HbA1c What's going on with HbA1c? What's going on with HbA1c? What's going on with HbA1c? its bow?

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Hull Royal Infirmary/Hull York Medical School

Hull and East Yorkshire Hospitals NHS Trust

H·Y·M·S

What's going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes

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HbA_{1c}: Historical Aspects

1962: Huisman and Dozy

Increases in minor fractions of haemoglobin in four diabetic patients treated with tolbutamide.

1968: Rahbar

'Diabetic haemoglobin component' found in 49 Iranian diabetic patients.

1968: Rahbar

Component the same structure as the previously described HbA_{1c}

Minor Components of HbA

Haemoglobin		Modification	Abundance (%)
A			95
HbA_1	A_{1a1}	fructose 1,6-diphosphate	0.2
	A_{1a2}	glucose-6-phosphate	0.2
	A_{1b}	carbohydrate (?)	0.5
	A_{1c}	glucose	4

HbA_{1c}: Historical Aspects

HbA_{1c} correlated with:

- Plasma 'glucose brackets'

  Koenig RJ *et al.* N Engl J Med 1976; 295: 417-420

- Daily mean plasma glucose

  Gonen B *et al.* Lancet 1977; ii; 734-737

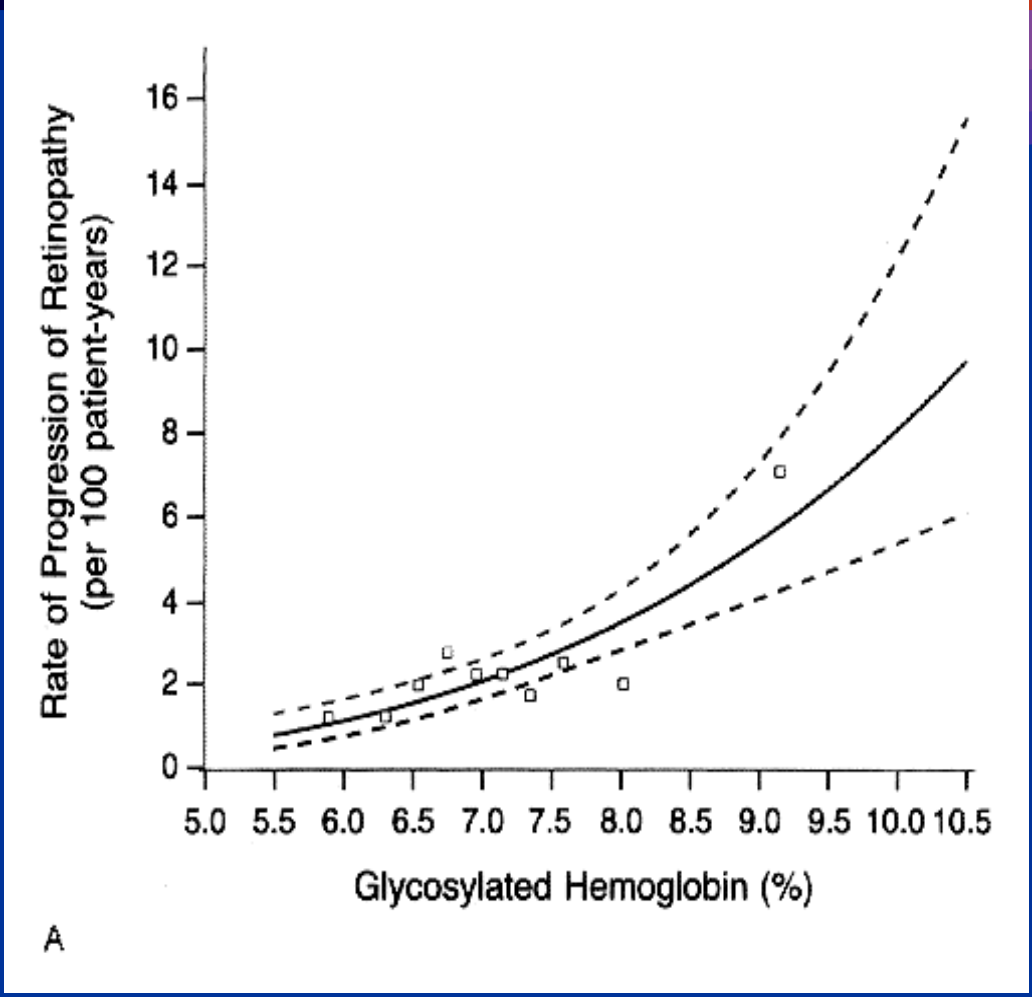
- 24 hour urinary glucose excretions

  Gabbay KH *et al.* J Clin Endocrinol Metab 1977; 44: 859-864

- Glucose control over past 6-8 weeks

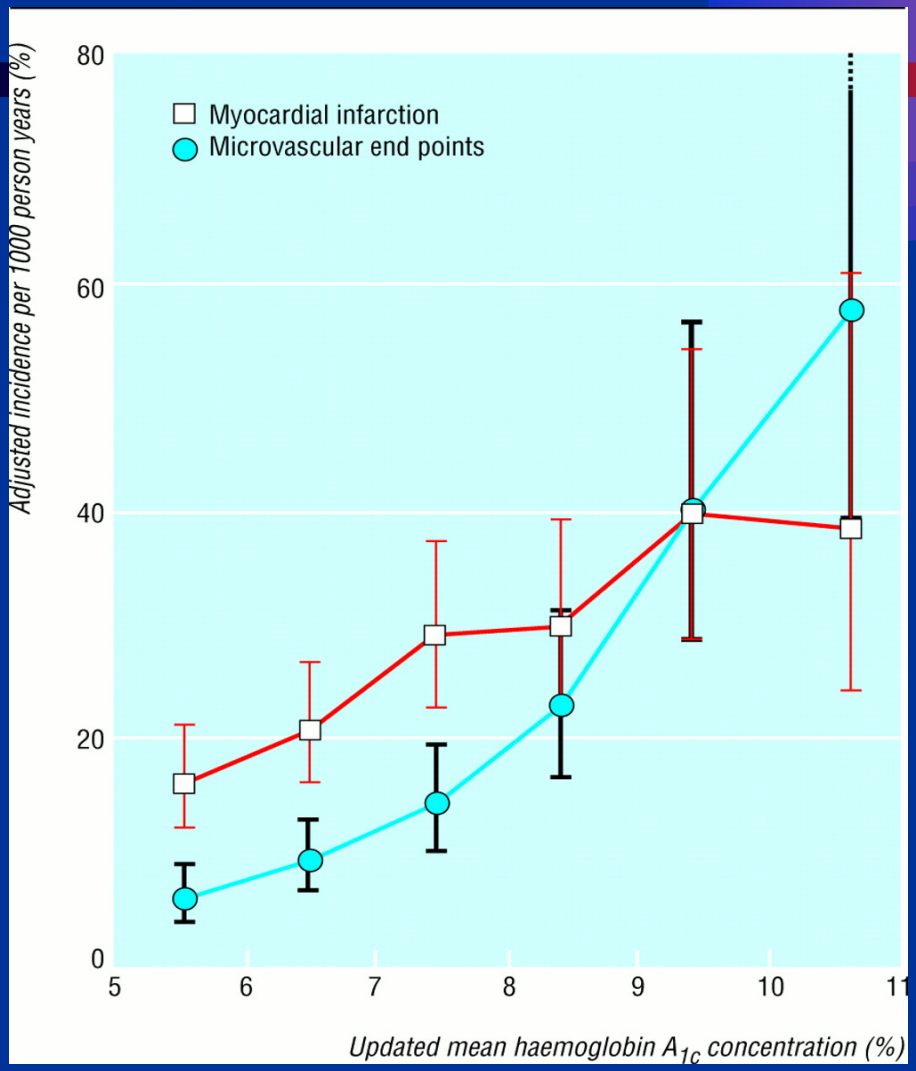
  Goldstein D *et al.* Clin Chem 1986; 32(Suppl): B64-70

DCCT: Risk of Microvascular Complications



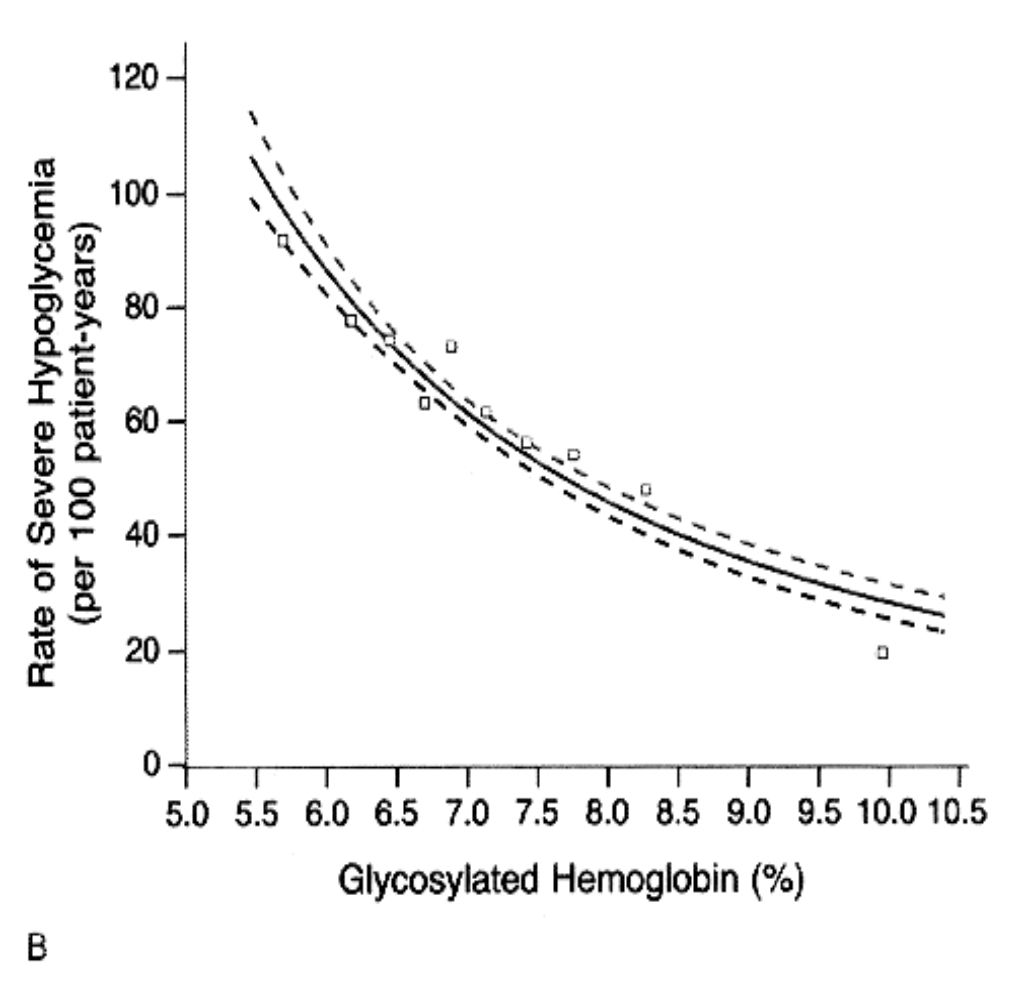
DCCT Group. *N Engl J Med*. 1993; **329:** 977-86

UKPDS: Risk of Macro and Microvascular Complications



UKPDS Group. *BMJ* 2000;321:405-412

DCCT: Risk of Severe Hypoglycaemia



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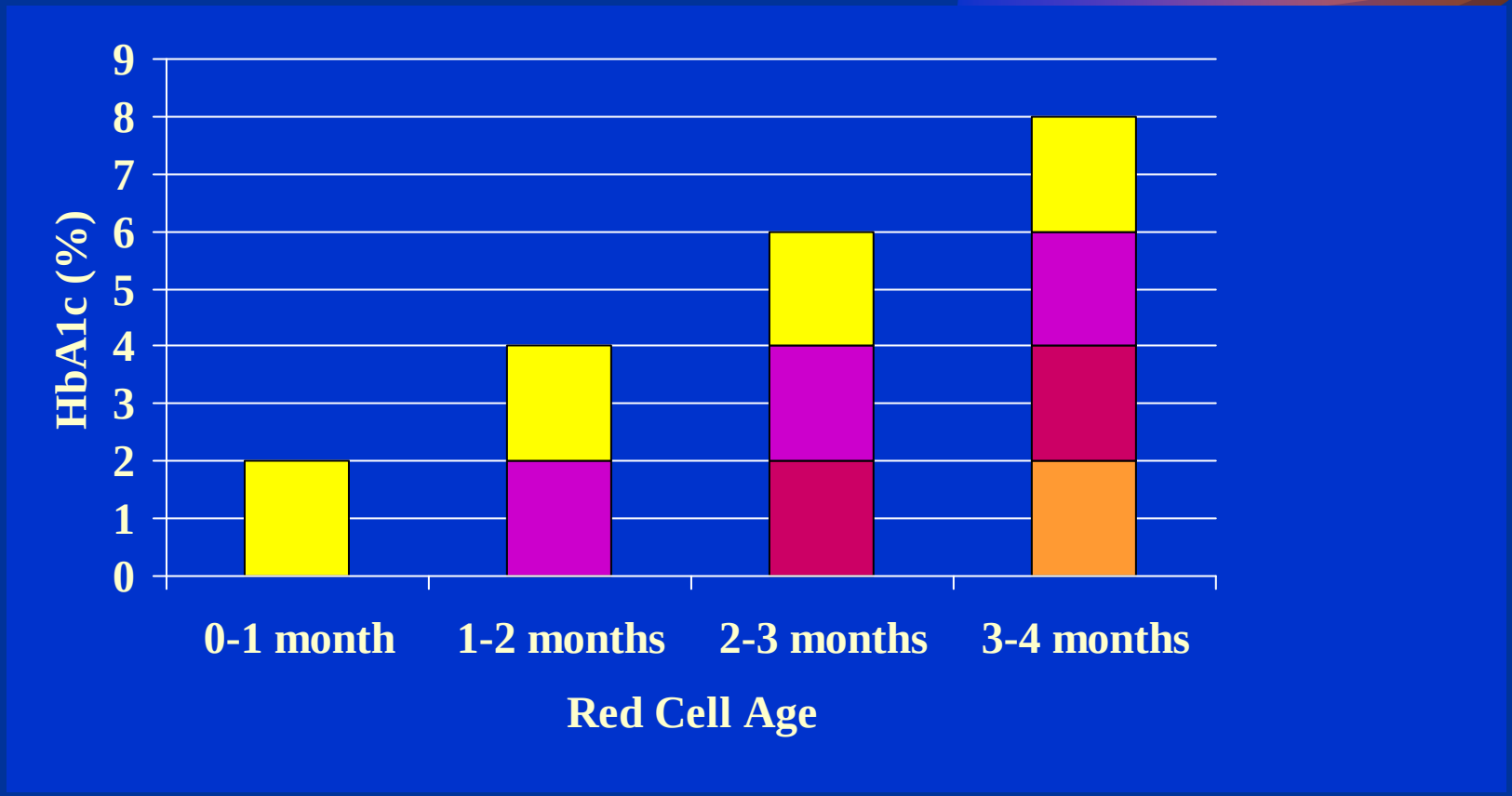
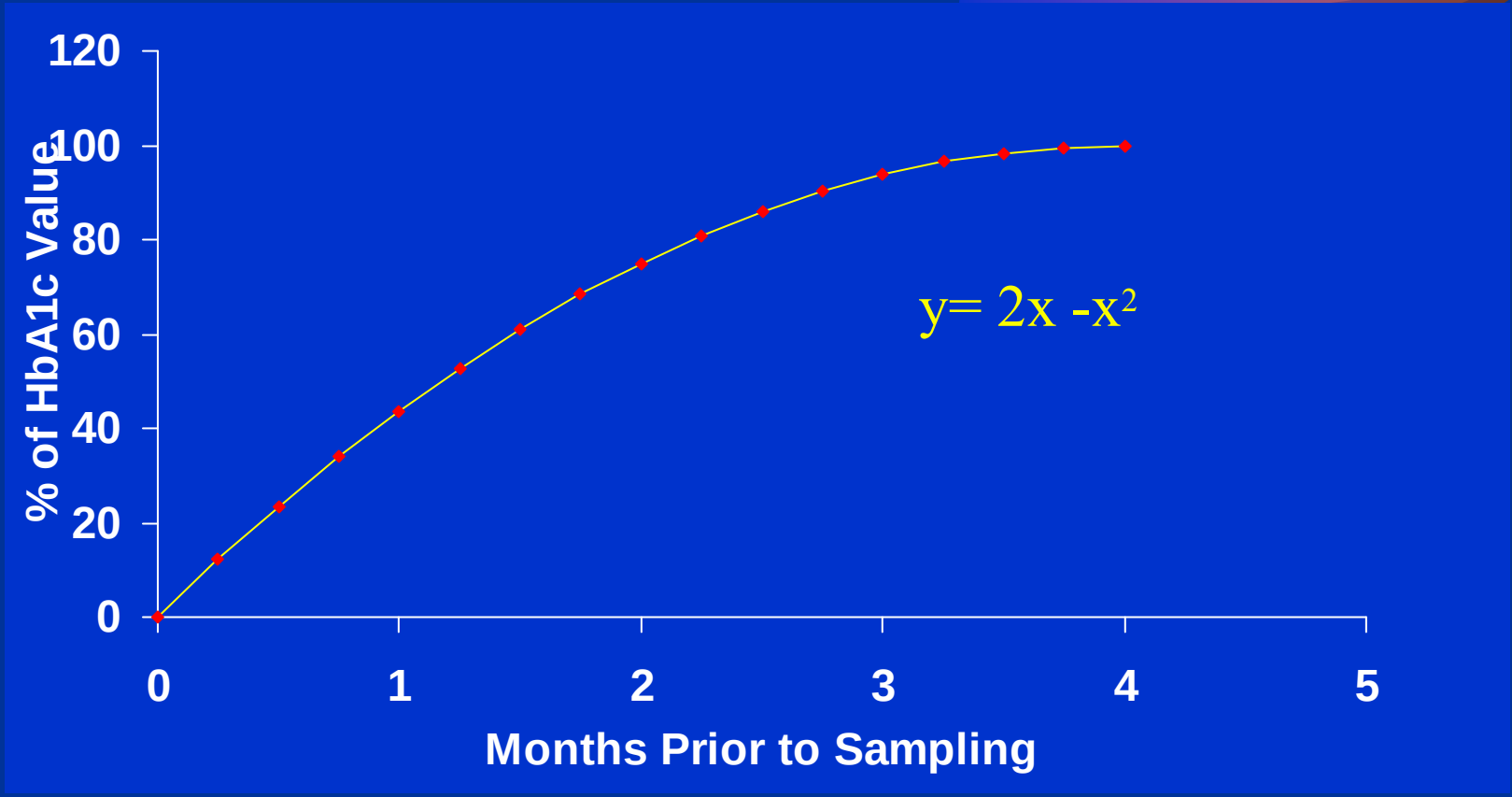
Model of Glycated Haemoglobin Formation



Model of Glycated Haemoglobin Formation

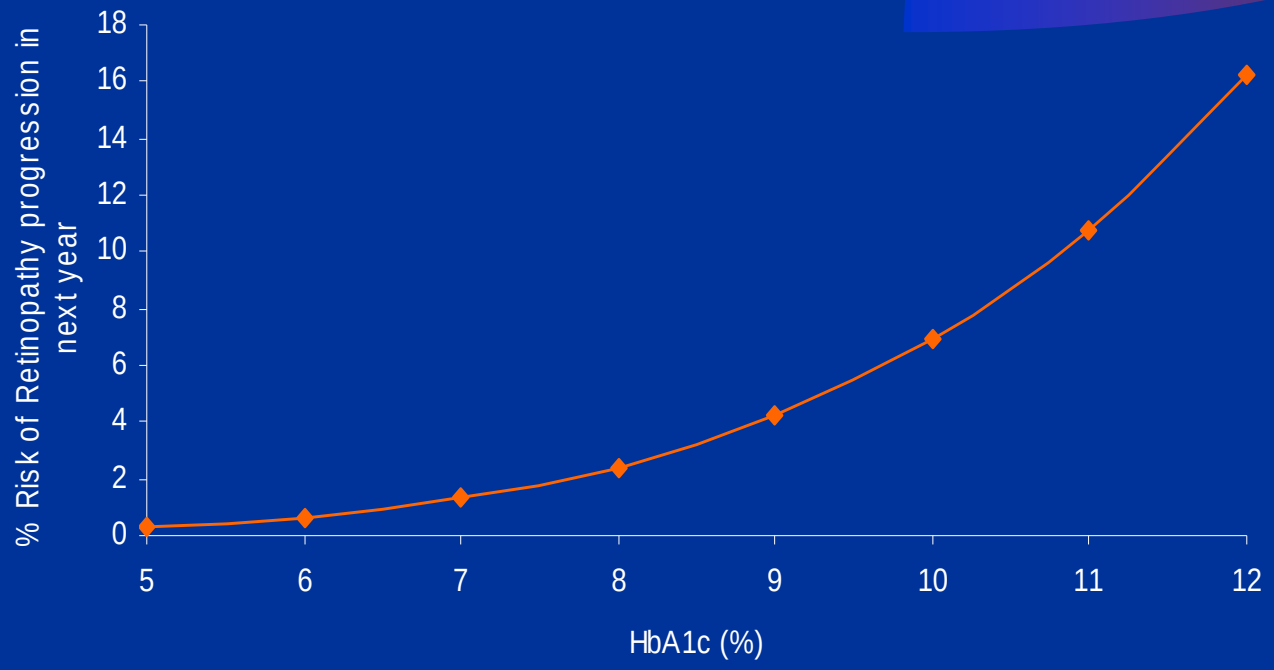


Playing the odds

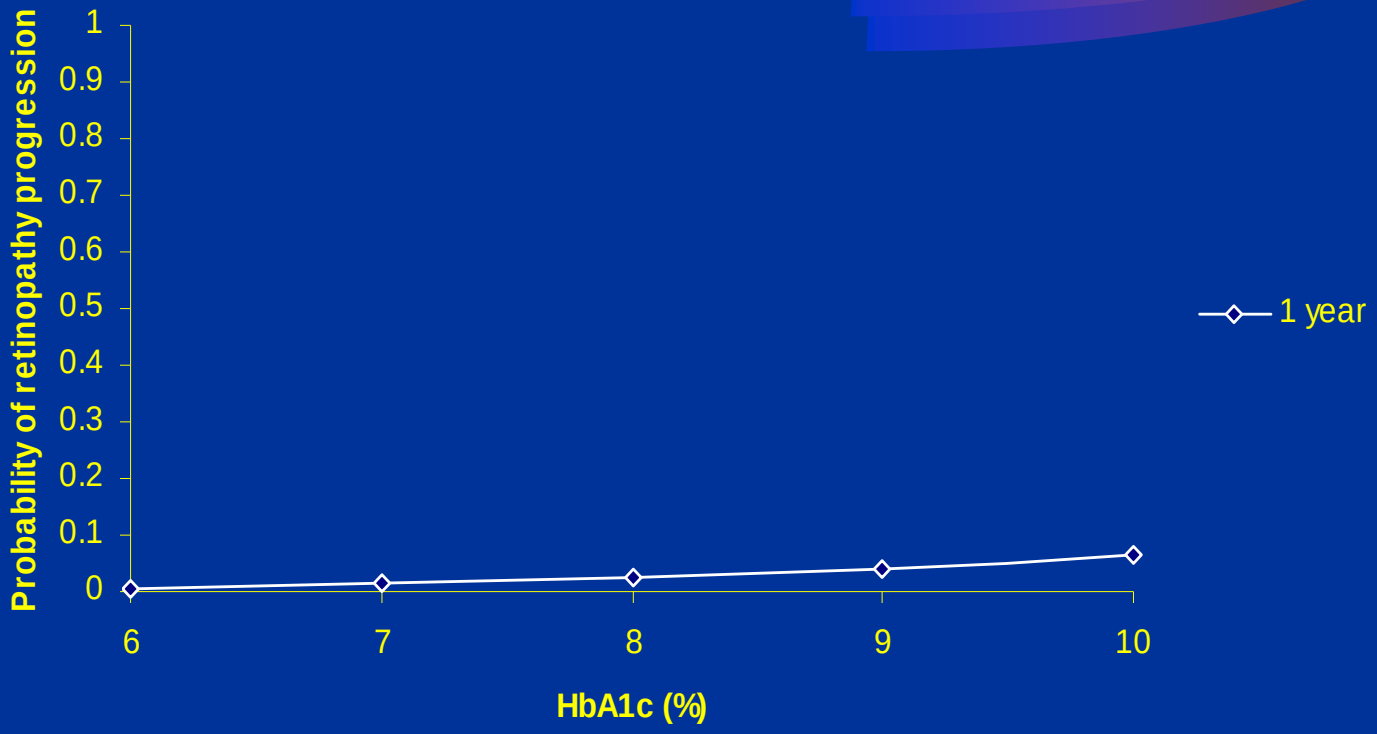
If I develop diabetes tomorrow

- What are the chances I will remain complication-free for the rest of my life?

DCCT: risk of retinopathy progression



Cumulative risk



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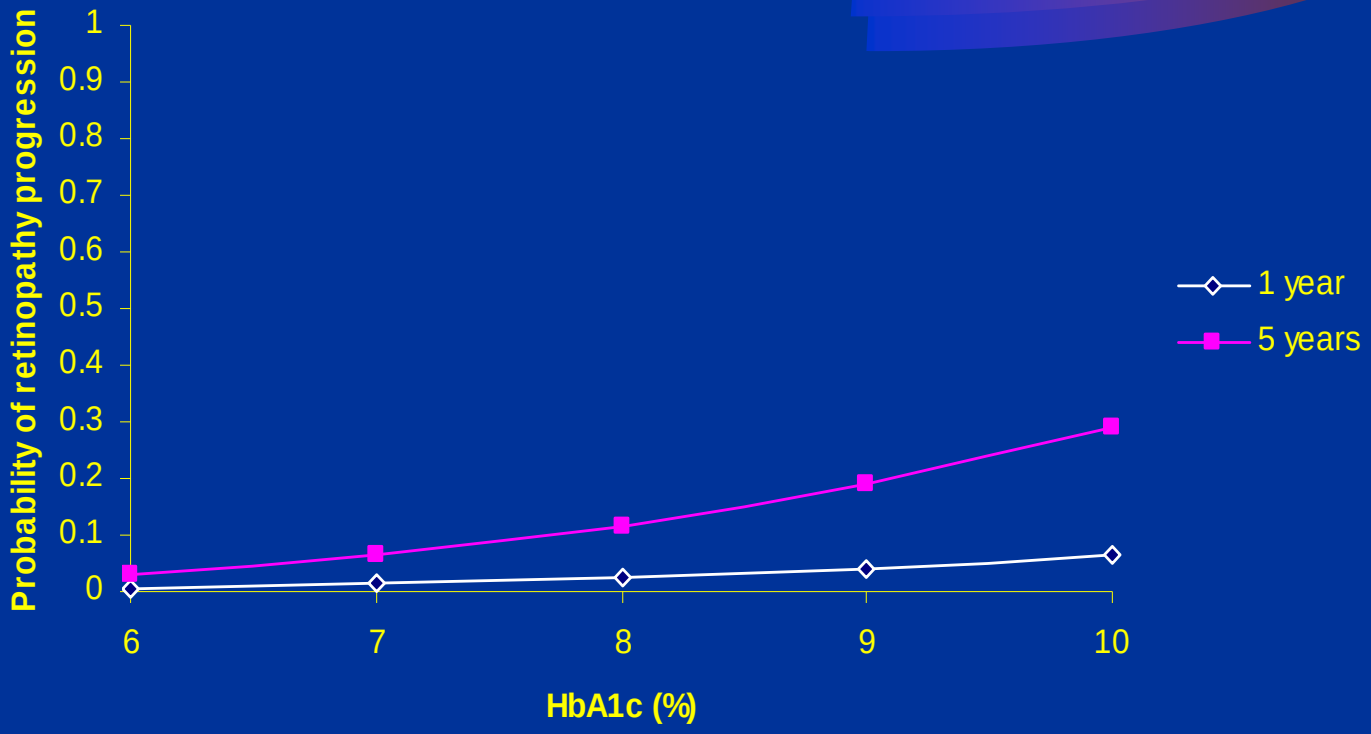
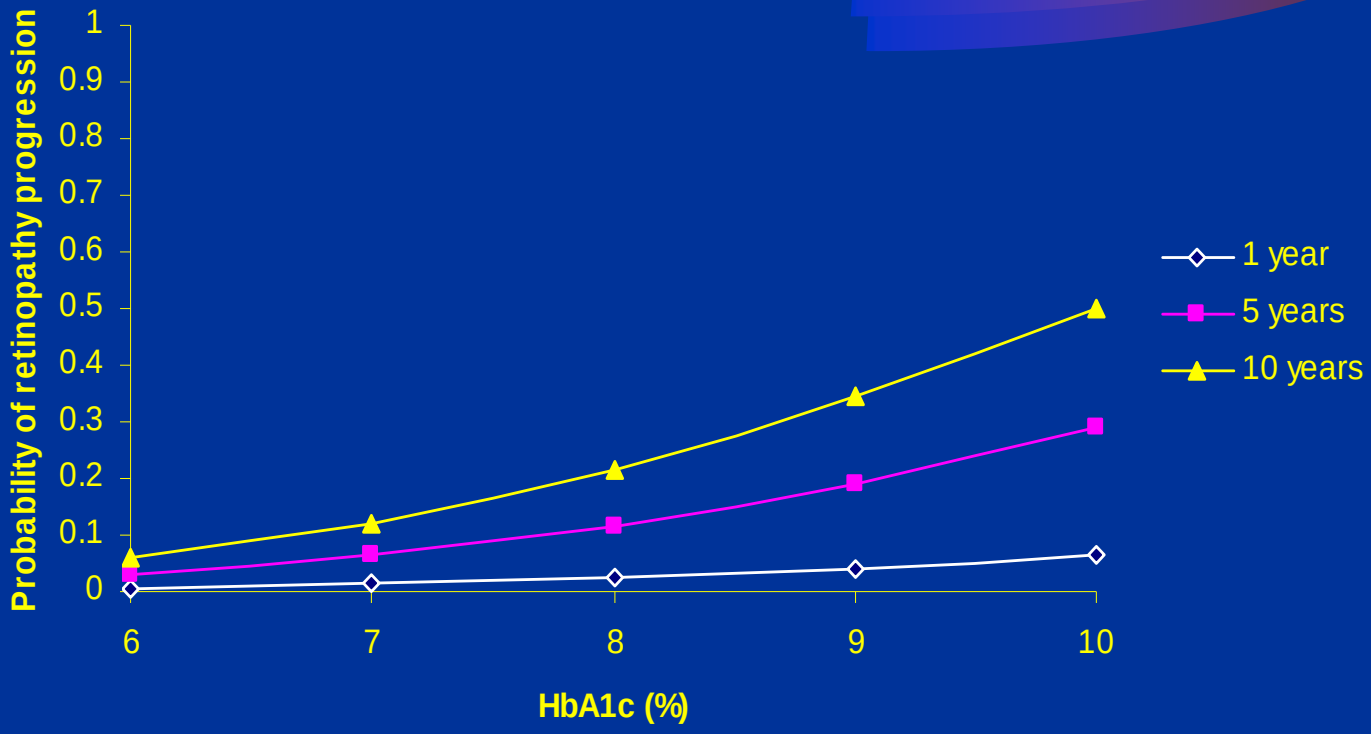
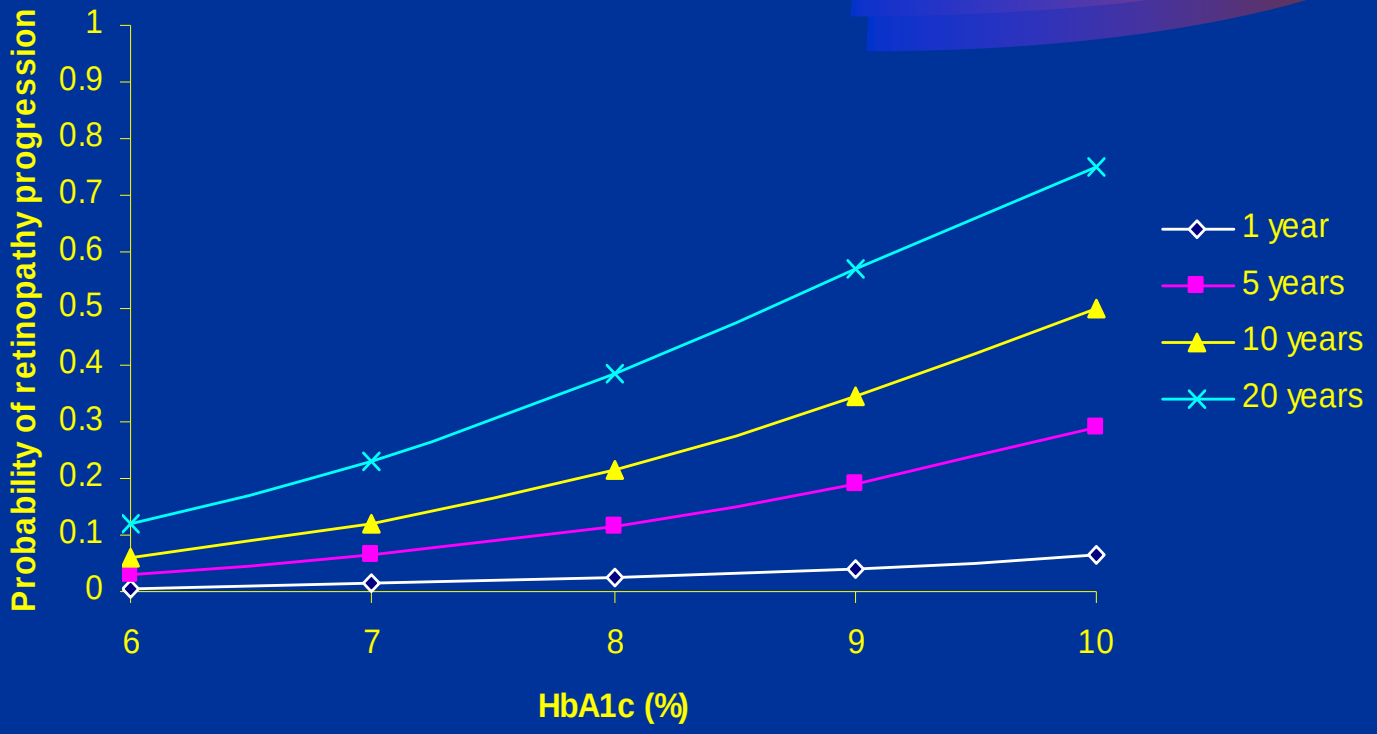


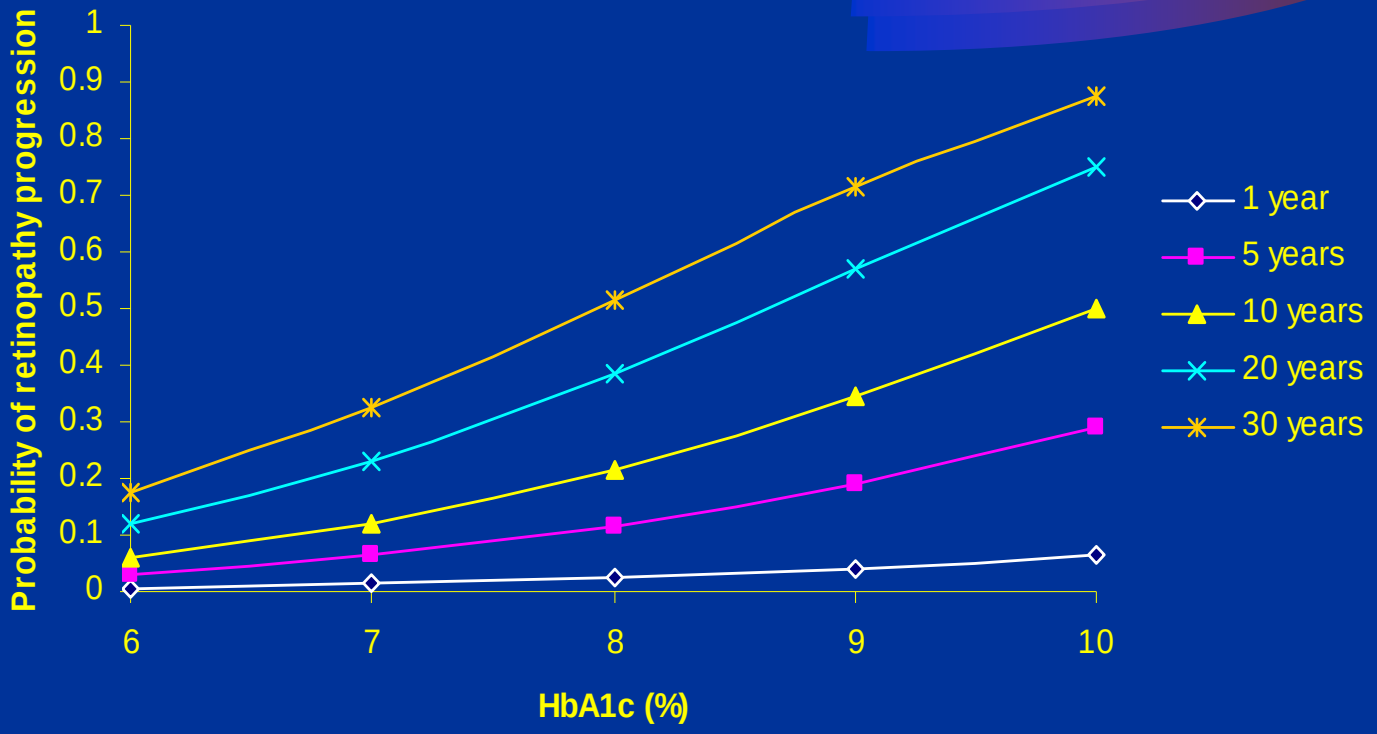
Cumulative risk



Cumulative risk



Cumulative risk



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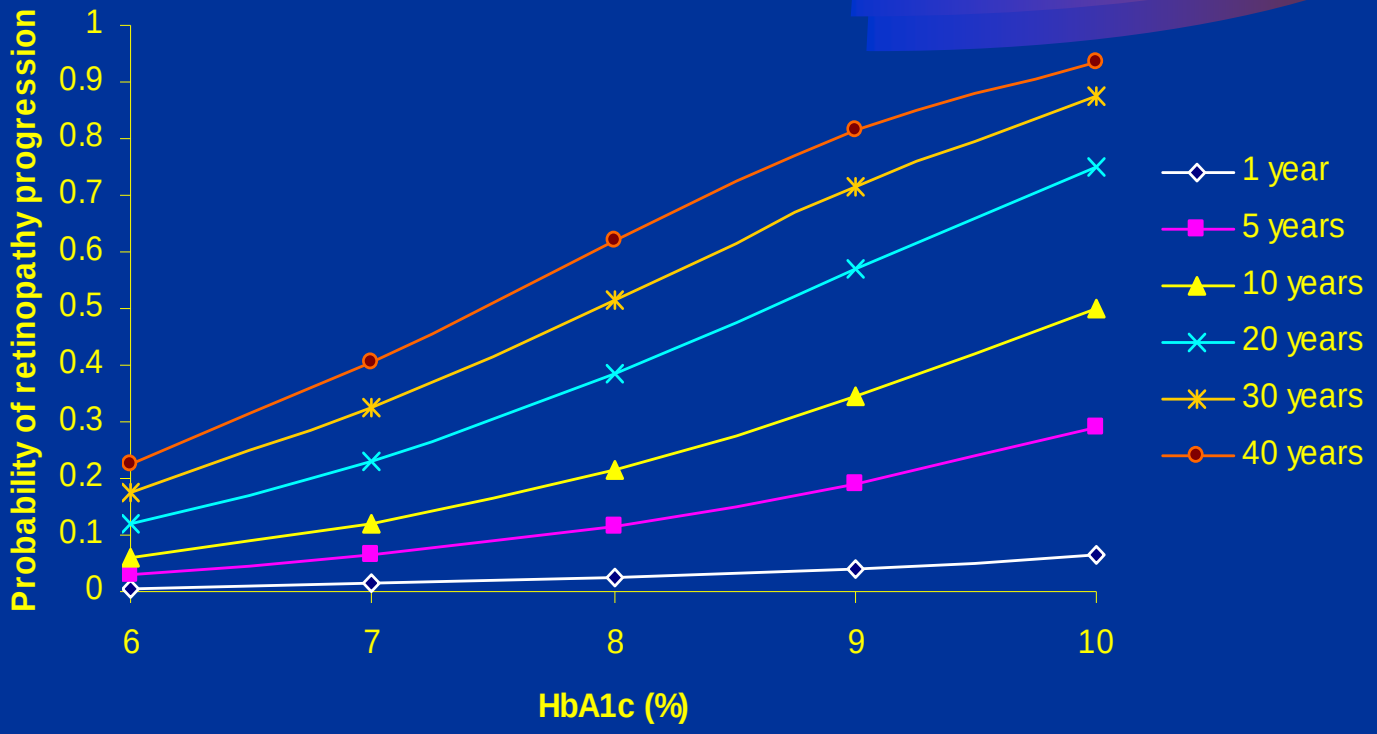

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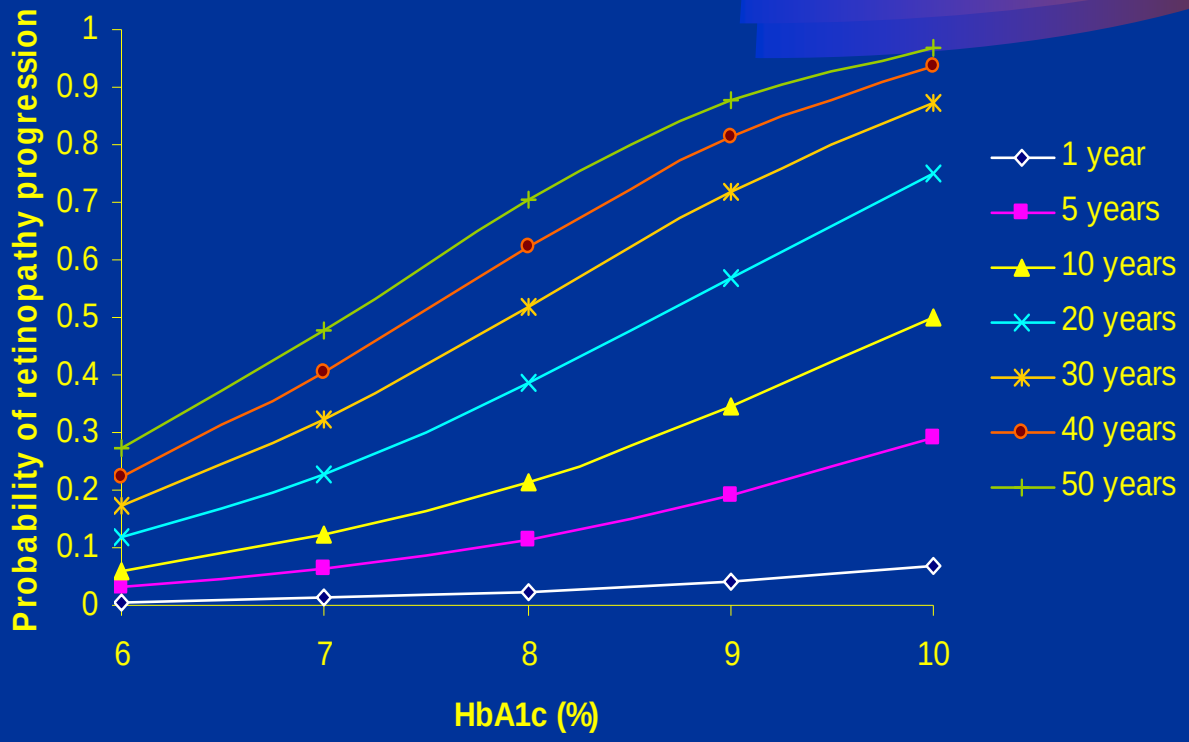
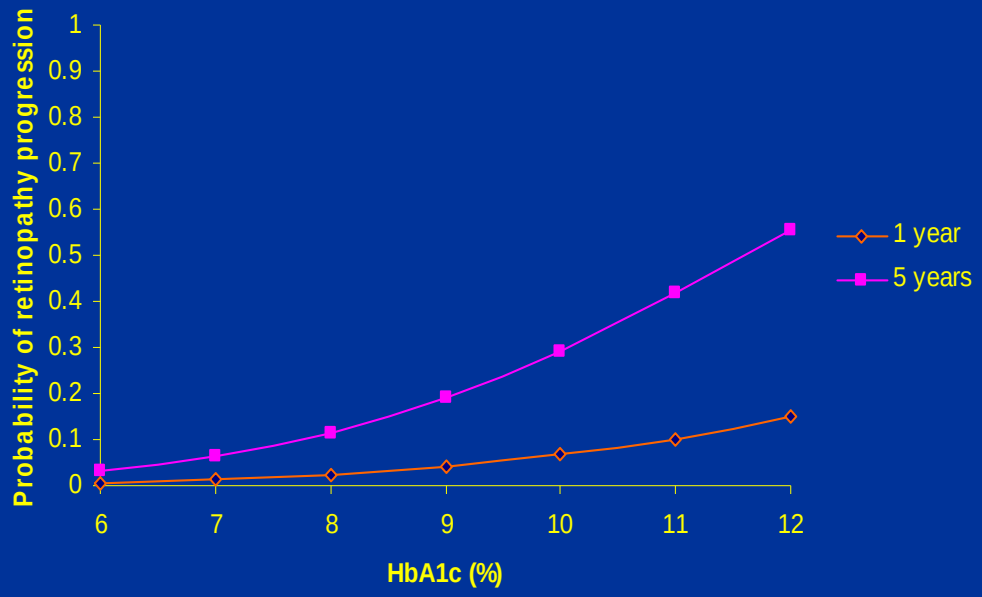


Playing the odds

- 46 years old

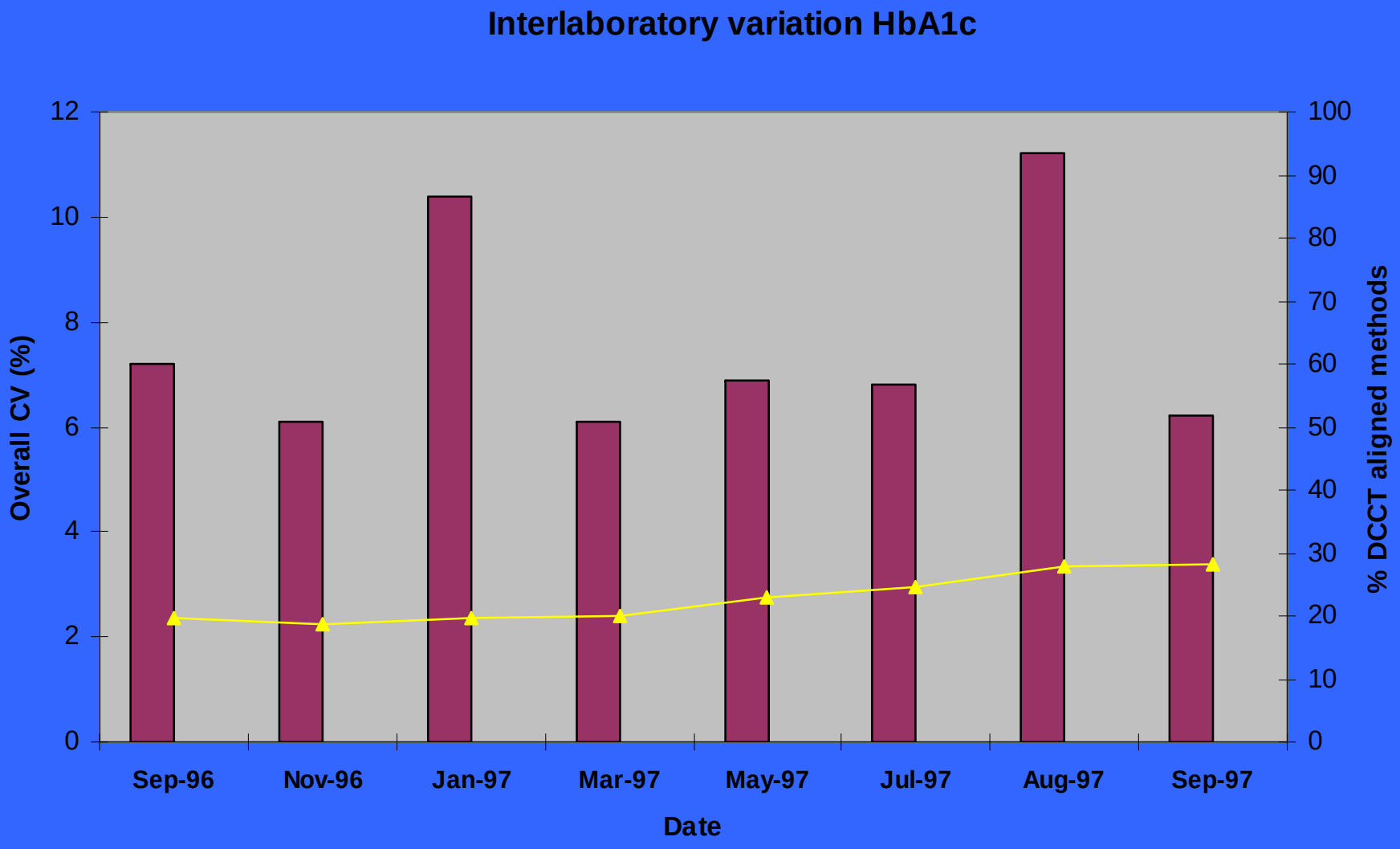


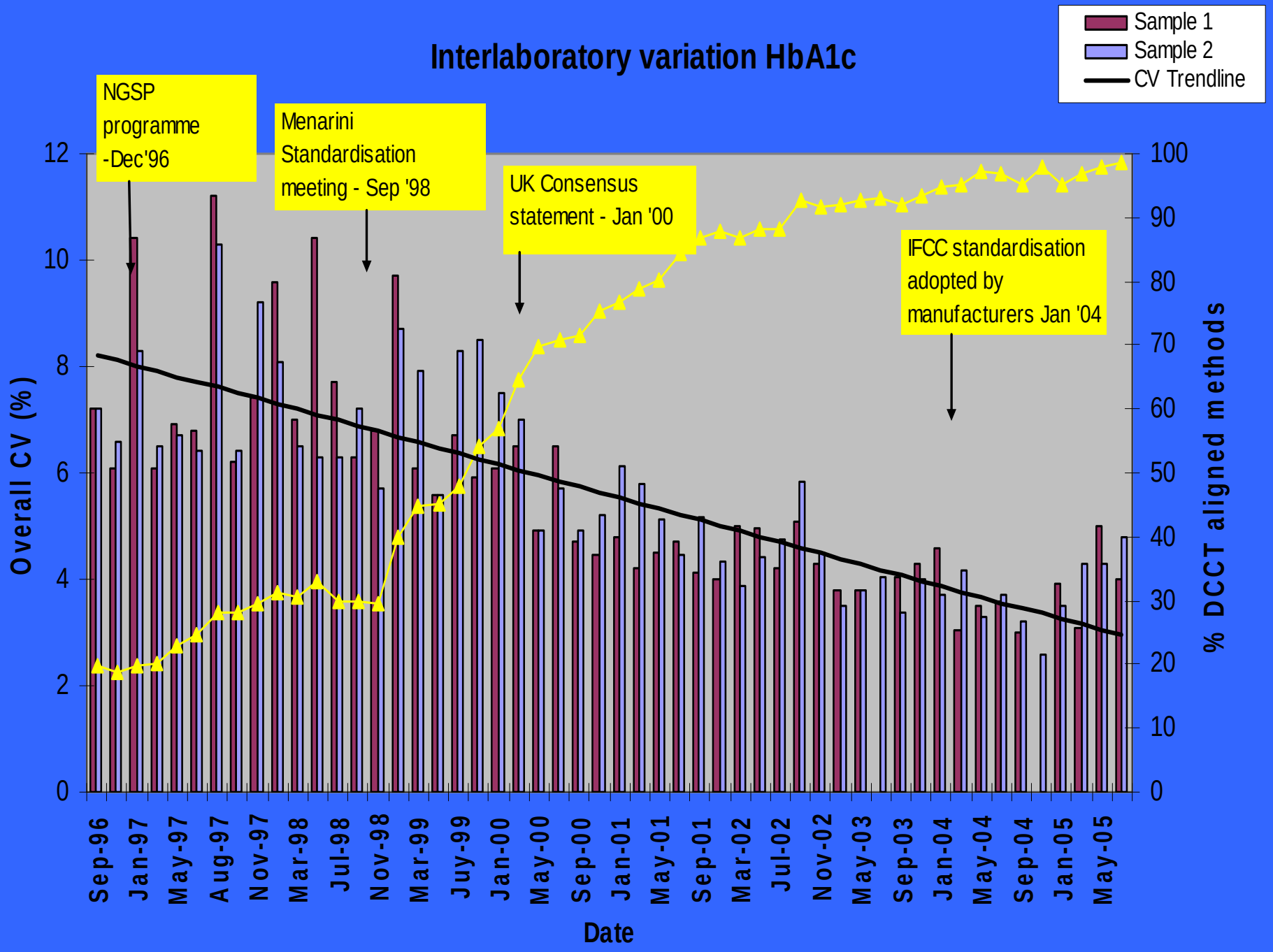
50:50 odds of developing retinopathy

HbA1c mmol/mol	Age (years)
108 (12%)	51
97 (11%)	52
86 (10%)	55
75 (9%)	61
64 (8%)	74
53 (7%)	98
42 (6%)	154

What's going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes


Interlaboratory variation HbA1c
Overall CV (%)
% DCCT aligned methods
0
2
4
6
8
10
12
0
10
20
30
40
50
60
70
80
90
100
Sep-96
Nov-96
Jan-97
Mar-97
May-97
Jul-97
Aug-97
Sep-97
Date


Interlaboratory variation HbA1c
Sample 1
Sample 2
CV Trendline
NGSP programme -Dec'96
Menarini Standardisation meeting - Sep '98
UK Consensus statement - Jan '00
IFCC standardisation adopted by manufacturers Jan '04
Overall CV (%)
% DCCT aligned methods
Date
0
2
4
6
8
10
12
0
10
20
30
40
50
60
70
80
90
100
Sep-96
Jan-97
May-97
Aug-97
Nov-97
Mar-98
Jul-98
Nov-98
Mar-99
Juy-99
Jan-00
May-00
Sep-00
Jan-01
May-01
Sep-01
Mar-02
Jul-02
Nov-02
May-03
Sep-03
Jan-04
May-04
Sep-04
Jan-05
May-05

DCCT calibration: the de facto *standard*

Cons

- Not a true standardised measurement
  - The best technology the 1980s could muster
  - Not the true HbA1c concentration
- Tracability of values to DCCT/UKPDS may be lost in time
  - Dependent on upkeep of the 1980s HPLC instrument

IFCC – Working Group on Standardisation of HbA1c

- Established in 1995
- Remit

  -To establish a definition of the analyte
  Hb that is irreversibly glycated at one or both N-terminal valines of the beta chains.

  -Establish a Primary Reference Material

  -Develop a Reference Method

  -Implement standardisation through a lab network

IFCC Reference Method for HbA1c

First step:

- haemoglobin is cleaved into peptides by the enzyme endoproteinase Glu-C

Second step:

- glycated and non-glycated N-terminal hexapeptides of the β-chain are separated and quantified by:

  1. HPLC and electrospray ionisation mass spectrometry OR
  2. two-dimensional approach using HPLC and capillary electrophoresis with UV-detection

Jeppsson JO Clin Chem Lab Med. 2002;40:78-89

DCCT vs. IFCC HbA1c

DCCT HbA1c (%)	IFCC HbA1c (%)
6	4.2
7	5.3
8	6.4
9	7.5
10	8.6

Middle J. Proceedings of the ACB National Meeting 2003

DCCT vs. IFCC HbA1c

DCCT HbA1c (%)	IFCC HbA1c (%)
6	4.2
7	5.3
8	6.4
9	7.4
10	8.5

DCCT vs. IFCC HbA1c

DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
6	4.2
7	5.3
8	6.4
9	7.4
10	8.5

DCCT vs. IFCC HbA1c

DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
6	42
7	53
8	64
9	74
10	85

Clin Chem Lab Med 2007;45:1081-1082

Consensus meeting on reporting glycated haemoglobin (HbA1c) and estimated average glucose (eAG) in the UK

- Convened at the request of Dr Sue Roberts, National Director for Diabetes
- Representatives of 18 UK professional organisations and of the diagnostic industry
- Meeting held on 23rd January 2008

HbA1c reporting in the UK

- IFCC and DCCT numbers to be ‘dual reported’ as of June 2009
- As of June 2011, removal of the DCCT numbers

DCCT vs. IFCC HbA1c

DCCT HbA1c (%)	IFCC HbA1c (mmol/mol)
6	42
7	53
8	64
9	74
10	85

Clin Chem Lab Med 2007;45:1081-1082

Middle's Manipulation

- 'I have discovered and easy way to remember how (to convert DCCT to IFCC numbers)'
- 'The master equation for the relationship between NGSP and IFCC HbA1c 'numbers' is
  IFCC% = 10x(NGSP% + 2.15) / 0.915'
- 'It turns out that this yields an easy to remember 'conversion guide' of:
  IFCC mmol/mol = (DCCT% x 11) – 24'

Jonathan Middle, ACB mailbase 29/1/08

Kilpatrick's Kludge

- minus 2 minus 2

DCCT

7%

Eric Kilpatrick, ACB mailbase 30/1/08

Kilpatrick's Kludge

- minus 2 minus 2

DCCT	-2
7%	5

Eric Kilpatrick, ACB mailbase 30/1/08

Kilpatrick's Kludge

- minus 2 minus 2

DCCT	-2	-2
7%	5	3

Eric Kilpatrick, ACB mailbase 30/1/08

Kilpatrick's Kludge

- minus 2 minus 2

DCCT	-2	-2	IFCC
7%	5	3	53mmol/mol

Eric Kilpatrick, ACB mailbase 30/1/08

Kilpatrick's Kludge

- DCCT
  4%
  5%
  6%
  7%
  8%
  9%
  10%

Kilpatrick's Kludge

DCCT	-2
4%	2
5%	3
6%	4
7%	5
8%	6
9%	7
10%	8

Kilpatrick's Kludge

DCCT	-2	-2
4%	2	0
5%	3	1
6%	4	2
7%	5	3
8%	6	4
9%	7	5
10%	8	6

Kilpatrick's Kludge

DCCT	-2	-2
4%	2	0
5%	3	1
6%	4	2
7%	5	3
8%	6	4
9%	7	5
10%	8	6

Kilpatrick's Kludge

DCCT	-2	-2
4%	20	
5%	31	
6%	42	
7%	53	
8%	64	
9%	75	
10%	86	

Kilpatrick's Kludge

DCCT	IFCC (mmol/mol)
4%	20
5%	31
6%	42
7%	53
8%	64
9%	75
10%	86

What's going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes

How do we diagnose diabetes currently?

- If a fasting plasma glucose (FPG) is ≥7.0mmol/L

  and/or

- A 2hr post-OGTT plasma glucose is ≥11.1mmol/L

SPECIAL FEATURE

Consensus Statements

A New Look at Screening and Diagnosing Diabetes Mellitus

Objective: Diabetes is underdiagnosed. About one third of people with diabetes do not know they have it, and the average lag between onset and diagnosis is 7 yr. This report reconsiders the criteria for diagnosing diabetes and recommends screening criteria to make case finding easier for clinicians and patients.

J Clin Endocrinol Metab **93: 2447–2453, 2008**

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

THE INTERNATIONAL EXPERT COMMITTEE*

An International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation was convened in 2008 to consider the current and future means of diagnosing diabetes in nonpregnant individuals. The report of the International Expert Committee represents the consensus view of its members and not necessarily the view of the organizations that appointed them. The International Expert Committee hopes that its report will serve as a stimulus to the international community and professional organizations to consider the use of the A1C [illegible] for the diagnosis of diabetes.

type 2 diabetes has a more gradual onset, with slowly rising glucose levels over time, and its diagnosis has required specified glucose values to distinguish pathologic glucose concentrations from the distribution of glucose concentrations in the nondiabetic population. Virtually every scheme for the classification and diagnosis of diabetes in modern times has relied on the measurement of plasma (or blood or serum) glucose concentrations in timed samples, such as fasting glucose; in casual samples independent of prandial status; or after a standardized metabolic stress test, such as the 75-g oral glucose tolerance test (OGTT).

relied on distributions of glucose levels, rather than on the relationship of glucose levels with complications, to diagnose diabetes despite emerging evidence that the microvascular complications of diabetes were associated with a higher range of fasting and OGTT glucose values (11,13–15). The diagnostic glucose values chosen were based on their association with decompensation to "overt" or symptomatic diabetes.

When selecting the threshold glucose values, the NDDG acknowledged that "there is no clear division between diabetics and nondiabetics in the FPG concentration or their response to an oral glucose load," and consequently, "an arbitrary decision has been made as to what level justifies the diagnosis of diabetes." The diagnosis of diabetes was made when *1*)

Diabetes Care 2009 32: 1327-1334

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

- Diabetes should be diagnosed when A1C is ≥6.5% (48mmol/mol). Diagnosis should be confirmed with a repeat A1C test.
- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.

Diabetes Care 2009 32: 1327-1334

POSITION STATEMENT

Diagnosis and Classification of Diabetes Mellitus

HbA1c ≥6.5% (48mmol/mol)

OR

FPG ≥ 7.0 mmol/l

OR

2-h plasma glucose ≥ 11.1 mmol/L during an OGTT

OR

In a patient with classic symptoms….
a random plasma glucose ≥ 11.1 mmol/L

‘The decision about which test to use to assess a specific patient for diabetes should be at the discretion of the healthcare professional’

Advantages in using HbA1c

- Assesses glycaemia over previous weeks/months
- Lower biological variability than FPG or 2hr
- Already used to guide management
- IFCC standardisation should help with harmonising results between labs

Advantages in using HbA1c

- Does not require a fasting sample
- Does not require a fasting sample
- Does not require a fasting sample
- Does not require a fasting sample
- Does not require a fasting sample
- Does not require a fasting sample

Problems in using HbA1c

- Can give spurious results in:
  - -Haemoglobinopathies
    - HbS, HbC etc
  - -Anaemia
    - haemolytic
    - iron deficiency
  - -Renal failure
  - -HIV infection
  - -Ethnicity
  - -Ageing

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Effect of haemoglobinopathies on HbA1c methods

Method (listed in alphabetical order by manufacturer)	Interference (Yes/No)					
	Hb C trait	*Hb S trait*	*Hb E trait*	*Hb D trait*	*Elevated HbF*	*Carbamyl-Hb*
Abbott Architect (Seradyn Reagents)	Yes	Yes	-		-	-
Axis-Shield Nycocard (Primus Nycocard)	No	No	-		-	-
Axis-Shield Afinion	No	No	No	No	-	-
Siemens (previously Bayer) Advia	Yes	Yes	-		-	-
Siemens (previously Bayer) DCA 2000	Yes/No	No	No	No	Yes	No
Beckman Diatrac	Yes	Yes	-		Yes	Yes
Beckman Synchron	No	No	No	No	-	-
Bio-Rad D-10 (short Program)	Yes/No	No	No	No	-	-
Bio-Rad D-10 (extended program)	No	No	No	No	-	-
Bio-Rad Variant A1c	No	Yes/No	No	No	-	Yes
Bio-Rad Variant II A1c	Yes/No	Yes/No	No	No	No	No
Bio-Rad Variant II Turbo	No	No	Yes	Yes	-	-
Dade Dimension	No	No	No	No	-	-
Diazyme Direct Enzymatic HbA1c	No	No	No	No	-	-
Drew Scientific DS5	No	Yes	-	-	-	-
Helena Glyco-Tek	Yes	No	-	-	-	-
Menarini HA8140	No	Yes	Yes	Yes	No	Yes/No
Menarini HA8160 (Diabetes Mode)	No	No	Yes	Yes	-	-
Menarini HA8160 (Thalassemia Mode)	-	-	No	Yes		
Microgenics	No	No	-	-	-	-
Bayer (previously Metrika) A1c Now	Yes	Yes	No	No	-	-
Olympus	Yes	Yes	No	No	Yes (>10%)	-
Ortho-Clinical Vitros	No	No	No	No	-	-
Pointe Scientific Hemoglobin A1c	No	No	No	No	-	-
Primus Boronate Affinity HPLC	No	No	No	No	Yes	No
Bio-Rad Deeside (previously Provalis) MicroMat (also sold by Cholestech as GDX)	Yes	No	-		-	-
Randox Haemoglobin A1c	Yes	Yes	-	-	Yes (>10%)	-
Roche Cobas Integra	Yes	Yes	-	-	-	-
Roche Cobas Integra Gen2	No	No	No	No	-	-

www.ngsp.org

For People of African, Mediterranean, or Southeast Asian Heritage: Important Information about Diabetes Blood Tests

When to Suspect that a Patient with Diabetes Has a Hemoglobinopathy

http://diabetes.niddk.nih.gov/dm/pubs/hemovari-A1C/index.htm

People who carry one gene for a hemoglobinopathy are often unaware. Several situations may indicate the presence of a hemoglobinopathy

- when results of self-blood-glucose monitoring have a low correlation with A1C results
- when an A1C result is different than expected
- when an A1C result is more than 15 percent
- when a patient's A1C test result is radically different from a previous test result following a change in laboratory A1C methods

http://diabetes.niddk.nih.gov/dm/pubs/hemovari-A1C/index.htm

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    - haemolytic
    - iron deficiency
  - -Renal failure
  - -HIV infection
  - -Ethnicity
  - -Ageing

Effect of Fe deficiency anaemia on HbA1c

- 50 patients (30 women, 20 men, mean age 35.7 ± 11.9 years) with IDA and 50 controls
- HbA1c in healthy group 5.9% ± 0.5%
- HbA1c in IDA 7.4% ± 0.8% ($p<0.001$)
- Following 3 months iron HbA1c 6.2% ± 0.6%

Acta Haematol 2004;112:126-128

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HbA1c and ethnicity in the Diabetes Prevention Programme

Mean HbA1c in subjects with IGT:

- 5.78% for whites
- 5.93% for Hispanics
- 6.00% for Asians,
- 6.12% for American Indians
- 6.18% for blacks

After adjusting for age, sex, BP, BMI, fasting glucose, glucose AUC, corrected insulin response, and insulin resistance

***Diabetes Care* 30:2453–2457, 2007**

HbA1c and ethnicity in Whitehall II Study

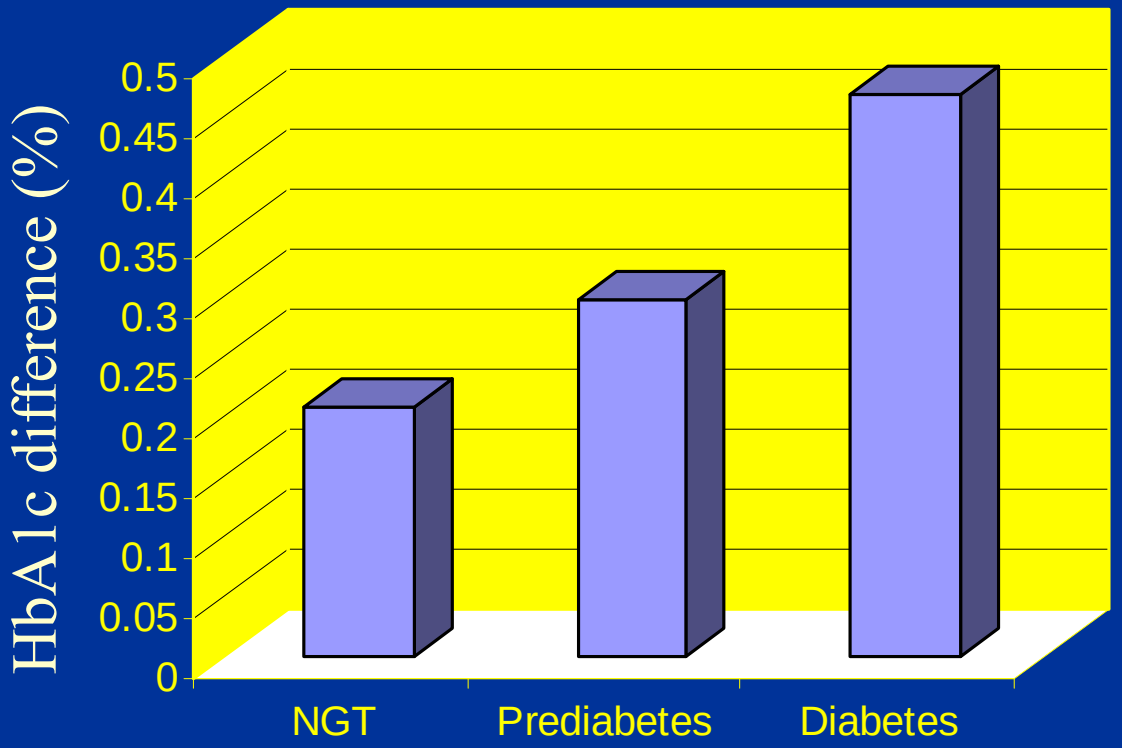
HbA1c ≥6.5%	Diabetes by OGTT
White	91%
Asian	61%
Black	50%

‘ A shift to an HbA1c-based diagnosis for diabetes will have substantially different consequences for diabetes prevalence across ethnic groups’

Diabetes Care 2010; **33:**580-582

Racial differences in HbA1c

HbA1c difference. Black vs. White, NHANES III



Ann Intern Med. 2010;152:770-7.

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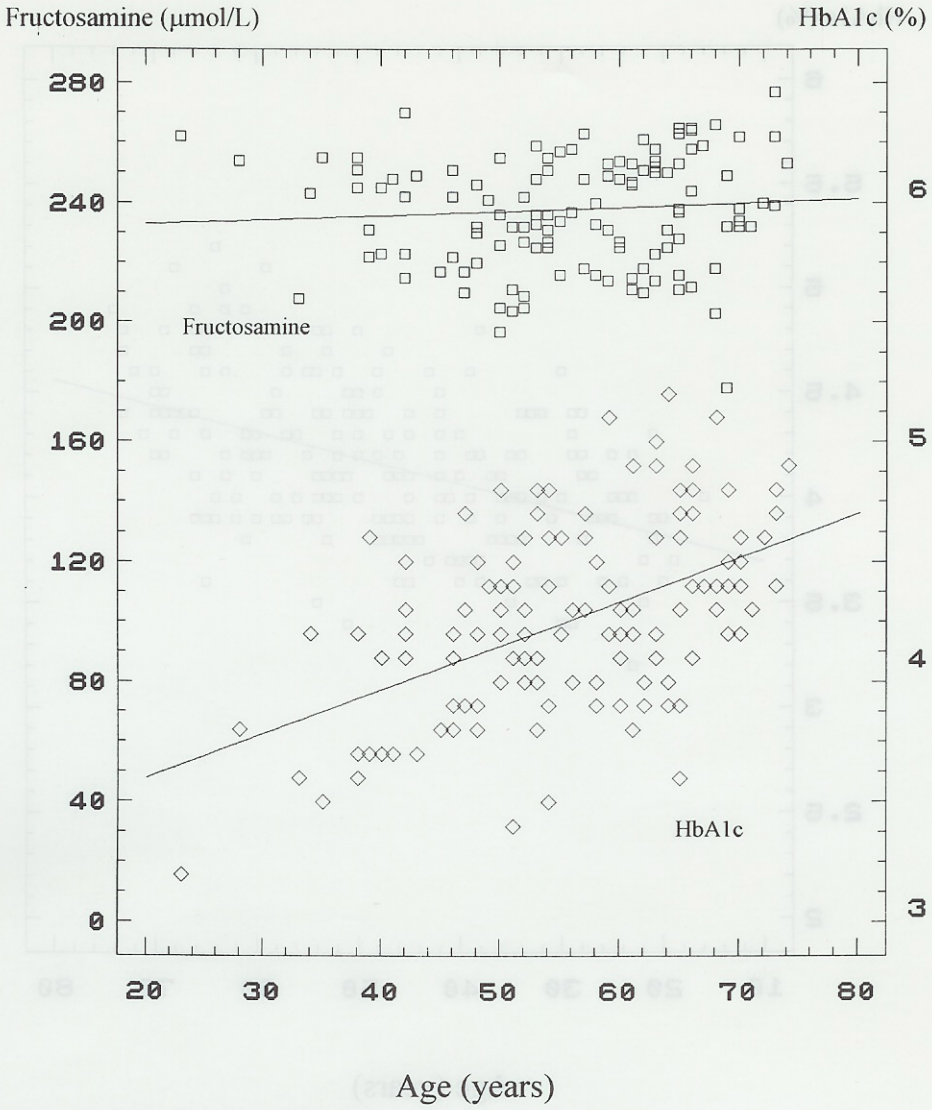
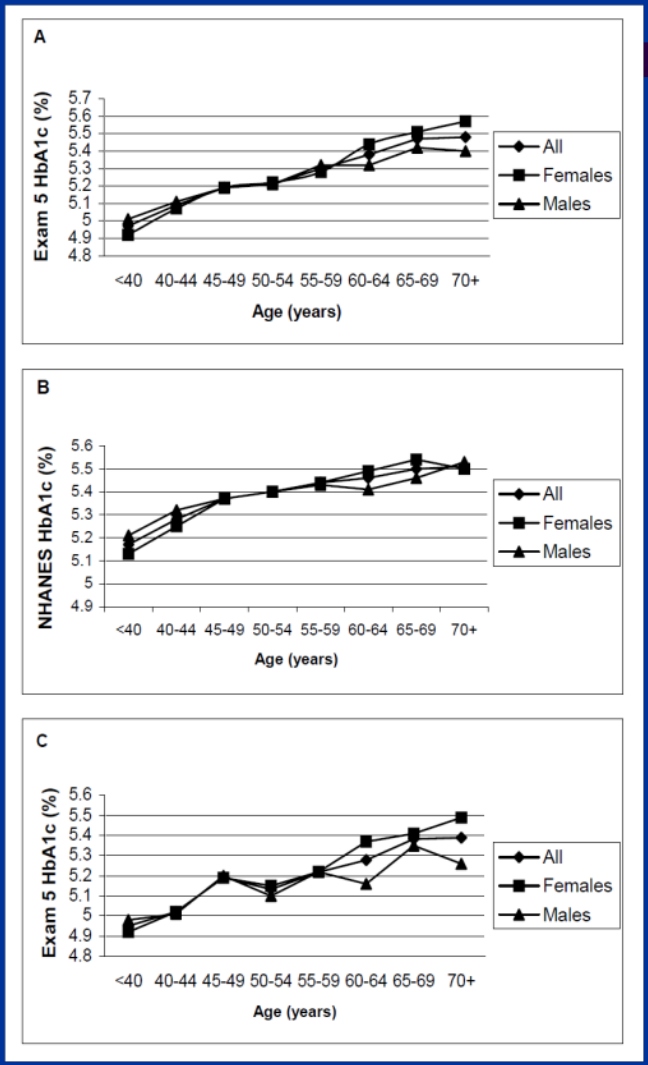
HbA1c and age



QJM 1996; **89: 307-312**

HbA1c and age



'A1C increases with age even after multivariate adjustments for gender, fasting and 2hPG……..

…… (it) suggests that non-glycemic factors may contribute to the relationship of A1C with age.'

Pandi…..and Nathan

Diabetes Care 2008; 31:1991-1996

HbA1c and diabetes diagnosis: ensuring the correct result

Further tests

- Haemoglobinopathy screen
- FBC, ferritin, haptoglobin
- Urea, creatinine

Other factors

- Ethnic background
- Age

Glucose and diabetes diagnosis: ensuring the correct result

- Make sure the patient is fasting

The proposed cut-off for diagnosis

SPECIAL FEATURE

Consensus Statements

A New Look at Screening and Diagnosing Diabetes Mellitus

Objective: Diabetes is underdiagnosed. About one third of people with diabetes do not know they have it, and the average lag between onset and diagnosis is 7 yr. This report reconsiders the criteria for diagnosing diabetes and recommends screening criteria to make case finding easier for clinicians and patients.

Conclusions: The main factors in support of using HbA1c as a screening and diagnostic test include:

J Clin Endocrinol Metab 93: 2447–2453, 2008

International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes

- Diabetes should be diagnosed when A1C is ≥6.5% (48mmol/mol). Diagnosis should be confirmed with a repeat A1C test.
- If A1C testing is not possible, previously recommended diagnostic methods (e.g., FPG or 2HPG, with confirmation) are acceptable.

Diabetes Care 2009 32: 1327-1334

HbA1c vs. OGTT

US NHANES

- 1.6% of the population had HbA1c ≥6.5%
- 5.1% undiagnosed using FPG or 2hr criteria

- 25% of patients with a +ve GTT had an HbA1c ≥6.5%
- 55% of patients with FPG ≥7mmol/L AND 2hr ≥11.1mmol/L had an HbA1c ≥ 6.5%

Diabetes Care 2010 33:562–568

HbA1c of ≥6.5% for diagnosis

- Will not identify half to two thirds of patients diagnosed using current criteria
- Will the ‘missing third’ now be the ‘missing two thirds’?
- Will it delay diagnosis in these two thirds?
- Is it acceptable that someone with a haemoglobinopathy etc is 2-3 times as likely to be diagnosed as someone without?

What about type 1 diabetes?

Could HbA1c criteria lead to a (critical) delay in diagnosis?

HbA1c to diagnose diabetes

- HbA1c for diagnosis has it's attractions
- Using a 'simple' HbA1c measurement to diagnose diabetes may not be so simple
- Individual patients risk being wrongly diagnosed because of non-glycaemic factors
- Populations risk having their diagnoses delayed

But Doctor, WHO

WHO, January 2011

Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus

Abbreviated Report of a WHO Consultation

www.who.int/cardiovascular_diseases/report-hba1c_2011_edited.pdf

Executive Summary

An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The expert group concluded that there is currently insufficient evidence to make any formal recommendation on the interpretation of HbA1c levels below 6.5%.

GRADE quality of evidence: moderate
GRADE strength of recommendation: conditional

www.who.int/cardiovascular_diseases/report-hba1c_2011_edited.pdf

What's going on with HbA1c?

- HbA1c: a brief history
- How should we report HbA1c?
- Using HbA1c to diagnose diabetes

Where from here?

- IFCC (SI) numbers seem destined to be widely used in most countries outside the US
- It seems likely HbA1c will become a diagnostic test for diabetes in the UK
- It is still unclear exactly how it will be implemented.