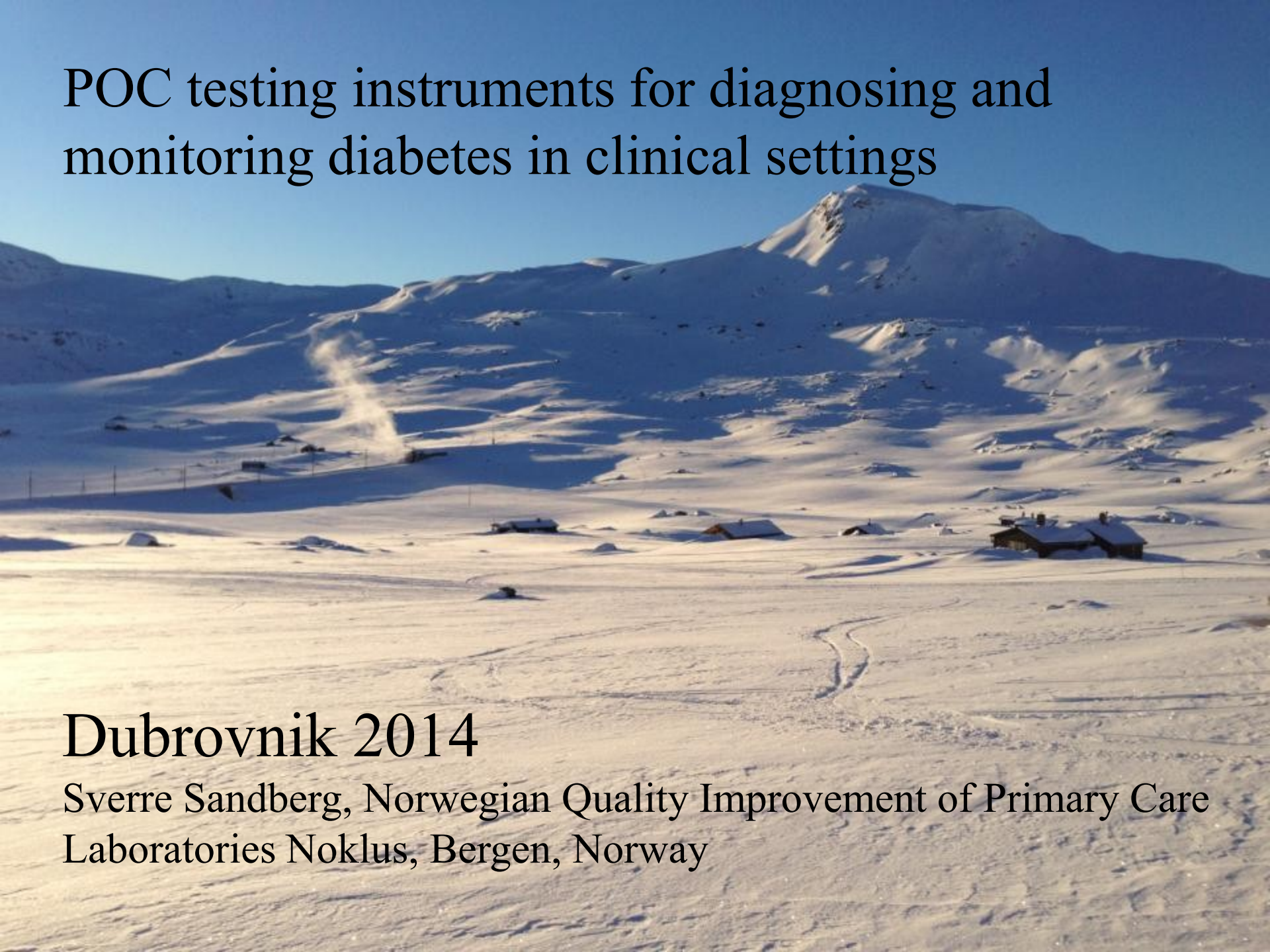
POC testing instruments for diagnosing and monitoring diabetes in clinical settings



Dubrovnik 2014

Sverre Sandberg, Norwegian Quality Improvement of Primary Care Laboratories Noklus, Bergen, Norway

Does HbA1c has a place in the diagnosis of diabetes mellitus?

Yes	80
No	20

What should be the first test to order for diagnosing DM?

HbA1c	26
F-glucose	67
OGTT	5

Should we screen the high risk population with HbA1c

Yes	60
No	40

Does HbA1c has a place in the diagnosis of diabetes mellitus?

Yes	80 / 68
No	20 / 32

What should be the first test to order for diagnosing DM?

HbA1c	26 / 29
F-glucose	67 / 79
OGTT	5 / 0

Should we screen the high risk population with HbA1c

Yes	60 / 52
No	40 / 48

What is in principle differences between monitoring and diagnosing

-

Monitoring

The test result is compared with previous test result(s) and differences between test results are compared to a change in the clinical condition.

When the level has been established, reproducibility is of most importance

Information about within-subject variation and analytical variation is important to calculate the reference change value (RCV).

Monitoring accuracy studies are important

Diagnosing

The test result is compared with a threshold target value.

Trueness is of most importance

Information about within-subject variation and analytical variation is important.

Diagnostic accuracy studies are important

Monitoring and Diagnosing

When constituents are used for monitoring the results are sometimes used to compare with certain thresholds. Typical examples are HbA1c and cholesterol.

It is then a “monitoring-diagnostic” situation where you have access to previous results.

Both trueness and imprecision are of importance (and pre-analytical conditions)

So for using an instrument for diagnosing we have to consider four different variables

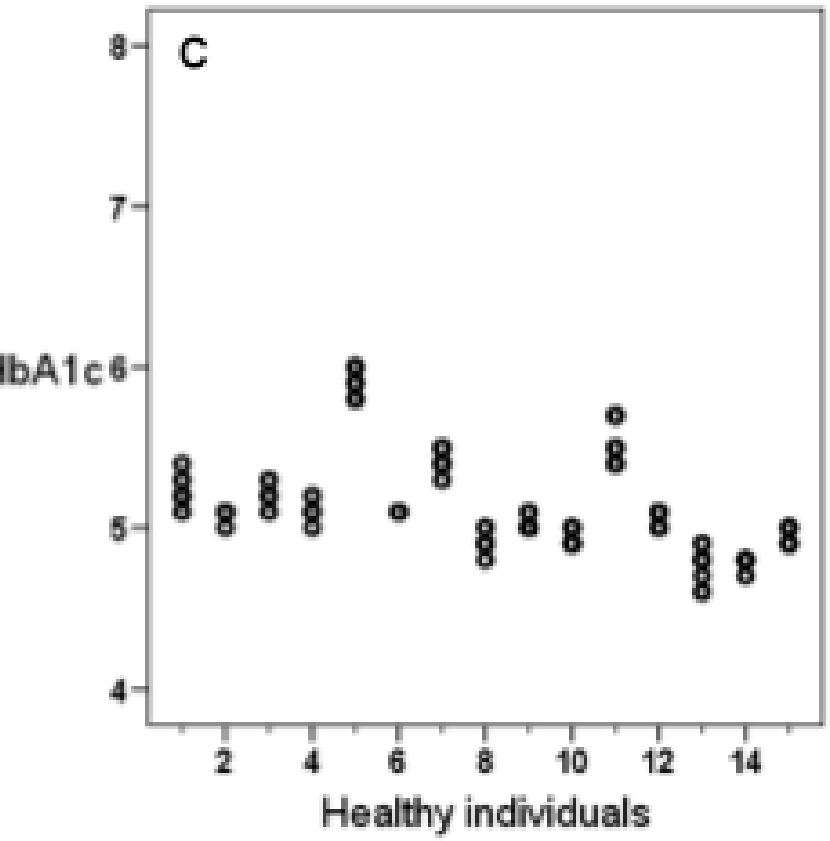
The trueness – standardization / harmonisation

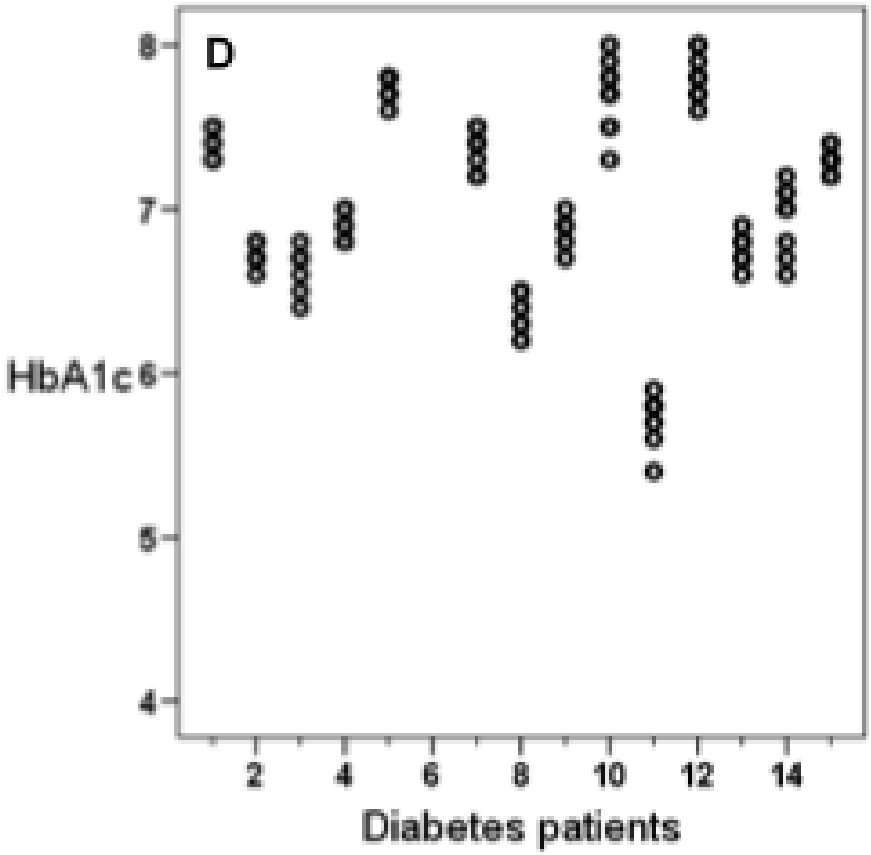
The imprecision

Pre-analytical variation

The within-subject variation

HbA1c in healthy and in persons with diabetes





Carlsen S et al Clin Chem Lab Med. 2011;49:1501-7.

HbA1c

Table 2 Between-subject, within-subject and analytical coefficients of variation of HbA_{1c} in healthy individuals and diabetes patients (95% CI).

	Number of person/ samples	HbA_{1c}, %/mmol/mol Grand mean	CVbs, %	CVws, %	CVa, %
HbA_{1c}					
Healthy individuals	15/148	5.1 (5.0–5.2)/32.0 (31.0–33.			-0.6)
Diabetes patients	14/135	7.0 (6.9–7.1)/53.0 (52.0–54.			-0.6)

HbA_{1c} is reported in NGSP HbA_{1c} (%)/IFCC HbA_{1c} (mmol/mol).

CVws for healthy 1.2
CVws for patients 1.7

Carlsen S et al Clin Chem Lab Med. 2011;49:1501-7.

Papers in Press. Published September 23, 2014 as doi:10.1373/clinchem.2014.227983
The latest version is at http://hwmaint.clinchem.org/cgi/doi/10.1373/clinchem.2014.227983

Clinical Chemistry 60:12
000–000 (2014)

Letters to the Editor

Biological Variation of Hemoglobin A_{1c}: Consequences for Diagnosing Diabetes Mellitus

To the Editor:

For optimal monitoring and diagnosing of patients with diabetes by use of glycated hemoglobin (Hb A_{1c})[1] measurements, the analytical CV (CVa) of the Hb A_{1c} assay and the within-person biological variamediately stored at −80 °C. Full analysis was performed at the end of the 2-month collection period. The samples were analyzed in a single run in duplicate using the following 4 SRMPs:

- Tina-quant Gen.2 HbA_{1c} on Integra 800, immunoassay, IFCC- and NGSP-certified (Roche Diagnostics);
- Premier Hb9210, boronate affinity chromatography HPLC, at the time not yet officially cer-

betes). Normality was checked using Shapiro–Wilk test (P > 0.006) for both within-person and analytical components for the 4 methods. The index of individuality was calculated as CVwp/between-person biological variation (CVbp).

The mean CVwp of 19 healthy individuals using 4 SRMP Hb A_{1c} methods was 1.3% in SI units (range 0.8% to 1.7%) and 0.8% in DCCT units (range 0.5%

Lenters-Westra, Røraas, Schindhelm, Slingerland, Sandberg, Clin. Chem 2014, in press

Within-person variation

	HbA_{1c} Grand mean		CVwp (%)
Ultra[2] (mmol/mol)	34.2 (33.8 – 34.6)		0.8 (0.4 – 1.2)*
Ultra[2] (%)	5.28 (5.24 – 5.32)	)	0.5 (0.3 – 0.7)#
Premier (mmol/mol)	32.5 (32.1 – 32.9)		1.3 (1.1 – 1.6)
Premier (%)	5.13 (5.09 – 5.16)		0.8 (0.6 – 0.9)
Tosoh G8 (mmol/mol)	33.4 (32.9 – 33.8)		1.7 (1.4 – 2.0)*
Tosoh G8 (%)	5.20 (5.17 – 5.24)		1.0 (0.8 – 1.2)#
TQ (mmol/mol)	32.6 (32.3 – 33.0)		1.4 (0.9 – 1.8)
TQ (%)	5.14 (5.10 – 5.17)		0.8 (0.5 – 1.1)

* and # significantly different from each other

Lenters-Westra, Røraas, Schindhelm, Slingerland, Sandberg, Clin Chem in press

Analytical uncertainty HbA1c

CVws	CV anal	Total var	Bias(%)	Unknown Bias (%)
1,2	2,0	2,33	0,0	2

		Meas. Value		Low lim	Upper lim
1 meas		7,0	TRUE	6,5	7,5
2 meas		7,0	TRUE	6,6	7,4
2 samp.		7,0	TRUE	6,6	7,4
4 samp.		7,0	TRUE	6,7	7,3
	30	7,0	TRUE	6,8	7,2

HbA1c

CVws	CV anal	Total var	Bias(%)	Unknown Bias (%)
1,2	2,0	2,33	0,0	2

		Meas. Value		Low lim	Upper lim
1 meas		6,0	TRUE	5,6	6,4
2 meas		6,0	TRUE	5,7	6,3
2 samp.		6,0	TRUE	5,7	6,3
4 samp.		6,0	TRUE	5,7	6,3
	30	6,0	TRUE	5,8	6,2

Advantages of HbA1c for the testing of diabetes

No need for fasting or timed samples

Relatively unaffected by acute changes in glucose levels

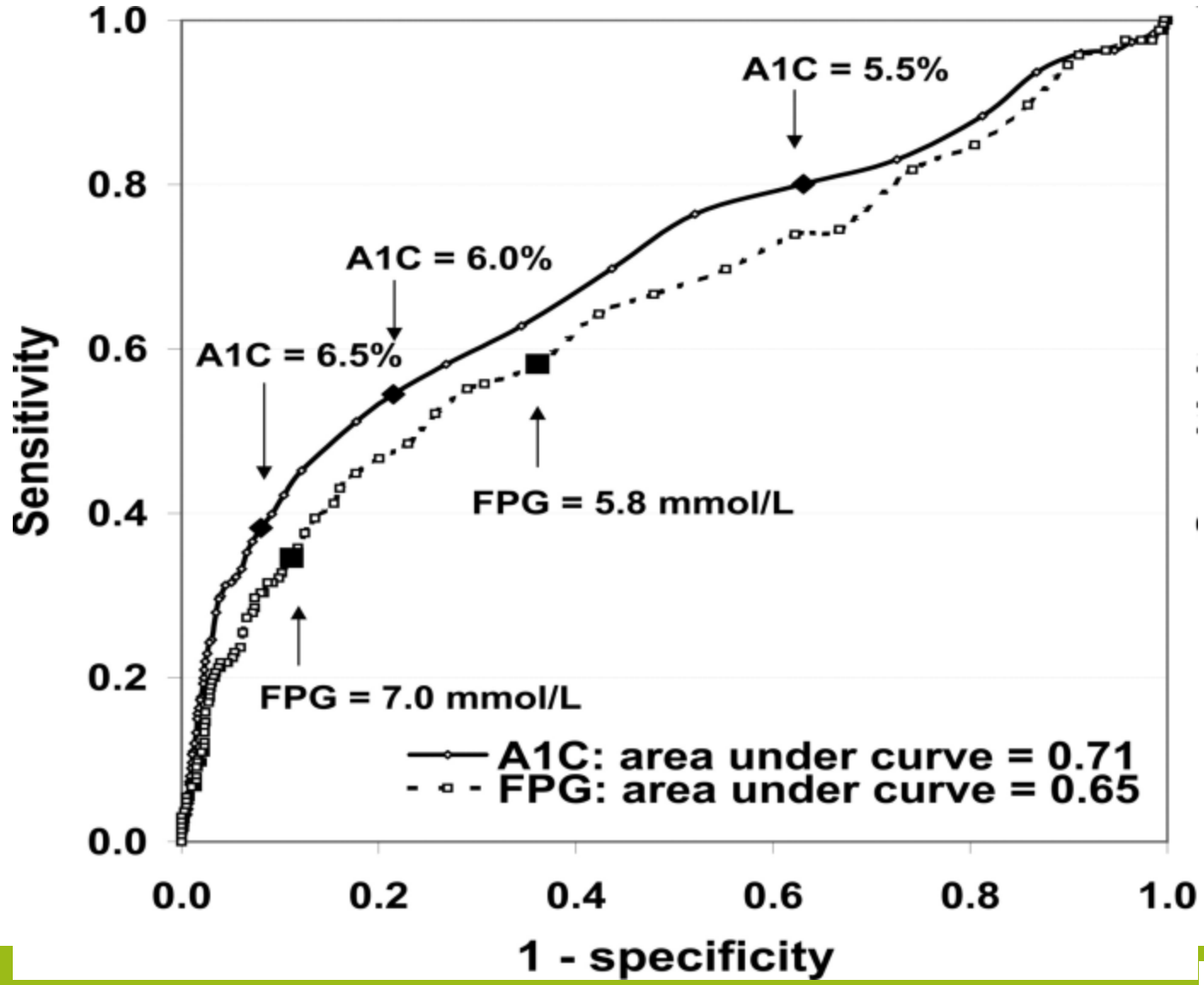
Standardized (IFCC-standard) and aligned to the DCCT/UKPDS

Better index of overall glycemic exposure and risk for long term complications

Less biologic variabillity than FPG/2HPG

Less preanalytical instabillity than FPG/2HPG

Cheng et al.
Diabetes Care, 2009



HbA1c: Quality specifications for diagnosing (will vary a little from country to country)

Methods used should be traceable to the IFCC referenc method.

Total error less than 6% at the level of 6.5

Day to day within-batch internal quality control should have a CV < 2%. (If impr=2%, bias can be 2%)

This is in NGSP (%) units. In IFCC units (mmol/mol) the numbers are larger!!!

POC instruments HbA1c

It is recommended that HbA1c is analysed on the Laboratory since (POC) instruments do not fulfill the quality specifications for diagnosing diabetes (*Diabetes Care 2009;32:1327-34*)

Only two of eight POC instruments *can* fulfill quality specifications for diagnosing diabetes mellitus (*Clin Chem 2010;56:44-52*)

Evaluation of HbA1c instruments

Evaluated under optimal conditions

Evaluated by the intended users

Evaluated after having been on the market

Criteria for using a POC instrument to diagnose diabetes

You can use whatever instrument you wish as long as you are aware of the “grey” zone or the “diagnostic paralytic” zone.

Three of 7 Hemoglobin A1c Point-of-Care Instruments Do Not Meet Generally Accepted Analytical Performance Criteria

CONCLUSION:

Afinion, DCA Vantage, Cobas B101, and B-analyst instruments met the generally accepted performance criteria for Hb A1c. Quo-Test, Quo- Laboratory, and InnovaStar met the criteria for precision but not for bias. Proficiency testing should be mandated for users of Hb A1c POC assays to ensure quality.

1. Lenters-Westra et al .Clin Chem. 2014.


SKUP
Scandinavian evaluation of laboratory equipment for prima
SKandinavisk Udprøvning af laboratorieudstyr til Primærsekt
SKandinavisk Utprøving av laboratorieutstyr for Primærh
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Evaluation both under optimal conditions and by the intended user

Post marketing evaluation

"Clearly, as noted in previous studies *(4,5)*, some methods that can perform well enough to pass NGSP certification when testing is performed by the manufacturer do not consistently achieve the same level of performance in the field".

Clinical Chemistry 59:12
1790–1801 (2013)

Diagnosing Diabetes Mellitus: Performance of Hemoglobin A_{1c} Point-of-Care Instruments in General Practice Offices

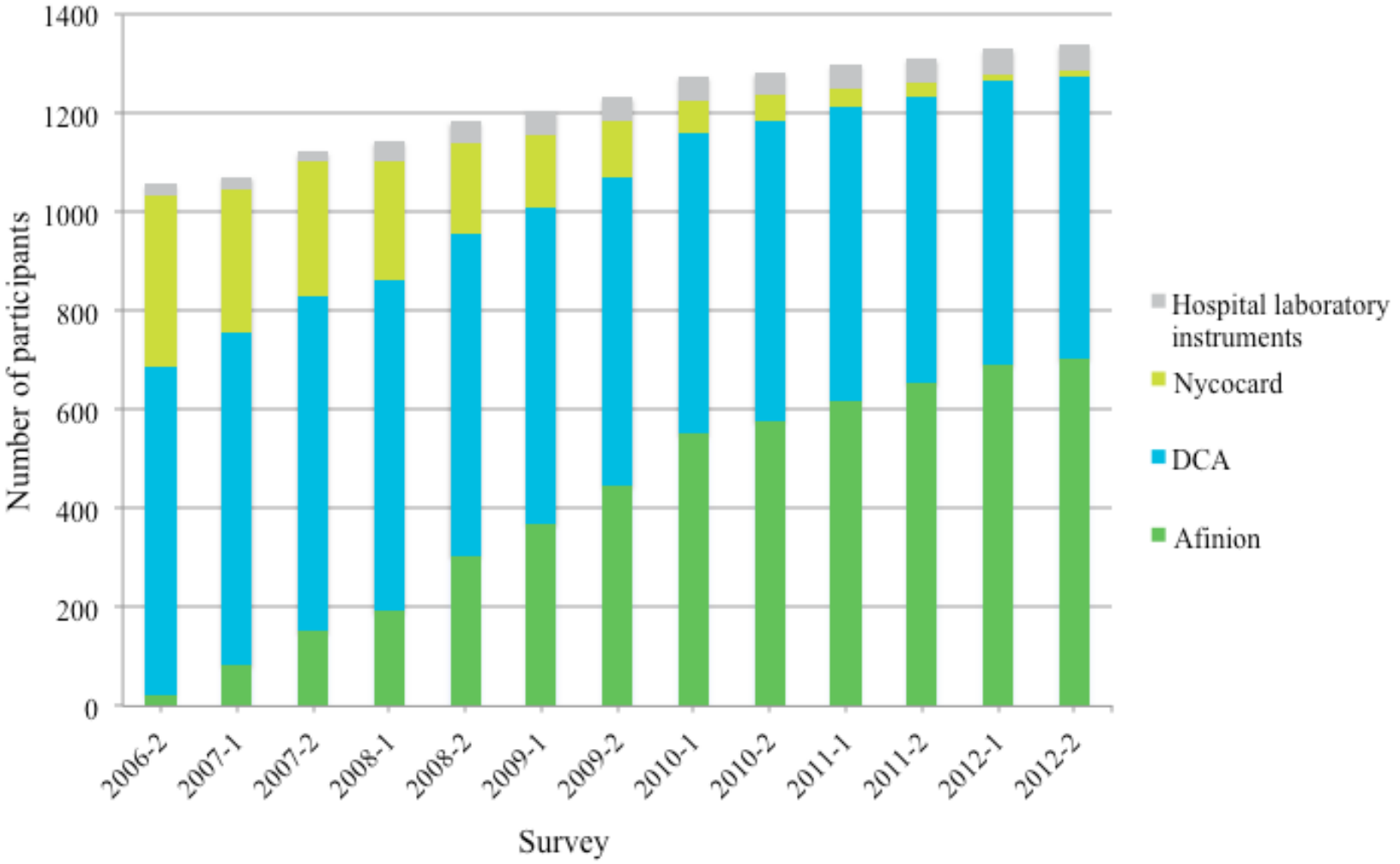
Una Ørvim Sølvik,[1*] Thomas Røraas,[2] Nina Gade Christensen,[2] and Sverre Sandberg[1,2,3]

BACKGROUND: Hemoglobin A_{1c} (Hb A_{1c}) measurement by hospital laboratory instruments, but not by point-of-care (POC) instruments, has been recommended for use to diagnose diabetes mellitus. We evaluated results from 13 Hb A_{1c} external quality assurance (EQA) surveys over a 6-year period in Norway, from both POC instruments used in general practice (GP) offices and instruments in hospital laboratories, against the A_{1c} measurements that meet analytical quality specifications, these measurements can be recommended for use to diagnose diabetes mellitus.

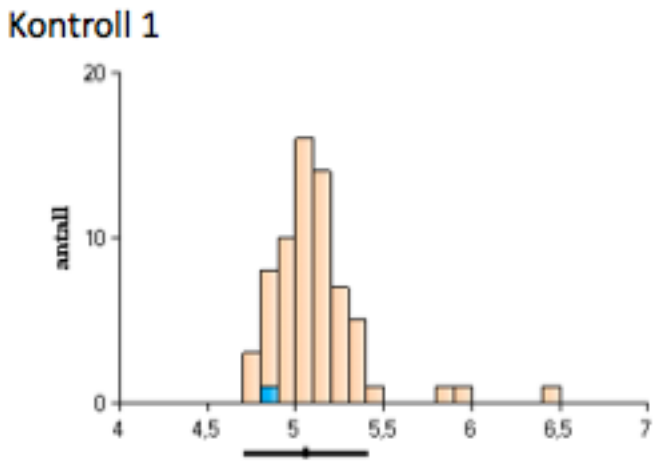
An expert committee officially recommended the use of hemoglobin Hb A_{1c} (Hb A_{1c})[4] for the diagnosis of

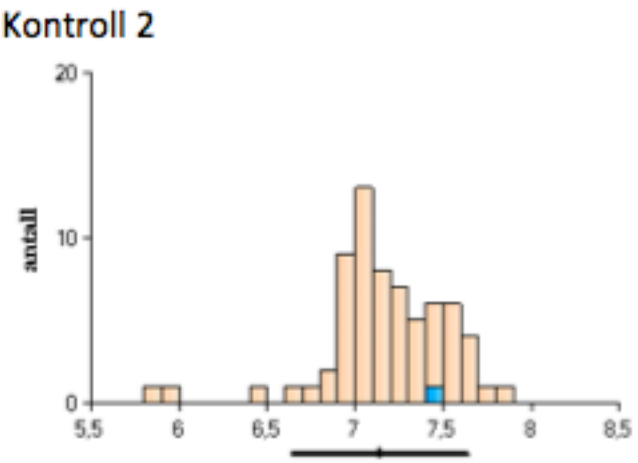
EQAS:
Fresh material from diabetes patients
Target value set by reference method

Number of participants

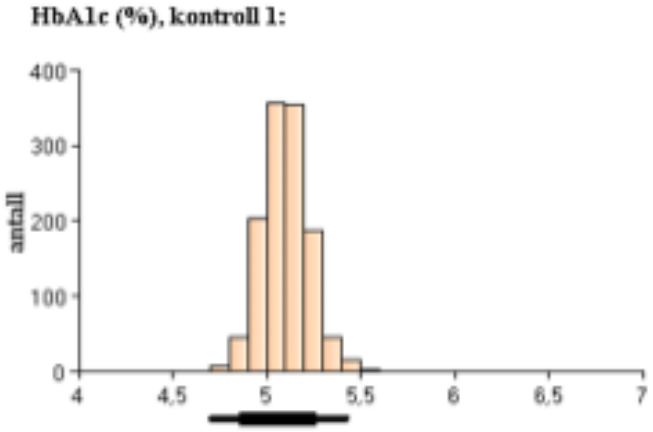


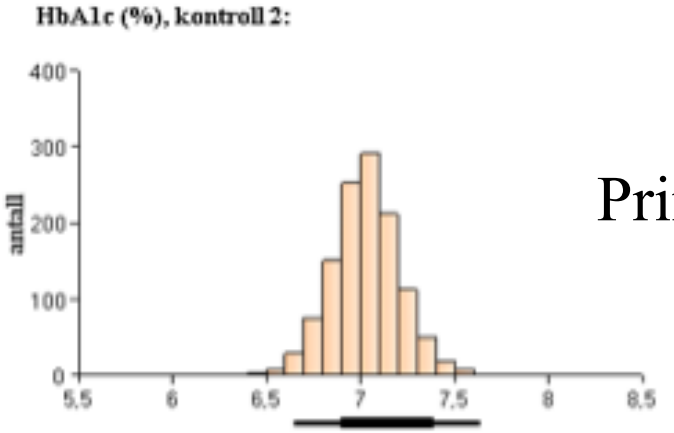
Solvik et al. Clin Chem 2013; 59: 1790-1801





Hospital

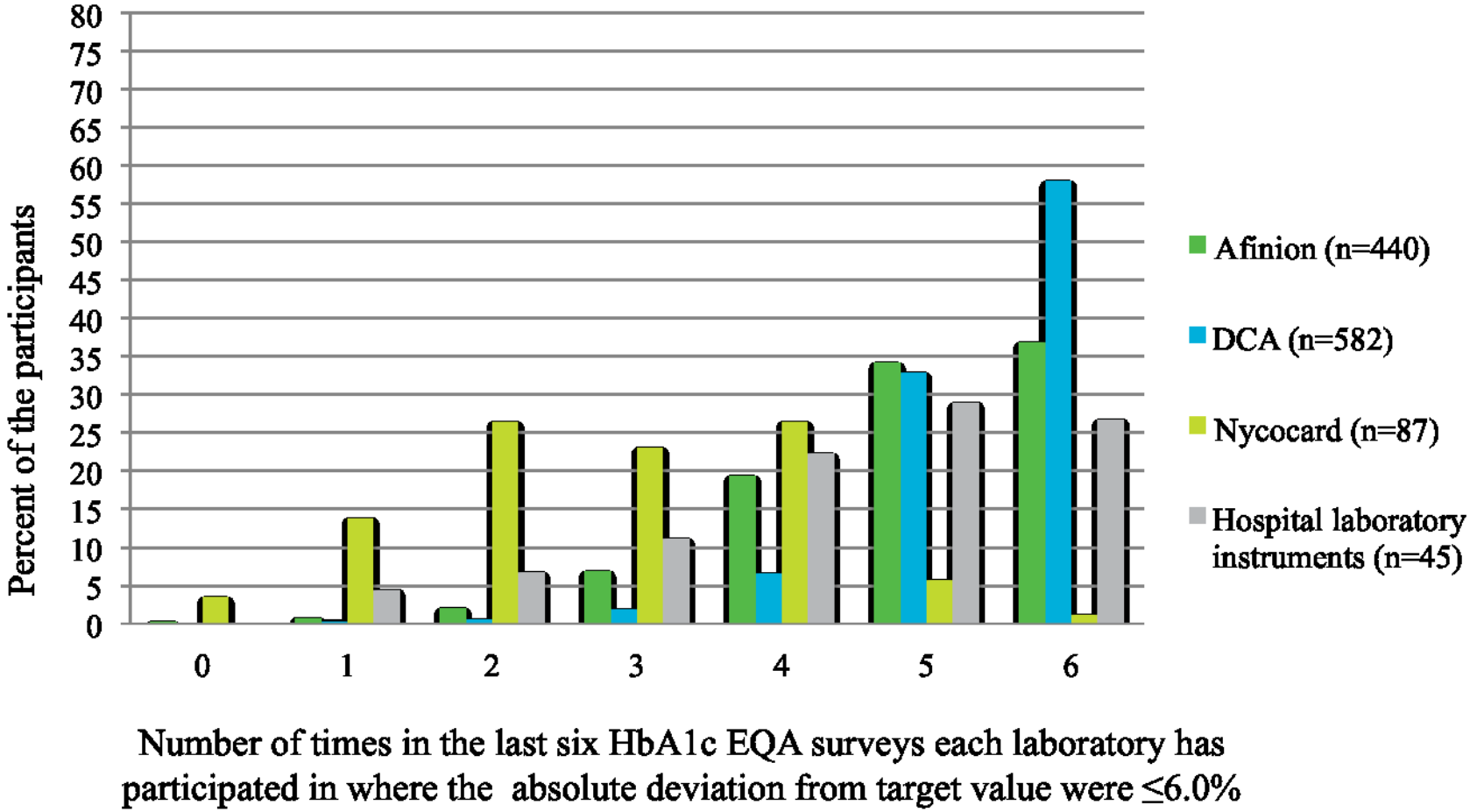




Primary health care

Figure 3A

PHC compared to hospital laboratories – total error



Solvik et al. Clin Chem 2013; 59: 1790-1801

Presuppositions for diagnosing DM with (POC) HbA1c

- EQAS with commutable control material
- Routines for internal quality control
- Recommendations concerning what actions that should be taken to obtain the necessary quality
- Advises on which instruments to buy

Internal quality control

For POC instruments, an internal quality control should be analysed each day HbA1c is analysed

Can we approve instruments for diagnosing?

The quality is not only dependent on the instrument, but also on the participant performance. Therefore it is extremely important with participant focused information.

The quality specifications as well as other information is given in letters to GPs

General question: Can we use POC instruments to *diagnose* DM

General answer:

"Yes" if you can document your quality. But there will always be a "grey" zone (also using hospital instruments).