The 23rd Spring Congress of the Korean Diabetes Association (KDA) 8th May 2010

# The Role Of HbA<sub>1</sub><sub>C</sub> In Diagnosing Diabetes

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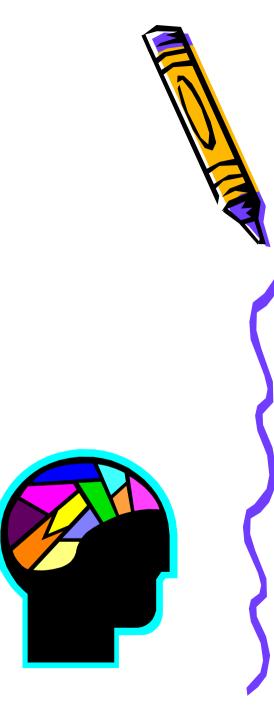
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# Outline

- 1. Diagnosing diabetes
  - 🗸 a quick review 🔺
- 2. PG & A1c for diabetes diagnosis
  - $\checkmark$  the Good, the Bad & the Ugly  $\bullet$
- 3. Suggestions from IEC/ADA 🍝
- 4. Ways forward in diagnosing diabetes





#### **Diabetes Mellitus**

"A group of metabolic diseases characterized by <u>hyperglycemia</u> - resulting from defects in insulin secretion, insulin action, or both."

ADA. Diabetes Care 2010;33(Suppl 1):562.



#### 'classic' criteria

	NDDG 1979 (National Diabetes Data Group)	WHO 1985	ADA 1996
Classical symptoms	$\checkmark$	±	±
FPG (venous)	≥7.8 mmol/l (140 mg/dl)	≥7.8 mmol/l (140 mg/dl)	≥7.8 mmol/l (140 mg/dl)
Random PG	-	≥11.1 mmol/l (200 mg/dl)	≥11.1 mmol/l (200 mg/dl)
OGTT 2hr PG	≥11.1 mmol/l	≥11.1 mmol/l	≥11.1 mmol/l
Values	Symptoms + 1 value	Preferably 2 values if asymptomatic	2 values if asymptomatic



NDDG. Diabetes 1979;28:1039-57 WHO. Tech. Rep. Ser. 727, 1985 ADA. Diabetes Care 1996;19:54

### • 2hr PG cutoff <u>11.1 mmol/L</u>: base on clinical outcome (retinopathy)

## I. The Whitehall Survey

Al Sayegh H et al. Lancet 1979;2:431-3. Reid DD et al. Lancet 1974;1:469-73.

### II. The Bedford Study

- On FU, retinal vascular changes was confined to individuals with 2-hr PG  $\geq$  200mg/dl

Jarrett RT et al. Lancet 1976;2:1009-12



<u>\*FPG value was "projected" from</u> <u>2hr PG value</u>

Sayetta et al. Diabetes Care 1979;2:105-19.

- FPG = <u>7.8 mmol/l (140 mg/dl)</u> is
  - too HIGH in corresponding to
     2hr-PG of <u>11.1 mmol/l (200 mg/dl)</u>



\*\*To achieve an optimal balance between sensitivity and specificity for diagnosing DM, a lower FPG value, ranging from <u>5.3 to 7.1 mmol/l</u>, has been suggested.



Cockram CS et al. Diabetes Care 1992;15:988-90. (5.7 mmol/l, HK Chinese) Hanson RL et al. Arch Intern Med 1993;153:2133-40. (6.8 mmol/l, Pima Indian) Ramachandran A et al. Diabet Med 1993;10:811-13 (7.1 mmol/l, South Indian) Clements JP et al. Acta Diabeto/1994;31:187-92 (6.4 mmol/l, North European) Bortheiry AL et al. Diabetes Care 1994;17:1269-72 (5.6 mmol/l, Brazilians) Larsson H et al. J Intern Med 1995;237:537-41 (5.3 mmol/l, Swedish women) Ko GT et al. Diabetes Care 1997;20:170-2 (5.4 mmol/I, HK Chinese)



FPG cutoff value of 7.8 mmol/l is too high to diagnose DM (for both Chinese & other populations) -

# Revised "magic figures": 7.0 7.8 11.1

	ADA 1997	WHO 1998
Classical symptoms	±	±
FPG (venous)	≥7.0 mmol/l	≥7.0 mmol/l
Random PG	≥11.1 mmol/l	≥11.1 mmol/l
OGTT 2hr PG	≥11.1 mmol/l	≥11.1 mmol/l
Values	Preferably 2 values if asymptomatic	2 values unless unequvico e.g. acute decompensatio
IFG	≥ <b>6.1</b> to <7.0 mmol/l (≥110 to <126 mg/dl) = impaired fasting glucose	<ul> <li>≥6.1 to &lt;7.0 mmol/l</li> <li>(≥110 to &lt;126 mg/dl)</li> <li>= impaired fasting glycaemia</li> </ul>
OGTT	Not recommended for routine use	Either FPG or 2hr PG ma be used

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Alberti KGMM et al. Diabet Med 1998;15:539-53

# DM - DIAGNOSIS ? Why 7.0 mmol/L:

1) FPG cutpoints corresponding to the 2hr PG criterion of 11.1 mmol/l in many populations

 Increased risk of retinopathy in persons with FPG ≥110-129 mg/dl (6.1-7.2 mmol/l)

> McCane DR et al. BMJ 1994;308:1323-8 Engelgau MM et al. Diabetes Care 1997;20:785-91 NHANES III

3) Increased incidence of CHD at FPG  $\geq$ 6.9 mmol/l

Jarrett RJ et al. Lancet 1976;ii:1009-12



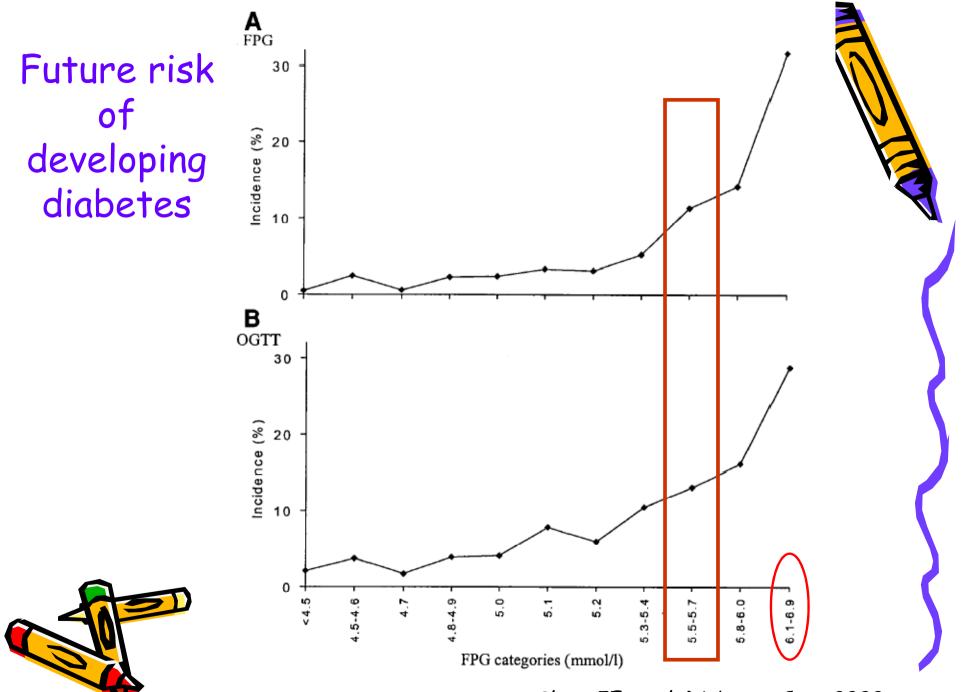
# Revised "magic figures": 6.1 7.0 7.8 11.1



## DM - DIAGNOSIS Added issues on IFG

- To predict future diabetes (metabolic outcome), using ROC curve analysis for best sensitivity and specificity:
  - Ducth 5.7
  - Pima Indian 5.4
  - Mauritius 5.4
  - San Antonio study 5.2





Shaw JE et al. Diabetes Care 2000

DM - ĎIA	GNOSIS	
	ADA 2003	WHO 1998
Classical symptoms	<u>±</u>	±
FPG (venous)	≥7.0 mmol/l	≥7.0 mmol/l
Random PG	≥11.1 mmol/l	≥11.1 mmol/l
OGTT 2hr PG	≥11.1 mmol/l	≥11.1 mmol/l
Values	Preferably 2 values if asymptomatic	2 values unless unequvicoo e.g. acute decompensatio
OGTT	Either FPG or 2hr PG may be used	Not recommended for routine use
IFG	≥ <b>5.6</b> to <7.0 mmol/l (≥100 to <126 mg/dl)	≥6.1 to <7.0 mmol/l (≥110 to <126 mg/dl)
HbA1c	NOT recommended	NOT recommended

ADA. Diabetes Care 2003;26:3160-7 Alberti KGMM et al. Diabet Med 1998;15:539-53

"magic figures" 5.6/6.1 NFG, IFG (FPG) DM (FPG) 7.0 IGT (OGTT) 7.8 11.1 DM (2hr or random PG)

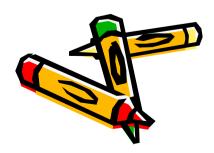
# PG or HbA<sub>1c</sub> to diagnose diabetes

The Good, the Bad and the Ugly

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# The BAD of PG

- Fasting &/or 2hr OGTT: need special arrangement
- Higher assay variability of PG as compared to A1c
- Variation between plasma, whole blood & capillary blood values



## Assay variability

- Biological variability with same subject:
  - Time of day, stress, timing to sample processing, ...
  - Intra-CV:
    - A1c = 3.6%
    - FPG = 5.7%
    - 2hr PG = 16.6%

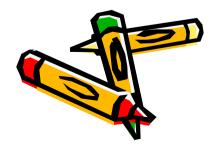
Selvin E et al. Arch Intern Med 2007 Rohlfing C et al. Clin Chem 2002



#### OGTT: 2hr PG

- 212 Hong Kong Chinese subjects (age 30-65):
  - 2 OGTTs in a 6-wk period
  - Reproducibility = 65.6%
     (139/212: 74 normal OGTT, 24 DM, 41 IGT on both occasions)
  - Among subjects with high HbA1c ( $\geq$ 5.8%) or high BMI ( $\geq$ 25 kg/m<sup>2</sup>):
    - reproducibility = 52.8% & 58.3% respectively

Ko GT et al. Ann Clin Biochem 1998;35:62-7.



#### OGTT: 2hr PG

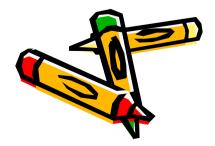


## •Reproducibility:

 Only 50% of OGTTs are reproducible in normal population



Ganda OP et al. Diabetes 1978;27:715-25. Troxler RG et al. Aviat Space Environ Med 1975;46:729-35.



### Drawback of OGTT (2hr PG)

- poor reproducibility
- laborious
- time consuming
- costy
- inconvenient to patients
- GI upset

(NOT recommended by ADA 1997/2003 & WHO 1998 guidelines)



#### Variations between types of samples

		Fas	ting	2	-hr
Plasma	Venous	6.1	7.0	7.8	11.1
Plasma	Capillary	6.1	7.0	8.9	12.2
Whole blood	Venous	5.6	6.1	6.7	10.0
Whole blood	Capillary	5.6	6.1	7.8	11.1

Plasma glucose > whole blood glucose
 venous glucose < capillary glucose</li>
 fasting: similar; post-meal: difference
 ~10% difference in each condition



# The GOOD of A1c

### Advantages of A1c for diagnosis of DM:

- No need for fasting or timed samples (convenient)
- Substantially less biologic variability; less preanalytic instability (reproducibility)
  - Relatively unaffected by acute (e.g. stress or illness related) perturbation in PG levels
- Assay: standardized and alignes to DCCT/UKPDS

(PG is less well standardized) 🔺

- Currently used to guide Mx and adjust Rx 💌
- Better index of overall glycemic exposure and risk for long-term complications / metabolic outcome



#### Assay standardization

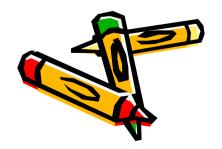
Standardization led by:

- the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)

Miedema K. Diabetologia 2004

College of American Pathologists (CAP)

- Average CV of A1c:
  - 6-7% in 2003 to ~4% in 2009
- Acceptable limits for error:
  - 10% in 2009
  - plan to reduce to 6% in coming years



Little RR et al. NGSP. ADA abstract 2009

#### Treatment targets

	ADA	IDF
HbA1c	<7%	<6.5%
Pre-prandial PG	5.2-7.0 mmol/L	<6 mmol/L
Post-prandial PG	<10.0 mmol/L	<8 mmol/L (1-2 hr after meal)

ADA. Diabetes Care 2007; 30 (Suppl 1): :51-5103.

IDF Clinical Guidelines Task Force, ed. Global Guideline for Type 2 Diabetes. Brussels: IDF 2005



#### Overall glycemic exposure

- Estimated Average Glucose (eAG)
- Mean Self-Monitored Blood Glucose (SMBG)
- A1c-Derived Average Glucose (ADAG) Equivalent (ADAGE)
- Continuous Glucose Monitoring (CGM) level
- 'Average glucose' = 28.7 × <u>A1c</u> 46.7
   R<sup>2</sup> = 0.84

Nathan DM et al. ADAG Study. Diabetes Care 2008

(? Ignored: age, ethnicity, Hb level, renal fx, ...)

#### Relationship of PG with outcomes / CVD / mortal

	Fasting PG	2hr or Pp-PG
Whitehall survey		$\checkmark$
Paris Prospective Study		$\checkmark$
Helsinki Policemen Study		$\checkmark$
Coutinho M 1999	$\checkmark$	$\checkmark$
Honolulu Heart Program 1999		$\checkmark$
Chicago Heart Study 1997		$\checkmark$
Rancho Bernardo Study 1998		$\checkmark$
Shaw JE 1999	×	$\checkmark$
DECODE 2003	×	$\checkmark$

#### A1c reflecting risk and outcomes

- A1c tertiles associated with CVD risk factors in subjects with NGT Ko GT et al. Diabet Med 1998
- $\Uparrow$  CVD risk with  $\uparrow$  A1c values among non-DM and DM

Khaw KT et al (Norfolk Study). Ann Intern Med 2004 Selvin E et al (ARIC Study). Arch Intern Med 2005 Pradham AD et al. Am J Med 2007 Brewer N et al (New Zealand linkage study). Diabetes Care 2008 Gerstein HC et al (CHARM Program). Arch Intern Med 2008

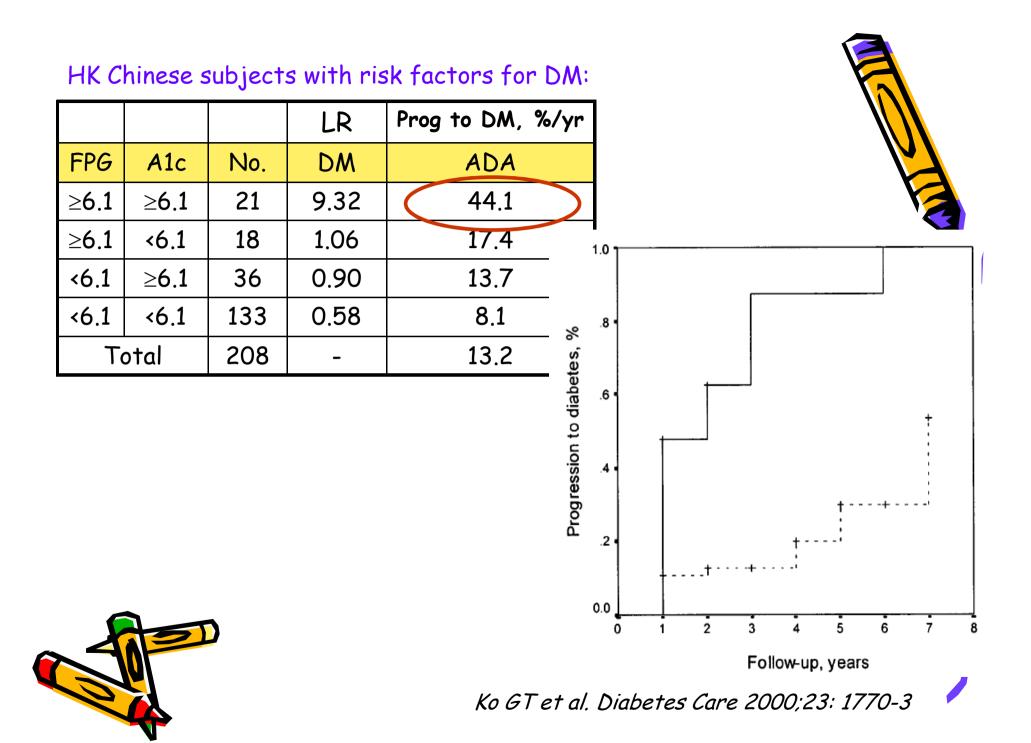


#### A1c vs. PG reflecting outcomes

- Hoorn Study
  - 2-h PG and to a lesser extent HbA1c, indicate a risk of all-cause and cardiovascular mortality in general population
  - RR for all-cause & CVD mortality
    - A1c 1.4 (1.2, 1.7) vs. 2hr PG 1.5 (1.3, 1.9)
    - A1c 1.5 (1.2, 1.9) vs. 2hr PG 1.6 (1.3, 2.1)

De Vegt et al. Diabetologia 1999



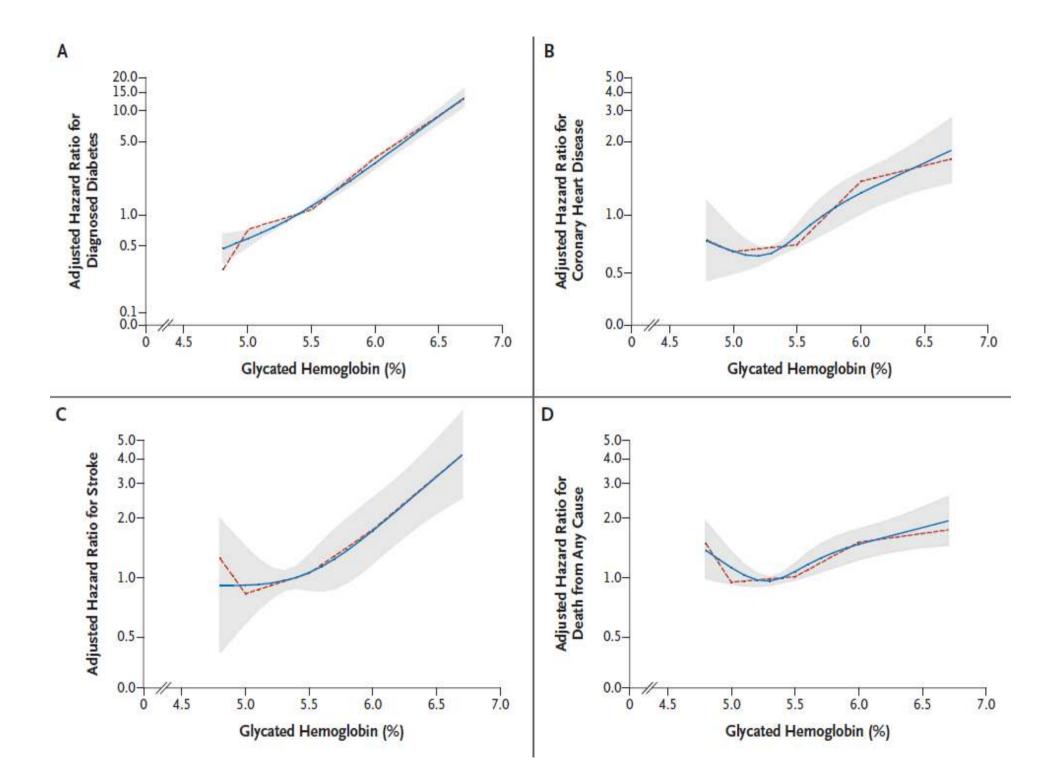


#### A1c vs. PG reflecting outcomes

- Atherosclerosis Risk in Communities (ARIC) Study
  - 11092 non-diabetic adults (1987-89)
  - Assessed prognostic value of A1c and FPG for DM, CVD, all-cause mortality
  - Median FU 14 years

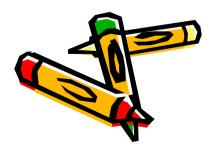
Selvin E et al. NEJM 2010;362:800-11





## A1c reflecting risk and outcomes

- ARIC Study
  - A1c:
    - DM/ CHD/ stroke: +ve association
    - All-cause death: J-shaped curve
    - Remained significant after adjusting baseline FPG
  - FPG:
    - DM/ CVD/ death: +ve association became non-significant when adjusted for A1c
- <u>Conclusions</u>: A1c was superior to FPG for assessing long-term CVD risk, and support use of A1c to diagnose DM



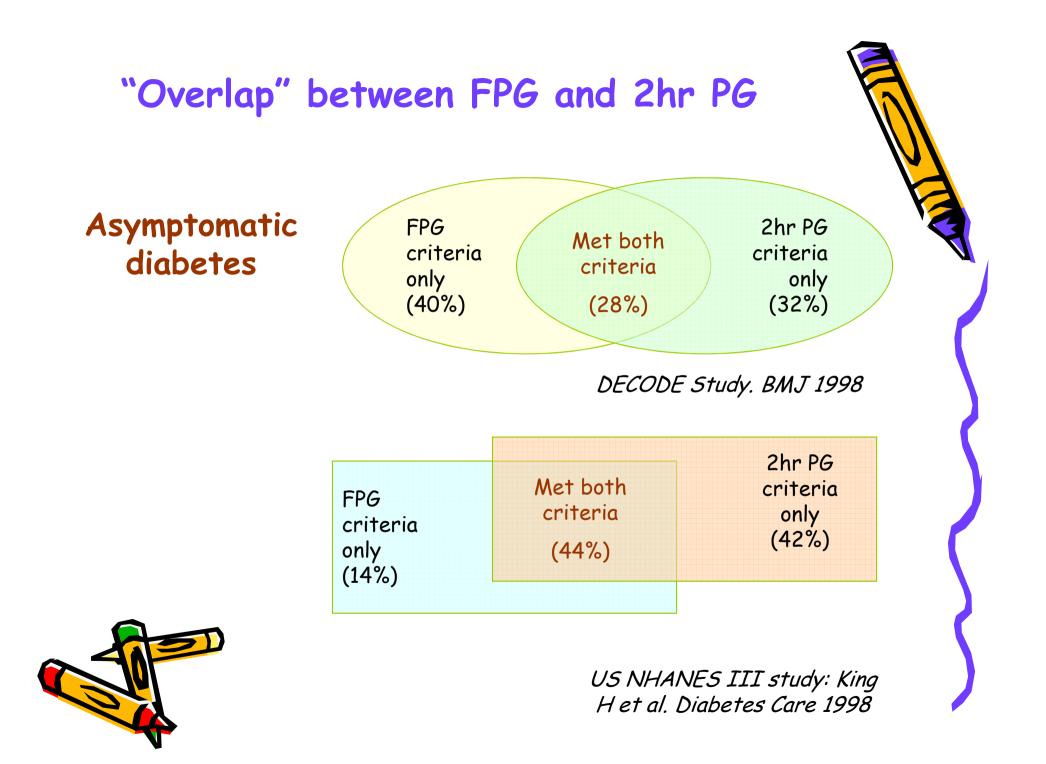
Selvin E et al. NEJM 2010;362:800-11

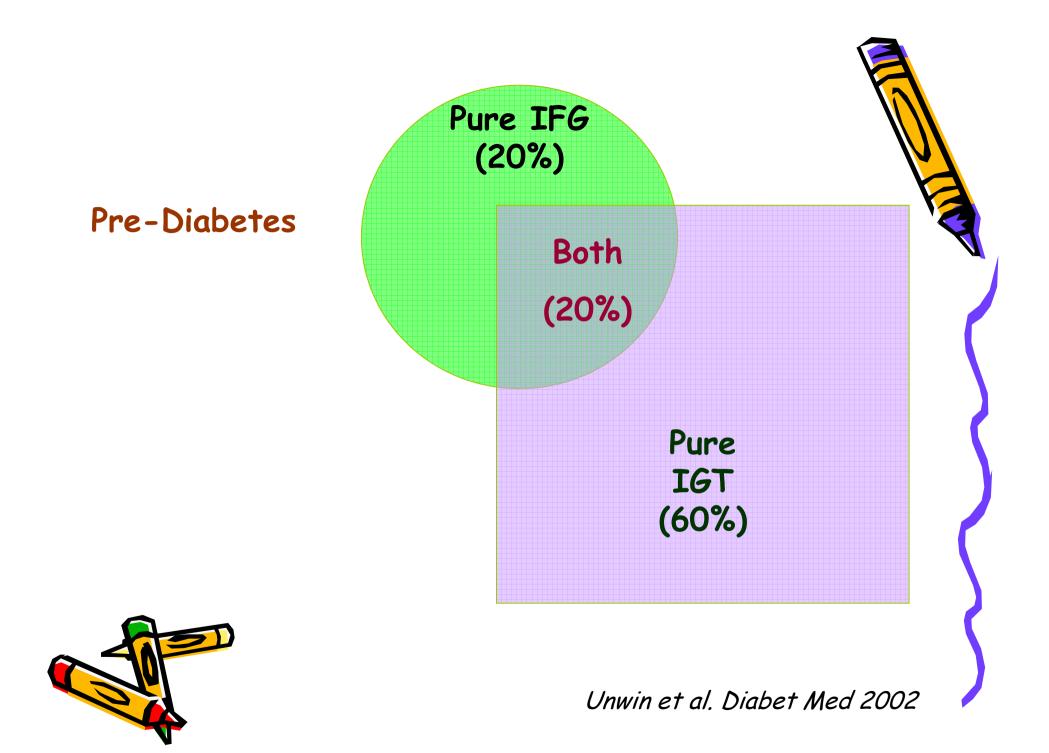
## Relationship of PG with outcomes / CVD / mortal

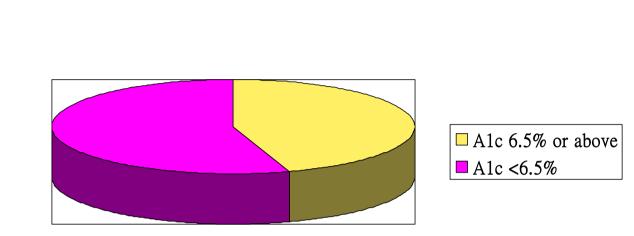
	FPG	2hr / Pp-PG	A1c
Whitehall survey		$\checkmark$	
Paris Prospective Study		√	
Helsinki Policemen Study		√	
Coutinho M 1999		√	
Honolulu Heart Program 1999		√	
Chicago Heart Study 1997		√	
Rancho Bernardo Study 1998		$\checkmark$	
Shaw JE 1999	×	√	
Hoorn Study 1999		√	
DECODE 2003	×		
Ko et al 2000; Norfolk Study 2004; NZ linkage study 2008; CHARM Program 2008			
ARIC Study 2010	+/-		

# The BAD of HbA1c

- ? Optimal cutoff
  - Sensitivity vs. specificity
  - Relationship / overlap with 'gold standard' 🔺
- Assay methods
- Confounding medical conditions e.g. hemoglobinopathies, anemia <u>\*</u>
- Cost (needs 2 values to make a diagnosis)
- Ethnic differences in A1c are independent of glycaemia
  - Inter-patient variability of Hb glycation







- A1c ≥6.5% for the Dx of DM based on FPG (NHANES data)
  - Sensitivity = 42.8-44.3%

DM with FPG  $\geq$ 7 mmol/L

- Specificity = 99.6%

Buell C et al. Diabetes Care 2007 Saudek C et al. J Clin endocrinol Metab 2008



A1c: UNDER-diagnose "DM"



# Other A1c assay

- DCCT not aligned yet
- "Point of care" A1c methods
  - Exempted from CAP quality standardization
- Modification of A1c units (mmol/mol)
  - Potential marked confusion to pts & users



#### 'Discrepancy' between A1c and PG

OVER-Dx by A1c ("falsely" high A1c value)	UNDER-Dx by A1c ("falsely" low A1c value)
(Tuisely night Aic value)	(Tuisely IOW AIC Vulue)
Fe deficiency	*Hemoglobinopathies
Following splenectomy	Pregnancy
Elderly	Uremia; on hemodialysis
Black subjects	HIV infection (antiretroviral drugs)
	"general populations"



\*HbS, HbC, HbE, HbD, ... traits

•>10% Africans, Asians, ...

NGSP. A1c & Hb variants. 2009 www.ngsp.org/

	A1c	FPG	2hrPG
Assay standardization	$\sqrt{\sqrt{2}}$	$\checkmark$	√ <b>\\</b>
Reproducibility: Intra-CV	3.6%	5.7%	16.6%
Lab to lab differences	+/- Large	Less	Less
Easy to measure	$\sqrt{\sqrt{2}}$	$\checkmark$	-
Cost	-	111	$\checkmark$
Global availability	$\checkmark$	~~~	$\sqrt{\sqrt{2}}$
Overall glycemia		-	-
Predicting long-term complications	$\sqrt{}$	$\sqrt{\sqrt{2}}$	$\sqrt{\sqrt{2}}$
DM monitoring/ Chronic M×	$\sqrt{\sqrt{2}}$	$\sqrt{\sqrt{2}}$	- / √
Overlap with diagnosis by 2hr PG	Limited	Limited	"Gold standard"
Clinical limitations	*RBC lifespan abnormalities; Fe def; pregnancy; age; ethnicity	Fasting; to be analyzed promptly	75g glucose loading; to be analyzed promptly; gastric surgery



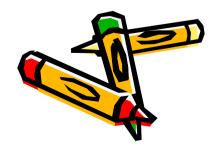
International Expert Committee on role of A1c assay in the diagnosis of DM, 2009

IEC. Diabetes Care 2009;32: 1327-34

IEC members (appointed by ADA, EASD and IDF) convened in 2008

### **IEC 2009**

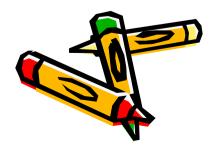
- Diabetes should be diagnosed when:
  - HbA1c ≥6.5%
    - Diagnosis should be confirmed with a repeat A1c test
      - Confirmation not required in symptomatic subjects with PG  $\geq\!\!11.1$  mmol/l
    - If A1c testing not possible, previously recommended methods on FPG &/or 2hr PG are acceptable
    - No age- or race-specific values (yet)



IEC. Diabetes Care 2009;31:1327-34

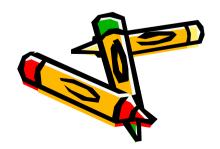
### **IEC 2009**

- Special groups:
  - Children:
    - A1c is also indicated if DM is suspected, and classic symptoms and a casual PG >11.1 mmol/l are not found
  - Diagnosis of DM in pregnancy:
    - Changes in RBC turnover make the A1c assay problematic, will continue to require PG
  - Other condition that changes RBC turnover e.g. hemolytic anemia, blood transfusion, etc
    - $\boldsymbol{\cdot}$  Continue to use PG



### **IEC 2009**

- High risk subjects:
  - "pre-diabetes" (IFG, IGT):
    - Will be phased out of use as A1c replace PG measurements
  - A1c ≥6 and <6.5%:
    - Likely at the highest risk for progression to DM
    - Should receive preventive interventions
  - A1c <6%:
    - May still be at risk
    - To see other DM risk factors



IEC. Diabetes Care 2009;31:1327-34

# Why 6.5%

- Risk of retinopathy, significantly rise if
  - 2hr PG  $\geq$ 11.1 mmol/L
  - FPG  $\geq$ 7.0 mmol/L

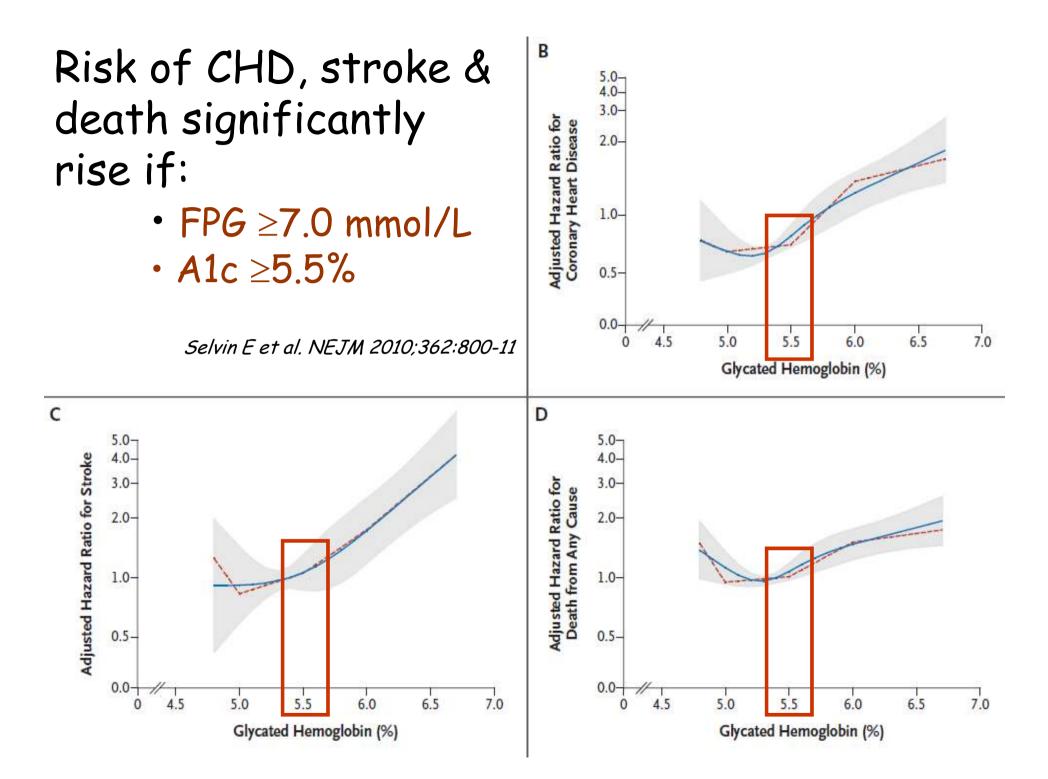
(Whitehall Survey, Bedford Study)

(McCane DR et al. BMJ 1994 Engelgau MM et al. Diabetes Care 1997)

- A1c ≥6.5%

(DETECT-2. Diabetes Voice 2003 Sabanayagam C et al. Diabetologia 2009)

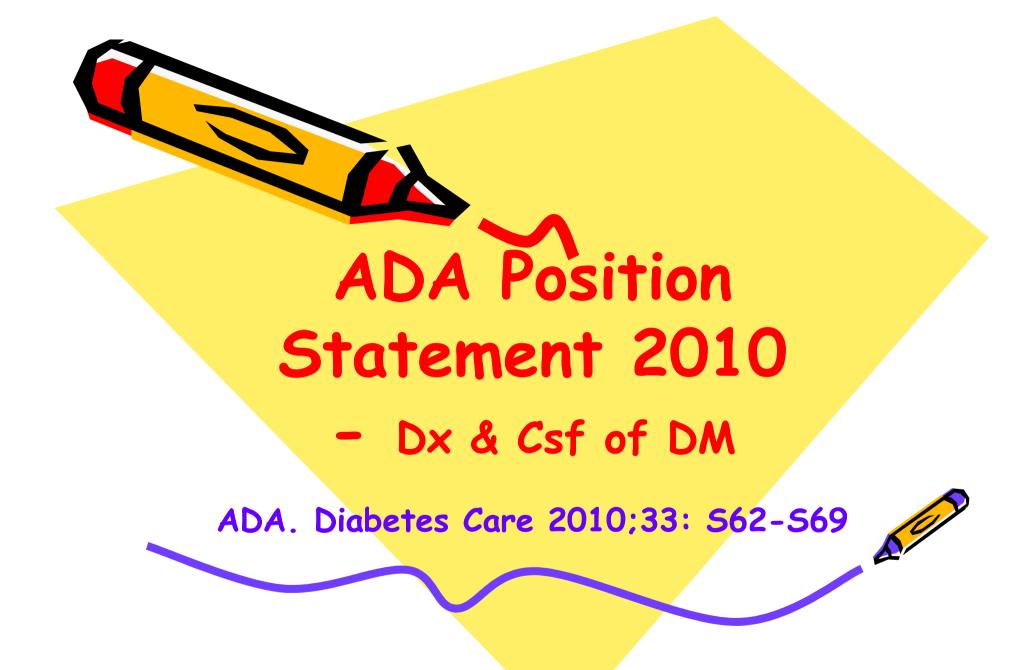




# DM - DIAGNOSIS

• IEC stressed the CONTINUUM of risk for diabetes with all glycemic measures





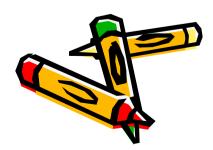
Criteria for DM Dx

Either one of the below:				
Random PG	≥11.1 mmol/l	& with symptoms		
FPG	≥7.0 mmol/l	Fasting >8 hrs	To be confirmed by	
2hr PG (OGTT)	≥11.1 mmol/l		repeat testing, if no unequivocal hyperglycemia	
A1c	≥6.5%	NGSP certified; DCCT assay standardized		

ADA. Diabetes Care 2010;33 (Suppl 1):562-9.

# Categories of increased risk for DM

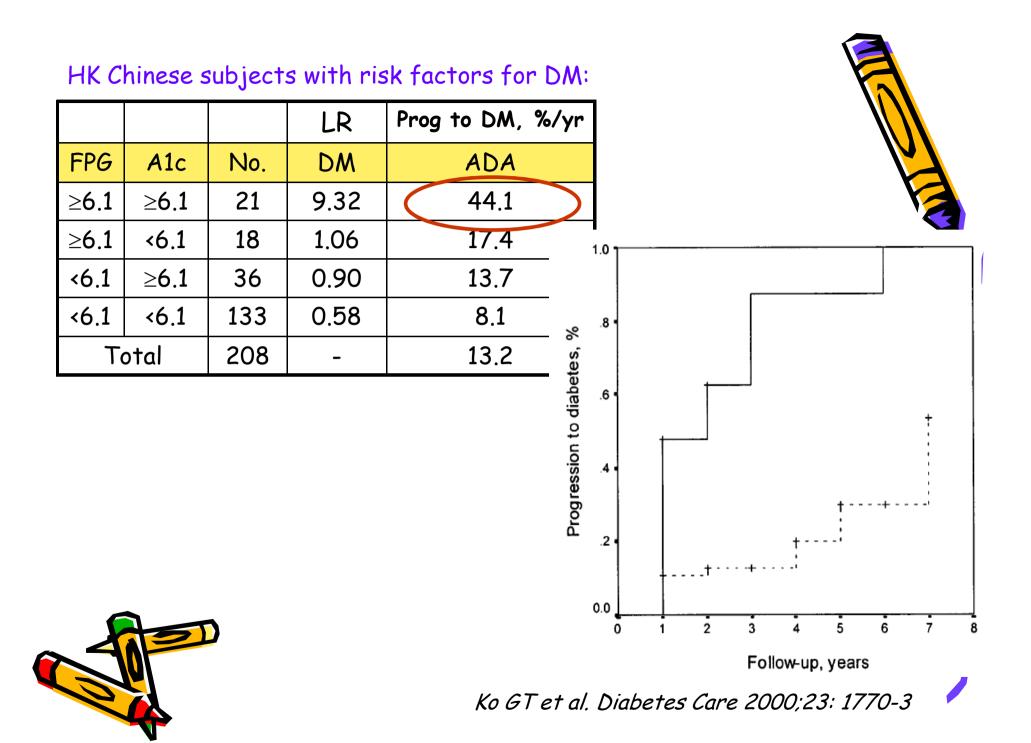
FPG	≥5.6 – 6.9 mmol/l	Fasting >8 hrs	* Continuous risk, extending below the
2hr PG (OGTT)	≥7.8 - 11.0 mmol/l		lower limit of the range and becoming disproportiona
A1c	≥5.7 - 6.4%	NGSP certified; DCCT assay standardized	tely greater at higher ends of the range



ADA. Diabetes Care 2010;33 (Suppl 1):562-9.

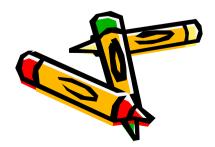
# Ways forward in diagnosing diabetes

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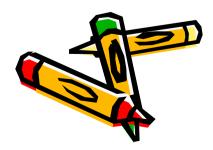
## FPG & A1c 'predicting' DM

FPGA1cNo.NormalIGTDM*AbnDMHK Chinese subjects with risk factors for DM $\geq 5.6$ $\geq 5.5$ 8801322215277.035.36 $\geq 6.1$ $\geq 6.1$ 551259643017.212.8HK Chinese subjects from community (ADA criteria) $\geq 6.1$ $\geq 6.1$ 181413141.974.7									
HK Chinese subjects with risk factors for DM $\geq 5.6$ $\geq 5.5$ 8801322215277.035.36 $\geq 6.1$ $\geq 6.1$ 551259643017.212.8HK Chinese subjects from community (ADA criteria)					OGTT		L	R	
$\geq 5.6$ $\geq 5.5$ 8801322215277.035.36 $\geq 6.1$ $\geq 6.1$ 551259643017.212.8HK Chinese subjects from community (ADA criteria)	FPG	A1c	No.	Normal	IGT	DM	*Abn	DM	
$\geq 6.1 \geq 6.1  551  25  96  430  17.2  12.8$ HK Chinese subjects from community (ADA criteria)	HK Chine	ese subje	cts with r	risk facto	rs for DN	٨			
HK Chinese subjects from community (ADA criteria)	≥5.6	≥5.5	880	132	221	527	7.03	5.36	
	≥6.1	≥6.1	551	25	96	430	17.2	12.8	
$\geq 6.1 \geq 6.1 $ 18 1 4 13 141.9 74.7	HK Chine	ese subje	cts from	communit	y (ADA c	riteria)			
	≥6.1	≥6.1	18	1	4	13	141.9	74.7	



Ko GT et al. Diabetes Care 1998:21: 1221-5 Ko GT et al. Diabetes Care 1998;21: 2032-3 Ko GT et al. Diabetes Care 1999;22: 1908-9

Categories	Choice of test
Diagnosing diabetes e.g. symptomatic pts	Fasting or random PG (on 2 separate occasions)
Epidemiological survey	Fasting or 2 hour PG after OGTT (one value only)
Diabetes screening:	
1. no risk factor	Fasting PG
2. risk factor present e.g. FH +ve	OGTT, or paired test of FPG + HbA <sub>1c</sub>
Selected subjects:	
1. pre-DM i.e. IGT or IFG	OGTT
2. FPG $\geq$ 5.6 mmol/L & HbA <sub>1c</sub> $\geq$ 5.5%	OGTT



Ko GT. Diagnosing diabetes mellitus in the Asian population. HK Med J 2000;6:53-9.

Categories	HK		ADA / IEC
Diagnosing diabetes	FPG or (twice		RPG / FPG / 2hPG / A1c (twice)
Epidemiological survey	FPG or (once)	· 2hPG	Not clear ( ? FPG / A1c, once )
Diabetes screening:			
1. no risk factor	FPG		FPG or A1c
2. at risk e.g. pre- diabetes; hx of borderline high A1c	OGTT FPG +	•	FPG / 2hPG / A1c (twice)



Ko GT. HK Med J 2000;6:53-9. ADA. Diabetes Care 2010;33 (Suppl 1):562-9.

# Decision on DM Dx test (I)

- Clinicians
  - Understanding on the tests
- Patients
  - Medical conditions e.g. hbopathy
  - Degree of DM Risk
  - Availability for vs. Preference to a test
- Test options
  - Availability vs. Practicality
  - Resources of testing centers
    - ? Further evidence-based information on the tests e.g. diagnostic cut-off level, confounders ...

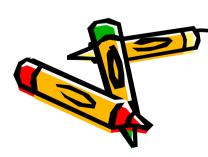


# Decision on DM Dx test (II)

- Most cases
  - FPG or RPG or A1c
  - Repeat testing (the abnormal test)
    - +  $\pm$  2hr PG with OGTT
- At risk patients

(i.e. high chance of the need for 2 tests to confirm Dx)

- FPG + A1c



Higher the risk, more the tendency to check 2 tests at the same time



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#### Dx of hyperglycemic disorders in pregnancy

First prenato	al visit					
Measure FPG	, A1c, or RPG on	all or only high	n-risk women			
	FPG A1c RPG					
Either one:	≥7 mmol/l	≥6.5%	≥11.1 mmol/l (+ confirmation by FPG/A1c)	Overt DM		
	≥5.1-6.9 mmol/l	-	-	GDM		
24-28 wks' g	gestation (2hr	75g OGTT)				
	FPG	1hr PG	2hr PG			
	≥7 mmol/l	-	-	Overt DM		
Either one:	≥5.1 mmol/l	≥10 mmol/l	≥8.5 mmol/l	GDM		



Int Asso of DM & Pregnancy Study Groups (IADPSG). Diabetes Care 2010;33:676-82.