

Part A:

**Glycated hemoglobin A1c as a screening tool
for detection of type 2 diabetes?**

Part B:

**Evaluation of point-of-care instruments for
glycated hemoglobin A1c testing in an
ambulant hospital setting**

Marieke Criel

11/03/2014

1. Inleiding
2. Hemoglobine A1c
3. Harmonisatie van hemoglobine A1c resultaten
4. Criteria voor de diagnose van diabetes mellitus
5. HbA1c als diagnostische test
6. Performantie van HbA1c toestellen
7. HbA1c point-of-care testing
8. Evaluatie van HbA1c POCT

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1. Inleiding

Key facts

- 347 million people worldwide have diabetes* (1).
 - In 2004, an estimated 3.4 million people died from consequences of high fasting blood sugar (2).
 - More than 80% of diabetes deaths occur in low- and middle-income countries (3).
 - WHO projects that diabetes will be the 7th leading cause of death in 2030 (4).
 - Healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use can prevent or delay the onset of type 2 diabetes.
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“Diabetes has increased dramatically over the past 10 years. That proves that diabetes is caused by global warming!”

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2. Hemoglobine A1c

- Onderscheid van “fast” hemoglobine (Huisman en Meyering 1958)
- Binding van hexose aan N-terminale groep van bèta-keten (Bookchin en Gallop 1968)
- Hogere waarden van fast hemoglobine fracties bij personen met diabetes mellitus (Rashbar, 1969)
- Relatie tussen HbA1c, gemiddelde glucoseconcentraties en lange termijn complicaties (Trivelli, 1971)
- Vorming van Schiffse base (Bunn, 1975)
- Aanbeveling van gebruik HbA1c in opvolging van diabetes mellitus patiënten door WHO (1985)

2. Hemoglobine A1c

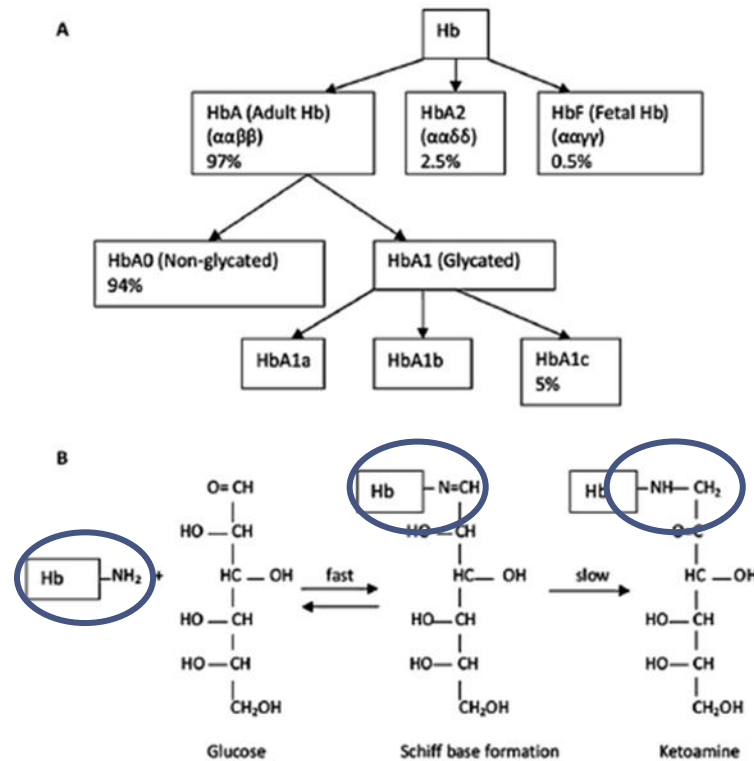


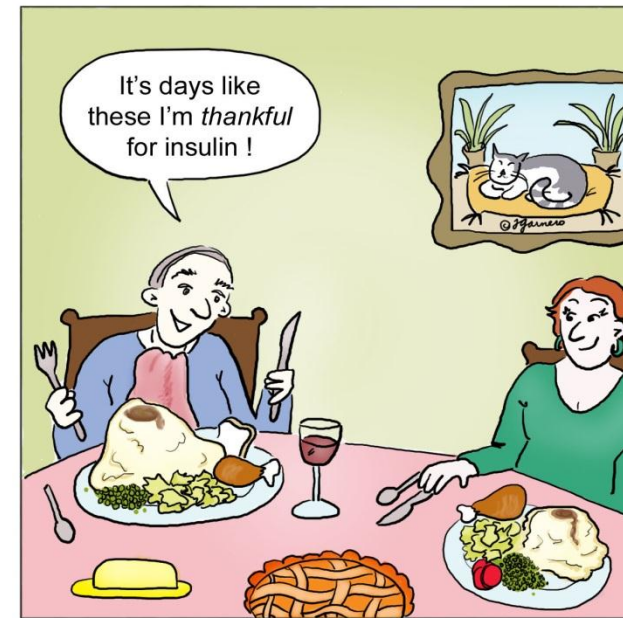
Fig. 1 - (A) Haemoglobin types of healthy adults. Haemoglobin in healthy individuals consists of approximately 97% adult haemoglobin (HbA), 2.5% HbA₂ and 0.5% foetal haemoglobin (HbF). In a healthy person, approximately 94% of HbA is non-glycated, while 6% is glycated. Glycated haemoglobin consists of HbA1a and HbA1b (minor components: taken together ~1%) and HbA1c (main component: ~5%). (B) The N-terminal valine of the β chain reacts with glucose to the aldimide (Schiff base or labile HbA1c), which undergoes an Amadori rearrangement to the stable ketoamine (HbA1c).

2. Hemoglobine A1c

- 1993: de 'Diabetes mellitus Control and Complications (DCCT)' – trial
- 1998: de 'UK Prospective Diabetes mellitus Study (UKPDS)'

Islets of Humor

by Theresa Garnero



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3. Harmonisatie van hemoglobine A1c resultaten

- **National Glycohemoglobin Standardization Program (NGSP)**
- International Federation of Clinical Chemistry (IFCC) working group on HbA1c standardization

3. Harmonisatie van hemoglobine A1c resultaten

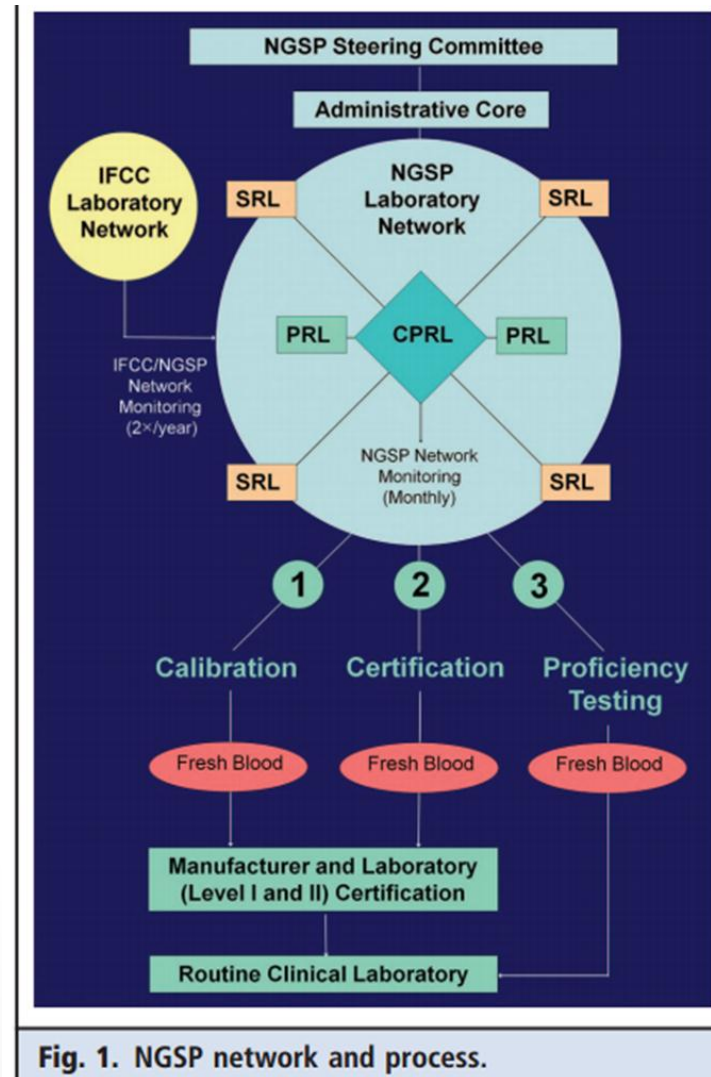


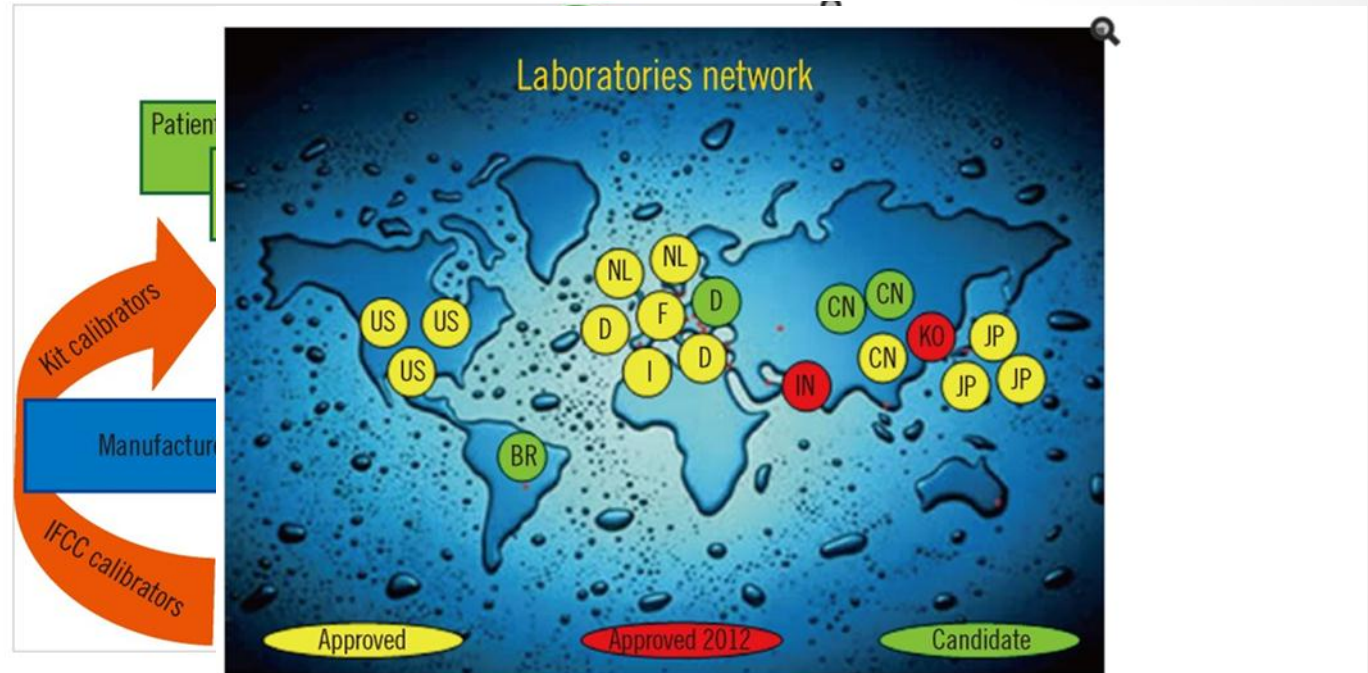
Fig. 1. NGSP network and process.

3. Harmonisatie van hemoglobine A1c resultaten

- National Glycohemoglobin Standardization Program (NGSP)
- **International Federation of Clinical Chemistry (IFCC) working group on HbA1c standardization**

3. Harmonisatie van hemoglobine A1c resultaten

mmol/mol



Quality chain of IFCC-RMI
the IFCC-RMP, to assign va
performance of the whole c
measures the correct HbA_{1c}
diabetologists can use unive

The global distribution of reference laboratories operating the IFCC-RMP.

Abbreviations: IFCC-RMP, International Federation of Clinical Chemistry Reference Measurement Procedure; US, the United States; BR, Brazil; NL, the Netherlands; D, Germany; F, France; I, Italy; IN, India; CN, China; KO, Korea; JP, Japan.

Abbreviations: IFCC-RMP, International Federation of Clinical Chemistry Reference Measurement Procedure; EQA, external quality assessment; PT, proficiency testing.

3. Harmonisatie van hemoglobine A1c resultaten

- NGSP-HbA1c: 0.915 (IFCC-HbA1c) + 2.15%
- JDS/JSCC-HbA1c: 0.927 (IFCC-HbA1c) + 1.73%
- Swedish-HbA1c: 0.989 (IFCC-HbA1c) + 0.88%

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4. Criteria voor de diagnose van diabetes mellitus

Criteria for the diagnosis of diabetes

1. A1C ≥ 6.5 percent. The test should be performed in a laboratory

540750 540761 Doseran van glycohemoglobine in hemolysaat B 250
 (Maximum 1) (Cumulregel 18) (Diagnoseregel 56)"

"K.B. 9.12.1994" (in werking 1.3.1995) + "K.B. 26.8.2010" (in werking 1.10.2010)

56

De verstrekking 540750 - 540761 mag enkel aangerekend worden aan de Z.I.V. voor een patiënt met diabetes mellitus, mucoviscidose of chronische pancreatitis.

Health O of 75-gr OR

2013: Belgische richtlijnen (Domus Medica) voegen HbA1c alsnog niet toe als diagnostische test voor DM

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

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5. HbA1c als diagnostische test

Rationale:

- Betrouwbare meting van chronische glucosespiegels
- Minder onderhevig aan kortdurende schommelingen
- Goede voorspeller van het optreden van complicaties

5. HbA1c als diagnostische test

VOORDELEN

Niet nuchter (>< FPG)

Minder voorbereiding (>< OGTT)

Kleinere intra-individuele variabiliteit dan glucose

Invloed van tijdelijke factoren (stress, ...) kleiner

Pre-analytisch stabiel(er) dan glucose

Standaardisatie

Gekende parameter

5. HbA1c als diagnostische test

Some of the factors that influence HbA1c and its measurement*.
Adapted from Gallagher et al (24)

1. Erythropoiesis

Increased HbA1c: iron, vitamin B12 deficiency, decreased erythropoiesis.

Decreased HbA1c: administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease.

2. Altered Haemoglobin

Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.

3. Glycation

Increased HbA1c: alcoholism, chronic renal failure, decreased intra-erythrocyte pH.

Decreased HbA1c: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH.

Variable HbA1c: genetic determinants.

4. Erythrocyte destruction

Increased HbA1c: increased erythrocyte life span: Splenectomy.

Decreased A1c: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.

5. Assays

Increased HbA1c: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use.

Variable HbA1c: haemoglobinopathies.

Decreased HbA1c: hypertriglyceridaemia.

5. HbA1c als diagnostische test

Advantages and disadvantages of various HbA1c assay methods

Assay	Principle	Advantages	Disadvantages
Ion Exchange Chromatography	HbA1c has lower isoelectric point and migrates faster than other Hb components.	Can inspect chromatograms for Hb variants. Measurements with great precision.	Variable interference from hemoglobinopathies, HbF and carbamylated Hb but the current ion exchange assays correct for HbF and carbamylated Hb does not interfere.
Boronate Affinity	Glucose binds to m-aminophenylboronic acid.	Minimal interference from haemoglobinopathies, HbF and carbamylated Hb.	Measures not only glycation of N-terminal valine on β chain, but also β chains glycated at other sites and glycated α chains.
Immunoassays	Antibody binds to glucose and between 4-10 N-terminal amino acids on β chain.	Not affected by HbE, HbD or carbamylated Hb Relatively easy to implement under many different formats.	May be affected by haemoglobinopathies with altered amino acids on binding sites. Some interference with HbF.

5. HbA1c als diagnostische test

NGSP
Harmonizing Hemoglobin A_{1c} Testing
A better A1C test means better diabetes care

Home | News | About the NGSP | **More About HbA_{1c}** | Obtaining Certification | Certified Methods and Laboratories | CAP GH2 and LN15 Data | Enter Monitoring Data | Links | Contact Us

ADA Recommendations | IFCC Standardization | HbA_{1c} and eAG | Convert between IFCC, NGSP and eAG | **HbA_{1c} Assay Interferences**

HbA_{1c} Assay Interferences

HbA_{1c} methods: Effects of Hemoglobin Variants (HbC, HbS, HbE and HbD traits) and Elevated Fetal Hemoglobin (HbF)
Updated July 2013

[More comprehensive information regarding HbA_{1c} assay interferences](#)

The following table lists the 20 methods most often used to measure A1C and whether the method is affected by HbC, HbS, HbE or HbD trait or by elevated HbF. Methods are listed in alphabetical order by manufacturer. The criteria used to determine whether or not a method shows interference that is clinically significant (indicated by "Yes") is $>\pm 7\%$ at 6 and/or 9% A1C. If your diabetes patient has a hemoglobin variant, your lab should use a method that does not show interference from that variant in order to produce an accurate A1C result.

Method	Interference from HbC	Interference from HbS	Interference from HbE	Interference from HbD	Interference from elevated HbF
Arkray ADAMS A1c HA-8180V (Menarini)	No	No	HbA _{1c} not quantified	HbA _{1c} not quantified	No

5. HbA1c als diagnostische test

Some of the factors
Adapted from Gallagher

A. Preanalytical

1. Erythropoiesis

Increased HbA1c: iron, v
Decreased HbA1c: admi
reticulocytosis, chronic liv

- Hogere kostprijs
- Beperkte beschikbaarheid wereldwijd

4. Erythrocyte destructi

Increased HbA1c: increa
Decreased A1c: decreas
splenomegaly, rheumat
ribavirin and dapsone.

5. Assays

Increased HbA1c: hypert
alcoholism, large doses c
Variable HbA1c: haemog
Decreased HbA1c: hyper

RECOMMENDATION: LABORATORIES SHOULD BE AWARE OF POTENTIAL INTERFERENCES, INCLUDING HEMOGLOBINOPATHIES, THAT MAY AFFECT HbA_{1c} TEST RESULTS, DEPENDING ON THE METHOD USED. IN SELECTING ASSAY METHODS, LABORATORIES SHOULD CONSIDER THE POTENTIAL FOR INTERFERENCES IN THEIR PARTICULAR PATIENT POPULATION. IN ADDITION, DISORDERS THAT AFFECT ERYTHROCYTE TURNOVER MAY CAUSE SPURIOUS RESULTS, REGARDLESS OF THE METHOD USED
GPP.

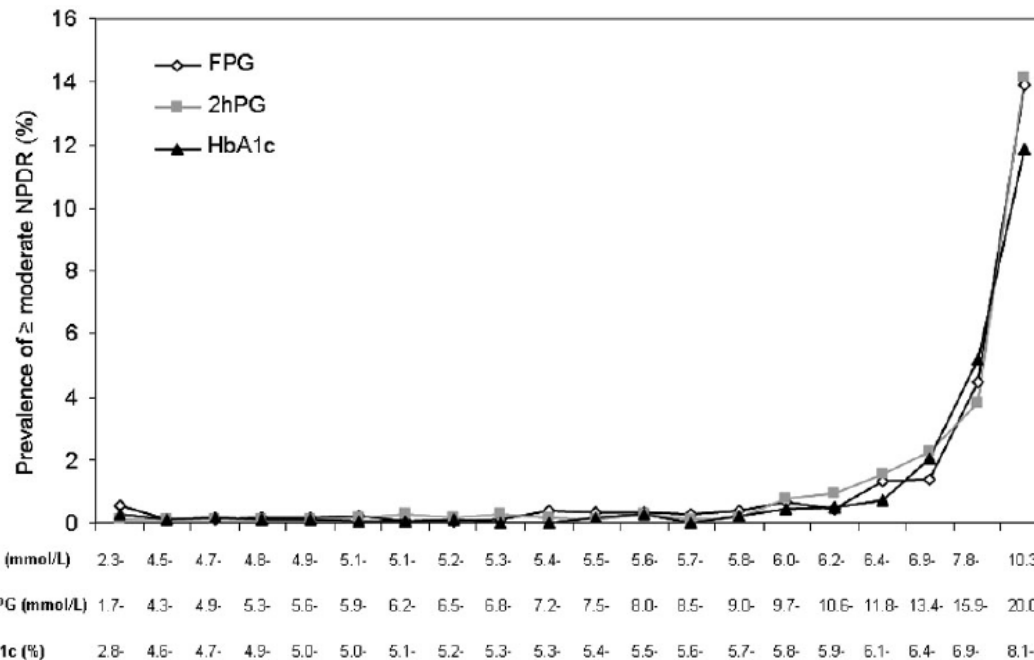
5. HbA1c als diagnostische test

Table 1. HbA1c, I

Study	Comp
Colagiuri et al. (Diabetes Care, in press)	Retin (ROC analy; Retin (visual of dec distrib
Engelgau et al. (1997)	Bi-mc - Enti popul Retin - Enti popul Retin
Expert Committee, (1997)	Retin
Ito et al. (2000a)	Retin
McCance et al. (1994)	Retin WHO ROC analy;
Miyazaki et al. (2004)	Retin
Tapp et al. (2006)	Retin Micrc Retin Micrc

* Significantly different

Figure 1. Prevalence of diabetes-specific retinopathy (\geq moderate non proliferative retinopathy) by vigintiles* of distribution of FPG, 2-h PG and HbA1c from DETECT-2.



*20 equally-sized groups.

Sensitivity (%)	Specificity (%)
83	83
NR	NR
90	100
NR	NR
NR	NR
NR	NR
88	81
88	76
87	90
NR	NR
NR	NR
NR	NR
NR	NR

NR = not reported; FPG = fasting

5. HbA1c als diagnostische test

Alternatieven voor diagnose obv HbA1c criteria:

- Combinatie van HbA1c en plasmaglucose metingen
- 'rule in' en 'rule out' criteria

Impact op prevalentie:

- HbA1c criterium categoriseert het kleinste aantal personen in de groep van diabetes mellitus
- HbA1c, FPG en 2-h PG meten verschillende aspecten van glycemie waardoor bij andere groepen personen de diagnose DM wordt gesteld

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6. Performantie van HbA1c toestellen

RECOMMENDATION: LABORATORIES SHOULD USE ONLY HbA_{1c} ASSAY METHODS THAT ARE CERTIFIED BY THE NATIONAL GLYCOHEMOGLOBIN STANDARDIZATION PROGRAM (NGSP) AS TRACEABLE TO THE DCCT REFERENCE. THE MANUFACTURERS OF HbA_{1c} ASSAYS SHOULD ALSO SHOW TRACEABILITY TO THE IFCC REFERENCE METHOD GPP.

NGSP News

Updated 08/30/2013

New NGSP Certification Criteria beginning Jan. 2014

Beginning January 2014, 37 of 40 results (38 of 40 for Level I laboratories) will need to be within +/-6% (relative) of the NGSP SRL in order to pass certification (current limits are +/-7%).

GPP.

6. Performantie van HbA1c toestellen

RECOMMENDATION: LABORATORIES

Change in CAP GH2 HbA1c Survey Grading

The College of American Pathologists began using accuracy grading based on target values set by the NGSP starting with the 2007A survey. In 2007 the acceptable limit was +/-15% of the target value; this limit was lowered to +/-12% in 2008, +/-10% in 2009, +/-8% in 2010 and +/-7% in 2011 and 2012. For 2013 the limit has been further reduced to +/-6%.

TRACEABILITY TO THE IFCC

REFERENCE METHOD

GPP.

RECOMMENDATION: LABORATORIES THAT
MEASURE HbA_{1c} SHOULD PARTICIPATE
IN A PROFICIENCY-TESTING PROGRAM,
SUCH AS THE COLLEGE OF AMERICAN
PATHOLOGISTS (CAP) HbA_{1c} SURVEY,
THAT USES FRESH BLOOD SAMPLES
WITH TARGETS SET BY THE NGSP
LABORATORY NETWORK
GPP.

6. Performantie van HbA1c toestellen

B. Analytical

RECOMMENDATION: DESIRABLE SPECIFICATIONS FOR HbA_{1c} MEASUREMENT ARE AN INTRALABORATORY CV <2% AND AN INTERLABORATORY CV <3.5%. AT LEAST TWO CONTROL MATERIALS WITH DIFFERENT MEAN VALUES SHOULD BE ANALYZED AS AN INDEPENDENT MEASURE OF ASSAY PERFORMANCE B (low).

6. Performantie van HbA1c toestellen

The reference change value (RCV) is defined as the critical difference between two consecutive HbA1c measurements representing a significant change in health status.

$$RCV(\%) = \sqrt{2} * 1.96 * \sqrt{[(CVa)^2 + (CVw)^2]}$$

Een A
behouder
vers
consecu
aa

Bij een veronderstelde CVw van 1,8% en een RCV van 5,0 mmol/mol (0,5 %) = maximaal aanvaardbare analytische CV, nl. 2,9% (IFCC) en 1,9% (DCCT) en maximaal toegelaten bias 2,0 mmol/mol (0,24% DCCT)

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7. HbA1c point-of-care testing

RECOMMENDATION: HbA_{1c} MAY BE USED FOR THE DIAGNOSIS OF DIABETES, WITH VALUES $\geq 6.5\%$ BEING DIAGNOSTIC. AN NGSP-CERTIFIED METHOD SHOULD BE PERFORMED IN AN ACCREDITED LABORATORY. ANALOGOUS TO ITS USE IN THE MANAGEMENT OF DIABETES, FACTORS THAT INTERFERE WITH OR ADVERSELY AFFECT THE HbA_{1c} ASSAY WILL PRECLUDE ITS USE IN DIAGNOSIS
A (moderate).



RECOMMENDATION: POINT-OF-CARE HbA_{1c} ASSAYS ARE NOT SUFFICIENTLY ACCURATE TO USE FOR THE DIAGNOSIS OF DIABETES
B (moderate).

7. HbA1c point-of-care testing

Cagliero et al. Ferenczi et al. Miller et al.

Verschillende studies toonden een verbetering in controle van de glycemie aan bij directe feedback van HbA1c resultaten bij DM type 1 patiënten en insuline-afhankelijke DM type 2 patiënten.

Al-Ansary et al.

Niet-significante reductie van 0,09% van HbA1c in POCT groep versus controle groep.

7. HbA1c point-of-care testing

Evaluatie van HbA1c point-of-care toestellen:

Lenters et al. 2 van de 8 POCT voldeden aan NGSP criteria

ørvik Sølvik et al. Tussen 60 – 90% van de Afinion en DCA gebruikers voldeden aan de kwaliteitseisen van juistheid (6,0%) en imprecisie ($CV \leq 2,0 \%$)

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Eigen evaluatie:

3 POC toestellen: cobas b101, Afinion en B-Analyst

Referentiemethode: eigen laboratorium HbA1c assay
(Adams Arkray HA-8160, Menarini)

Precisie volgens CLSI EP-5 protocol

Bias volgens CLSI EP-9 protocol

Besluit

Afinion en B-analyst voldoen aan eisen voor precisie.

Cobas b101, Afinion en B-analyst hebben alle drie een statistisch niet-significante bias tegenover onze eigen referentiemethode.

Eigen referentiemethode positieve bias tegenover SRMs.

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"My diabetic research shows that test subjects are 98% more likely to take their diabetic pills if the pills are covered in chocolate."