



**Children's Hospital**  
New Orleans  
LCMC Health

**LSU Health**  
NEW ORLEANS  
**School of Medicine**  
Department of Pediatrics

# How to Keep Score in Pediatric Diabetes: Is Use of Hemoglobin A1c Obsolete and Dangerous ???

**Presenter: Stuart Chalew, M.D.**  
**Professor of Pediatrics**





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**NO DISCLOSURES**



# Objectives

- Why monitoring glycemia/keeping score is relevant
- Compare the two major ways of keeping score
- Has HbA1c been transcended by new technology



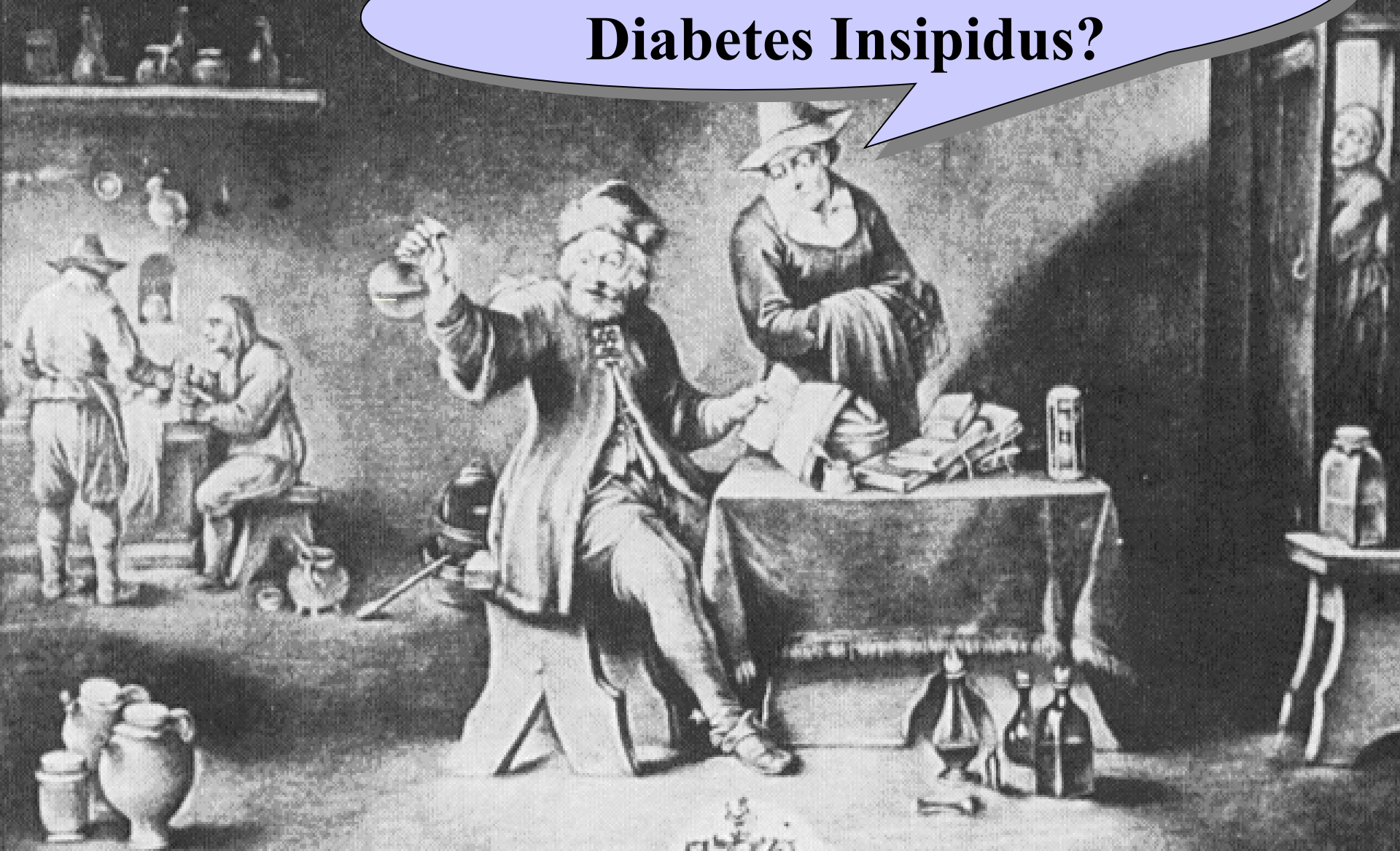
# Diabetes

\Di`a\*be"tes\, n. [NL., from Gr. a siphon?]

A disease ... attended with a persistent, excessive discharge of urine = POLYURIA.



**Diabetes Mellitus?  
Diabetes Insipidus?**



**Great Moments in Clinical Chemistry**



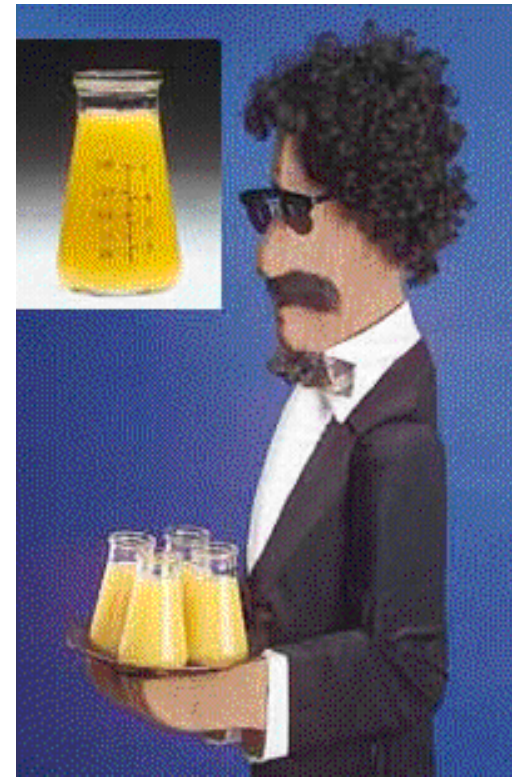
**Qualitative Analysis:**

**Diabetes MELLITUS**

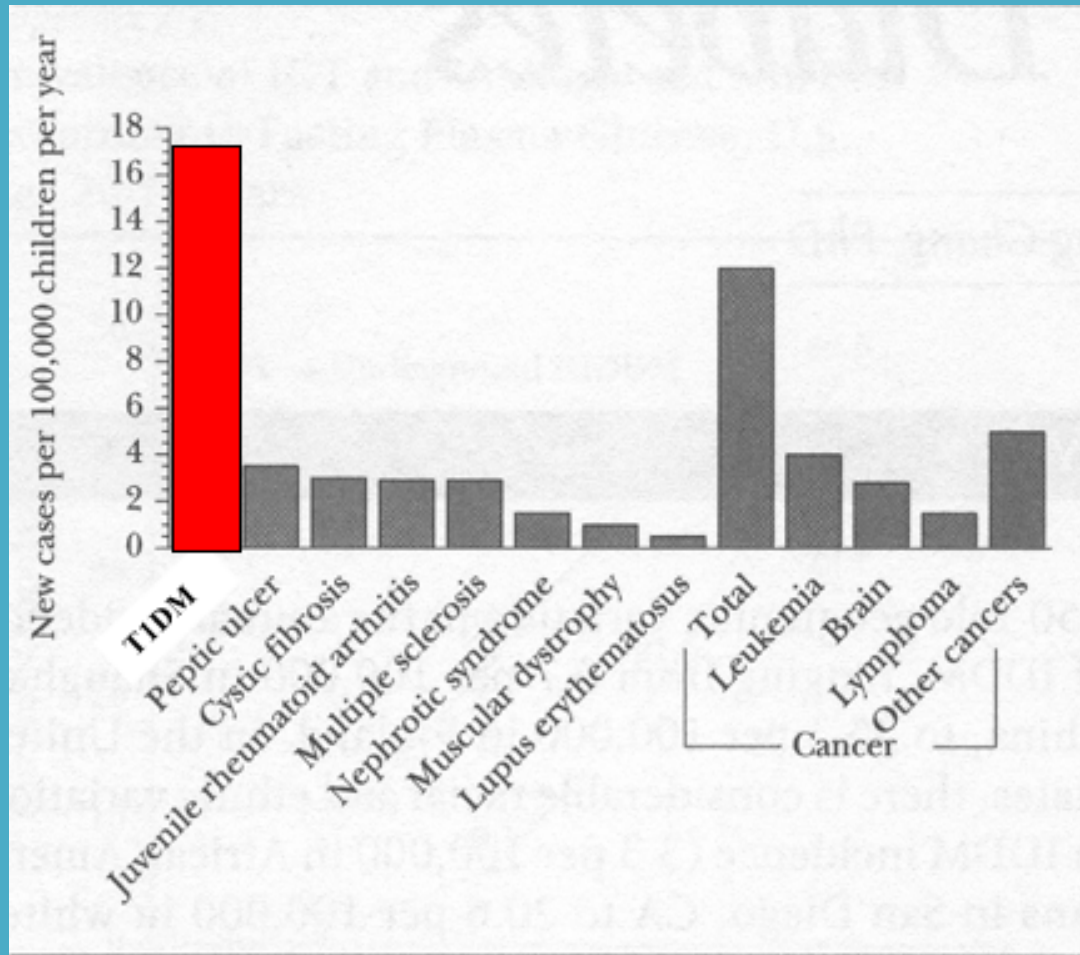
=sweet urine and  
blood

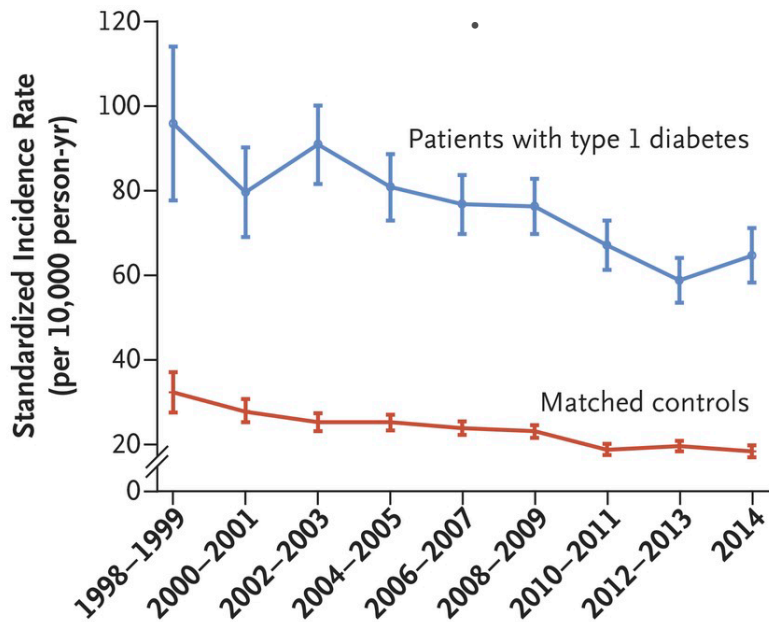
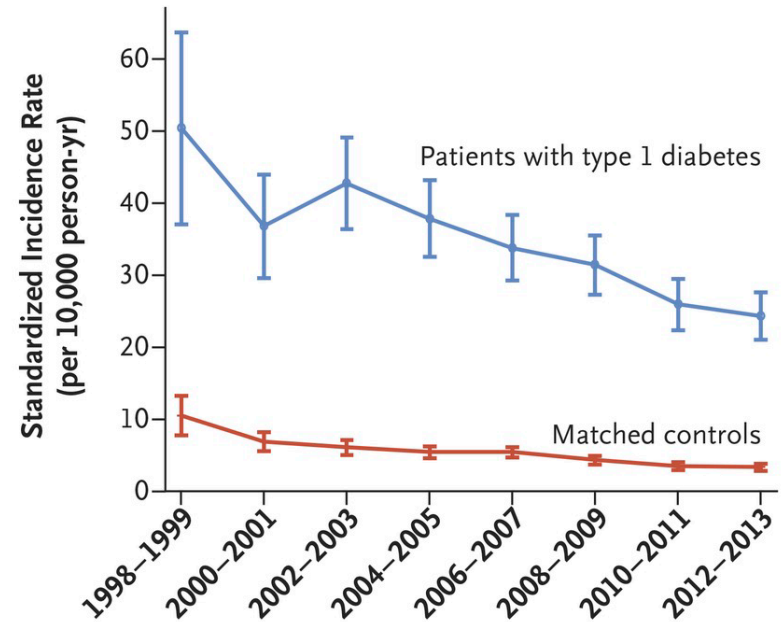
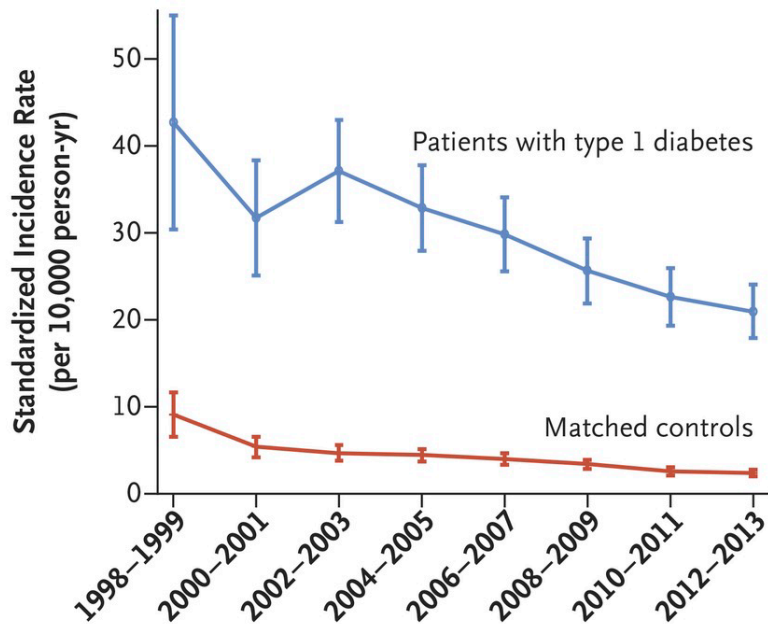
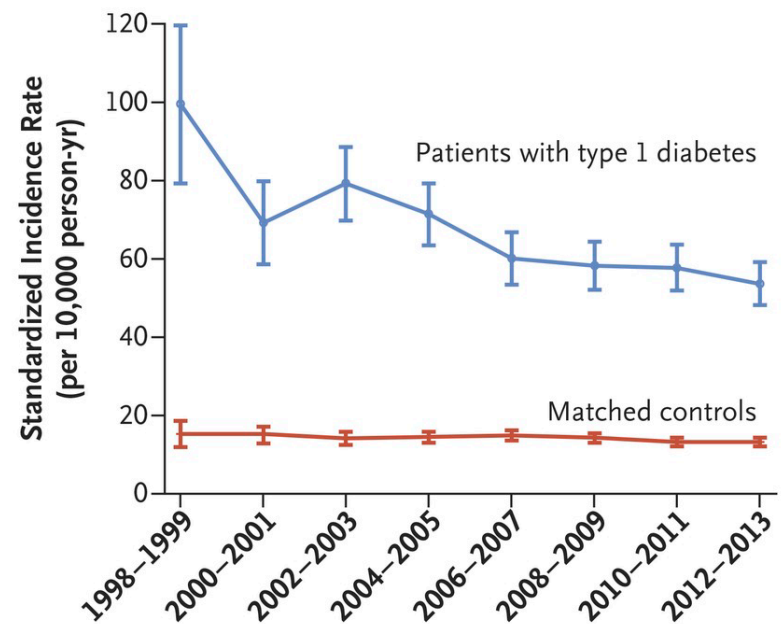
**Diabetes INSIPIDUS**

=tasteless urine.



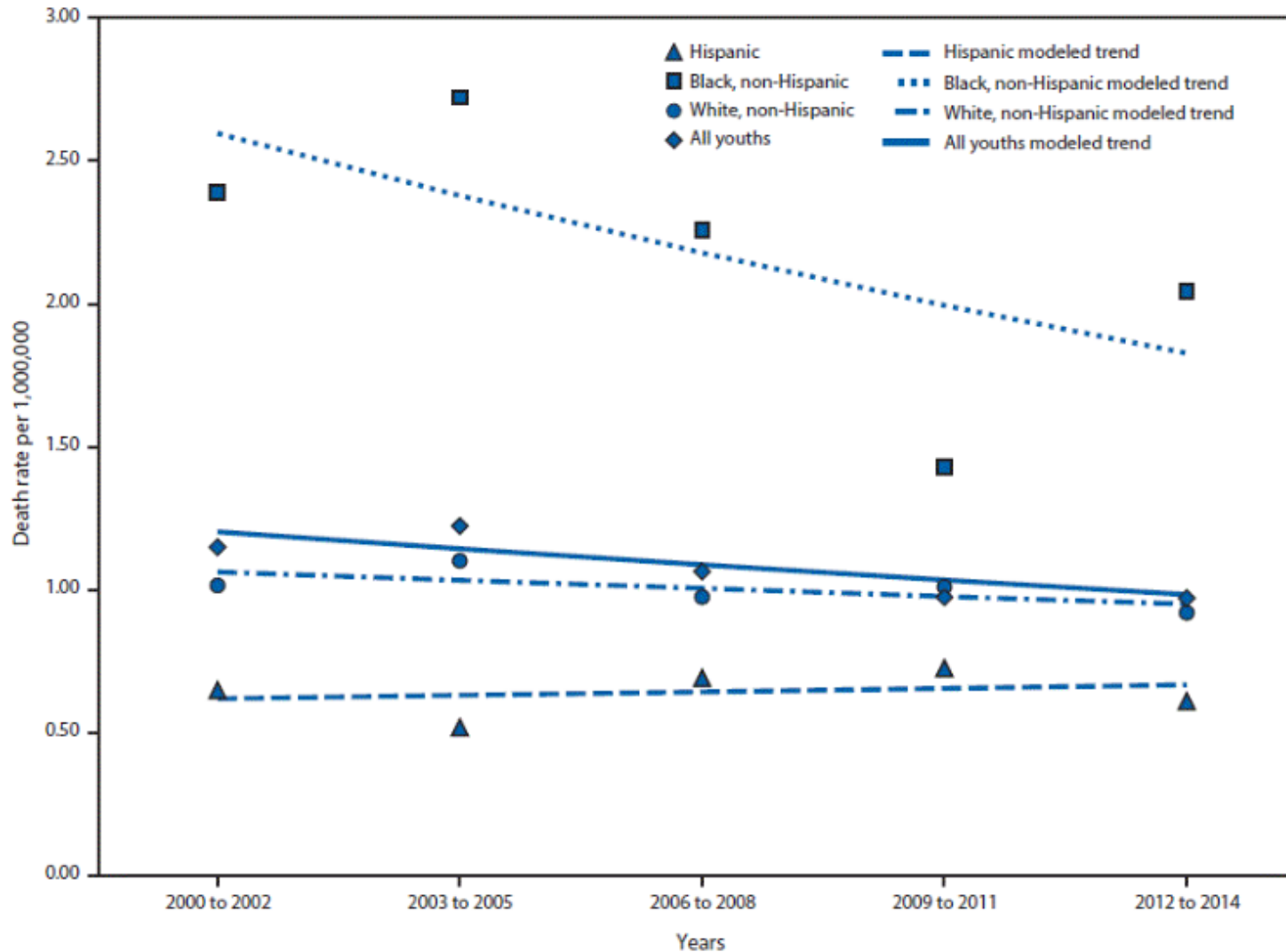
# T1D One of Most Common Incurable Diseases of Childhood



**A Death from Any Cause****B Death from Cardiovascular Disease****C Death from Coronary Heart Disease****D Hospitalization for Cardiovascular Disease**



# Diabetes Mortality Persons 1–19 Yrs, By Race/Ethnicity — US



Black, non-Hispanic

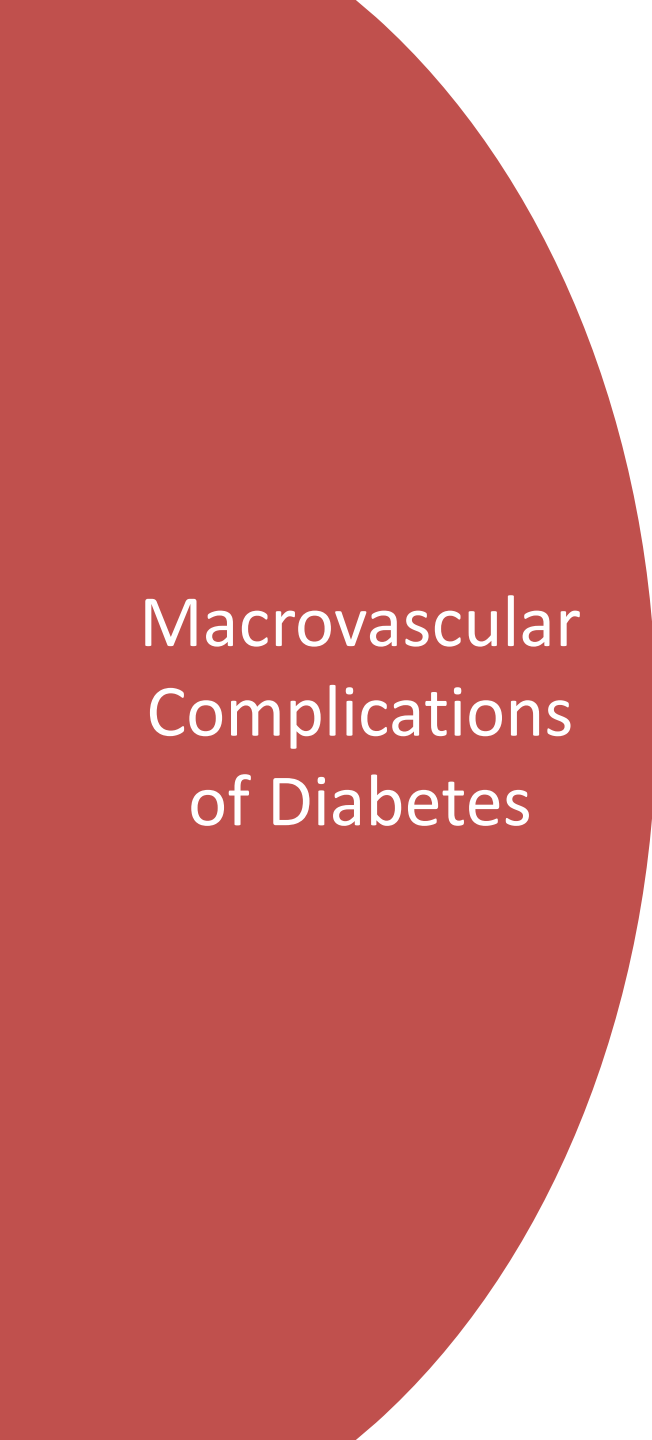
White, non-Hispanic

# Microvascular Complications of Diabetes


**Retinopathy**

**Nephropathy**

**Neuropathy**



Macrovascular  
Complications  
of Diabetes

- **Coronary Artery Disease**
  - **Stroke**
  - **Peripheral Vascular Disease**
- 

# **Why Do Bad Things Happen: GLUCOSE HYPOTHESIS**



**Chronic elevated glucose  
levels due to diabetes  
cause complications**

# DCCT



**Can normalization of blood glucose levels prevent complications of diabetes?**

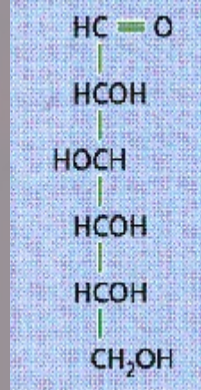


“You can’t manage what you don’t measure” -Peter Drucker.



- **Multiple Sticks To Assess Glucose Control**
  - **How Many Needed To Get Complete Assessment?**
  - **Poorly Tolerated**
  - **Time Consuming and Expensive**

# Non-Enzymatic Hb Glycation

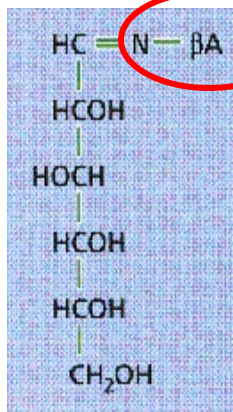


Plasma  
**GLUCOSE**

Glut1

RBC Membrane

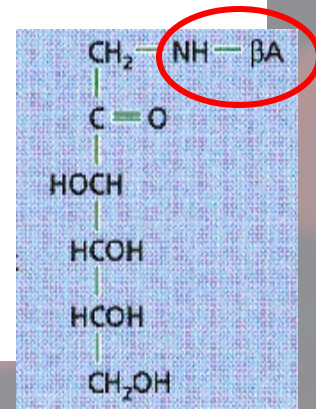
Intracellular  
**GLUCOSE** + **HbA**



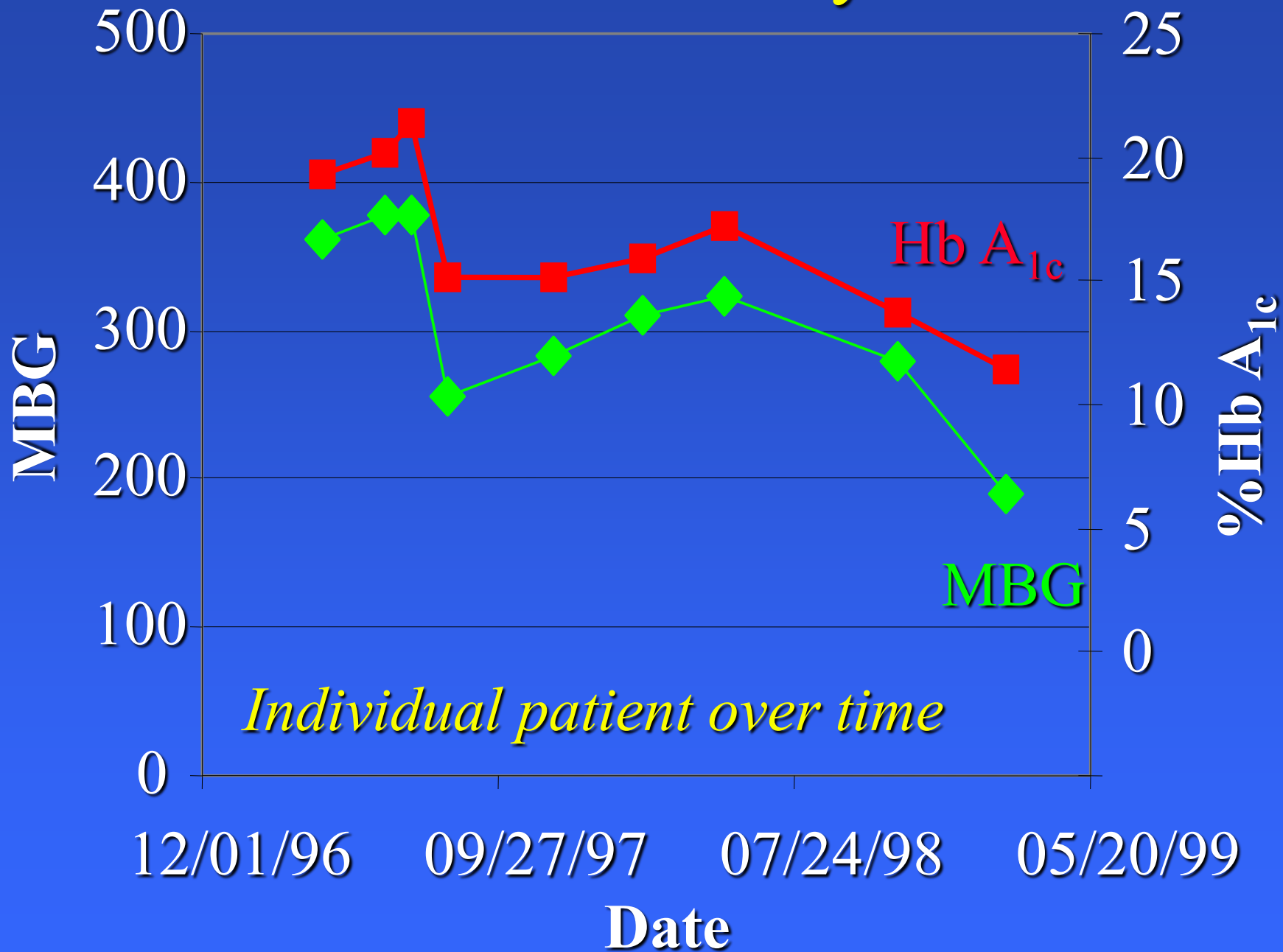
**Labile HbA1c**  
(Schiff Base, Aldimine)

Amadori Rearrangement

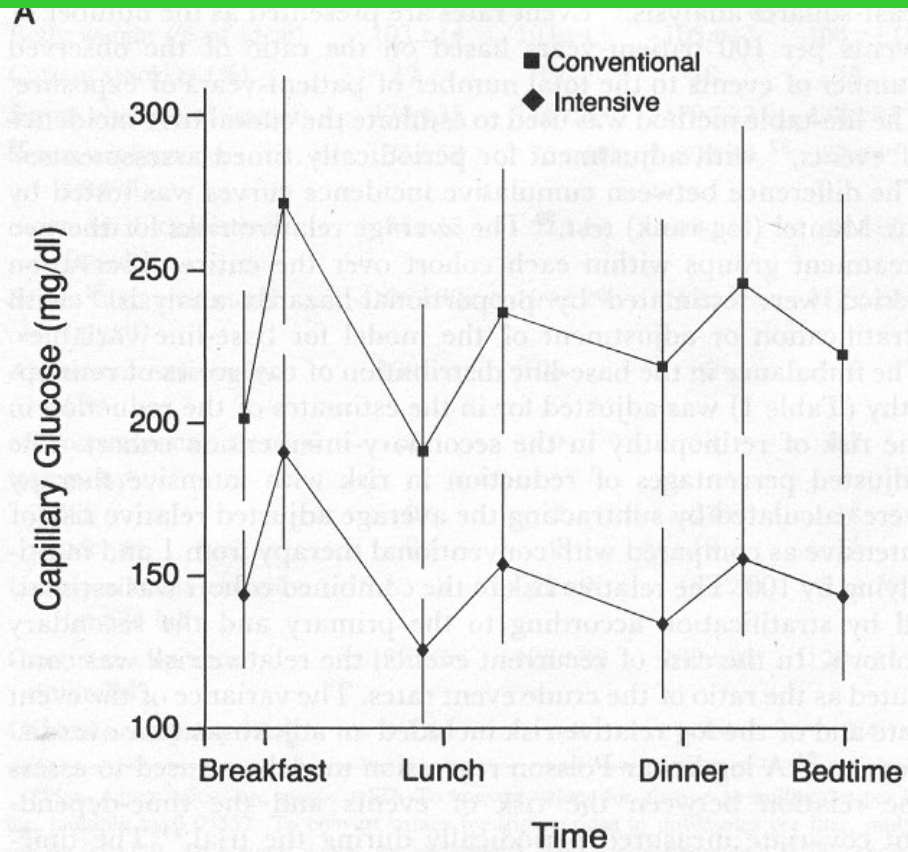
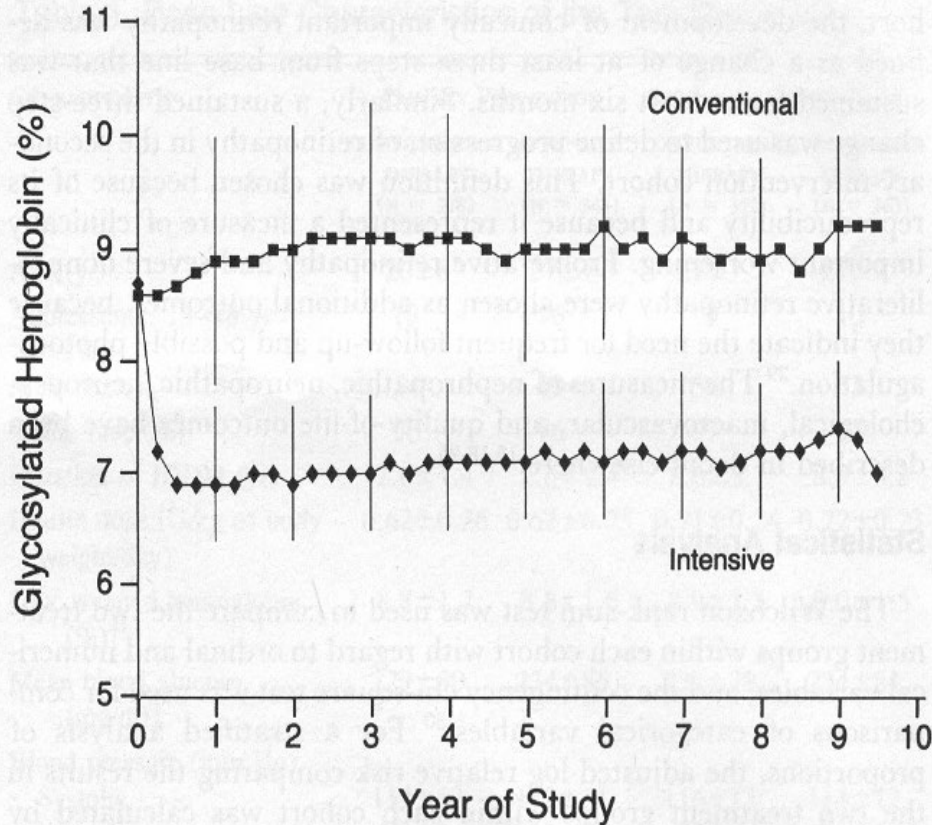
**Stable HbA1c**  
(Amadori Product, Ketoamine)



# Correlation of MBG and Glycated Hb



# Differences in Glycemic Control between Intensive and Conventional Therapy in the DCCT



B

HbA1c was the Primary Metric

# FINDINGS OF DCCT

Participants in Intensive Arm with Reduced HbA1c

Retinopathy	↓	76%
Albuminuria	↓	54%
Neuropathy	↓	60%






# IMPLICATIONS OF DCCT

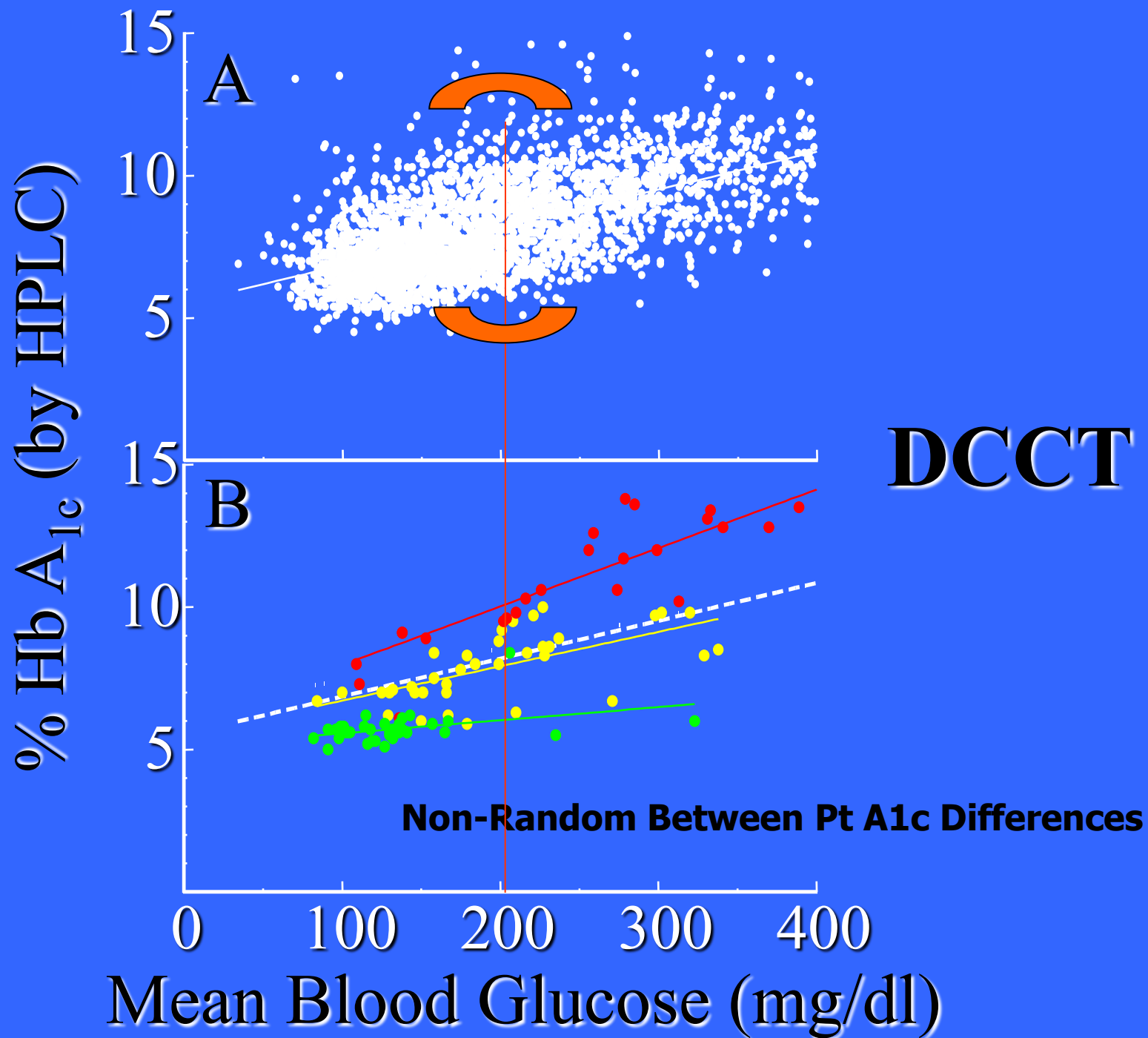
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- Rationale and Impetus for Glycemic Management Goals
- Enshrined HbA1c as the Metric for Management and Predictor of Complications

AFTER DCCT  
HbA1c BECAME  
THE MAJOR WAY  
TO KEEP SCORE  
ON DIABETES  
MANAGEMENT

HbA1c		MEAN BLOOD GLUCOSE		
test score		mg/dL	mmol/L	
	 action needed	14.0	380	21.1
		13.0	350	19.3
		12.0	315	17.4
		11.0	280	15.6
		10.0	250	13.7
		9.0	215	11.9
		8.0	180	10.0
		7.0	150	8.2
		6.0	115	6.3
		5.0	80	4.7
	excellent	4.0	50	2.6

**THE RELATIONSHIP BETWEEN HbA1c  
and GLUCOSE IS MORE COMPLEX**



# Table 1 Conditions associated with misleading HbA<sub>1c</sub>

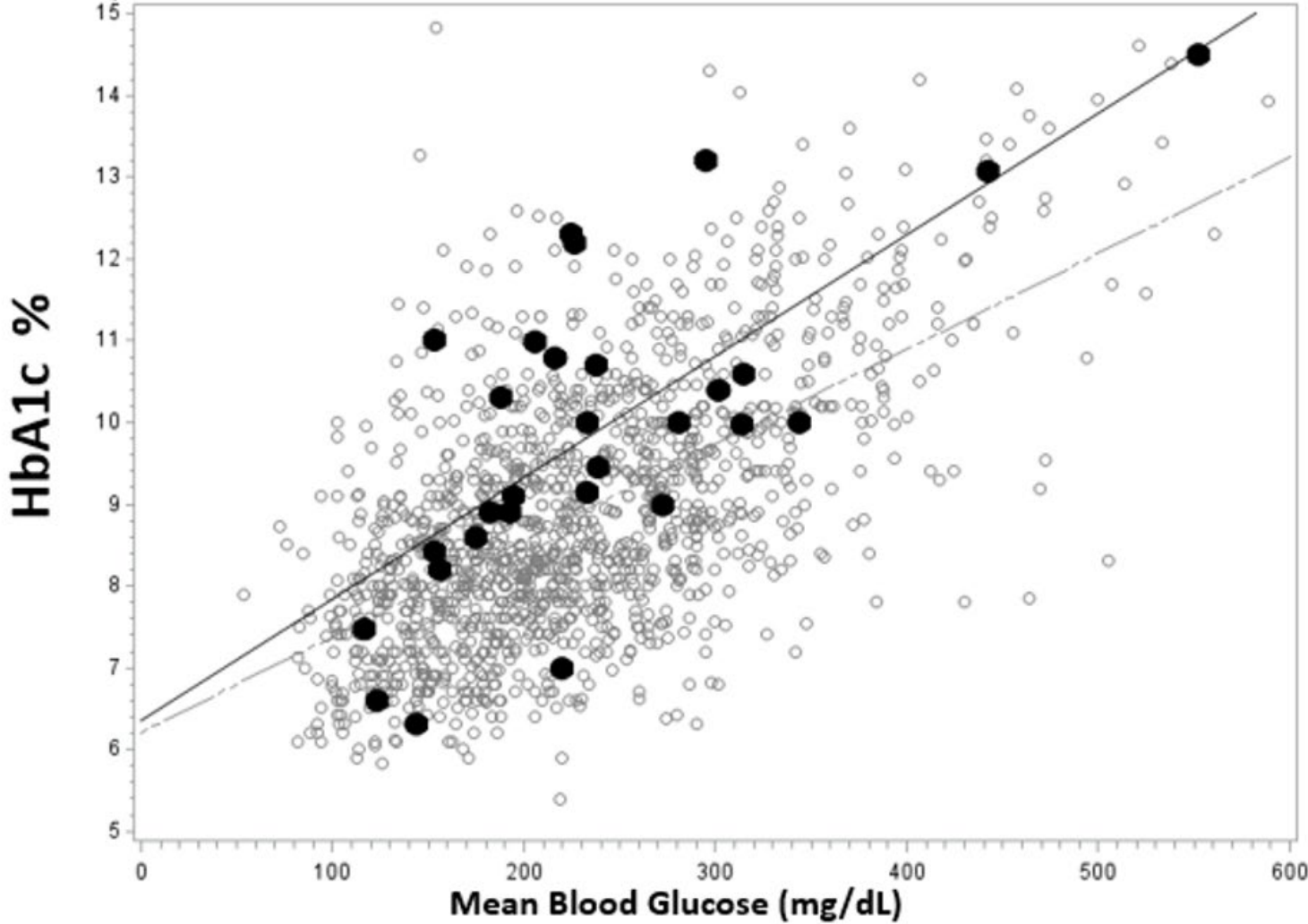
**Table 1** | Conditions associated with misleading HbA<sub>1c</sub> results and potential mechanisms

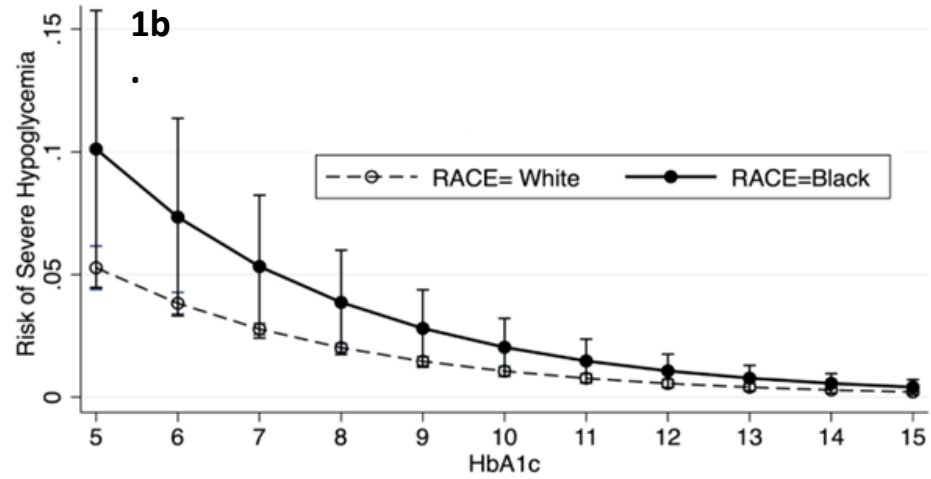
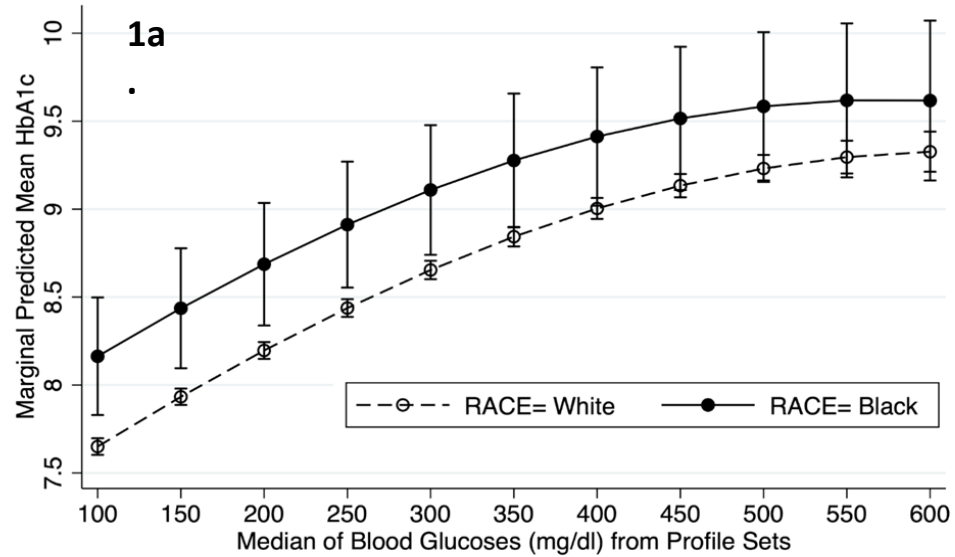
Disease or condition	Effect on HbA <sub>1c</sub> level	Potential mechanism
Rapid erythrocyte turnover	Falsely low	Unstable erythrocyte pool
Hemolytic states	Falsely low	Unstable erythrocyte pool
Iron deficiency anemia	Falsely high	Unknown
Hemoglobin SS, SC or CC disease	Falsely low	Unstable erythrocyte pool
Variant hemoglobin trait	Variable	Assay interference
Fetal hemoglobin	Variable	Assay interference
Blood transfusions	Falsely low	Unstable erythrocyte pool
Aging	Falsely high	Unknown
Cirrhosis	Falsely low	Unknown
Uremia	Falsely low	Carbamylated hemoglobin
Hemodialysis	Falsely low	Multiple
HIV infection	Falsely low	Occult hemolysis
Pregnancy	Falsely low	Hemodilution?
Dyslipidemia	Variable	Assay interference
Hyperbilirubinemia	Variable	Assay interference
Aspirin use (large doses)	Variable	Acetylated hemoglobin
Vitamin C	Variable	Interference with glycation
Vitamin E	Falsely low	Interference with glycation
Alcohol excess	Variable	Assay interference
Opiate use	Variable	Assay interference



**ETHNICITY INFLUENCES HbA1c**

# INDIVIDUAL VARIATION IN HbA1c AT THE SAME MEAN BLOOD GLUCOSE





# ISSUES WITH HbA1c

Between Patient  
Difference at Same MBG

Ethnic Differences at  
Same MBG

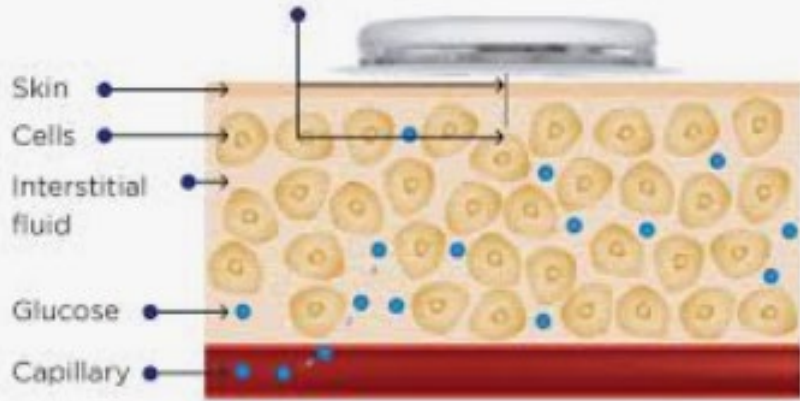
- Excess hypoglycemia with Treat to HbA1c
- Different Threshold for Dx of Diabetes

Factors Besides MBG  
Can Affect

Doesn't Give Good  
Detail to Adjust Insulin

# Continuous Glucose Monitoring

At less than 0.4 mm thick, the sensor measures glucose in the interstitial fluid, which surrounds the cells just below the skin. It does not enter the blood vessel further down.



## GLUCOSE STATISTICS AND TARGETS

26 Feb 2019 - 10 Mar 2019

% Time CGM is Active

13 days

99.9%

### Glucose Ranges

### Targets [% of Readings (Time/Day)]

Target Range 70-180 mg/dL ..... Greater than 70% (16hr 48min)

Below 70 mg/dL ..... Less than 4% (58min)

Below 54 mg/dL ..... Less than 1% (14min)

Above 250 mg/dL ..... Less than 5% (1hr 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

### Average Glucose

173 mg/dL

### Glucose Management Indicator (GMI)

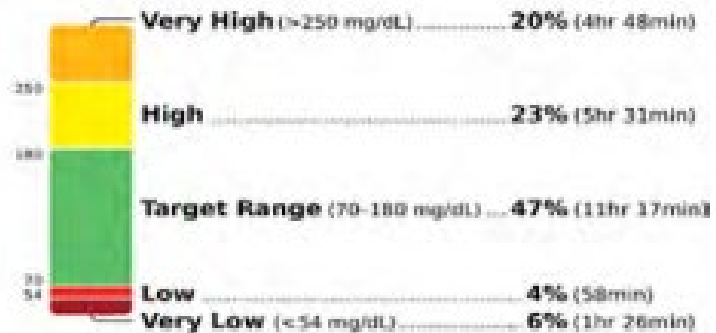
7.6%

### Glucose Variability

49.5%

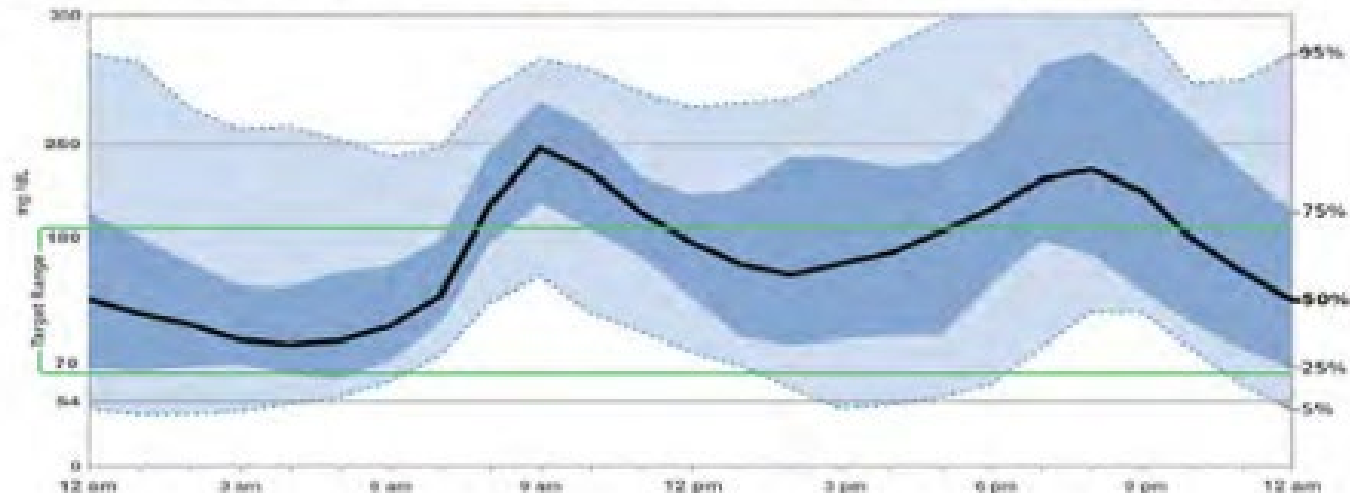
Defined as percent coefficient of variation (%CV); target  $\leq 36\%$

## TIME IN RANGES

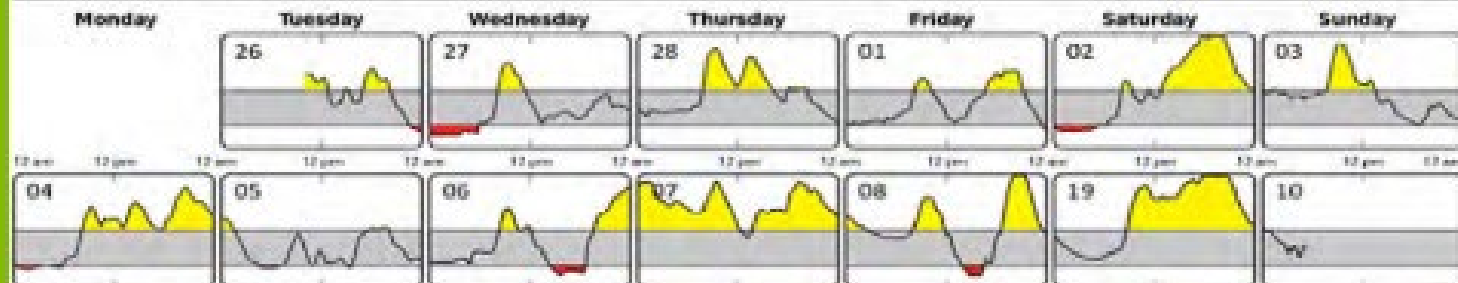


## AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

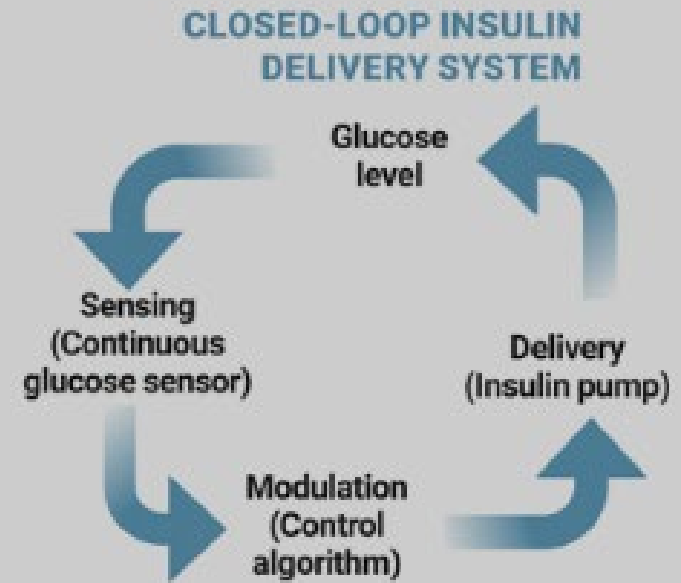
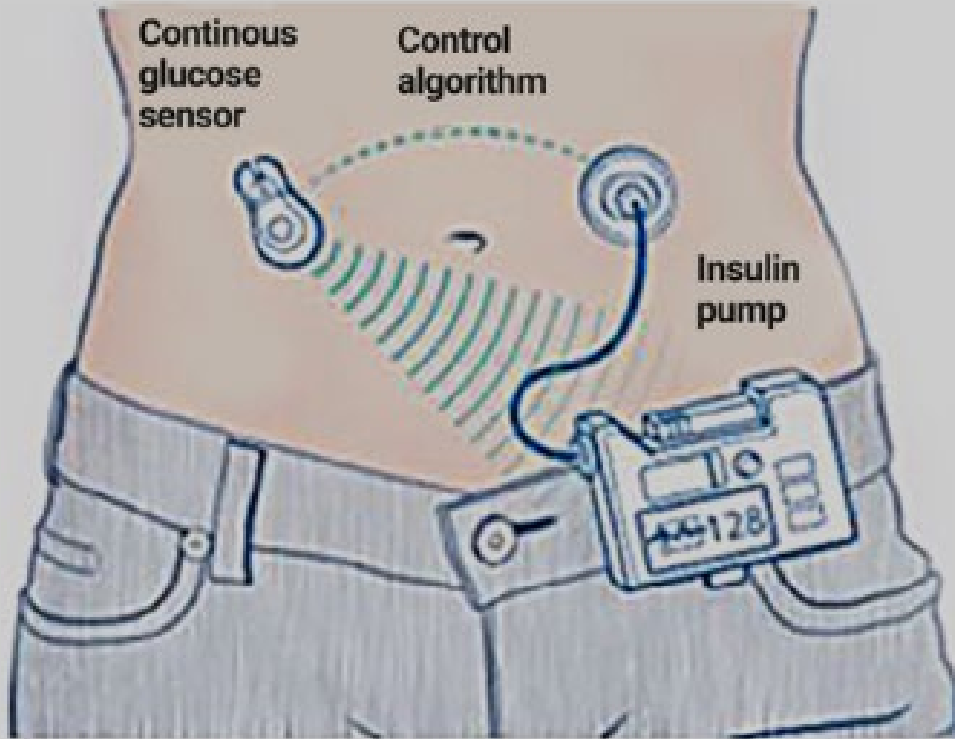


## DAILY GLUCOSE PROFILES

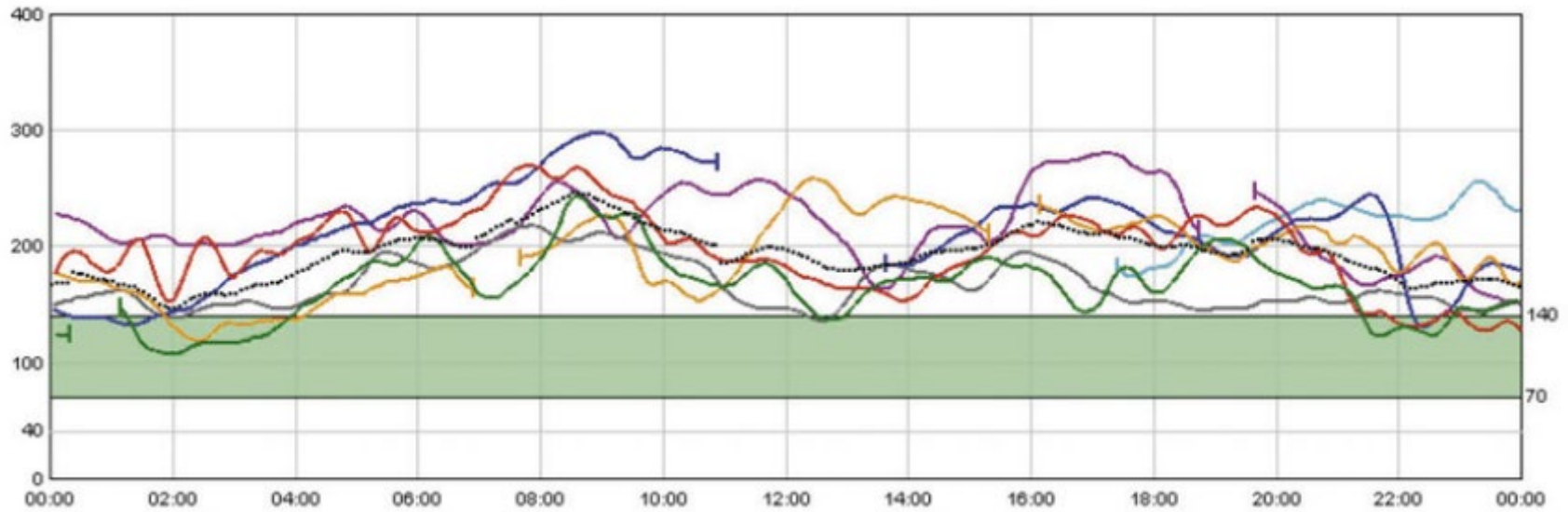


Each daily profile represents a midnight to midnight period.





# Continuous Glucose Monitoring

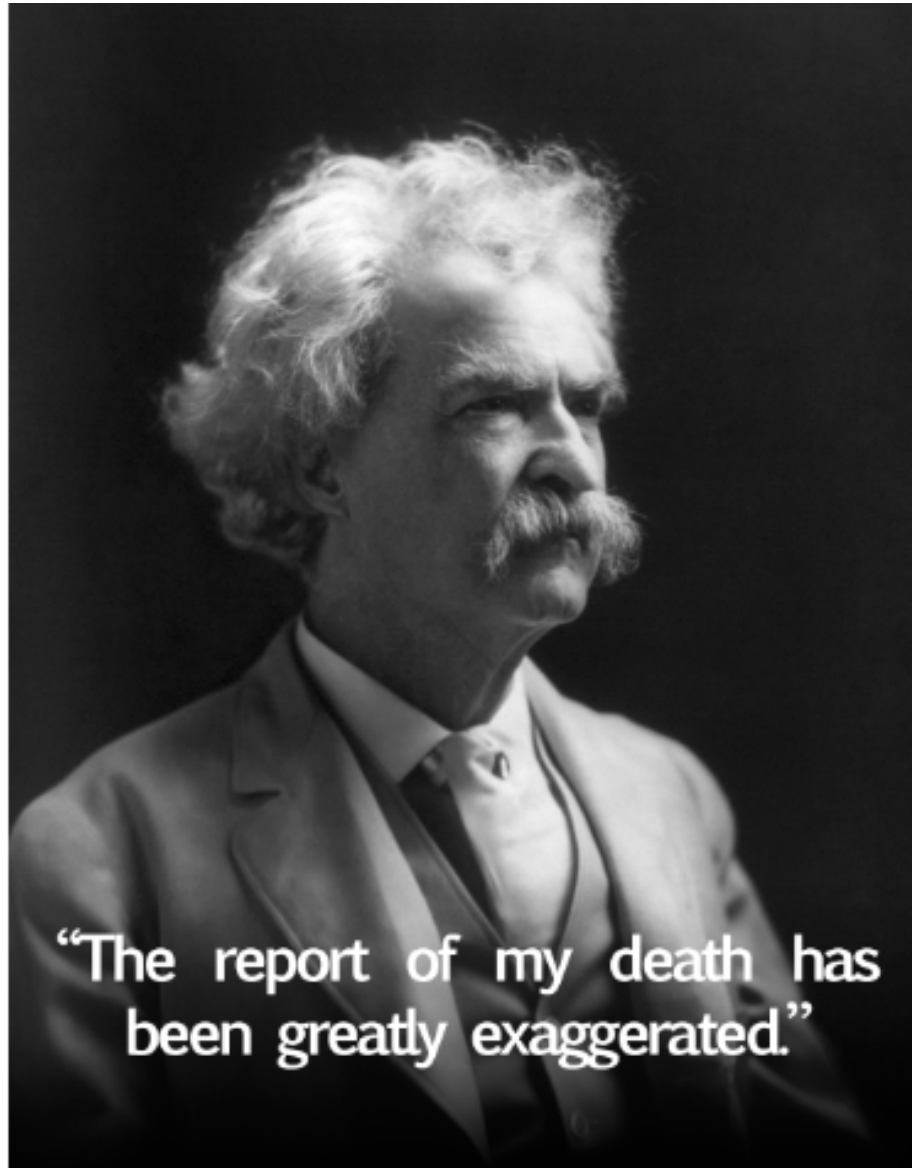


- Majority of Patients Now Have
- Real time glucose levels
- Very detailed Glucose Trends and Stats
- Ability to More Precisely Direct Insulin Rx
- No Ethnic Excess of Hypoglycemia

A grey granite gravestone with a rectangular top and a wider base. The stone is set on a grassy field. In the background, other gravestones and a building are visible under a clear sky. The text is overlaid in the center of the stone.

**RIP**

**Is Hemoglobin A1c  
Dead??**

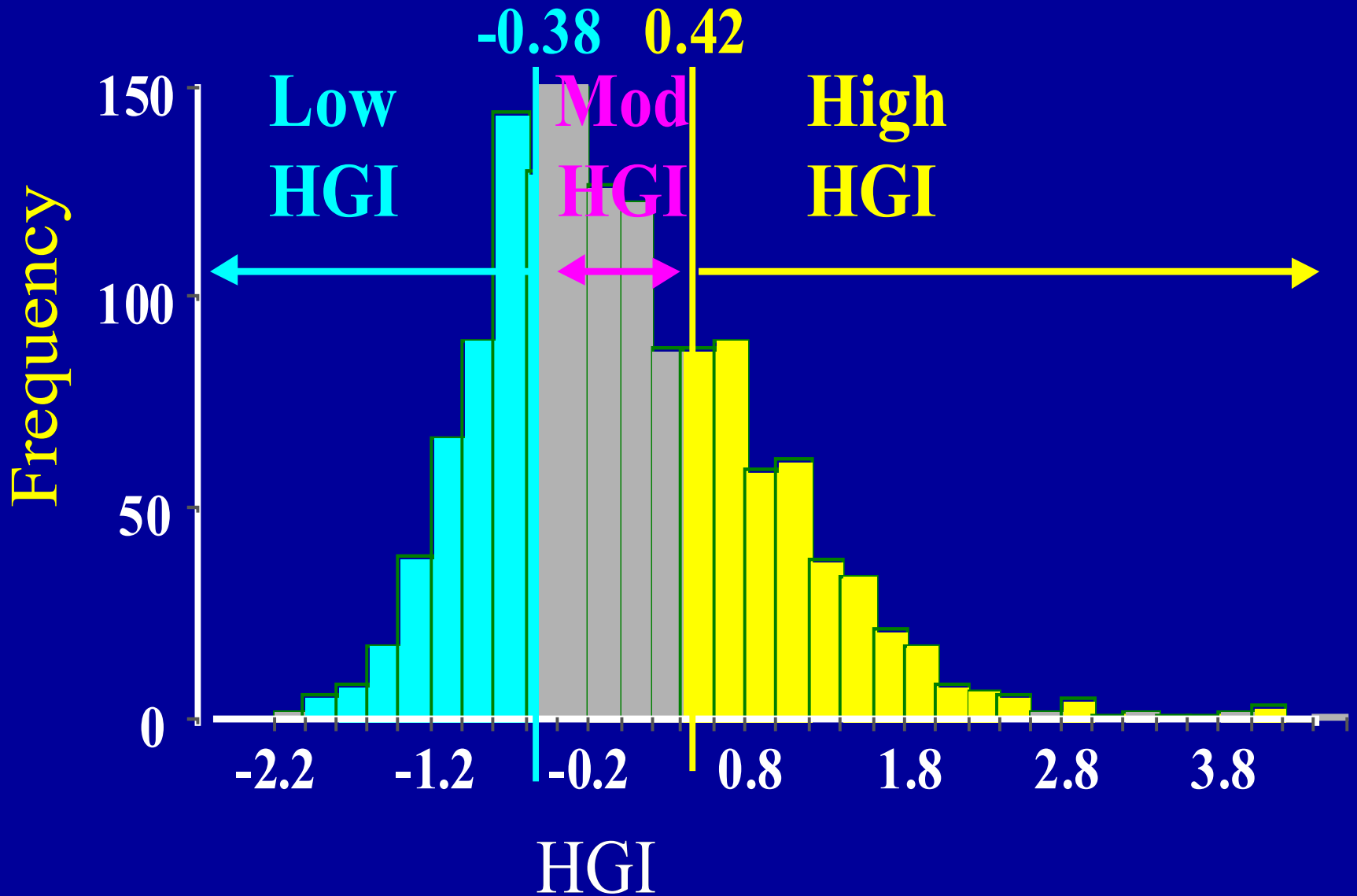


“The report of my death has  
been greatly exaggerated.”

**HbA1c Is A Better Predictor of  
Complications Than MBG**

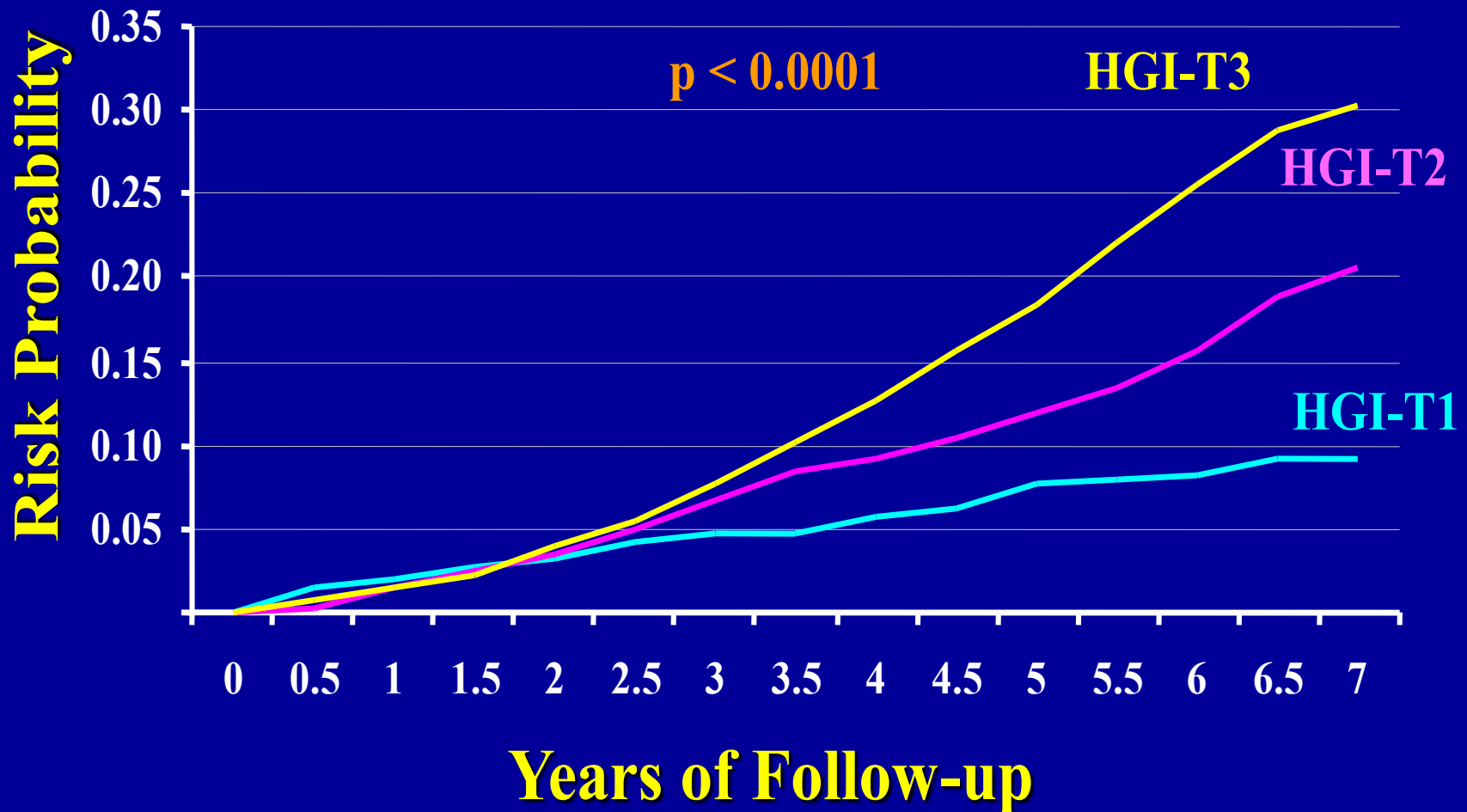
# DCCT HGI Tertiles

Groups Differ By HbA1c But Each Group Has Same MBG

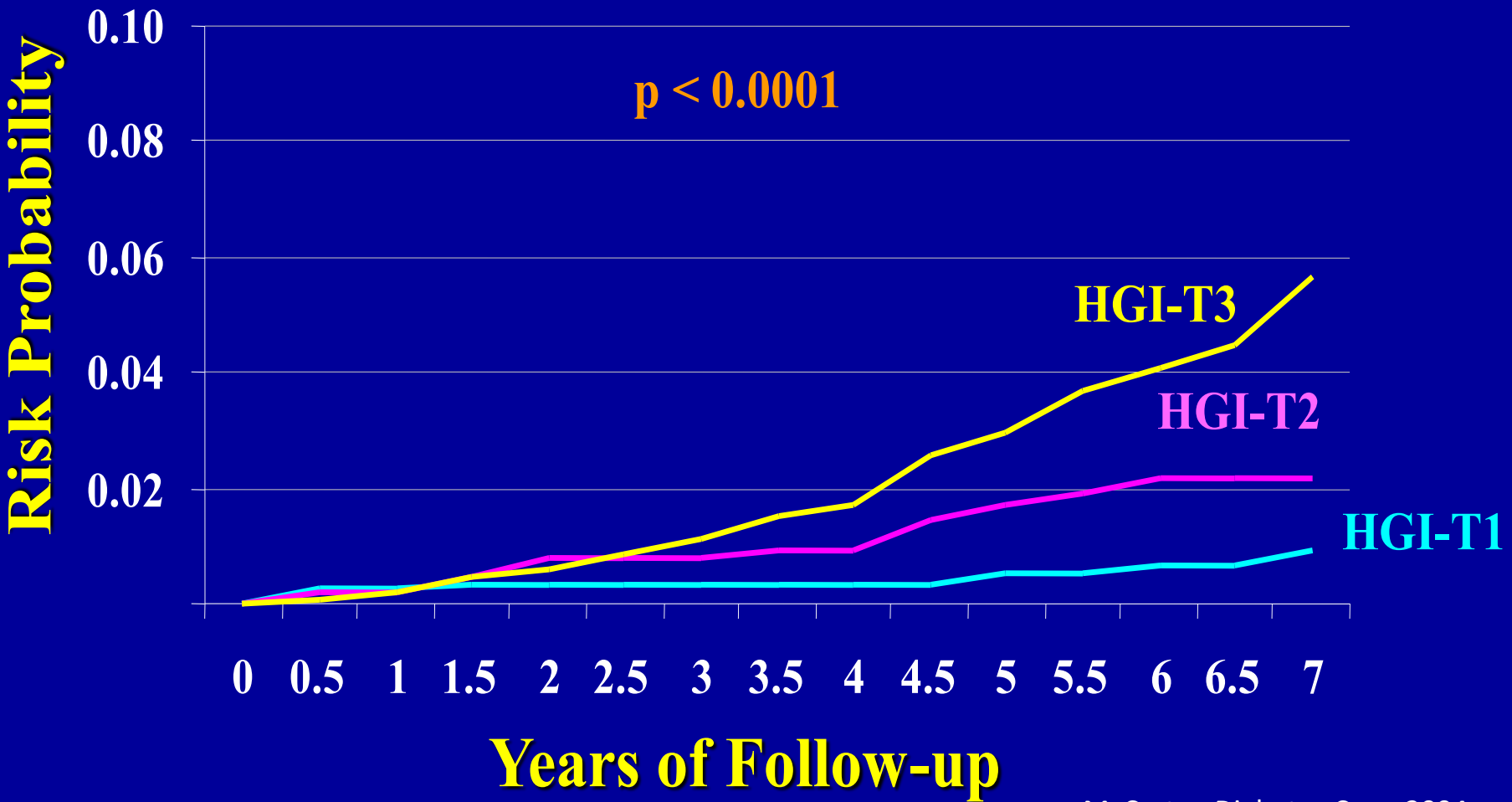




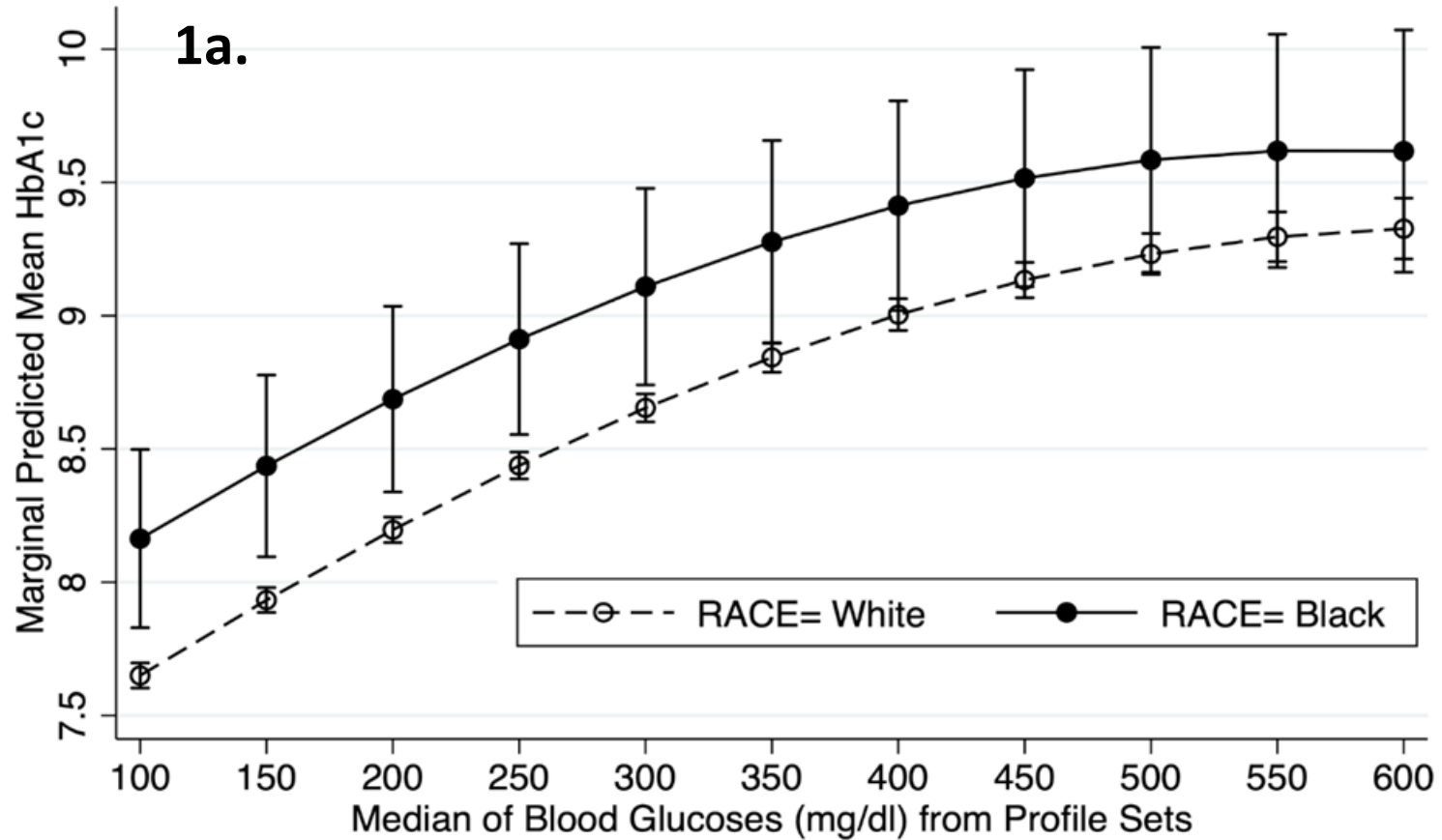
# Relationship Between HGI and Retinopathy (Incidence or Progression) In the DCCT



# HGI and Albuminuria or Advanced Microalbuminuria In the DCCT





# Blacks Have Higher HbA1c at Any Given Level of MBG Compared to Whites



## Research: Epidemiology

### **Retinopathy develops at similar glucose levels but higher HbA<sub>1c</sub> levels in people with black African ancestry compared to white European ancestry: evidence for the need to individualize HbA<sub>1c</sub> interpretation**

L. R. Staimez<sup>1</sup> , M. K. Rhee<sup>2,3</sup> , Y. Deng<sup>4</sup>, S. E. Safo<sup>5</sup>, S. M. Butler<sup>6</sup>, B. T. Legvold<sup>7</sup>, S. L. Jackson<sup>8</sup>, C. N. Ford<sup>1</sup>, P. W. F. Wilson<sup>1,2,9</sup>, Q. Long<sup>10</sup> and L. S. Phillips<sup>1,2,3</sup>

# HbA1c May Still Have a Place

Better Predictor Of Complications Than MBG Alone

May Reflect Glycation/Damage of Vital Proteins

Cheaper in Resource Poor Areas of the World

Need For Novel Therapy To Stop Glycation Related Complications Besides Glucose Lowering??

Will Be Secondary To CGM And Done Less Often

## One Last Thought....

- So What About That Obese Kid You Just Saw For An Annual Visit Who Has HbA1c =6.5%???





**THANK YOU**

