

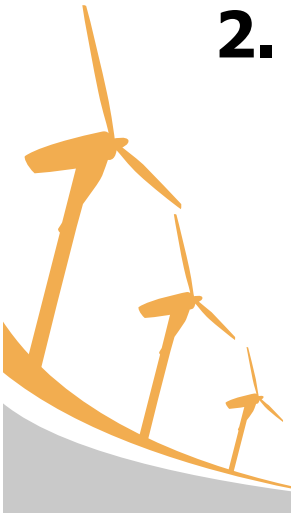


The Role of HbA1C Testing in Diagnosing Diabetes

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School of Medicine
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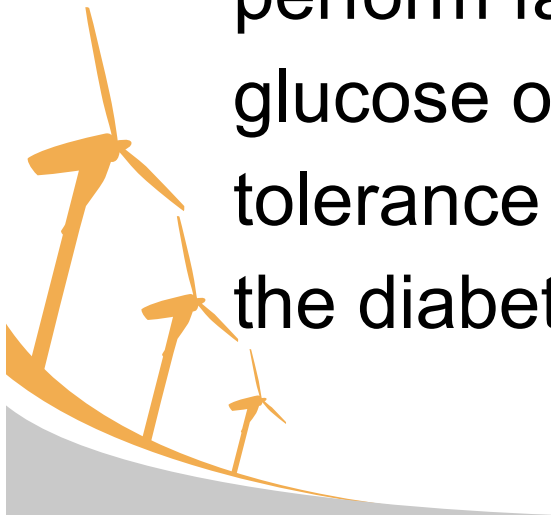
Contents

- 1. Overview of New Diagnostic Criteria of Diabetes – HbA1C**
- 2. The role of HbA1C testing in diagnosing diabetes in Korean adults**

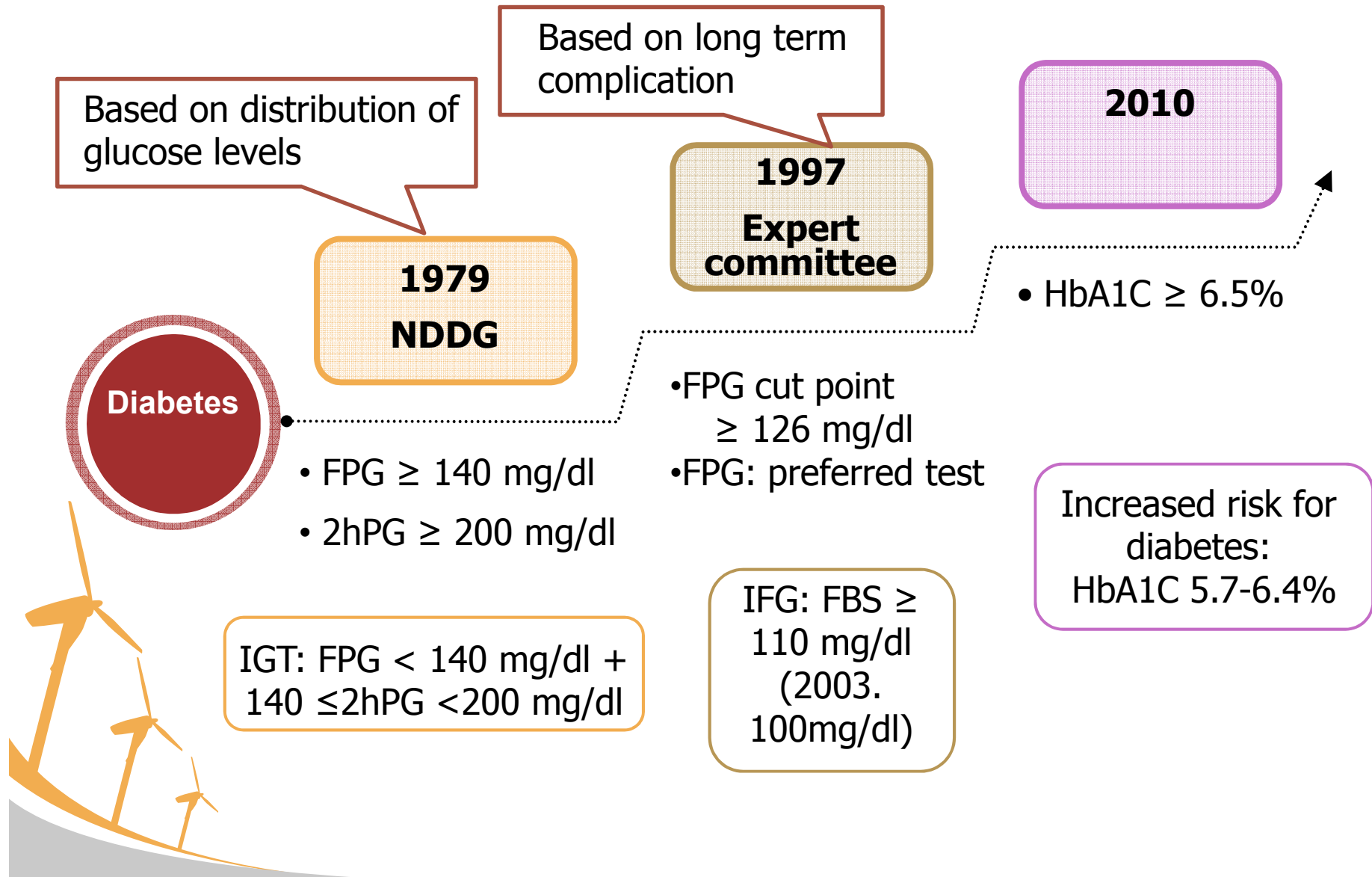


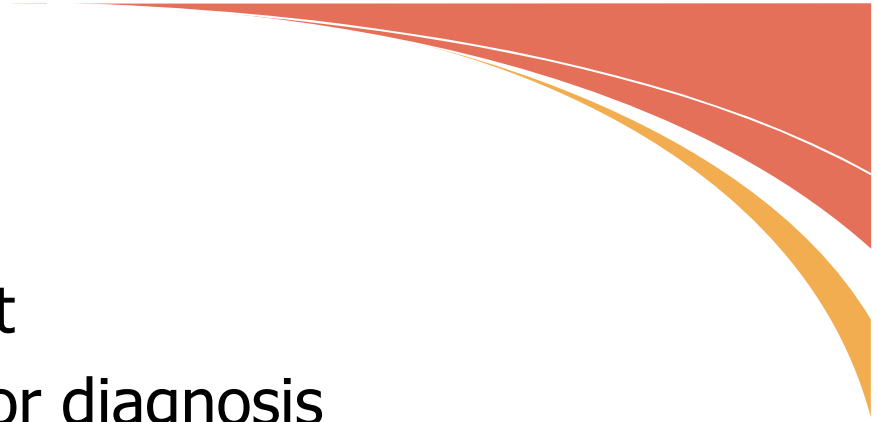
A Typical Patient Encounter

“So, Mrs. Lee, it looks like you do have diabetes. Your random blood sugar was 195 mg/dl, but you have to perform fasting blood glucose or oral glucose tolerance test to diagnose the diabetes.”



Diagnosis of Diabetes



- 
- 1997 expert committee report
 - against using A1C values for diagnosis
 - because of the lack of assay standardization
 - 2003 follow-up report
 - A1C not be used to diagnose diabetes
 - “What has changed” → “continued and further **standardization of the A1C assay**”





CAN THE HBA1C BE USED TO DIAGNOSE DIABETES?

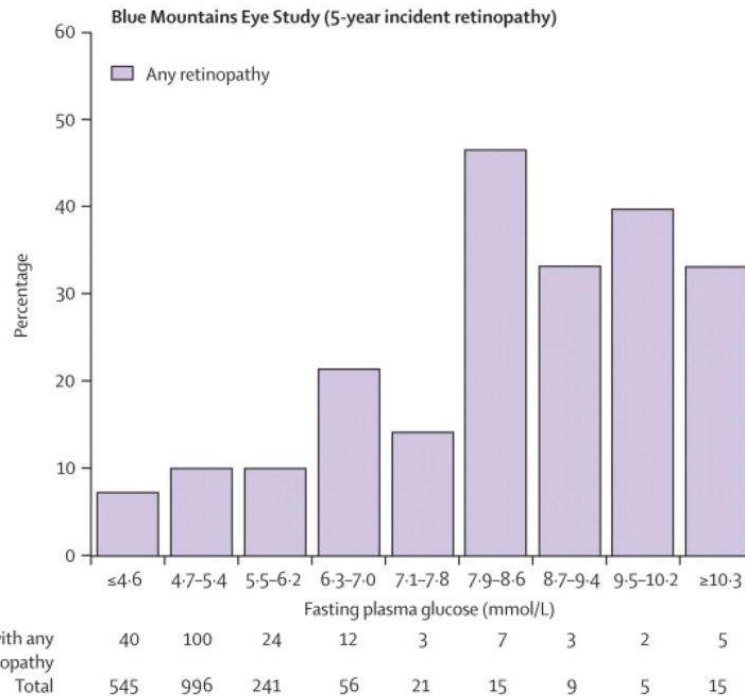


Longterm complication

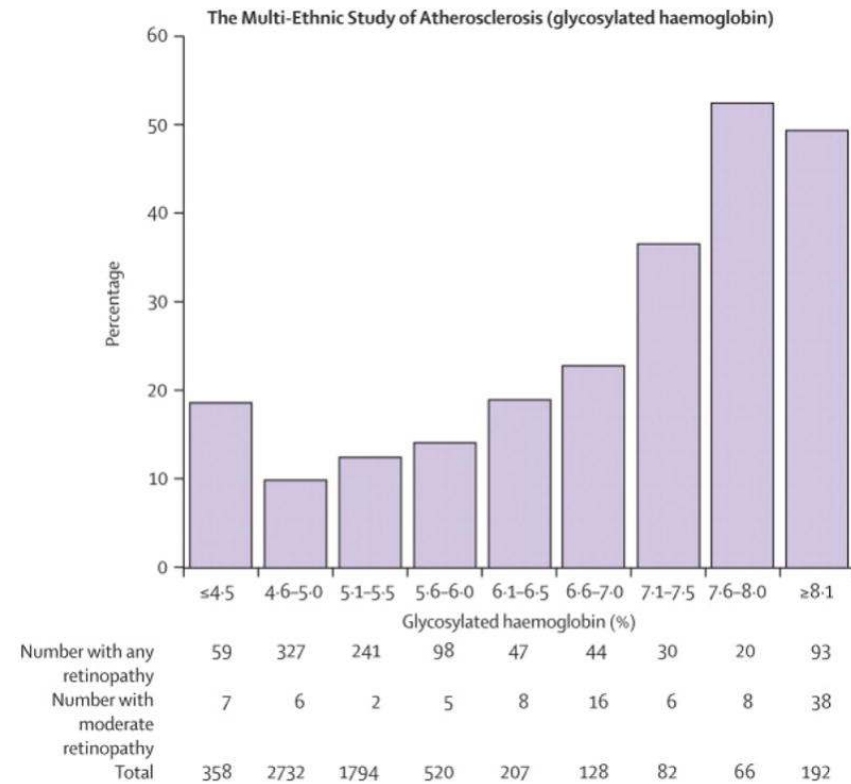
- Laboratory measures that capture long-term glycemic exposure : better marker of the disease than single measures of glucose concentration.
- Strong correlation between retinopathy and A1C but a less consistent relationship with fasting glucose level.



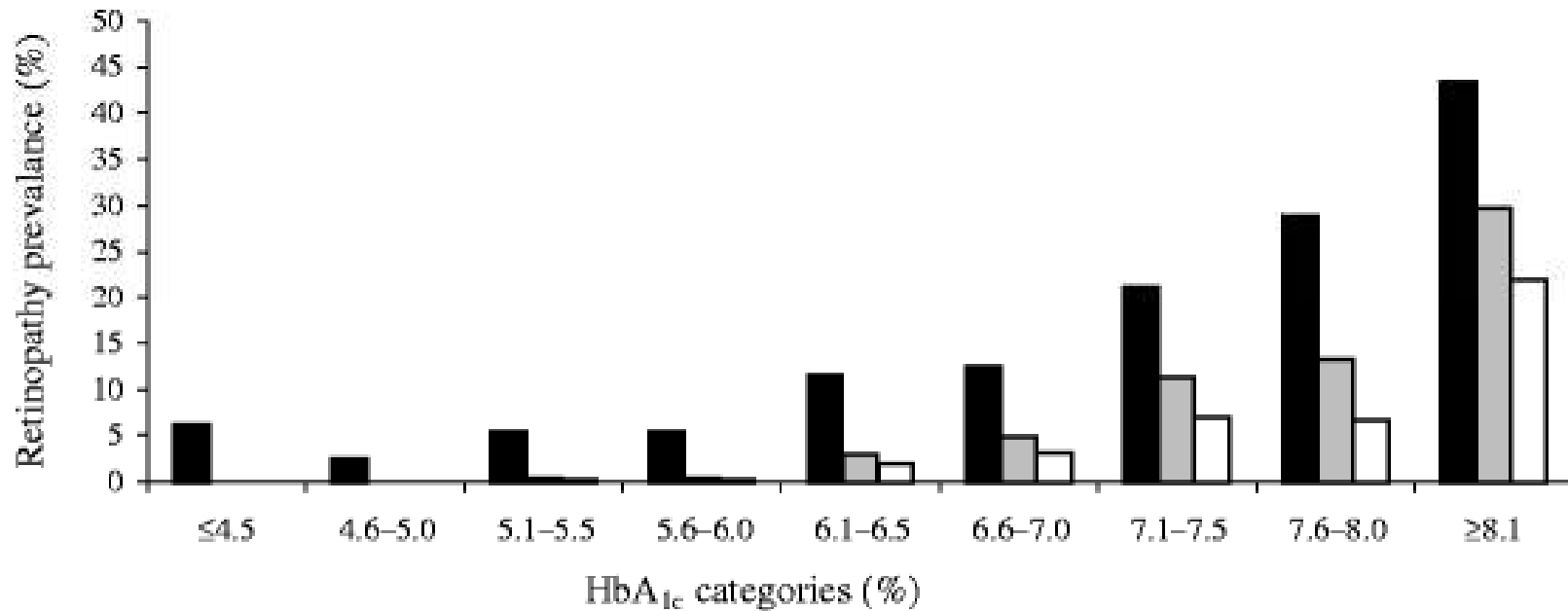
Relationship of retinopathy and FPG



Relationship of retinopathy and HbA1C

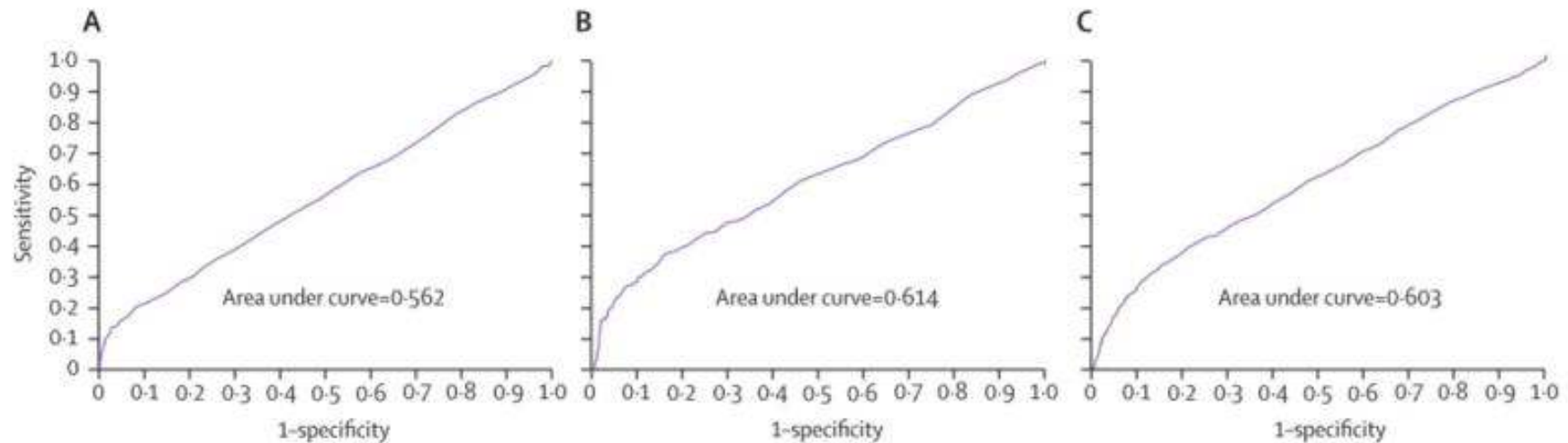


Relationship between HbA1c and any retinopathy (black), mild retinopathy (grey) and moderate retinopathy (white)



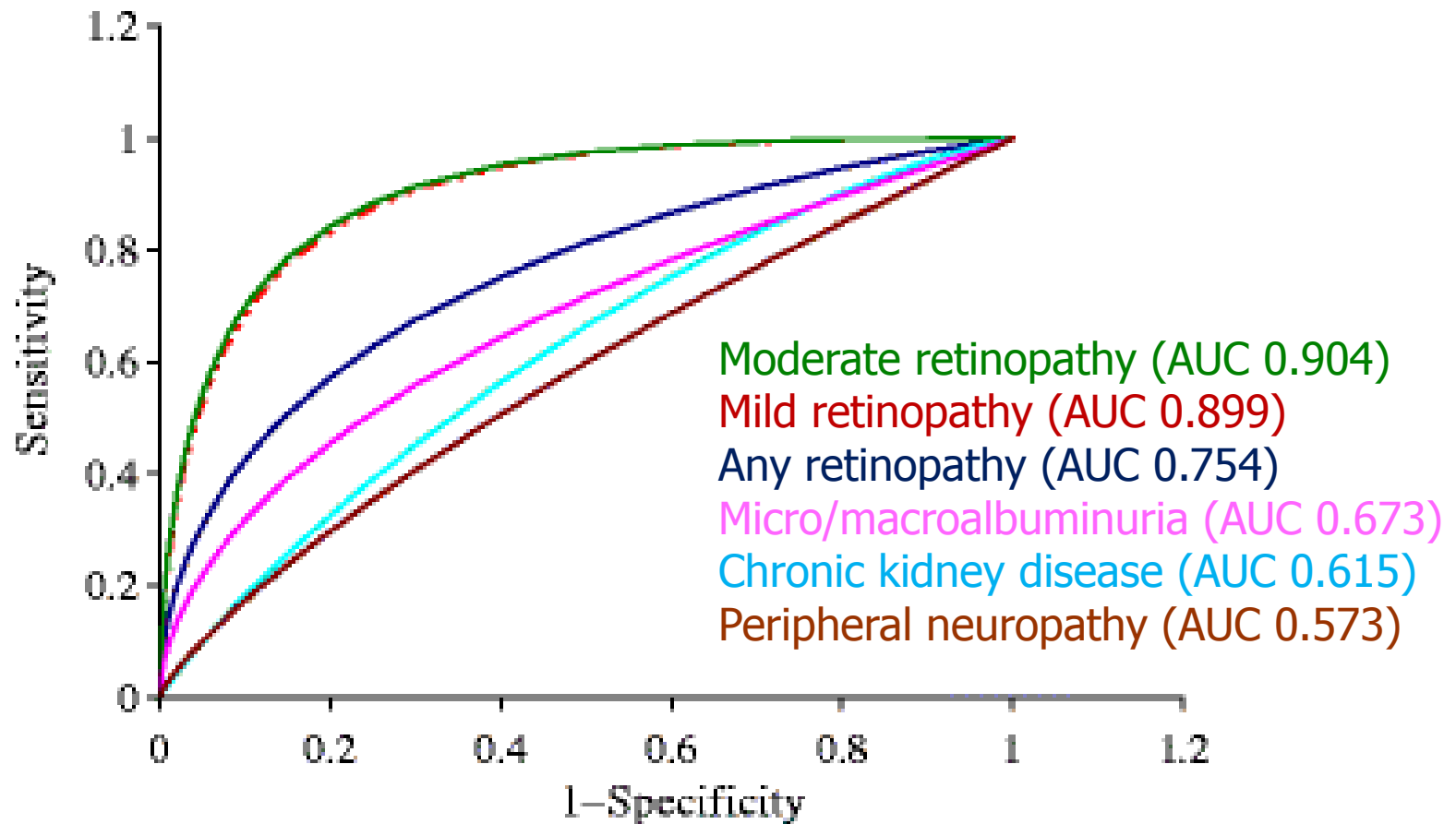
Any retinopathy	1	3	31	61	63	28	30	26	167
Mild retinopathy	0	0	2	5	16	11	16	12	115
Moderate retinopathy	0	0	1	3	11	7	10	6	85
No. at risk	16	118	566	1,104	543	225	142	90	386

ROC curves for FPG and Prevalent Retinopathy



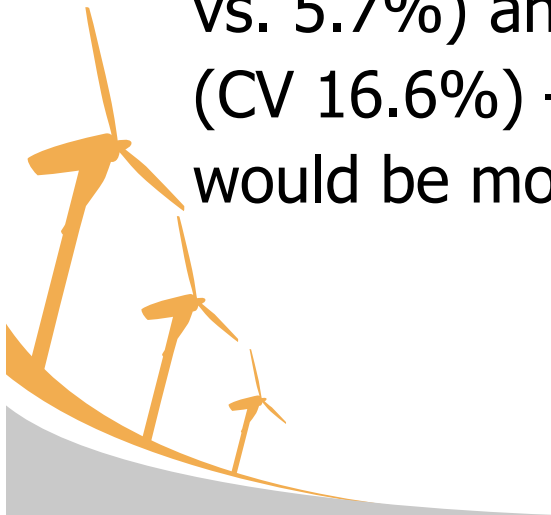
(A: Blue Mountains Eye Study, B: The AusDiab Study
C: The MESA Study)

ROC curves for HbA1c (%) and the various microvascular complications.



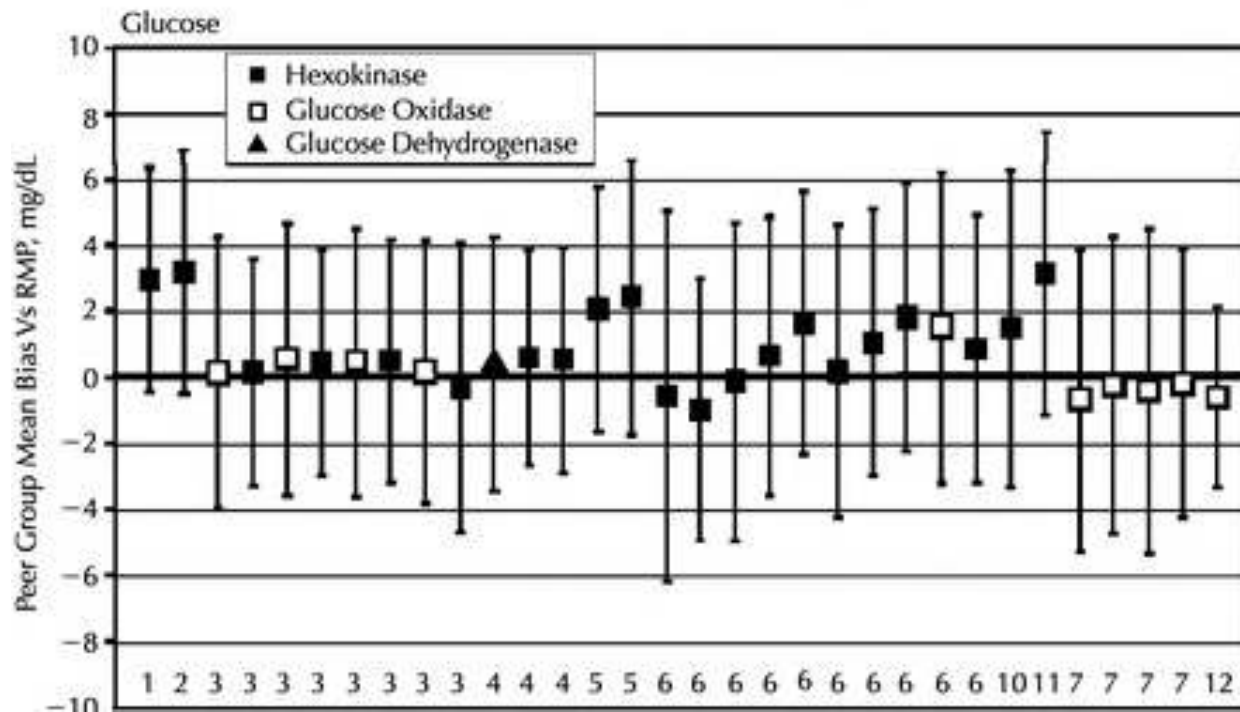
Accuracy

- laboratory measurements of glucose and A1C
: accuracy and precision of A1C assays at least match those of glucose assays.
- Biological variability of A1C 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 A1C.



The measurement of glucose itself is less accurate and precise than most clinicians realize!

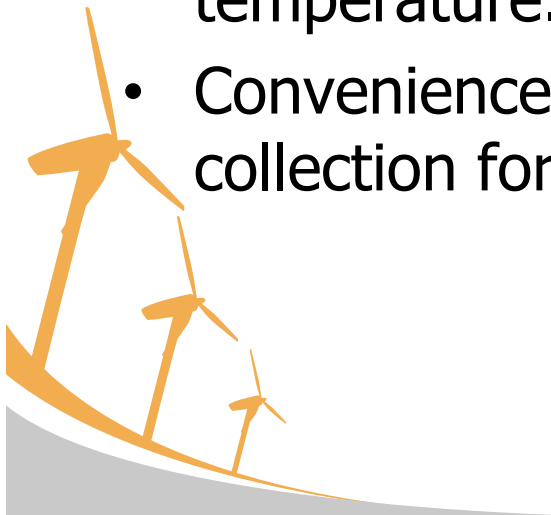
- 41% of instruments have a significant bias from the reference method that would result in potential misclassification of > 12% of patients.





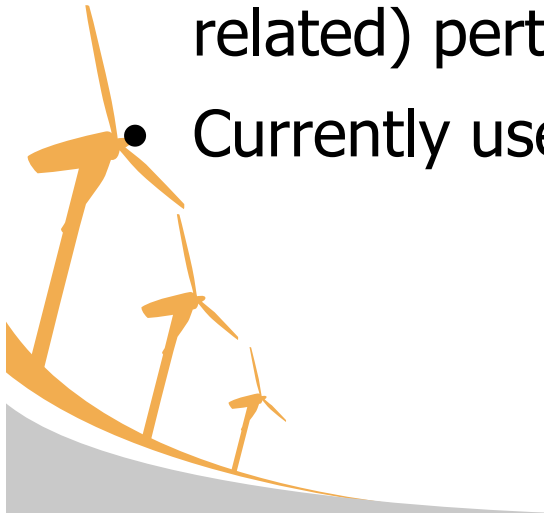
Stability of glucose vs. Relative stable HbA1C values

- Variability of HbA1C : less than that of FPG
day-to-day within-person variance of <math><2\%</math> for HbA1C
but 12-15% for FPG.
- Potential preanalytic errors owing to sample handling
and lability of glucose in the collection tube at room
temperature.
- Convenience for the patient and ease of sample
collection for A1C



Advantages of A1C testing compared with FPG or 2hPG for the diagnosis of diabetes

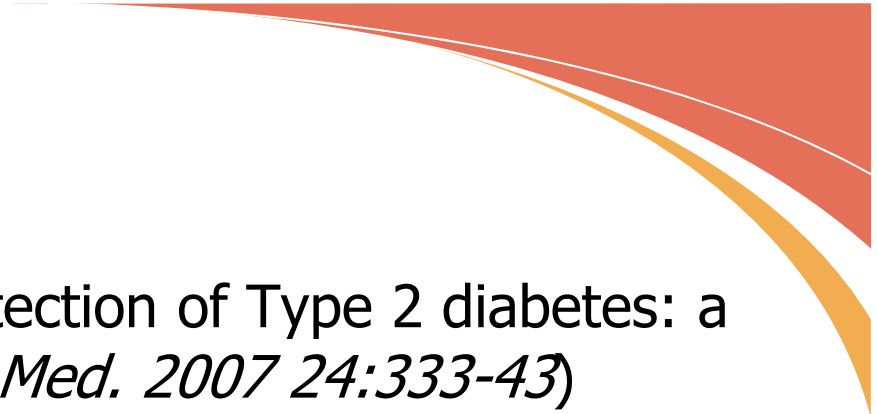
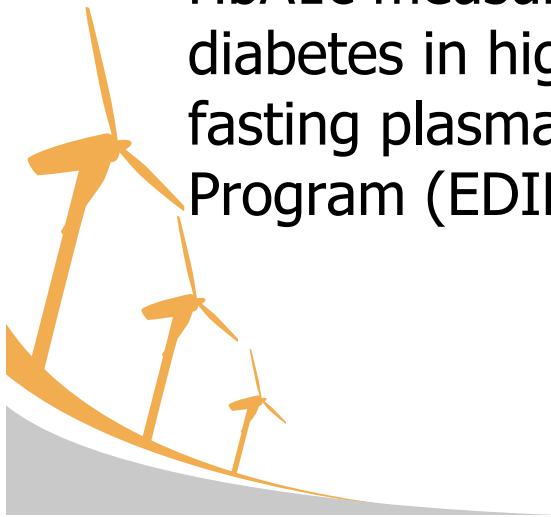
- Better index of overall glycemic exposure and risk for long-term complications
- Substantially less biologic variability
- Substantially less preanalytic instability
- No need for fasting or timed samples
- Relatively unaffected by acute (e.g. stress or illness related) perturbations in glucose levels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



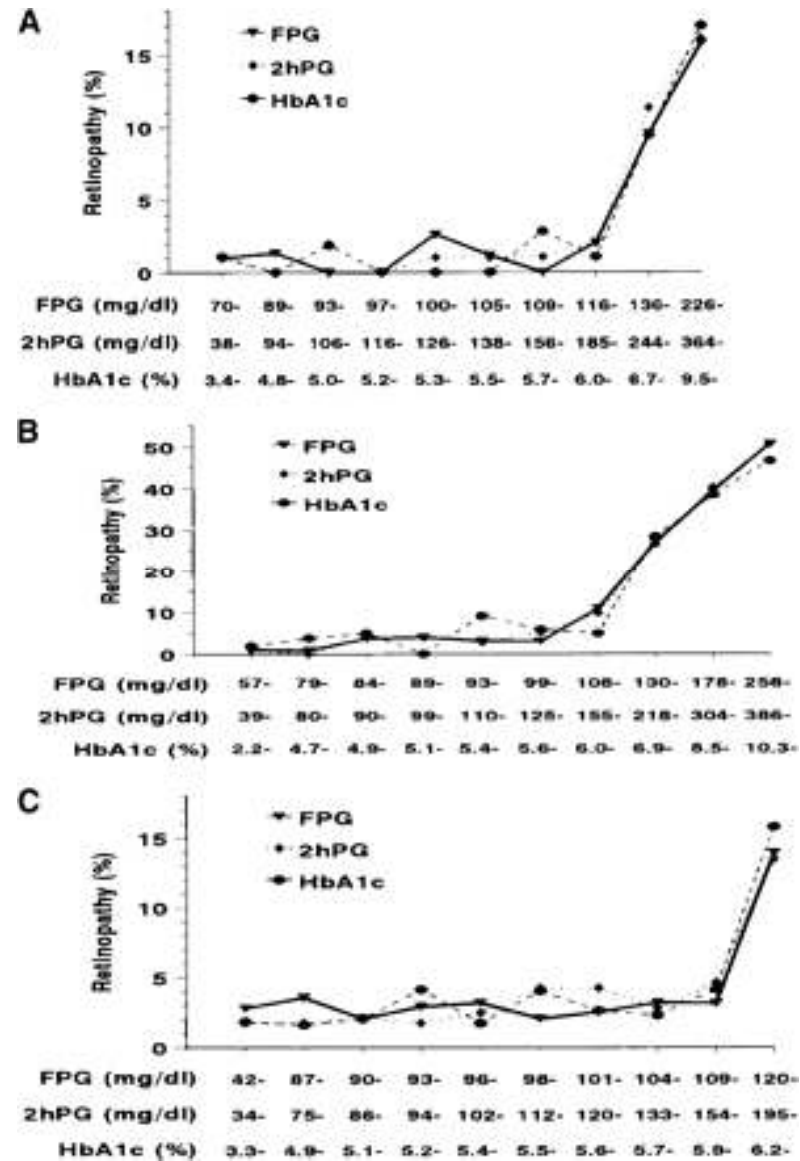


**WHAT IS THE MOST APPROPRIATE A1C
CUT POINT FOR THE DIAGNOSIS OF
DIABETES?**



- 
- HbA1C as a screening tool for detection of Type 2 diabetes: a systematic review: **6.1%** (*Diabet Med. 2007 24:333-43*)
 - Correlation among fasting plasma glucose, two-hour plasma glucose levels in OGTT and HbA1c. : **6.1%** (*Diabetes Res Clin Pract. 2000 50:225-30*)
 - Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke: **6.2%** (*Age Ageing. 2004 33:71-7*)
 - HbA1c measurement improves the detection of type 2 diabetes in high-risk individuals with nondiagnostic levels of fasting plasma glucose: the Early Diabetes Intervention Program (EDIP) : **6.1%** (*Diabetes Care. 2001 24:465-71*)
- 

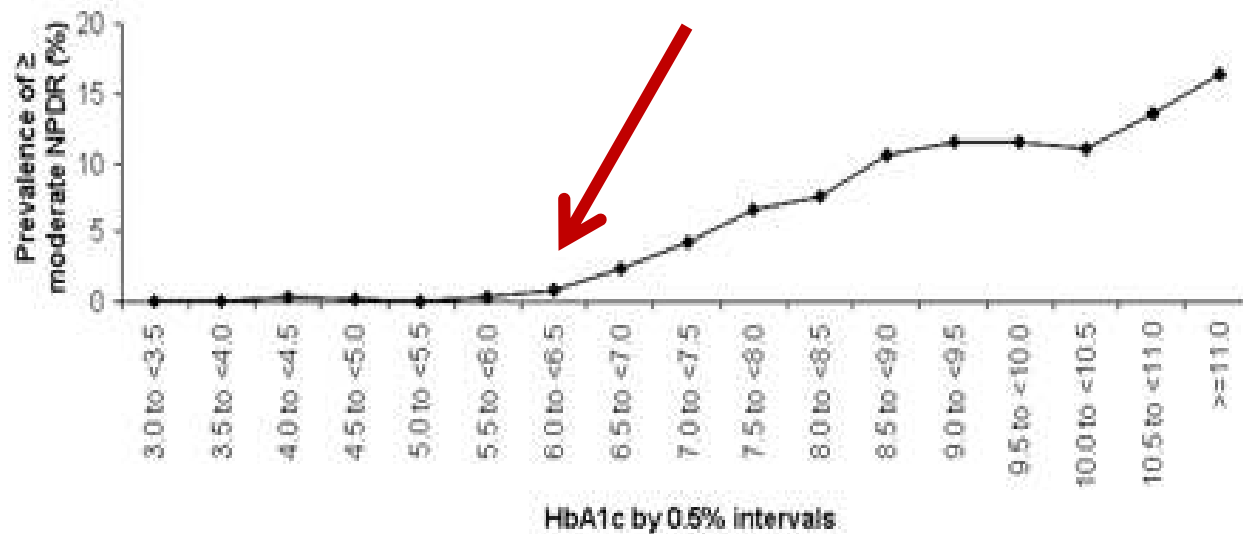
'97 committee report:
prevalence of
retinopathy increase
substantially at **A1C**
between 6.0 and 7.0%.



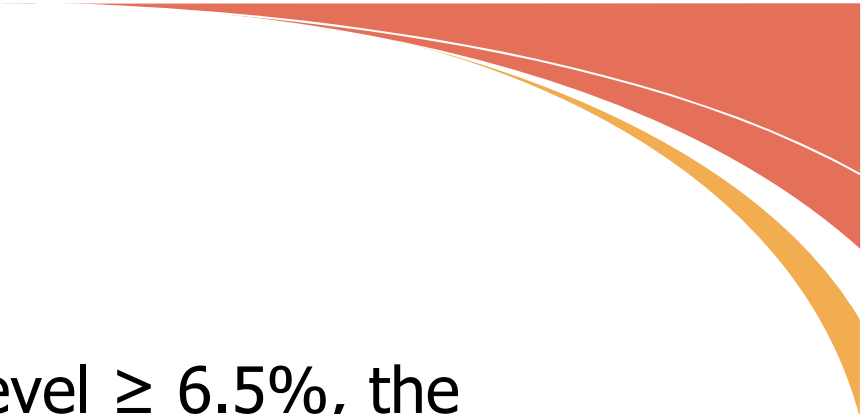
International Expert Committee, Diabetes care. 1997



DETECT-2 + '97 report (~28,000 subjects from 9 countries)
the prevalence of "moderate retinopathy"
begins to rise at 6.5%



International Expert Committee, Diabetes care. 2009

- 
- In selecting a diagnostic A1C level $\geq 6.5\%$, the international Expert Committee balanced the stigma and costs of mistakenly identifying individuals as diabetic against the minimal clinical consequences of delaying the diagnosis in someone with an A1C level $< 6.5\%$
 - Emphasize specificity rather than sensitivity





LIMITATIONS OF A1C AS THE RECOMMENDED MEANS OF DIAGNOSING DIABETES



Some

HbS, Hb

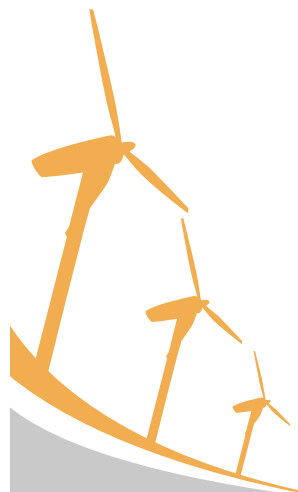
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presen

- affi

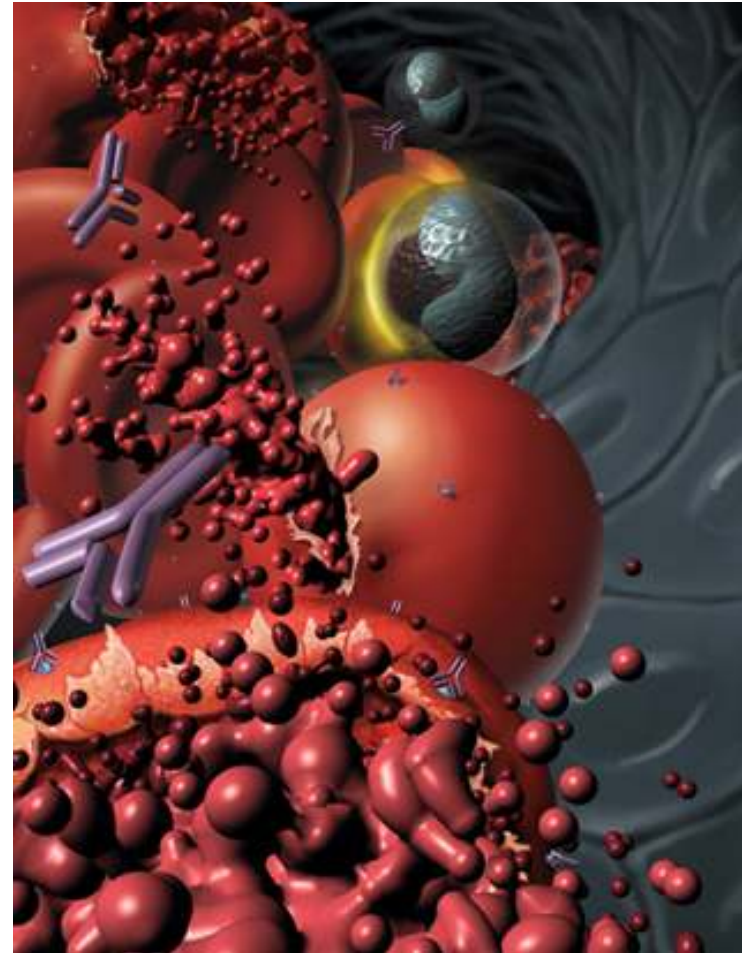
traits

Method	Interference from			
	HbAS	HbAC	HbAE	HbAD
Abbott Architect/Aeroset	Yes	Yes	-	-
Axis-Shield Afinion	No	No	No	No
Bayer (Metrika) A1cNOW	Yes	Yes	No	No
Beckman Synchron System	No	No	No	No
Bio-Rad D-10	No	No	No	No
Bio-Rad Variant A1c	No	No	No	Yes
Bio-Rad Variant II A1c	No	No	No	No
Bio-Rad Variant II Turbo A1c	No	No	Yes	Yes
Dade Dimension	No	No	No	No
Olympus AU system	Yes	Yes	No	No
Ortho-Clinical Vitros	No	No	No	No
Primus HPLC (affinity)	No	No	No	No
Roche Cobas Integra Gen.2	No	No	No	No
Roche/Hitachi (Tina Quant II)	No	No	No	No
Siemens (Bayer) Advia HbA1c # (original version)	Yes	Yes	-	-
Siemens (Bayer) Advia A1c (new version)	No	No	-	-
Siemens (Bayer) DCA 2000	No	No	-	-
Tosoh A1c 2.2 Plus	No	No	Yes	No
Tosoh G7	No	No	Yes	No
Tosoh G8	No	No	-	-



Any Condition that Changes Red Cell Turnover

hemolytic anemia
chronic malaria
major blood loss
blood transfusions

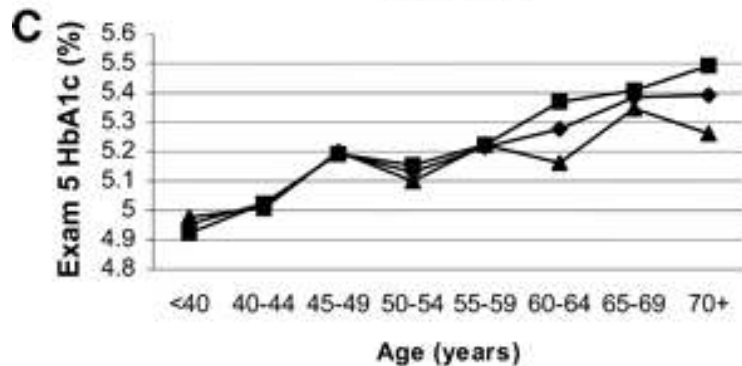
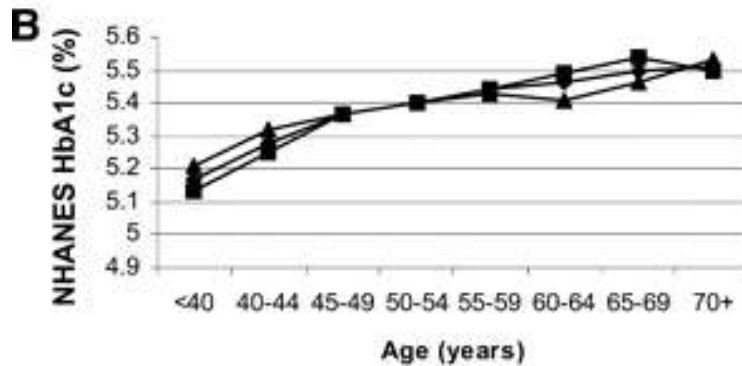
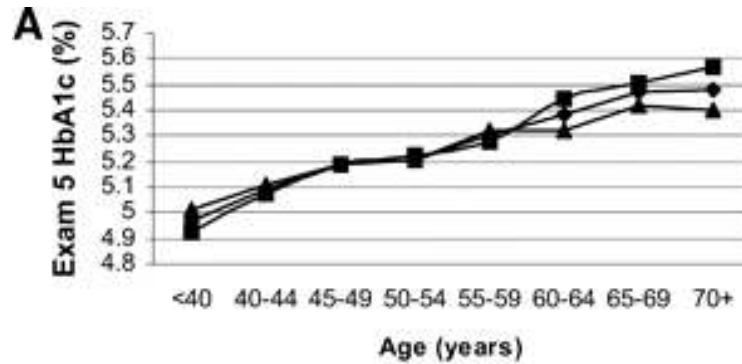


Age

A1C 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



Effect of **Aging** on HbA1C levels in Individuals without Diabetes

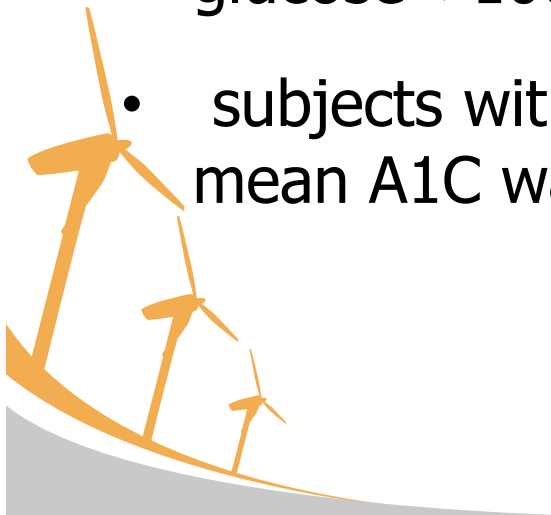


- ◆ all
- women
- ▲ men



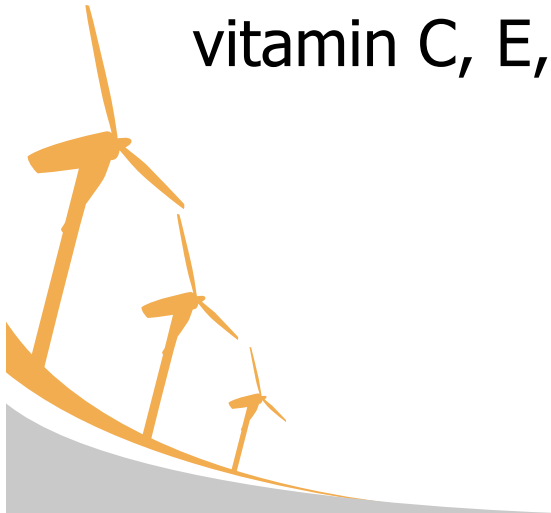
Race

- racial disparities in A1C: 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.



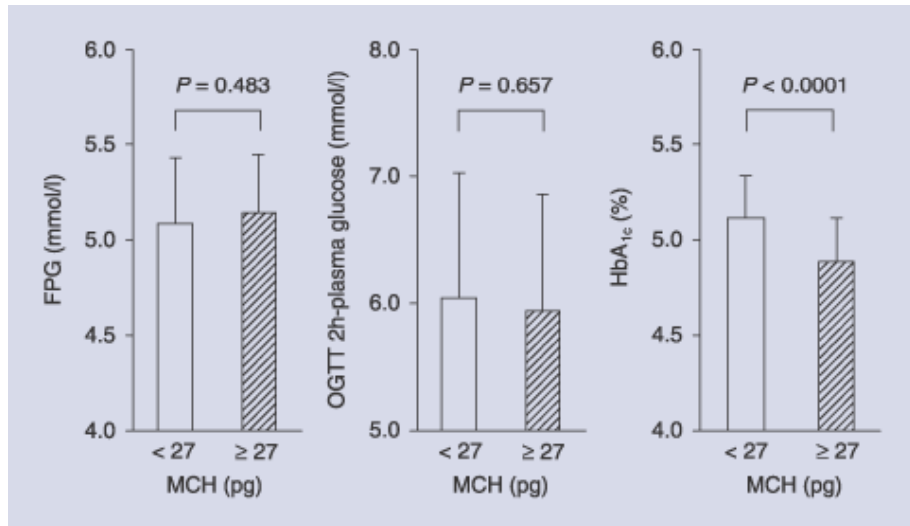
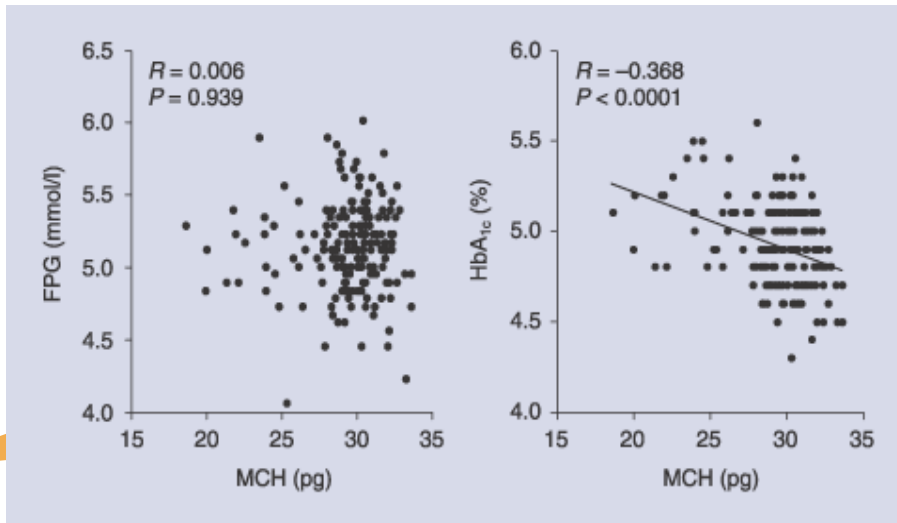
Other conditions

- rapidly evolving type 1 diabetes: diabetes should be diagnosable with typical symptoms and casual glucose levels ≥ 200 mg/dl
- Iron deficiency anemia, effects of HIV therapy, renal failure, dapsons therapy, high dose salicylates, vitamin C, E, splenectomy and aplastic anemia



Iron deficiency anemia

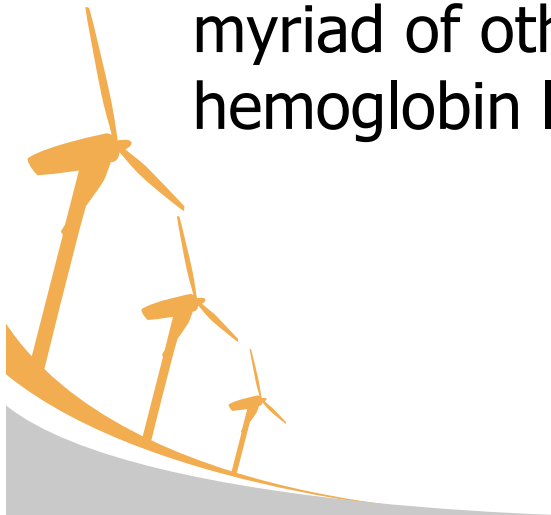
: increase in HbA1C by 1-1.5%
that subsequently falls following iron treatment.



Diabet Med. 2007 24:843-7

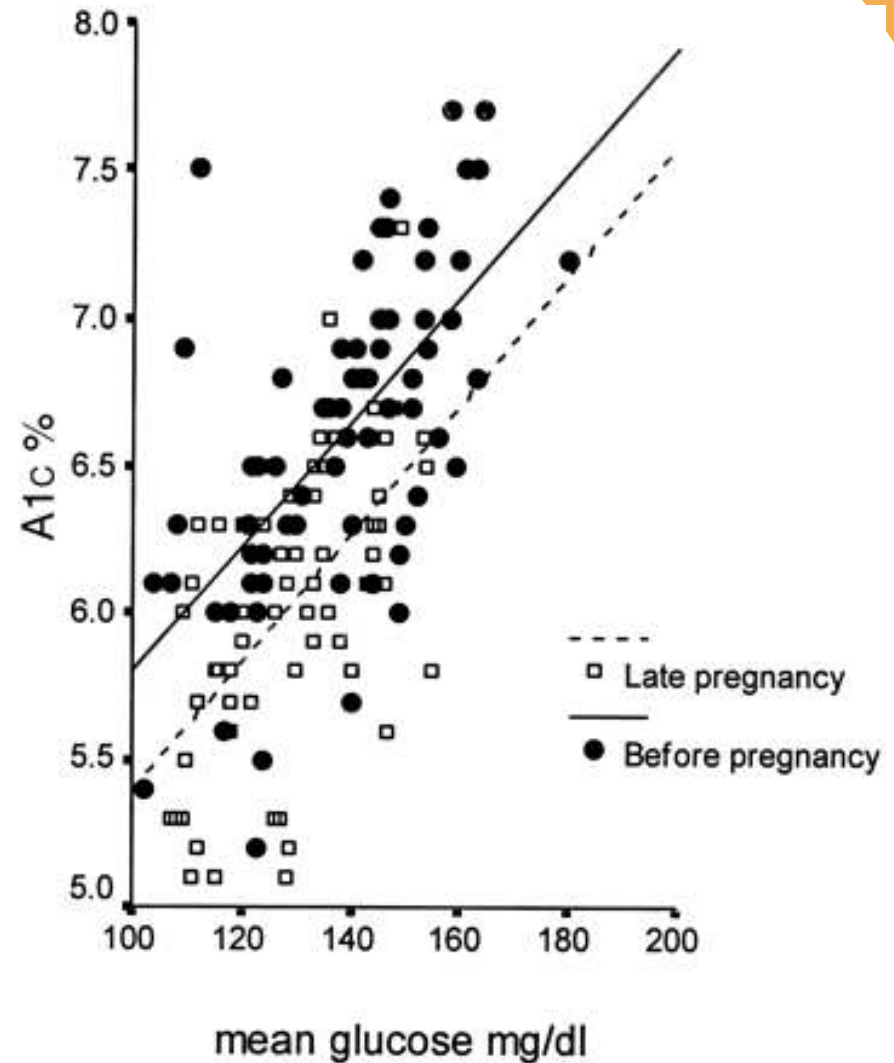
Discrepancies between HbA1C and glucose levels

- HbA1C represents glycation of hemoglobin, localized to a specific biologic compartment, the erythrocyte cytoplasm, which is potentially rather different from the entire glucose distribution volume.
- Erythrocyte turnover, cell membrane permeability to glucose, hemoglobin glycation and deglycation, and a myriad of other processes will change glycated hemoglobin levels.



Pregnancy

- reduction in HbA1C levels, perhaps as a function of hemodilution or increased erythrocyte turnover
- during late pregnancy, A1C levels decrease by $\sim 0.5\%$ at every level of mean plasma glucose.



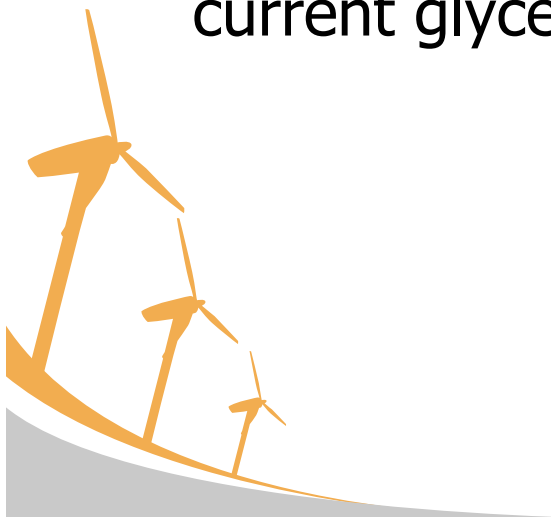
Diabetes Care. 2007, 30:1579-80


Underdiagnosis v. Overdiagnosis

NHANES data

50-60% of patients with fasting plasma glucose ≥ 126 mg/dl had HbA1C $< 6.5\%$

- suggesting that HbA1C might reduce the number of people diagnosed as having diabetes from that using current glycemic criteria.



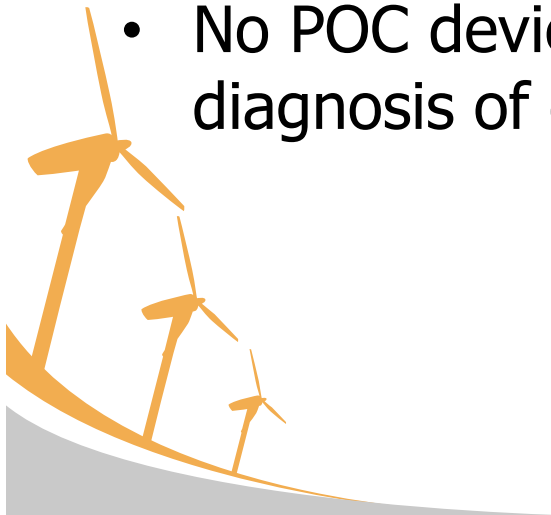


HbA1C will lead to overdiagnosis among the elderly, blacks, subject with iron deficiency, and individuals genetically predisposed to greater levels of hemoglobin glycation, whereas those with anemia, renal insufficiency, and many hemoglobinopathies, as well as those with other genetic variations, will be incorrectly told that they do not have diabetes.

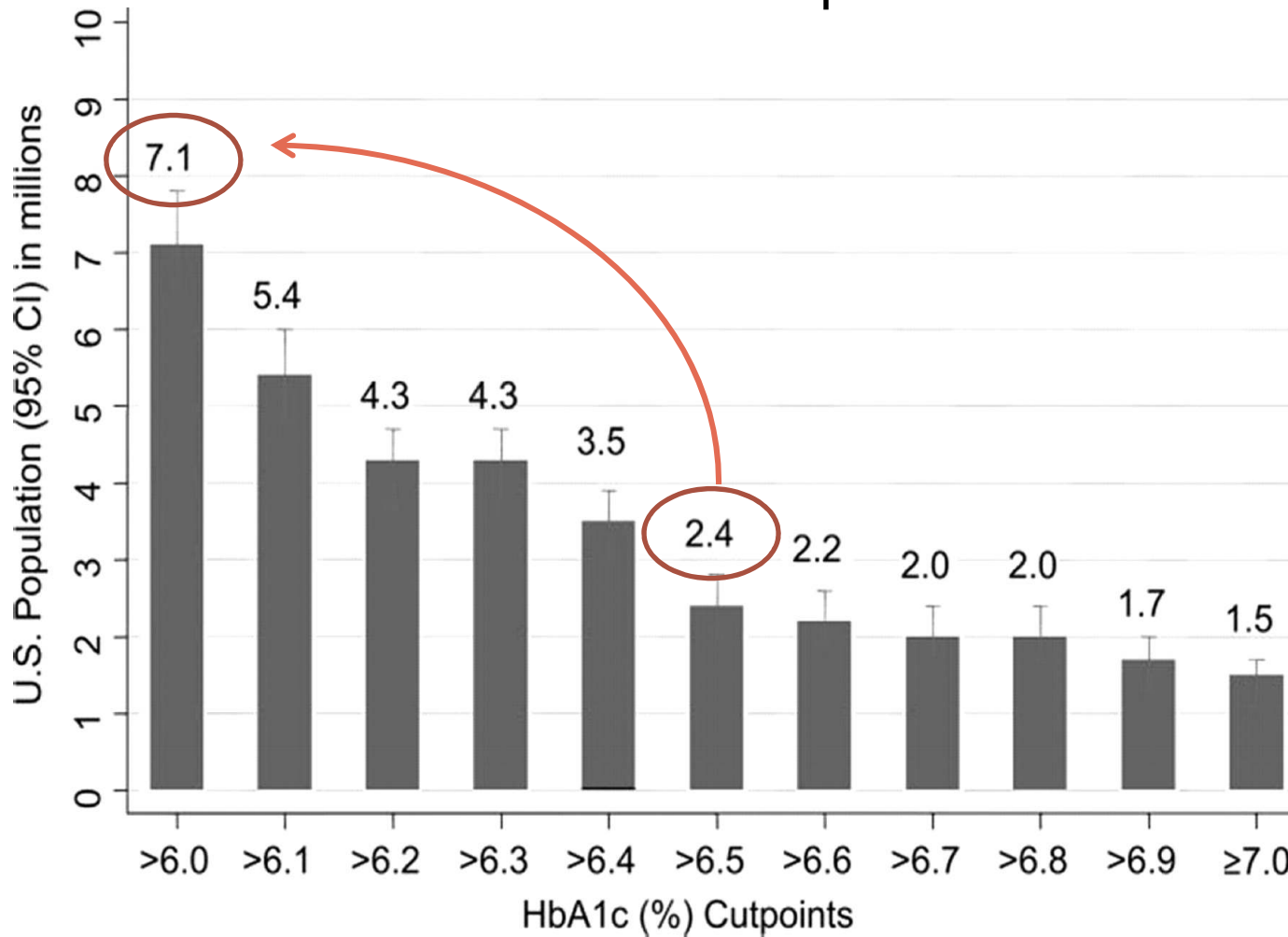


Practical Issues related to A1C Testing

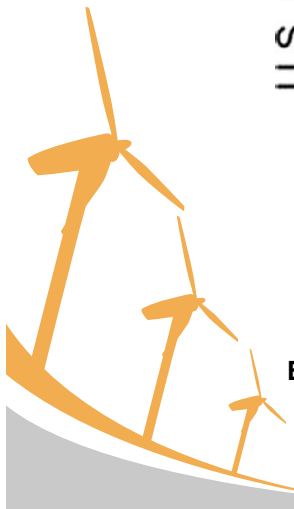
- Testing be performed in a laboratory using a method that is NGSP certified, POC (point of care) instruments have not yet been shown to be sufficiently accurate or precise for diagnosing diabetes
- POC devices
: biases ranged from approximately 0.9 to 0.4%.
- No POC device for measuring HbA1C be used for the diagnosis of diabetes.



Distribution of estimated numbers of persons without a history of diabetes in the US 2000 Census population (age ≥ 20 years) at different HbA1C cutpoints



Bruns, D. E. et al. Clin Chem 2010;56:4-6



Criteria for the diagnosis of diabetes

2010 ADA Recommendation

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

OR

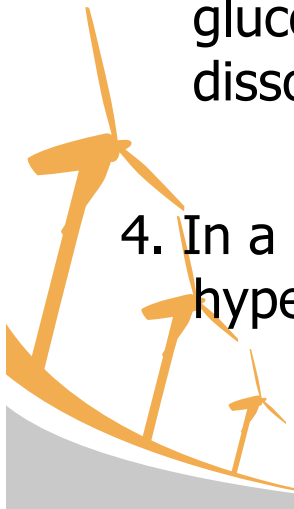
2. FPG \geq 126 mg/dl. Fasting is defined as no caloric intake for at least 8h.

OR

3. 2-h plasma glucose \geq 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 \geq 200 mg/dl

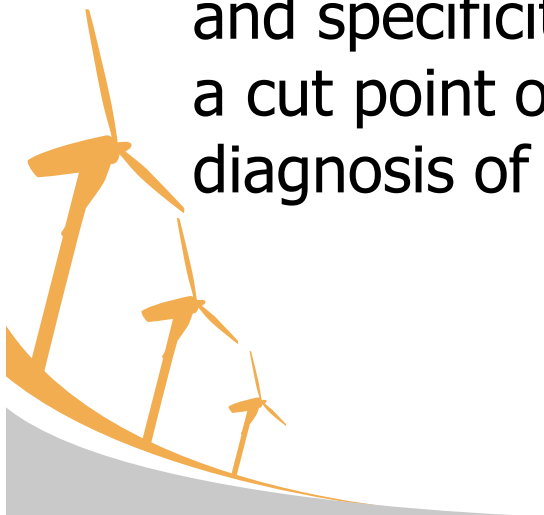


2010 studies

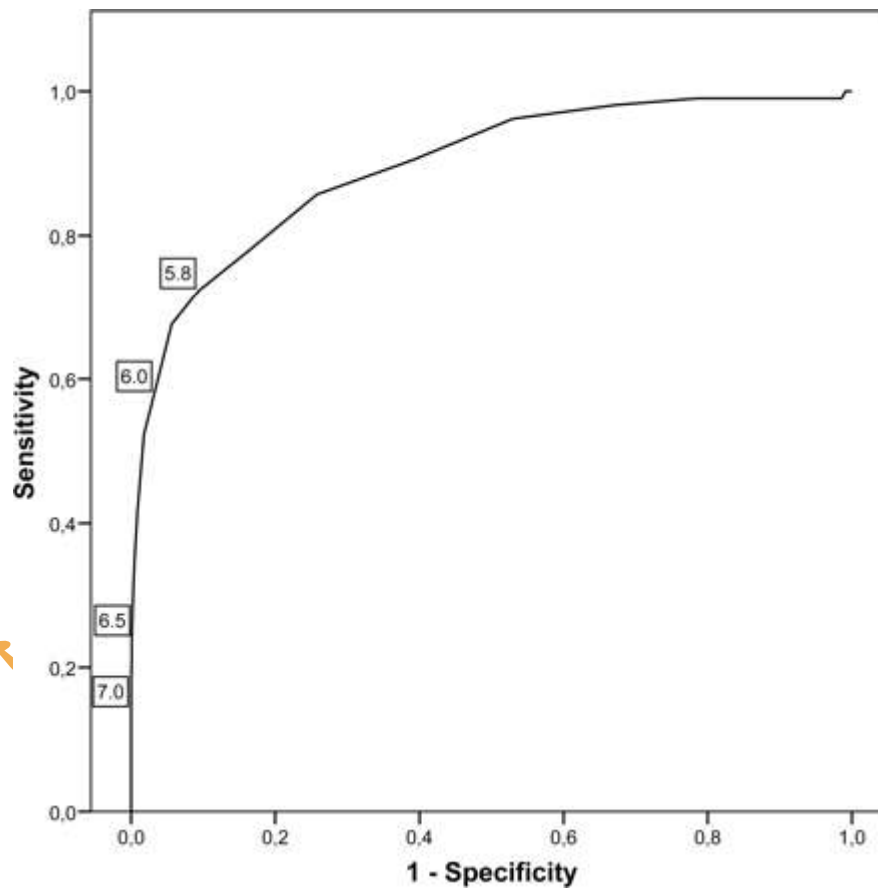


- Utility of Glycated hemoglobin in diagnosing type 2 diabetes mellitus: a community-based study.
: HbA1C cut point of **6.1%** has an optimal sensitivity and specificity and can be used as a screening test, and a cut point of **6.5%** has optimal specificity of 88% for diagnosis of diabetes.

(J Clin Endocrino Metab 2010, e-published)



Relationship Between A1C and Glucose Levels in the General Dutch Population The New Hoorn Study

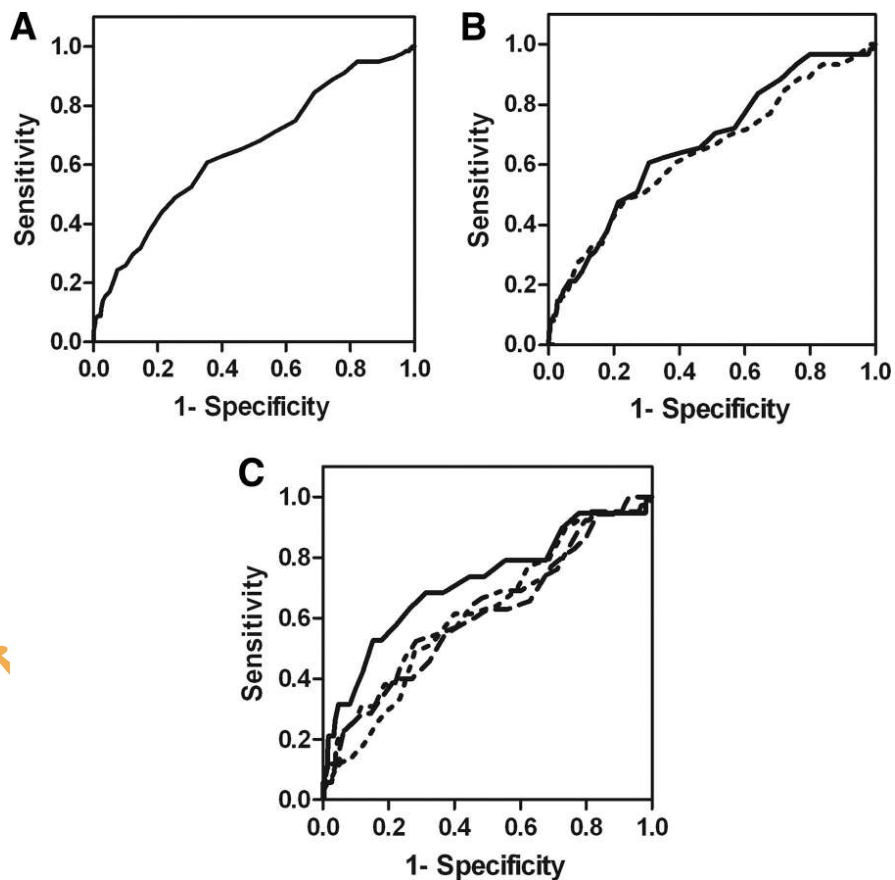


An A1C level of \geq **5.8%** had highest combination of sensitivity (72%) and specificity (91%) for identifying newly diagnosed diabetes.



Diabetes Care

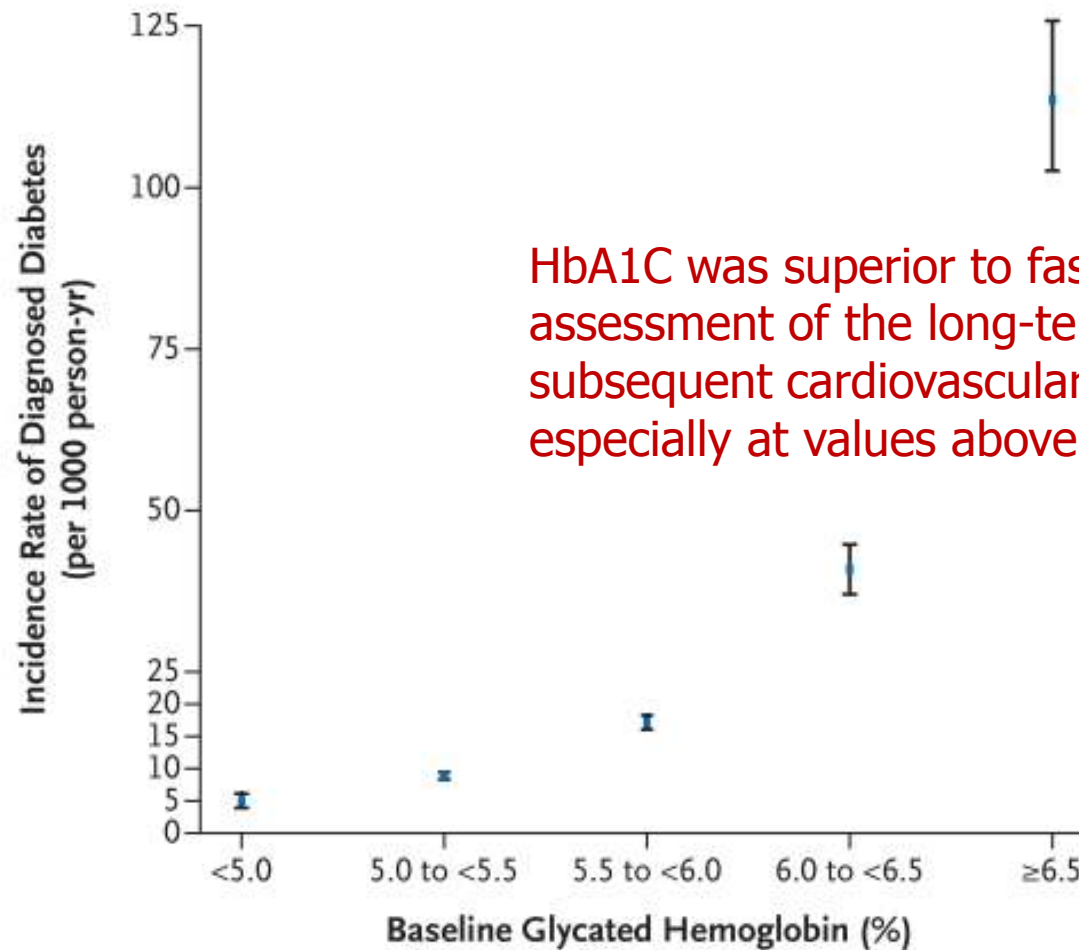
A1C and Diabetes Diagnosis: The Rancho Bernardo Study



The A1C cut point of **6.15%** yielded the highest combination of sensitivity (63%) and specificity (60%).

ORIGINAL ARTICLE

Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults



HbA1C was superior to fasting glucose for assessment of the long-term risk of subsequent cardiovascular disease, especially at values above 6.0%

Brief report

New diagnosis criteria for diabetes with hemoglobin A1c and risks of macro-vascular complications in an urban Japanese cohort: The Suita Study

Incident rates and adjusted HRs with 95% CIs for cardiovascular diseases by HbA1c levels in a cohort study of the Japanese men and women, 1989–2005.

HbA1c levels	N	Number of events	Person-years	Crude incidence rates (per 1000 person-years)	Age-adjusted		Multivariate-adjusted ^a	
					HRs	95%CIs	HRs	95%CIs
All cardiovascular diseases								
≤5.9	1451	54	18627	2.9	1	(reference)	1	(reference)
6.0–6.4	108	9	1289	7.0	1.5	(0.7–3.0)	1.2	(0.6–2.5)
≥6.5	48	7	479	14.6	3.5	(1.6–7.7)	3.0	(1.2–7.4)
					Trend $P = 0.003$		Trend $P = 0.04$	

(*Diabetes Res and Clin Pract*, 2010)



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/m²)

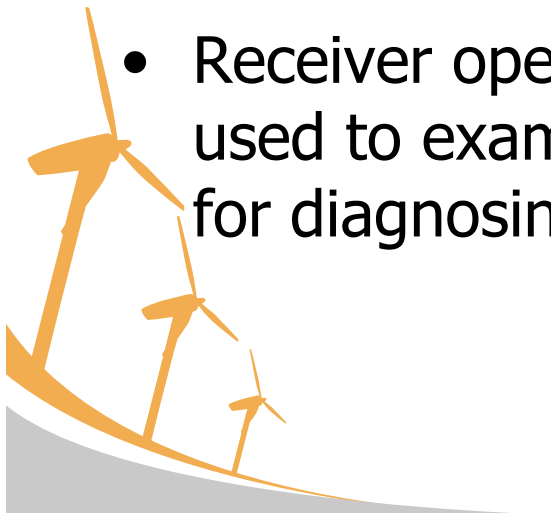
without a self-reported history of diabetes

from 8 university hospitals in 2009



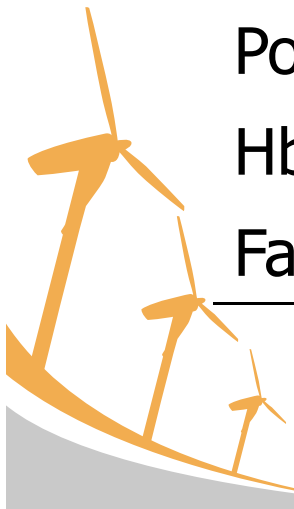
Method

- 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.

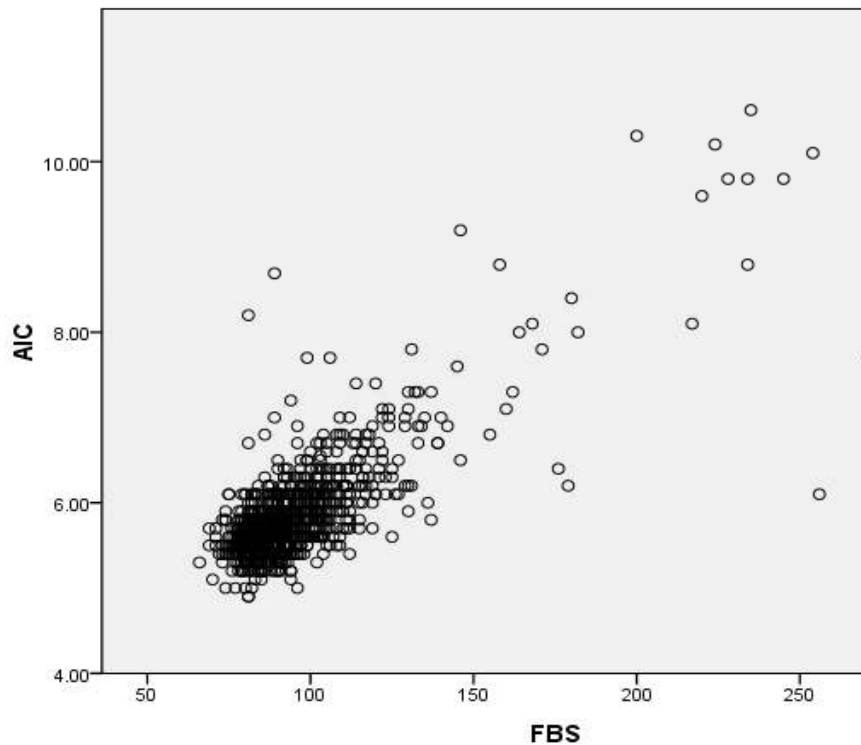


Clinical characteristics of subjects

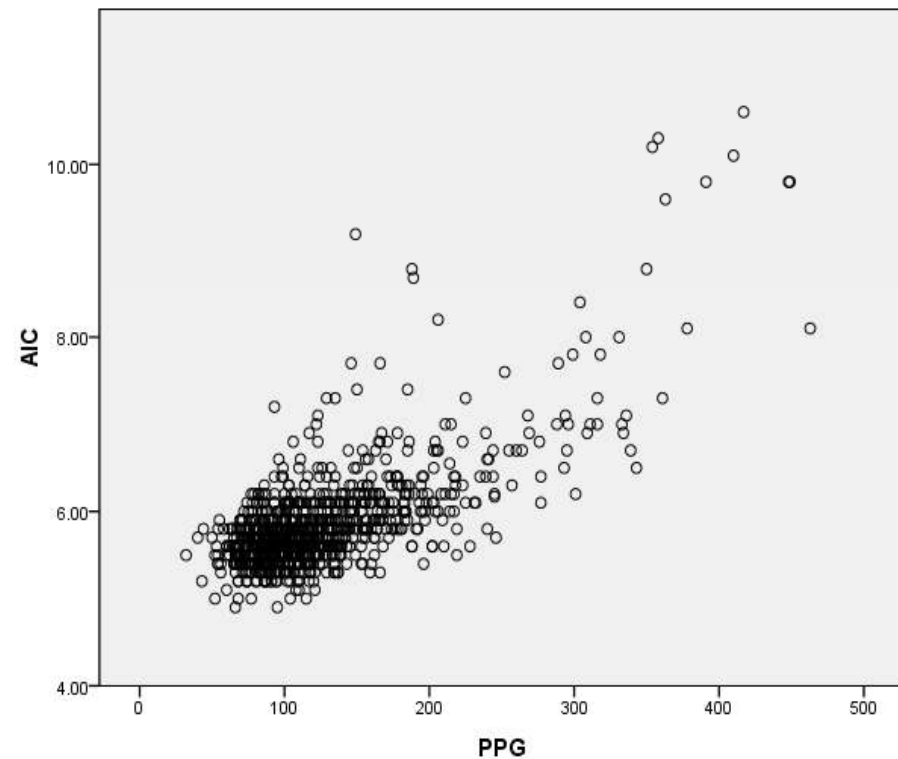
Age (years)	41 ± 14
Sex (male/female)	203/ 793
BMI (kg/m ²)	23.1 ± 3.5
Systolic BP (mmHg)	115 ± 14
Diastolic BP (mmHg)	73 ± 9
Fasting glucose (mg/dl)	95 ± 21
Post 2hr glucose (mg/dl)	125 ± 58
HbA1C (%)	5.9 ± 0.6
Family history of diabetes (yes/no)	237/ 759



Scatter plots of FPG and 2h postload glucose in relation to A1C



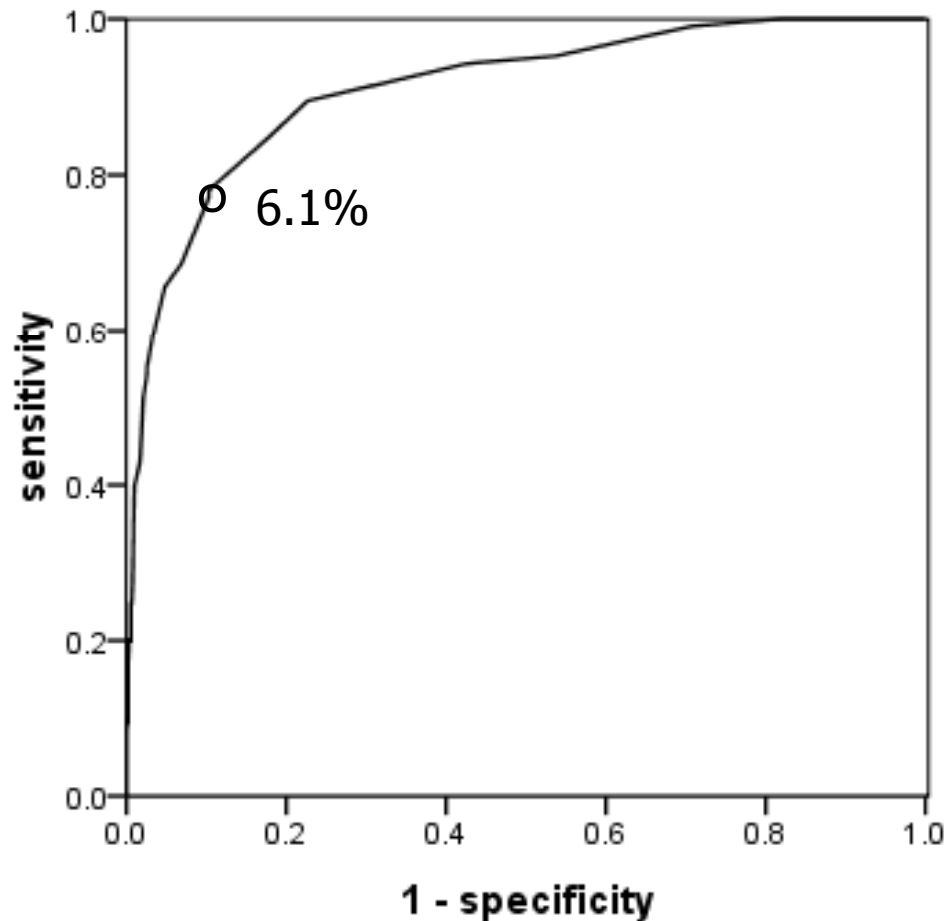
$r=0.782, p<0.01$



$r=0.726, p<0.01$

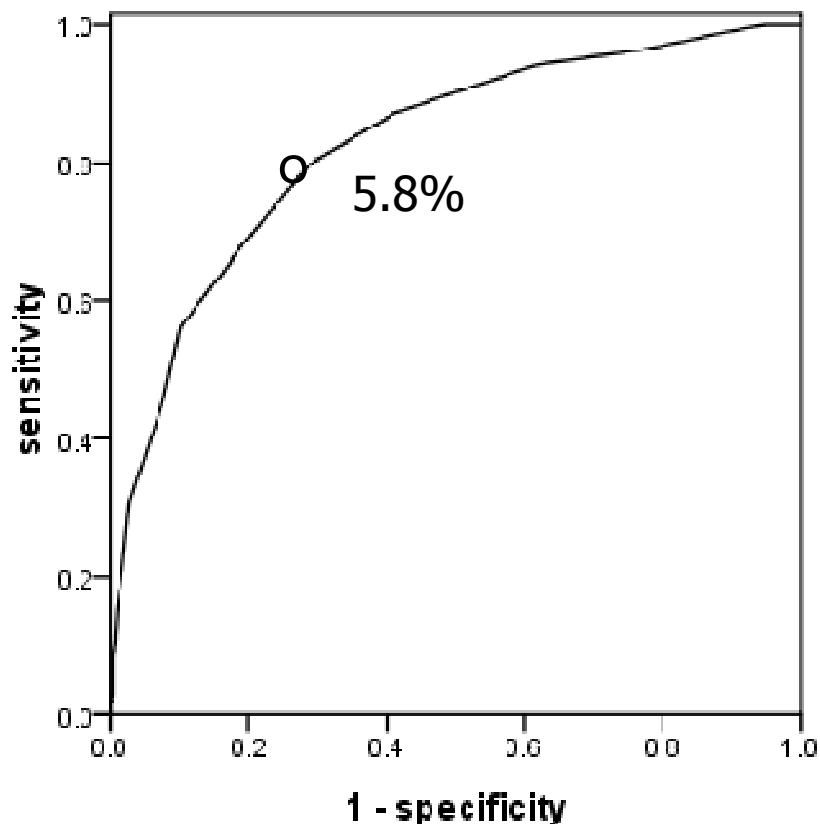


ROC curve for identification of participants with previously undiagnosed diabetes, using HbA1C for diagnosis and an OGTT as criterion.



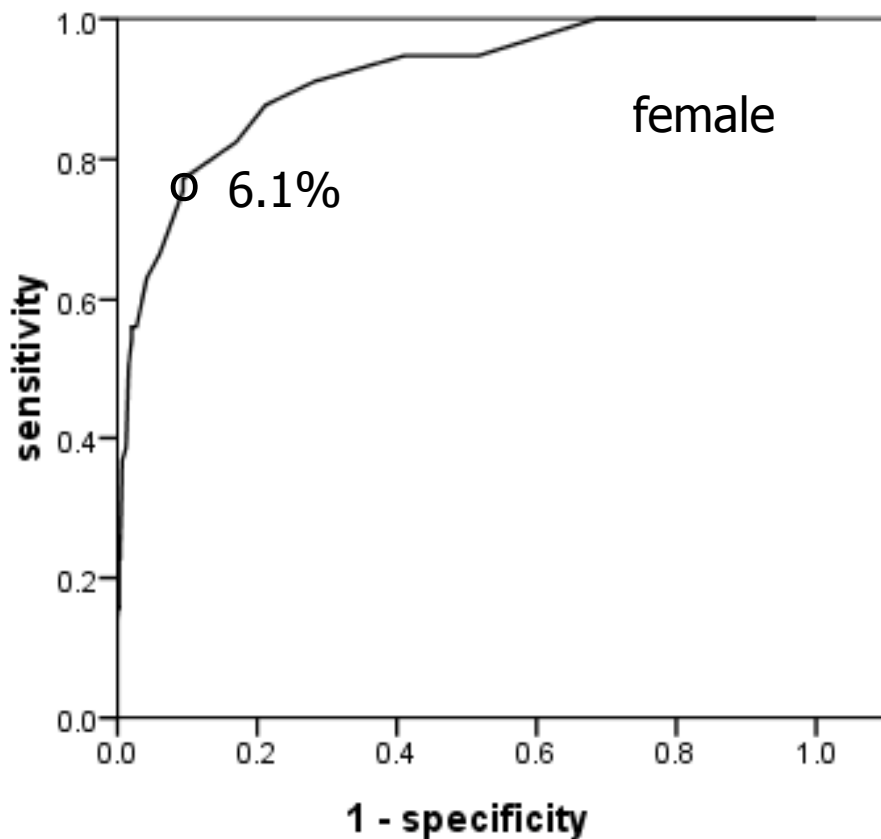
	AUC	95% CI
HbA1C	0.911	0.880-0.942

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

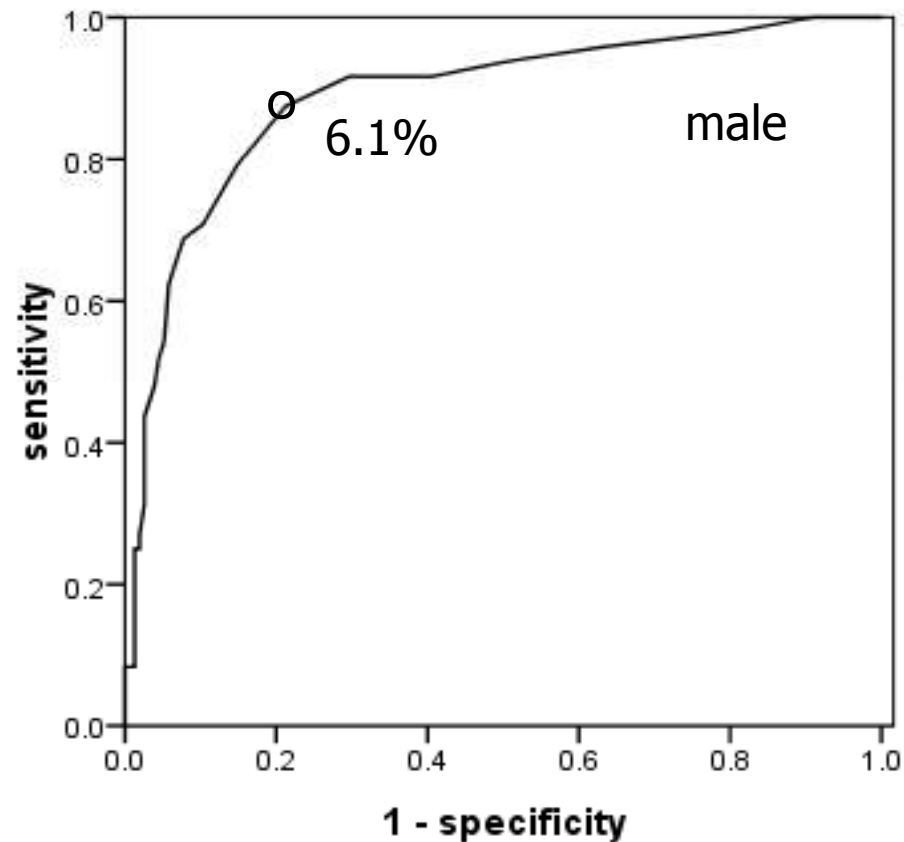


	AUC	95% CI
HbA1C	0.825	0.794-0.856

ROC curve analysis for HbA1C according to sex

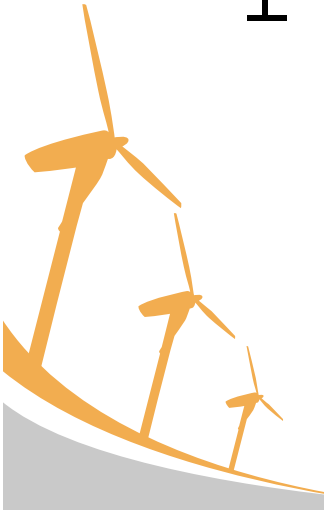
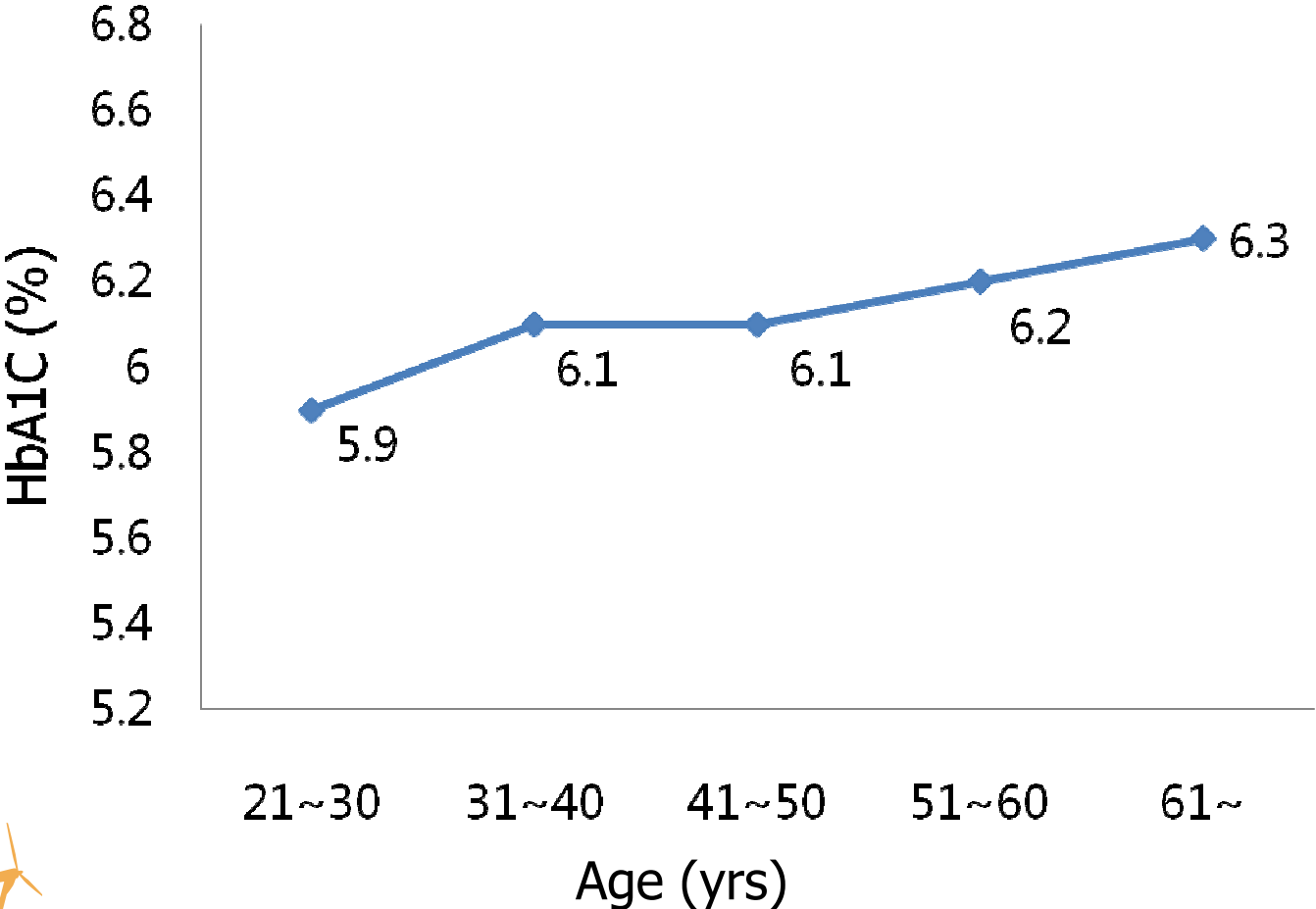


	AUC	95% CI
HbA1C	0.914	0.874-0.953



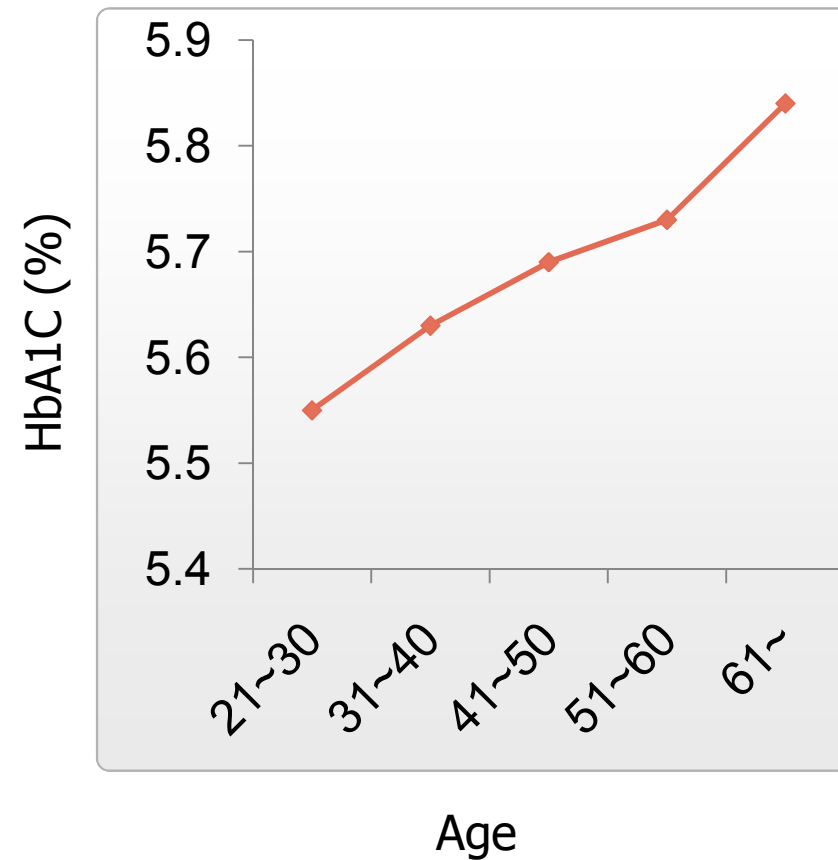
	AUC	95% CI
HbA1C	0.888	0.831-0.945

Cutoff value of HbA1C according to age



Mean HbA1C by age categories in subjects with NGT

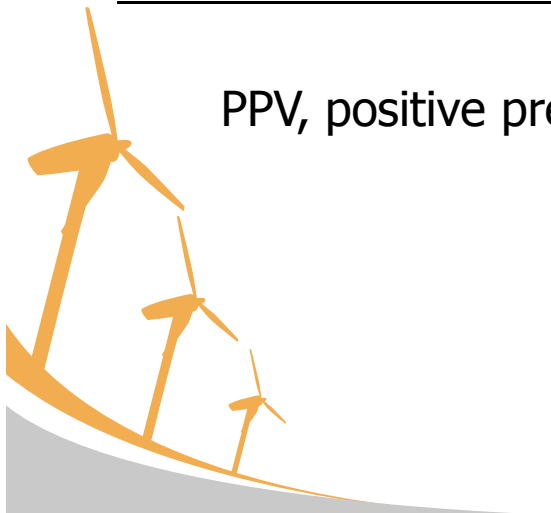
Age (n)	HbA1C (mean \pm SD)
21~30 (288)	5.55 \pm 0.21
31~40 (269)	5.63 \pm 0.24
41~50 (139)	5.69 \pm 0.29
51~60 (170)	5.73 \pm 0.29
61~ (122)	5.84 \pm 0.36



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

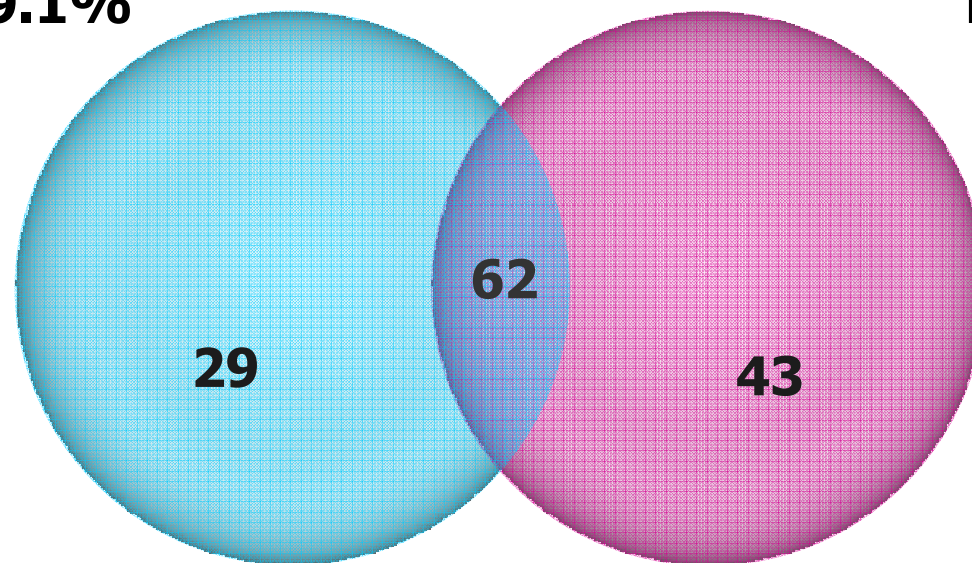
Cut-off point	PPV	NPV	sensitivity	specificity
6.1%	36.1%	97.9%	84.8%	82.3%
6.5%	68.1%	96.0%	59.0%	97.5%

PPV, positive predictive value; NPV, negative predictive value



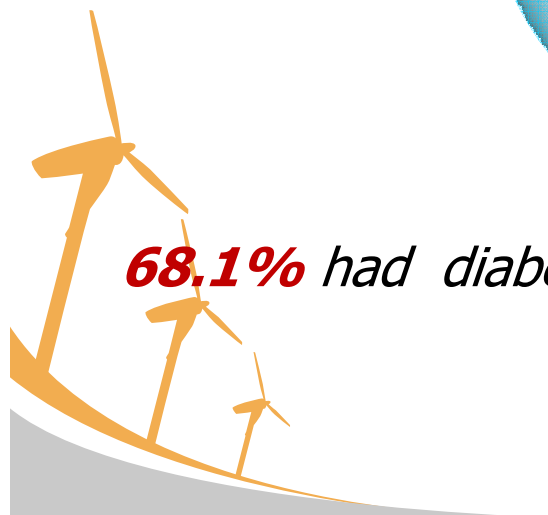
**HbA1C (6.5%)
based DM: 9.1%**

**OGTT based
DM: 10.5%**



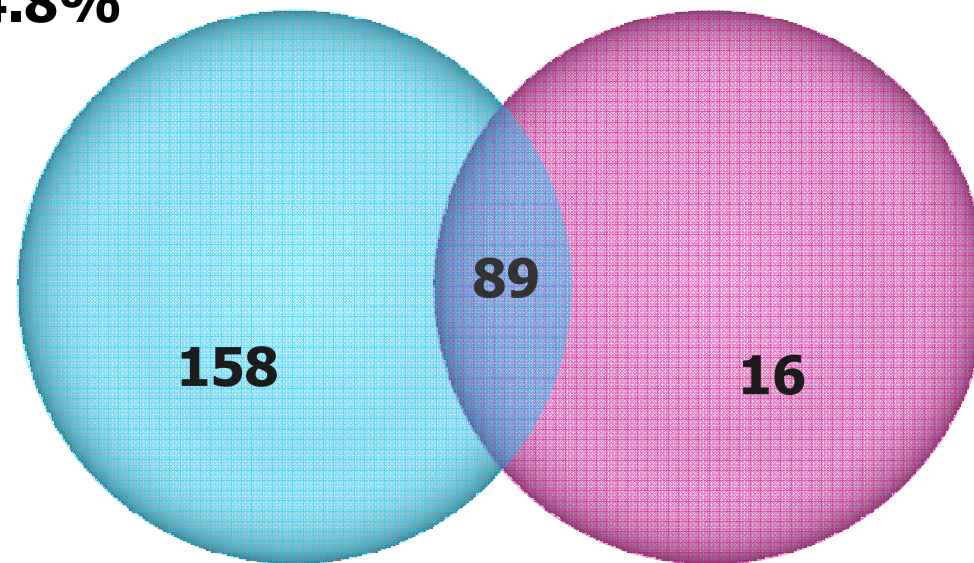
68.1% had diabetic glucose levels

Total 996



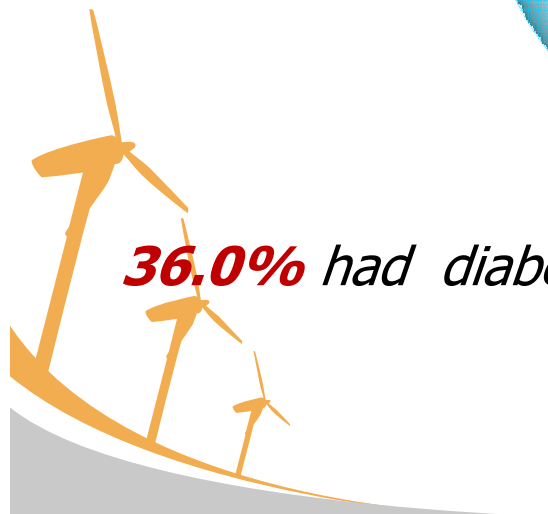
**HbA1C (6.1%)
based DM: 24.8%**

**OGTT based DM:
10.5%**



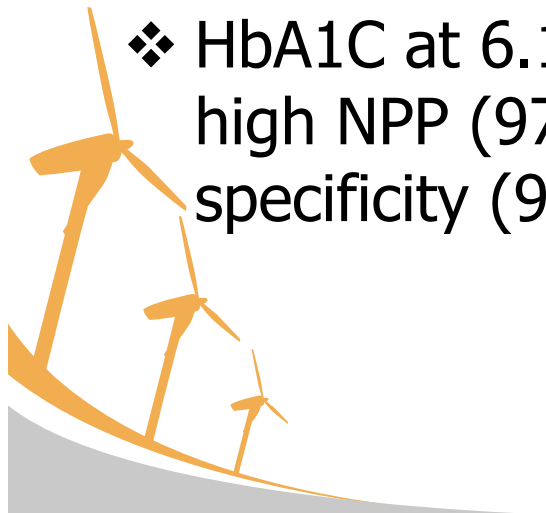
36.0% had diabetic glucose levels

Total 996



summary

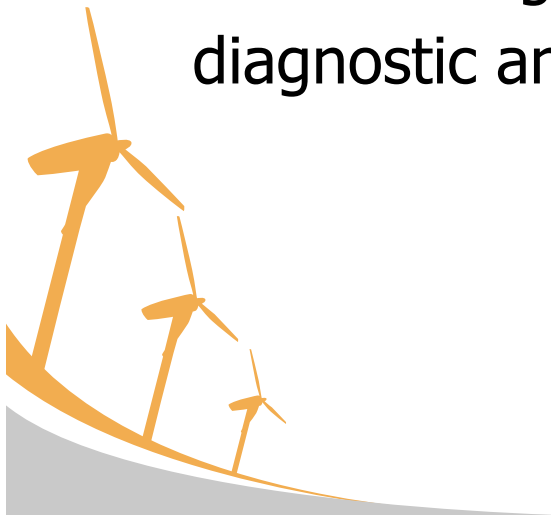
- ❖ The cutoff point for diagnosing for diabetes with the highest sum of sensitivity and specificity in our data was an HbA1C level of 6.1%.
- ❖ HbA1C levels positively associated with age, but results in sex-stratified analysis were similar.
- ❖ Of all subjects with an HbA1C > 6.1%, 36% had diabetic glucose levels.
- ❖ HbA1C at 6.1% provided high sensitivity (84.8%) and high NPP (97.9%), while HbA1C at 6.5% gave high specificity (97.5%) and high PPV (68.1%).



Conclusion

Further studies should be undertaken to determine

- the population-specific HbA1C cut-offs points
- whether the increase in HbA1C associated with age is of clinical significance and to clarify whether age-specific diagnostic and treatment criteria would be appropriate.



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Thank You!

