Insulin Analogues and SMBG

Messages from Dalhousie CME

Academic Detailing

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Presentation to Diabetes Care Program of Nova Scotia

April 15, 2010
Disclosure statements

The Academic Detailing Service is operated by Dalhousie Continuing Medical Education and funded by the Nova Scotia Department of Health. Dalhousie University Office of Continuing Medical Education has full control over content.

Pam and Jill provide drug evaluation support to the Nova Scotia Department of Health
Outline

• Clinical Questions
• Background information
• Insulin Analogue Therapy
  – Evidence
  – COMPUS and CDA recommendations
• Blood Glucose Test Strips
  – Evidence
  – COMPUS and CDA recommendations
Three questions

1. Do the insulin analogues provide any clinically important reduction in A1C levels compared to human insulins?

2. Do the insulin analogues provide any clinically important reduction in hypoglycemia compared to human insulins?

3. Who should be self-monitoring their blood glucose? How often should they monitor?
Academic Detailing Program

• Managed by Dalhousie CME and funded by the Department of Health.

• Trained health care professionals visit practitioners individually to provide evidence-based CME on a particular topic in brief educational sessions.

• Material developed with the assistance of an advisory board consisting of four family physicians and topic-specific specialists from across NS.

• Academic detailing is available to all Nova Scotia family physicians and interested specialists, but participation is completely voluntary and confidential.

• To date, over 65% of Nova Scotia family physicians have participated in one or more AD programs.
• Canadian Optimal Medication Prescribing and Utilization Service
  – program of CADTH
  – Pan-Canadian service funded by Health Canada
  – In partnership with the Federal, Provincial, and Territorial Health Ministries, COMPUS identifies and promotes optimal drug therapy

• COMPUS Expert Review Committee
  – 12 member panel
  – Including endocrinologists, pharmacists, family physicians
Considering the evidence

• Step 1: Evidence of clinical benefit and harm
  • Safety, efficacy, and clinically-important differences

• Step 2: Economic evidence
  • Cost-effectiveness

• Step 3: Recommendations formulated
  “GRADE” process
  • quality of evidence: low, moderate, high
  • strength of each recommendation: weak or strong

• Step 4: Feedback from stakeholders such as advocacy groups and industry

Two recent COMPUS topics

- Insulin Analogue Therapy
- Blood Glucose Test Strips

We will consider:

A. What is the evidence for their use?
B. What are the recommendations for their use?
<table>
<thead>
<tr>
<th>Insulin</th>
<th>Start</th>
<th>Peak effect</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Analog</td>
<td>10 to 20 mins</td>
<td>45 min to 3 hours</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Regular HI</td>
<td>30 - 60 mins</td>
<td>1 to 5 hours</td>
<td>5 to 7.5 hours</td>
</tr>
<tr>
<td>NPH</td>
<td>1 to 3 hours</td>
<td>6 to 12 hours</td>
<td>12 to 16 hours</td>
</tr>
<tr>
<td>LA analog</td>
<td>1 to 2 hours</td>
<td>Even effect over 24 hrs</td>
<td>24 hours</td>
</tr>
</tbody>
</table>
Insulin price comparison

Outcomes

• **Glycemia**
  • A1c, Fasting plasma glucose, 2 hour PC glucose

• **Hypoglycemia**
  • Severe, nocturnal, overall

• **Clinical**
  • Mortality, CHD, stroke, PVD, retinopathy, nephropathy, neuropathy

• **Metabolic**
  • Body weight, BMI

• **Quality of life**
  • Satisfaction with care, quality of life
Question 1  Insulin Analogues

Do the insulin analogues provide any **clinically important reduction** in A1C levels compared to human insulins?

**NO**
Statistical vs clinical significance

A1c clinically significant difference

= 0.7 to 1.0 percentage point
A1C: summary of evidence

• Meta-analyses indicate no clinically significant difference in A1C levels between insulin analogues and human insulin in any population.

  – Adults or children with type 1 diabetes or
  – Adults with type 2 diabetes (children with type 2 diabetes have not been studied)

• No statistically significant difference was greater than 0.3 percentage points.
Question 2   Insulin Analogues

Do the insulin analogues provide any **clinically important reduction** in **hypoglycemia** compared to human insulins?  

???
Hypoglycemia as a clinical trial outcome

- Different Categories
  - Overall vs. Severe vs. Nocturnal

- Different ways to report each outcome
  - Risk ratios and / or Rate ratios

- Limitations of individual studies
  - Lack of clear definitions for hypoglycemia
  - Studies were unblinded

  - patients with history of recurrent severe hypoglycemia were EXCLUDED (mostly for detemir)
• Overall
  – Benefit from the insulin analogues in hypoglycemia was **INCONSISTENT** in clinical trials

• One outcome with most consistent benefit
  – Nocturnal hypoglycemia in two populations
    1. **Rapid-acting** analogues in adults and adolescents with **type 1** diabetes
    2. **Long-acting** analogues in adults with **type 2** diabetes.
There were no consistent differences between the analogues and human insulin in overall or severe hypoglycaemia.

<table>
<thead>
<tr>
<th>Population</th>
<th>Nocturnal Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting</strong> analogues in adults and adolescents with <strong>type 1</strong> diabetes</td>
<td>Relative Rate Reduction ≈ 40%</td>
</tr>
<tr>
<td><strong>Long-acting</strong> analogues in adults with <strong>type 2</strong> diabetes.</td>
<td>Risk was <strong>not</strong> reported</td>
</tr>
<tr>
<td></td>
<td>Absolute Risk Reduction ≈ 6 to 14%</td>
</tr>
<tr>
<td></td>
<td>NNT ≈ 6 to 13</td>
</tr>
</tbody>
</table>

There are limitations of nocturnal hypoglycemia as a clinical trial outcome.
## Insulin analogues vs human insulins: Summary of COMPUS findings

<table>
<thead>
<tr>
<th></th>
<th>A1C</th>
<th>Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
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<tr>
<td>Adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolus Insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
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</tr>
</tbody>
</table>

### Benefit with analogue

- No significant difference
- Inconsistent results
For a patient with type 1 diabetes which basal (background) insulin would you choose?

Analogue or NPH?

What about a patient with type 2 diabetes?
COMPUS recommendations for human insulins and insulin analogues

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Type 1 diabetes</th>
<th>Type 2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>Adults</td>
<td>Adolescents</td>
</tr>
<tr>
<td></td>
<td>NPH</td>
<td>NPH</td>
</tr>
<tr>
<td>Bolus</td>
<td>Reg HI or IA</td>
<td>IA</td>
</tr>
</tbody>
</table>

Strong recommendation
Weak recommendation
Comparison to CDA 2008 Recommendations

• COMPUS and CDA recommendations are similar
  – CDA: “consider”, “may be considered”
  – COMPUS: “suggested”

• Potential differences to highlight
  – The use of rapid-acting analogues in type 2 diabetes
  – Wording of recommendations for Basal insulins
<table>
<thead>
<tr>
<th>Type 2 adults</th>
<th>CDA Recommendations 2008</th>
<th>COMPUS Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid/short acting</strong></td>
<td>Use rapid-acting insulin analogues instead of short-acting insulin to lower postprandial blood glucose levels.(^a)</td>
<td>Regular human insulin is <strong>suggested</strong> over the rapid acting analogues.(^b)</td>
</tr>
<tr>
<td><strong>Grade B, Level 2</strong></td>
<td><strong>Weak recommendation; low quality evidence</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td>When basal insulin is added to antihyperglycemic agents, long-acting analogues <strong>may be considered</strong> instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia.</td>
<td>NPH is <strong>recommended over</strong> long acting insulin analogues.</td>
</tr>
<tr>
<td></td>
<td><strong>Strong recommendation; low / moderate quality evidence</strong></td>
<td></td>
</tr>
</tbody>
</table>

**IMPORTANT:** COMPUS recommendations consider cost-effectiveness
Summary

1. BASAL or long-acting analogs
   – NPH recommended first in type 1 and type 2 diabetes

2. BOLUS or rapid-acting analogs
   – Type 1: Regular insulin OR rapid-acting analogs recommended as first line except for adolescents
     • Adolescents: Rapid-acting analog suggested as first line over regular human insulin
   – Type 2: Regular human insulin suggested as first line over rapid-acting analogs

3. Reasons for considering analogues
   – Convenience or episodes of hypoglycemia

4. No preference for one analog over another
<table>
<thead>
<tr>
<th>Insulin</th>
<th>Regular Benefit</th>
<th>Exception Status</th>
<th>Non-Benefit Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>children ≤ 18 yrs old</td>
<td>adults ≥ 19 years old</td>
<td></td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
<td>✗</td>
</tr>
<tr>
<td>Determir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACADEMIC DETAILING MESSAGES
SELF MONITORING OF
BLOOD GLUCOSE
(SMBG)

Pam McLean-Veysey
"The first commandment is: Thou shalt not shoot the messenger."
WHY SMBG?

• The main reasons for self-monitoring of blood glucose are to
  – Improve adherence to glycemic targets
  – Reduce episodes of hypoglycemia
  – Monitor hyperglycemia in acute situations

• SMBG should be used when linked to specific patient actions such as
  – Prevention or treatment of hypoglycemia
  – Self-directed medication dosage adjustment
Role of SMBG in Self Management

Ref: CDA 2008
AD messages based on COMPUS material

http://www.cadth.ca/index.php/en/compus/blood-glucose
COMPUS recommendations vary depending on whether the patient is using insulin.

Generally, it is recommended that

- Patients *using insulin* perform SMBG
- Most adults *not using insulin* do **not** require **routine** SMBG
**Type 1 or type 2 diabetes using basal-bolus insulin:**

- SMBG should be **individualized** to guide adjustments in insulin therapy to achieve optimal blood glucose control.

**Adults with type 2 diabetes using basal insulin**

- Testing of **up to 14 times per week** should be sufficient for most patients at most times.
Basal Insulin

Why up to 14 tests per week?

• COMPUS rated evidence as low quality and this is a weak recommendation.
  – It is based on standards of practice and a cost-effectiveness analysis
  – Testing 14 times per week may be cost-effective if it leads to a decrease in A1C of 0.5% to 0.75%.
    • Approximately $50,000 - $75,000 /QALY (ICUR)

• CDA 2008 recommendation is to test at least once a day, at variable times in this population.
More frequent testing?

Based on clinical experience and accepted standards of practice, some conditions may require more frequent testing. For example:

- Multiple daily insulin injections (i.e., three or more per day)
- History of hypoglycemia
- Occupation where hypoglycemia poses safety concerns
  - testing is mandated by an employer (e.g., pilots, air-traffic controllers, critical positions in railways)
- Private and commercial drivers
  - jurisdictional regulations concerning SMBG, hypoglycemia, and operation of motor vehicles.
- Newly initiated on insulin
- Experiencing acute illness
- Undergoing changes in insulin dose/regimen or significant changes in routine.
- Poorly controlled or unstable blood glucose levels
- Pregnant or planning a pregnancy
Routine use of SMBG is **not recommended** for **most adults**
with type 2 diabetes using oral antihyperglycemic drugs.

- Strong recommendation; low to moderate level of evidence
- **Periodic testing in selected patients, for example**
  - Unstable glucose levels
  - acute illness, unplanned physical activity
  - pharmacotherapy changes
  - risk of hypoglycemia with insulin secretagogues (e.g., Glyburide, gliclazide, etc.)
  - Pregnant or planning a pregnancy
Efficacy Outcome Measure
A1C

Type 1
• Study which reported the largest reduction in the trials reviewed by COMPUS. Karter 2001
  – Mean difference in A1C reduction:
    • 0.78% (95% CI: 0.55 to 1.01) in favor of testing ≥ 3 times per day vs. once per day.
    • Very low quality retrospective cohort study.

Type 2 (oral agents or no pharmacotherapy)
• 7 RCTs (n= 2270)
  – Mean difference in A1C reduction
    • 0.25% (95% CI: 0.15 to 0.36) for SMBG vs. no monitoring
  – Statistically significant but not clinically significant
  – Similar results in patients using sulfonylureas
Efficacy Outcomes
Hypoglycemic Events/Well being

Type 2 not requiring insulin (SMBG vs no SMBG)
3 RCTs (n=1752)
  • Increase in at least one overall hypoglycemic event with SMBG.
    – Risk 15% vs. 7.6%, relative risk increase 99%, absolute risk increase 7.4%;
    – Number needed to test 13 (95% CI: 7 to 36).
    – Most mild or asymptomatic
    – Increase COULD BE due to detecting hypoglycemia with monitoring.
    – No affect on severe or nocturnal hypoglycemia (studies were not powered to detect such differences.)

2 RCTs (n=794) patients found a decrease in the rate of hypoglycemic events:
  – Rate ratio 0.73 (95% CI: 0.55 to 0.98).

• SMBG was not associated with improvements in well-being or satisfaction with treatment and showed increased levels of depression and poorer quality of life.
Daily SMBG in all patients with type 2 diabetes not using insulin does not represent an efficient use of finite healthcare resources.

Daily use is associated with an incremental cost of

- $113,643 per QALY gained.

Periodic use (e.g., one to two test strips per week) may be cost-effective.

Reducing the price of test strips would significantly improve cost-effectiveness.
**COMPUS Key Message**

**Diabetes controlled by diet**

Most adults with type 2 diabetes controlled by diet alone should not require **routine SMBG**
Efficacy Outcome

A1C

Type 2 using no antihyperglycemic drugs

- 1 RCT (n=124)
  - Mean difference in A1C
    - 0.05% (95% CI -0.33 to 0.23)
    - Not statistically significant
## Similarities and differences in recommendations

<table>
<thead>
<tr>
<th>Type 1 adults and children</th>
<th>CDA SMBG Recommendations 2008</th>
<th>COMPUS SMBG Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended as an essential part of diabetes self management</td>
<td>Grade A, Level 1</td>
<td>The optimal daily frequency should be individualized for adults and children with type 1 diabetes</td>
</tr>
<tr>
<td>- at least 3 times per day</td>
<td>Grade C, Level 3</td>
<td>Strong recommendation; low-quality evidence</td>
</tr>
<tr>
<td>include both pre- and postprandial tests</td>
<td>Grade C, Level 3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 adults using insulin</th>
<th>CDA SMBG Recommendations 2008</th>
<th>COMPUS SMBG Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using Insulin</td>
<td>SMBG recommended as an essential part of diabetes self-management</td>
<td>Frequency should be individualized for most adults with type 2 diabetes using insulin with or without oral antidiabetes drugs</td>
</tr>
<tr>
<td>- at least 3 times per day</td>
<td>Grade C, Level 3</td>
<td>Strong recommendation; low quality evidence</td>
</tr>
<tr>
<td>- include both pre- and postprandial tests</td>
<td>Grade C, Level 3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 Once daily Insulin Plus oral agents</th>
<th>CDA SMBG Recommendations 2008</th>
<th>COMPUS SMBG Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-daily insulin plus oral antihyperglycemic Agents</td>
<td></td>
<td>Suggested maximum average weekly frequency of SMBG for most adults with type 2 diabetes using [basal] insulin with or without oral antidiabetes drugs</td>
</tr>
<tr>
<td>- test at least once a day at variable times</td>
<td>Grade D, Consensus</td>
<td></td>
</tr>
<tr>
<td>14 tests per week.</td>
<td>Weak recommendation; low quality evidence</td>
<td></td>
</tr>
</tbody>
</table>
Similarities and differences in recommendations

CDA SMBG
Recommendations 2008

COMPUS SMBG
Recommendations 2009

Type 2  Controlling with diet alone or oral agents

• The frequency of SMBG should be **individualized** depending on glycemic control and type of therapy.
  – Should include both **pre- and postprandial** measurements

• **Routine** use of blood glucose test strips for SMBG is
  – **not recommended** for most adults with type 2 diabetes using oral antidiabetes drugs or diet alone

  *Grade D, Consensus.*

  *Strong recommendation; low / moderate quality evidence*
Financial Considerations

• In 2008 spending within the NS Pharmacare program was:
  – Diabetes medications $8,532,000
  – Glucose test strips $8,522,200
• > $4,000,000 for patients where routine testing is not recommended (oral antidiabetes drugs or no drugs).
  – $870,000 in those on no drugs.
Total Spending in Canadian Publicly and Privately Funded Drug Plans on Blood Glucose Test Strips Exceeded **$330 Million*** in 2006

- **Patients with diabetes who are using insulin**: $144,000,000
- **Patients with diabetes who are not using insulin**: $188,000,000

*This estimate is based on data from eight publicly funded drug plans in Canada (British Columbia, Manitoba, Newfoundland and Labrador, Non-Insured Health Benefits, Nova Scotia, Ontario, Quebec, and Saskatchewan) plus data from 67% of privately funded drugs plans that submitted data to Brogan Inc. Some patients in the dataset could not be classified by province or territory, therefore, the estimate is underreported.
Summary

• There is little evidence to guide recommendations on SMBG
  – Evidence is of low/moderate quality, mostly observational studies.

• Recommendations are primarily based on consensus and usual care.

• COMPUS includes cost considerations in recommendations.

• Consider opportunity costs
  – resources can be used elsewhere.
"Your blood sugar is too high."