

Clinical Need for Tighter Performance Requirements

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FDA/CDRH Public Meeting: Blood Glucose Meters

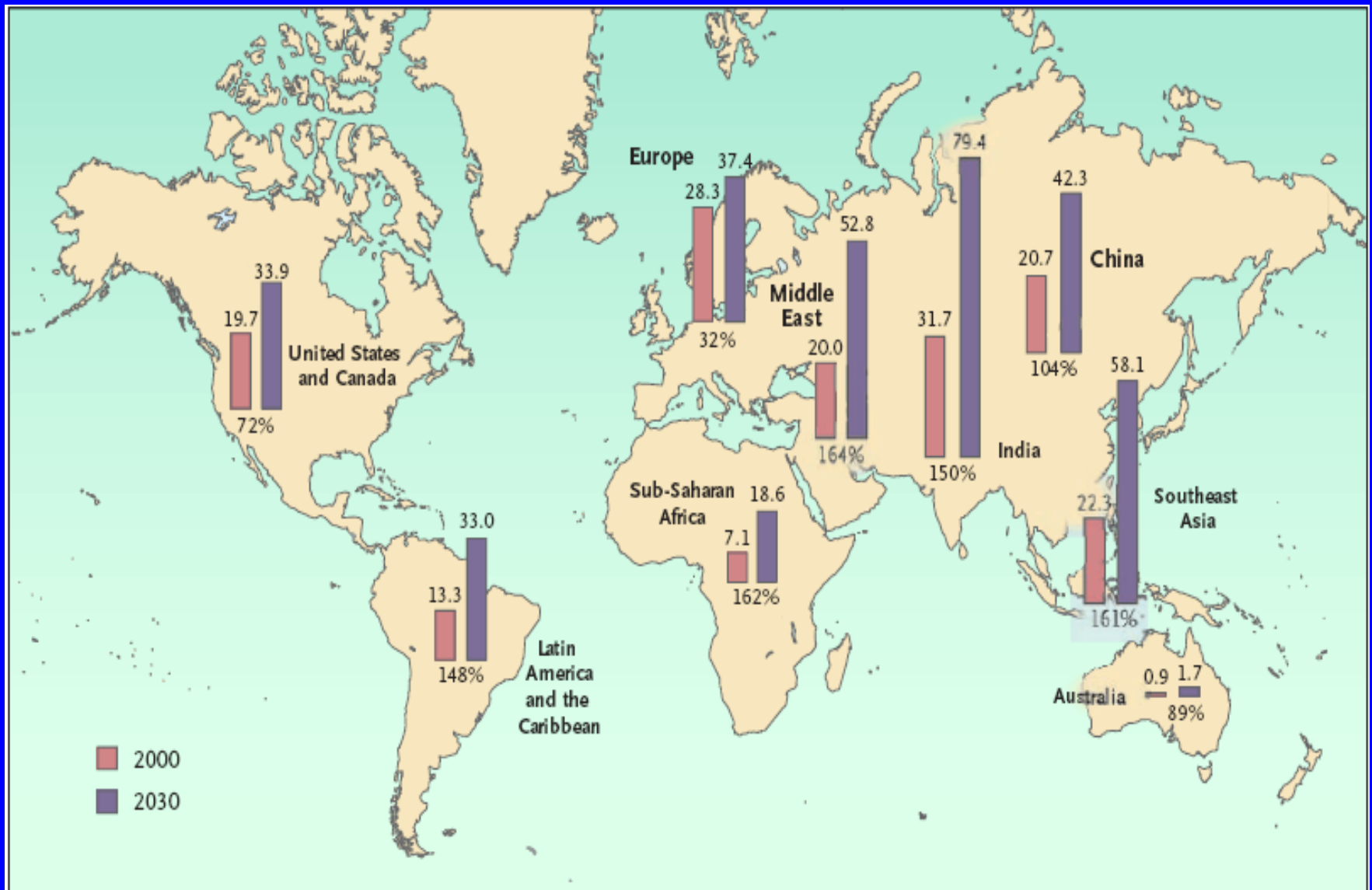
Washington DC

16th March, 2010

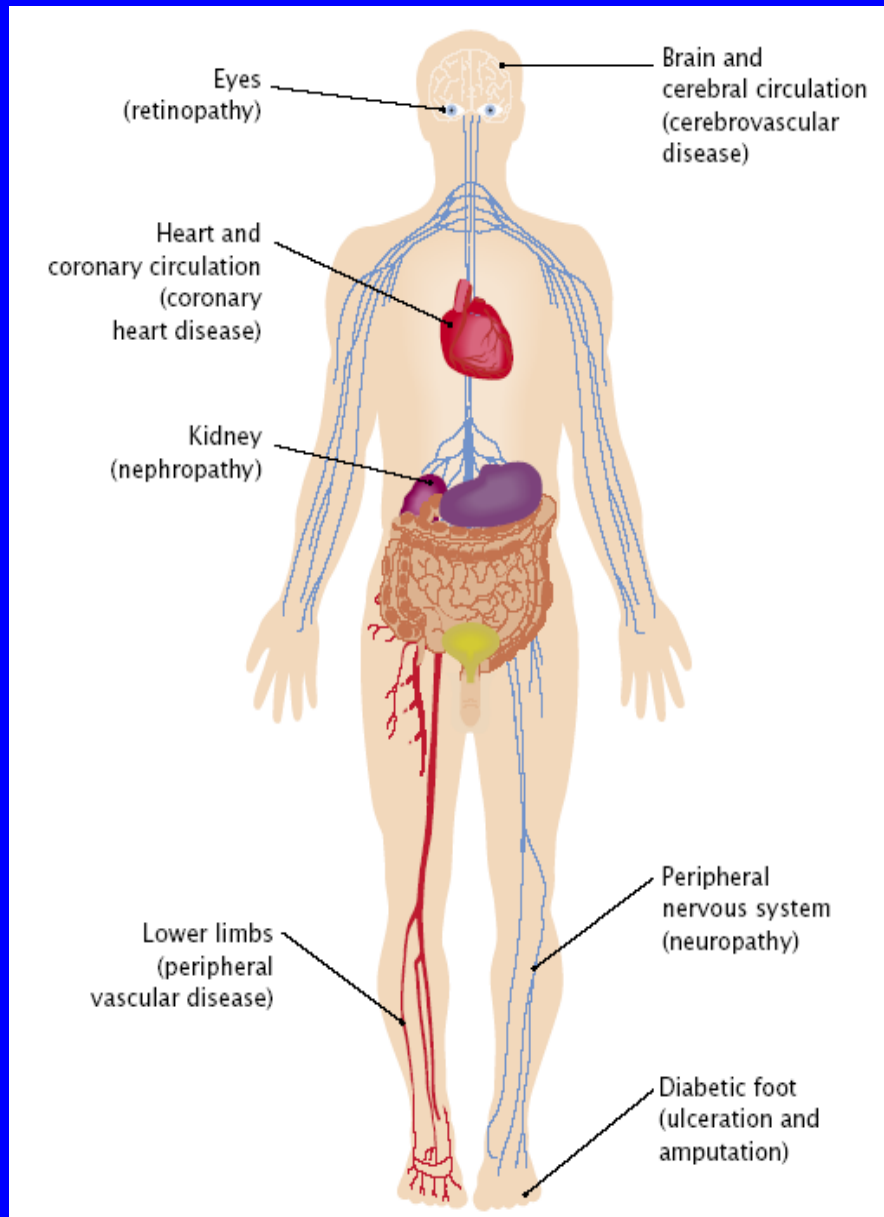
Overview

- 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)



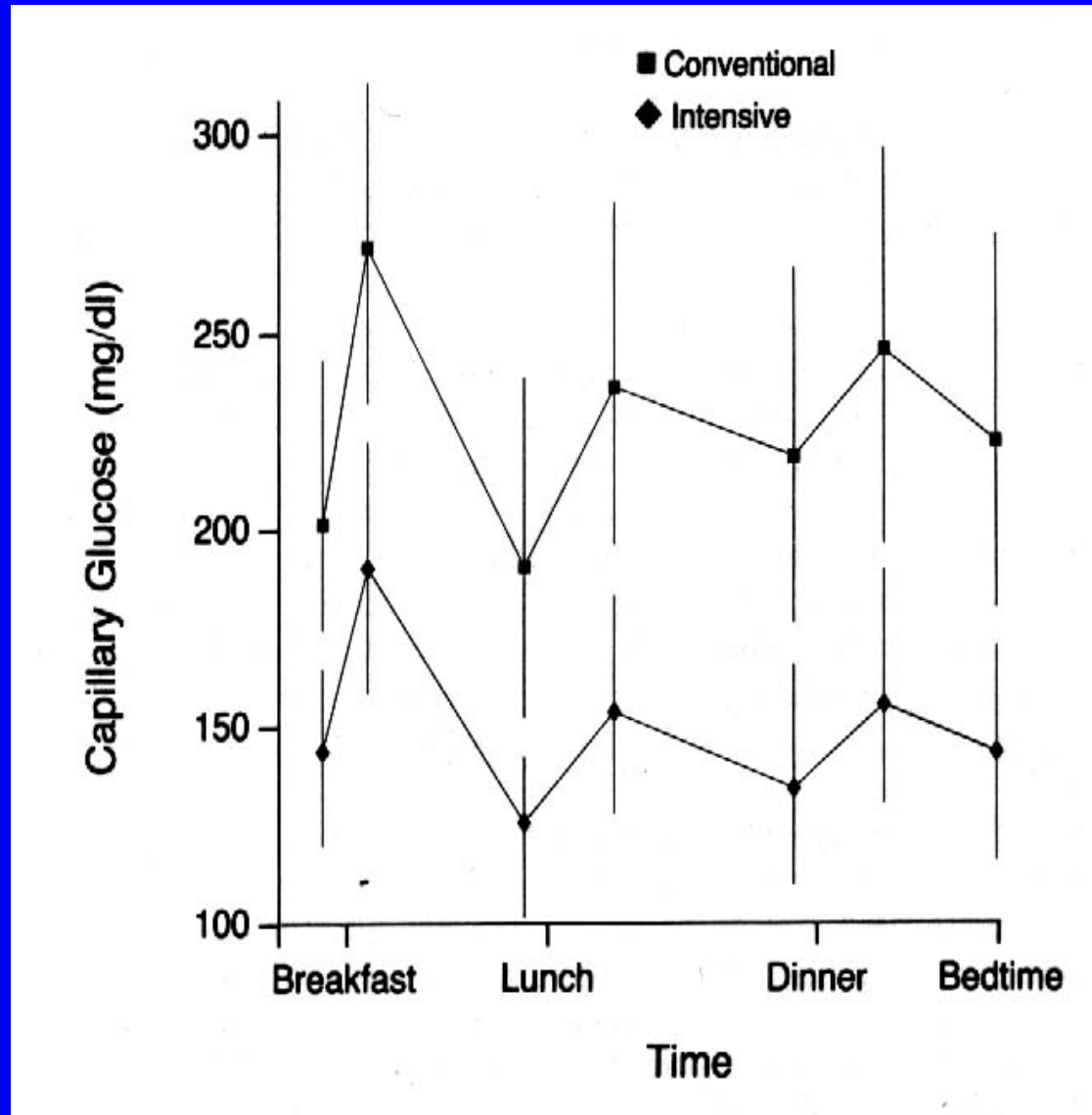
The Major Complications of Diabetes



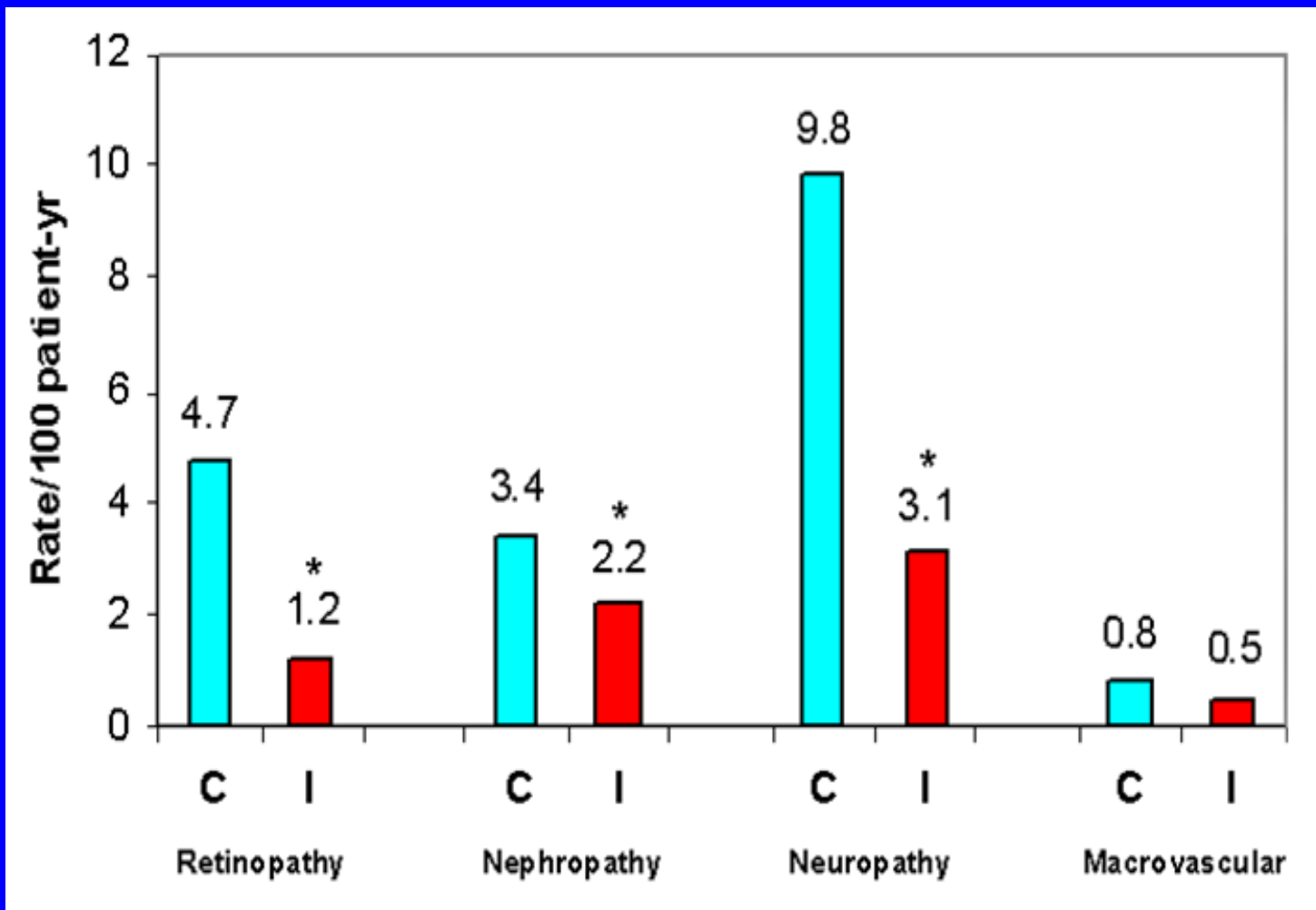
Diabetes Control and Complications Trial (DCCT)

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

Measurement of Glucose in DCCT



Development of Complications - DCCT



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**

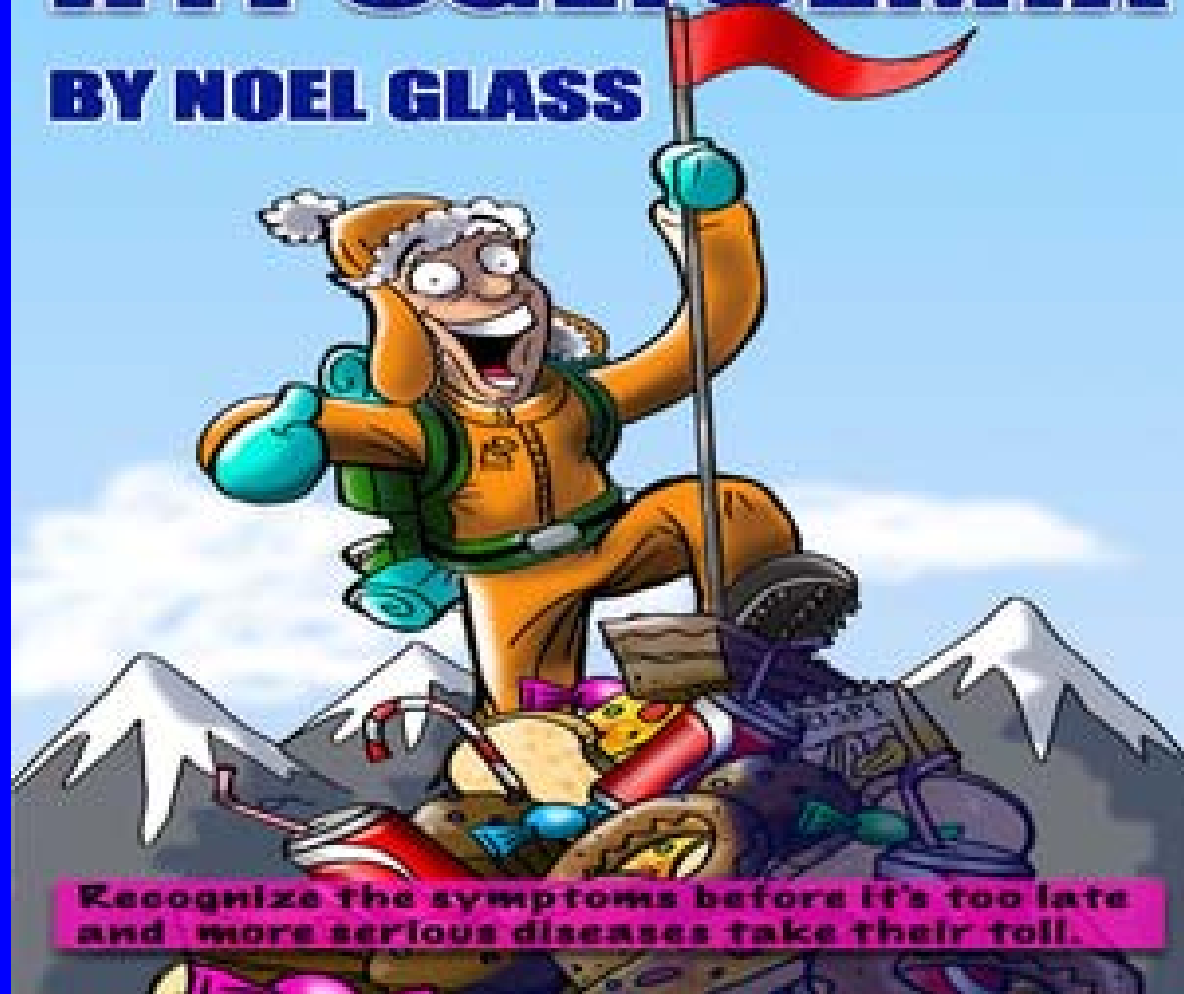
Does meter performance meet clinical needs?

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.

The facts you need to
manage your blood sugar and feel better

Hypoglycemia

FOR DUMMIES[®]

2nd Edition

**A Reference
for the
Rest of Us!**

FREE eTips at dummies.com[®]

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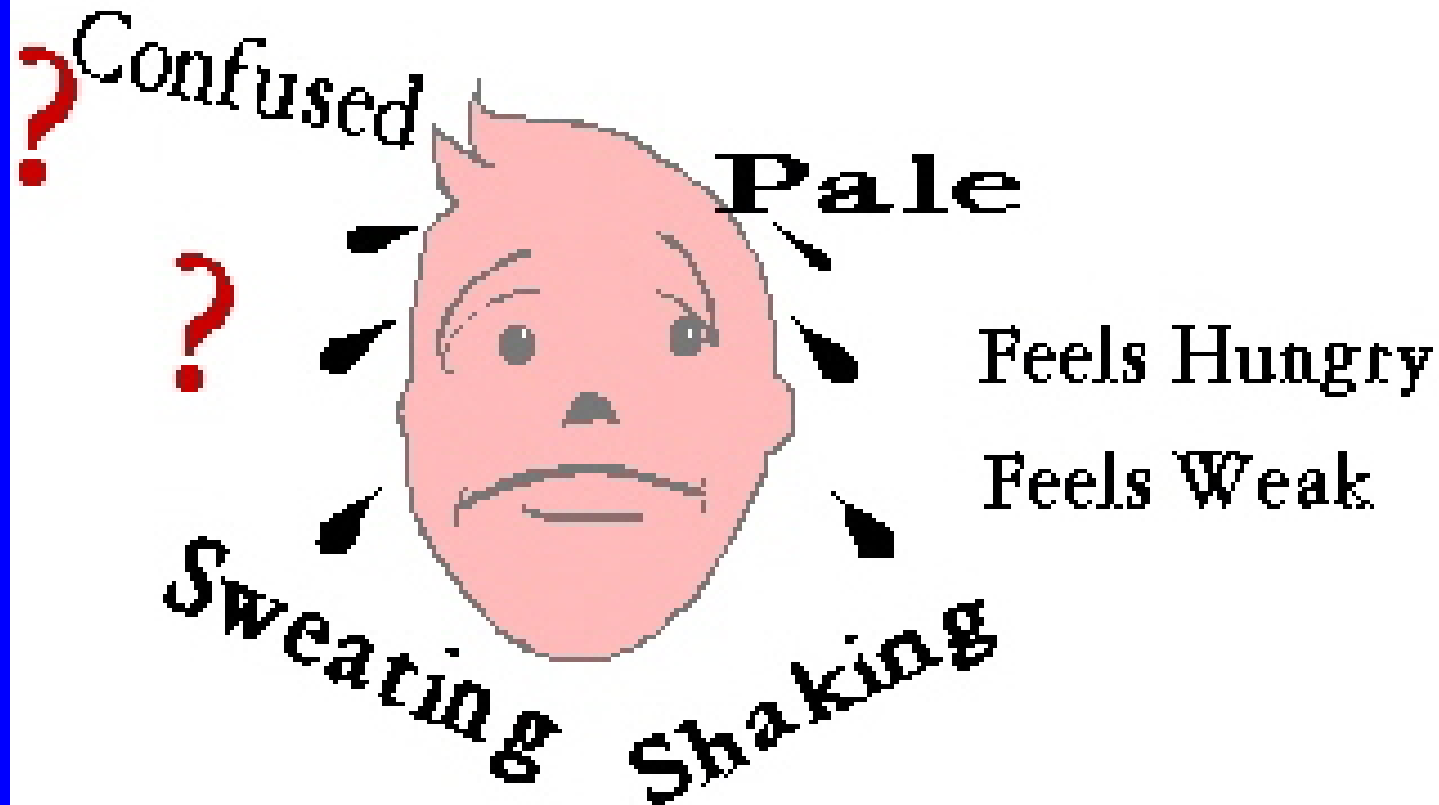
Now updated with
the latest medical
information



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



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**

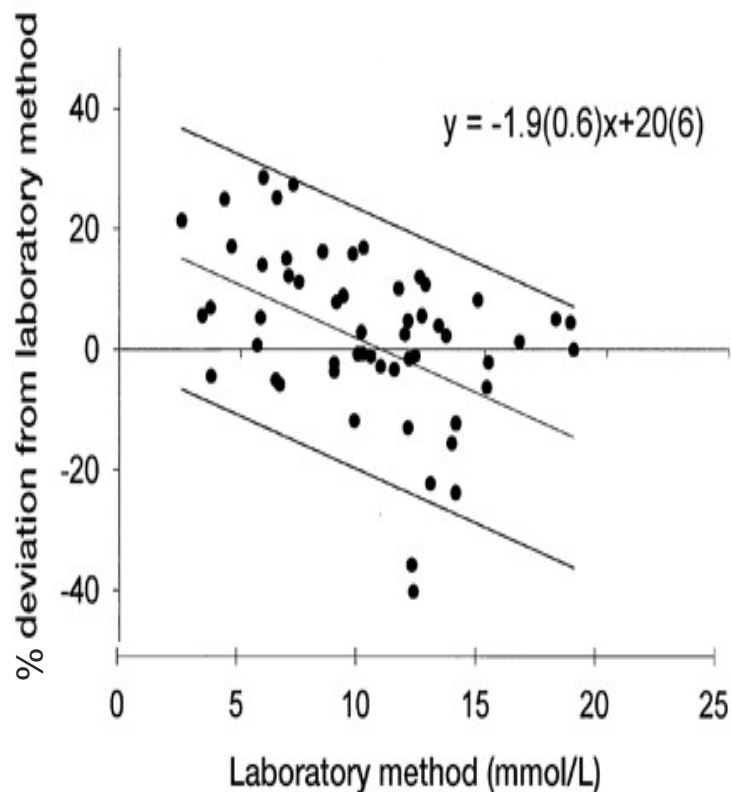
Meter Performance

- 1. Current meters have performance superior to prior generations**
- 2. Technological advances decrease operator error**
- 3. Performance by patients inferior to medical technologists**

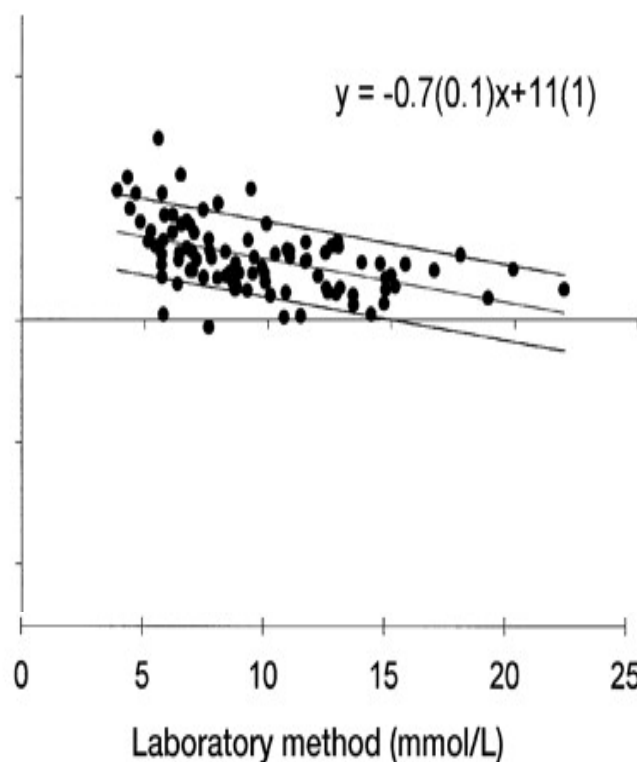
(CVs: patients 7-20%; techs 2.5-5.9% for 5 meter types)

Technologists Perform Better Than Patients

Patients



Technologist



Patients failed to meet ISO criteria

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%

Patient-derived SMBG Criteria

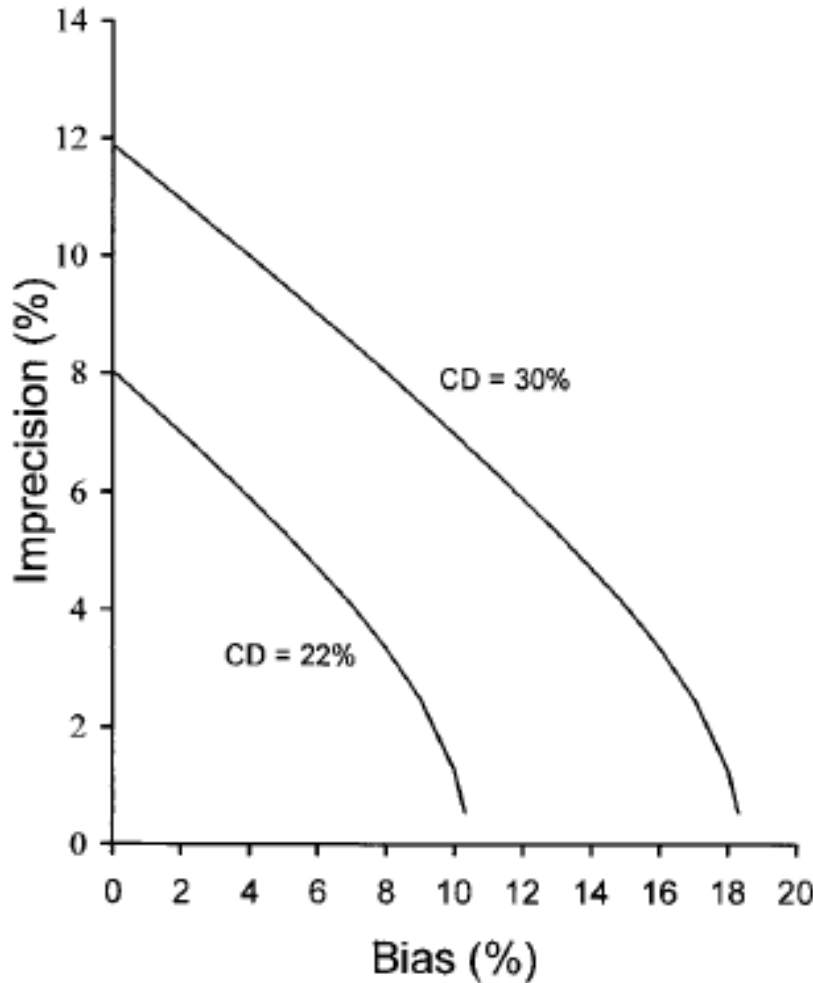


Fig. 2. Relationship between allowable imprecision and bias when the CD is 22% (reflecting optimum quality) or 30% (reflecting desirable quality).

Analytical CV 6.4-9.7% needed

For hypoglycemia, CV 3.1%

CV $\leq 5\%$ and bias $\leq 5\%$ are required to meet expectations of 75% of patients (excluding hypoglycemia)

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

Source	Year	Goal
NCCLS/CLSI	1994	$>100 \text{ mg/dL} \pm 20\%$ for 95% of results $\leq 100 \text{ mg/dL} \pm 15 \text{ mg/dL}$
ISO/TC212	2003	$\geq 75 \text{ mg/dL} \pm 20\%$ for 95% of results $\leq 75 \text{ mg/dL} \pm 15 \text{ mg/dL}$

Addendum to Meter Performance Criteria

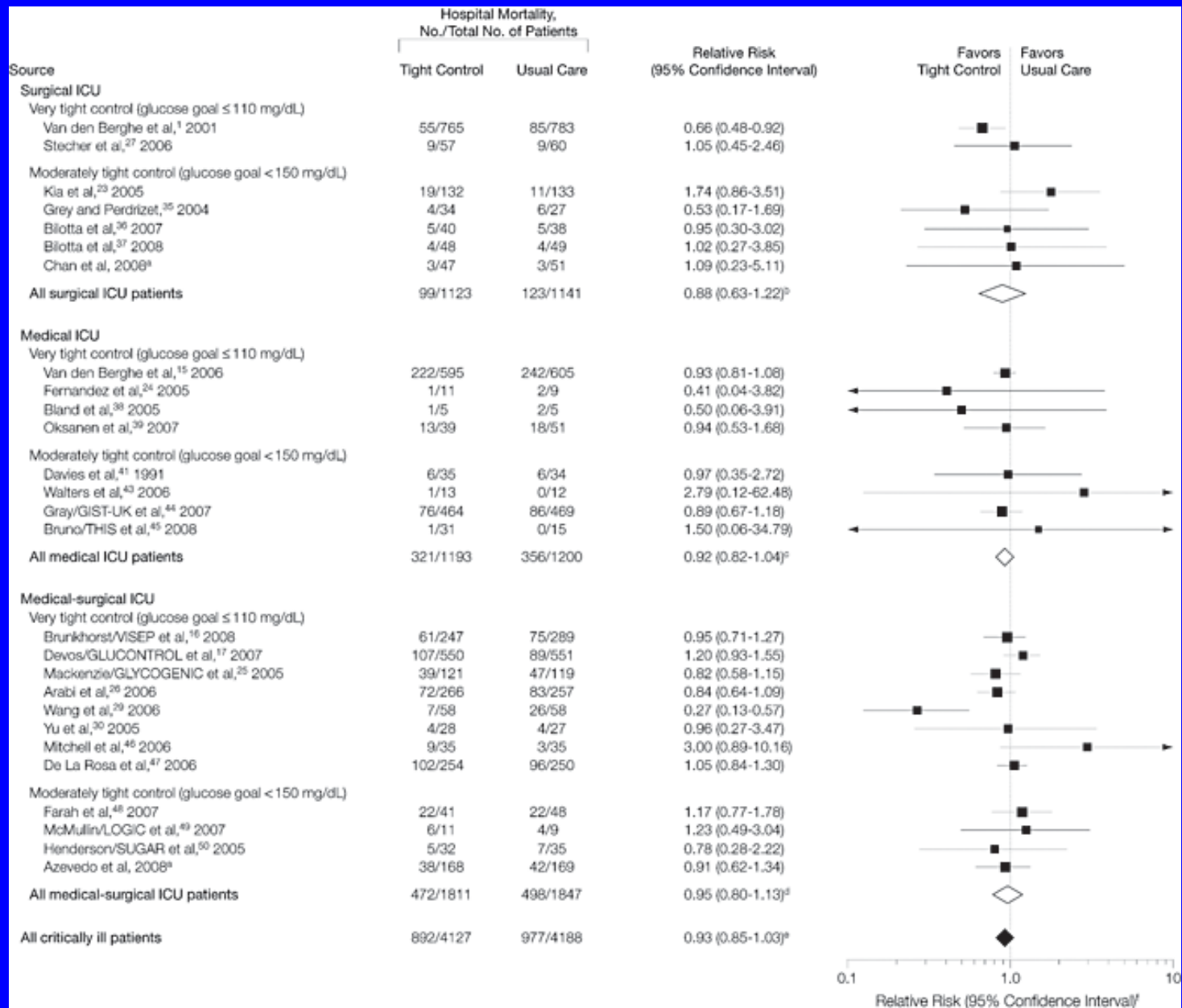
- 1. 5% of results excluded from accuracy criteria**
- 2. Values can be essentially anything**
- 3. If patient does SMBG 4x/d, expect 1 result outside analytical limit every 5 days**
- 4. Need to define criteria that include these values**

Tight glycemic control



**Does meter performance meet clinical
needs in TGC?**

Association of Tight Glucose Control vs Usual Care



NICE-SUGAR

- 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 mmol/L)**
 - conventional - ≤ 180 mg/dL (10 mmol/L)**

NICE-SUGAR Results

	Intensive	Conventional
Mean time-weighted glucose	115 ± 18 mg/dL (6.4 ± 1.0 mmol/L)	144 ± 23 mg/dL (8 ± 1.3 mmol/L)
Mortality	27.5%	24.9%
Severe hypoglycemia ≤40 mg/dL (2.2 mmol/L)	6.8%	0.5%

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

Meter Bias

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)

NICE-SUGAR Analysis (ctd)

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 blood glucose concentrations very important role in patient management**
- 2. Accurate identification of hypoglycemia is essential**
- 3. Current performance criteria for glucose meters inadequate for clinical needs**
- 4. Recommended accuracy criteria for meters:**

minimum	$\pm 15\%$
desirable	$\pm 10\%$
optimum	$\pm 5\%$

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 $< 10\%$**

NICE-SUGAR Analysis (ctd)

1. Meter performance criteria : $\pm 20\%$ 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)

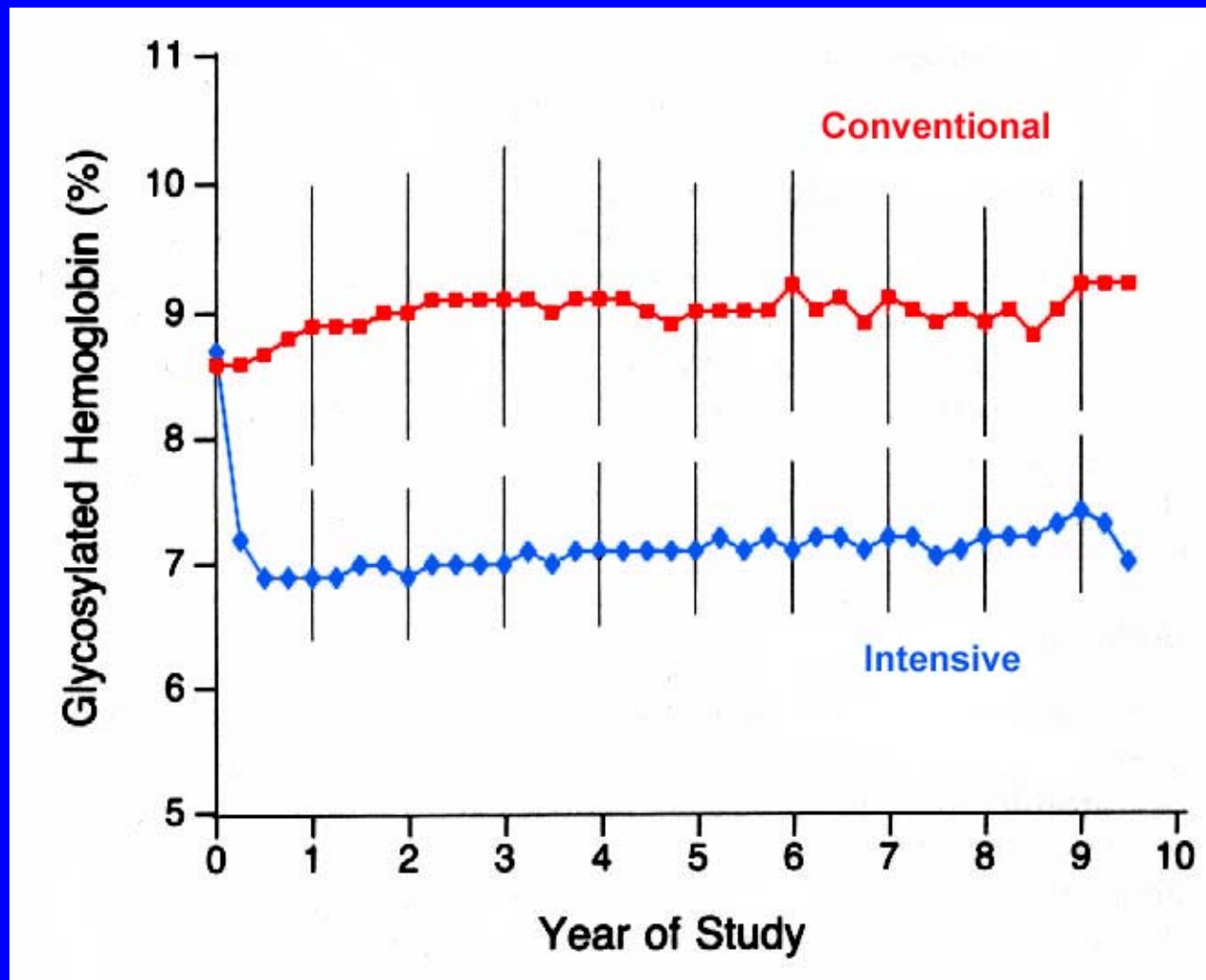
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3. Difference in mean glucose between intensive and conventional groups in NICE-SUGAR was 29 mg/dL (1.6 mmol/L)
4. Therefore, bias can be twice the difference in mean glucose between intensive and conventional groups
5. If meter has high bias, results 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 ≥ 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



NICE-SUGAR Results

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%

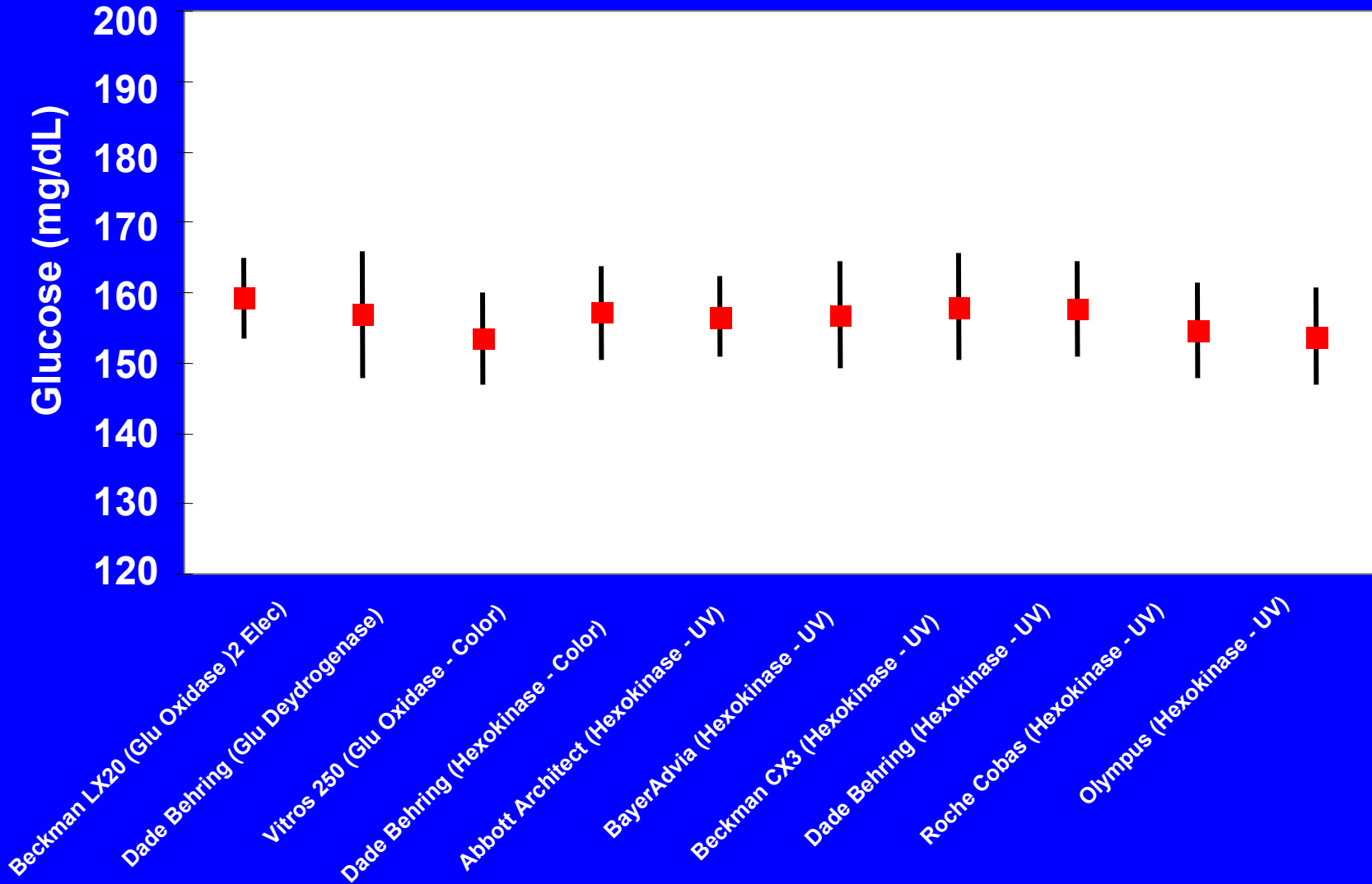
Limitations of POC Glucometers

- 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%)**

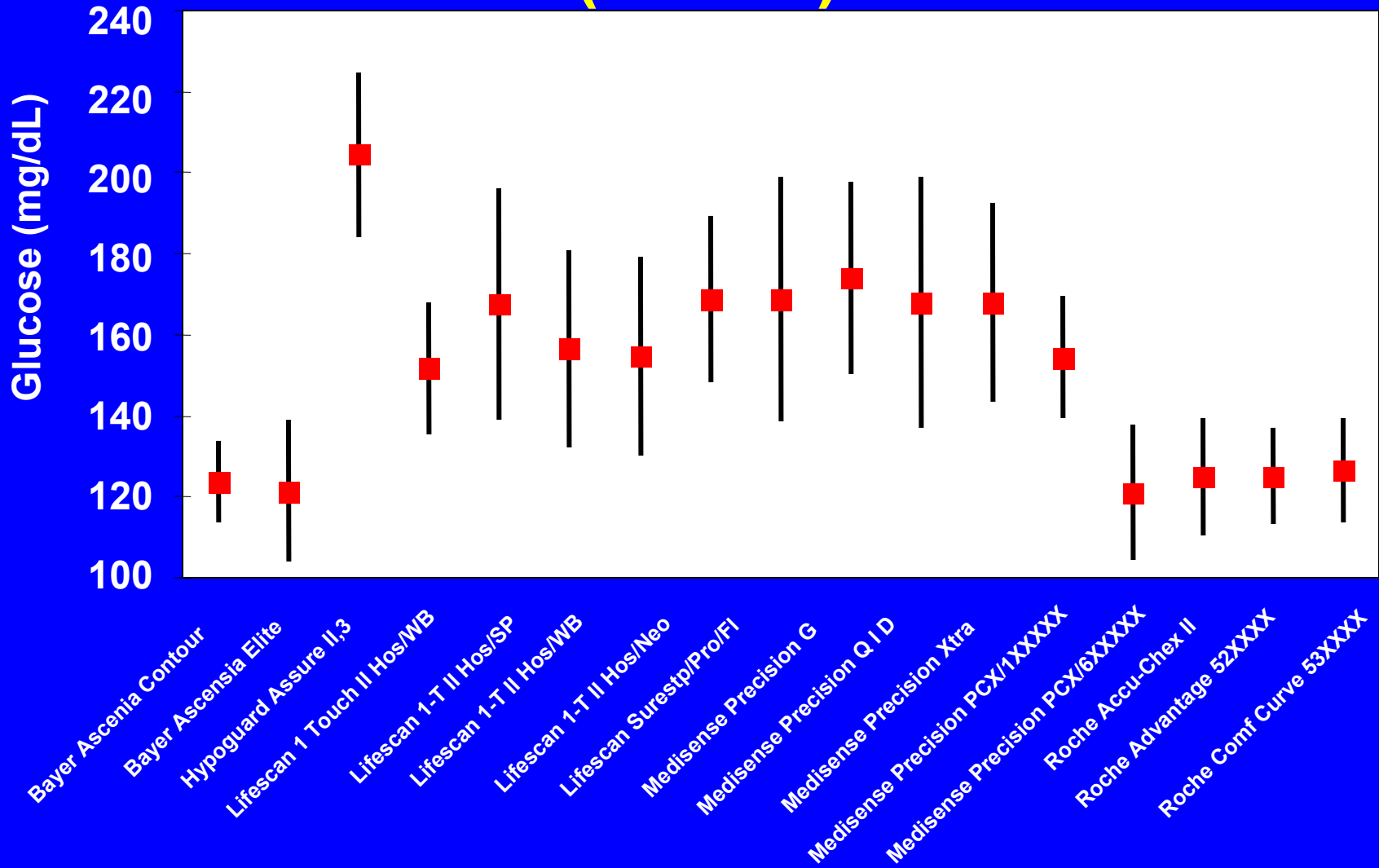
Limitations of POC Glucometers (ctd)

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

CAP - Plasma Glucose C 2005



CAP - Whole Blood Glucose C 2005 (POCT)



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

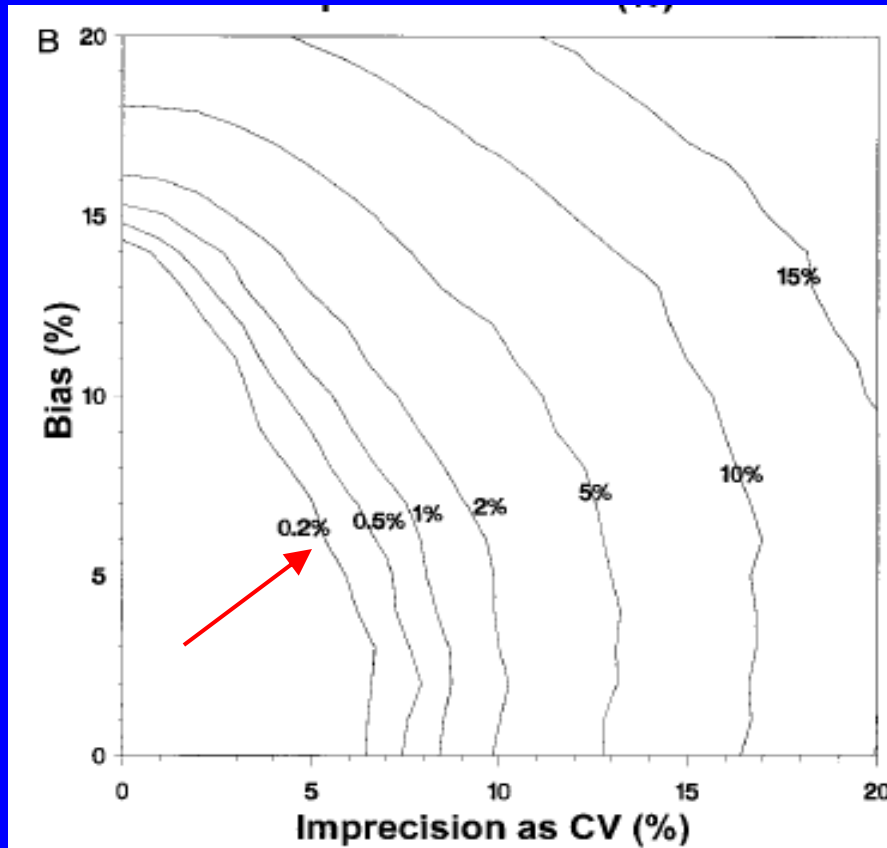
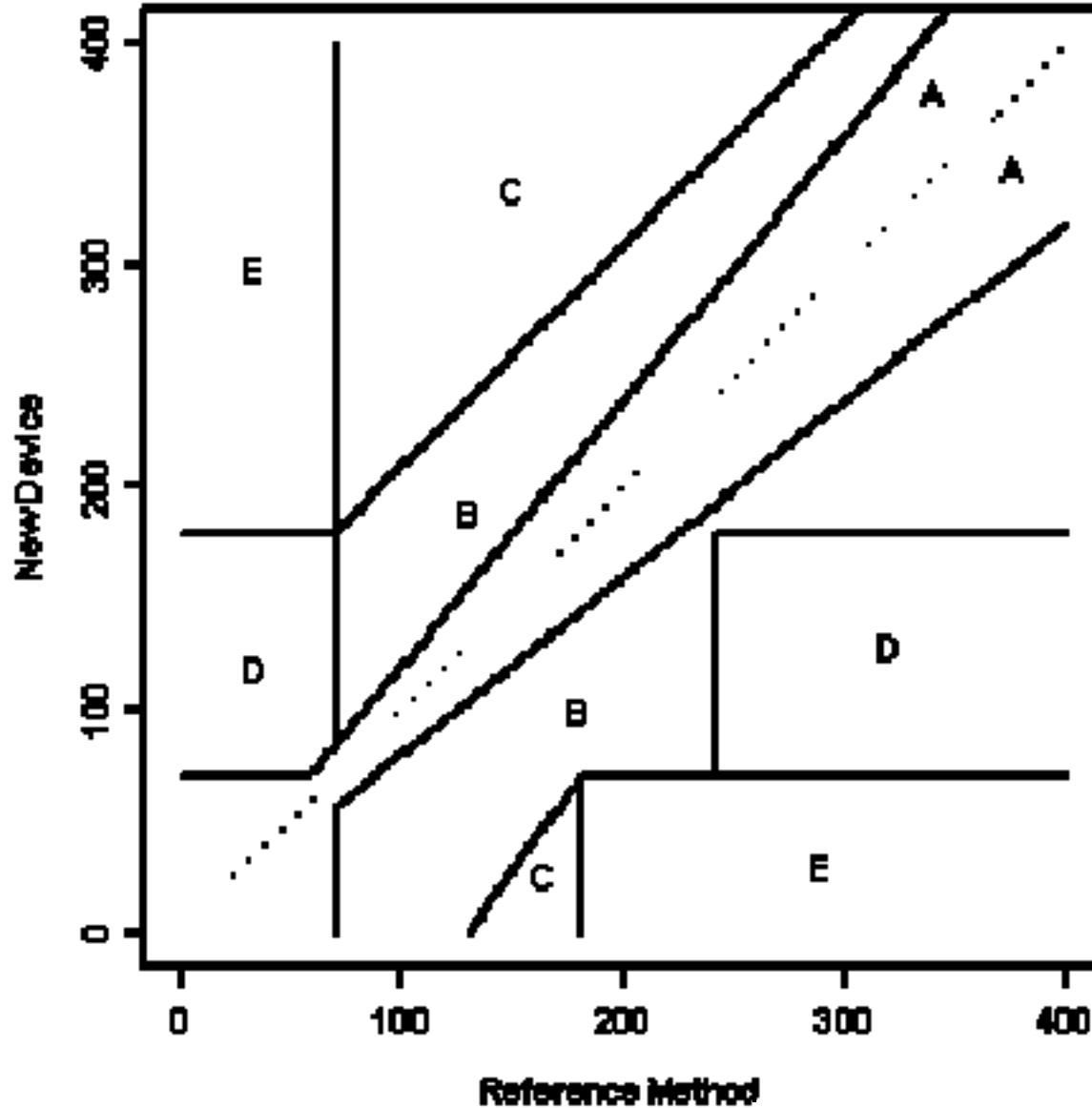


Fig. 3. Contour plots of insulin-dosage error rates as a function of assay bias and imprecision (CV).

- 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%

Clarke Error Grid



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

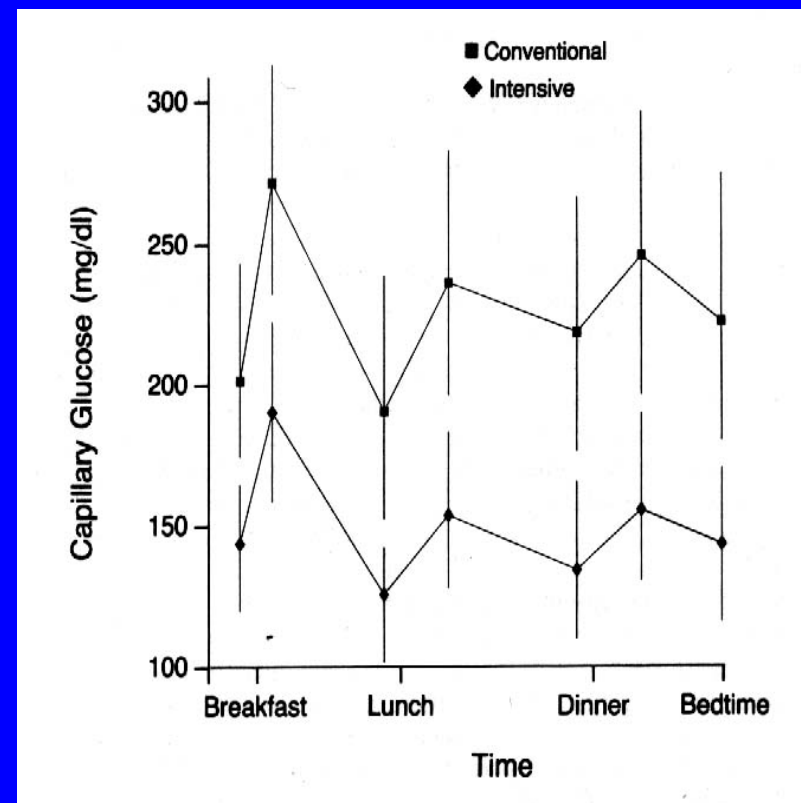
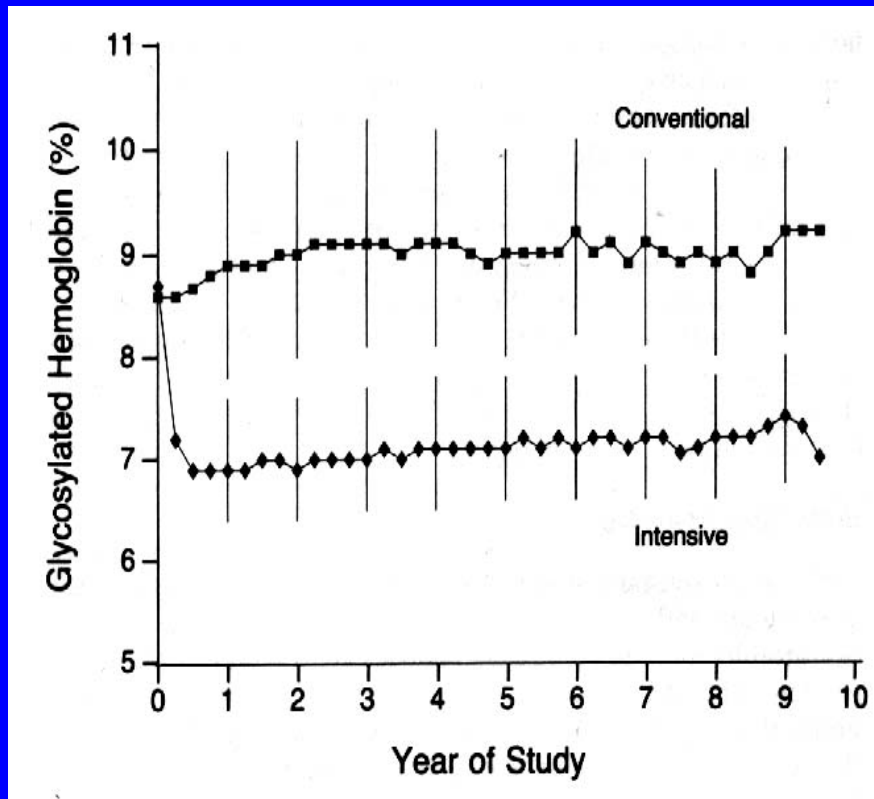


**A sure sign someone is unclear on the
concept of tight blood glucose control.**





Measurement of GHb and Glucose in DCCT





"...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 ≥ 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

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