Meters have limited measurement range

7. Measurement accurate only within defined hematocrit range

8. Operator variability
Acceptable Glucose Results in Practice

1. Use current ISO criteria
2. True glucose 45 mg/dL (2.5 mmol/L)
3. Acceptable results 30-60 mg/dL (1.7-3.3 mmol/L)
4. 5% of time values may be <30 or >60 mg/dL
5. These results cannot reliably detect hypoglycemia
Insulin Dose Error-Based Criteria

- Computer Modeling of 20,000 data points

- Total Error < 10% would lead to two-step errors in insulin dose ~ 0.2% of time

- However, one-step errors would occur 16-45% of time

- To provide intended insulin dose 95% of the time, CVs need to be <1-2%

Whoopie!! Hey honey, I did it! I finally got this darned meter over 400!! Wow! I wonder how high this baby can go!

A sure sign someone is unclear on the concept of tight blood glucose control.
Measurement of GHb and Glucose in DCCT

NEJM 1993; 329:977
"...and our lucky super lotto winner has just told us his winning five numbers '75-83-89-80-90' were the results of his last five blood glucose tests..."
Recommended Accuracy Criteria (based on biological variation)

1. **At minimum**: +/-15% of reference value at glucose $\geq 100$ mg/dL (5.6 mmol/L) and +/- 15 mg/dL (0.83 mmol/L) at glucose $< 100$ mg/dL (5.6 mmol/L)

2. **Desirable**: +/- 10%

3. **Optimal**: +/- 5%
A Case

1. 34-year-old accountant with type 1 diabetes
2. On once-daily glargine plus pre-meal lispro
3. Mealtime insulin dosing:
   1 unit per 15 grams of carbohydrate plus 1 unit for every 30 mg/dL above upper limit of his pre-meal target blood glucose (120 mg/dL)
4. Plans to eat a turkey sandwich on whole wheat bread plus a small apple (45 grams of CHO)
5. Blood glucose by meter is 140 mg/dL
6. How much lispro should he take?
Another Case

1. 24-year-old woman with type 1 diabetes who is 20 weeks pregnant

2. Goals for BG while pregnant:
   - Pre-meal 60-99 mg/dL (3.3-5.4 mmol/L)
   - Peak post-prandial glucose 100-129 mg/dL (5.4-7.1 mmol/L)

3. About to drive home from work; usual commute time is 50 minutes

4. BG by meter is 65 mg/dL (3.6 mmol/L)
Fear of Hypoglycemia

1. Hypoglycemia greatest barrier to good glycemic control

2. Severe hypoglycemia (requiring assistance) feared by patients and families

3. Annual prevalence in type 1 diabetes is ~30%

4. Causes embarrassment
Fear of Hypoglycemia

“I live in constant fear that one day my hypoglycemic episodes will end up on YouTube.”
Criteria to Establish Goals

1. Expert Opinion
2. Opinion of clinicians
3. Regulation
4. Biological criteria
Biological Criteria

1. Imprecision should not exceed $\frac{1}{2}$ of within-subject biological CV
2. Total error $\leq 6.9\%$
3. Imprecision (CV over days/weeks) $\leq 2.9\%$
4. Bias $\leq 2.2\%$
Accuracy Based on Biology

1. Recommendation to use biological criteria for analytical goals
2. Imprecision $\leq \frac{1}{2} CV_i$
3. $CV_a \leq 2.2\%$ suggested

i.e., at 126 mg/dL (7.0 mmol/L), instrument should give 120-132 mg/dL (6.7-7.3 mmol/L)
## Analytical Goals for Glucose Meters

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<th>Source</th>
<th>Year</th>
<th>Goal</th>
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<tbody>
<tr>
<td>ADA</td>
<td>1986</td>
<td>TE &lt;10% for 100% of the time</td>
</tr>
<tr>
<td>ADA</td>
<td>1996</td>
<td>±5% total analytical error</td>
</tr>
<tr>
<td>CLIA ‘88</td>
<td>1988</td>
<td>±10% or ±6 mg/dL 80% of time</td>
</tr>
<tr>
<td>NCCLS/CLSI</td>
<td>1994</td>
<td>&gt;100 mg/dL ± 20%</td>
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<td></td>
<td></td>
<td>≤100 mg/dL ± 15 mg/dL</td>
</tr>
<tr>
<td>FDA</td>
<td>1998</td>
<td>&lt;100 mg/dL ± 20 mg/dL</td>
</tr>
<tr>
<td>ISO/TC212</td>
<td>2003</td>
<td>≥75 mg/dL ± 20% for 95% of time</td>
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