UF UNIVERSITY of FLORIDA
Health Science Center

Glucose monitoring and control in hospitalized patients: How we got here and where we might be going

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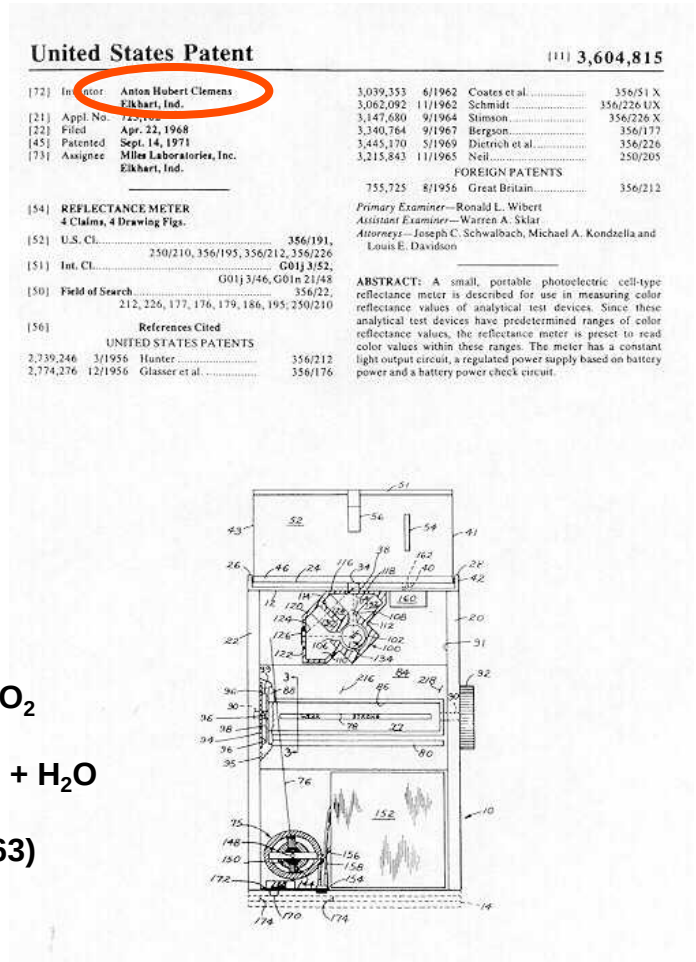
In The Beginning . . . (*circa* 1963)

George Orr
VP, Prof Prod Grp

Walter Ames Compton, MD
CEO, Miles Laboratories



United States Patent [11] 3,604,815

[72] Inventor: Anton Hubert Clemens, Elkhart, Ind.
[21] Appl. No.
[22] Filed: Apr. 22, 1968
[45] Patented: Sept. 14, 1971
[73] Assignee: Miles Laboratories, Inc., Elkhart, Ind.

[54] REFLECTANCE METER
4 Claims, 4 Drawing Figs.

[52] U.S. Cl. 356/191, 250/210, 356/195, 356/212, 356/226
[51] Int. Cl. G01j 3/52, G01j 3/46, G01n 21/48
[50] Field of Search 356/22, 212, 226, 177, 176, 179, 186, 195; 250/210

[56] References Cited
UNITED STATES PATENTS

2,739,246	3/1956	Hunter	356/212
2,774,276	12/1956	Glasser et al.	356/176
3,039,353	6/1962	Coates et al.	356/51 X
3,062,092	11/1962	Schmidt	356/226 UX
3,147,680	9/1964	Stimson	356/226 X
3,340,764	9/1967	Bergson	356/177
3,445,170	5/1969	Dietrich et al.	356/226
3,215,843	11/1965	Neil	250/205

FOREIGN PATENTS

755,725	8/1956	Great Britain	356/212

Primary Examiner—Ronald L. Wibert
Assistant Examiner—Warren A. Sklar
Attorneys—Joseph C. Schwalbach, Michael A. Kondzella and Louis E. Davidson

ABSTRACT: A small, portable photoelectric cell-type reflectance meter is described for use in measuring color reflectance values of analytical test devices. Since these analytical test devices have predetermined ranges of color reflectance values, the reflectance meter is preset to read color values within these ranges. The meter has a constant light output circuit, a regulated power supply based on battery power and a battery power check circuit.

$$\text{glucose} + O_2 \xrightarrow{GO} \text{gluconic acid} + H_2O_2$$

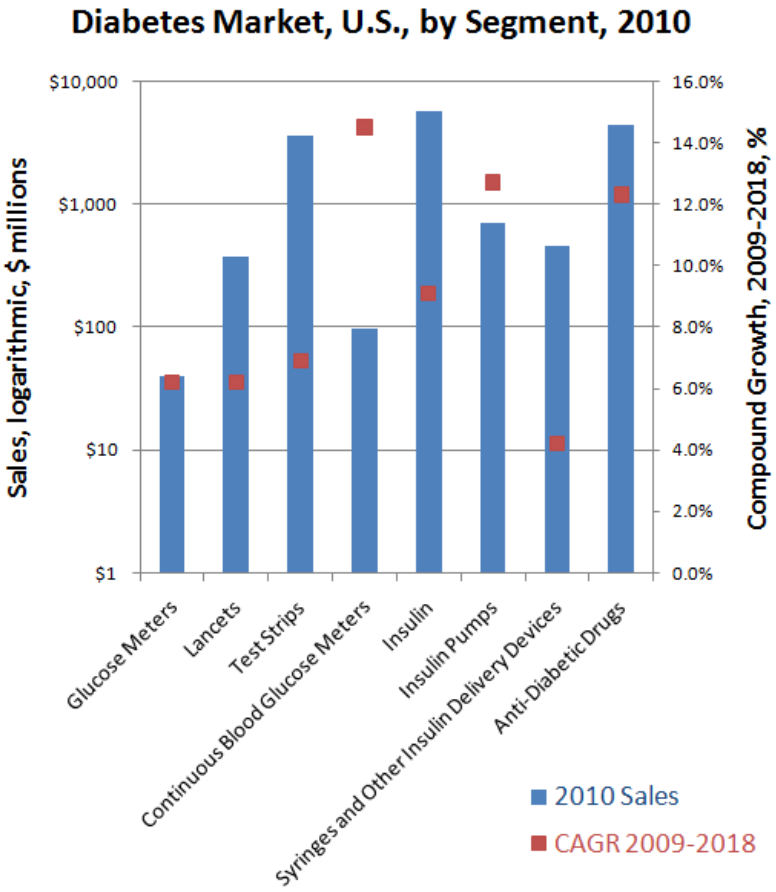
$$H_2O_2 + \textit{o}\text{-tolidine} \rightarrow \text{oxidized } \textit{o}\text{-tolidine} + H_2O$$

U.S. Patent #3,092,465 (June 4, 1963)

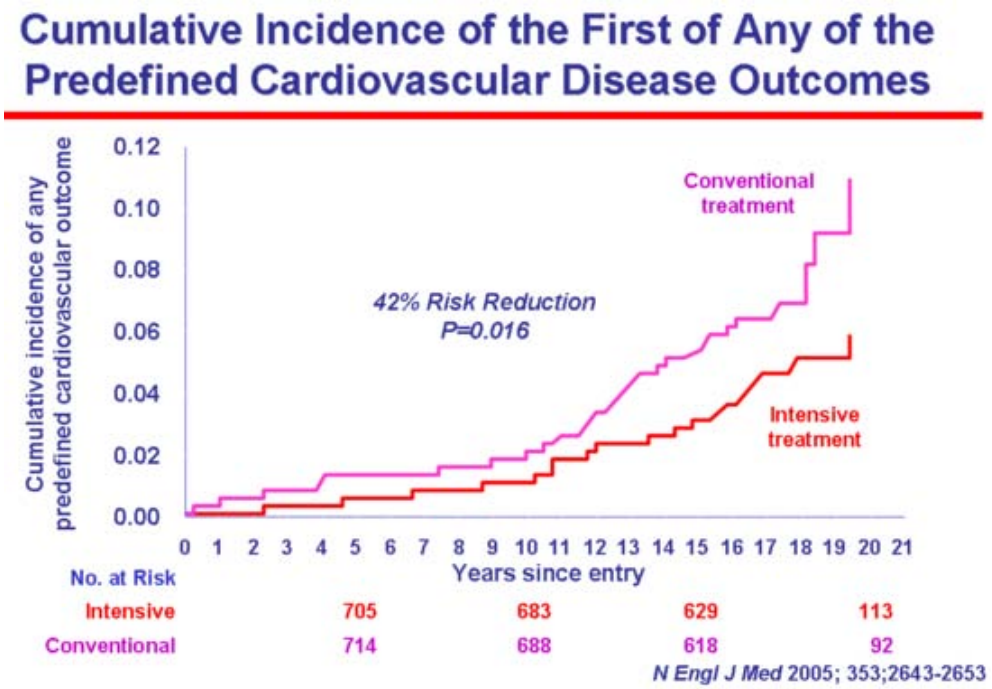
(Ernie Adams)

Self-Monitoring of Blood Glucose (1978)

Danowski TS and Sunder JH. Jet injections of insulin during self-monitoring of blood glucose. Diabetes Care **1978**;1:27-33.



DCCT (1993)



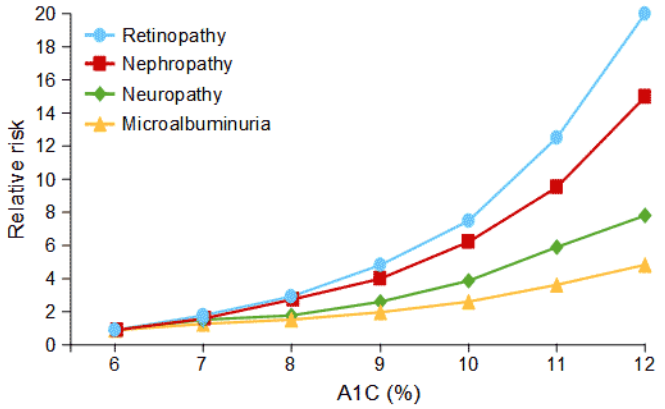
1,441 patients with Type 2 diabetes randomized to either:

Intensive therapy: insulin (pump or injection) 3-4 times per day based on BG 4 times daily

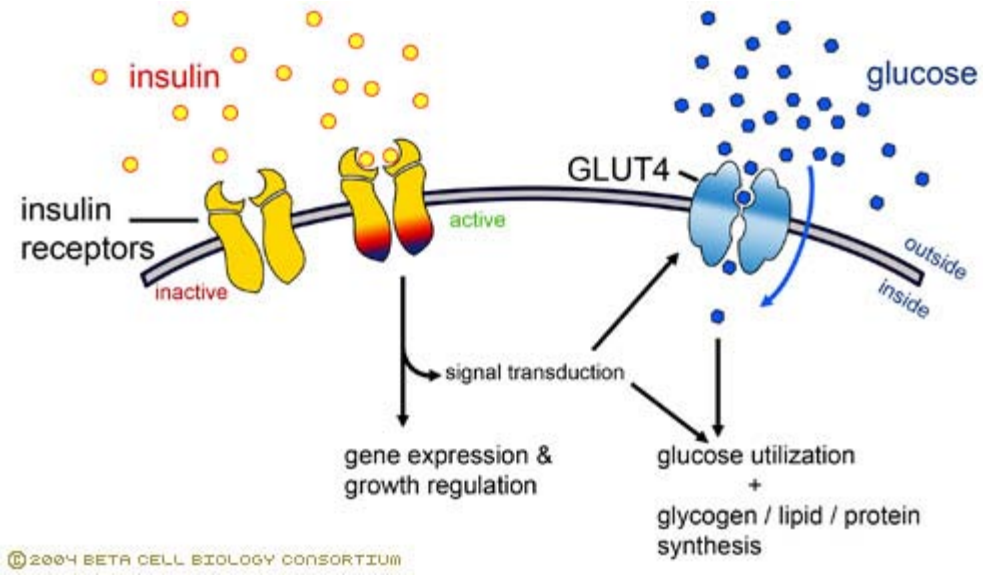
Conventional therapy: insulin twice daily with urine or BG daily.

Goals of intensive therapy:

Preprandial BG 70-120 mg/dL
Postprandial BG <180 mg/dL
Monthly HbA1c <6.05%



Regulation of Cellular Uptake of Glucose



There are four glucose transport proteins: **GLUT1-GLUT4**

Only **GLUT4** is insulin-responsive

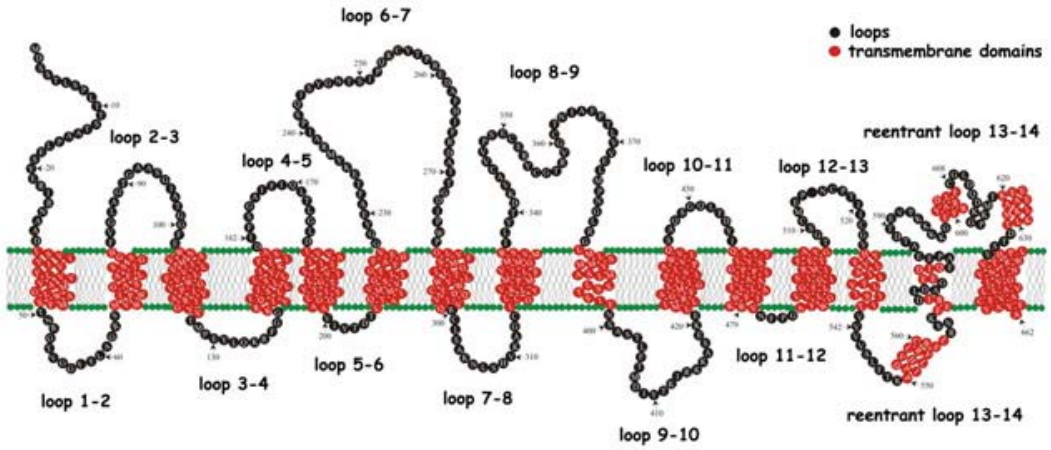
GLUT1-3 proteins facilitate non-insulin dependent glucose transport

GLUT1: Fetal tissue; RBCs; endothelium (BBB)

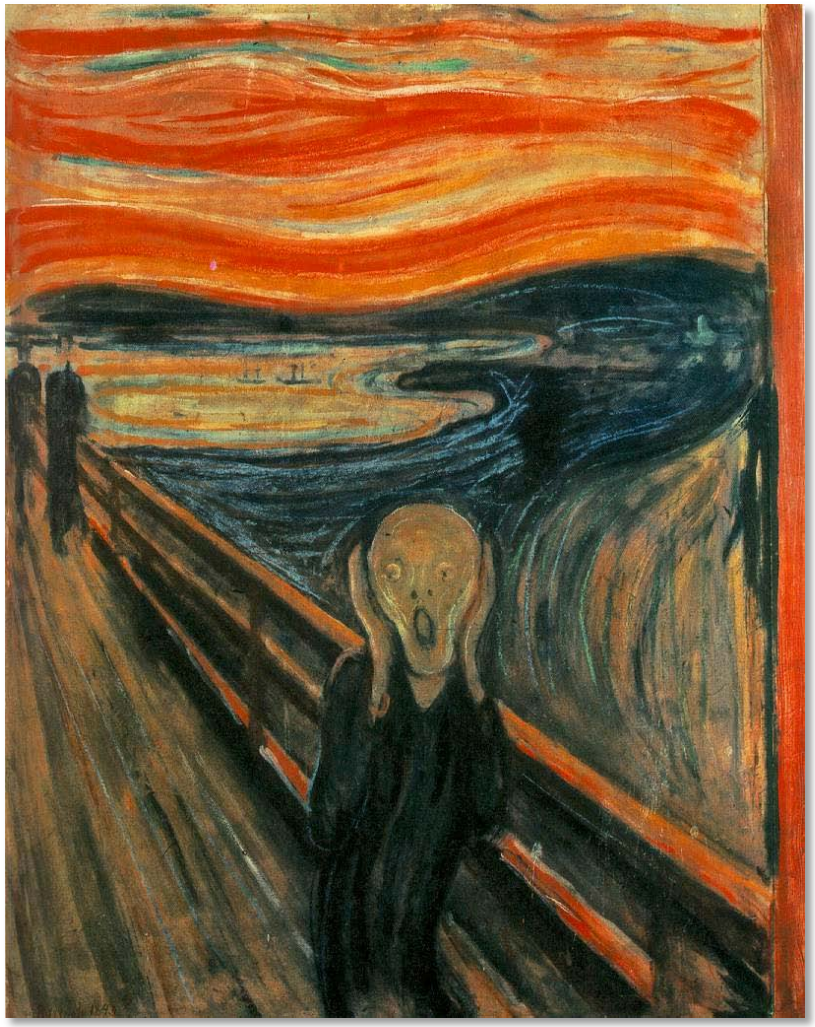
GLUT2: Renal tubules

GLUT3: Neurons, placenta

GLUT4: Adipose tissue and striated muscle



Stress and Hyperglycemia



- Increased glucose uptake
- Increased gluconeogenesis
- Lower glycogenesis
- Glucose intolerance
- Insulin resistance
- Up-regulation of glycolysis

- Are these changes beneficial?

Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. Am J Med 1995;98:75-84.

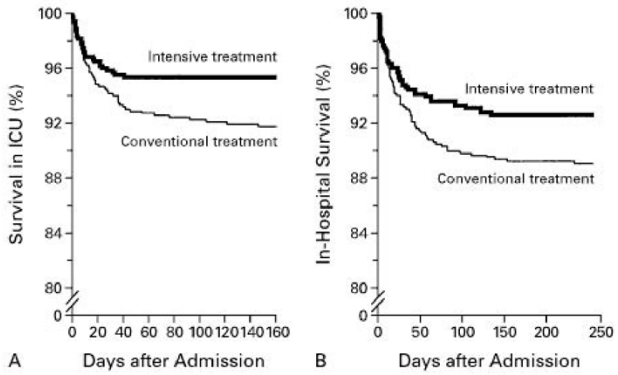
Intensive Insulin Therapy (2001)

Maintained of BG between 80-110 mg/dL.

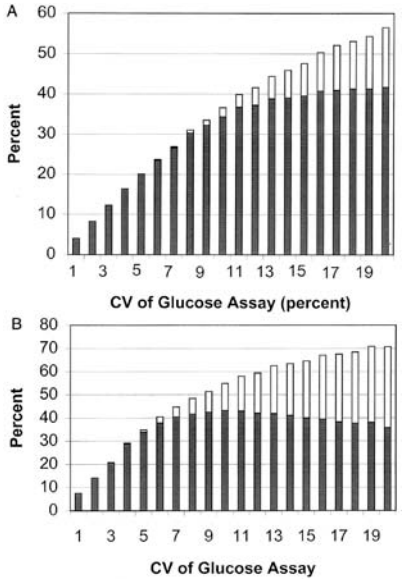
Controls treated with insulin only when BG exceeded 215 mg/dL.

Mortality with IIT = 4.6%, vs. 8.0% in controls

(BG measurements by ABL700 analyzer on arterial blood collected from central line)



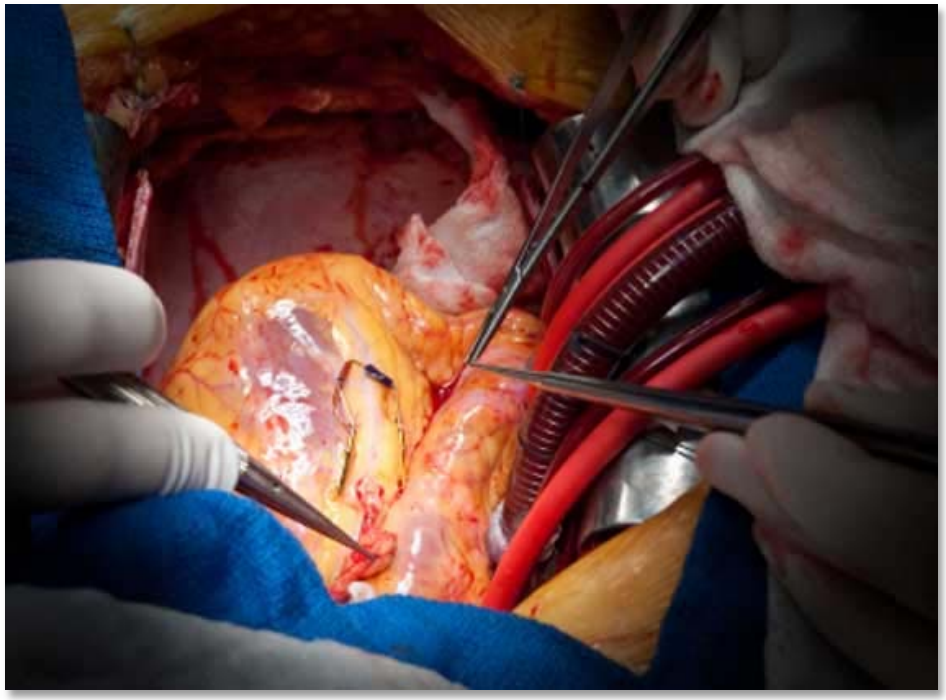
The First Sign of Trouble (2001)



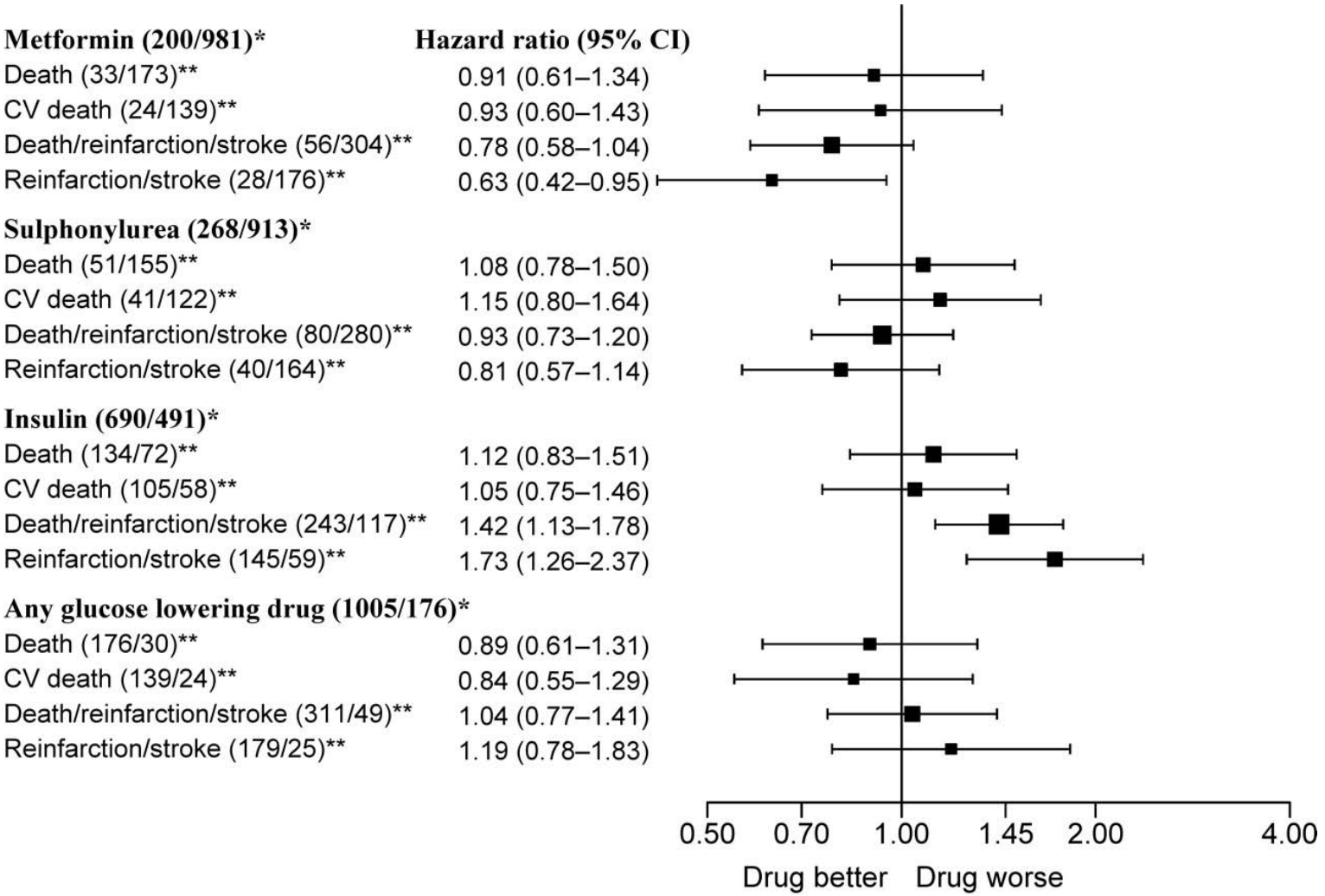
The Portland Protocol (2003)

Observed mortality with continuous insulin infusion was 2.5%, vs. 5.3% with subcutaneous insulin.

CII ⇒ better glucose control ⇒ lower mortality



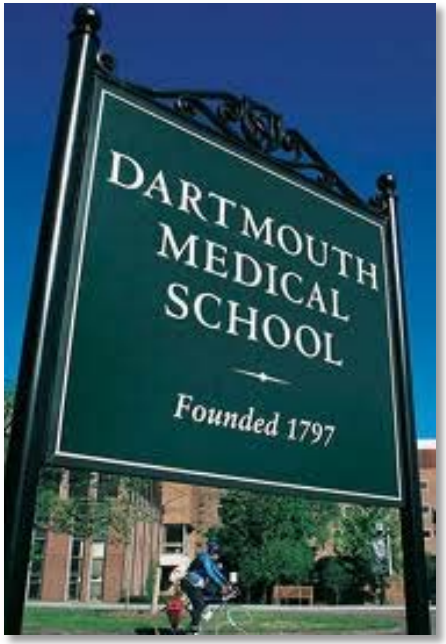
The DIGAMI 2 Trial (2008)



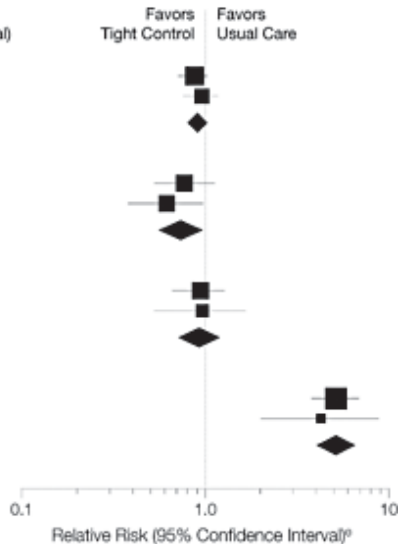
*Number of patients using drug/number of patients not using drug at discharge.
**Number of endpoints for patients using drug/number of endpoints for patients not using drug.

Mellbin L G et al. Eur Heart J 2008;29:166-176

What The . . . ?!?!



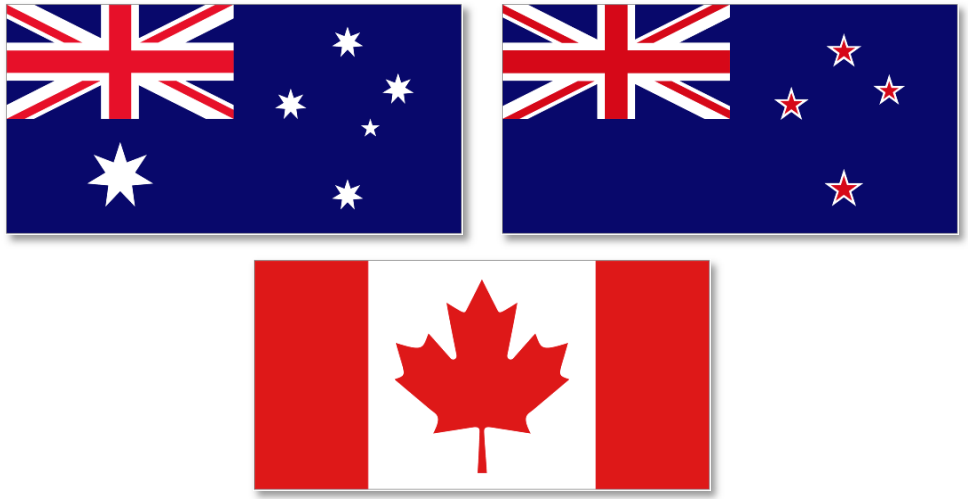
Subgroup	No. of Studies	Outcome, No./Total No. of Patients (%)		Relative Risk (95% Confidence Interval)
		Tight Control	Usual Care	
Hospital mortality[a]				
Very tight control	14	702/3031 (23.2)	781/3099 (25.2)	0.90 (0.77-1.04)
Moderately tight control	13	190/1096 (17.3)	196/1089 (18.0)	0.99 (0.83-1.18)
Overall	27	892/4127 (21.6)	977/4188 (23.3)	0.93 (0.85-1.03)
Septicemia[b]				
Very tight control	4	186/1654 (11.2)	221/1672 (13.2)	0.80 (0.57-1.11)
Moderately tight control	5	26/295 (8.8)	43/295 (14.6)	0.64 (0.41-1.00)
Overall	9	212/1949 (10.9)	264/1967 (13.4)	0.76 (0.59-0.97)
New need for dialysis[c]				
Very tight control	5	172/1424 (12.1)	193/1475 (13.1)	0.95 (0.70-1.29)
Moderately tight control	4	28/366 (7.7)	29/364 (8.0)	0.98 (0.59-1.61)
Overall	9	200/1790 (11.2)	222/1839 (12.1)	0.96 (0.76-1.20)
Hypoglycemia (glucose ≤40 mg/dL)[d]				
Very tight control	11	409/2895 (14.1)	75/2952 (2.5)	5.23 (4.12-6.64)
Moderately tight control	4	41/380 (10.8)	9/386 (2.3)	4.37 (2.19-8.72)
Overall	15	450/3275 (13.7)	84/3338 (2.5)	5.13 (4.09-6.43)



Wiener, R. S. et al. JAMA 2008;300:933-944.

"In critically ill adult patients, tight glucose control is not associated with significantly reduced hospital mortality, but is associated with an increased risk of hypoglycemia."

NICE-SUGAR* (2009)

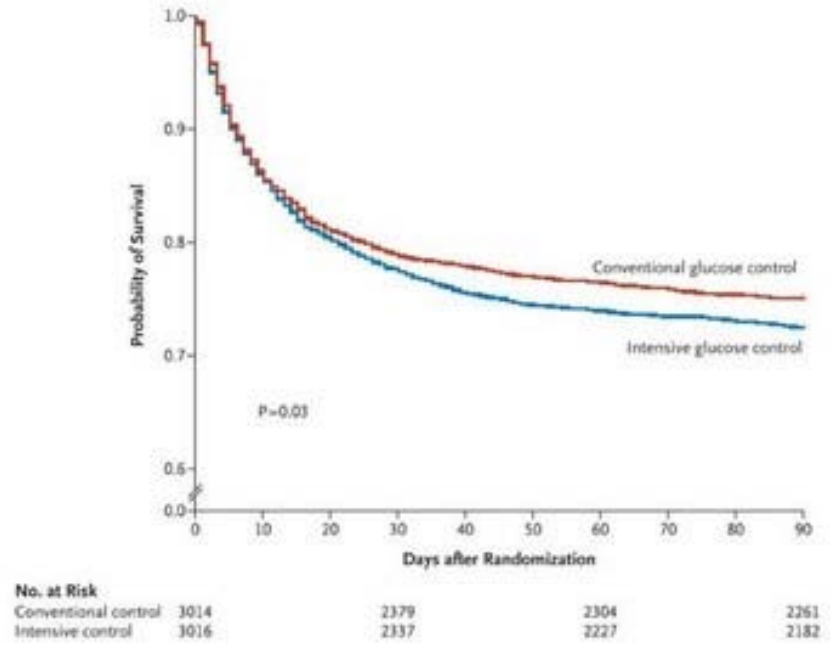


"Severe hypoglycemia (blood glucose ≤40 mg/dL) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001)."

6,104 patients randomized to:

Intensive control: 81-108 mg/dL

Conventional control: ≤180 mg/dL



*Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation

OMG, What Are We Going To Do?

The FDA Steps In

15197

± 15 mg/dL at < 75 mg/dL

± 20% at ≥ 75 mg/dL

(accuracy, not precision)

Public Hearing, March 16-17, 2010

Jeffrey E. Shuren, MD, JD, Director, Center for Devices and Radiological Health, FDA:

"[The] FDA receives approximately 12,000 adverse event reports associated with blood glucose meters each year."

"Despite the fact that these devices have not been approved for this use, glucose meters are increasingly being used to achieve tight glycemic control."

Patricia Bernhardt, MT(ASCP), Scientific Reviewer, FDA:

". . . currently there is no distinction between the performance requirements for over-the-counter and professional use glucose meters. So when a glucose meter is cleared for over-the-counter use, it can also be used in professional settings."

Performance of Approved Glucose Meters

Table 4 — Example of presentation of system accuracy results for glucose concentration < 4,2 mmol/L (75 mg/dL)

Within ± 0,28 mmol/L (Within ± 5 mg/dL)	Within ± 0,56 mmol/L (Within ± 10 mg/dL)	*Within ± 0,83 mmol/L (Within ± 15 mg/dL)*
18/40 (45 %)	28/40 (70 %)	*38/40 (95 %)*

Table 5 — Example of presentation of system accuracy results for glucose concentration ⩾ 4,2 mmol/L (75 mg/dL)

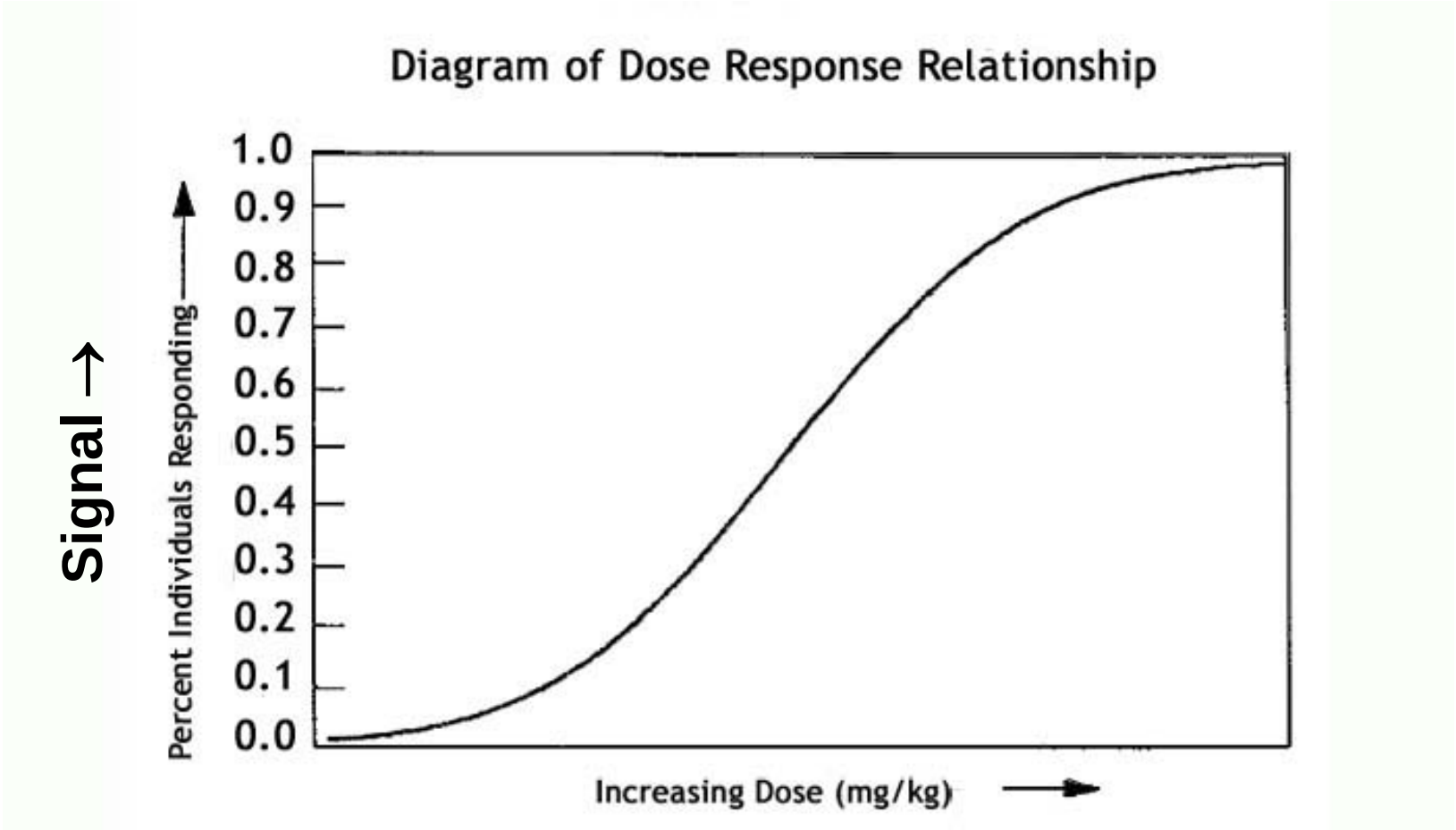
Within ± 5 %	Within ± 10 %	Within ± 15 %	*Within ± 20 %*
36/160 (22 %)	78/160 (49 %)	136/160 (85 %)	*156/160 (97 %)*

A recent evaluation of glucose meters cleared in last 2 years showed that approximately 72% would meet ±10 mg/dL at <75 mg/dL and approximately 50% would meet ±15% at ≥75 mg/dL.

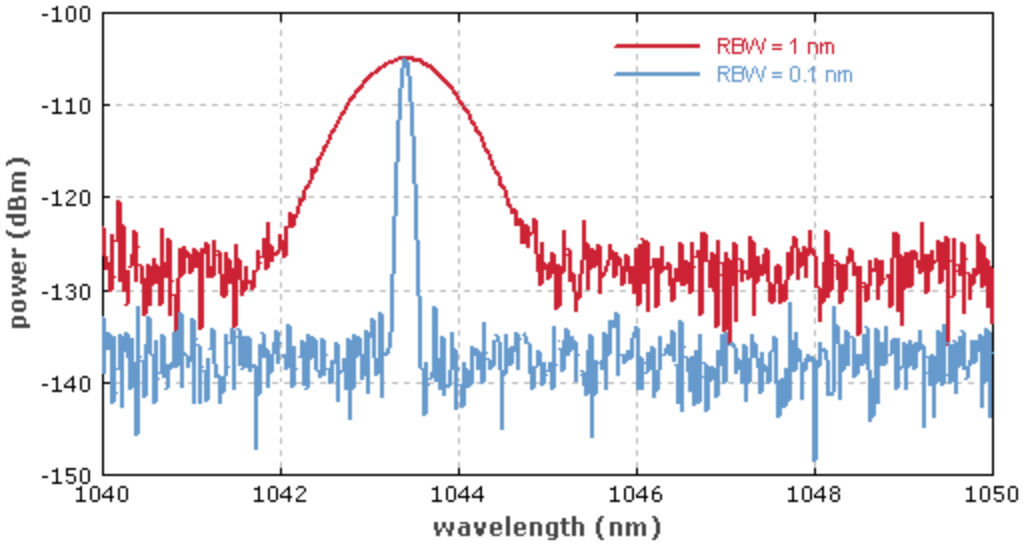
Why are glucose meters so imprecise?

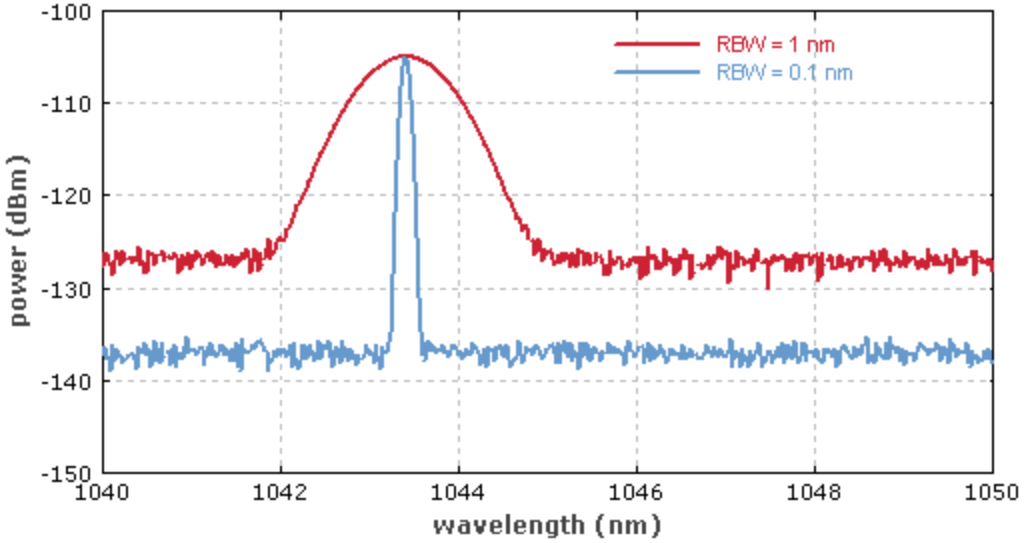
- Operator variability
- Hospitalized patients
  - Hypotension; decreased capillary blood flow
  - High or low pO_2
  - Anemia; hematocrit
  - DKA
  - Renal failure; uremia
  - Hepatic failure; azotemia
  - Drugs
- The “Design Conundrum”

Optimizing analytical methods

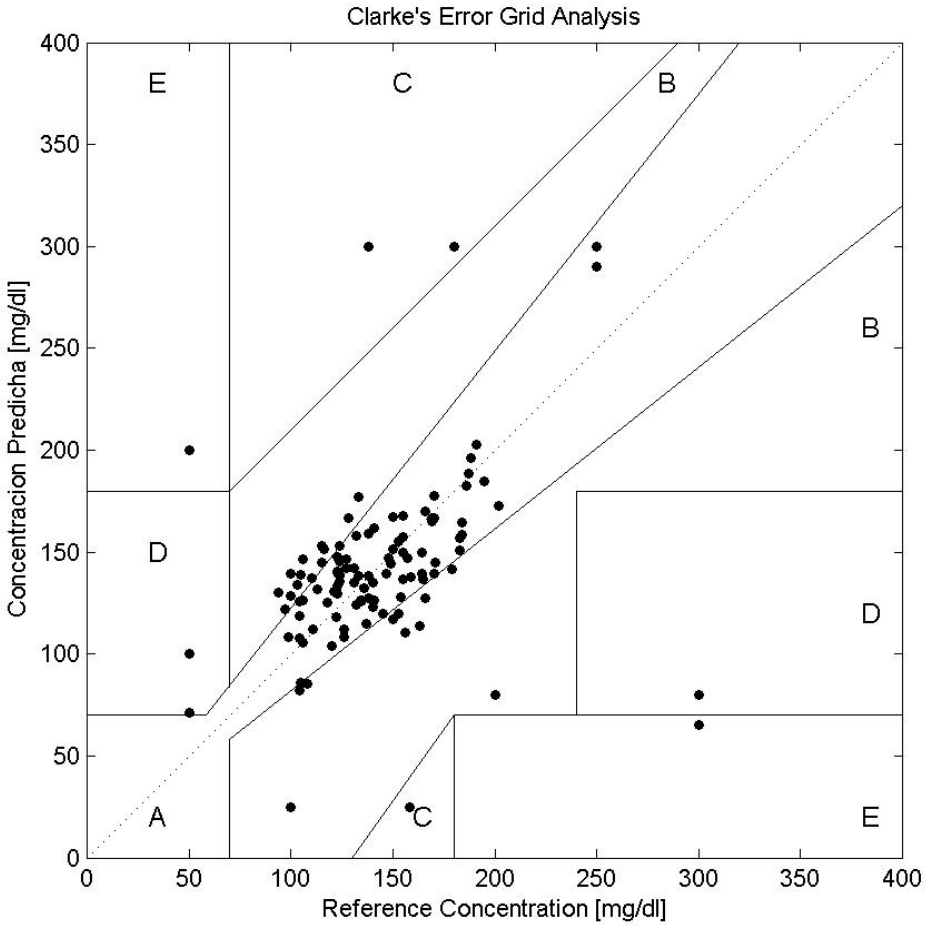


Optimizing analytical methods





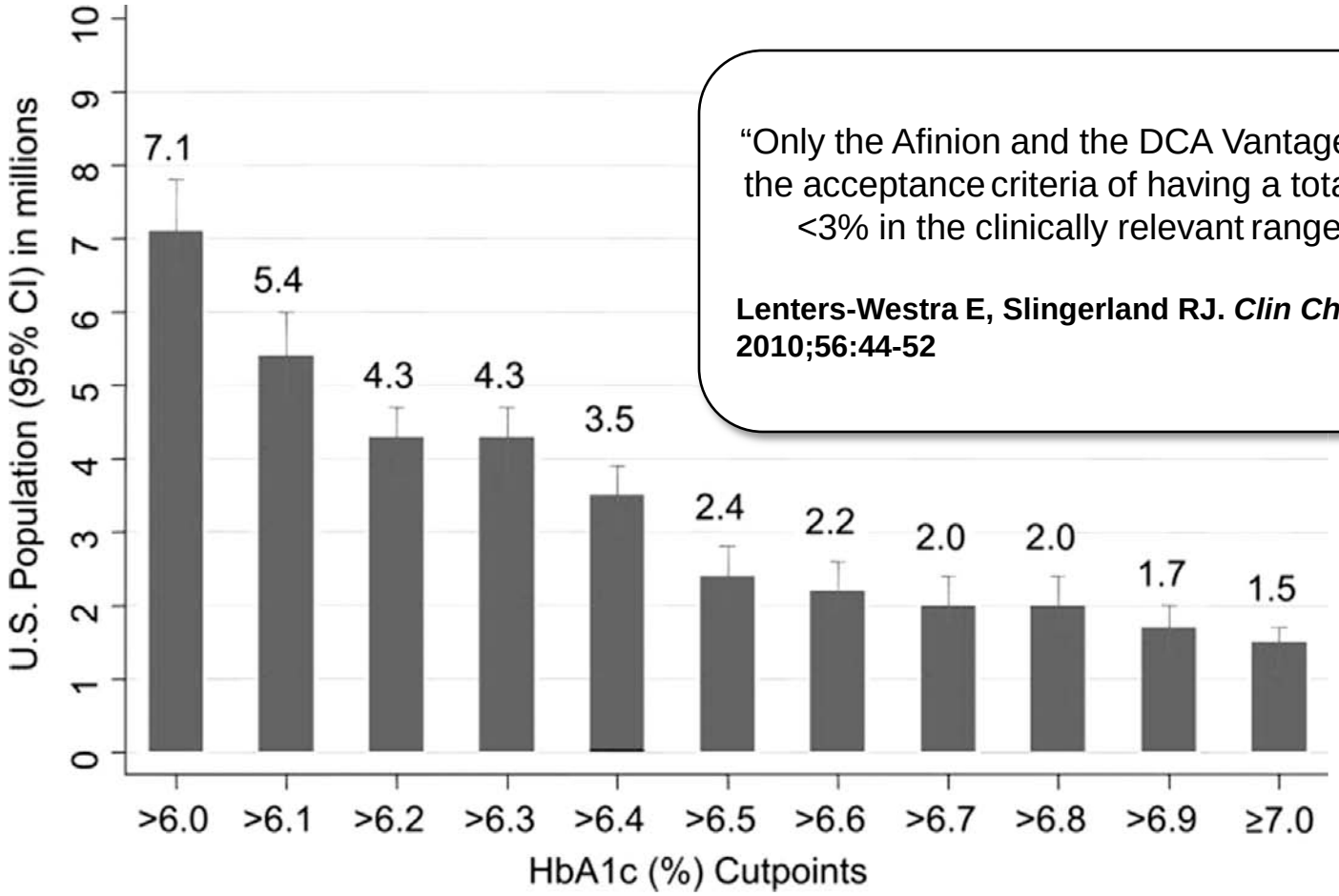
Clarke's error grid for glucose measurement



A = no error
B = ≥ 20% error, but benign
C = overcorrection
D = dangerous failure to detect
E = erroneous treatment

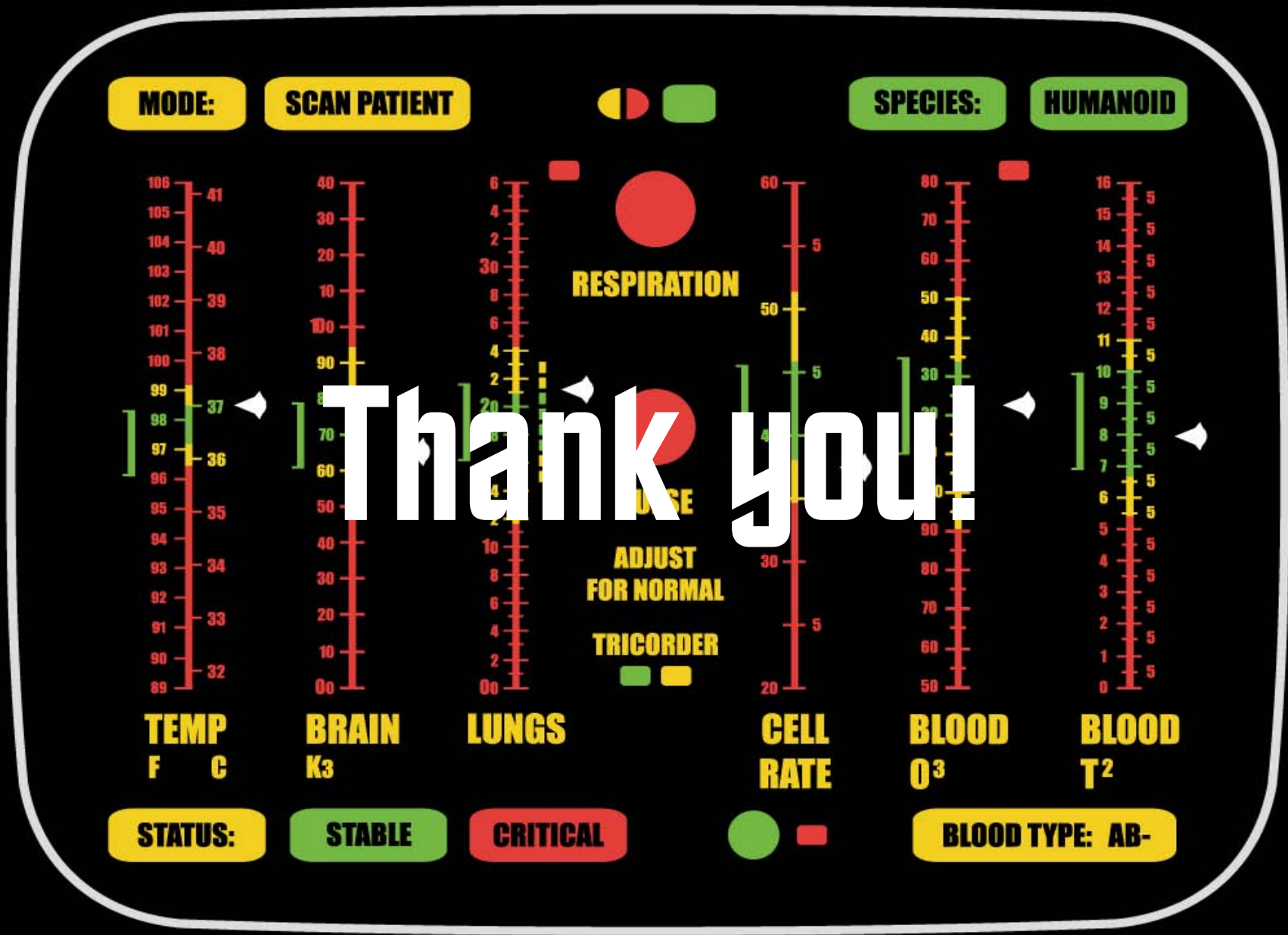
What about HbA_{1c}?

Distribution of estimated numbers of persons without a history of diabetes in the US 2000 Census population (age >=20 years) at different Hb A1C cutpoints



"Only the Afinion and the DCA Vantage met the acceptance criteria of having a total CV <3% in the clinically relevant range."

Lenters-Westra E, Slingerland RJ. *Clin Chem* 2010;56:44-52


MODE:
SCAN PATIENT
SPECIES:
HUMANOID
RESPIRATION
ADJUST
FOR NORMAL
TRICORDER
TEMP
F C
BRAIN
K3
LUNGS
CELL
RATE
BLOOD
O3
BLOOD
T2
STATUS:
STABLE
CRITICAL
BLOOD TYPE: AB-

Thank you!