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Performance of strategies using one and two HbA1c cut-points for diagnosis of Type 2 diabetes: WHO or ABCD?

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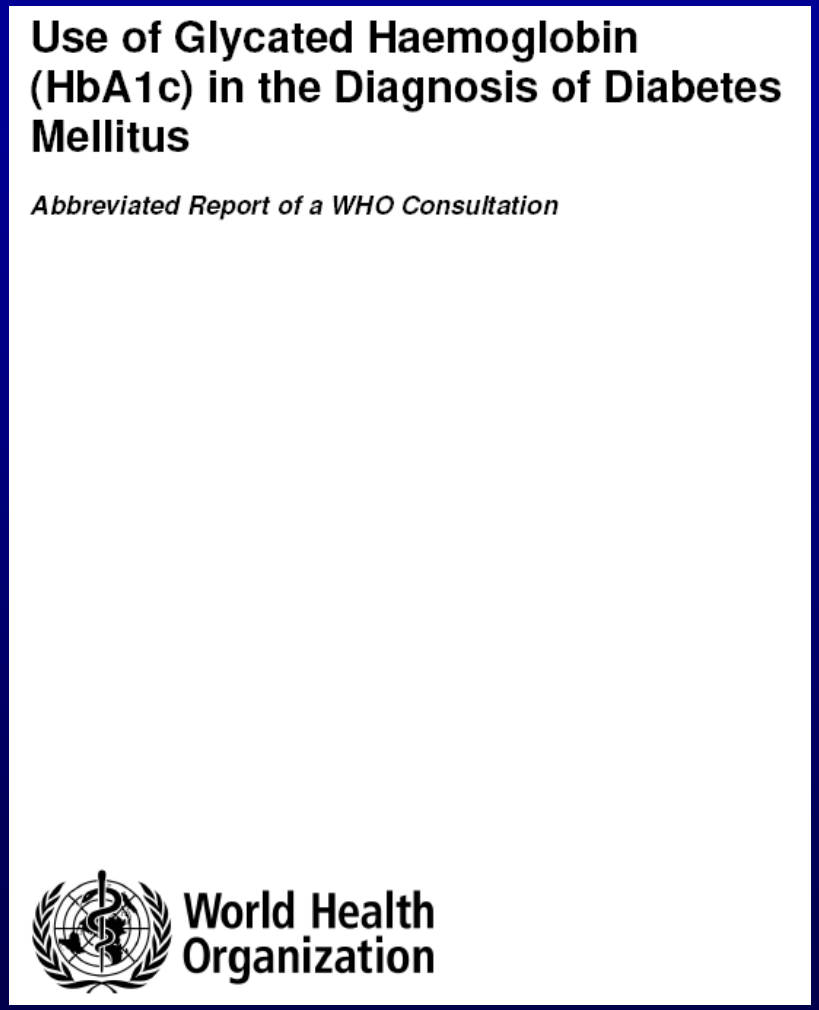
Background – 1: Burden of undiagnosed DM

- Need to simplify screening tests for T2DM to reduce burden of undiagnosed disease
- Existing screening tests may have barriers
- HbA1c actively considered as a diagnostic tool (2009)[1-3]
- Logistical advantages

1) Diabetes Care 2009:32(7);1327-1334 2) Diabetes Care 2010:33:S4-S10

3) Abbreviated Report of a WHO Consultation 2011

Background – 1: Breakthrough



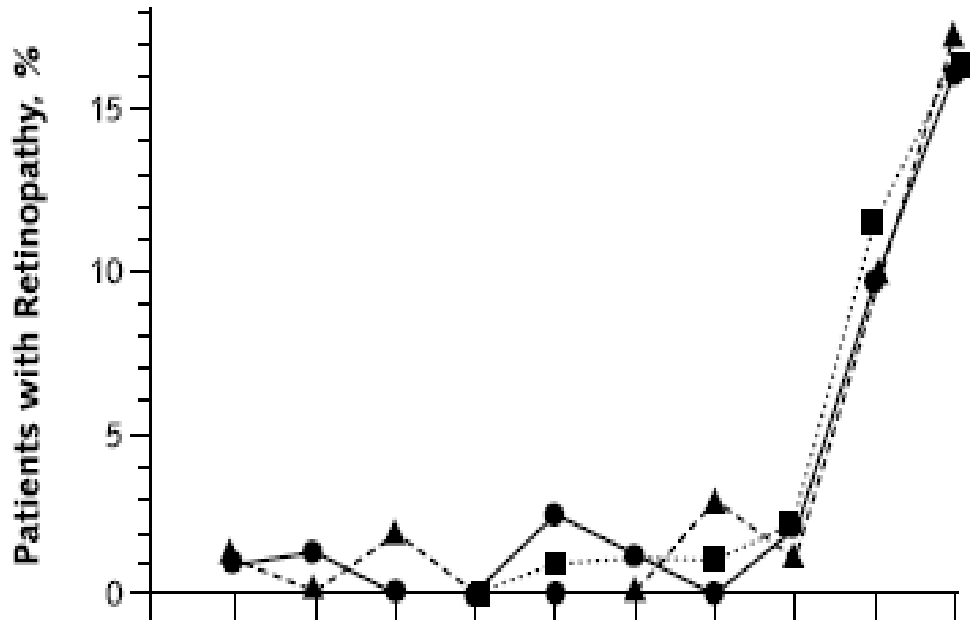
- ADA 2010 [1]
- WHO 2011 [2]
- recommend using HbA1c ≥ 6.5% (48mmol/mol)
- to detect T2DM in non-pregnant adults
- in addition to previous glucose criteria

- IGR: ADA: HbA1c 5.7 - 6.4% 'high risk'

  WHO: not enough evidence

1) Diabetes Care 2010:33:S4-S10 2) Abbreviated Report of a WHO Consultation 2011

HbA1c≥ 6.5% reflects onset of diabetic retinopathy



Fasting plasma glucose level, *mg/dL*	70	89	93	97	100	105	109	116	136	226
2-hour plasma glucose level, *mg/dL*	38	94	106	116	126	138	156	185	244	364
Hemoglobin A_{1c} level, %	3.4	4.8	5.0	5.2	5.3	5.5	5.7	6.0	6.7	9.5

Study	HbA1c
DETECT-2 [2] n=28,010	6.3 – 6.7%
NHANES [3] n=1066	≥ 5.5%
Malaysia [4] n=3190	6.6 – 7.0%

1) Diabetes Care 2009:32(7);1327-1334 2) Diabetes Care2011:34(1):145-50.

3) Diabetes Care 2009;32(11):2027-32 4) Diabetologia 2009 Jul;52(7):1279-89.

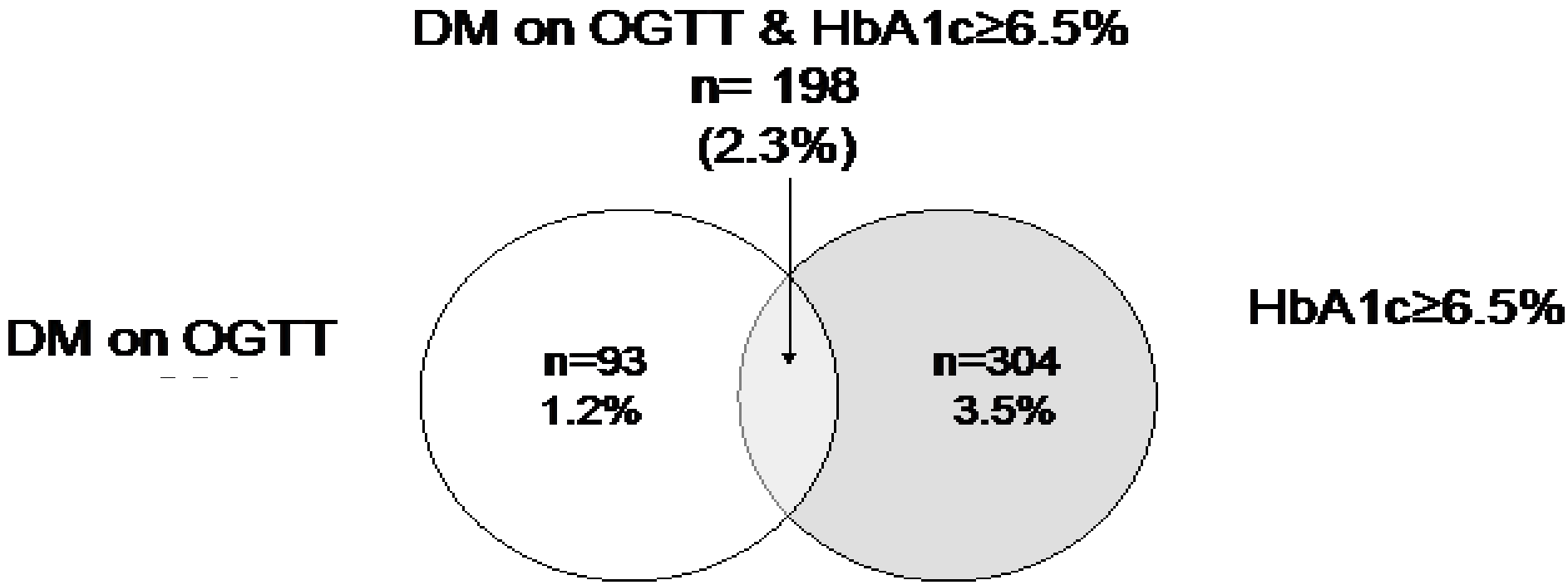
Background – 2: OGTT or HbA1c

- Two Discordant tests = different people detected
- Sensitivity: HbA1c ≥ 6.5% to detect OGTT defined T2DM can be as low as 20% [1-2]
- ? Which correct or 'better' test to use.
- HbA1c better predictor of micro + macro-vascular complications [3-4]
- Caution remains about using HbA1c 6.5% for diagnosis

1) Diabetes Care 2010:33(3):580-582. 2) Diabetes Research Clinical Practice 2007: 76(2):251-256.

3) PLos Medicine 2010: 7(5). E1000278. 4) N Engl J Med. 2010;362(9): 800-11

Figure 1. Venn diagram of prevalence of HbA1c vs. OGTT



MOSTAFA et al. Diabetic Medicine 2010

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ABCD position statement on haemoglobin A1c for the diagnosis of diabetes

ES Kilpatrick, PH Winocour; on behalf of the Association of British Clinical Diabetologists (ABCD). Endorsed by the Association for Clinical Biochemistry (ACB)*

- Concerns: lack of standardisation of HbA1c techniques
- UK NEQAS (2009)

  – same sample of HbA1c 6.5% sent to UK laboratories

  - 251 instruments gave HbA1c measurements varying from 5.8 – 7.2%

1 Pract Diab Int 2010: 27 (7): 306-310

ABCD 2010: a two HbA1c cut-point strategy?

- Principle: decrease false negative/ positive diagnoses
- The 1st cut-point 'rules out' diabetes: HbA1c ≤ 5.7% [1]
- The 2nd cut-point 'rules in' diabetes: 2 x HbA1c ≥ 7.3%[1]
- Any value between 5.8 - 7.2% = 'Intermediate HbA1c'. [1]
- People with 'intermediate HbA1c' may have diabetes and require a confirmatory glucose test [1-2]

1 Pract Diab Int 2010: 27 (7): 306-310 2 Endocrine Practice 2010; 16 (2): 155-6.

Two HbA1c cut-point strategies

	Rule out cut-point	Rule in cut-point	Intermediate HbA1c range
ABCD [1]	≤ 5.7%	≥ 7.3%	5.8 to 7.2%
Australian group [2]	≤ 5.5%	≥ 7.0%	5.6 to 6.9%
AACE/ACE [3]	≤ 5.4%	≥ 6.5%	5.5 to 6.4%

1) Practical Diabetes International 2010. 27(7):306–310. 2) Diabetes Care 2010:33(4):817-9. 3) Endocrine Practice 2010;16(2):155-6.

In the UK, two options……

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

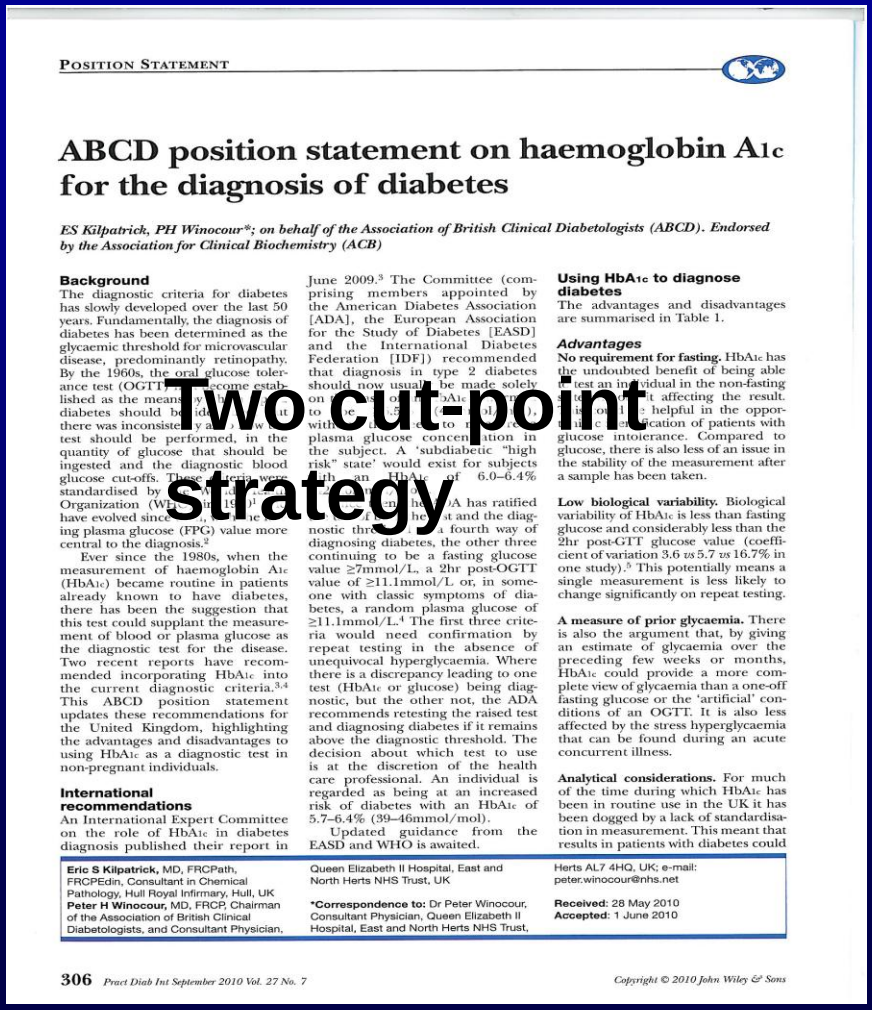
Abbreviated Report of a WHO Consultation

Single cut-point ≥ 6.5%

World Health Organization

Vs.

Two cut-point strategy



POSITION STATEMENT

ABCD position statement on haemoglobin A1c for the diagnosis of diabetes

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Background

The diagnostic criteria for diabetes has slowly developed over the last 50 years. Fundamentally, the diagnosis of diabetes has been determined as the glycaemic threshold for microvascular disease, predominantly retinopathy. By the 1960s, the oral glucose tolerance test (OGTT) had become established as the means by which diabetes should be identified but there was inconsistency as to how the test should be performed, in the quantity of glucose that should be ingested and the diagnostic blood glucose cut-offs. These criteria were standardised by the World Health Organization (WHO) in 1980 but have evolved since to the current fasting plasma glucose (FPG) value more central to the diagnosis.[2]

Ever since the 1980s, when the measurement of haemoglobin A1c (HbA1c) became routine in patients already known to have diabetes, there has been the suggestion that this test could supplant the measurement of blood or plasma glucose as the diagnostic test for the disease. Two recent reports have recommended incorporating HbA1c into the current diagnostic criteria.[3,4] This ABCD position statement updates these recommendations for the United Kingdom, highlighting the advantages and disadvantages to using HbA1c as a diagnostic test in non-pregnant individuals.

International recommendations

An International Expert Committee on the role of HbA1c in diabetes diagnosis published their report in June 2009.[3] The Committee (comprising members appointed by the American Diabetes Association [ADA], the European Association for the Study of Diabetes [EASD] and the International Diabetes Federation [IDF]) recommended that diagnosis in type 2 diabetes should now usually be made solely on the basis of HbA1c to be [illegible] with [illegible] to the plasma glucose concentration in the subject. A 'subdiabetic "high risk" state' would exist for subjects with an HbA1c of 6.0–6.4% [illegible] HbA1c has ratified [illegible] the test and the diagnostic threshold as a fourth way of diagnosing diabetes, the other three continuing to be a fasting glucose value ≥7mmol/L, a 2hr post-OGTT value of ≥11.1mmol/L or, in someone with classic symptoms of diabetes, a random plasma glucose of ≥11.1mmol/L.[4] The first three criteria would need confirmation by repeat testing in the absence of unequivocal hyperglycaemia. Where there is a discrepancy leading to one test (HbA1c or glucose) being diagnostic, but the other not, the ADA recommends retesting the raised test and diagnosing diabetes if it remains above the diagnostic threshold. The decision about which test to use is at the discretion of the health care professional. An individual is regarded as being at an increased risk of diabetes with an HbA1c of 5.7–6.4% (39–46mmol/mol).

Updated guidance from the EASD and WHO is awaited.

Using HbA1c to diagnose diabetes

The advantages and disadvantages are summarised in Table 1.

Advantages

No requirement for fasting. HbA1c has the undoubted benefit of being able to test an individual in the non-fasting [illegible] affecting the result. [illegible] helpful in the opportunistic identification of patients with glucose intolerance. Compared to glucose, there is also less of an issue in the stability of the measurement after a sample has been taken.

Low biological variability. Biological variability of HbA1c is less than fasting glucose and considerably less than the 2hr post-GTT glucose value (coefficient of variation 3.6 *vs* 5.7 *vs* 16.7% in one study).[5] This potentially means a single measurement is less likely to change significantly on repeat testing.

A measure of prior glycaemia. There is also the argument that, by giving an estimate of glycaemia over the preceding few weeks or months, HbA1c could provide a more complete view of glycaemia than a one-off fasting glucose or the 'artificial' conditions of an OGTT. It is also less affected by the stress hyperglycaemia that can be found during an acute concurrent illness.

Analytical considerations. For much of the time during which HbA1c has been in routine use in the UK it has been dogged by a lack of standardisation in measurement. This meant that results in patients with diabetes could

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Aims

- 1) Compare performance of:

  ABCD ‘rule-out, rule-in’ HbA1c strategy: 5.7%/ 7.3%
  (confirmatory test = OGTT)

  vs. WHO 2011: HbA1c ≥ 6.5%

  - to detect OGTT defined T2DM [1]

- 2) To determine the optimal two cut-points in our cohort

1. WHO 1999 report

Patients and Methods

- Analysis of LEADER cohort [1-2]
- Leicestershire, UK: 2002-8.
- Undiagnosed primary care individuals
- Aged 40-75 years
- All underwent OGTT and HbA1c.

1) Diabetic Medicine 2010:27(7):762-769. 2) Diabetes Research Clinical Practice.2010: 90(1):100-8.

Methods-2: Laboratory Assays

- HbA1c - measured on HPLC assay
  - DCCT aligned: CV 1.9% at HbA1c 5.3%
  - recognise variant Hb S and C (excluded)
- Glucose samples:
  - Abbott Aeroset clinical chemistry analyzer (hexokinase method):
  - CV 1.61% at 6.8mmol/l

Results – Cohort demographics

- Cohort size: n = 8696
- Mean age: 57.3 years (SD 9.7)

White Europeans (WE):	74.7%
South Asians (SA):	22.8%

- Mean cohort HbA1c: 5.71% (SD 0.61): High
- OGTT : T2DM n = 291 (3.3%).

Results 1 - White Europeans

Strategy	Single cut-point	2 cut-point	
Sensitivity	62.1%	93.4%	+31%
Specificity	97.7%	98.9%	
PPV	44.8%	85.5%	+41%
NPV	98.9%	99.6%	

Single cut-point: 6.5% 2 cut-points: 5.7% and 7.3%

Results 2- South Asians

Strategy	Single cut-point	2 cut-point	
Sensitivity	78.9%	98.9%	+20%
Specificity	92.8%	99.7%	
PPV	36.2%	87.5%	+51%
NPV	98.8%	99.9%	

Single cut-point: 6.5% 2 cut-points: 5.7% and 7.3%

‘Intermediate HbA1c’ 5.8-7.2%

- Whole cohort
- Intermediate HbA1c: 5.8 – 7.2%: n = 3447

  39.6% of cohort

5.8 – 6.4%: n = 3060

35.2% of cohort

Optimal ‘rule-out’ and ‘rule-in’ cut-points

- Principle: reduce % requiring a subsequent test.

- ‘RULE-OUT’ = HbA1c ≤ 5.8%
- ‘RULE-IN’ = HbA1c ≥ 6.8%

‘Intermediate HbA1c’ 5.9 – 6.7%:

n = 2505 (28.2% of total cohort)

Optimal ‘rule-out/ rule-in’ cut-points: 5.8 and 6.8%

	White Europeans	South Asians	
Sensitivity	91.8%	97.9%	✓
Specificity	99.4%	98.9%	
PPV	69.8%	53.6%	+/-
NPV	99.6%	99.8%	

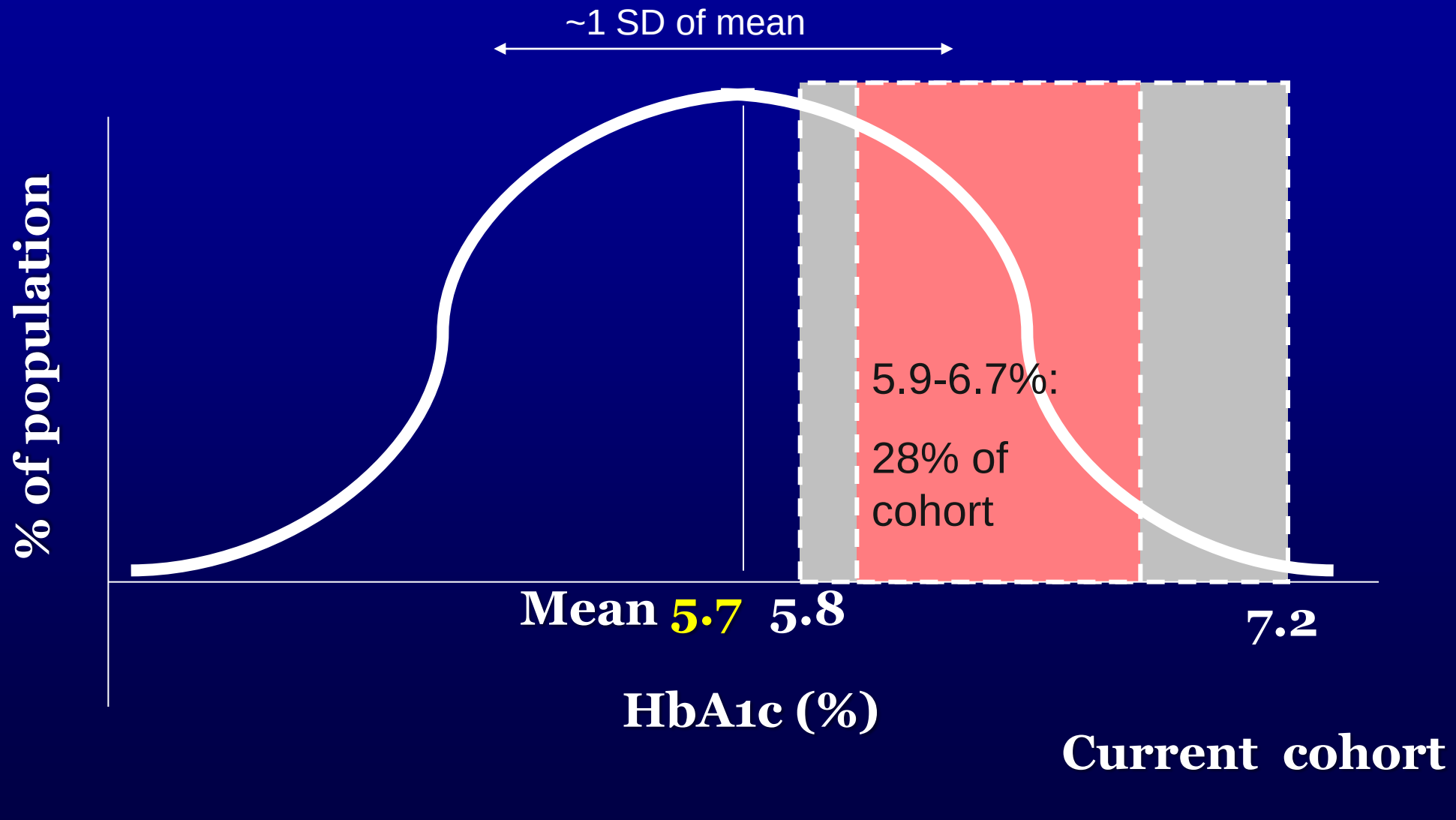
Conclusion

- Using HbA1c ≥ 6.5% to detect T2DM is a reasonable option
- Using the ABCD two cut-point strategy is more accurate
- Potential limitation = % of cohort requiring subsequent test
- If HbA1c 5.8 and 7.2%: ~ 40%

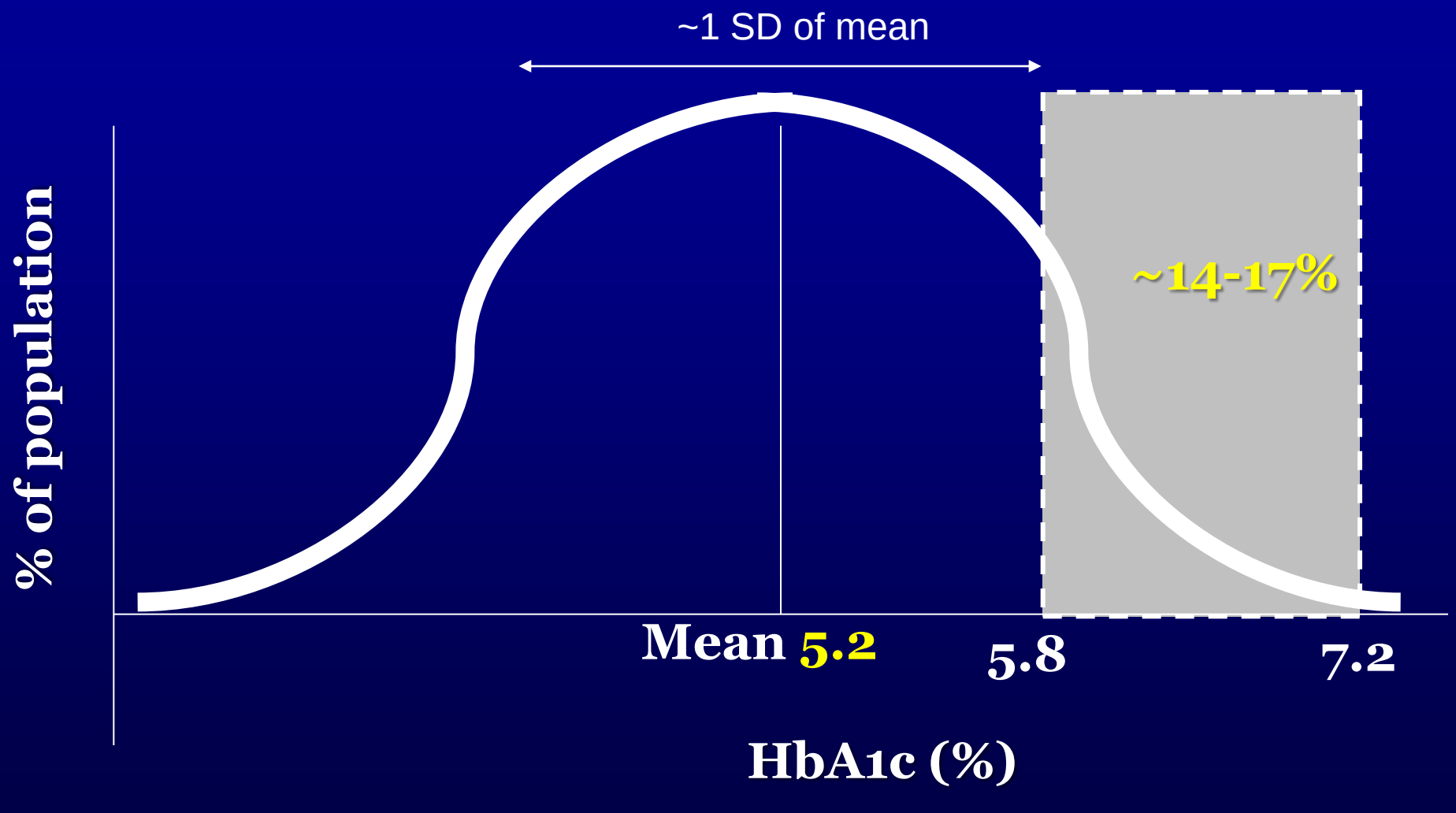
  - ? feasible to implement in clinical practice

- Using HbA1c 5.9% and 6.7%: maintains high diagnostic accuracy only ~ 25% subsequent testing.

Can we estimate what % have 'intermediate HbA1c' and require subsequent test?



The key influence is the mean HbA1c and SD



WHITEHALL cohort [1]

1 Diabetes Care 33(3), 580-582 (2010)

Screening Study	Mean Cohort HbA1c %, (SD)
LEADER	5.7 (0.6)
Inter 99 [1]	5.8 (0.5)
CURES [1]	5.9 (1.2)
HOORN [2]	5.5 (0.5)
NHANES [3]	5.2
EPIC-NORFOLK[4]	5.25 (0.6)
WHITEHALL [1]	5.2 (0.5)
AuSDiab [1]	5.1 (0.4)

Mean Cohort HbA1c for undiagnosed populations

If a two cut-point is employed: Different areas may need to set their own 'rule-in' and 'rule-out' cut-points

1 Diab Care 33(3), 580-582 (2010). 2. Diab Care. 2010: 33(1): 61-66. 3. Diab Res Clin Pract 2010; 87(3), 415-421.
4. Personal communication: Dr. SJ Griffin MRC Cambridge

Cost – estimations of using one vs. two cut-points for T2DM: modelling data

- Cost per case for one person with Type 2 DM
- HbA1c 6.5% vs. HbA1c 5.8 – 6.8%
- Assumptions:

- 60% of people uptake 1st screening test [1]

1) Family Practice 2008;25(5):370-5

Costs based on regional prices

- HbA1c = £2.66
- OGTT = £0.94
- (Risk score = £2.17)
- Estimated administrative cost for any blood test = £5.32
- Cost of HCP = £18 per hour

  estimated HbA1c = 10mins, OGTT = 30mins

- **Total cost of one HbA1c = £10.98, OGTT = £15.26**

White European: Costs per case of diabetes

Strategy	Stage 1 (60%)	Stage2	Total Cost (£)	Cost per case, £ (95% CI)	Difference in cost per case: £ (95% CI)
1 cut-point	HbA1c	-	41,800.86	616.41 (556.38 to 698.52)	- 55.30 (-104.40 to - 14.17)
2 cut-point	HbA1c	OGTT	56,249.03	561.11 (542.21 to 594.12)	

Strategy	1 cut-point	2 cut-point
Sensitivity	62.1%	91.8%

+29.7%

Mostafa et al. under review

South Asians: Costs per case of diabetes

Strategy	Stage 1	Stage 2	Total Cost (£)	Cost per case, £ (95% CI)	Difference in cost per case £ (95% CI)
1 cut-point	HbA1c	-	12,780.72	284.19 (260.72 to 322.16)	+ 68.89 (53.15 to 85.63)
2 cut-point	HbA1c	OGTT	19,702.66	353.08 (346.35 to 375.31)	

Strategy	1 cut-point	2 cut-point
Sensitivity	78.9%	97.9%

Application of filter (risk score [1]) at stage 1

Strategy	Stage 1 (60%)	Stage 2	Stage 3	Total Cost (£)	Cost per case, £ (95% CI)	Difference in cost per case £ (95% CI)
WE 1 cut point	Risk score	HbA1c	-	35,298.30	613.24 (541.33 to 708.69)	- 82.24 (- 40.89 to -133.45)
2 cut-point	Risk Score	HbA1c	OGTT	46,184.78	530.99 (500.44 to 575.24)	
SA 1 cut-point	Risk score	HbA1c	-	12,857.11	310.56 (279.86 to 358.61)	+ 52.32 (37.21 to 66.33)
2 cut-point	Risk Score	HbA1c	OGTT	18,726.10	363.01 (346.18 to 395.82)	

Risk score ≥ 14 = positive screen 1) Gray et al. Diabetic Medicine 2010

Potential cost savings in WE using 2 cut-point strategy

Thank You!

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