بسم الله الرحمن الرحيم

Moving to an A1C-Based Screening & Diagnosis of Diabetes

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A1C

is the nonenzymatic glycated product of the hemoglobin beta-chain at the valine terminal residue.

*Clin Chem*32 : B64-B70,1986

1c

The number following HbA represents the order in which this hemoglobin is detected on chromatography.

Hence, other hemoglobin peaks are referred to as HbA1a, HbA1b, and so...

It is normally present at low levels (approximately **4-6%** in healthy non-diabetics) because of the glycosylation reaction between hemoglobin and circulating glucose.

In the presence of excess plasma glucose, the hemoglobin beta-chain becomes increasingly glycosylated, making the A1C
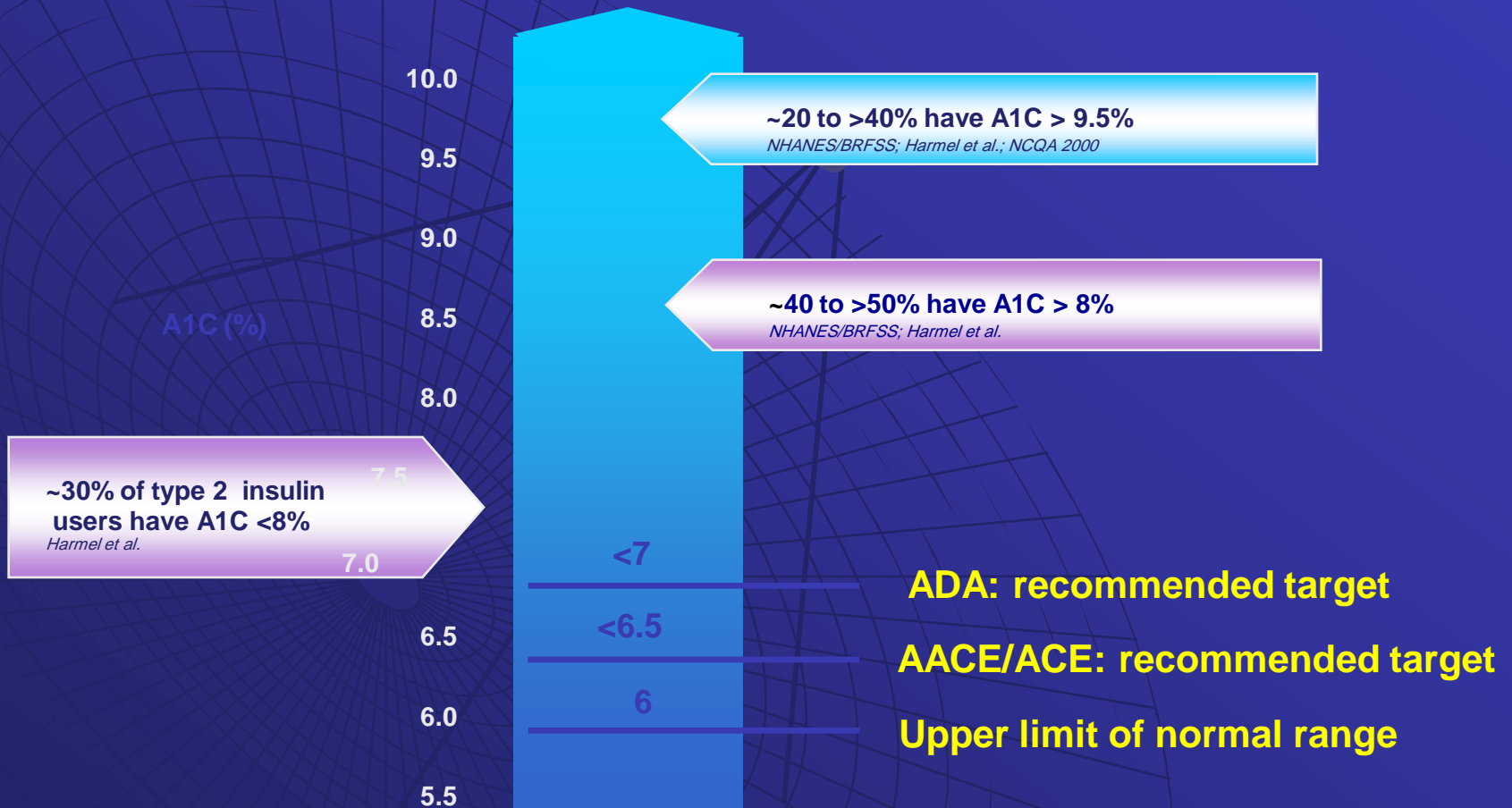
a useful index of glycemic control

Correlation of A1C with Estimated Average Glucose (eAG)

	Mean plasma glucose	
A1C (%)	mg/dl	mmol/l
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

These estimates are based on ADAG data of ~2,700 glucose measurements over 3 months per A1C measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A1C and average glucose was 0.92. A calculator for converting A1C results into estimated average glucose (eAG), in either mg/dl or mmol/l, is available at http://professional.diabetes.org/GlucoseCalculator.aspx.

American Diabetes Association®

A1C Goals For Clinical Practice

A1C (%)

10.0

9.5

9.0

8.5

8.0

7.5

7.0

6.5

6.0

5.5

~20 to >40% have A1C > 9.5%
NHANES/BRFSS; Harmel et al.; NCQA 2000

~40 to >50% have A1C > 8%
NHANES/BRFSS; Harmel et al.

~30% of type 2 insulin users have A1C <8%
Harmel et al.

<7 — ADA: recommended target

<6.5 — AACE/ACE: recommended target

6 — Upper limit of normal range

ADA. *Diabetes Care* 2003; 26(S1):S33-S50
ACE Consensus Conference on Guidelines for Glycemic Control. Endocrine Practice, 2002
HEDIS 2000. Washington: National Committee for Quality Assurance, 1999
State of Managed Care Quality. National Committee for Quality Assurance, 2000

HbA1c correlates well with **development of complications** related to diabetes mellitus

Lower A1C Reduces Incidence of Complications

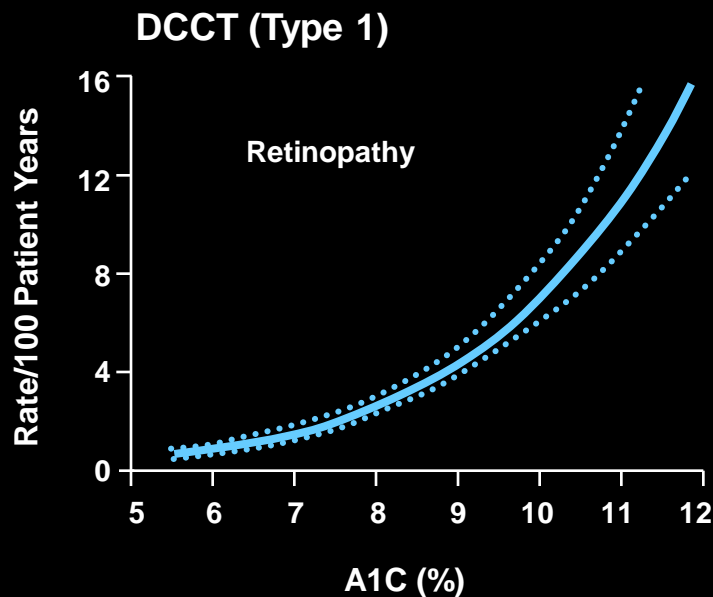| A1C	DCCT $9 \rightarrow 7\%$	Kumamoto $9 \rightarrow 7\%$	UKPDS $8 \rightarrow 7\%$
Retinopathy	63%	69%	17-21%
Nephropathy	54%	70%	24-33%
Neuropathy	60%	–	–
Macrovascular disease	41%*	–	16%*

*Not statistically significant.

Diabetes Control and Complications Trial (DCCT) Research Group. *N Engl J Med.* 1993;329:977-986.
Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117.
UK Prospective Diabetes Study Group (UKPDS) 33. *Lancet.* 1998;352:837-853.

DCCT and UKPDS:
No Glycemic Threshold

- Continuous relationship between A1C and complication risk
- Lower A1C associated with lower complication risk
- No glycemic threshold…the lower the better

DCCT (Type 1)

Retinopathy

UKPDS (Type 2)

Microvascular

DCCT Research Group. *Diabetes* 1996; 45:1289-1298
Adapted from Stratton IM, et al. *Br Med J* 2000; 321:405-412
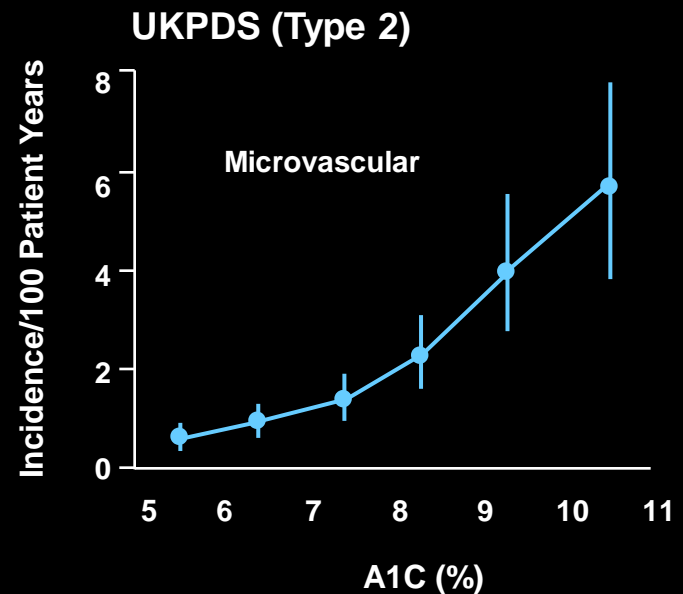
Utility of Hemoglobin A1c in Predicting Diabetes

Systematic screening for diabetes
is a potentially useful intervention

because diabetes is a common, costly, and highly morbid illness

and because there is a long asymptomatic phase prior to the illness.

"Ticking Clock" Hypothesis

For	The "clock starts ticking"
Microvascular complications	At onset of hyperglycemia
Macrovascular complications	Before the diagnosis of hyperglycemia

WHO. *Diabetologia* 1985;28:615-640; Haffner SM et al. *JAMA* 1990;263:2893-2898.

Early treatment will add benefit over treatment at the time of symptomatic diagnosis, most likely in the form of added years of complication-free life.
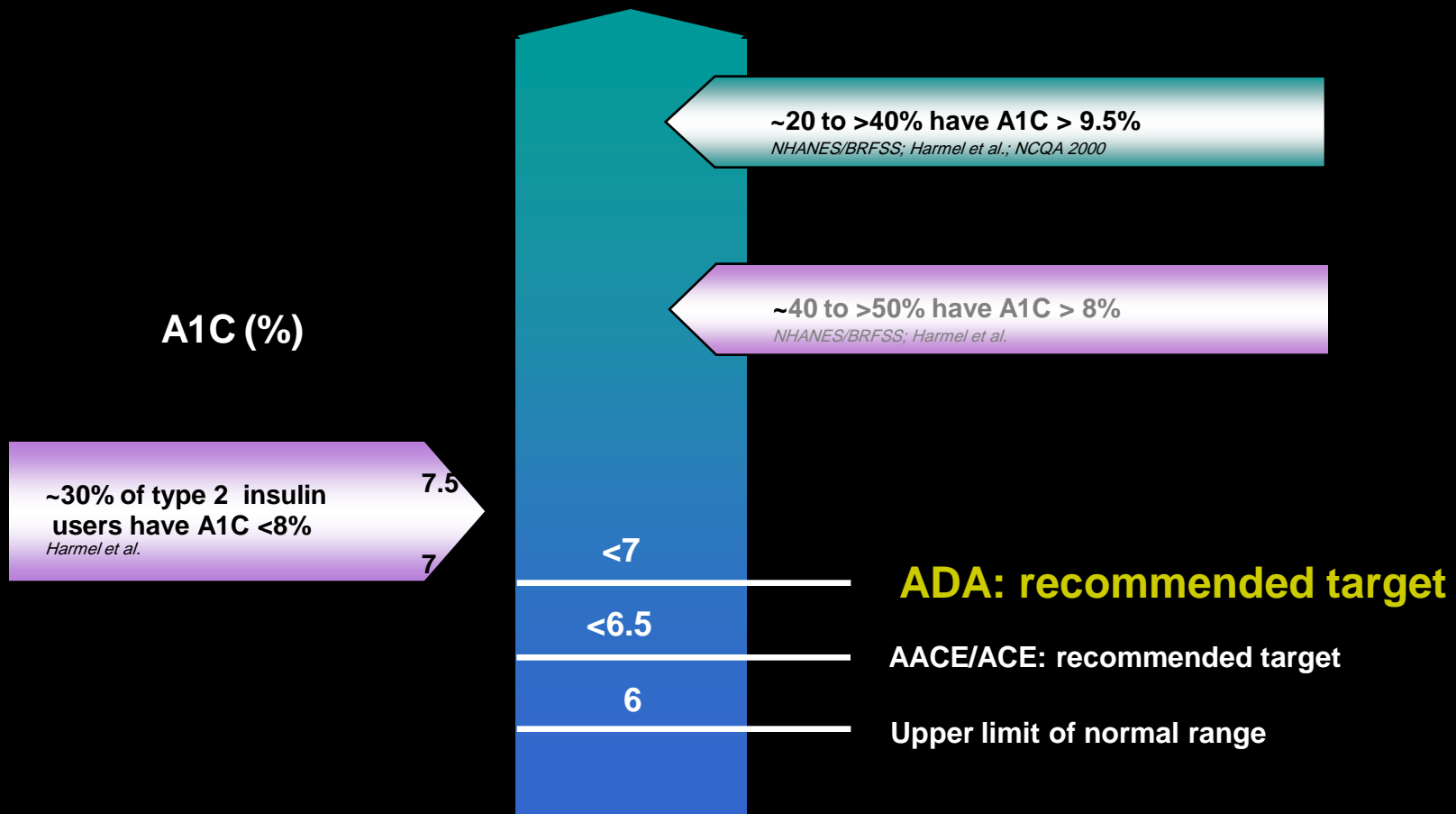
HbA1c is attractive as a screening test

because it is used to;

  define treatment targets in diabetes,

  and predict complications.

A1C Goals For Clinical Practice

A1C (%)

~20 to >40% have A1C > 9.5%
NHANES/BRFSS; Harmel et al.; NCQA 2000

~40 to >50% have A1C > 8%
NHANES/BRFSS; Harmel et al.

~30% of type 2 insulin users have A1C <8%
Harmel et al.

7.5

7

<7

<6.5

6

ADA: recommended target

AACE/ACE: recommended target

Upper limit of normal range

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Lower A1C Reduces Incidence of Complications

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If HbA1c was both able to predict future diabetes and to predict future complications

It would be an attractive test for screening, as it would allow screening to both risk of incident diabetes and complication risk once diabetes is developed.

The objective of this work was to measure the incidence of new diabetes among outpatients enrolled in a health care system

and to determine whether hemoglobin A1c (A1c) values would allow risk stratification for patients' likelihood of developing diabetes over 3 years.

1,253 outpatients

without diabetes,

age 45 to 64,

with a scheduled visit at the Veterans Affairs Medical Center (VAMC)

were screened for diabetes.

At the baseline screening

diabetes case was defined as HbA1c >/= 7.0% or FPG >/= 7.0 mmol/L (126 mg/dl).

These patients were then excluded from analysis of diabetes incidence.

Additional Measures

At enrollment, multiple demographic measures and patient-reported family history of diabetes and hypertension were obtained.
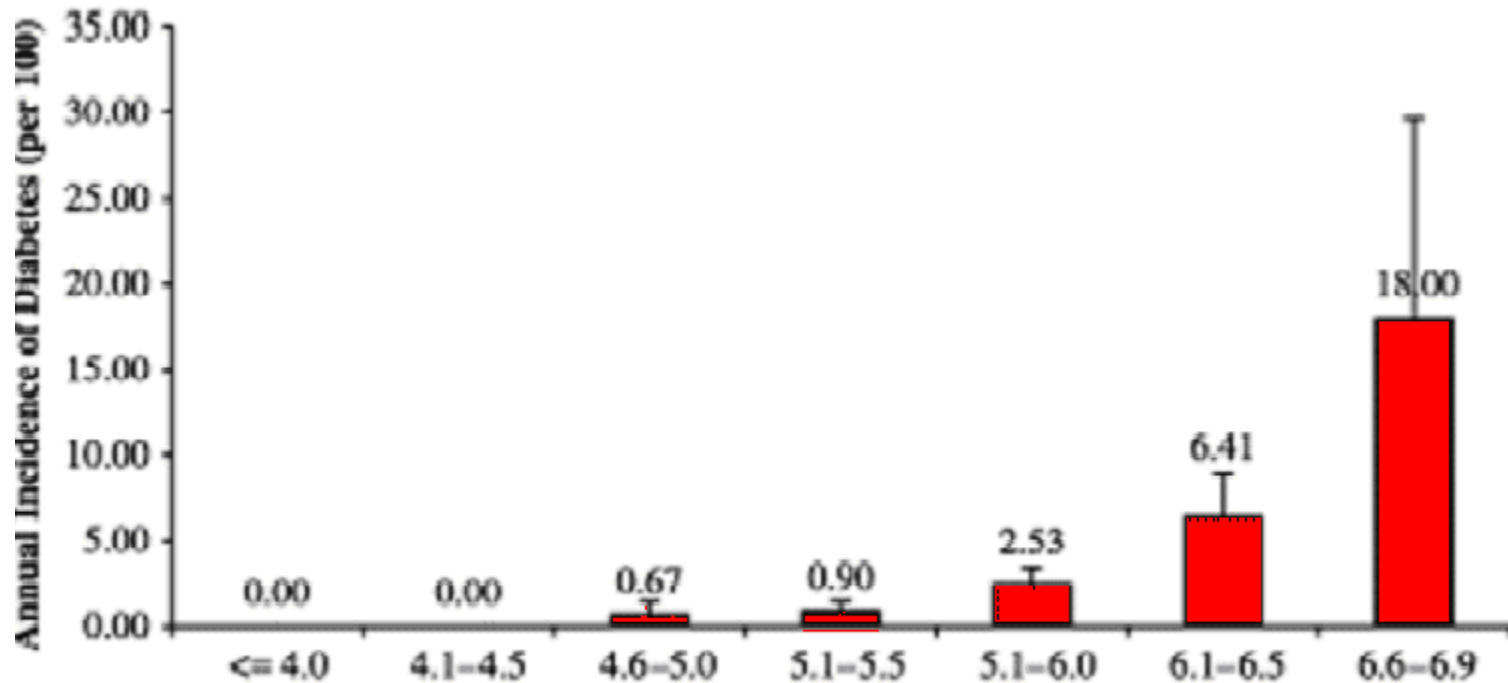
Also, height and weight of all subjects, and calculated body mass index (BMI) were obtained.

New cases of diabetes were defined by HbA1c $\geq$ 7.0% or FPG $\geq$ 126 mg/dl. at 3-year follow-up.
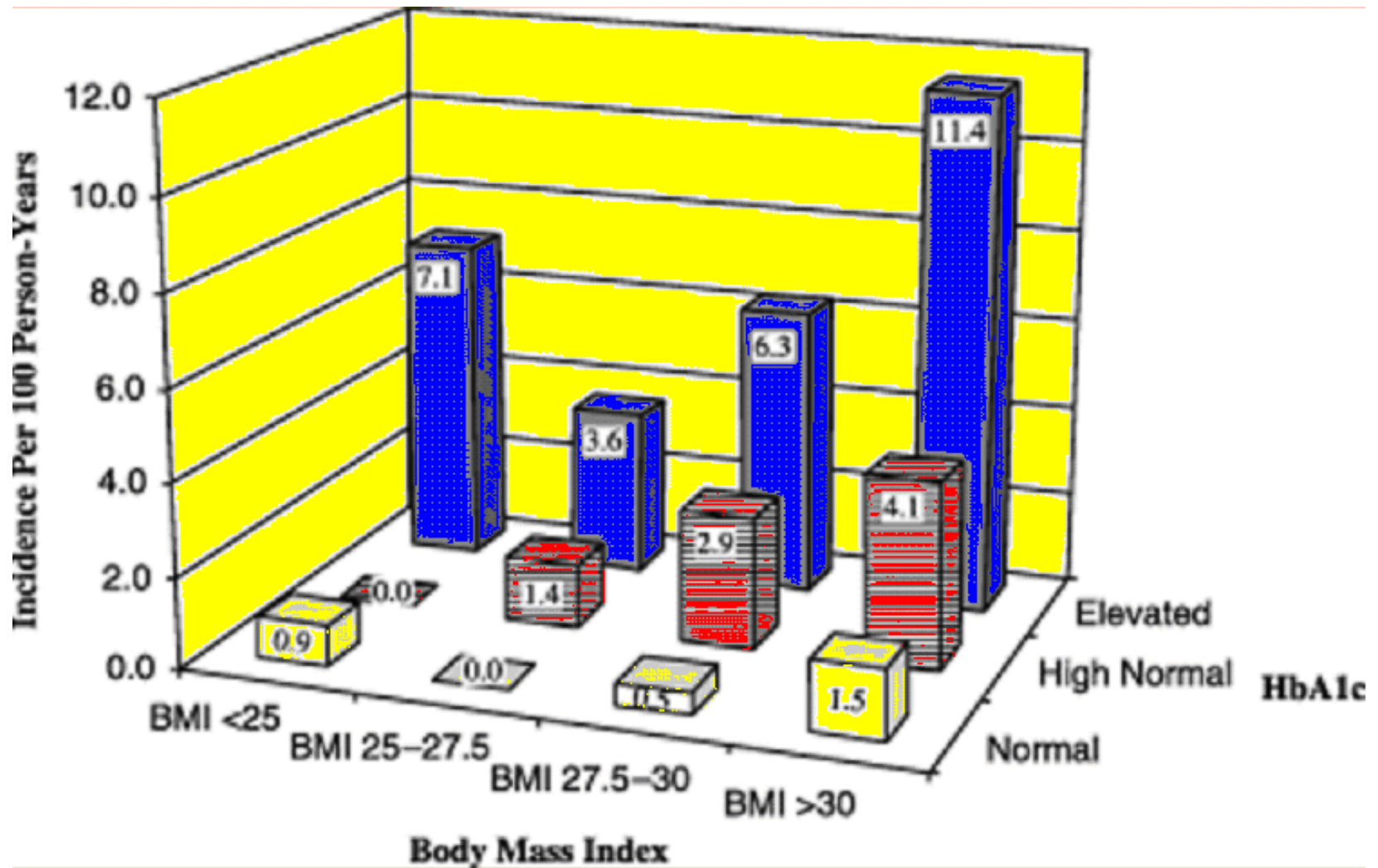
The incidence of diabetes was calculated as the number of new cases per person-year of follow-up.

Annual incidence of diabetes based on baseline HbA1c.

Baseline A1c and incidence of diabetes

Relationship of body mass index and baseline HbA1c to annual incidence of diabetes.
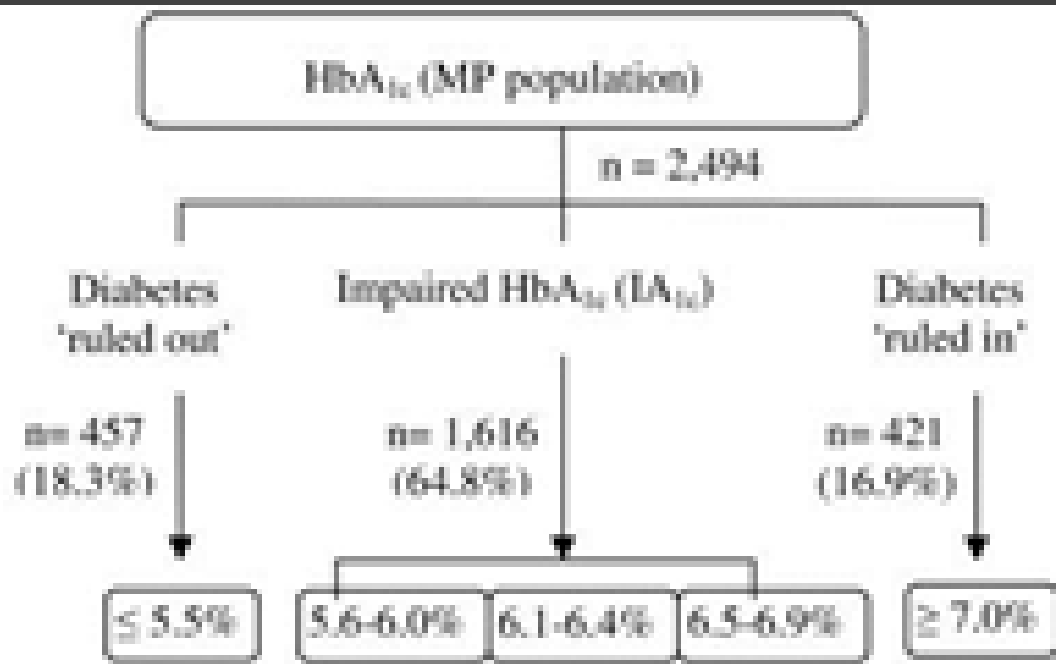
This predictive value suggests that

HbA1c

may be a useful test for

periodic diabetes screening.

A1C for Screening and Diagnosis of Type 2 Diabetes in Routine Clinical Practice.

- Application of A1c cut offs to screen or diagnose diabetes in a clinical group (MP population, n=2494) and in a national population-based group(Ausdiab population,n=6014).

A

HbA$_{1c}$ (MP population)

n = 2,494

Diabetes 'ruled out'	Impaired HbA$_{1c}$ (IA$_{1c}$)	Diabetes 'ruled in'
n= 457 (18.3%)	n= 1,616 (64.8%)	n= 421 (16.9%)

≤ 5.5%	5.6-6.0%	6.1-6.4%	6.5-6.9%	≥ 7.0%

Classified by ADA:

	≤ 5.5%	5.6-6.0%	6.1-6.4%	6.5-6.9%	≥ 7.0%
Normal (n):	275	342	123	31	2
IFG and or IGT (n):	163	290	255	121	28
Diabetes (n):	19	100	144	210	391
Total (n):	457	732	522	362	421
Diabetes prevalence:	4.2%	13.7%	27.6%	58.0%	92.9%

B

HbA$_{1c}$ (AusDiab population)

n = 6,014

Diabetes 'ruled out' — Impaired HbA$_{1c}$ (IA$_{1c}$) — Diabetes 'ruled in'

n= 4,534 (75.4%)　　n= 1,449 (24.1%)　　n= 31 (0.5%)

≤ 5.5% | 5.6–6.0% | 6.1–6.4% | 6.5–6.9% | ≥ 7.0%

Classified by ADA:	≤ 5.5%	5.6–6.0%	6.1–6.4%	6.5–6.9%	≥ 7.0%
Normal (n):	3,388	548	4	0	0
IFG and or IGT (n):	1,100	653	39	4	0
Diabetes (n):	46	102	58	41	31
Total (n):	4,534	1,303	101	45	31
Diabetes prevalence:	1.0%	7.8%	57.4%	91.1%	100%

CONCLUSIONS

- A1C <=5.5% and >=7.0% predicts absence or presence of type 2 diabetes, respectively.

- while at A1C 6.5–6.9%, diabetes is highly probable.

CONCLUSIONS

- For those with <u>impaired A1C</u> (5.5–6.9%), the prevalence of diabetes increases as A1C increases.

People with A1C5.6–6.0% were more likely to have either normoglycemia or pre-diabetes than diabetes

People with an A1C of 6.1–6.4% were more likely to have pre-diabetes or diabetes than normoglycemia

Among those with a A1C of 6.5–6.9%, diabetes was highly probable

CONCLUSIONS

- For those with an A1C >=6.5%, screening for **retinopathy** is also necessary.

- **The overall efficiency of using A1C as a first line for diabetes screening may facilitate early diagnosis and reduce the health burden associated with diabetes complications.**

CONCLUSIONS

- **A1C as a screening/diagnostic tool has some limitations;**
  - ✓ <u>method bias</u>, which is now being addressed by Internation Federation of Clinical Chemistry standardization.

  - ✓ certain confounding medical conditions (hemoglobinopathies and anemia). Most new A1C methods can identify or are unaffected by hemoglobinopathies. Anemia is also readily identifiable.

Glucose Testing and Interpretation

Test	Result	Diagnosis
Fasting plasma glucose, mg/dL	≤99	Normal
	100-125	Impaired fasting glucose
	≥126	Diabetes, confirmed by repeating the test on a different day
Glucose, mg/dL (oral glucose tolerance test, 2 hours after ingestion of 75-g glucose load)	≤139	Normal
	140-199	Impaired glucose tolerance
	≥200	Diabetes, confirmed by repeating the test on a different day
Hemoglobin A_{1c}, % (as a screening test)	≤5.4	Normal
	5.5-6.4	High risk/prediabetes; requires screening by glucose criteria
	≥6.5	Diabetes, confirmed by repeating the test on a different day

THANK YOU

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