Should HbA1C measured by POC instruments be used for diagnosis of diabetes?

Sverre Sandberg, Norwegian Quality Improvement of Primary Care Laboratories Noklus, Bergen, Norway
NOKLUS – a POC organisation -
2855 participants, voluntarily participation
1725 GPs offices (99.8%)
848 (96%) nursing homes
31 military installations
48 oil platforms
120 others
88 Norwegian Hospitals

60% of the participants have been visited
350 courses with 5254 participants
34 surveys (20 schemes) for EQAS
External quality control surveys by NOKLUS

- Urine stix
- Glucose
- CRP
- Haemoglobin
- LCG
- Fecal occult blood
- Streptococcus A
- PT-INR
- HbA1c
- Urine albumin
- Leucocytes
- Urine dip-slide
- Haematology
- Helicobacter Pylori
- Haematology (Hospitals)
- Cholesterol
- Coagulation (Hospitals)
- Clinical Chemistry
- D-Dimer
- Post analytical Haematology (Hospitals)
Should HbA1C measured by POC instruments be used for diagnosis of diabetes?

- And if yes – what are the presuppositions for doing it.
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

Table 2  Between-subject, within-subject and analytical coefficients of variation of HbA1c in healthy individuals and diabetes patients (95% CI).

<table>
<thead>
<tr>
<th></th>
<th>HbA1c, %/mmol/mol</th>
<th>CVbs, %</th>
<th>CVws, %</th>
<th>CVa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of person/samples</td>
<td>Grand mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy individuals</td>
<td>5.1 (5.0–5.2)/32.0 (31.0–33.2)</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes patients</td>
<td>7.0 (6.9–7.1)/53.0 (52.0–54.1)</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HbA1c is reported in NGSP HbA1c (%) / IFCC HbA1c (mmol/mol).

CVws for healthy  1.2
CVws for patients 1.7
Within-person variation

<table>
<thead>
<tr>
<th></th>
<th>HbA$_{1c}$ Grand mean</th>
<th>CV$_{wp}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultra$^2$ (mmol/mol)</strong></td>
<td>34.2 (33.8 – 34.6)</td>
<td>0.8 (0.4 – 1.2)*</td>
</tr>
<tr>
<td><strong>Ultra$^2$ (%)</strong></td>
<td>5.28 (5.24 – 5.32)</td>
<td>0.5 (0.3 – 0.7)#</td>
</tr>
<tr>
<td><strong>Premier (mmol/mol)</strong></td>
<td>32.5 (32.1 – 32.9)</td>
<td>1.3 (1.1 – 1.6)</td>
</tr>
<tr>
<td><strong>Premier (%)</strong></td>
<td>5.13 (5.09 – 5.16)</td>
<td>0.8 (0.6 – 0.9)</td>
</tr>
<tr>
<td><strong>Tosoh G8 (mmol/mol)</strong></td>
<td>33.4 (32.9 – 33.8)</td>
<td>1.7 (1.4 – 2.0)*</td>
</tr>
<tr>
<td><strong>Tosoh G8 (%)</strong></td>
<td>5.20 (5.17 – 5.24)</td>
<td>1.0 (0.8 – 1.2)#</td>
</tr>
<tr>
<td><strong>TQ (mmol/mol)</strong></td>
<td>32.6 (32.3 – 33.0)</td>
<td>1.4 (0.9 – 1.8)</td>
</tr>
<tr>
<td><strong>TQ (%)</strong></td>
<td>5.14 (5.10 – 5.17)</td>
<td>0.8 (0.5 – 1.1)</td>
</tr>
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</table>

* and # significantly different from each other
<table>
<thead>
<tr>
<th></th>
<th>CVws</th>
<th>CV anal</th>
<th>Total var</th>
<th>Bias(%)</th>
<th>Unknown Bias (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2</td>
<td>2,0</td>
<td>2,33</td>
<td>0,0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
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<table>
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<tr>
<th>Meas. Value</th>
<th>Low lim</th>
<th>Upper lim</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 meas</td>
<td>7,0</td>
<td>TRUE</td>
</tr>
<tr>
<td>2 meas</td>
<td>7,0</td>
<td>TRUE</td>
</tr>
<tr>
<td>2 samp.</td>
<td>7,0</td>
<td>TRUE</td>
</tr>
<tr>
<td>4 samp.</td>
<td>7,0</td>
<td>TRUE</td>
</tr>
<tr>
<td>30</td>
<td>7,0</td>
<td>TRUE</td>
</tr>
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</table>
## HbA1c

<table>
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<tr>
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<td>TRUE 5,7</td>
</tr>
<tr>
<td>30</td>
<td>6,0</td>
<td>TRUE 5,8</td>
</tr>
</tbody>
</table>
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 variability than FPG/2HPG
Less preanalytical instability than FPG/2HPG
Better measure of long-term complications?

Cheng et al. Diabetes Care, 2009

- A1C: area under curve = 0.71
- FPG: area under curve = 0.65
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.

Lenters-Westra et al Clin Chem, in press
Evaluation of glucometers

Evaluation both under optimal conditions and by the intended user
**HbA1c**

<table>
<thead>
<tr>
<th>Evaluation #</th>
<th>Instrument/testkit</th>
<th>Summary</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKUP/2012/91</td>
<td>Quo-Test A1c</td>
<td>🇬🇧</td>
<td>Download PDF</td>
</tr>
<tr>
<td>SKUP/2010/78</td>
<td>in2it</td>
<td>🇬🇧</td>
<td>Download PDF</td>
</tr>
<tr>
<td>SKUP/2008/65</td>
<td>Afinion HbA1c</td>
<td>🇬🇧</td>
<td>Download PDF</td>
</tr>
<tr>
<td>SKUP/1999/4</td>
<td>DCA 2000</td>
<td>🇳🇴</td>
<td>Download PDF</td>
</tr>
<tr>
<td>SKUP/1999/3</td>
<td>Nycocard</td>
<td>🇳🇴</td>
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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”.

Little, R Clin Chem, in press (editorial)
Diagnosing Diabetes Mellitus: Performance of Hemoglobin A$_{1c}$ Point-of-Care Instruments in General Practice Offices

Una Ørvim Sølvik, Thomas Røraas, Nina Gade Christensen, and Sverre Sandberg

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.

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An expert committee officially recommended the use of hemoglobin Hb A$_{1c}$ (Hb A$_{1c}$) for the diagnosis of
EQAS:
Fresh material from diabetes patients
Target value set by reference method
Number of participants

Hospital

Primary health care
PHC compared to hospital laboratories – total error

Number of times in the last six HbA1c EQA surveys each laboratory has participated in where the absolute deviation from target value were ≤6.0%
PHC compared to hospital laboratories – precision

Number of times in the last six HbA1c EQA surveys each laboratory has participated in where the absolute difference between duplicates were ≤0.3% HbA1c

PHC compared to hospital laboratories – total error and precision

Number of times in the last six HbA1c EQA surveys each laboratory has participated in where the absolute deviation from target were ≤6.0% and the absolute difference between duplicates were ≤ 0.3% HbA1c

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).
09:00-11:00  SYMPOSIUM
POCT: ITS IMPACTS ON PATIENTS AND LABORATORIES
Chairs: D.E. Bruns (USA), S. Sandberg (Norway)

09:00-09:30  A new POC paradigm: Continuous glucose monitoring to enable accurate control of glycemia
             D.E. Bruns (USA)

09:30-10:00  What is important in quality control for POC instruments
             S. Sandberg (Norway)

10:00-10:30  Past, current and continuing controversies in monitoring glycemic control in critical care settings
             D. Sacks (USA)

10:30-10:45  Point of Care Testing (POCTs): the importance of critical problems reporting
             A. Aita (Italy)

10:45-11:00  Implementation of C-reactive protein (CRP) point of care testing in the primary care: a pilot study
             A.Y. Demir (The Netherlands)
1st EFLM Strategic Conference

Defining analytical performance goals 15 years after the Stockholm Conference

8th CIRME International Scientific Meeting

Milan (IT)
24-25 November 2014