Global Standardization of HbA1c

Impact of the Consensus Statement of International Professional Organizations

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Network Coordinator IFCC Working Group for Standardization of HbA1c
EQA organiser HbA1c in The Netherlands,
Berlin, EQALM, 1 July 2009
Obesitas

Diabetes

Long Term Complications

Glucose Memory

$HbA1c$: Risc factor

$HbA1c$: Standardization
Prevalence of Obesity Among U.S. Adults

JAMA 2003; 298:76

With permission of Prof. David Sacks, Harvard School of Medicine
Prevalence of Diagnosed Diabetes Among Adults in the U.S.

JAMA 2003; 298:76

With permission of Prof. David Sacks, Harvard School of Medicine
THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

The Diabetes Control and Complications Trial Research Group*

Abstract  Background. Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM). We examined whether intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range could decrease the frequency and severity of these complications.

Methods. A total of 1441 patients with IDDM — 726 with no retinopathy at base line (the primary-prevention interval, 62 to 85 percent), as compared with conventional therapy. In the secondary-intervention cohort, intensive therapy slowed the progression of retinopathy by 54 percent (95 percent confidence interval, 39 to 66 percent) and reduced the development of proliferative or severe nonproliferative retinopathy by 47 percent (95 percent confidence interval, 14 to 67 percent). In the two cohorts combined, intensive therapy reduced the occurrence of microalbuminuria (urinary albumin excretion of ≥40 mg
Distribution of HbA1c - EDIC

With permission of Prof. David Sacks, Harvard Medical School
Prevalence of Albuminuria

With permission of Prof. David Sacks, Harvard Medical School

JAMA 2003; 290:2159
DCCT: HbA1c = Risk Factor

Relative Risk

Poor, Fair, Good

5.5% 8.5% 11.5%
Reliable Risk Prediction = Reliable HbA1c

Standardization

Relative Risk

HbA1c

5.5%  8.5%  11.5%
National Initiatives Standardisation

Approach

USA: NGSP
Japan: JDS/JSCC
Scandinavia: Mono-S
Comparison
National Reference Methods

* Arbitrarily Chosen
* Not Specific
* Different numbers

Confusion!
Summary Situation

* Confusion Different Numbers in USA, Japan, Scandinavia, Europe

* Many Countries not standardized at all

* Traceability required by The European Law (IVD Directive)
The IFCC: This is unacceptable

We want someone.......  

......To develop an scientifically sound Reference Method

......As the anchor to achieve worldwide Harmonization of HbA1c
Where to find Fools to do this Job?

Scientists
Europe-USA-Japan-Australia

IFCC
Reference Method
HbA1c

European Union
Roche-Boehringer
IFCC Working Group at Work

- Pure HbA1c HbA0
- Reference Method
- Worldwide Network
- Clinical Studies
- Implementation
Conclusions:

- highly reproduceable over 8 years
- linear relationship
- tight relationship (low uncertainty)

Similar results for Japanese and Scandinavian DCM’s
The IFCC Reference Measurement System for HbA1c: A 6-Year Progress Report

Cas Weykamp (1*), W. Garry John (2), Andrea Mosca (3)
Tadao Hoshino (4), Randie Little (5), Jan-Olof Jeppsson (6)
Kor Miedema (8), Gary Myers (9), Hans Reinauer (10)
David Sacks (11), Robbert Slingerland (8), Carla Siebelder (1)
IFCC Definition of the Analyte

Primary Calibrator
Pure HbA1c/HbA0 mix

Secondary Calibrator
Blood Panels

Manufacturer’s Working Calibrator

Manufacturer’s Product Calibrator

Patient Sample

Primary Reference MP
Gravimetry

Secondary Refer. MP
IFCC Reference Meth.

Manufacturer’s Internal MP

Manufacturer’s Standing MP

Routine MP in Lab

Interpretation
Patient Result

For HbA1c
IFCC Working Group at Work

- Pure HbA1c HbA0
- Reference Method
- Worldwide Network
- Clinical Studies
- Implementation
…..The IFCC Reference Method is ready for Implementation.....
Does the World love The IFCC?
But........
The first Debate
But.........in General

<table>
<thead>
<tr>
<th>Fahrenheit</th>
<th>Celcius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark</td>
<td>Euro</td>
</tr>
<tr>
<td>Miles</td>
<td>Kilometers</td>
</tr>
<tr>
<td>Pints*</td>
<td>Liters</td>
</tr>
<tr>
<td>mg/dL</td>
<td>μmol/L</td>
</tr>
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</table>

* Except Beer
<table>
<thead>
<tr>
<th>Fahrenheit</th>
<th>Celcius</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark</td>
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</tr>
<tr>
<td>mg/dL</td>
<td>μmol/L</td>
</tr>
</tbody>
</table>

**NGSP Numbers** | **IFCC Numbers**

That is the Question!
Debate on HbA1c Numbers

Purists

Conservatives

Strategists
Debate on HbA1c Numbers

Implement the new IFCC numbers
We have a new method: use it!

Purists  Conservatives  Strategists
Debate on HbA1c Numbers

Keep the old DCCT numbers
We are used to it: never change a winning team!

Purists  Conservatives  Strategists
Consensus Statement!

IFCC  = International Federation Clinical Chemistry
IDF   = International Diabetes Federation
EASD  = European Association Study of Diabetes
ADA   = American Diabetes Association

Milan, 4 May 2007
1. We agree that the HbA1c results should be standardized worldwide, including the reference system and results reporting.

2. We agree that the IFCC reference system for HbA1c represents the only valid anchor to implement standardisation of the measurement.

3. We agree that the HbA1c assay results be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.

4. We agree that if the ongoing “average plasma glucose study” fulfills its a priori specified criteria, an HbA1c-derived average plasma glucose (APG) value should also be reported as an interpretation of the HbA1c result.

5. We recommend that all clinical guidelines be expressed in IFCC units, derived NGSP units, and APG.

6. We agree that these recommendations should be implemented globally as soon as possible.
# HbA1c Dictionary

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Average Plasma Glucose (APG)*</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-S</td>
<td>JDS/JSCC</td>
<td>NGSP</td>
</tr>
<tr>
<td>Sweden</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>7.2</td>
<td>7.6</td>
<td>8.0</td>
</tr>
<tr>
<td>6.1</td>
<td>6.6</td>
<td>7.0</td>
</tr>
<tr>
<td>5.0</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>2.9</td>
<td>3.6</td>
<td>4.0</td>
</tr>
</tbody>
</table>

*From provisional results ADAG Study*

C. Weykamp
Patient Chart

**HbA1c**
- mmol/mol (% NGSP)
  - 64 (8.0%)
  - 53 (7.0%)
  - 42 (6.0%)

**eAG***
- mmol/L (mg/dL)
  - 10.2 (183)
  - 8.6 (154)
  - 7.0 (126)

**Change Therapy**
- Jan 06
- April 06
- July 06
- Oct 06
- Jan 07
- Apr 07
- Jul 07
- Oct 07

**Target Therapy**
- Jan 06
- April 06
- July 06
- Oct 06
- Jan 07
- Apr 07
- Jul 07
- Oct 07

**Upper Normal**
- Jan 06
- April 06
- July 06
- Oct 06
- Jan 07
- Apr 07
- Jul 07
- Oct 07

C. Weykamp  *From Provisional Data ADAG Study
1. HbA1c Standardised Worldwide

2. IFCC is the Anchor

3. HbA1c reported IFCC and NGSP

4. HbA1c also reported eAG

5. IFCC, NGSP, eAG in Guidelines

6. Implementation Soon
But......
The second Debate
Laboratory Report

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Conversion</th>
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<tr>
<td>Glucose</td>
<td>5.9 mmol/L (106 mg/dL)</td>
<td>6.0 % (NGSP units)</td>
</tr>
<tr>
<td>Na</td>
<td>142 mmol/L (327 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>4.6 mmol/L (18 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>42 mmol/mol (IFCC Units)</td>
<td>6.0 % (NGSP units)</td>
</tr>
<tr>
<td></td>
<td>7.0 mmol/L (Average Plasma Glucose)</td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>5.6 mmol/L (34 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>83 μmol/L (0.94 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>2.1 mmol/L (8.4 mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>2.1 mmol/L (8.4 mg/dL)</td>
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## Laboratory Report

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Value</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>5.9 mmol/L (106 mg/dL)</td>
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<tr>
<td>Na</td>
<td>142 mmol/L (327 mg/dL)</td>
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<td>2.1 mmol/L (8.4 mg/dL)</td>
</tr>
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</table>
Implementatation: Many parties Involved

- Patient
- Diabetologists
- Clinical Chemist
- Manufacturer
- EQAS Organizer
- Consensus Statement
- Kit Calibrators
- IFCC Calibrators
- Proficiency Test
- Value Assignment
One Analyte – Three Numbers!?

* This is what We want
One Analyte Three Numbers!? 

* Scientifically Sound?
* Technically Possible?
* Do my Physicians want this?
One Analyte – Three Numbers !?

* Not too Fast
Our Opinion
Is…….
One Analyte – One Number !?

* Know My Number….

…..What Number?
One Analyte – Three Numbers !?

Manufacturer

Give Us Time
- Traceable 31 Dec 2009
- IFCC and NGSP “1-1-1-1”
  1 January 2011
- eAG not business
Analytical Instruments
(but lab information system like eGFR)
Lessons Learned

It is an Illusion to think that The Consensus Statement will be uniformly implemented Worldwide: the views in the respective countries are too different.

Implementation is not an issue for a single group but must be a concerted action of all parties involved (diabetologists, clinical chemists, patients, manufacturers, EQA organisers).

As global implementation is not achieveable, try at least uniform implementation at the national level.
Implementation National Level

• National Committee of stakeholders

• Define: final situation, transition period, deadlines

• Consensus and Commitment of Stakeholders

• Tasks of respective Stakeholders

• (Communication) Plan
## Decisions National Level

<table>
<thead>
<tr>
<th>Country</th>
<th>IFCC</th>
<th>NGSP</th>
<th>eAG</th>
<th>Other</th>
<th>Remark</th>
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<tr>
<td>UK</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Germany</td>
<td>X</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>by Law</td>
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<tr>
<td>France</td>
<td>(X)</td>
<td>-</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>Small EU</td>
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<td>Transition</td>
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<td>-</td>
<td>JDS</td>
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<td>-</td>
<td>X</td>
<td>X</td>
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</table>
One Analyte – Three Numbers!?  

EQA Organiser  

* Make a Policy
EQA Organiser
(External Quality Assessment Programme)
(Proficiency Testing)

Role?

Implementation Consensus Statement
## Trend Quality in 15 years

<table>
<thead>
<tr>
<th>Year</th>
<th>Deviation</th>
<th>Intralab CV</th>
<th>Interlab CV</th>
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</thead>
<tbody>
<tr>
<td>1993</td>
<td>----</td>
<td>5.2%</td>
<td>22.0%</td>
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<tr>
<td>1999</td>
<td>+0.3%</td>
<td>4.9%</td>
<td>11.2%</td>
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<tr>
<td>2002</td>
<td>-0.1%</td>
<td>3.4%</td>
<td>8.5%</td>
</tr>
<tr>
<td>2005</td>
<td>-0.2%</td>
<td>2.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>2008</td>
<td>0.0%</td>
<td>2.1%</td>
<td>4.1%</td>
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Summary

1. Diabetes is emerging
2. HbA1c Anchor for Therapy
3. HbA1c requires Standardisation
4. Reference Method is in place
5. Global Debate on Units
6. EQA Organiser: Make your Decision
   implement in Concerted Action Stakeholders
7. EQA Organiser: Play a role
   in education and check Implementation
Thank you for your Attention