Clinical Need for Tighter Performance Requirements

David B. Sacks

FDA/CDRH Public Meeting: Blood Glucose Meters

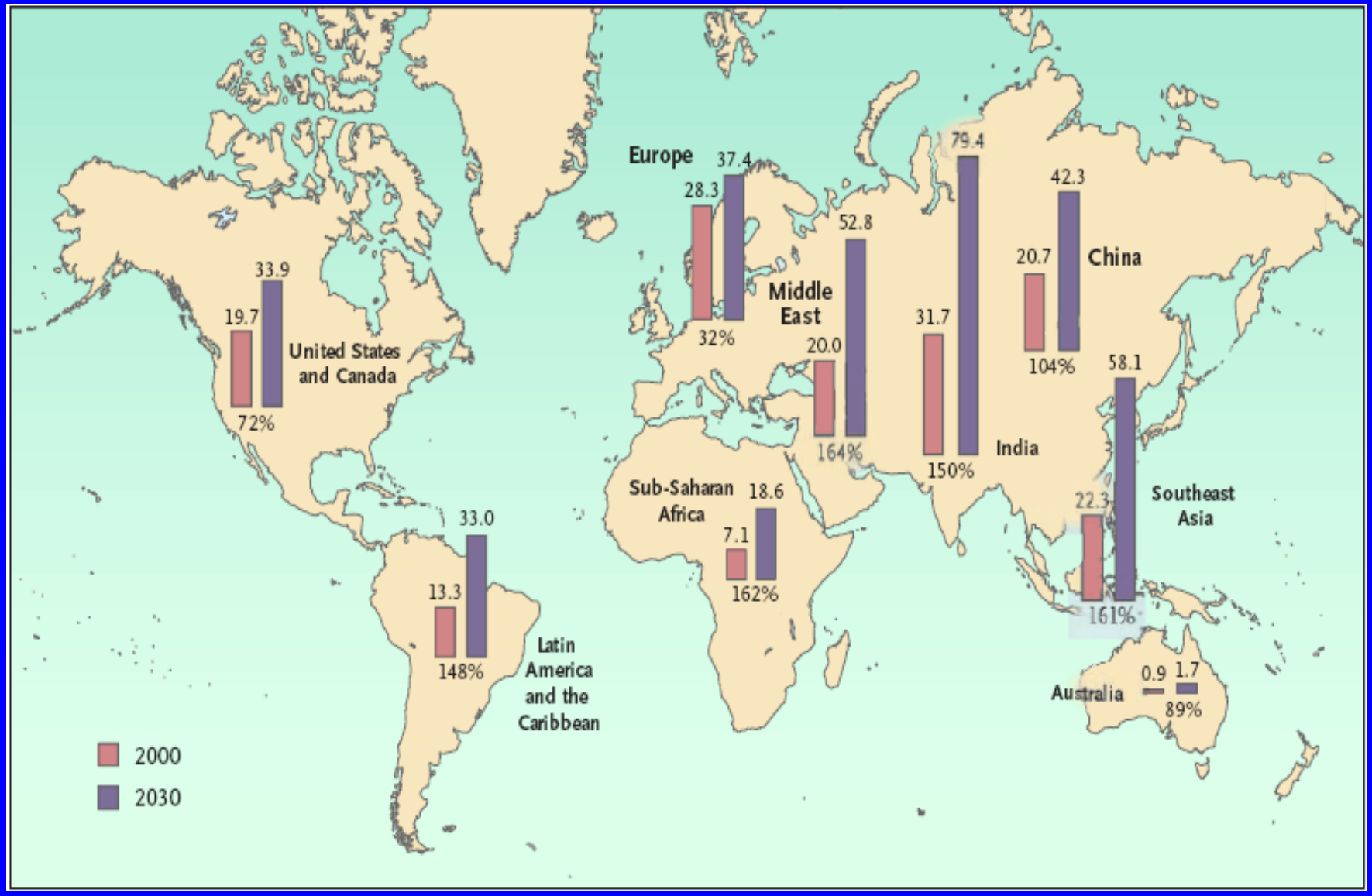
Washington DC

16th March, 2010

Overview

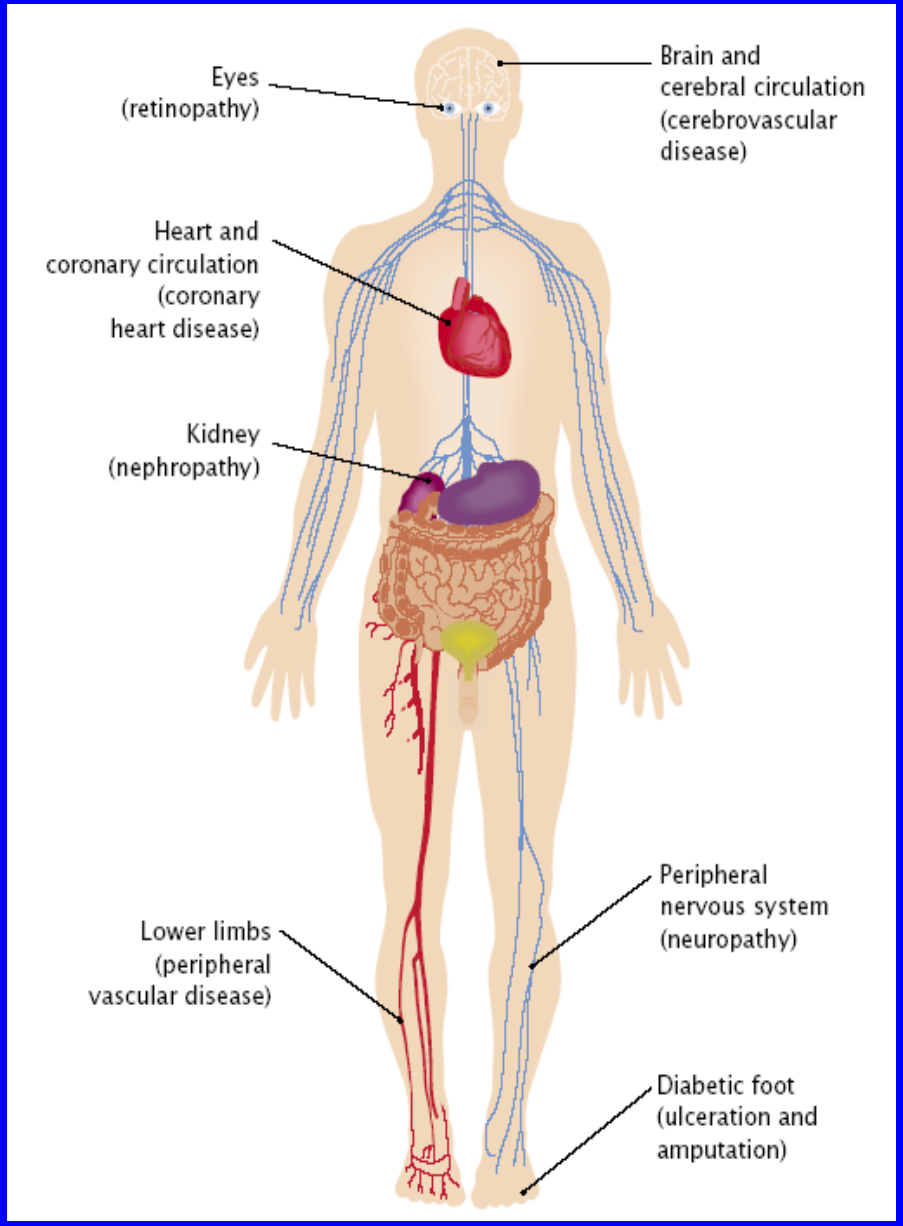
1. Need for near-normoglycemia
2. Clinical use of meters:
    A. Self-monitoring of blood glucose (SMBG)
    B. Tight glycemic control (in ICUs)

Millions of Cases of Diabetes (in 2000 and projections for 2030)



NEJM 2007; 356:213

The Major Complications of Diabetes



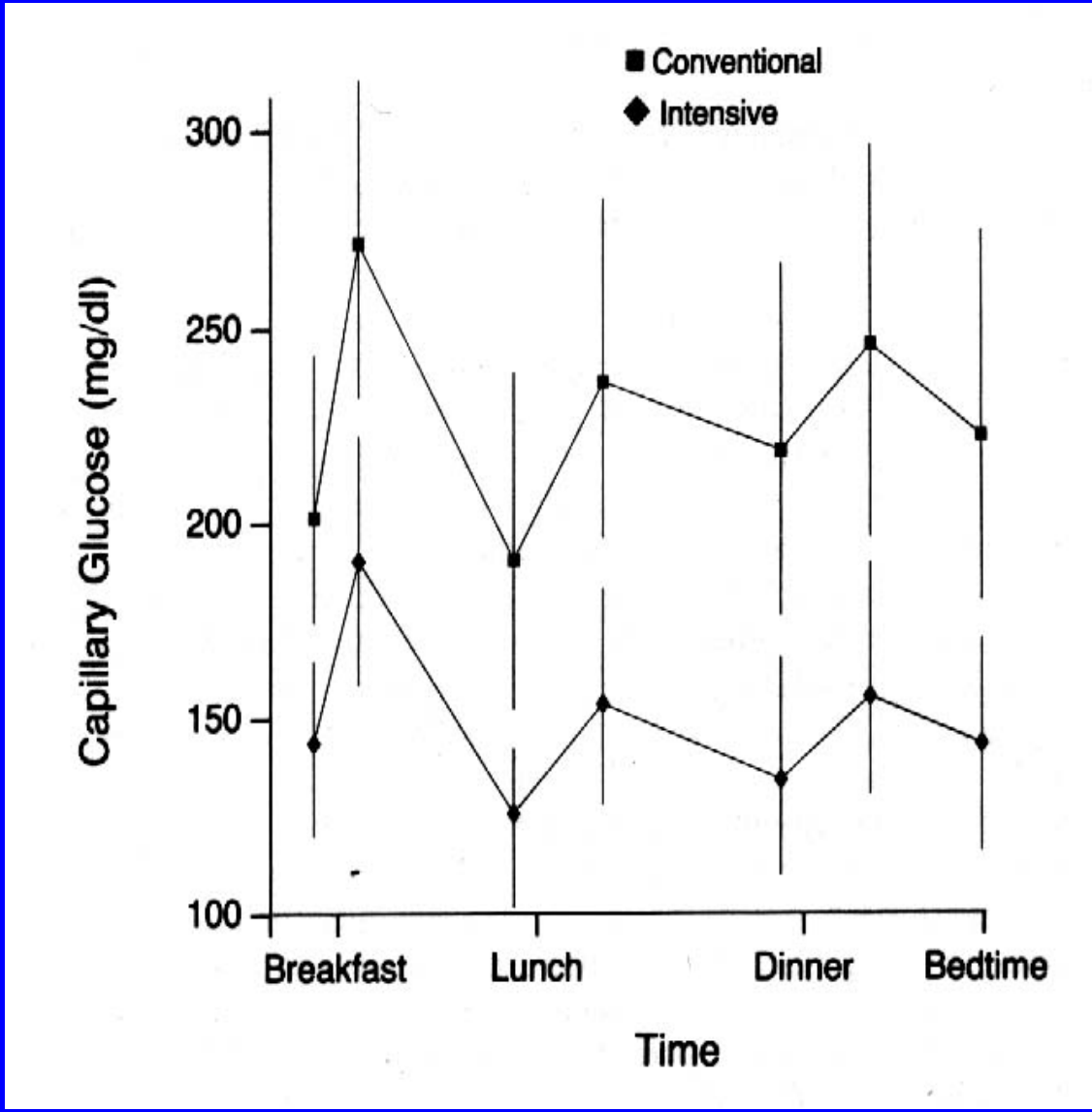
Diabetes Atlas 2nd Ed.: IDF 2003

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

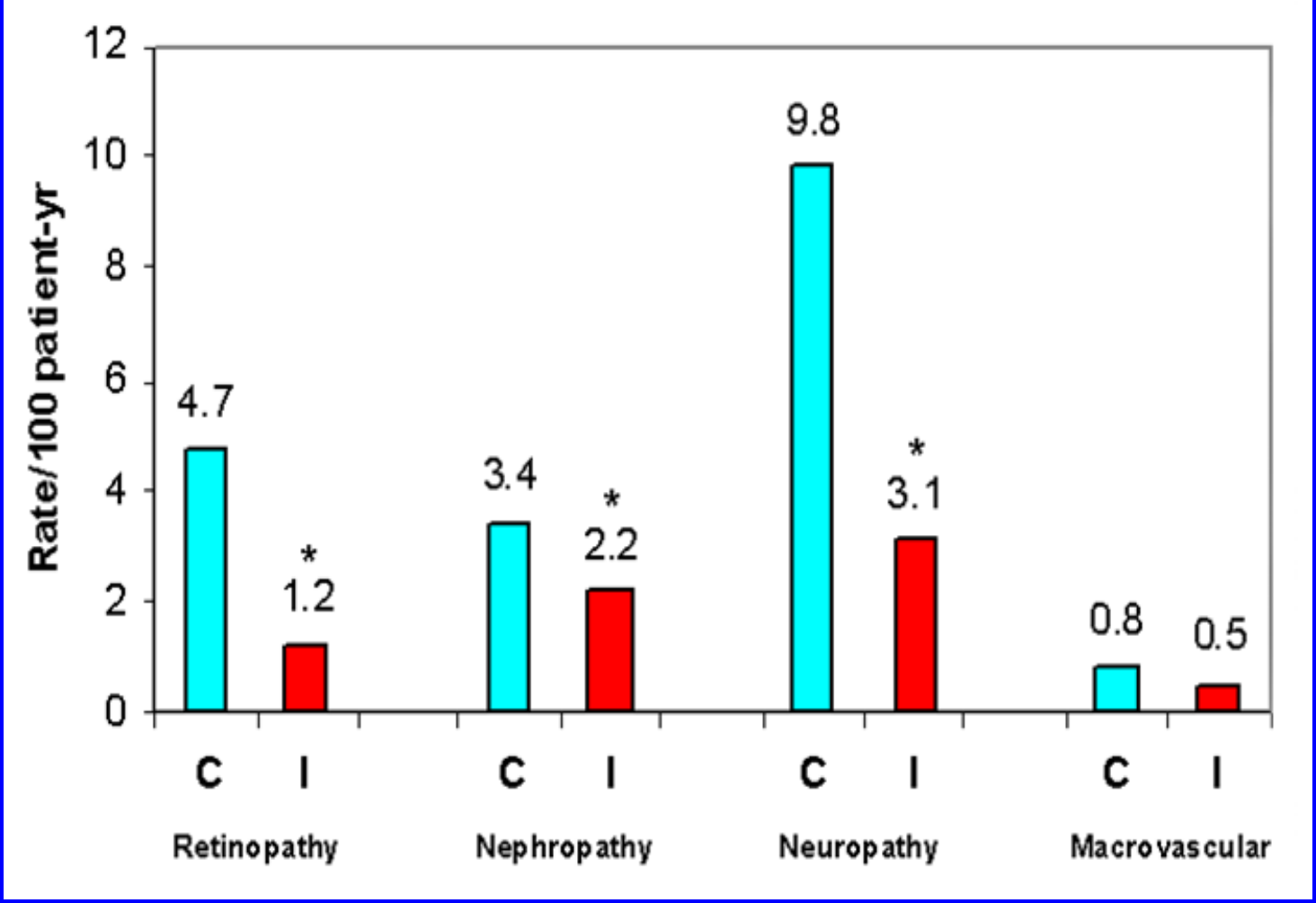
NEJM 1993;329:977

Measurement of Glucose in DCCT



NEJM 1993; 329:977

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

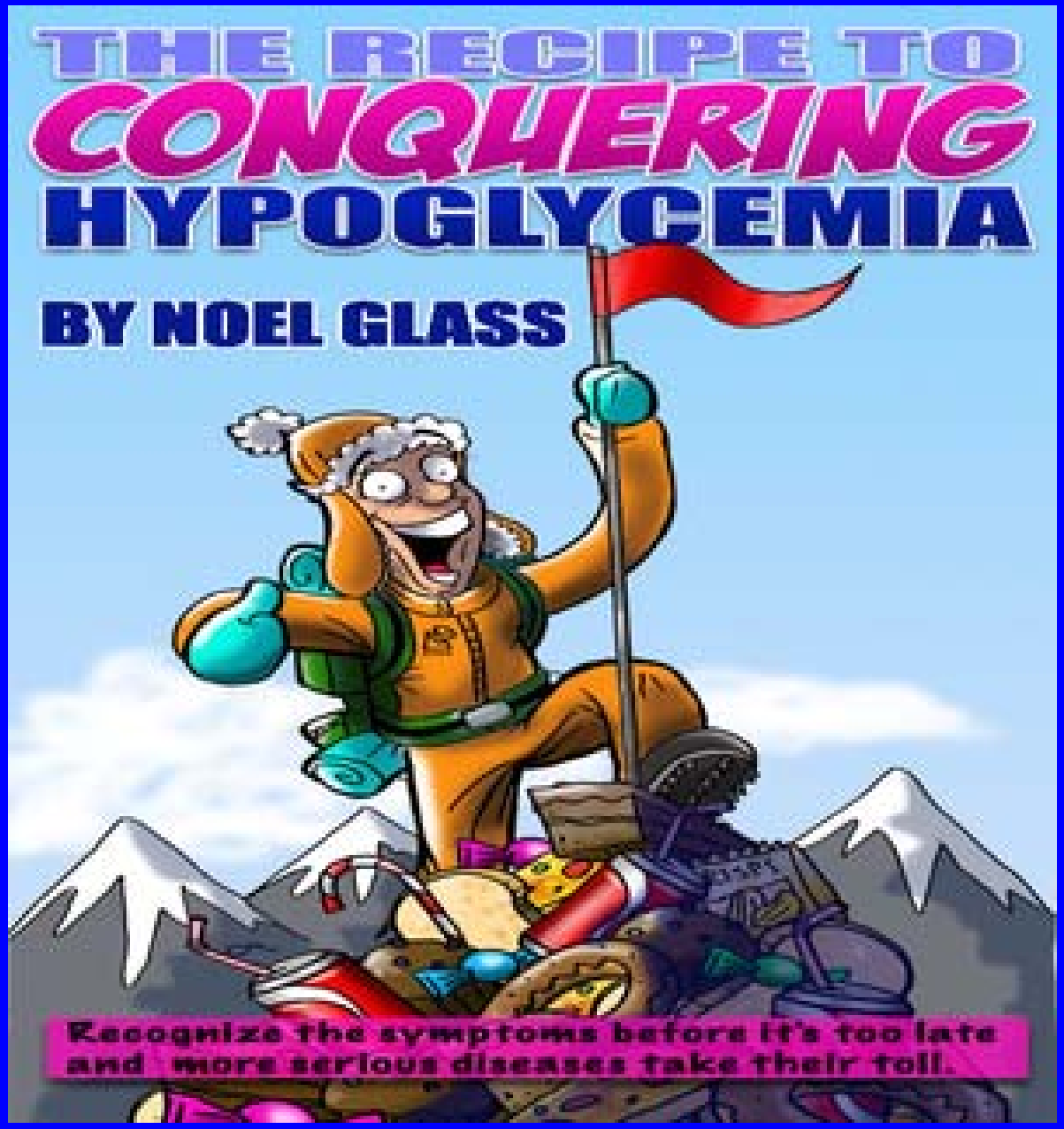
1. Determine insulin doses at meals (at least 3X daily if multiple insulin injections; glycemic control worsens with less)
2. Determine insulin dose in gestational diabetes
3. Achievement of glycemic goals
4. Detection and avoidance of hypoglycemia

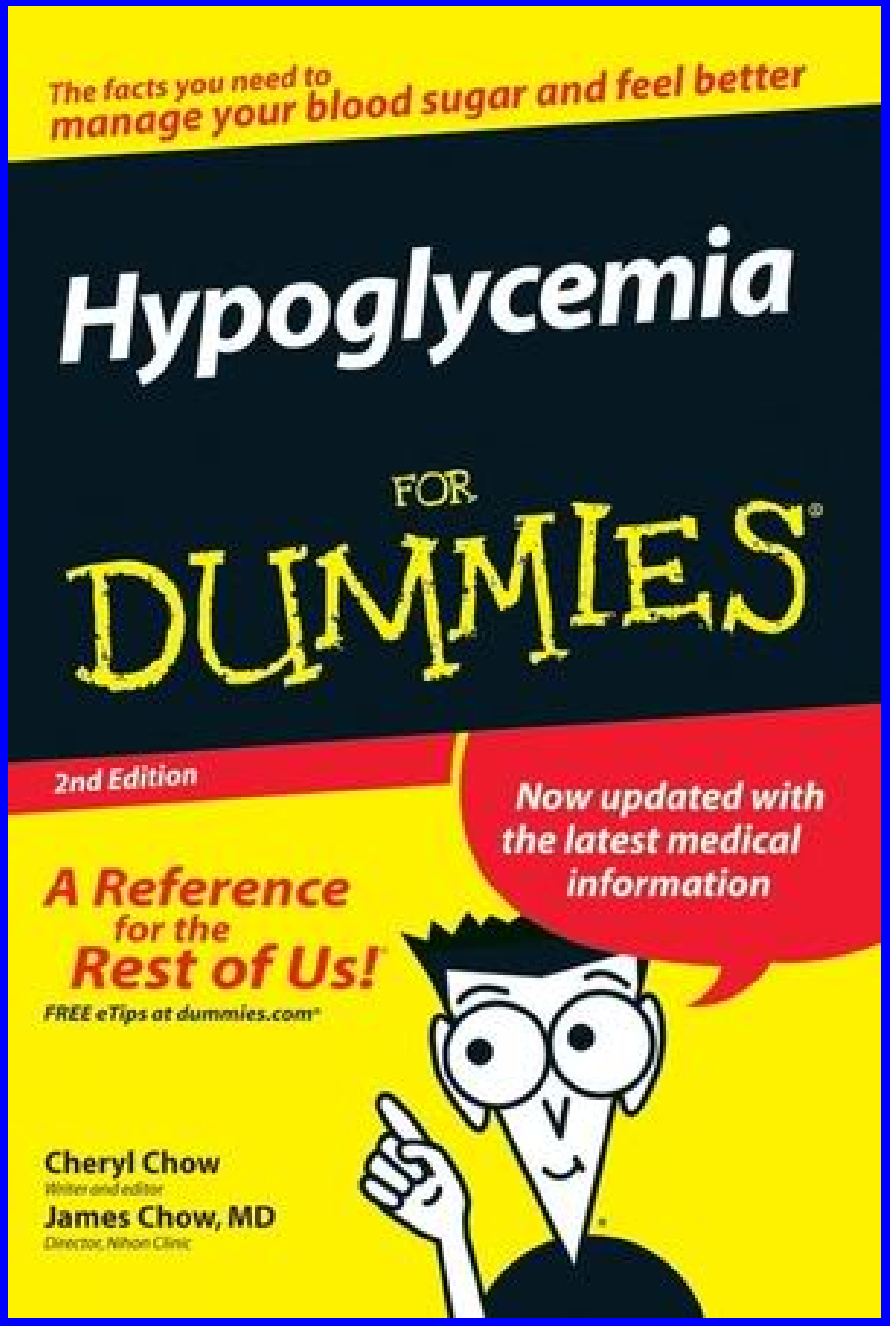
Diabetes Care 2010;33:S11

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)

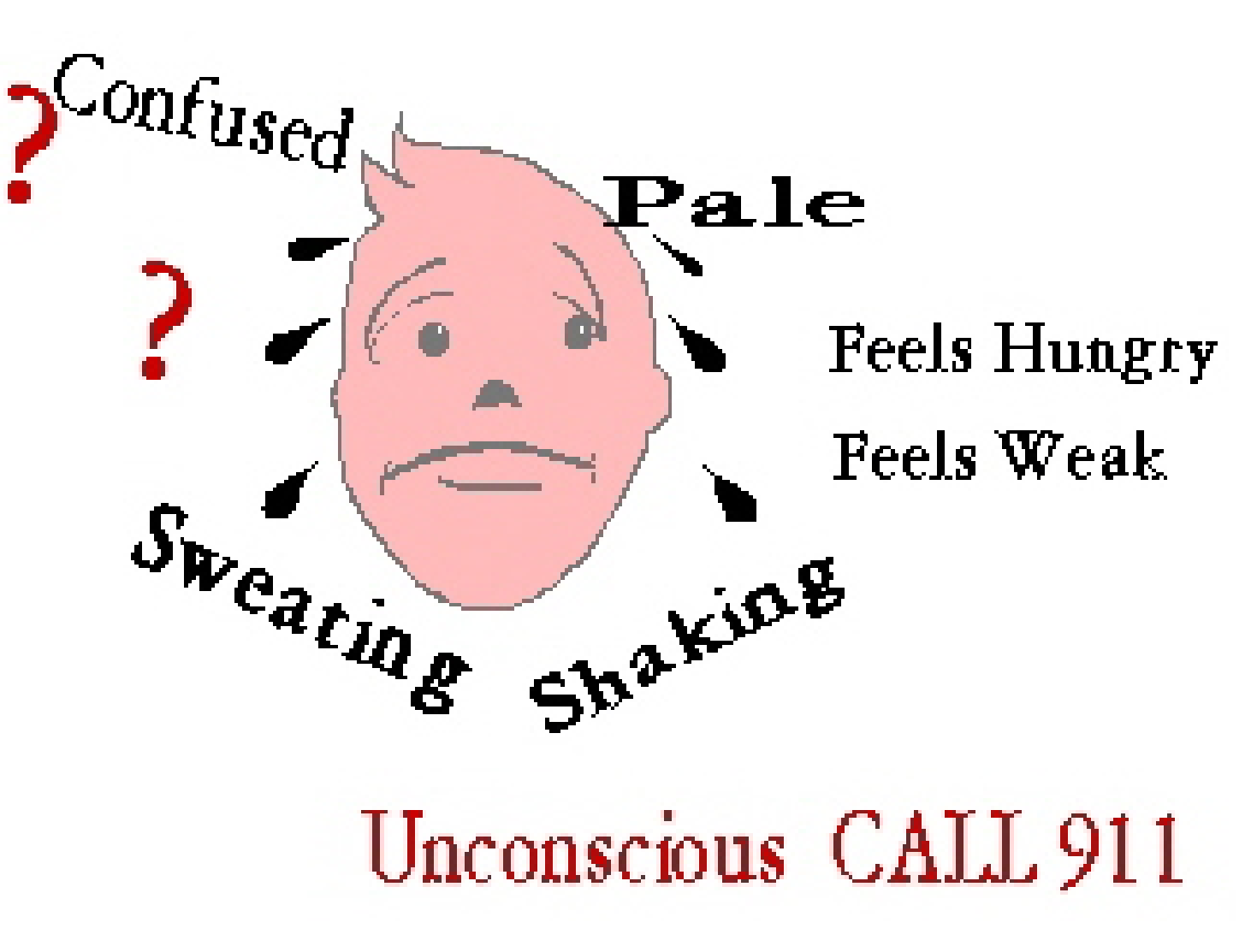

THE RECIPE TO
CONQUERING
HYPOGLYCEMIA
BY NOEL GLASS
Recognize the symptoms before it's too late
and more serious diseases take their toll.


The facts you need to
manage your blood sugar and feel better
Hypoglycemia
FOR
DUMMIES
2nd Edition
Now updated with the latest medical information
A Reference for the Rest of Us!
FREE eTips at dummies.com
Cheryl Chow
Writer and editor
James Chow, MD
Director, Nihon Clinic

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



Meter Use in Practice

1. Accuracy criteria excusively 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

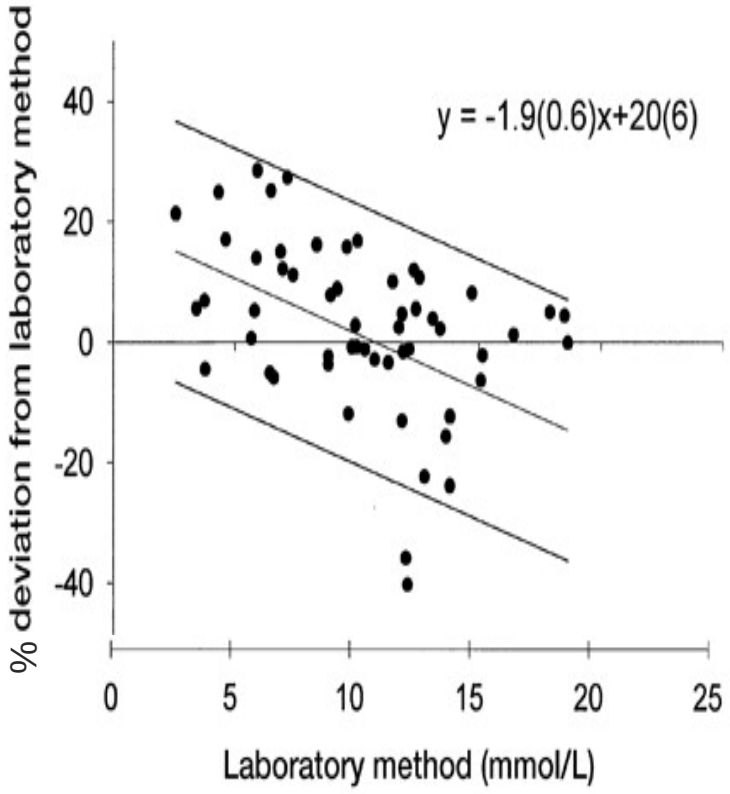
1. Current meters have performance superior to prior generations
2. Technological advances decrease operator error
3. Performance by patients inferior to medical technologists

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

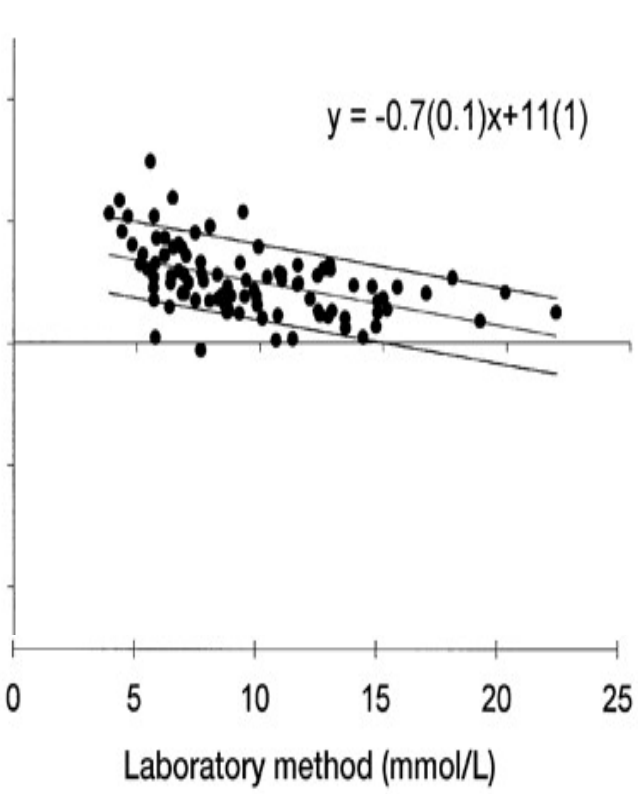
Clin Chem 2002;48:994

Technologists Perform Better Than Patients

Patients



Technologist



Patients failed to meet ISO criteria

Clin Chem 2002;48:994

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

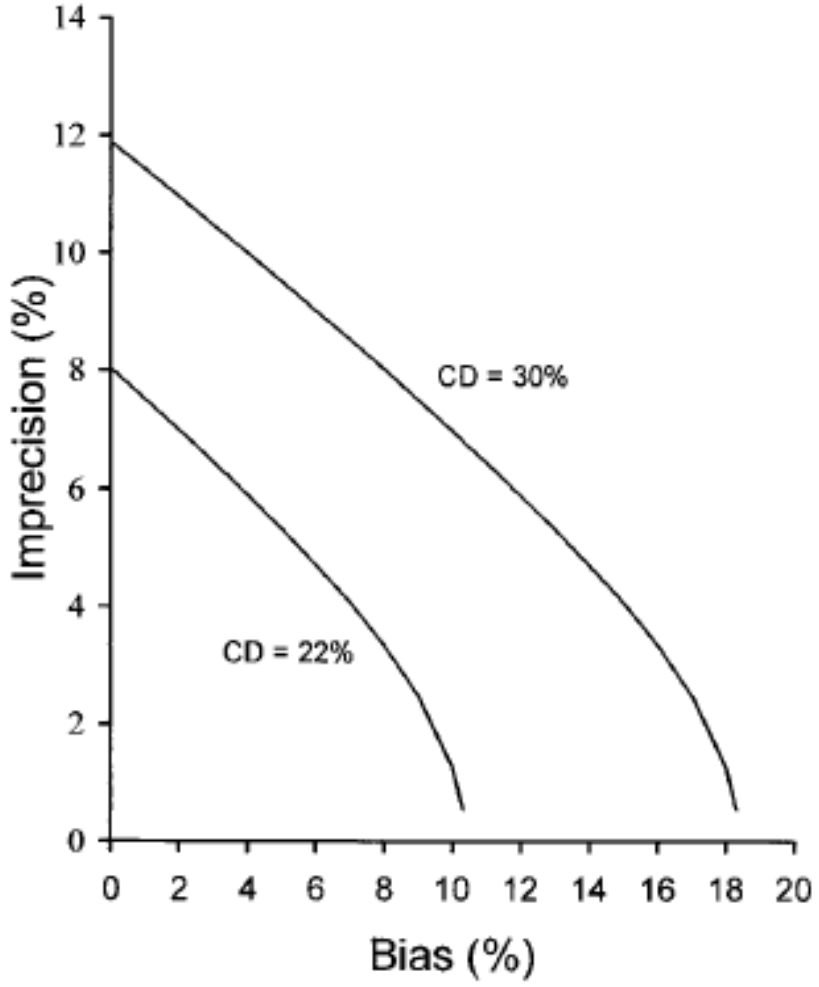


Fig. 2. Relationship between allowable imprecision and bias when the CD is 22% (reflecting optimum quality) or 30% (reflecting desirable quality).

Analytical CV 6.4-9.7% needed

For hypoglycemia, CV 3.1%

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

Clin Chem 2001; 47:67

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 mg/dL ± 20% for 95% of results ≤100 mg/dL ± 15 mg/dL
ISO/TC212	2003	≥75 mg/dL ± 20% for 95% of results ≤ 75 mg/dL ± 15 mg/dL

Addendum to Meter Performance Criteria

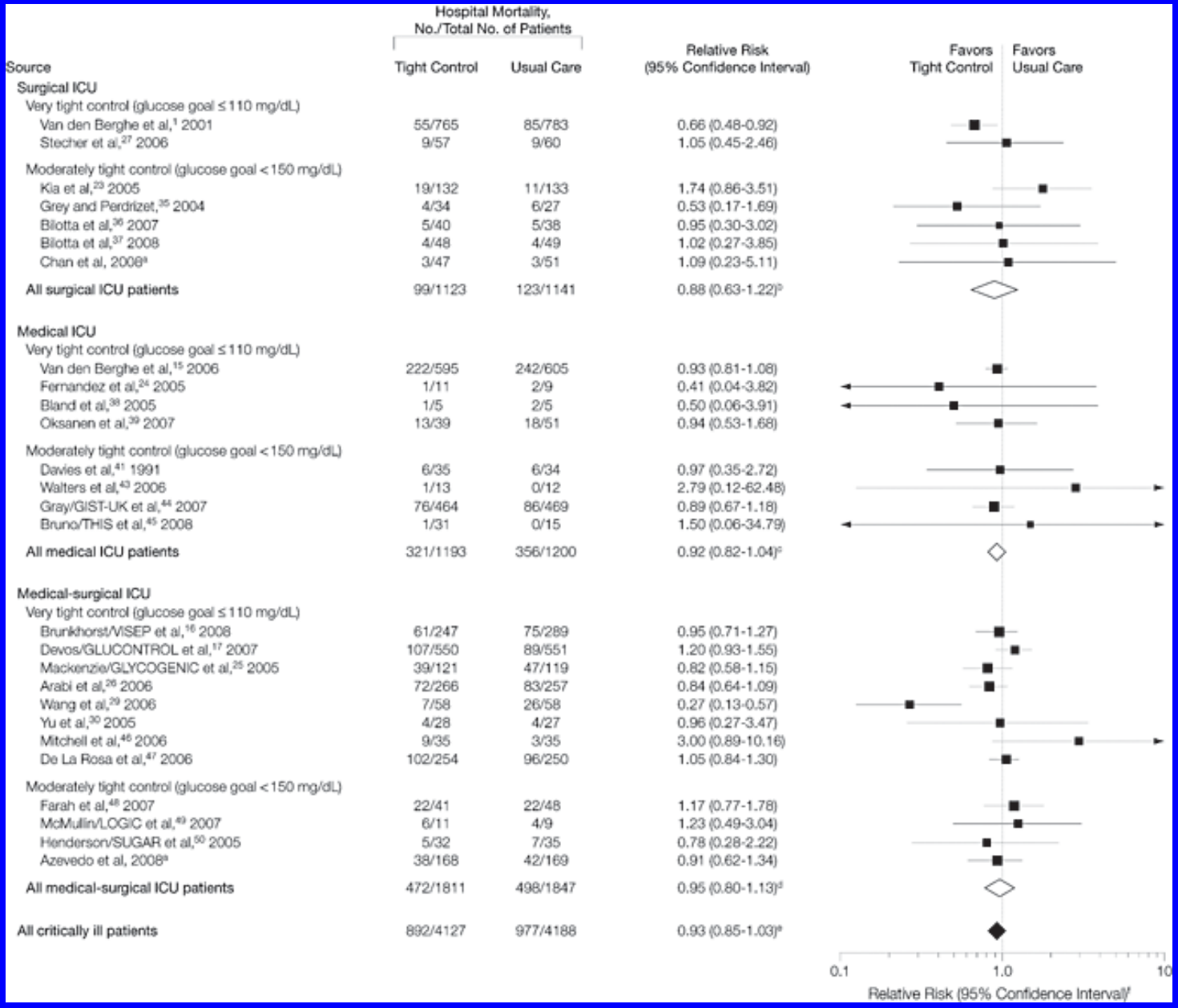
1. 5% of results excluded from accuracy criteria
2. Values can be essentially anything
3. If patient does SMBG 4x/d, expect 1 result outside analytical limit every 5 days
4. Need to define criteria that include these values

Tight glycemic control

Nature Rev Endocrinol 2009;5:473

Does meter performance meet clinical needs in TGC?

Association of Tight Glucose Control vs Usual Care



Source	Hospital Mortality, No./Total No. of Patients: Tight Control	Hospital Mortality, No./Total No. of Patients: Usual Care	Relative Risk (95% Confidence Interval)
Surgical ICU			
Very tight control (glucose goal ≤ 110 mg/dL)			
Van den Berghe et al,[1] 2001	55/765	85/783	0.66 (0.48-0.92)
Stecher et al,[27] 2006	9/57	9/60	1.05 (0.45-2.46)
Moderately tight control (glucose goal <150 mg/dL)			
Kia et al,[23] 2005	19/132	11/133	1.74 (0.86-3.51)
Grey and Perdrizet,[35] 2004	4/34	6/27	0.53 (0.17-1.69)
Bilotta et al,[36] 2007	5/40	5/38	0.95 (0.30-3.02)
Bilotta et al,[37] 2008	4/48	4/49	1.02 (0.27-3.85)
Chan et al, 2008[a]	3/47	3/51	1.09 (0.23-5.11)
All surgical ICU patients	99/1123	123/1141	0.88 (0.63-1.22)[b]
Medical ICU			
Very tight control (glucose goal ≤ 110 mg/dL)			
Van den Berghe et al,[15] 2006	222/595	242/605	0.93 (0.81-1.08)
Fernandez et al,[24] 2005	1/11	2/9	0.41 (0.04-3.82)
Bland et al,[38] 2005	1/5	2/5	0.50 (0.06-3.91)
Oksanen et al,[39] 2007	13/39	18/51	0.94 (0.53-1.68)
Moderately tight control (glucose goal <150 mg/dL)			
Davies et al,[41] 1991	6/35	6/34	0.97 (0.35-2.72)
Walters et al,[43] 2006	1/13	0/12	2.79 (0.12-62.48)
Gray/GIST-UK et al,[44] 2007	76/464	86/469	0.89 (0.67-1.18)
Bruno/THIS et al,[45] 2008	1/31	0/15	1.50 (0.06-34.79)
All medical ICU patients	321/1193	356/1200	0.92 (0.82-1.04)[c]
Medical-surgical ICU			
Very tight control (glucose goal ≤ 110 mg/dL)			
Brunkhorst/VISEP et al,[16] 2008	61/247	75/289	0.95 (0.71-1.27)
Devos/GLUCONTROL et al,[17] 2007	107/550	89/551	1.20 (0.93-1.55)
Mackenzie/GLYCOGENIC et al,[25] 2005	39/121	47/119	0.82 (0.58-1.15)
Arabi et al,[26] 2006	72/266	83/257	0.84 (0.64-1.09)
Wang et al,[29] 2006	7/58	26/58	0.27 (0.13-0.57)
Yu et al,[30] 2005	4/28	4/27	0.96 (0.27-3.47)
Mitchell et al,[46] 2006	9/35	3/35	3.00 (0.89-10.16)
De La Rosa et al,[47] 2006	102/254	96/250	1.05 (0.84-1.30)
Moderately tight control (glucose goal <150 mg/dL)			
Farah et al,[48] 2007	22/41	22/48	1.17 (0.77-1.78)
McMullin/LOGIC et al,[49] 2007	6/11	4/9	1.23 (0.49-3.04)
Henderson/SUGAR et al,[50] 2005	5/32	7/35	0.78 (0.28-2.22)
Azevedo et al, 2008[a]	38/168	42/169	0.91 (0.62-1.34)
All medical-surgical ICU patients	472/1811	498/1847	0.95 (0.80-1.13)[d]
All critically ill patients	892/4127	977/4188	0.93 (0.85-1.03)[e]

JAMA 2008;300:933

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

NEJM 2009; 360:1283

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%

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

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	± 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%

NICE-SUGAR Analysis (ctd)

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)

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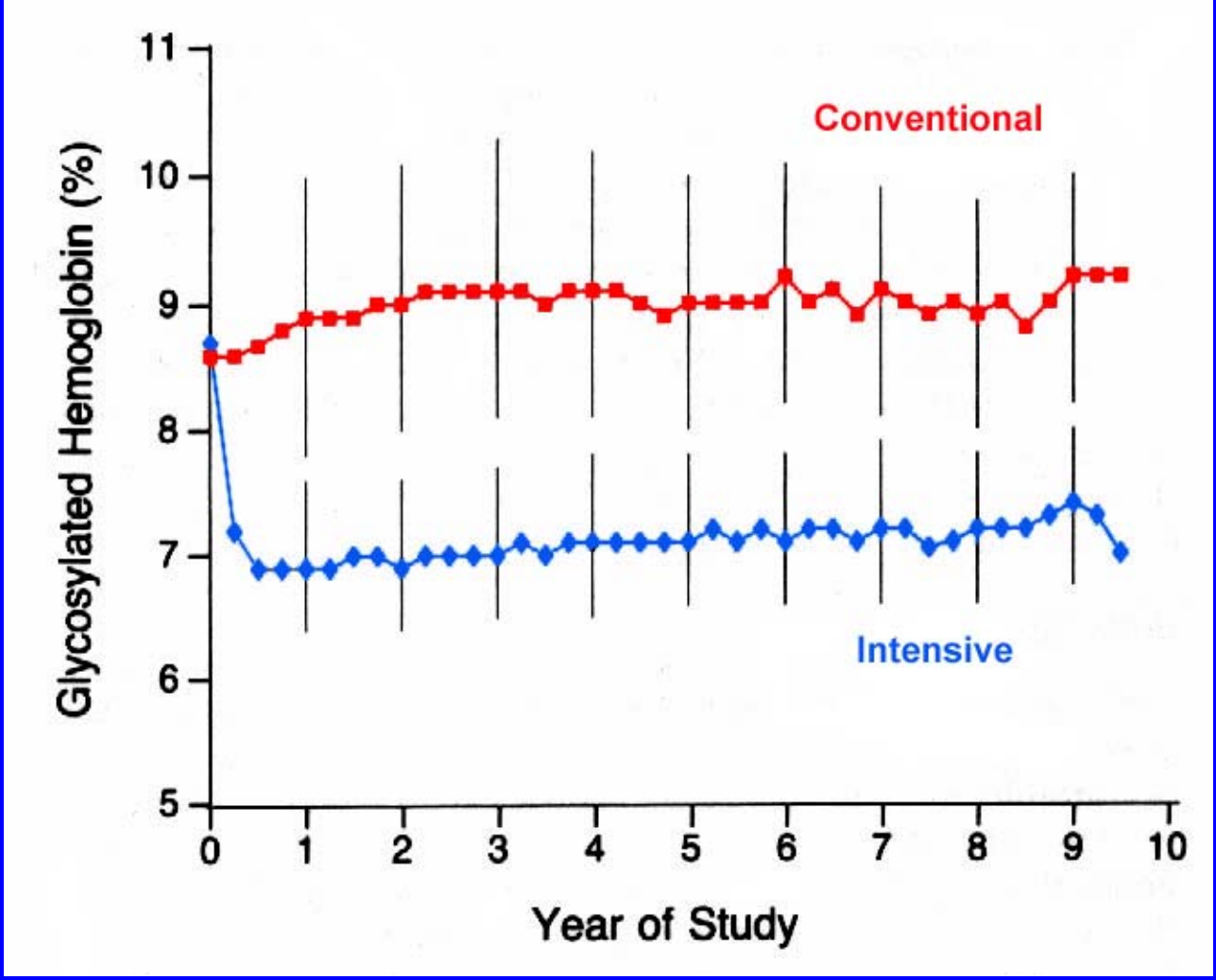
5. If meter has high bias, results will be higher than patient's actual glucose and patient will receive too much insulin, producing hypoglycemia (which might not be detected)

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



NEJM 1993; 329:977

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%

NEJM 2009; 360:1283

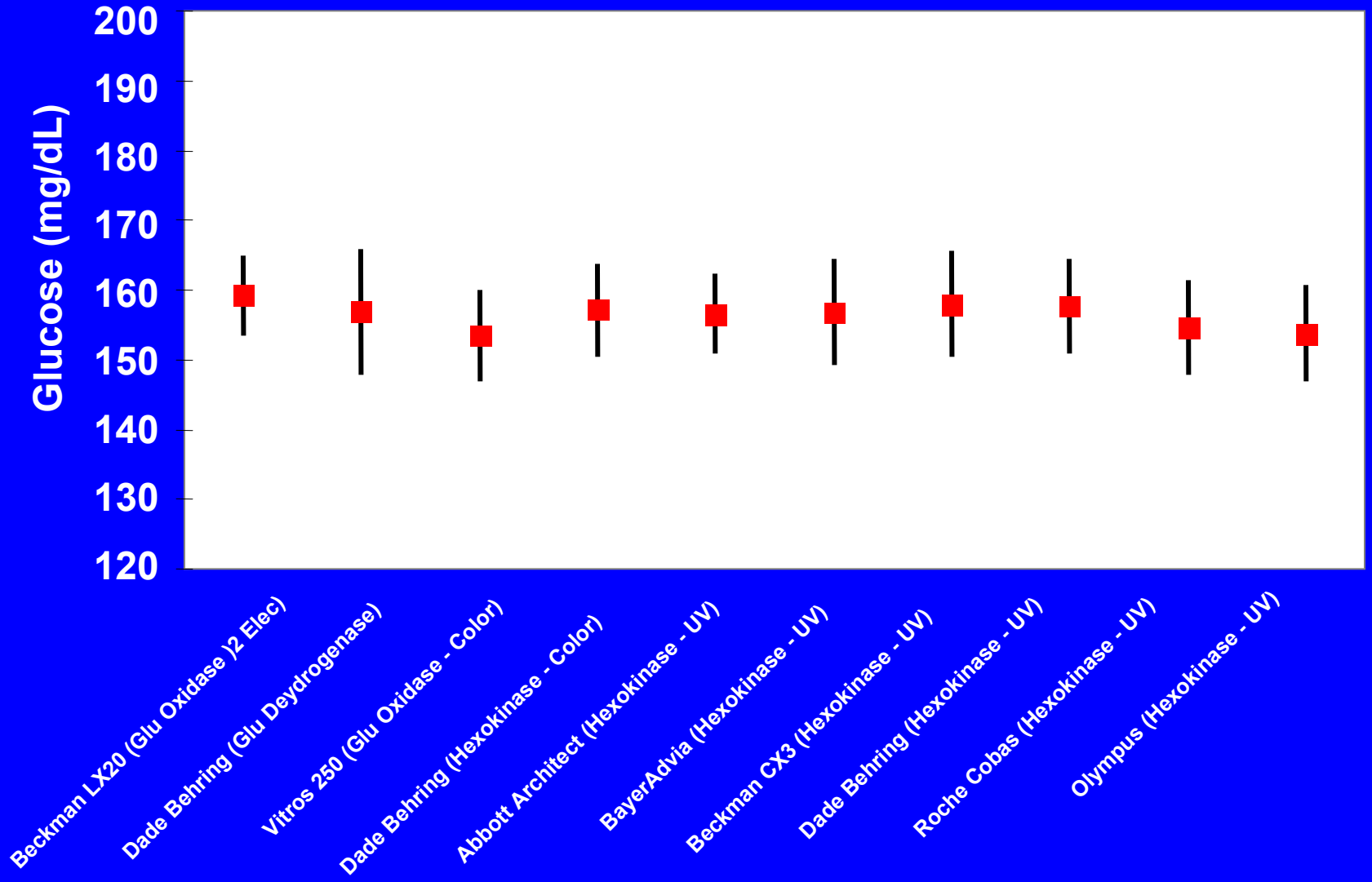
Limitations of POC Glucometers

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%)

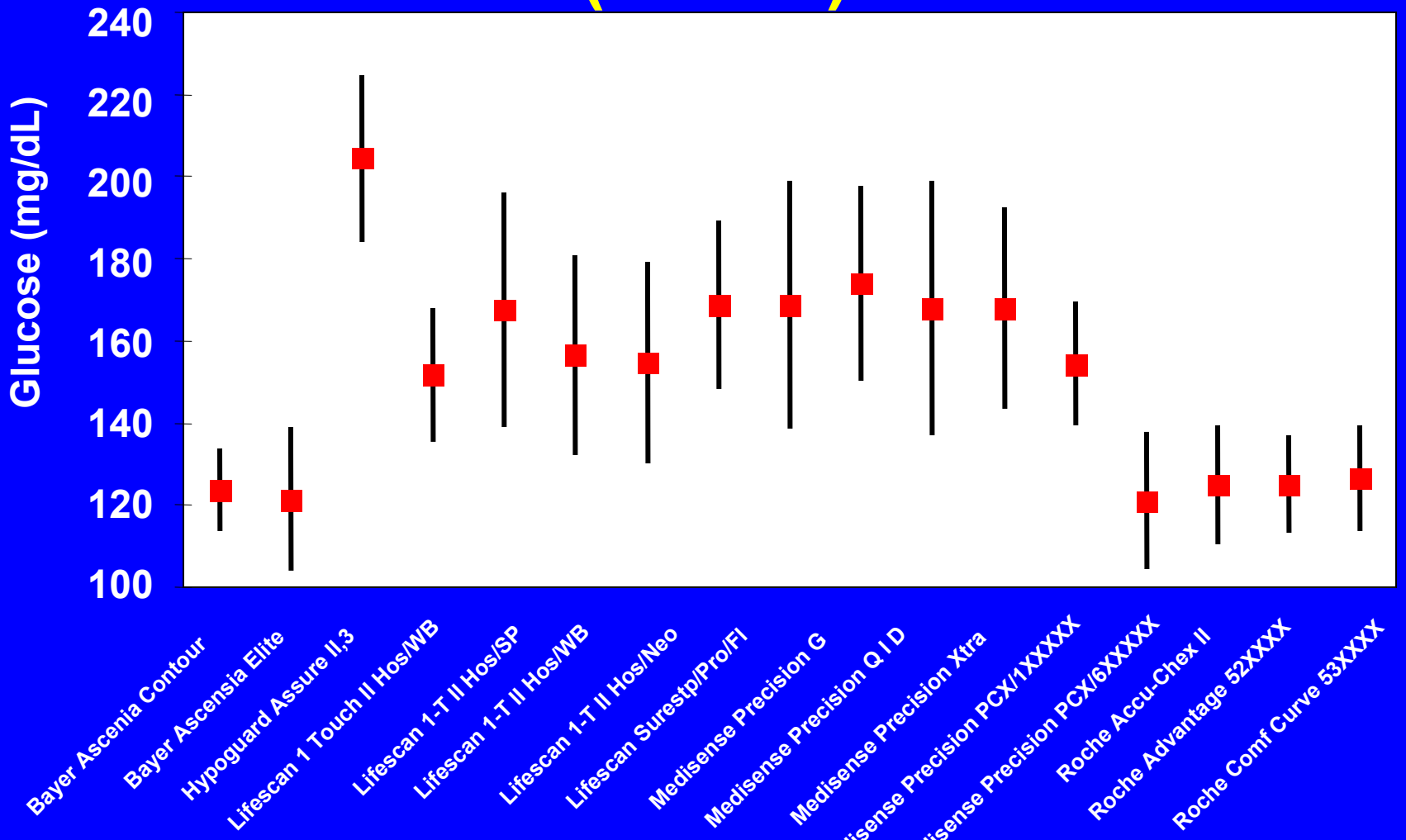
Limitations of POC Glucometers (ctd)

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

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

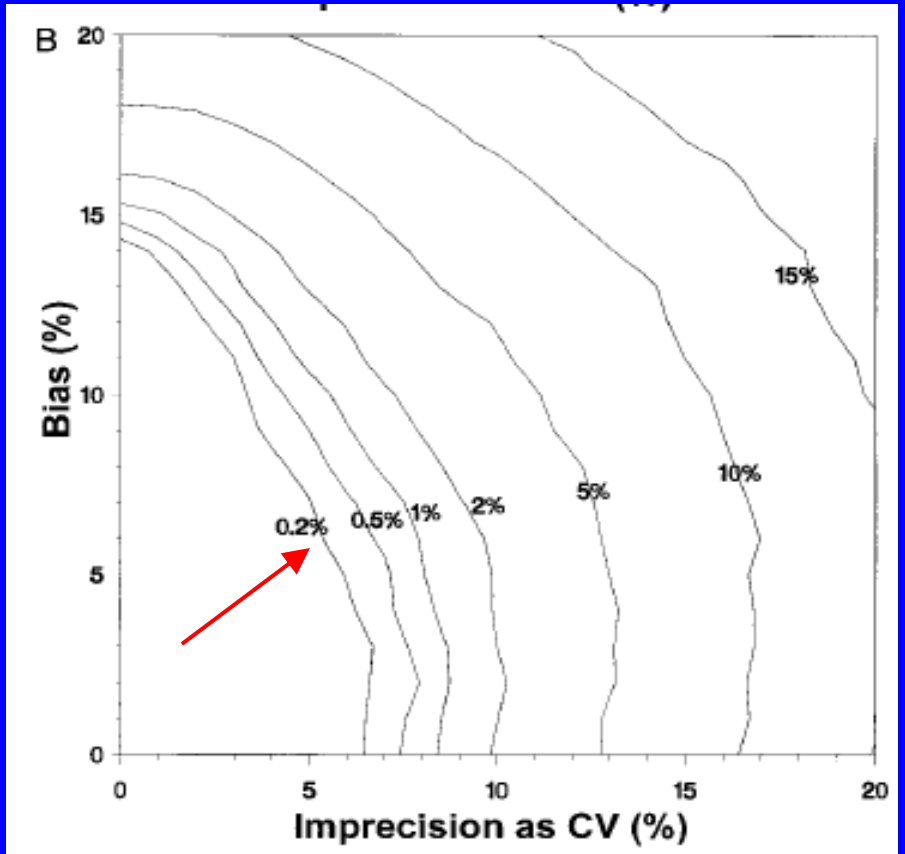


Fig. 3. Contour plots of insulin-dosage error rates as a function of assay bias and imprecision (CV).

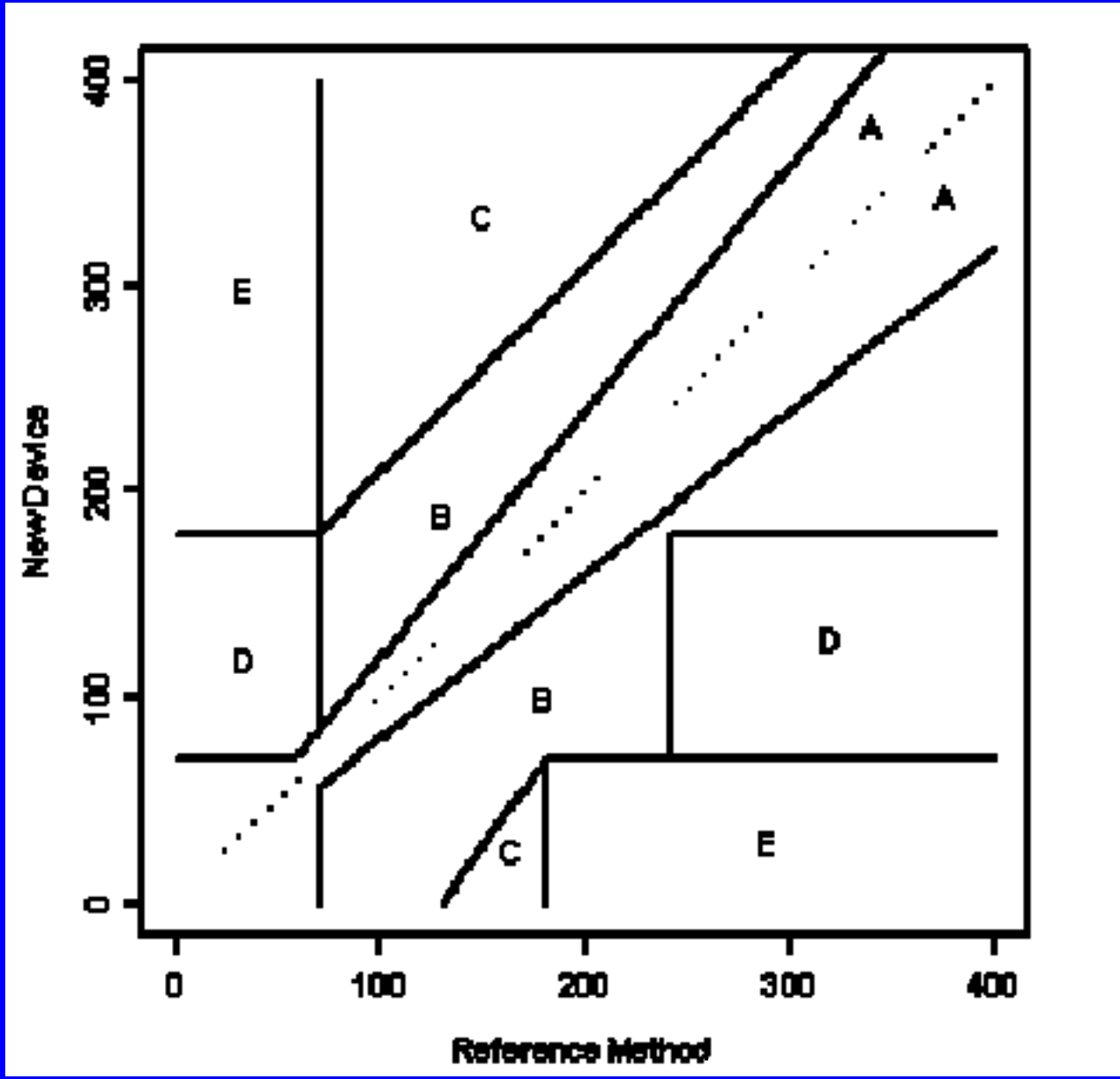
-Total Error < 10% would lead to two-step errors in insulin dose ~ 0.2% of time

- 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%

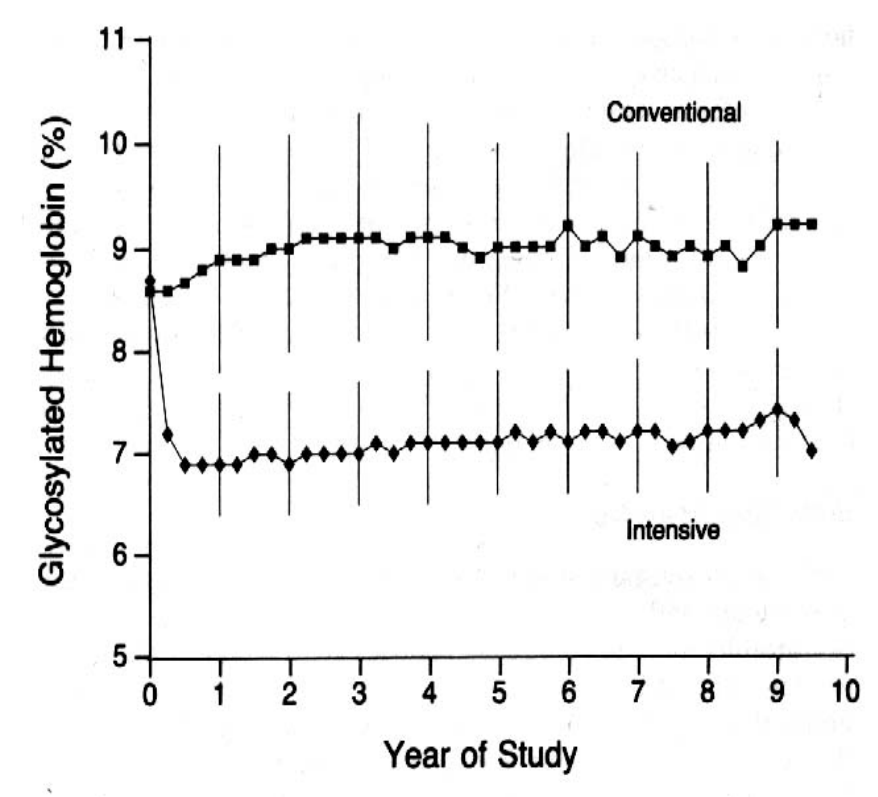
Boyd, Clin Chem 2001;47:209

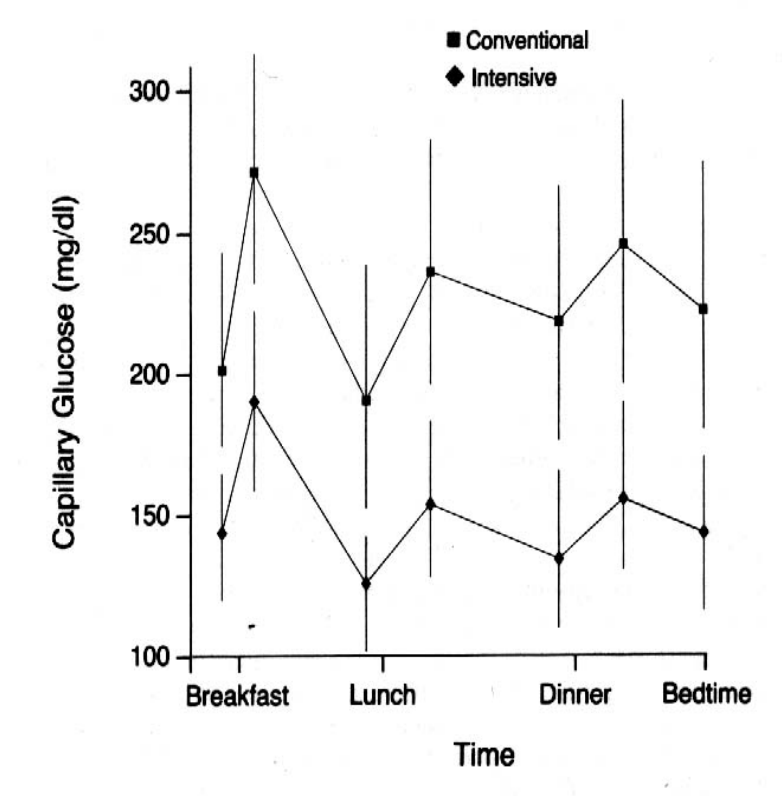
Clarke Error Grid



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 ≥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 embarassment

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 ½ 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 ≤ ½ CV_i
3. CV_a ≤ 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