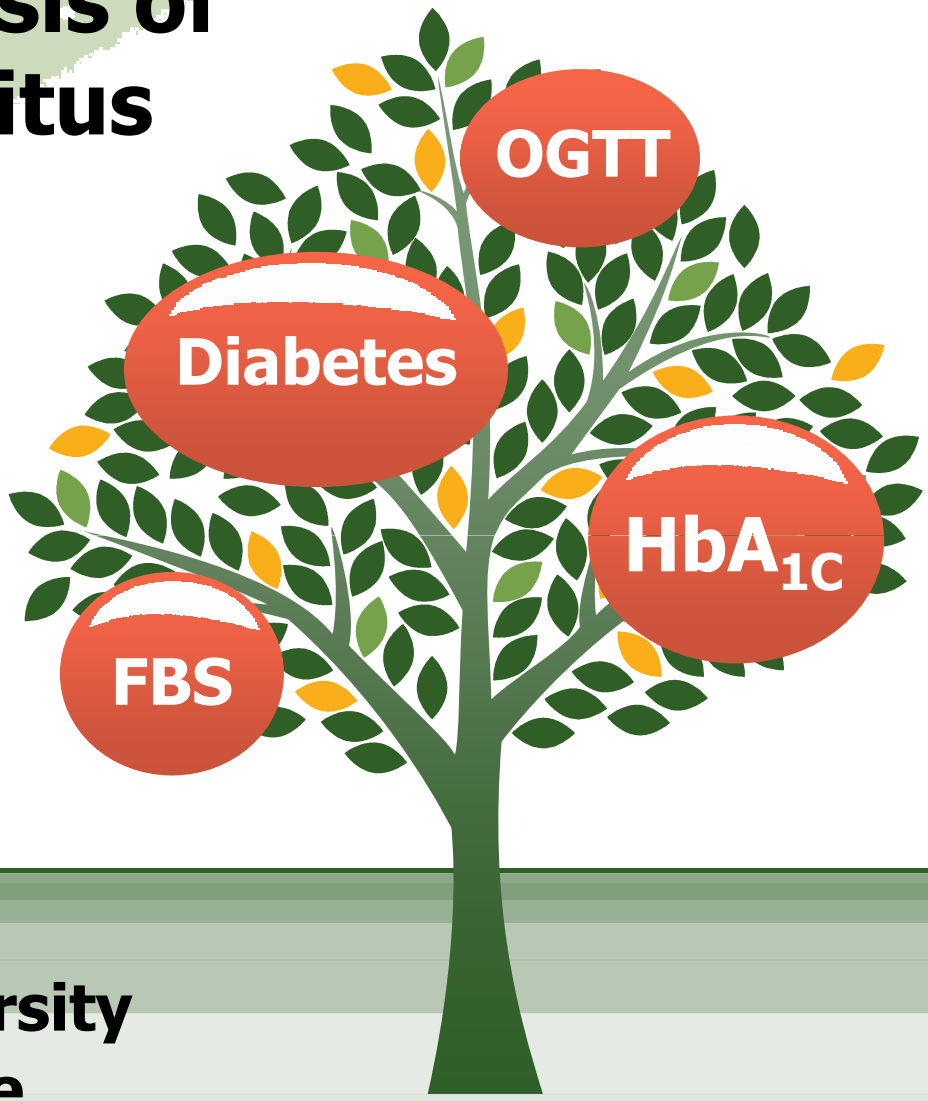
HbA_{1C} for the Diagnosis of Type 2 Diabetes Mellitus



Ewha Womans University
School of Medicine
LEE HYE JIN

Diagnosis of Diabetes

Based on distribution of glucose levels

1979
NDDG

Based on long term complication

1997
Expert committee

2010

Diabetes

- FPG ≥ 140 mg/dl
- 2hPG ≥ 200 mg/dl

- FPG cut point ≥ 126 mg/dl
- FPG: preferred test

- HbA_{1c} ≥ 6.5%

IGT: FPG < 140 mg/dl + 140 ≤2hPG <200 mg/dl

IFG: FBS ≥ 110 mg/dl (2003. 100mg/dl)

Increased risk for diabetes: HbA_{1c} 5.7-6.4%

ADA
Endo Society, AACE

Recommendation of International Expert Committee - *with members appointed by ADA, EASD, and IDF, 2009*

For the diagnosis of diabetes

- The A1C assay is an accurate, precise measure of chronic glycemic levels and correlates well with the risk of diabetes complications.
- The A1C assay has several advantages over laboratory measures of glucose.
- Diabetes should be diagnosed when A1C is 6.5%. Diagnosis should be confirmed with a repeat A1C test. Confirmation is not required in symptomatic subjects with plasma glucose levels 200 mg/dl.
- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.
- A1C testing is indicated in children in whom diabetes is suspected but the classic symptoms and a casual plasma glucose 200 mg/dl are not found.

Criteria for the diagnosis of diabetes
2010 ADA Recommendation

1. A1C≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay

or

2. FPG≥126 mg/dl. Fasting is defined as no caloric intake for at least 8h.

or

3. 2-h plasma glucose≥200 mg/dl during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water

or

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose≥200 mg/dl

AACE/ACE Statement on the Use of A1c for the Diagnosis of Diabetes

AACE/ACE support the ADA recommendations for use of a confirmed A1c as an available option to diagnose diabetes, with the following recommendations:

1. A1c should be considered as an additional optional criterion, not as the primary criterion.
2. AACE/ACE suggest using traditional glucose criteria for diagnosis when feasible.
3. A1c is not recommended for diagnosing type 1 diabetes.
4. A1c is not recommended for diagnosing gestational diabetes.
5. A1c may be misleading in several ethnic populations (e.g. African-Americans).
6. A1c may be misleading in the setting of various hemoglobinopathies, iron deficiency, hemolytic anemias, thalassemias, spherocytosis, and severe hepatic and renal disease.
7. AACE/ACE endorse using only standardized, validated assays for A1C testing.

The Endocrine Society Statement on the Use of A1c for Diabetes Diagnosis and Risk estimation

- The Endocrine Society supports the ADA recommendations for use of A1C as an option to diagnose diabetes, because of its close correlation with microvascular complications, and its ease of use.
- Clinicians should also be aware that there are a number of clinical conditions in which A1C and average blood glucose do not correlate well. (iron deficiency and hemolytic anemia, various hemoglobinopathies, thalassemias, hereditary spherocytosis, malignancies, and severe chronic hepatic and renal disease)
- Only standardized, validated techniques for A1C testing should be used. The point-of-service tests will need to be validated individually.
- A1C should not replace the use of fasting and all other glucose testing which are beneficial in the diagnosis of patients with Type 1 diabetes, in pediatrics, and in pregnancy.

THE ROLE OF HBA1C TESTING IN DIAGNOSING DIABETES IN KOREAN ADULTS

Subject

- Recruited 996 adults

  (mean age 41 ± 14 years, mean BMI 23.1 ± 3.5 kg/m^2)

  without a self-reported history of diabetes

  from 8 university hospitals in 2009

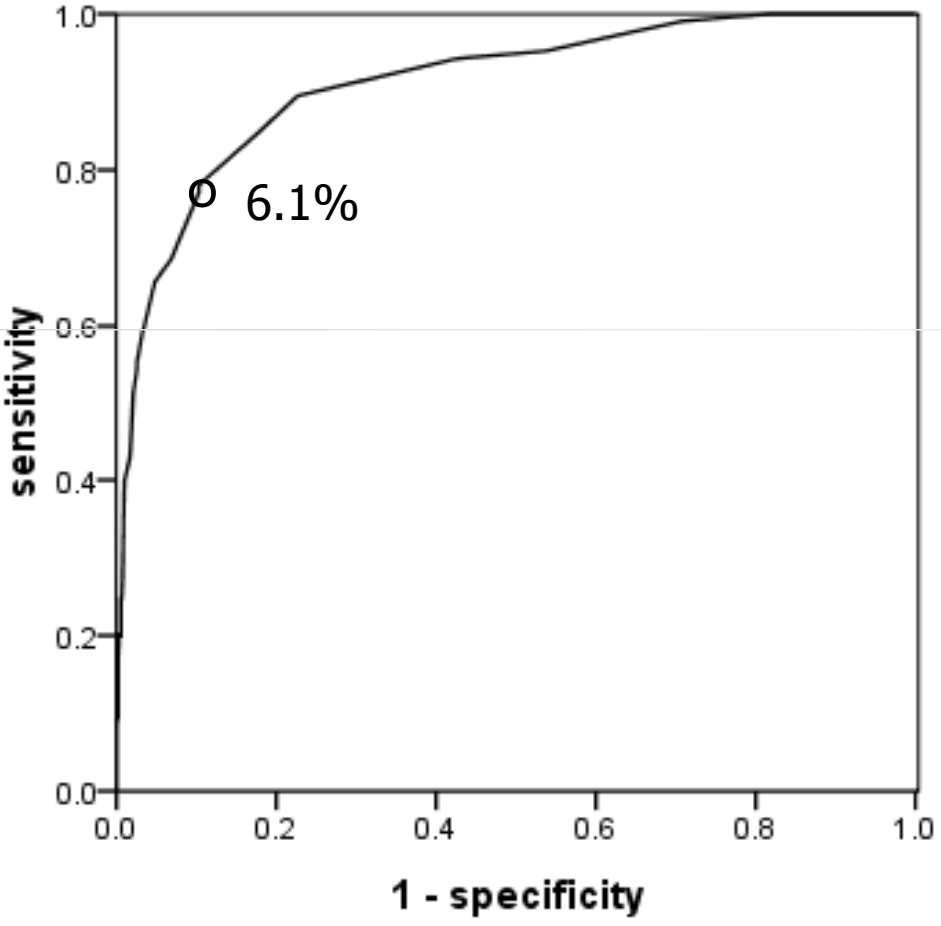
Method

- 75-g OGTT and HbA1C sampling were performed in all examinees.
- Glucose concentrations were measured by colorimetry method (ADVIA2400 autoanalyzer)

  HbA1C, by immunoturbidimetric method (Cobas integra800, Roche, Switz)

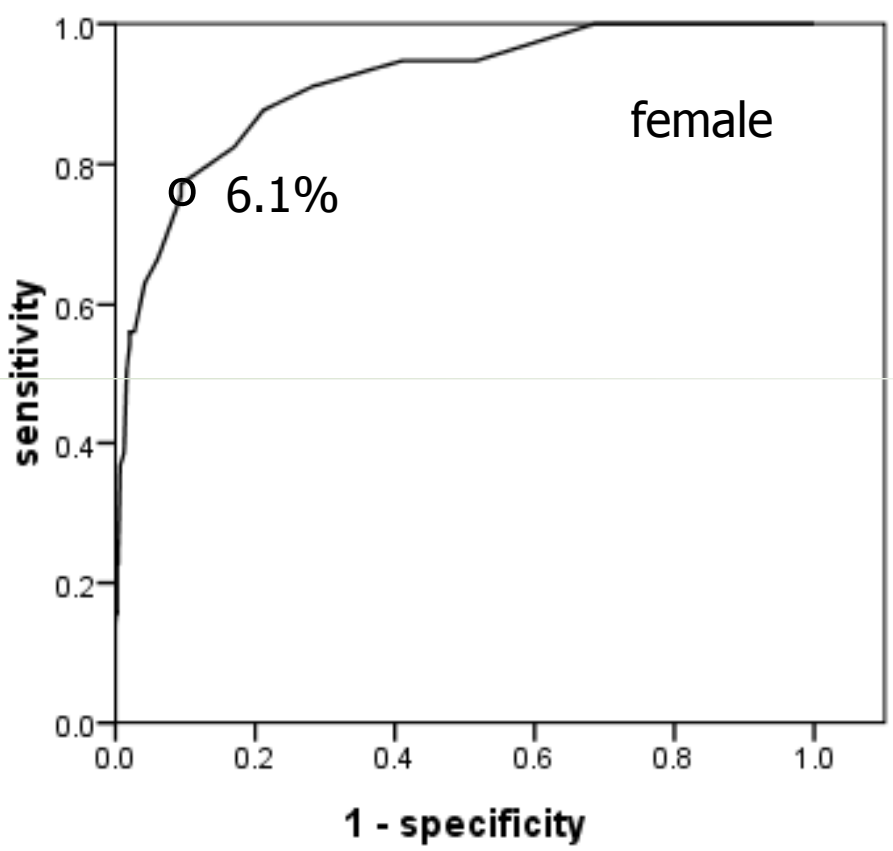
  - at the central laboratory.
- Receiver operating characteristic curve analysis was used to examine the sensitivity and specificity of HbA1C for diagnosing diabetes.

ROC curve for identification of participants with previously undiagnosed diabetes, using HbA1C for diagnosis and an OGTT as criterion.

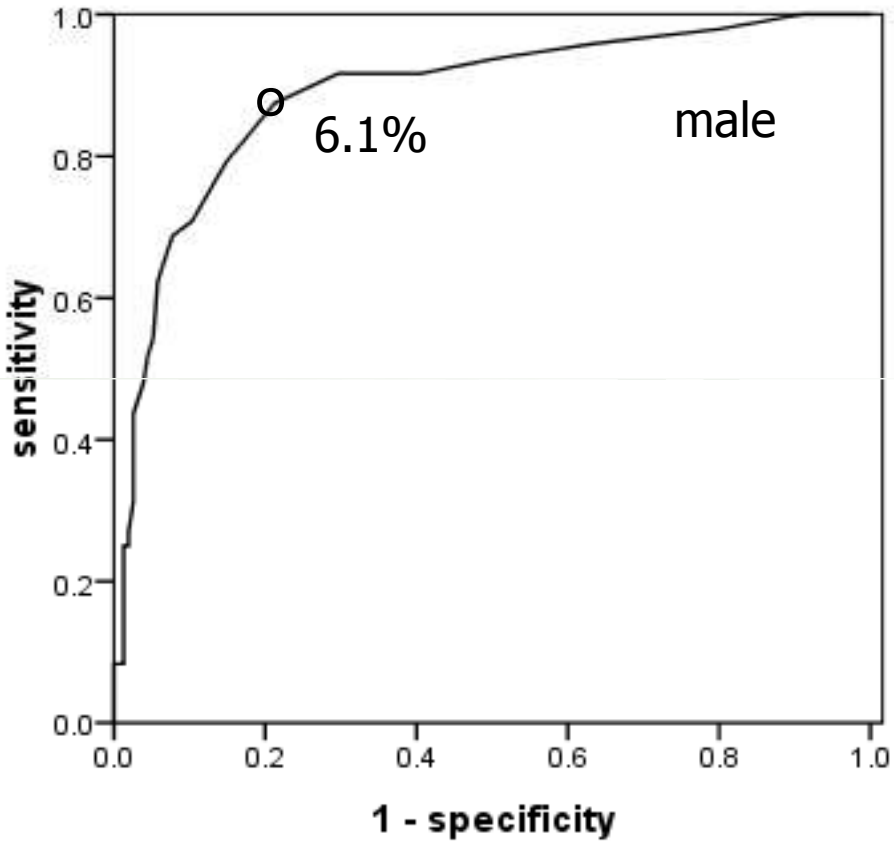


	AUC	95% CI
HbA1C	0.911	0.880-0.942

ROC curve analysis for HbA1C according to sex

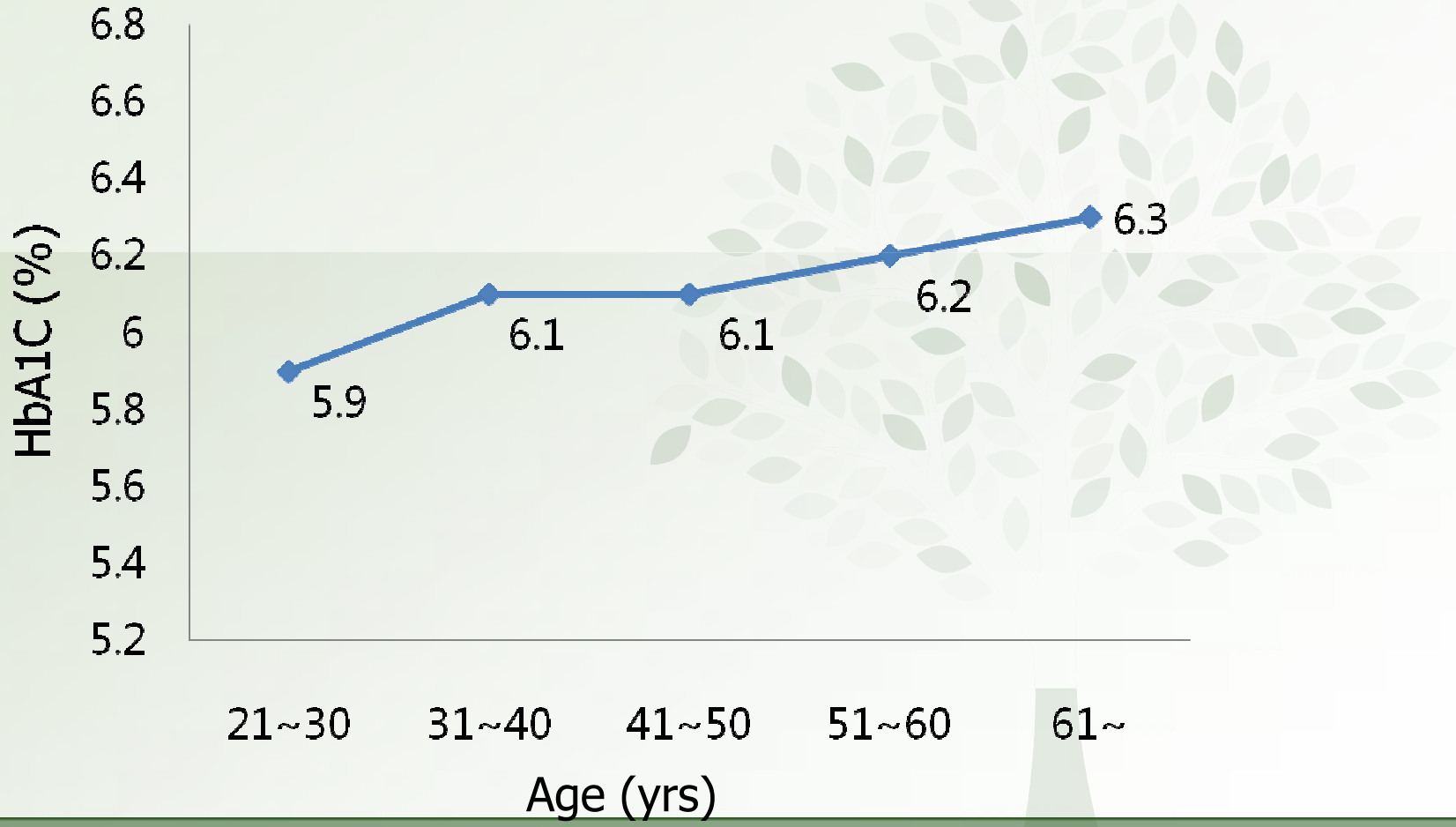


	AUC	95% CI
HbA1C	0.914	0.874-0.953



	AUC	95% CI
HbA1C	0.888	0.831-0.945

Cutoff value of HbA1C according to age



Sensitivity and specificity of HbA1C 6.1%, 6.5% as cut-off points for diagnosing the diabetes

Cut-off point	PPV	NPV	sensitivity	specificity
6.1%	56.1%	97.9%	84.8%	82.3%
6.5%	68.1%	96.0%	59.0%	97.5%

PPV, positive predictive value; NNV, negative predictive value

HbA_{1C}

- **New diagnostic Criteria of Diabetes**

1. Advantage

2. Limitation

CAN THE HBA_{1C} BE USED TO DIAGNOSE DIABETES?

Evidence that Favors the Use of HbA_{1c} in the Diagnosis of Diabetes

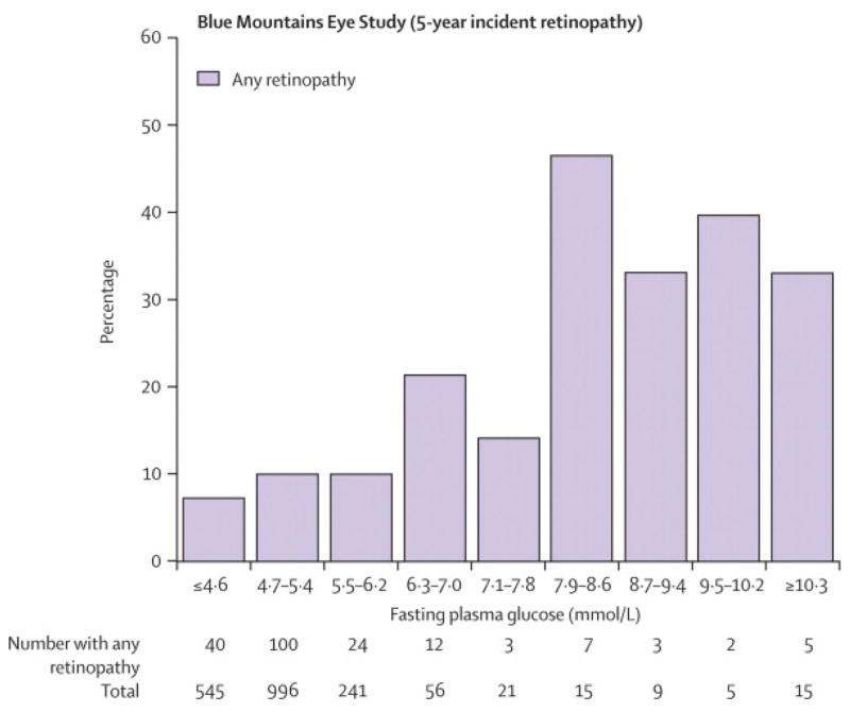
- Better index of overall glycemic exposure and risk for long-term complications
- Substantially less biologic variability
- Low interindividual or intraindividual variability
- Substantially less preanalytic instability
- No need for fasting or timed samples
- Relatively unaffected by acute (e.g. stress or illness related) perturbations in glucose levels
- Currently used to guide management and adjust therapy
- Standardization

Longterm complication

- Laboratory measures that capture long-term glycemic exposure : better marker of the disease than single measures of glucose concentration.

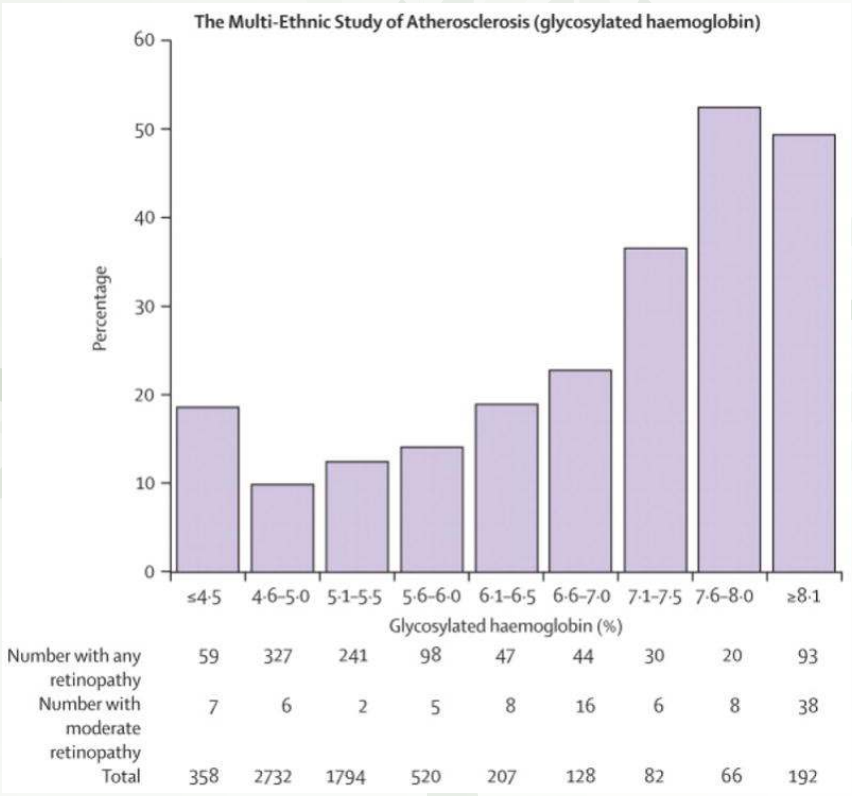
- Strong correlation between retinopathy and HbA_{1c} but a less consistent relationship with fasting glucose level.

Relationship of retinopathy and FPG



	≤4·6	4·7–5·4	5·5–6·2	6·3–7·0	7·1–7·8	7·9–8·6	8·7–9·4	9·5–10·2	≥10·3
Number with any retinopathy	40	100	24	12	3	7	3	2	5
Total	545	996	241	56	21	15	9	5	15

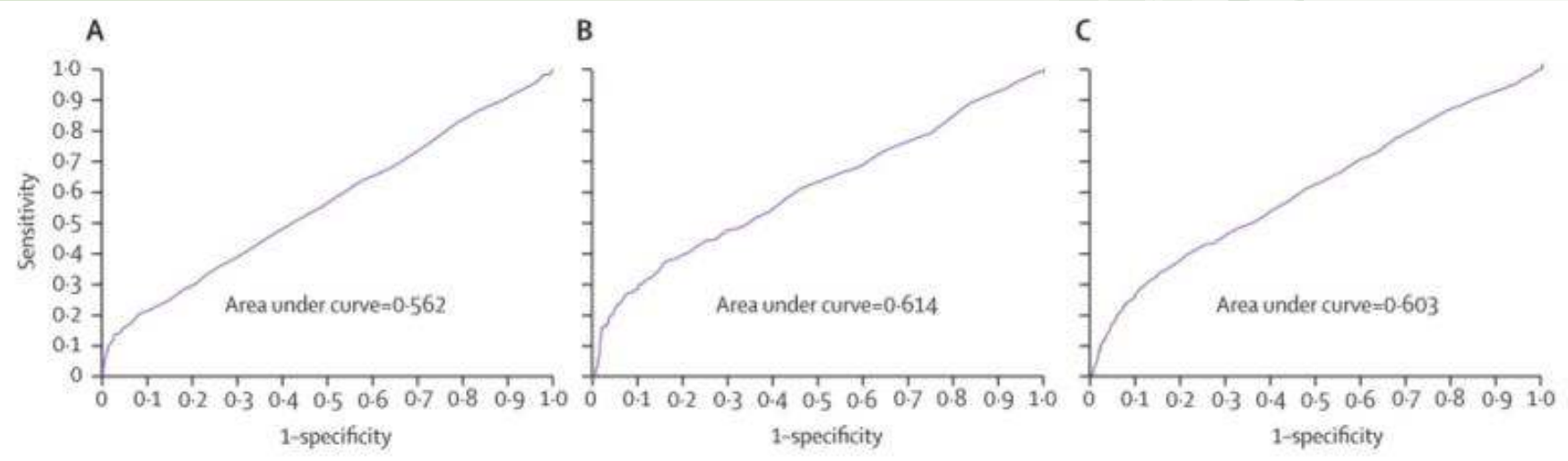
Relationship of retinopathy and HbA_{1c}



	≤4·5	4·6–5·0	5·1–5·5	5·6–6·0	6·1–6·5	6·6–7·0	7·1–7·5	7·6–8·0	≥8·1
Number with any retinopathy	59	327	241	98	47	44	30	20	93
Number with moderate retinopathy	7	6	2	5	8	16	6	8	38
Total	358	2732	1794	520	207	128	82	66	192

Wong T.Y, Lancet 2008

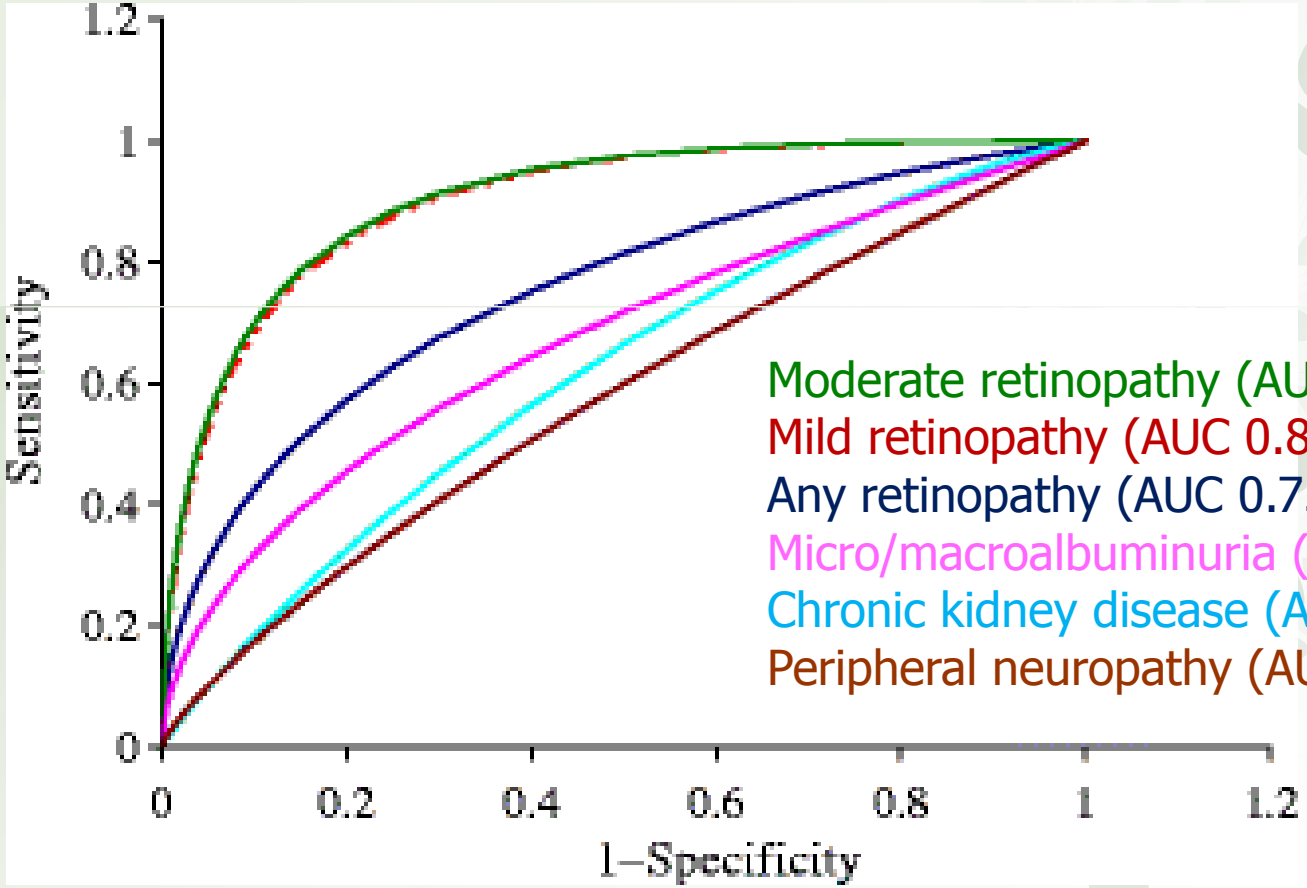
ROC curves for FPG and Prevalent Retinopathy



(A: Blue Mountains Eye Study, B: The AusDiab Study C: The MESA Study)

Wong T.Y, Lancet 2008

ROC curves for HbA_{1c} (%) and the various microvascular complications.



Sabanayagam C, Diabetologia 2009

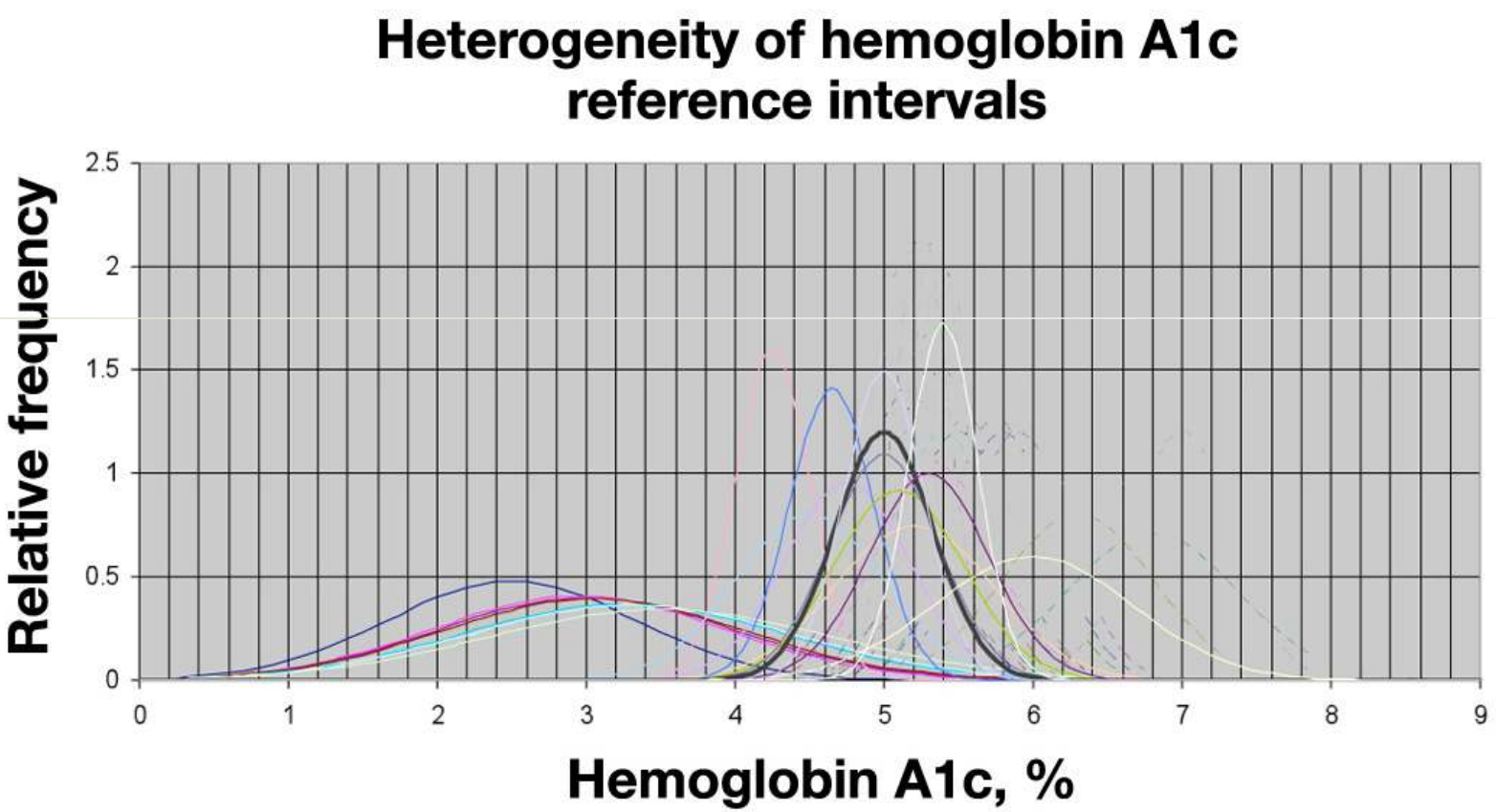
Accuracy

- laboratory measurements of glucose and HbA_{1c}

  : accuracy and precision of HbA_{1c} assays at least match those of glucose assays.

- Biological variability of HbA_{1c} within an individual is somewhat smaller than that of fasting glucose (CV 3.6 vs. 5.7%) and considerably less than that of 2-h glucose (CV 16.6%) – suggesting that repeated measurements would be more consistent using HbA_{1c}.

Standardization



Standardization

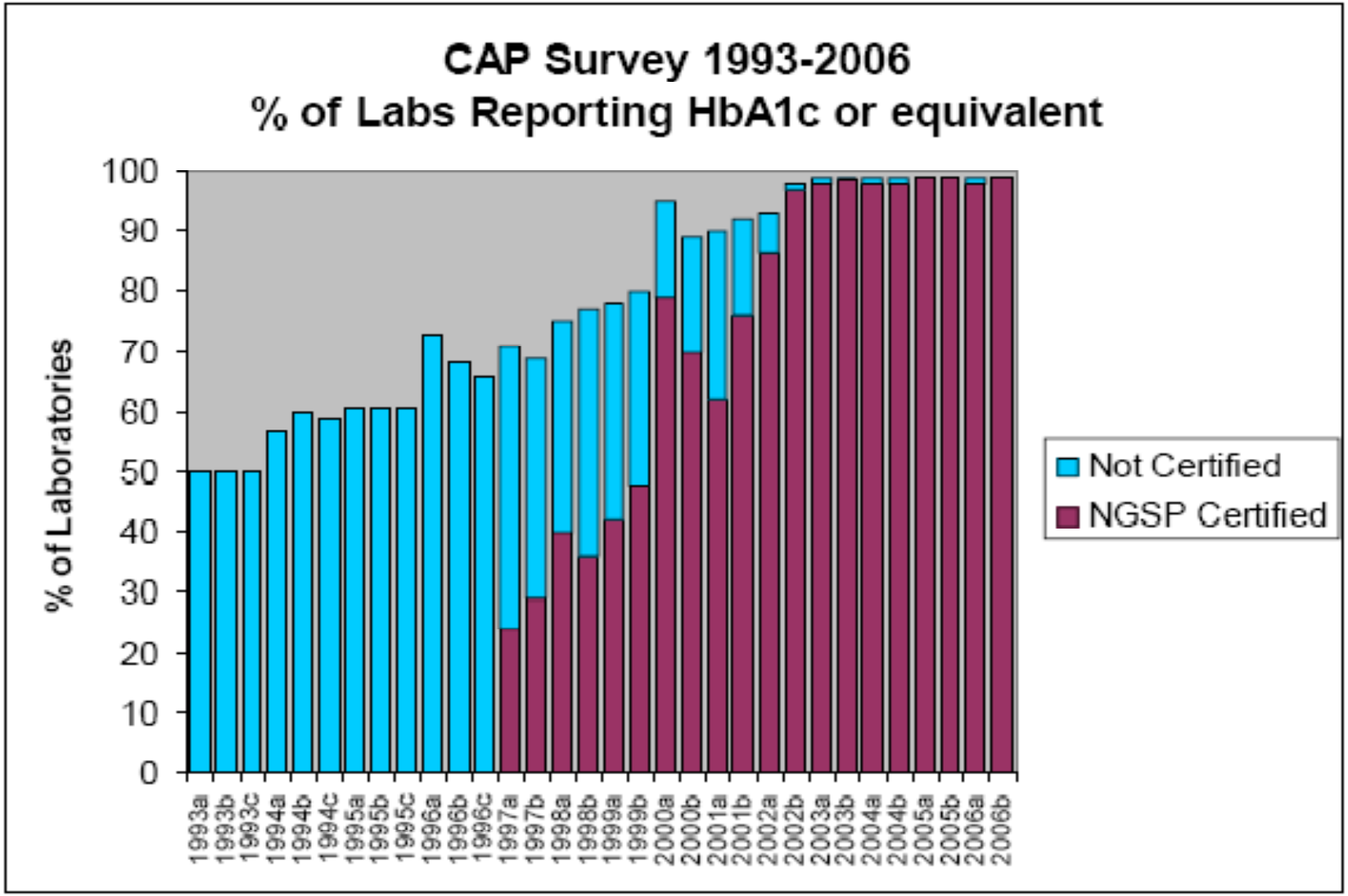
- National Standardization Programs

1. In the US, the National Glycohemoglobin Standardization Program (NGSP), with the DCCT HPLC method used as primary reference method
2. In Sweden, the Mono S ion exchange chromatography designated as the comparison method
3. In Japan, use of common calibrators (six calibrators available for use) with HbA_{1c} values assigned by the Japan Diabetes Society

- *NOT INTERNATIONAL* -

standardization

- ADA recommends that laboratories use only HbA_{1c} assay methods that have been NGSP certified.
- ADA recommends that all laboratories performing HbA_{1c} testing participate in the College of American Pathologist (CAP) fresh sample proficiency testing survey.


CAP Survey 1993-2006
% of Labs Reporting HbA1c or equivalent
% of Laboratories
100
90
80
70
60
50
40
30
20
10
0
1993a
1993b
1993c
1994a
1994b
1994c
1995a
1995b
1995c
1996a
1996b
1996c
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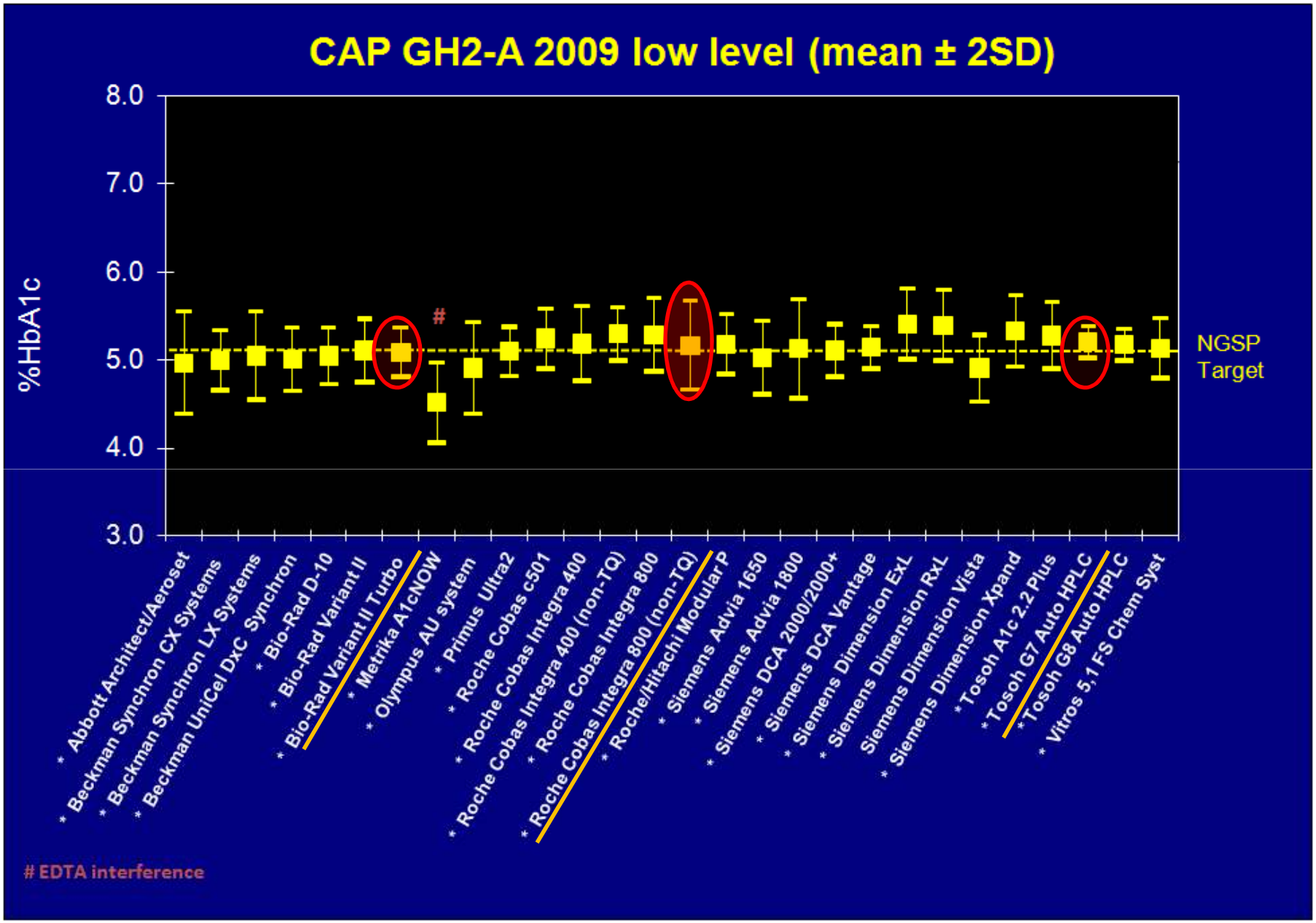
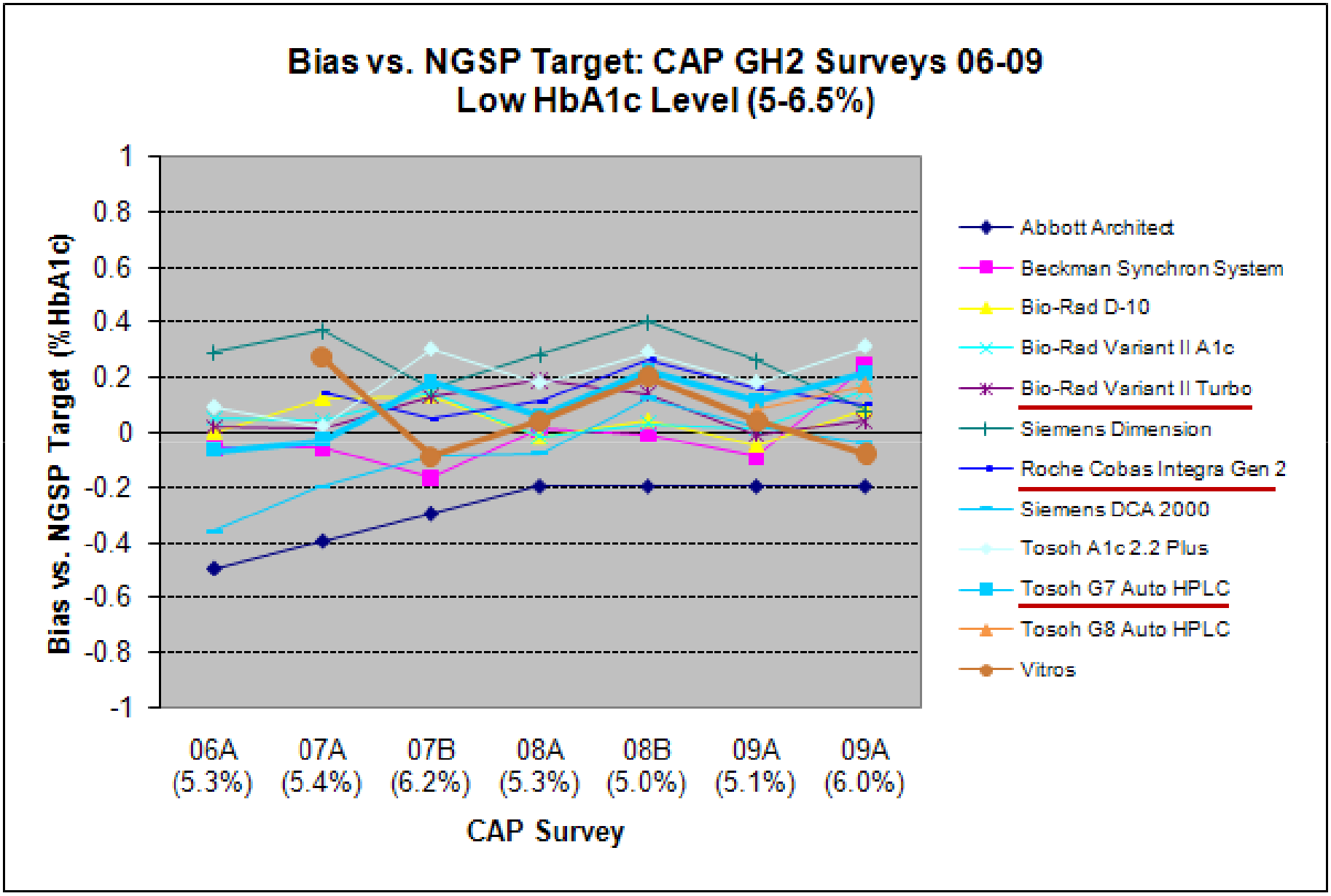
2002a
2002b
2003a
2003b
2004a
2004b
2005a
2005b
2006a
2006b
Not Certified
NGSP Certified


CAP GH2-A 2009 low level (mean ± 2SD)
%HbA1c
8.0
7.0
6.0
5.0
4.0
3.0
#
NGSP Target
* Abbott Architect/Aeroset
* Beckman Synchron CX Systems
* Beckman Synchron LX Systems
* Beckman UniCel DxC Synchron
* Bio-Rad D-10
* Bio-Rad Variant II
* Bio-Rad Variant II Turbo
* Metrika A1cNOW
* Olympus AU system
* Primus Ultra2
* Roche Cobas c501
* Roche Cobas Integra 400
* Roche Cobas Integra 400 (non-TQ)
* Roche Cobas Integra 800
* Roche Cobas Integra 800 (non-TQ)
* Roche/Hitachi Modular P
* Siemens Advia 1650
* Siemens Advia 1800
* Siemens DCA 2000/2000+
* Siemens DCA Vantage
* Siemens Dimension ExL
* Siemens Dimension RxL
Siemens Dimension Vista
* Siemens Dimension Xpand
*Tosoh A1c 2.2 Plus
*Tosoh G7 Auto HPLC
*Tosoh G8 Auto HPLC
* Vitros 5,1 FS Chem Syst
# EDTA interference


Bias vs. NGSP Target: CAP GH2 Surveys 06-09
Low HbA1c Level (5-6.5%)
Bias vs. NGSP Target (%HbA1c)
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
06A (5.3%)
07A (5.4%)
07B (6.2%)
08A (5.3%)
08B (5.0%)
09A (5.1%)
09A (6.0%)
CAP Survey
Abbott Architect
Beckman Synchron System
Bio-Rad D-10
Bio-Rad Variant II A1c
Bio-Rad Variant II Turbo
Siemens Dimension
Roche Cobas Integra Gen 2
Siemens DCA 2000
Tosoh A1c 2.2 Plus
Tosoh G7 Auto HPLC
Tosoh G8 Auto HPLC
Vitros

국내현황

Method	제조사	품명 (Reagent or Instrument)
Immunoassay	ABBOTT	ABBOTT CLINICAL CHEMISTRY MULTIGENTHEMOGLOBIN A1C
	Dade-Behring	DIMENSION HEMOGLOBIN A1C
	DIAZYME	DIAZYME ENZYMATIC HBA1C ASSAY
	Fujirebio Inc.	RAPIDIA AUTO HBA1C
	J&J	VITROS CHEMISTRY PRODUCTS D%A1C REAGENT KIT
	Nordia	Nordia HbA1c
	Pointe Scientific	POINTE-HEMOGLOBIN A1C REAGENT SET
	RANDOX	RANDOX HAEMOGLOBIN A1C
	ROCHE	COBAS INTEGRA HBA1C
		TINA-QUANT HBA1C II
	Thermo Clinical Systems	THERMO-HBA1C
	WAKO	AUTO WAKO HBA1C
HPLC	ARKRAY	HA-8140
	BIORAD	D-10
		DIASTAT
		VARIANT
		VARIANT II
		VARIANT II TURBO
	TOSOH	HLC-723 GHb V, A1c 2.2
		HLC-723 G7
POC	Axis-Shield	NYCOCARD HBA1C
	Yongdong	Yongdong HbA1c
	BAYER	DCA 2000 HEMOGLOBIN A1C
	BIORAD	MICROMAT II HBA1C

Survey 분석결과 (1)

Instrument/method group	08-1-01			08-1-02	
	기관수	평균	CV(%)	평균	CV(%)
ADVIA System	1	4.90		7.40	
Dimension	6	5.55	4.5	7.82	2.4
Rapidia Auto HbA1c	9	4.51	4.0	7.26	6.7
Nordia HbA1c	3	4.50	4.4	6.73	1.8
Olympus AU640/640e	3	4.93	11.6	7.77	6.3
Pointe-HbA1c Reagent Set	1	5.10		7.90	
Randox HbA1c	1	6.00		8.80	
Cobas Integra HbA1c	13	5.10	3.3	7.76	4.5
Tina-Quant HbA1c II	16	5.41	10.9	7.77	4.2
Auto Wako HbA1c	3	5.00	9.2	7.50	4.8
D-10	16	5.01	3.4	8.01	2.2
DiaStat	1	5.10		7.40	
Variant II	7	4.80	5.8	8.06	1.9
Variant II Turbo	48	5.04	2.4	7.87	2.2
HLC-723 GHbV, A1c 2.2	3	4.70	2.1	8.13	1.5
HLC-723 G7	49	4.79	2.7	8.14	1.7
NycoCard HbA1c	36	5.27	7.4	7.77	7.2
DCA2000 HbA1c	6	5.18	2.9	7.55	2.6
Micromat II A1C	1	4.90		7.20	
Other	6	5.42	15.7	7.72	6.6

Survey 분석결과 (2)

Instrument/method group	08-2-01			08-2-02		08-2-03	
	기관수	평균	CV(%)	평균	CV(%)	평균	CV(%)
ADVIA System	2	5.45	1.3	9.10	3.1	12.20	10.4
Dimension	6	5.55	3.2	8.63	2.7	11.33	2.5
Rapidia Auto HbA1c	7	4.76	2.9	7.84	3.6	10.14	4.3
Nordia HBA1c	4	4.68	3.6	7.63	6.7	10.03	4.9
Olympus AU640/640e	2	4.85	13.2	7.95	13.3	9.80	14.4
Cobas Integra HbA1c	12	5.27	2.7	8.58	3.3	11.05	3.4
Tina-Quant HbA1c II	8	5.39	3.0	8.43	2.7	11.10	2.8
Modular Tina-Quant Gen.2	3	5.30	1.9	8.40	1.2	10.73	2.9
Tina-Quant HbA1c Gen.2	5	5.36	5.0	8.36	7.5	10.74	7.8
Auto Wako HbA1c	3	4.73	12.1	7.57	10.3	10.57	13.2
HA-8140	1	5.30		8.60		11.60	
D-10	15	5.13	4.5	8.55	2.5	11.30	2.9
DiaStat	1	4.80		7.80		10.30	
Variant II	7	5.23	3.3	8.70	3.1	11.36	4.1
Variant II Turbo	49	5.30	1.7	8.51	1.3	11.00	1.4
HLC-723 GHbV, A1c 2.2	4	5.30	2.3	8.48	1.5	10.83	0.9
HLC-723 G7	49	5.26	1.5	8.62	2.3	11.08	2.8
DCA2000 HbA1c	6	5.23	4.0	8.28	4.1	10.52	4.6
Micromat II A1C	1	5.70		8.60		11.10	
NycoCard HbA1c	31	5.56	8.1	8.72	6.9	11.02	7.8
Other	6	5.67	9.0	9.15	12.2	11.22	7.0

LIMITATIONS OF HBA1C AS THE RECOMMENDED MEANS OF DIAGNOSING DIABETES

Arguments Against the Use of HbA_{1C} as a Tool for the Diagnosis of Diabetes

- Lack of universal threshold for the diagnosis of diabetes
  - Problems for the selection of the HbA_{1c} threshold: methodological and ethnic issues
- Absence of the standardization network in the majority of the countries and uncertanties in the diagnosis resulting from the use of nonstandardized methods
- Low sensitivity of the HbA_{1c} criterion may leave undetected a significant proportion of cases seeking attention because they are considered at risk for having diabetes.

Race

- Different sensitivity and specificity for HbA_{1c} occurs among ethnic groups, which may be related to genetic differences in the concentration of hemoglobin, rates of glycation and the lifespan or amount of red blood cells.
- racial disparities in HbA_{1c}

  : premature to establish race-specific diagnostic values
- multivariate analysis of 15,934 nondiabetic participants in the 1999-2006 NHANES,

  - non hispanic blacks had 2.4 fold increase in likelihood of A1C > 6% among subjects with fasting glucose< 100mg/dl.
- subjects with IGT in the Diabetes Prevention Program, mean A1C was 5.78% for whites and 6.18% for blacks.

Abnormal Hemoglobins

- HbA (adult hemoglobin): 2α + 2β chains
- HbF (fetal hemoglobin): 2α + 2γ chains
- Most common Hb variants: HbS, HbE, HbC, HbD

  single amino acid substitutions in the β chain.

  - some variants can affect either the net charge of the Hb and /or the recognition of glycated N terminus by antibodies, resulting in erroneous HbA_{1c} values for some methods
  - affect ionic charge of the Hb molecule → cause interference with ion-exchange methods
  - S,C variant: close to the N terminus on the β chain → some immunoassays are affected.

Interference of Heterozygous Variants S, C, D, E, and Elevated HbF with Specific HbA1c Methods

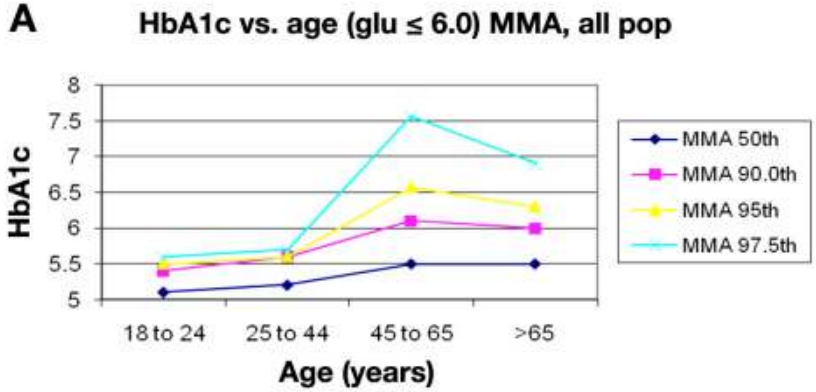
Manufacturer	Method	Interference from HbAS	HbAC	HbAE	HbAD	↑ HbF
Immunoassay						
Abbott	Architect/Aeroset	Yes ↑	Yes ↑	—*b*	—*b*	—*b*
Bayer (Metrika)	A1cNOW	Yes ↑	Yes ↑	No	No	—*b*
Beckman	Synchron System	No	No	No	No	—*b*
Dade	Dimension	No	No	No	No	—*b*
Olympus	AU system	Yes ↑	Yes ↑	No	No	—*b*
Ortho-Clinica	lVitros	No	No	No	No	—*b*
Point Scientific	HbA1c on Modular P	No	No	No	No	—*b*
Roche	Cobas Integra	Yes ↑	Yes ↑	—*b*	—*b*	—*b*
Roche	**Cobas Integra Gen.2**	**No**	**No**	**No**	**No**	**—*b***
Roche/Hitachi	Hitachi (Tina Quant)	No	No	No	No	—*b*
Siemens (Bayer)	Advia	Yes ↑	Yes ↑	—*b*	—*b*	—*b*
Siemens (Bayer)	DCA 2000	No	No	No	No	Yes[c]

Manufacturer	Method	Interference from HbAS	HbAC	HbAE	HbAD	↑ HbF
Ion-exchange HPLC						
Bio-Rad	D-10 (short)	No	No	No	No	—*b*
Bio-Rad	D-10 (extended)	No	No	No	No	—*b*
Bio-Rad	Variant A1c	No	No	No	Yes ↓	—*b*
Bio-Rad	**Variant II A1c**	**No**	**No**	**No**	**No**	**No**
Bio-Rad	**Variant II Turbo A1c**	**No**	**No**	**Yes ↑**	**Yes ↑**	**—*b***
Menarini	HA8140 (diabetes mode)	Yes ↑	No	—*b*	—*b*	—*b*
Menarini	HA8160 (diabetes mode)	No	No	Yes ↓	Yes ↓	—*b*
Menarini	HA8160 (TP mode)	No	No	No	Not quantified	—*b*
Tosoh	A1c 2.2 Plus	No	No	Yes ↓	No	Yes[c]
Tosoh	**G7**	**No**	**No**	**Yes ↓**	**No**	**No[d]**
Tosoh	G8	—*b*	—*b*	*Yes ↓*	*No*	—*b*
Boronate affinity						
Axis-Shield	Afinion	No	No	No	No	—*b*
Primus	Boronate affinity HPLC	No	No	No	No	Yes[c]
Other						
Diazyme	Direct enzymatic A1c	No	No	No	No	—*b*

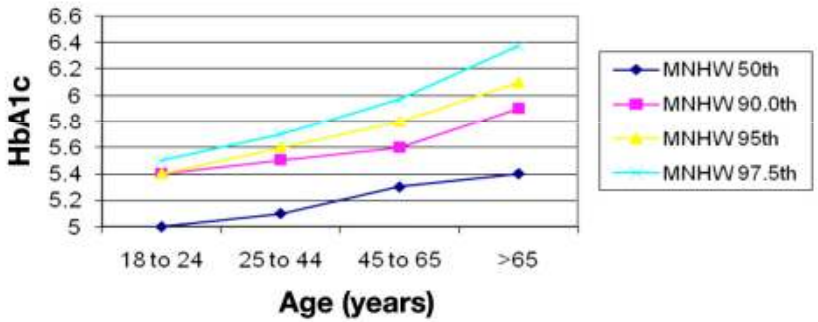
Age

HbA_{1c} levels appear to increase with age, but the extent of the change, whether it relates to factors other than glucose metabolism, and the effect of the age-related increases on the development of complications are not sufficiently clear to adopt age-specific values in a diagnostic scheme

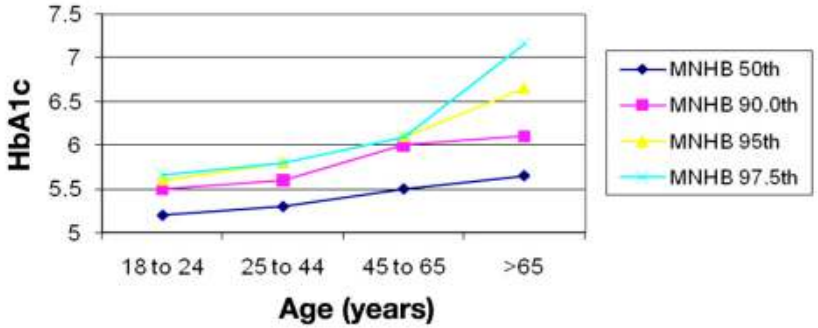
A


HbA1c vs. age (glu ≤ 6.0) MMA, all pop
HbA1c
8
7.5
7
6.5
6
5.5
5
18 to 24
25 to 44
45 to 65
>65
Age (years)
MMA 50th
MMA 90.0th
MMA 95th
MMA 97.5th

B


HbA1c vs. age (glu ≤ 6.0) MNHW, all pop
HbA1c
6.6
6.4
6.2
6
5.8
5.6
5.4
5.2
5
18 to 24
25 to 44
45 to 65
>65
Age (years)
MNHW 50th
MNHW 90.0th
MNHW 95th
MNHW 97.5th

C


HbA1c vs. age (glu ≤ 6.0) MNHB, all pop
HbA1c
7.5
7
6.5
6
5.5
5
18 to 24
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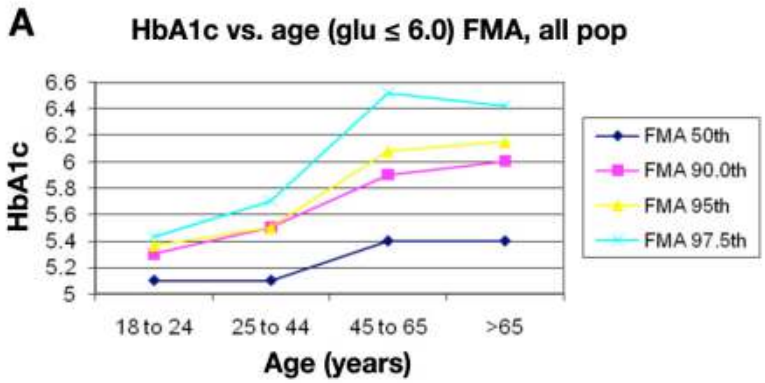
45 to 65
>65
Age (years)
MNHB 50th
MNHB 90.0th
MNHB 95th
MNHB 97.5th

A


HbA1c vs. age (glu ≤ 6.0) FMA, all pop
HbA1c
6.6
6.4
6.2
6
5.8
5.6
5.4
5.2
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25 to 44
45 to 65
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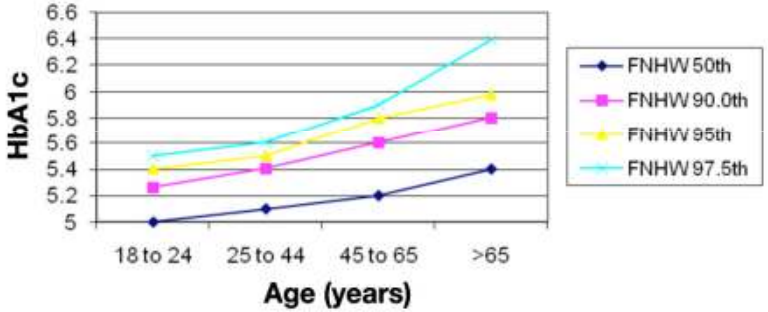
Age (years)
FMA 50th
FMA 90.0th
FMA 95th
FMA 97.5th

B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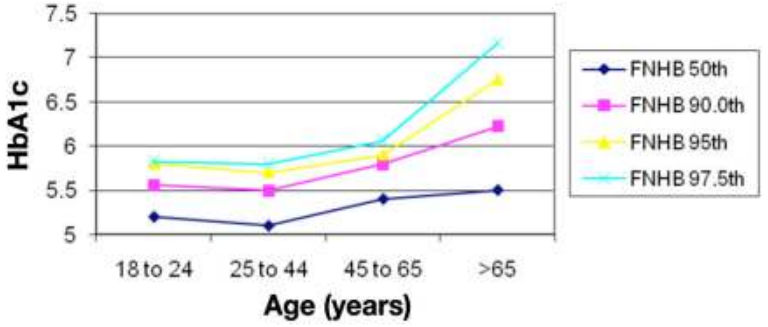
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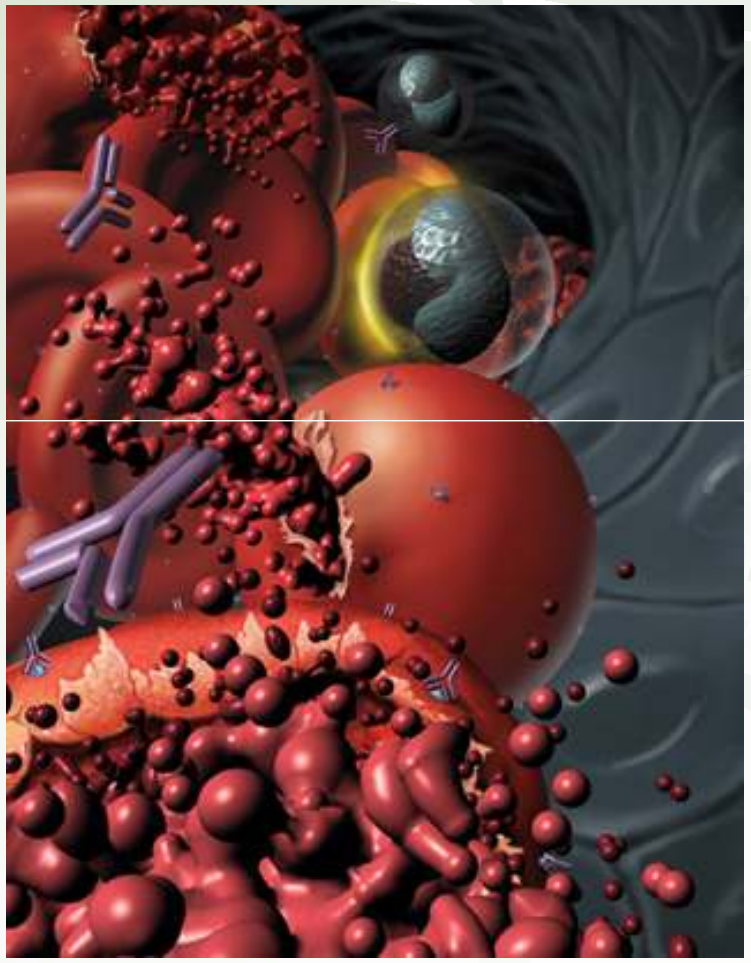
FNHB 95th
FNHB 97.5th

Any Condition that Changes Red Cell Turnover

hemolytic anemia
chronic malaria
major blood loss
blood transfusions



- Condition that shortens erythrocyte survival (hemolytic anemia, spherocytosis, pregnancy); proportionally decrease HbA_{1c} because hemoglobin in younger red cells has less time of exposure to glycemia.
- Bleeding and the resulting increased reticulocyte production: decreased the half-life of erythrocyte and will lower HbA_{1c}
- Any factor that prolong the erythyrocyte half life: increase the level of HbA_{1c} (i.e., splenectomy, aplastic anemia)
- Iron deficiency: rises in HbA_{1c} up to 2% that can be reversed with iron supplementation

Other conditions

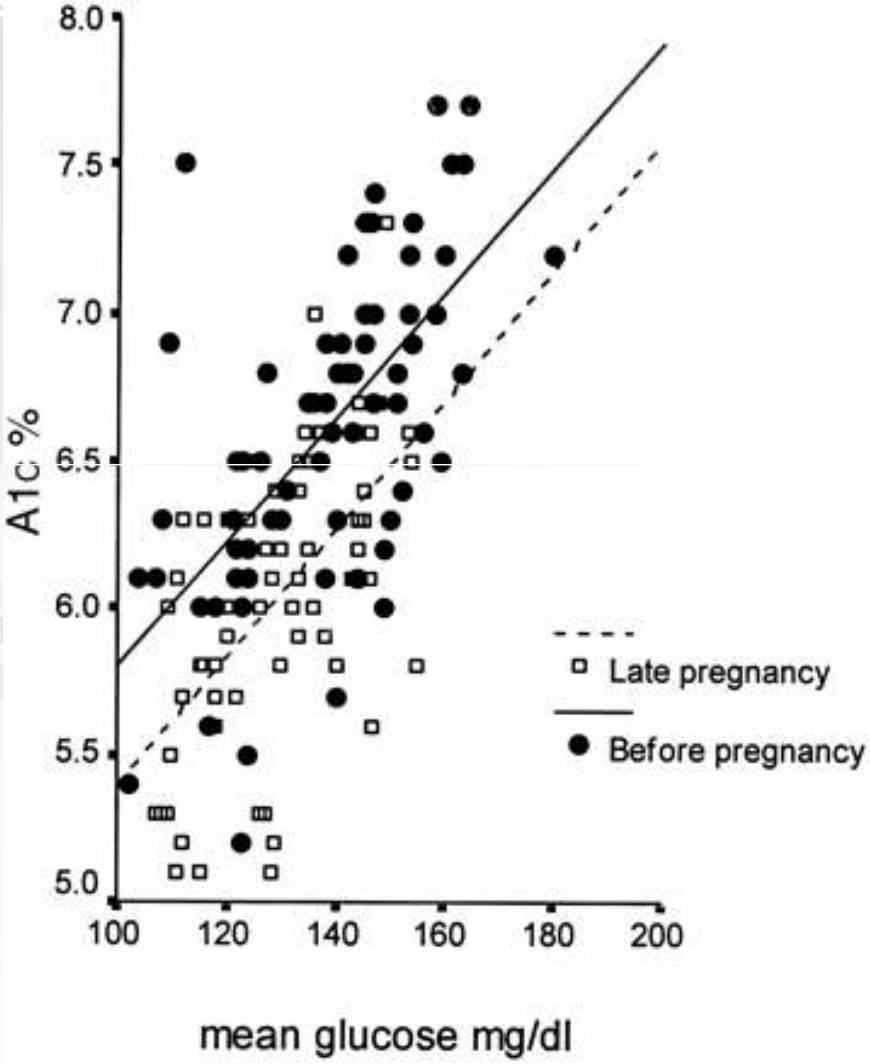
- rapidly evolving type 1 diabetes: diabetes should be diagnosable with typical symptoms and casual glucose levels ≥ 200 mg/dl

- effects of HIV therapy, renal failure, dapsone therapy, high dose salicylates, vitamin C, E, splenectomy and aplastic anemia

Pregnancy

- reduction in HbA_{1c} levels, perhaps as a function of hemodilution or increased erythrocyte turnover

- during late pregnancy, HbA_{1c} levels decrease by ~0.5% at every level of mean plasma glucose.



Diabetes Care. 2007, 30:1579-80

Underdiagnosis vs. Overdiagnosis

NHANES data

50-60% of patients with fasting plasma glucose ≥126 mg/dl had HbA_{1c} < 6.5%

- suggesting that HbA_{1c} might reduce the number of people diagnosed as having diabetes from that using current glycemic criteria.

HbA_{1c} will lead to overdiagnosis among the elderly, blacks, subject with iron deficiency, and individuals genetically predisposed to greater levels of hemoglobin glycation, whereas those with anemia, renal insufficiency, and many hemoglobinopathies, as well as those with other genetic variations, will be incorrectly told that they do not have diabetes.

Practical Issues related to HbA_{1c} Testing

- Testing be performed in a laboratory using a method that is NGSP certified, POC (point of care) instruments have not yet been shown to be sufficiently accurate or precise for diagnosing diabetes
- POC devices

  : biases ranged from approximately 0.9 to 0.4%.
- No POC device for measuring HbA_{1c} be used for the diagnosis of diabetes.

Point of Care

- May improve the glycemic control of people with diabetes by providing a rapid result if the performance of the instruments used is acceptable.

- Six of eight HbA_{1c} Point-of-Care instruments do not meet the general accepted analytical performance criteria

(Clinical Chemistry 56:1, 2010)

- Only two met the < 0.85% error criterion of the NGSP
- HbA_{1c} estimated with POC analyzers are not suitable for diagnosis of diabetes.

Advantage vs. Limitation

Advantage

- Better index of long-term complication
- Less biologic variability
- Low interindividual or intraindividual variability
- Less preanalytic instability
- No need for fasting
- Relatively unaffected by acute perturbation
- Currently used
- Standardization

Limitation

- Lack of universal threshold
- Absence of standardization network
- Low sensitivity of the HbA_{1c}
- Race
- Age
- Abnormal hemoglobin
- Change of RBC turnover
- Pregnancy
- Under/Over diagnosis

Thank You!