Diabetes 2010...

Insulin Analogues & Self-monitoring

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“Seek simplicity, and mistrust it.”
Alfred North Whitehead
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Definitions


- **Basal insulin**: Intermediate- or long-acting insulin or insulin analogue preparations designed to mimic the action of basally secreted endogenous insulin. Examples are:
  - Human insulin neutral protamine Hagedorn (NPH)
  - Insulin analogues detemir (Levemir), glargine (Lantus)

- **Biphasic insulin preparation**: Pre-mixed insulin containing both a bolus and basal insulin in the same vial or cartridge (e.g., regular human insulin and insulin NPH) Examples are:
  - Human insulin: regular/NPH (e.g. Novolin 30/70, Humulin 30/70)
  - Insulin analogues: lispro/lispro protamine (Humalog Mix) aspart/aspart protamine (Novo Mix)

- **Bolus insulin**: Short- or rapid-acting insulin or insulin analogue preparations designed to mimic the endogenous secretion of insulin in response to food intake. Examples are:
  - Human insulin regular human insulin
  - Insulin analogues lispro (Humalog), aspart (NovoRapid)

- **Continuous subcutaneous insulin infusion**: A method of insulin administration designed to mimic endogenous insulin secretion through continuous subcutaneous delivery of basal doses of short- or rapid-acting insulin via an insulin pump, and user-controlled bolus doses prior to food intake.

- **Diabetes mellitus**: A group of common metabolic disorders characterized by hyperglycemia and caused by insufficient insulin secretion, reduced insulin sensitivity of target tissues, or both.

- **Diabetic ketoacidosis**: An acute complication of marked hyperglycemia (due to uncontrolled diabetes) characterized by increased fatty acid metabolism, accumulation of ketone bodies, and acidosis.

- **Fasting plasma glucose**: Plasma glucose level measured at least eight hours after caloric intake.

- **Gestational diabetes mellitus**: Defined as glucose intolerance with first onset during pregnancy; usually a temporary condition.

- **Hemoglobin A1C**: A glycated form of hemoglobin. Hemoglobin A1C levels correlate with glycemia over the course of 90 to 120 days, and are, therefore, commonly used as a measure of long-term glycemic control in persons with diabetes. We will refer to this as A1C.

- **Heterogeneity (I²)**: This statistic describes the degree of variation, as a percentage, between the results of individual studies within a meta-analysis. A low I² is better because it represents low heterogeneity. I² values of
  - <50% represent low heterogeneity
  - 50% to <75% represent moderate heterogeneity
  - ≥ 75% represent high heterogeneity

- **Hyperglycemia**: A qualitative term to describe blood glucose above the normal range.
• **Hypoglycemia**: A qualitative term describing blood glucose below the normal range.
  
  Definitions vary across studies, although one or both of the following is usually required to define a hypoglycemic event: autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake, and/or a plasma glucose level below a specific value (threshold is usually between 3.4 to 4.0 mmol/L).

• **Hypoglycemia unawareness**: Hypoglycemia occurring in the absence of typical symptoms. More common in people with long-standing type 1 diabetes and those who attempt to maintain glucose levels which are closer to normal. Contributing factors include autonomic neuropathy, desensitization of the brain to hypoglycemia, and use of drugs that mask the hypoglycemic symptoms.

• **Insulin analogue**: Pharmaceutical agents produced through alterations of the amino acid sequence of regular human insulin with the intent to alter the pharmacokinetic properties of regular human insulin while maintaining its pharmacological effects.

• **Long-acting insulin analogues**: A class of insulin analogues — produced by introducing alterations in the amino acid sequence and/or molecular structure of regular human insulin — which mimics the action of basal endogenous insulin secretion by providing a prolonged, basal level of insulin activity.

• **Multiple daily injection**: A method of insulin administration involving three or more daily subcutaneous injections of insulin (i.e., both basal and bolus insulins, in various combinations) designed to mimic endogenous insulin secretion.

• **Neutral protamine Hagedorn (NPH)**: An insulin preparation with an intermediate duration of action produced through combination of regular human insulin with protamine.

• **Nocturnal hypoglycemia**: Hypoglycemic events that occur at night, usually between midnight and 6:00 a.m. May be symptomatic (night sweats, tremors, nightmares) or asymptomatic with unexplained high morning fasting blood glucose values. Occasionally checking 2 AM blood glucose (specifically in type 1 DM) may help prevent unrecognized nighttime lows.

• **Overall hypoglycemia**: Defined in most studies by signs or symptoms of hypoglycemia, and/or blood glucose below a certain threshold (e.g., < 4 mmol/L).

• **Rapid-acting insulin analogue**: A class of insulin analogues — produced through alterations of the amino acid sequence of regular human insulin — designed to closely mimic the short duration of action of meal-induced endogenous insulin secretion.

• **Severe hypoglycemia**: Severe hypoglycemia is defined as an event with characteristic hypoglycemic symptoms requiring assistance of another person. Some studies also require the presence of blood glucose values below a certain threshold (e.g., < 4 mmol/L).

• **Type 1 diabetes mellitus**: Diabetes characterized by a lack of insulin secretion caused by pancreatic beta cell destruction. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

• **Type 2 diabetes mellitus**: Diabetes characterized by insulin resistance and varying degrees of insulin deficiency, especially as the disease progresses.
Measures of treatment effect

To illustrate the following measures of treatment effect:
- Consider a 1-year study measuring the effect of a treatment on mortality.
  - There were 100 patients in the control group
  - 100 patients in the treatment group

Risk or event rate
- These terms mean the same thing.
- In the control group, 20 patients died
  - Therefore the risk or event rate was 20/100 or 20% or 0.20
- In the treatment group, 15 patients died
  - Therefore the risk or event rate was 15/100 or 15% or 0.15

Relative risk (RR)
- Sometimes called risk ratio.
- Relative risk is the risk in the treatment group divided by the risk in the control group
  - In the example RR = 15%/20% = 75% (or 0.15/0.25 = 0.75)
  - Patients in the treatment group have 75% of the risk of dying compared to patients in the control group.
- If the treatment increases risk, the RR will be greater than 1 (or >100%).
- If the treatment decreases risk, the RR will be less than 1 (or <100%).

Relative Risk Reduction (RRR)
- RRR is a measure of the percent of events prevented by the treatment.
- RRR is calculated as 100% minus the RR (if expressed as a percentage) or 1 minus the RR (if expressed as a proportion)
  - In the example: RRR = 100% - 75% = 25% 25% of deaths are prevented by the treatment.

Absolute Risk Reduction (ARR)
- Sometimes called risk difference
- ARR is an absolute measure of the percent of events prevented by the treatment.
- Generally, the ARR is a more accurate reflection of treatment effect than RRR.
  - In the example: ARR = 20% - 15% = 5% 5% of people will be saved from dying by the treatment.

Number needed to treat (NNT)
- The NNT indicates the number of patients who need to be treated to prevent one bad outcome. It is calculated as the inverse of the absolute risk reduction:
  - NNT = 100%/ARR (if ARR is a percent) or NNT=1/ARR (if ARR is a proportion).
  - In the example: NNT = 100%/5% or 1/0.05 = 20.
    - Therefore, 20 people need to be treated for one year to avoid one death.

Number needed to harm (NNH)
- Absolute risk increase and NNH are calculated the same way.
  - If 60% of patients in the treatment group experienced a headache compared with 20% in the control group then the absolute risk increase is 40%.
    - The NNH is 100%/40% or 1/0.4 = 2.5. You need to treat only 2-3 people with the new treatment to cause one to have a headache.


**Rate ratio**

- Like the relative risk, the rate ratio provides a measure of the relative benefit of a treatment.
- However, it takes into account the amount of **time** that subjects in the control and treatment groups experienced before having an event and the number of events they have.
- The rate ratio is used
  1. When subjects are followed up for differing lengths of time\(^1\) or
  2. If subjects have more than one event during the study.\(^2\)
- It is the ratio of the **rates** that events occurred in the control and treatment groups.
- Rates are expressed as events per 100 or 1000 person-years.
- Person-years reflect the total time spent by subjects in each group, standardized to 100 or 1000 person-years.

1. For an example of subjects being followed **for different lengths of time**, in the example remember the study was 1 year long. Suppose
   - In the control group 20 patients died after 6 months (0.5 years)
   - In the treatment group 15 patients died after 9 months (0.75 years)
   - All the survivors stayed in the study for the full year.

**In the control group**
- Those who died were exposed for 20 \times 0.5 \text{ years} = 10 \text{ person-years}
- Those who lived were exposed for 80 \times 1.0 \text{ years} = 80 \text{ person-years}
- Total exposure = 90 \text{ person-years}
- There were 20 deaths in 90 person-years = **22.2 deaths per 100 person yrs**

**In the treatment group**
- Those who died were exposed for 15 \times 0.75 \text{ years} = 11.25 \text{ person-years}
- Those who lived were exposed for 85 \times 1.0 \text{ years} = 85 \text{ person-years}
- Total exposure = 96.25 \text{ person-years}
- There were 15 deaths in 96.25 person-years = **15.6 deaths per 100 person yrs**

**Rate ratio** = \(\frac{15.6}{22.2} = 0.70\)
- Note the rate ratio which takes into account **when** events happened in each group shows more benefit than indicated by the relative risk (0.75) which just shows **if** they occurred.
2. For an example of subjects having **more than one event** during the study, in the example imagine we are measuring the number of episodes of hypoglycemia.
   - Suppose all 100 subjects in each group stay in the study for 1 year.
   - There will be 100 person-years in the control group and in the drug group.

**In the control group**
- 10 subjects have 40 episodes of hypoglycemia
  - The **risk** is 10/100 = 10%
  - The **rate** is 40 per 100 person-years

**In the treatment group**
- 10 subjects have 20 episodes of hypoglycemia
  - The **risk** is 10/100 = 10%
  - The **rate** is 20 per 100 person-years

- The **relative risk** is 10%/10% = 1
  indicating no benefit from the treatment in the **number of subjects** having an episode of hypoglycemia.

- The **rate ratio** is 20/40 = 0.5
  indicating that the treatment decreases the **number of episodes** of hypoglycemia.

- Both measures are important to consider in evaluating the efficacy of a therapy.
  - The **relative risk** estimates the likelihood that **any subject** in the study may benefit.
  - The **rate ratio** estimates the likelihood that fewer **episodes** of hypoglycemia will occur but doesn’t give an estimate of how many subjects will benefit.
SUMMARY STATEMENTS

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

- A1C is the most frequently reported measure of long-term glycemic control in studies of anti-diabetes agents, including insulin analogues.
- It is important to consider the minimal difference in A1C that is considered clinically relevant (i.e., a therapy may lead to a statistically significant lowering of A1C but it may not be enough to be clinically relevant).
- COMPUS agreed on a minimal clinically important difference in A1C between 0.7 and 1 percentage points. The FDA considers 0.7 percentage points to be clinically significant.

Meta-analyses indicate **no clinically significant difference** in A1C levels between insulin analogues (rapid or long-acting) and human insulin (regular or NPH) in
- Adults or children with type 1 diabetes or
- Adults with type 2 diabetes (children with type 2 diabetes have not been studied.)

Rapid-acting insulin analogues
- Lispro – Humalog
- Glulisine – Apidra
- Aspart – NovoRapid

Long-acting insulin analogues
- Detemir – Levemir
- Gliptine – Lantis
Question 2: Do the insulin analogues provide any clinically important reduction in hypoglycemia compared to human insulins?

- Definitions of hypoglycemia vary across studies and are usually reported as:
  - **Overall hypoglycemia**: Defined in most studies by signs or symptoms of hypoglycemia, and/or blood glucose below a certain threshold (e.g., < 4 mmol/L).
  - **Nocturnal hypoglycemia**: Hypoglycemic events that occur at night, usually between midnight and 6:00 a.m. In most studies, nocturnal hypoglycemia was not well defined and blood glucose levels were not measured.
  - **Severe hypoglycemia**: An event with characteristic hypoglycemic symptoms requiring assistance of another person (medical or non-medical personnel). Some studies also require the presence of blood glucose values below a certain threshold (e.g., < 4 mmol/L).

- Hypoglycemia, particularly severe and nocturnal episodes, poses a substantial barrier to achieving glycemic control in patients with diabetes.

- Hypoglycemia is more likely if patients strive for tight glucose control, in those with long-standing, more advanced diabetes (type 1), and in the presence of hypoglycemia unawareness.

- Hypoglycemia in the frail elderly may be more severe and prolonged and lead to falls, confusion, and impaired cognition.

- Some studies showed a reduced risk of hypoglycemia with insulin analogues versus human insulins. However statistically significant effects were not observed consistently across all studies and studies generally had limitations such as:
  - Lack of clear definitions for hypoglycemia
  - Unblinded
  - Short duration
  - Exclusion of patients with history of recurrent severe hypoglycemia (mostly for detemir)

- In most populations, (e.g., type 1 diabetes, type 2 diabetes, adults, children) benefits in hypoglycemia from insulin analogues were *inconsistent*.

- Benefits of insulin analogues were most consistently found in **nocturnal** hypoglycemia, particularly
  - **Rapid-acting** analogues in adults and adolescents with **type 1** diabetes
  - **Long-acting** analogues in adults with **type 2** diabetes
Summary and COMPUS recommendations based on Questions 1 and 2

COMPUS Recommendations

For basal insulin

- NPH should be the first line basal insulin in most patients with type 1 and type 2 diabetes.

For bolus insulin

- In type 1 diabetes
  - Adults and children can use either rapid-acting analogues or regular human insulin.
  - Adolescents can use rapid-acting analogues in preference to regular human insulin.

- In type 2 diabetes regular human insulin can be used in preference to rapid-acting analogues.

- In type 1 and type 2 diabetes, insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using human insulins or for whom hypoglycemia is a major concern.

- Long-acting analogues are 2 to 3 times the cost of NPH insulin.
  - Because long-acting analogues are much more expensive than NPH insulin, and their benefits are uncertain, COMPUS recommends NPH insulin as the first line basal insulin in most patients with type 1 and type 2 diabetes.

- Rapid-acting analogues are approximately 1.4 times more expensive than regular human insulin.
  - They may be more convenient in terms of flexibility of administration and may lead to less hypoglycemia in type 1 patients.
  - Because the rapid-acting analogues are somewhat but not markedly more expensive than human insulin, COMPUS recommends that adults and children with type 1 diabetes can use either rapid-acting insulin analogues or regular human insulin.
  - Evidence from the one reported study indicates benefit with rapid-acting analogues for adolescents in nocturnal hypoglycemia and COMPUS suggests that analogues be used in preference to regular human insulin in this age group. (This is a weak recommendation. See page 15.)

- There is inconsistent evidence of benefit in hypoglycemia in adults with type 2 diabetes, and COMPUS suggests that regular human insulin be used in preference to insulin analogues in this population.

- Based on clinical opinion and limited evidence, insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using human insulins or for whom hypoglycemia is a major concern.
Question 3: Who should be self-monitoring their blood glucose and how frequently?

- 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 dosage adjustment.
- There is little evidence to guide recommendations on self-monitoring of blood glucose and much of the evidence is of low quality, coming from observational studies. Observational studies may overestimate the benefit of self-monitoring of blood glucose because patients who self-test frequently may be more likely to engage in other behaviours such as following dietary and exercise routines.
- Outcomes reported are generally limited to A1C and hypoglycemia.
- Some recommendations come from consensus and usual care.

**COMPUS recommendations vary depending on whether the patient is using insulin.**

- Generally, it is recommended that
  - Patients using insulin perform self-monitoring of blood glucose.
  - Most adults **not using** insulin do **not** require routine self-monitoring of blood glucose.

- For patients with type 1 and type 2 diabetes using **basal and bolus** insulin, self-monitoring of blood glucose should be **individualized**.
- For most adults with type 2 diabetes using **basal** insulin with or without oral antidiabetes drugs, the suggested **maximum** average weekly frequency of testing is **14** times per week.
- For adults with type 2 diabetes not taking insulin, routine self-monitoring of blood glucose is **not** recommended.

Rapid-acting insulin analogues
- Lispro – Humalog
- Aspart – NovoRapid

Long-acting insulin analogues
- Detemir – Levemir
- Giargine – Lantus
- For patients with type 2 diabetes some conditions may require more frequent testing or initiation of testing. Examples would be patients
  - Using multiple daily insulin injections (i.e., three or more per day)
  - At risk of hypoglycemia (taking insulin secretagogues, instances of inadequate caloric intake, unforeseen or unplanned physical activity)
  - With a history of hypoglycemia or hypoglycemia unawareness
  - 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
  - Working in an occupation where hypoglycemia poses safety concerns or where testing is mandated by an employer or jurisdictional requirements (e.g., commercial drivers, pilots, air-traffic controllers, critical positions in railways)
    - See Appendix 3 for list of Canadian recommendations for self-monitoring of blood glucose for special populations.

- SMBG is only part of diabetes self-management which includes proper diet and physical activity, monitoring blood pressure and lipids, and follow-up for diabetes complications.

- SMBG is not always associated with positive outcomes and has been associated with a decreased quality of life and increased depression.

- In some cases recommendations made by the Canadian Diabetes Association differ from those made by COMPUS (Table 9).
Introduction

- This topic has been developed based on an extensive review conducted by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS). COMPUS is a branch of the Canadian Agency for Drugs and Technology in Health (CADTH), Canada’s national health technology assessment agency.
  - **CADTH** is an independent, not for profit agency funded by the Canadian federal, provincial, and territorial governments to provide credible, impartial advice and evidence-based information about the effectiveness of drugs and other health technologies to Canadian health care decision makers.
  - **COMPUS** identifies and promotes optimal drug therapy and provides strategies, tools, and services to encourage the use of evidence-based clinical and cost-effectiveness information in decision making among health care providers and consumers.
- COMPUS reviewed randomized controlled trials and observational studies about insulin analogues and self-monitoring of blood glucose in type 1 and type 2 diabetes. A 12-member panel of endocrinologists, family physicians, pharmacists, epidemiologists, and others helped interpret the evidence. Panel members are in Appendix 1. Nova Scotian physicians may recognize 2 panel members:
  - Dr Ehud Ur, endocrinologist, now at University of British Columbia, formerly at Dalhousie
  - Dr Michael Allen, family physician and Director of Evidence-based Programs at Dalhousie CME.
- Most information in this document is based on
  - COMPUS optimal prescribing reports of insulin analogues and self-monitoring of blood glucose (SMBG).
  - Recent CMAJ meta-analyses of the efficacy of insulin analogues which are based on the COMPUS optimal prescribing report.
- Glulisine (Apidra) was not reviewed by COMPUS as it was not marketed in Canada at the time of the review.
- The Common Drug Review examines both published and unpublished clinical trial data, including additional data submitted by the manufacturer. Its 2009 recommendation states that clinical trials suggest that insulin glulisine is associated with similar efficacy and safety compared with
  - Other rapid acting insulin analogues and regular human insulin in Type 1 diabetes and
  - Regular human insulin in Type 2 diabetes.
- We have also worked closely with the Diabetes Care Program of Nova Scotia.
- Finally, we will present recommendations from the 2008 Canadian Diabetes Association Guidelines.

**Rapid-acting insulin analogues**
- Lispro – Humalog
- Aspart – NovoRapid

**Long-acting insulin analogues**
- Detemir – Levemir
- Giargin – Lantus
This review will address three questions:

1. Do the insulin analogues provide any clinically important reduction in A1C levels in any population 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 and how frequently?

Background information

Levels of Evidence and Strength of Recommendations

GRADE

- Different organizations use different systems to rate their levels of evidence and strengths of recommendations. This leads to confusion and uncertainty when reading different guidelines.
- To address this problem, over the past several years, experts in guideline development have formulated a standardized rating system called GRADE - Grading of Recommendations Assessment, Development and Evaluation system.

Quality of evidence in GRADE

- In GRADE, evidence is initially rated as high or low quality.
  - High quality evidence comes from randomized controlled trials.
  - Low quality evidence comes from observational studies such as cohort or case-control studies.
- The quality of evidence can be upgraded or downgraded according to specific criteria.
- Evidence may be downgraded due to
  - Methodological limitations (lack of blinding; lack of allocation concealment; large losses to follow-up; analysis not by intention to treat; stopping early for benefit; or failure to report outcomes.)
  - Inconsistent results
  - Imprecision of results – indicated by wide confidence intervals
  - Reporting bias – tendency for favourable results to be published
  - Studies not directly addressing the population or comparison of interest
- Evidence may be upgraded if
  - There is a very large treatment effect.
  - There is a dose-response relationship.
  - All plausible biases would decrease the magnitude of an apparent treatment effect.
- After upgrading or downgrading, evidence is rated as high, moderate, low, or very low quality.
Strength of recommendations in GRADE

In GRADE, recommendations are rated as either weak or strong as outlined in Table 1.

Table 1 Description of weak and strong recommendations in GRADE

<table>
<thead>
<tr>
<th>Description</th>
<th>Strong Recommendation</th>
<th>Weak Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are confident the desirable effects of adhering to the recommendation outweigh the undesirable effects.</td>
<td>The desirable effects of adhering to the recommendation probably outweigh the undesirable effects but we are less confident.</td>
<td></td>
</tr>
<tr>
<td>Most people (90%) would want the recommended course of action and only a small proportion would not.</td>
<td>Most people in this situation would want the suggested course of action, but many would not.</td>
<td></td>
</tr>
<tr>
<td>Most people should receive the intervention.</td>
<td>Examine the evidence or summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences.</td>
<td></td>
</tr>
<tr>
<td>More likely if high quality evidence is available.</td>
<td>More likely if low quality evidence is available.</td>
<td></td>
</tr>
<tr>
<td>More likely if costs and resource requirements are low.</td>
<td>More likely if costs and resource requirements are high.</td>
<td></td>
</tr>
<tr>
<td>Can often be implemented as policy.</td>
<td>Is likely to require debate and involvement of multiple stakeholders before policy can be determined.</td>
<td></td>
</tr>
</tbody>
</table>

Use of GRADE

- GRADE is now being used by more than 25 organizations including the World Health Organization, the American College of Physicians, the American Thoracic Society, UpToDate, and the Cochrane Collaboration.
- COMPUS too has adopted the GRADE system. In this document, we will report COMPUS recommendations according to the GRADE system.

### COMPUS first assessed the evidence for clinical efficacy of insulin analogues and self-monitoring of blood glucose, and then the evidence for cost-effectiveness.

- The strength of recommendations is reflected in the wording:
  - Weak recommendations are worded as “suggested”. E.g., therapy A is suggested over therapy B.
  - Strong recommendations are worded as “recommended”. E.g., therapy A is recommended over therapy B.
- For comparison, we will also report recommendations from the 2008 CDA guidelines which use the system for rating evidence and recommendations in Table 2.
- The CDA guidelines do not consider cost-effectiveness.
### Table 2 CDA system for rating evidence and strength of recommendations

<table>
<thead>
<tr>
<th>CDA rating of evidence</th>
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</thead>
<tbody>
<tr>
<td>Level 1A</td>
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<td>Level 1B</td>
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<tr>
<td>Level 2</td>
</tr>
<tr>
<td>Level 3</td>
</tr>
<tr>
<td>Level 4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDA rating of strength of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
</tr>
<tr>
<td>Grade B</td>
</tr>
<tr>
<td>Grade C</td>
</tr>
<tr>
<td>Grade D</td>
</tr>
</tbody>
</table>

### Rationale for the insulin analogues

- Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both.
- **Type 1 diabetes** is primarily a result of pancreatic beta cell destruction. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.
- **Type 2 diabetes** may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.
- Endogenous insulin secretion is characterized by continuous basal insulin secretion and meal-related peaks.
- Treatment with insulin often may involve
  - **Longer-acting** insulin to control blood glucose levels between meals and overnight.
  - **Rapid-acting** insulin to provide the boost of insulin needed to stop the rise in blood glucose levels that occurs after meals.
- Insulin analogues are produced through alterations of the amino acid sequence of human insulin with the intent to alter the pharmacokinetic properties while maintaining its pharmacological effects.
- **Long-acting** insulin analogues mimic the action of basal endogenous insulin secretion by providing a prolonged, basal level of insulin activity.
- **Rapid-acting** insulin analogues mimic the short duration of action of meal-induced endogenous insulin secretion.

### Rapid-acting insulin analogues
- Lispro – Humalog
- Aspart – NovoRapid

### Long-acting insulin analogues
- Detemir – Levemir
- Giargin – Lantus
The **theoretical** benefits of insulin analogues over human insulin are convenience and lower risk of hypoglycemia because of differences in onset of action, peak effect, and duration of action (Table 3).

### Table 3 Pharmacodynamics of human insulins and insulin analogues

<table>
<thead>
<tr>
<th>Pharmacodynamics</th>
<th>Short-acting human insulin</th>
<th>Rapid-acting insulin analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>Approximately 30 minutes after injection</td>
<td>Approximately 10 to 15 minutes after injection</td>
</tr>
<tr>
<td></td>
<td>Should be given 30 minutes before meals</td>
<td>Can be given immediately before meals</td>
</tr>
<tr>
<td>Peak effect</td>
<td>2 to 4 hours</td>
<td>1 to 2 hours</td>
</tr>
<tr>
<td>Duration of action</td>
<td>5 to 8 hours</td>
<td>4 to 5 hours</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediated-acting human insulin</th>
<th>Long-acting insulin analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>1 to 2 hours</td>
</tr>
<tr>
<td>Peak effect</td>
<td>No discernible peak</td>
</tr>
<tr>
<td>Duration of action</td>
<td>Approx 24 hours</td>
</tr>
</tbody>
</table>

### Table 4 Selected insulins and costs in Nova Scotia

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Approx cost for 3mL (cartridge or penfill)*</th>
<th>NS formulary coverage (April 2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>NovoRapid</td>
<td>$12</td>
<td></td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog</td>
<td>$11.70</td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Apidra</td>
<td>$10.30</td>
<td></td>
</tr>
<tr>
<td><strong>Regular insulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>Humulin R</td>
<td>$8.60</td>
<td>Regular benefit</td>
</tr>
<tr>
<td></td>
<td>Novolin GE Tor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long-acting insulin analogues</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>$19</td>
<td>Not a benefit</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Levemir</td>
<td>$24</td>
<td>Not a benefit</td>
</tr>
<tr>
<td><strong>NPH insulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Humulin N</td>
<td>$8.60</td>
<td>Regular benefit</td>
</tr>
<tr>
<td></td>
<td>Novolin GE NPH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* – costs from McKesson Feb to April 2010  
<sup>b</sup> – not discussed in COMPUS review

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**Rapid-acting insulin analogues**
- Lispro – Humalog
- Glulisine – Apidra
- Aspart – NovoRapid

**Long-acting insulin analogues**
- Detemir – Levemir
- Giargine – Lantus
Important outcomes

- When evaluating the evidence for insulin analogues and SMBG, COMPUS identified the following outcomes as being important in making recommendations:
  - Long-term microvascular and macrovascular complications of diabetes (e.g., mortality, cardiovascular disease, nephropathy, retinopathy, neuropathy)
  - Surrogate outcomes related to glycemic control (i.e., hemoglobin A1C)
  - Severe, nocturnal, and overall hypoglycemia
  - Quality of life and patient satisfaction with diabetes care
  - Body weight

- COMPUS also considered resource use and costs in making recommendations.

Reported outcomes

- The most consistently reported outcomes were A1C and various types of hypoglycemia, so we will concentrate on them.
- Considering the proposed benefits of insulin analogues include patient satisfaction and quality of life, there is little evidence reporting these outcomes.
- There were no studies that were adequately powered and long enough to evaluate the long-term efficacy of insulin analogues on microvascular and macrovascular complications of diabetes.

Reported outcomes: hemoglobin A1C

- Definition: A glycated form of hemoglobin. Hemoglobin A1C levels correlate with glycemia over the course of 90 to 120 days and are used as a measure of long-term glycemic control in people with diabetes.
- A1C is the most frequently reported measure of long-term glycemic control in studies of anti-diabetes agents, including insulin analogues.
- It is important to consider the minimal difference in A1C that is considered clinically relevant.
  - A therapy may lead to a statistically significant lowering of A1C but it may not be enough to be clinically relevant in decreasing macro and microvascular complications of diabetes.
  - COMPUS agreed on a minimal clinically important difference in A1C between 0.7 and 1 percentage points. The FDA considers 0.7 percentage points to be clinically significant.

Hemoglobin A1C as a surrogate for clinical outcomes.

- A surrogate outcome is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives.\(^\text{10}\)
  - For example, cholesterol levels are associated with ischemic heart disease. When studying the efficacy of a drug that lowers cholesterol, it is important to know whether the drug decreases important clinical outcomes like myocardial infarction and death.
• Similarly when considering A1C, it is important to note if lowering A1C has been shown in randomized controlled trials to decrease micro and macrovascular outcomes such as:
  • Microvascular: neuropathy, nephropathy, retinopathy
  • Macrovascular: myocardial infarction, stroke, peripheral artery disease
• A related issue is whether tight control of diabetes (i.e., lowering A1C) results in better clinical outcomes.
• We shall consider these issues in type 1 and type 2 diabetes.

Lowering A1C in type 1 diabetes
• Most evidence for tight control of A1C in type 1 diabetes comes from the Diabetes Control and Complications Trial which followed 1441 patients for a mean of 6.5 years.\(^1\)
  • Intensively treated subjects achieved an A1C level of approximately 7% vs approximately 9% in the conventionally treated group.
  • For microvascular outcomes, there were statistically significant benefits found in the intensively treated group in retinopathy, albuminuria, and neuropathy with relative risk reductions of approximately 40% to 60%. Of note, retinopathy and albuminuria are themselves surrogate outcomes for visual loss and renal failure.
  • For macrovascular outcomes, there were no statistically significant differences between the types of treatment in mortality and in cardiovascular and peripheral vascular events.
    • However, a long-term (mean follow-up 17 years) observational study which included patients having participated to the DCCT trial showed that intensive therapy reduced the risk of any cardiovascular disease event.\(^1\) Over 17 years:
      • The event rate was 7.1% in the conventional therapy group vs 4.4% in the intensive therapy group.
      • RRR 42%, ARR 2.8%, NNT 36 (95% CI: 19 to 271)
    • For nonfatal myocardial infarction, stroke, or death from cardiovascular disease:
      • The event rate was 3.4% in the conventional therapy group vs 1.5% in the intensive therapy group.
      • RRR 57%, ARR 1.9%, NNT 53 (95% CI: 29 to 362)

Lowering A1C in type 2 diabetes
• Much evidence for tight control of A1C in type 2 diabetes comes from the UKPDS study, an unblinded RCT that followed 3,867 newly diagnosed patients with type 2 diabetes for 10 years (median age 54 years).\(^1\)
  • The objective was to determine whether the risk of microvascular and macrovascular complications was lower with intensive glycemic management using a sulfonylurea or insulin vs conventional management with diet.
  • The conventional management group received drugs if there were hyperglycemic symptoms or if their fasting glucose was > 15 mmol/L.
• In the main analysis
  • Median A1C was significantly lower in the intensive management arm (7% vs. 7.9%, p<0.0001).
  • Intensive management resulted in a 12% reduction in any diabetes-related endpoint. NNT over 10 years was 20 (95% CI: 10-500).
• For microvascular outcomes, intensive management resulted in
  • 25% risk reduction in total microvascular endpoints (p=0.0099) most of which was due to fewer cases of retinal photocoagulation.
    • For total microvascular events over 10 years
      • Event rates 10.6% vs 8.2%, RRR 25%, ARR 2.4%, NNT 42 95% CI (22 to 312)
    • For retinal photocoagulation over 10 years
      • Event rates 10.3 vs 7.6%, RRR 29%, ARR 2.7%, NNT 37 (95% CI 21 to 149)
  • A statistically significant reduction in microalbuminuria and risk of doubling of plasma creatinine. These are surrogate markers for renal failure.
  • No statistically significant reductions in vitreous hemorrhage, blindness in one eye, cataract extraction, death from renal disease, renal failure, proteinuria.
• For macrovascular outcomes, there was no statistically significant reduction in myocardial infarction, any diabetes-related death, or all-cause mortality.

• An epidemiological analysis of UKPDS data showed that for each percentage point reduction in A1C there were reductions of\textsuperscript{14}
  • 12-21% in the risk of cardiovascular events and death
  • 37% in risk reduction in combined microvascular endpoints
  • 43% reduction in amputation

These results should be treated with caution since the analysis was not adjusted for BMI or waist circumference which could affect the results.

We cannot report absolute risk reduction and numbers needed to treat due to limitations of published data.

• There is uncertainty about the validity of the results of UKPDS because
  • It was not blinded.
  • The main driver of statistically significant results was frequency of retinal photocoagulation. It is possible there was bias in the perceived need for this procedure.\textsuperscript{15}
  • Lack of pre-defined study duration.
  • Numerous interim analyses and multiple comparisons.
  • Rescue protocols that diluted differences between treatment arms.
  • Changes in the definitions of outcomes as the study progressed.\textsuperscript{15-17}
• A follow-up of UKPDS analyzed data from patients during the 10 years following the end of the study. No attempt was made to maintain patients’ previously assigned therapy.
  • Patients originally assigned to the intensive therapy group did not maintain their lower A1C levels compared to conventional therapy but had lower rates of any diabetes-related endpoint including myocardial infarction and microvascular disease.\textsuperscript{18}
  • The explanation given for this finding is that there is a “legacy-effect” from the lowering of A1C at the beginning of the study. However, it could also be interpreted to indicate that A1C was not a predictor for clinical outcomes.

• Other data on the association between A1C levels and clinical outcomes come from the \textbf{ACCORD}\textsuperscript{19} and \textbf{ADVANCE}\textsuperscript{20} studies both of which compared intensive glucose-lowering with standard care.
  • \textbf{ACCORD} (n=10,251), 3.5 years, A1C target <6%
    • The study was scheduled for 5 years but was ended at 3.5 years because of an increase in all cause mortality in the intensive care group.
      • Event rate 5\% vs 4\%; hazard ratio 1.22, 95\% CI: 1.01 to 1.46; number needed to harm 95 (95\% CI: 54 to 403)
    • At the end of 3.5 years:
      • A1C in intensive care group = 6.4\% vs 7.5\% in standard care group
      • There was no statistically significant difference in the primary outcome of non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes.
      • The intensive care group showed statistically significant increases in:
        • Hypoglycemia needing medical help \(10.5\%\ vs 3.5\%\)
        • Hypoglycemia needing any help \(16.2\%\ vs 5.1\%\)
        • Weight gain > 10 kg \(18\%\ vs 14\%\)
  • \textbf{ADVANCE} (n=11,140), median 5 years follow-up, A1C target <6.5%
    • At the end of median 5 years follow-up
      • A1C in intensive care group = 6.5\% vs 7.3\% in standard care group
      • The intensive care group showed statistically significant benefits in:
        • The primary outcome of combined major macrovascular and microvascular events \(20.0\%\ vs 18.1\%\)
        • Major microvascular events \(10.9\%\ vs 9.4\%\)
        • The benefit in microvascular events was driven by reduction in nephropathy, particularly microalbuminuria.
      • There was no benefit shown in
        • Major macrovascular events
        • Retinopathy
      • The intensive care group showed a statistically significant increase in severe hypoglycaemia \(1.5\%\ vs 2.7\%\)
A summary of ACCORD and ADVANCE is in Table 5.

Due to differences between the two trials, it is difficult to explain these contradictory results.\(^{21}\) For example in ACCORD:
- Patients had more non-glycemic risk factors.
- The rate of glucose lowering was faster.
- The frequency of rosiglitazone prescribing was higher.
- Treatment targets were lower.
- Duration of follow-up was shorter due to early termination and differences in primary endpoints.

Nonetheless, these trials are consistent in finding that targeting A1C to <6.5% in patients with long-standing diabetes is not associated with fewer cardiovascular events over 3.5 to 5 years.

The Veterans Affairs Diabetes Trial (VADT) assigned United States veterans with type 2 diabetes to intensive or standard glycemic therapy.\(^{54}\)
- N = 1791, median duration 5.6 years, A1C goal was an absolute reduction of 1.5% in intensive therapy group compared to standard therapy group. (The study was unblinded.)
- Mean achieved A1C was 6.9% in intensive therapy group vs 8.4% in standard therapy group.
- There was no statistically significant reduction in the primary outcome of major cardiovascular events, myocardial infarction, or any microvascular outcomes except for albuminuria.

The investigators of UKPDS, ACCORD, ADVANCE, and VADT collaborated to conduct a meta-analysis of the four studies.\(^{55}\)
- To standardize duration, they considered only the first five years of UKPDS.
- There was a statistically significant improvement in the intensive major cardiovascular events (death from CV causes, non-fatal MI and stroke)
  - HR 0.91 (95% CI: 0.84 to 0.99)
  - This result was mainly because of decreased risk of MI
  - HR 0.85 (95% CI: 0.76 to 0.94)
- There were no reductions in overall mortality, stroke, or cardiovascular death.
- Intensively treated subjects had more severe hypoglycemic events
  - HR 2.48 (95% CI: 1.91 to 3.21)
- An exploratory subgroup analysis suggested that patients with major cardiovascular disease did not show a benefit for the intensive therapy, but those without major cardiovascular disease did show a benefit.
- Another meta-analysis of the same four studies plus PROactive\(^{56}\) (pioglitazone vs placebo) had similar findings.\(^{57}\)
- In both meta-analyses the difference in A1C between the intensive and standard therapy groups was 0.9%
A recent retrospective cohort study analyzed the relation between A1C and mortality and large-vessel disease (myocardial infarction, angina, stroke, revascularization). Subjects came from the UK General Practice Research Database and were grouped into two cohorts: patients switched from

1. Oral monotherapy to a sulfonylurea plus metformin
   N = 27,965 mean follow-up 4.5 years
2. Oral agents alone to insulin with or without concomitant oral drugs
   N = 20,005 mean follow-up 5.2 years

In both cohorts, mortality showed a U-shaped curve with mortality and large-vessel disease being lowest at an A1C of 7.5%.

- Mortality and large-vessel disease were increased at A1C levels above and below 7.5%.
- Causes of death were not provided in the publication.
- Our content expert suggests results should be treated with caution because the authors did not adjust for decreased renal function which has been shown to be associated with increased mortality.
- There was also increased mortality and progression to large-vessel disease in the cohort taking insulin compared to the cohort not taking insulin.
- The authors speculate that the increased mortality at low A1C may be from severe hypoglycemia which may lead to
  - Cardiac arrhythmias secondary to adrenergic stimulation and hypokalemia
  - Glucose variability leading to oxidative stress and vascular inflammation resulting in atherosclerotic plaque destabilisation and vascular dysfunction.
- It may also be that patients who develop hypoglycemia are sicker and more likely to die.

Conclusions for A1C as a surrogate outcome

- The relationship between A1C and microvascular outcomes has been demonstrated in RCT evidence from the DCCT, the ADVANCE trial and possibly UKPDS.
- There is less certainty as to whether A1C is a reasonable surrogate outcome for macrovascular outcomes, particularly in type 2 diabetes.
- When considering the efficacy of drugs such as the insulin analogues or the self-monitoring of blood glucose, both of which require long-term use, studies should demonstrate long-term effectiveness on clinical outcomes rather than relying on a surrogate outcome like A1C.
- A related point arising from the above data is that aiming for tighter A1C control is associated with more episodes of hypoglycemia.
Table 5 Summary of ACCORD\textsuperscript{19} and ADVANCE\textsuperscript{20} studies

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10,251</td>
<td>11,140</td>
</tr>
<tr>
<td>Duration</td>
<td>3.5 yrs (stopped early because of increased mortality in the intensive treatment group)</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Included patients</td>
<td>A1C ≥ 7.5% 40 to 79 yrs with CV disease or 55 to 79 yrs at significant risk of CV disease</td>
<td>≥ 55 years old with a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease. Onset of type 2 diabetes at 30 yrs or older</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Non-fatal MI, non-fatal stroke, death from CV causes</td>
<td>Non-fatal MI, non-fatal stroke, death from CV causes, new or worsening nephropathy or retinopathy</td>
</tr>
<tr>
<td>A1C targets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care Standard care</td>
<td>&lt; 6% 7% to 7.9%</td>
<td>&lt;6.5% Variable – allowed to follow local guidelines</td>
</tr>
<tr>
<td>A1C achieved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care Standard care</td>
<td>6.4% 7.5%</td>
<td>6.5% 7.3%</td>
</tr>
<tr>
<td>Outcomes with stat sig benefit</td>
<td>Non-fatal MI 4.6% vs 3.6% RRR 21% ARR 1.0% NNT 104, 95% CI: 58 to 521</td>
<td>Primary outcome 20.0% vs 18.1% RRR 9.6% ARR 1.9% NNT 52, 95% CI: 30 to 213</td>
</tr>
<tr>
<td>Outcomes with no stat sig difference</td>
<td>Primary outcome (major macrovasc events) Non-fatal stroke</td>
<td>Major macrovascular events Retinopathy</td>
</tr>
<tr>
<td>Outcomes with stat sig harm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality Hypoglycemia</td>
<td>Event rates RRI ARI NNH (95%CI)</td>
<td>Event rates RRI ARI NNH (95%CI)</td>
</tr>
<tr>
<td>needing medical aid</td>
<td>5% vs 4% 27% 1% 95 (54 to 403)</td>
<td>2.7% vs 1.5% 85% 1.2% 81 (57 to 141)</td>
</tr>
<tr>
<td>Hypoglycemia needing any aid</td>
<td>11% vs 3.5% 200% 7% 14 (13 to 17)</td>
<td></td>
</tr>
<tr>
<td>Weight gain &gt;10 kg</td>
<td>16% vs 5.1% 218% 11% 9 (8 to 10)</td>
<td></td>
</tr>
<tr>
<td>Weight gain 10 kg</td>
<td>18% vs 14% 96% 14% 7 (6 to 8)</td>
<td></td>
</tr>
</tbody>
</table>

ARR = absolute risk reduction  
ARI = absolute risk increase  
NNT = number needed to treat  
RRR = relative risk reduction  
ARI = absolute risk increase  
NNH = number needed to harm  
RRI = relative risk increase

Rapid-acting insulin analogues  
Lispro – Humalog  
Glulisine – Apidra  
Aspart – NovoRapid

Long-acting insulin analogues  
Detemir – Levemir  
Giargine – Lantus
Reported outcomes: postprandial glucose

- There is evidence from observational studies that there is a correlation between the level of 2-hour PC glucose on an oral glucose tolerance test and the development of cardiovascular disease in patients with impaired glucose tolerance.\textsuperscript{24,25}
  - However, it is important to note that the 2-hour PC glucose on an oral glucose tolerance test is not necessarily equivalent to a postprandial glucose which can vary depending on type and amount of food.
  - Also, these are observational studies that may not take into account all potential confounders that could affect results.
- Two cohort studies of patients with type 2 diabetes had inconsistent findings.
  - A 5-year study of 529 patients found that blood glucose levels after lunch were significantly associated with risk of cardiovascular events, while blood glucose levels after breakfast and before dinner, and fasting glucose, were not.\textsuperscript{26}
  - The Diabetes Intervention Study, an 11-year follow-up of 1,139 newly-diagnosed patients with type 2 diabetes found that postprandial hyperglycemia (after breakfast) was not a risk factor for myocardial infarction, but was a risk factor for death from any cause.\textsuperscript{27}
  - An important consideration is that while the above studies may suggest an association between postprandial glucose and cardiovascular events, they do not confirm that lowering postprandial glucose to a specific level will decrease cardiovascular events.
  - STOP-NIDDM, a 3.3-year double-blind randomized controlled trial studied acarbose vs placebo in prevention of type 2 diabetes in patients with impaired glucose tolerance. Acarbose led to a slight decrease in postprandial glucose (mean difference 0.037 mmol/L) and a 2.5% absolute decrease in cardiovascular events (placebo 4.7% vs acarbose 2.2%).
    - However, the trial was not designed to test the relationship between acarbose and the reduction of post-prandial hyperglycemia and the incidence of cardiovascular diseases.\textsuperscript{28}
  - All the above studies are of patients with type 2 diabetes.
  - We will not report on postprandial glucose in our document because
    - Studies of insulin analogues infrequently reported postprandial glucose.
    - The significance of postprandial glucose is uncertain.
    - There is no trial data indicating that a strategy targeted at lower post-prandial glucose will improve clinical microvascular or macrovascular outcomes compared with other active therapy.
Reported outcomes: hypoglycemia

- Definitions vary across studies, although one or both of the following is usually required to define a hypoglycemic event:
  - Autonomic or neuroglycopenic symptoms characteristic of low blood glucose (e.g., trembling, sweating, hunger, confusion, weakness) that respond to carbohydrate intake, and/or a
  - Plasma glucose level below a specific value (threshold is usually between 3.4 to 4.0 mmol/L).
- Overall hypoglycemia: Defined in most studies by signs or symptoms of hypoglycemia, and/or blood glucose below a certain threshold (e.g., < 4 mmol/L).
- Nocturnal hypoglycemia: Hypoglycemic events that occur at night, usually between midnight and 6:00 a.m. In most studies, nocturnal hypoglycemia was not well defined and blood glucose levels were not measured.
- Severe hypoglycemia: An event with characteristic hypoglycemic symptoms requiring assistance of another person (medical or non-medical personnel). Some studies also require the presence of blood glucose values below a certain threshold (e.g., < 4 mmol/L).

- Hypoglycemia, particularly severe and nocturnal episodes, poses a substantial barrier to achieving glycemic control in patients with diabetes.
- Patients who manage their diabetes with insulin place a high relative importance on avoiding hypoglycemia. Fear of hypoglycemia may manifest itself in behavioural changes such as purposefully running higher blood glucose levels.
- Hypoglycemia is more likely if patients strive for tight glucose control, in those with long-standing, more advanced diabetes (type 1), and in the presence of hypoglycemia unawareness.
- Hypoglycemia in the frail elderly may be more severe and prolonged and lead to falls, confusion, and impaired cognition.

Patient populations

- Since diabetes affects all ages it is important to consider studies that involve adults and children.
- There are no studies of insulin analogues in children with type 2 diabetes.
- For the purposes of this document and recommendations, an adolescent is someone aged 9 to 18 years who has reached Tanner stage II puberty (genital or breast development).29
Question 1: Do the insulin analogues provide any clinically important reduction in A1C levels in any population compared to human insulins?

- Meta-analyses indicate no clinically significant difference in A1C levels between insulin analogues (rapid or long-acting) and human insulin (regular or NPH) in
  - Adults or children with type 1 diabetes or
  - Adults with type 2 diabetes (children with type 2 diabetes have not been studied.)

- COMPUS agreed that a minimal clinically important difference in A1C is between 0.7 and 1 percentage points. The FDA considers 0.7 percentage points to be clinically significant.
- Most studies were done in adults with type 1 diabetes (Table 6).

Table 6 Number of studies and subjects analyzed for A1C in Singh meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>Numbers of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children and</td>
<td>11</td>
<td>2,289</td>
</tr>
<tr>
<td>adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>49</td>
<td>15,285</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children and</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>35</td>
<td>11,330</td>
</tr>
</tbody>
</table>

Type 1 Diabetes

- Meta-analyses indicate no clinically significant difference in A1C levels between insulin analogues (rapid or long-acting) and human insulin (regular or NPH) in any type 1 population.
  - For comparisons between an insulin analogue and human insulin, pooled differences in A1C ranged from
    - A decrease of 0.40 percentage points (95% CI decrease of 0.91 to increase of 0.11) glargine + lispro vs NPH + regular in adolescents
    - To
    - An increase of 0.14 percentage points (95% CI decrease of 0.18 to increase of 0.46) lispro vs regular in children
      - Neither result was statistically significant.
  - There were statistically significant differences found in some comparisons, but mean differences did not approach clinical significance (mean difference ranged from a decrease of 0.09 to 0.23 percentage points).
  - Studies included adults, children, and/or adolescents.
Type 2 Diabetes

- Meta-analyses indicate no clinically significant difference in A1C levels between insulin analogues (rapid or long-acting) and human insulin (regular or NPH) in adults with type 2 diabetes.
- For comparisons between an insulin analogue and human insulin, pooled differences in A1C ranged from
  - A decrease of 0.09 percentage points (95% CI decrease of 0.21 to increase of 0.04; not statistically significant) aspart vs regular
  - To
    - An increase of 0.28 percentage points (95% CI increase of 0.07 to an increase of 0.49; statistically significant but not clinically significant) glargine vs NPH without oral antidiabetes therapy
- There were no statistically significant differences in A1C levels found between rapid acting insulin analogues and regular insulin in adults with type 2 diabetes.
- There were some statistically significant differences in favour of NPH vs long-acting analogues in some populations / situations.
  - However, mean differences in A1C were not clinically significant (mean difference ranging from 0.13 to 0.28).
- Studies included only adults. No studies were available in children or adolescents with type 2 diabetes.
- Detailed results for effects of insulin analogues on A1C are in the CMAJ meta-analysis.\(^5\)
Question 2: Do the insulin analogues provide any clinically important reduction in hypoglycemia compared to human insulins?

- In most populations, (e.g., type 1 diabetes, type 2 diabetes, adults, children) benefits in hypoglycemia from insulin analogues were inconsistent.
- Benefits of insulin analogues were most consistently found in nocturnal hypoglycemia, particularly
  - Rapid-acting analogues in adults and adolescents with type 1 diabetes
  - Long-acting analogues in adults with type 2 diabetes.
  
- Hypoglycemia outcomes are reported as:
  - **Relative risk**: measure of how likely an individual patient is to experience 1 or more episodes of hypoglycemia during the study period.
  - **Rate ratio**: measure of the number of episodes of hypoglycemia that occur per patient per unit time e.g., episodes per patient year. (See page 7.)
  - If only rate ratios of hypoglycemia are reported, we do not know if most of the benefit was seen in only a few patients or if it was more widely distributed in the study population.

- Some studies showed a reduced risk or incidence of hypoglycemia with insulin analogues versus human insulins. However:
  - Some effects were marginal and of uncertain clinical significance.
  - Statistically significant effects were not observed consistently across all studies in terms of
    - Route of administration (multiple dose injection or continuous infusion)
    - Measures (relative risk, rate ratio)
    - Types of hypoglycemia (severe, nocturnal, overall)

- Studies generally had limitations such as:
  - Lack of clear definitions for hypoglycemia
  - Unblinded
  - Short duration
  - Exclusion of patients with history of recurrent severe hypoglycemia (mostly for detemir)
Type 1 diabetes
Adults and adolescents

Rapid-acting insulin analogues (lispro, aspart)
- There is evidence of some benefit of fewer episodes of nocturnal hypoglycemia with rapid-acting insulin analogues compared to regular insulin in adults and adolescents with type 1 diabetes.
  - Studies were generally of low quality and nocturnal hypoglycemia was not well defined.
  - The rate ratios were approximately 0.60 for rapid acting analogues vs regular human insulin in both adults and adolescents.
  - Relative risks were not reported so we do not know if
    - Most benefit occurred because a few patients had reductions in frequent episodes of hypoglycemia or
    - Many patients had reductions in infrequent episodes of hypoglycemia.
- In adults there was no consistent benefit demonstrated in severe or overall hypoglycemia.
- In adolescents one study found a small statistically significant benefit with lispro in reduction of overall hypoglycemia (rate ratio 0.90, 95% CI 0.88 to 0.93).
  - There was no benefit in severe hypoglycemia.
- Expert opinion acknowledges the lack of evidence, but recommends insulin analogues because of their onset, time to peak effect, and duration of action.

Long-acting insulin analogues (detemir, glargine)
- The overall evidence does not demonstrate a consistent reduction in relative risk or rate ratio in any form of hypoglycemia between long acting insulin analogues and NPH insulin in adults with type 1 diabetes.
- Studies suggest that detemir may produce benefit in all types of hypoglycemia compared to NPH insulin. A single head-to-head study showed benefit from detemir compared to glargine in severe hypoglycemia.
  - Limitations about detemir studies make it difficult to draw firm conclusions about its efficacy compared to NPH and glargine.
    - In many studies, subjects with a history of recurrent severe hypoglycemia were excluded. This makes it difficult to determine if benefits from detemir apply to such patients.
    - In the head-to-head study comparing detemir to glargine
      - Detemir was dosed twice daily while glargine was dosed once daily.
      - The average daily dose of bolus insulin was slightly lower in the detemir group than the glargine group (0.36 units/kg vs 0.39 units/kg).
      - The average daily dose of detemir was higher than the dose of glargine (0.47 units/kg vs 0.35 units/kg). This may be a reflection of the twice daily dosing.
• Although there is some evidence of reduced relative risk and rate ratio of severe, nocturnal, and overall hypoglycemia with insulin detemir, the overall quality of the evidence is low and nocturnal hypoglycemia is not well defined.
• It may be helpful to have some idea of the potential benefit in decreasing severe hypoglycemia from using detemir compared to NPH insulin in a typical population of patients with type 1 diabetes. The relative risk reduction found in the COMPUS meta-analysis was applied to the risk in populations experiencing severe hypoglycemia according to 2 definitions:
  1. Severe enough to require assistance from medical personnel
     • We applied the relative risk reduction found in the COMPUS meta-analysis to a Scottish population-based study of patients with diabetes. In this study, 7.1% of patients had at least one episode per year of hypoglycemia severe enough to require medical attention from ambulance personnel or at an emergency department. The relative risk reduction was 26% (95% CI: 4% to 42%) = NNT of 54 (95% CI: 34 to 352) over 1 year.
  2. Severe enough to require assistance from anyone
     • COMPUS applied the relative risk reduction found in its COMPUS meta-analysis to the mean event rate in the NPH group found in the studies. The mean event rate in the NPH group was 10%. The relative risk reduction was 26% (95% CI: 4% to 42%); NNT of 37 (95% CI: 23 to 250) over 16 to 52 weeks.
• Expert opinion favours individualizing treatment to meet challenges or patient preferences for diabetes care.
  • Thus basal insulin analogues may be used when it is desirable to provide more mealtime flexibility or to meet certain challenges in glucose variability.

Type 1 diabetes
Children
Rapid-acting insulin analogues (lispro, aspart)
• There is little evidence of benefit in reducing hypoglycemia from using rapid acting insulin analogues over regular insulin in children.
• Expert opinion acknowledges the lack of evidence, but recommends insulin analogues because of their onset, time to peak effect, and duration of action.

Long-acting insulin analogues (detemir, glargine)
• COMPUS found the overall evidence does not demonstrate a consistent risk reduction in any form of hypoglycemia for long-acting insulin analogues in children with type 1 diabetes.
• One published RCT showed no statistically significant benefit for glargine vs NPH in reducing severe or nocturnal hypoglycemia.
• One published RCT compared insulin detemir vs NPH in children and adolescents.\textsuperscript{33}
  • Duration 26 weeks (The first 6 weeks were for titration, the latter 20 weeks for evaluation of maintenance therapy).
  • N = 232 in detemir group, 115 in NPH group
  • There was no consistent benefit in severe or overall hypoglycemia.
  • For confirmed nocturnal hypoglycemia (measured and found to be < 3.1 mmol/L) there was a benefit from detemir vs NPH during the latter 20 weeks (maintenance period), RRR 36\% (95\% CI: 10\% to 55\%) but event rates were not reported so we could not calculate NNT.
  • During the complete study period there did not appear to be a statistically significant benefit from detemir vs NPH in percentage of patients with confirmed nocturnal hypoglycemia. (The study publication did not report a p-value but our calculations indicate results were not statistically significant.)
    • Event rate 65\% vs 57\%; RRR 13\%; ARR 8\%

• Expert opinion favours individualizing treatment to meet challenges or patient preferences for diabetes care.
  • Thus basal insulin analogues may be used when it is desirable to provide more mealtime flexibility or to meet certain challenges in glucose variability.
  • Glargine is often favoured over detemir because it can often be given once daily.

• COMPUS clinical notes state:
  • Long-acting insulin analogues potentially require more injections throughout the day because they cannot be mixed with bolus insulins.
  • Since insulin NPH has an onset of effect of between 2 and 4 hours, a morning dose may be sufficient to control post-lunch glucose levels, thereby eliminating the need to administer an injection of bolus insulin at lunchtime.
  • In contrast, long-acting insulin analogues do not have a pronounced peak; therefore, an injection of bolus insulin is required before lunch. This may be impractical during school hours for young children (<14 years of age).
Type 2 diabetes
Adults
Rapid-acting insulin analogues (lispro, aspart)

- Results were **inconsistent** when comparing rapid-acting analogues to human insulin in hypoglycemia.
- There was **no relative risk** reduction in any form of hypoglycemia.
- There was benefit in **rate ratio** in nocturnal (0.58, 95% CI 0.48 to 0.70) and **overall** hypoglycemia (0.72, 95% CI 0.64 to 0.80).
  This indicates there were **fewer episodes** of nocturnal and overall hypoglycemia in some subjects.
  However, there was **no difference** in the percentages of **subjects** experiencing any form of hypoglycemia.

Long-acting insulin analogues (detemir, glargine)

- There is no consistent benefit from the long-acting insulins in decreasing risk of **overall** or **severe** hypoglycemia.
- Generally, detemir and glargine both reduced the risk of **nocturnal hypoglycemia** compared to NPH, when they were given with oral agents or with bolus insulins.
- There is some consistency in the reported benefits of long-acting analogues in nocturnal hypoglycemia so rather than report each individual comparison Table 7 provides the range of event rates and treatment effects reported by COMPUS.

### Table 7 Efficacy of long-acting insulin analogues vs NPH insulin in decreasing nocturnal hypoglycemia in type 2 diabetes

<table>
<thead>
<tr>
<th>Nocturnal hypoglycemia (percent patients experiencing)</th>
<th>RRR</th>
<th>ARR</th>
<th>Time</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH Insulin analogue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22% to 40%</td>
<td>15% to 31%</td>
<td>22% to 47%</td>
<td>6% to 14%</td>
<td>20 to 28 wks</td>
</tr>
</tbody>
</table>

ARR absolute risk reduction  
RRR relative risk reduction  
NNT number need to treat  
CI confidence intervals
• COMPUS and a recent Cochrane review\textsuperscript{34} point out reasons for caution when interpreting this benefit in nocturnal hypoglycemia.
• Some effects were marginal and of uncertain clinical significance.
• Benefit was not observed consistently across all studies, comparisons, and types of hypoglycemia (i.e., severe, nocturnal, overall).
• Studies generally had limitations such as:
  • Methods of randomization were poorly reported in most studies.
  • Patients or caregivers were not blinded in any studies.
  • No studies indicated if outcome assessment was blinded.
  • Lack of clear definitions for hypoglycemia.
    • Interpretation of "requirement of assistance from another person" is susceptible to bias.
  • Heterogeneity in reporting of hypoglycemia including failure to confirm hypoglycemia by blood glucose testing.
  • Exclusion of patients with history of recurrent major hypoglycemia (mostly for detemir).

**Cochrane and COMPUS conclusions based on CLINICAL evidence (not cost)**

• Based on clinical evidence alone, the Cochrane and COMPUS reviews acknowledge there may be some benefit from long-acting analogues in nocturnal hypoglycemia.
• The Cochrane Review concludes
  "Our analysis suggests, if at all only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2 treated with "basal" insulin regarding symptomatic nocturnal hypoglycaemic events.
  Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir."

• The COMPUS review based on clinical evidence alone concludes
  • Adults with type 2 diabetes who are using a pre-meal bolus insulin can use:
    • Either insulin NPH or long acting insulin analogues
  • Adults with type 2 diabetes who are concurrently using oral antidiabetes agents can use
    • Insulin detemir over insulin NPH
    • Either insulin NPH or insulin glargine

• No studies were found comparing rapid acting or long-acting insulin analogues to human insulins in children or adolescents with type 2 diabetes.
• COMPUS recommendations that consider cost-effectiveness are on the following page.
Summary and COMPUS recommendations based on Questions 1 and 2

COMPUS Recommendations

For basal insulin
- NPH should be the first line basal insulin in most patients with type 1 and type 2 diabetes.

For bolus insulin
- In type 1 diabetes
  - Adults and children can use either rapid-acting analogues or regular human insulin.
  - Adolescents can use rapid-acting analogues in preference to regular human insulin.
- In type 2 diabetes regular human insulin can be used in preference to rapid-acting analogues.
- In type 1 and type 2 diabetes, insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using human insulins or for whom hypoglycemia is a major concern.

- COMPUS recommendations consider both clinical efficacy and cost-effectiveness.

- For A1C
  - Insulin analogues provide no clinically significant benefit in glucose control as measured by A1C.

- For hypoglycemia
  - In most populations, (e.g., type 1 diabetes, type 2 diabetes, adults, children) benefits in hypoglycemia from insulin analogues were inconsistent with respect to
    - Type of hypoglycemia (severe, nocturnal, overall)
    - Measures of efficacy (rate ratio, relative risk)
  - Benefits of insulin analogues were most consistently found in nocturnal hypoglycemia, particularly
    - Rapid-acting analogues in adults and adolescents with type 1 diabetes
    - Long-acting analogues in adults with type 2 diabetes
  - Long-acting analogues are 2 to 3 times the cost of NPH insulin.
    - Because long-acting analogues are much more expensive than NPH insulin, and their benefits are uncertain, COMPUS recommends NPH insulin as the first line basal insulin in most patients with type 1 and type 2 diabetes.
    - However, patients who are experiencing significant hypoglycemia while using insulin NPH may benefit from long-acting insulin analogues.

Rapid-acting insulin analogues
- Lispro – Humalog
- Glulisine – Apidra
- Aspart – NovoRapid

Long-acting insulin analogues
- Detemir – Levemir
- Giargin – Lantus
- **Rapid-acting** analogues are approximately 1.4 times more expensive than regular human insulin.
  - They may be more convenient in terms of flexibility of administration and may lead to less hypoglycemia in type 1 patients.
  - Because the rapid-acting analogues are somewhat but not markedly more expensive than human insulin, COMPUS recommends that **adults and children** with **type 1** diabetes can use **either** rapid-acting insulin analogues or regular human insulin.
    - Evidence from the one reported study indicates benefit with rapid-acting analogues for **adolescents** in nocturnal hypoglycemia and COMPUS suggests that **analogue** be used in preference to regular human insulin in this age group. (This is a weak recommendation.)
  - There is **inconsistent** evidence of benefit in hypoglycemia in adults with **type 2** diabetes, and COMPUS suggests that **regular** human insulin be used in **preference** to insulin analogues in this population.
  - Based on clinical opinion and limited evidence, insulin analogues can be tried in patients who experience significant hypoglycemia, particularly nocturnal and severe hypoglycemia, while using human insulins or for whom hypoglycemia is a major concern.
  - COMPUS does not recommend one insulin analogue over another in either the rapid-acting or long-acting classes.

Rapid-acting insulin analogues
Lispro – Humalog  Glulisine – Apidra
Aspart – NovoRapid

Long-acting insulin analogues
Detemir – Levemir  Gliargine – Lantus
Comparison of COMPUS and CDA recommendations for insulin analogues

- The main difference is in use of rapid-acting analogues in type 2 diabetes:
  - COMPUS makes a weak recommendation that regular human insulin be used in preference to rapid-acting analogues.
  - The text of the CDA guideline states that short-acting insulin or rapid-acting analogues may be required as type 2 diabetes progresses.9
  - However, in its recommendations CDA recommends that rapid-acting analogues instead of regular insulin be used when considering lowering post-prandial glucose.
  - This is a Grade B, Level 2 recommendation, indicating it is based on inadequately designed randomized controlled trials (see Table 2).
    - The CDA recommendation is based on lowering postprandial glucose and cites three studies:
      - One was three days duration.35
      - Two studies showed benefit of insulin analogues in lowering postprandial glucose. Treatment difference in post-dinner glucose was 0.51\textsuperscript{36} and 1.3 mmol/L\textsuperscript{37} in the two studies. However, both were based on self-measured values, not laboratory values.
      - Neither study showed clinically significant differences in A1C (0.16\%\textsuperscript{36} and 0.2\%\textsuperscript{37}) or statistically significant differences in hypoglycemia.

- Other recommendations are similar:
  - CDA recommendations suggest considering insulin analogues to minimize hypoglycemia. Most CDA recommendations are Grade B, Level 2.
  - While COMPUS generally suggests human insulins be used in preference to analogues, clinical notes in its report state that insulin analogues can be tried in patients experiencing hypoglycemia.

- Table 8 summarizes COMPUS and CDA recommendations.
Table 8 Comparison of CDA and COMPUS recommendations for insulin analogues

See pages 15 and 16 for levels of evidence

<table>
<thead>
<tr>
<th>Type 1 adults</th>
<th>CDA Recommendations 2008</th>
<th>COMPUS Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid/short acting</td>
<td>Consider rapid-acting insulin analogues with basal insulin over regular insulin to improve A1C while minimizing hypoglycemia and to achieve postprandial glucose targets.</td>
<td>When bolus insulin is required, either regular human insulin or rapid acting insulin analogues are recommended in most patients.</td>
</tr>
<tr>
<td></td>
<td>Grade B, Level 2</td>
<td>Strong recommendation; low/moderate quality evidence</td>
</tr>
<tr>
<td>Long acting</td>
<td>A long-acting insulin analogue may be considered as an alternative to NPH to reduce risk of hypoglycemia including nocturnal hypoglycemia.</td>
<td>NPH is recommended over long acting insulin analogues.</td>
</tr>
<tr>
<td></td>
<td>Grade B, Level 2 for detemir Grade C, Level 3 for glargine</td>
<td>Strong recommendation; low/moderate quality evidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 1 children</th>
<th>CDA Recommendations 2008</th>
<th>COMPUS Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid/short acting</td>
<td>Children with new-onset diabetes should be started on at least 2 daily injections of short-acting insulin or rapid acting insulin analogues combined with an intermediate or long-acting insulin.</td>
<td>When bolus insulin is required, either regular human insulin or rapid acting insulin analogues are suggested in most patients.</td>
</tr>
<tr>
<td></td>
<td>Grade D, Consensus</td>
<td>Weak recommendation; low quality evidence</td>
</tr>
<tr>
<td>Long acting</td>
<td>Ongoing assessment should include consideration of change in the type of basal (long-acting analogue) and/or prandial (rapid-acting analogue) insulin.</td>
<td>NPH is suggested over long acting insulin analogues.</td>
</tr>
<tr>
<td></td>
<td>Grade B, Level 2 adolescents Grade D, Consensus younger children</td>
<td>Weak recommendation; low quality evidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 2 adults</th>
<th>CDA Recommendations 2008</th>
<th>COMPUS Recommendations 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid/short acting</td>
<td>Use rapid-acting insulin analogues instead of short-acting insulin to lower postprandial blood glucose levels.</td>
<td>Regular human insulin is suggested over the rapid acting analogues.</td>
</tr>
<tr>
<td></td>
<td>Grade B, Level 2</td>
<td>Weak recommendation; low quality evidence</td>
</tr>
<tr>
<td>Long acting</td>
<td>When basal insulin is added to antihyperglycemic agents, long-acting analogues may be considered instead of NPH to reduce the risk of nocturnal and symptomatic hypoglycemia.</td>
<td>NPH is recommended over long acting insulin analogues.</td>
</tr>
<tr>
<td></td>
<td>Grade A, Level 1A</td>
<td>Strong recommendation; low/moderate quality evidence</td>
</tr>
</tbody>
</table>

a The text of the CDA guideline states that short-acting insulin or rapid-acting analogues may be required as type 2 diabetes progresses.9

b COMPUS could not include postprandial glucose levels when making recommendations because it was infrequently reported, and in studies it was self-measured not laboratory measured.
Potential for increased cancer risk with insulin analogues – recent evidence

- There is biological plausibility for a link between insulin and cancer, and in particular glargine and cancer due to their effects on the receptor for insulin-like growth factor 1 (IGF-1).
  - IGF-1 mediates the effect of growth hormone and leads to cell proliferation in many tissues. Insulin, and to varying degrees the insulin analogues, activate the IGF-1 receptor which can lead to increased cell growth and reduced cell apoptosis. 38,39
  - When cells undergo malignant change, they may produce more receptors for insulin and IGF-1, leading to acceleration of their own growth. This tendency is common in cancers of the breast, colon, pancreas, and prostate. 39
  - Of note, activation of the IGF-1 receptor may lead to proliferation of pre-existing cancers rather than new cancer cell formation. 39
  - An in vitro study has shown that glargine has a six to eight-fold increase in affinity for IGF-1 receptors and for mitogenicity than human insulin. 40 However, there is also evidence that glargine is partially degraded at the injection site to forms that have less mitogenicity than glargine itself. 39
  - These conflicting findings emphasize the need for clinical studies.

- A series of retrospective cohort studies has examined the relation between glargine and cancer in Germany, 41 Scotland, 42 Sweden, 43 and the United Kingdom. 44 Results were inconsistent.
  - Two studies found an increased risk of all cancers 42 or breast cancer 43 in patients using glargine alone. However, this increased risk was not found in patients using glargine along with other insulins. This may be because patients taking glargine with other insulins were more likely to have type 1 diabetes and be younger, therefore at lower risk of developing cancer.
  - Two studies found no increased risk of all cancers with glargine 43,44 while two found evidence of increased risk. 41,42

- Observational studies like these cannot completely control for potential confounders such as smoking, socio-economic status, or diet.
- The studies are short with approximately 2 to 3 years exposure to glargine. This is a very short period of time for an increase in cancer risk to become manifest. 39
- Two industry-sponsored meta-analyses have been published in response to these observational studies.
  - A meta-analysis of 31 glargine studies (N = 10,880) found no increased risk of cancers associated with glargine. 45
  - A meta-analysis of detemir using individual patient data (21 studies, N = 8,693) found 46
    - An increased risk of cancer with NPH insulin compared to detemir OR 2.44 (95% CI: 1.01 to 5.89, p = 0.048)
    - No statistically significant increase in risk of cancer associated with detemir compared to glargine OR 1.47 (95% CI: 0.55 to 3.94)
• While these findings are reassuring, the RCTs in these meta-analyses are not designed to detect differences in risk of developing cancer and are not large enough or long enough to determine if insulin analogues lead to an increased cancer risk. Also, patients at increased risk of developing malignancies may be excluded from such studies.

• In July 2009, Health Canada, the European Medicines Agency (EMA) and the US Food and Drug Administration started safety reviews on the possible link between insulin glargine and cancer.\textsuperscript{47-49}

• The EMA reviewed the studies and published their conclusion on July 23, 2009.\textsuperscript{48}
  • Due to methodological limitations the studies were found to be inconclusive and did not allow a relationship between insulin glargine and cancer to be confirmed or excluded.
  • The Committee noted that the results of the studies were not consistent.

• As of April 2010 no further communication has been released by Health Canada or the FDA.
Question 3: Who should be self-monitoring their blood glucose and how frequently?

**COMPUS recommendations vary depending on whether the patient is using insulin.**
- Generally, it is recommended that
  - Patients using insulin perform self-monitoring of blood glucose.
  - Most adults **not using** insulin do **not** require routine self-monitoring of blood glucose.

- 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
- SMBG is only part of diabetes self-management which includes proper diet and physical activity, medication adherence, managing blood pressure and lipids, and follow-up for diabetes complications.
- There is little evidence to guide recommendations on self-monitoring of blood glucose and much of the evidence is of low quality, coming from observational studies. Observational studies may overestimate the benefit of self-monitoring of blood glucose because patients who self-test frequently may be more likely to engage in other behaviours such as following dietary and exercise routines.
- Outcomes reported are generally limited to A1C and hypoglycemia.
- Some recommendations come from consensus and usual care.

**COMPUS recommendations vary depending on whether the patient is using insulin.**
- Generally, it is recommended that
  - Patients using insulin perform self-monitoring of blood glucose.
  - Most adults **not using** insulin **do not** require routine self-monitoring of blood glucose.

- We will provide some brief summaries of evidence and recommendations from the COMPUS Optimal Therapy Report[^4] and some RCTs.
  - COMPUS considered cost-effectiveness in its recommendations.
- We will also provide the 2008 CDA recommendations which do not consider cost-effectiveness.

[^4]: COMPUS considered cost-effectiveness in its recommendations.
Patients with type 1 diabetes

- **COMPUS recommends that the optimal daily frequency of SMBG be individualized for adults and children with type 1 diabetes.**
  - This is a **strong** recommendation based on clinical opinion and accepted standards of practice even though the quality of evidence is low.
  - A1C was the only outcome for which evidence was available.\(^4\)
    - The greatest reduction in A1C found was a difference of 0.78% (95% CI: 0.55 to 1.01) in favor of testing ≥ 3 times per day vs. once per day. This came from a **very low quality** retrospective cohort study.\(^4\)
    - There was insufficient evidence to make a recommendation regarding **optimal** or **maximum** testing in this population.\(^4\)

Patients with type 2 diabetes taking insulin

- **COMPUS recommends the optimal daily frequency of testing be individualized for most adults with type 2 diabetes using insulin with or without oral antidiabetes drugs.**
  - This is a **strong** recommendation based on clinical opinion and accepted standards of practice even though the quality of evidence is low (limited to one non-randomized study and two observational studies).
  - **COMPUS suggests the maximum average weekly frequency of testing for MOST adults with type 2 diabetes using basal insulin is 14 tests per week.**
    - This is a **weak** recommendation and was based on standards of practice and a cost-effectiveness analysis that assessed frequencies of 4 times per week, 7 times per week, 14 times per week, and 21 times per week.
      - Testing 21 times per week is cost-effective only if it is assumed that testing at that frequency leads to a decrease in A1C of 1% which is unlikely.
      - COMPUS decided on testing 14 times per week because this frequency may be cost-effective if it leads to a decrease in A1C of 0.5% to 0.75%.
        - While this decrease only approaches clinical significance, COMPUS decided to err on the side of caution to allow the maximum possible cost-effective benefit that may arise from testing.
    - Based on clinical experience and accepted standards of practice, COMPUS also recognized that some conditions may require **more** frequent testing. For example
      - Using multiple daily insulin injections (i.e., three or more per day)
      - With a history of hypoglycemia
      - Working in an occupation where hypoglycemia poses safety concerns or where testing is mandated by an employer (e.g., pilots, air-traffic controllers, critical positions in railways)(see Appendix 3)
- Private and commercial drivers who should abide by 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

Patients with type 2 diabetes NOT requiring insulin
(controlled with diet, with or without oral antidiabetes agents)

- **COMPUS recommends that most adults with type 2 diabetes who do not require insulin do not perform routine self-monitoring of blood glucose.**
  - This is a strong recommendation.
  - Testing may be required in some situations but only if it helps to determine a specific course of action by the patient.
- Evidence was moderate quality for patients using oral antidiabetes drugs and low quality for patients not using oral antidiabetes drugs.
- Seven RCTs with a total of 2270 patients found a mean difference in A1C reduction of 0.25% (95% CI: 0.15 to 0.36) for self-monitoring of blood glucose vs no monitoring which is statistically significant but not clinically significant (i.e., did not achieve a difference of 0.7% to 1%). The overall quality of evidence was considered moderate.
- Results of the meta-analysis were similar for various sensitivity analyses i.e., by limiting analysis to select studies. For example results were similar when considering only
  - High quality studies
  - Studies in which all patients used sulfonylureas
  - Studies in which all patients used oral drugs
    This consistency of results indicates the findings are robust.
- Three RCTs with a total of 1752 patients found an increase in patients experiencing at least one overall hypoglycemic event with self-monitoring vs no monitoring.
  - Risk of having ≥ 1 event 15% vs. 7.6%, relative risk increase 99%, absolute risk increase 7.4%; number needed to test 13 (95% CI: 7 to 36).
  - Most episodes were mild or asymptomatic and it is not clear if the increase was due to detecting hypoglycemia with monitoring.
- SMBG testing did not affect severe or nocturnal hypoglycemia compared with the groups that performed no testing though studies were not powered to detect such differences.
- Two RCTs with a total of 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 patient well-being or satisfaction with treatment compared with no SMBG in patients with type 2 diabetes not taking insulin. Increased levels of depression and poorer quality of life have been reported.\(^4,50\)

There is **insufficient** evidence to recommend an **optimal** frequency of testing in this population (Appendix 2).

Based on clinical experience and accepted standards of practice, COMPUS recognized that **some** patients may benefit from self-monitoring of blood glucose including those:

- At risk of hypoglycemia with insulin secretagogues
- At increased risk of hypoglycemia (e.g., due to a history of severe hypoglycemia or hypoglycemia unawareness, instances of inadequate caloric intake, unforeseen or unplanned physical activity)
- Experiencing acute illness
- Undergoing changes in pharmacotherapy or significant changes in routine
- With poorly controlled or unstable blood glucose levels
- Who are pregnant or planning a pregnancy
- Working in an occupation where hypoglycemia poses safety concerns
  - See Appendix 3 for list of Canadian recommendations for self-monitoring of blood glucose for special populations such as
    - Commercial and private vehicle drivers
    - Pilots and air traffic controllers
    - Railway workers who operate or control the movement of trains
- A summary of the COMPUS evidence for blood glucose testing in patients with type 2 diabetes not taking insulin is in Appendix 2.

### Risk of hypoglycemia with secretagogues

Estimating the risk of hypoglycemia associated with secretagogues is somewhat difficult because of differing definitions of hypoglycemia. Two studies of patients with type 2 diabetes taking sulfonylureas found incidence rates of:

- **~1% per year**: Scottish population-based study, **severe** hypoglycemia defined as requiring medical attention.\(^31\)
- **~0.1% per year**: Nested case-control study from the United Kingdom, **mild to moderate** hypoglycemia defined as requiring treatment from a family physician.\(^52\)

One 27-week study of patients taking gliclazide found no statistically significant differences of relative risk or rate of overall hypoglycemia with SMBG vs no SMBG. No patients experienced severe hypoglycemia.\(^53\)
Comparison of COMPUS and CDA recommendations for SMBG

- In **type 1 diabetes**, the CDA is more specific in its recommendation than COMPUS, specifying that testing be done
  - At least 3 times daily and
  - Include both pre- and postprandial measurements
    COMPUS recommends testing be **individualized**.

- In patients with **type 2 diabetes using insulin**, CDA makes different recommendations depending on the insulin regimen.
  - For patients **using insulin**, CDA again makes a specific recommendation that testing be done at least 3 times daily.
  - For patients **using once daily (basal) insulin** plus oral agents CDA recommends testing at least once daily.
    - The CDA guideline acknowledges that the benefits and optimal frequency of SMBG in type 2 diabetes are less clear than for type 1 and states that current evidence is at times contradictory, and methodological and conceptual limitations exist in the literature.\(^9\)
      COMPUS recommends the optimal daily frequency of testing be **individualized** for most adults with type 2 diabetes using insulin.
      COMPUS suggests the **maximum** average weekly frequency of SMBG for most adults with type 2 diabetes using basal insulin is **14 tests per week**.

- In patients with **type 2 diabetes NOT using insulin**, CDA recommends that testing should be **individualized** and include pre- and postprandial measurements.
  - COMPUS recommends that most adults do **not need** routine SMBG.

- The above CDA recommendations are Grade C, Level 3 or Grade D, Consensus and do not consider cost-effectiveness.

- Most COMPUS recommendations are strong recommendations but based on low to moderate quality evidence and do consider **cost-effectiveness**.

- Table 9 summarizes the CDA and COMPUS recommendations.
Table 9 Comparison of CDA and COMPUS recommendations for SMBG

See pages 15 and 16 for levels of evidence

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

Type 2 adults

<table>
<thead>
<tr>
<th>Using Insulin</th>
<th>SMBG recommended as an essential part of diabetes self-management</th>
<th>The optimal daily frequency of testing should be individualized for most adults with type 2 diabetes using insulin with or without oral antidiabetes drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade C, Level 3</td>
<td>Strong recommendation; low quality evidence</td>
</tr>
<tr>
<td></td>
<td>- should be undertaken at least 3 times per day</td>
<td>The suggested maximum average weekly frequency of SMBG for most adults with type 2 diabetes using [basal] insulin with or without oral antidiabetes drugs is 14 tests per week a</td>
</tr>
<tr>
<td></td>
<td>Grade C, Level 3</td>
<td>Weak recommendation; low quality evidence</td>
</tr>
<tr>
<td></td>
<td>- and should include both pre- and postprandial measurements</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>In those on once-daily insulin plus oral antihyperglycemic agents, testing at least once a day at variable times is recommended</td>
<td>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.b</td>
</tr>
<tr>
<td>Once daily</td>
<td>Grade D, Consensus.</td>
<td>Strong recommendation; low / moderate quality evidence</td>
</tr>
<tr>
<td>insulin plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oral agents</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type 2 Controlling with diet alone or oral agents

| For individuals treated with oral antihyperglycemic agents or lifestyle alone, the frequency of SMBG should be individualized depending on glycemic control and type of therapy and 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.b |
| Grade D, Consensus. | Strong recommendation; low / moderate quality evidence |

Based on clinical experience and accepted standards of practice, COMPUS recognized that some patients may benefit from initiating

a – More frequent testing (See page 43 for list.)

b – Self-monitoring of blood glucose (See page 45 for list.)
Glycemic targets

The 2008 CDA glycemic targets for most patients with type 1 and type 2 diabetes are listed in Table 10.

The guidelines suggest that

- Clinical judgment is required to determine which people can reasonably and safely achieve these targets.
- Treatment goals and strategies must be tailored to the patient, with consideration given to individual risk factors (e.g. the patient’s age, prognosis, level of glycemic control, duration of diabetes, the presence of diabetes complications or comorbidities, and their risk for and ability to perceive hypoglycemia).
- To make the guidelines easier to incorporate into clinical practice, a single A1C target is provided, and plasma glucose targets have been rounded to whole numbers.

Table 10 Glycemic targets recommended by CDA

<table>
<thead>
<tr>
<th></th>
<th>A1C %</th>
<th>FPG or preprandial PG (mmol/L)</th>
<th>2-hour postprandial PG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 and Type 2 diabetes</td>
<td>≤ 7.0</td>
<td>4.0 to 7.0</td>
<td>5.0 to 10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 to 8.0 if A1C targets not met</td>
</tr>
</tbody>
</table>

a Treatment goals and strategies must be tailored to the individual with diabetes, with consideration given to individual risk factors.

PG = plasma glucose

Glycemic targets for children ≤12 years of age and pregnant women differ from these targets. See relevant guidelines for further details.

An A1C of 7.0% corresponds to a laboratory value of 0.070. Where possible, Canadian laboratories should standardize their A1C values to Diabetes Control and Complications Trial levels (reference range: 0.040 to 0.060). However, as many laboratories continue to use a different reference range, the target A1C value should be adjusted based on the specific reference range used by the laboratory that performed the test.

As a useful guide, an A1C target of 7.0% refers to a threshold that is approximately 15% above the upper limit of normal.

A1C = glycated hemoglobin  FPG = fasting plasma glucose  PG = plasma glucose

CDA recommendations for achieving glycemic targets

1. Glycemic targets must be individualized; however, therapy in most individuals with type 1 or type 2 diabetes should aim to achieve an A1C ≤7.0% to reduce the risk of

   - Microvascular  
     and  
   - In individuals with type 1 diabetes, macrovascular complications

   Grade A, Level 1A
   Grade C, Level 3
2. A target A1C of \( \leq 6.5\% \) may be considered in some patients with type 2 diabetes to further lower the risk of nephropathy Grade A, Level 1A but this must be balanced against the risk of hypoglycemia Grade A, Level 1A and increased mortality in patients who are at significantly elevated risk of cardiovascular disease Grade A, Level 1A.

3. To achieve A1C of \( \leq 7.0\% \), people with diabetes should aim for:
   - An FPG or preprandial PG target of 4.0 to 7.0 mmol/L Grade B, Level 2 and
   - A 2-hour postprandial PG target of 5.0 to 10.0 mmol/L Grade B, Level 2

   If A1C targets cannot be achieved with a postprandial target of 5.0 to 10.0 mmol/L, further postprandial BG lowering to 5.0 to 8.0 mmol/L can be considered. Grade D, Consensus, for type 1 diabetes Grade D, Level 4 for type 2 diabetes

**Glycemic targets in the frail elderly in long-term care facilities**

- The usual glycemic targets apply to otherwise healthy elderly as to younger people with diabetes. However, CDA recommends that glycemic targets should be less stringent in the frail elderly such as those living in long-term care facilities and with multiple comorbidities, a high level of functional dependency and limited life expectancy.\(^9\)

- The Diabetes Care Program of Nova Scotia has published some recommendations for glycemic targets in the frail elderly in long-term care facilities.\(^51\)
  - Clinicians should try to avoid symptoms of hyperglycemia and prevent hypoglycemia.
    - Prolonged hyperglycemia can cause
      - Polyuria, which can aggravate nocturia and incontinence
      - Dehydration, weight loss, falls, infection, and impaired cognition
    - Nevertheless, frail elderly in long-term care facilities with type 2 diabetes have fewer hyperglycemic-related symptoms compared to younger people with type 1 diabetes and it is not clear that better glycemic control will improve these non-specific symptoms that are common in elderly people.
• **Recommended glycemic targets** were developed from this perspective.

<table>
<thead>
<tr>
<th>If random blood glucose (BG):</th>
<th>Treatment recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 7 mmol/L</td>
<td>Notify physician to decrease diabetes treatment.</td>
</tr>
<tr>
<td>7.0 - 9.9 mmol/L</td>
<td>This range may be acceptable. There is risk for hypoglycemia with glyburide, gliclazide, and glimepiride or insulin therapy. If the resident has hypoglycemia (more than once a month), notify the physician to decrease treatment.</td>
</tr>
</tbody>
</table>
| 10.0 - 20.0 mmol/L            | This range is acceptable if the resident has no reversible symptoms such as polyuria or nocturia.  
If the resident has reversible symptoms, notify the dietician to assess food intake. Notify physician to assess the diabetes treatment. Increased treatment may not improve symptoms if due to other causes. |
| Greater than 20.0 mmol/L      | Notify physician to increase diabetes treatment. |
| Greater than 33.0 mmol/L with stupor or coma | Notify the physician. |

- When the health care team discusses an individual’s overall health status and prognosis with either the patient or the family, a review of glycemic targets and the importance of avoiding hypoglycemia would be beneficial. If glycemic targets are different from the diabetes guidelines, this should be clearly documented and include the rationale.

- Please refer to [http://www.diabetescareprogram.ns.ca/](http://www.diabetescareprogram.ns.ca/) for further details and updates.

<table>
<thead>
<tr>
<th>Rapid-acting insulin analogues</th>
<th>Long-acting insulin analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro – Humalog</td>
<td>Detemir – Levenir</td>
</tr>
<tr>
<td>Glulisine – Apidra</td>
<td>Gliargine – Lantus</td>
</tr>
<tr>
<td>Aspart – NovoRapid</td>
<td></td>
</tr>
</tbody>
</table>
Utilization of blood glucose test strips in Nova Scotia

- In Nova Scotia, almost as much money is spent on glucose test strips as on diabetes medication (Table 11).
- In 2008 spending within the Pharmacare program was:
  - Diabetes medications $8,532,000
  - Glucose test strips $8,522,200
- Of note, over $4,000,000 was paid for patient groups where routine testing is not recommended (oral antidiabetes drugs or no drugs).

Table 11 Nova Scotia Pharmacare utilization of glucose test strips 2008

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Amount paid for test strips (rounded)</th>
<th>Number of claimants (rounded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>$2,356,000</td>
<td>3,600</td>
</tr>
<tr>
<td>Oral antidiabetes drugs (OAD)</td>
<td>$3,461,000</td>
<td>12,100</td>
</tr>
<tr>
<td>Both insulin and OAD</td>
<td>$1,834,000</td>
<td>3,300</td>
</tr>
<tr>
<td>No drugs</td>
<td>$871,000</td>
<td>4,100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$8,522,000</strong></td>
<td><strong>23,100</strong></td>
</tr>
</tbody>
</table>

- Cost per strip varies between 40 cents and 80 cents.
- The average number of strips per day ranged from
  - Less than 1 per day (in non-drug users) to
  - Approximately 2 per day in insulin users.
- The ranges were very broad, with some patients using up to 24 strips per day. There was wide variation in all patient groups, including the non-drug users, where the maximum number of strips per day was 10.
  - The minimum number for all patient groups was 0.1 strip per day.
Appendix 1

COMPUS Expert Review Committee

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### Appendix 2 Effect of self-monitoring of blood glucose on A1C and hypoglycemia in persons with type 2 diabetes not taking insulin

#### Summary of Findings for A1C From Studies Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of Studies (Sample Size)</th>
<th>WMD (95% CI) in A1C (%)</th>
<th>I² (%)</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence from RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall estimate of effect</td>
<td>7 RCTs&lt;sup&gt;53,54,57-59&lt;/sup&gt; (n = 2,270)</td>
<td>-0.25% (-0.36, -0.15)</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Good quality RCTs only</td>
<td>3 RCTs&lt;sup&gt;53,54,57&lt;/sup&gt; (n = 1,247)</td>
<td>-0.21% (-0.34, -0.08)</td>
<td>0</td>
<td>High</td>
</tr>
<tr>
<td>RCTs in which all subjects used OADs</td>
<td>3 RCTs&lt;sup&gt;53,54,57&lt;/sup&gt; (n = 1,628)*</td>
<td>-0.24% (-0.36, -0.11)</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>RCT in which all patients use sulfonylureas</td>
<td>1 RCT&lt;sup&gt;57&lt;/sup&gt; (n = 610)</td>
<td>-0.24% (-0.43, -0.05)</td>
<td>N/A</td>
<td>High</td>
</tr>
<tr>
<td>More intensive education</td>
<td>3 RCTs&lt;sup&gt;47&lt;/sup&gt; (n = 710)</td>
<td>-0.28% (-0.47, -0.08)</td>
<td>17.8</td>
<td>Moderate</td>
</tr>
<tr>
<td>Less intensive or unspecified education</td>
<td>5 RCTs&lt;sup&gt;53,54,57,59&lt;/sup&gt; (n = 1,712)</td>
<td>-0.22% (-0.34, -0.10)</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Evidence from retrospective cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one strip per day versus no SMBG</td>
<td>1 R. cohort&lt;sup&gt;55&lt;/sup&gt; (n = 8,735)</td>
<td>-0.68% (-0.77, -0.59)*</td>
<td>N/A</td>
<td>Very low</td>
</tr>
<tr>
<td>Less than one strip per day versus no SMBG</td>
<td>1 R. cohort&lt;sup&gt;55&lt;/sup&gt; (n = 10,243)</td>
<td>-0.21% (-0.30, -0.12)</td>
<td>N/A</td>
<td>Very low</td>
</tr>
<tr>
<td>Prescription of two to four strips per week versus no prescription of strips</td>
<td>1 R. cohort&lt;sup&gt;55&lt;/sup&gt; (n = 115)</td>
<td>-0.20% (-0.37)</td>
<td>N/A</td>
<td>Very low</td>
</tr>
<tr>
<td>Prescription of 0.56 strips per day versus no prescription of strips</td>
<td>1 R. cohort&lt;sup&gt;55&lt;/sup&gt; (n = 299)</td>
<td>-0.13% (-0.28, 0.02)*</td>
<td>N/A</td>
<td>Very low</td>
</tr>
</tbody>
</table>

A1C = hemoglobin A1C; CI = confidence interval; N/A = not applicable; OADs = oral antidiabetes drugs; R. cohort = retrospective cohort; RCT = randomized controlled trial; SMBG = self-monitoring of blood glucose; WMD = weighted mean difference

*Farmer et al. (2007)* presented data for a subgroup of patients treated with oral antidiabetes drugs.

† Data were adjusted for age, sex, ethnicity, educational attainment, annual income and occupational class, years since diabetes diagnosis, diabetes therapy refill adherence, number of daily insulin injections (insulin users only), clinic appointment "no show" rate, annual eye exam attendance, self-reported exercise and diet as diabetes treatment, smoking status, alcohol consumption, and hospitalization and emergency room visits during the baseline year.

‡ Data were not adjusted for any confounder and baseline A1C was not reported; however, age, weight, dose of glyburide, serum creatinine, and proteinuria were similar between the two groups.

¶ Data were not adjusted for any possible confounders, although baseline A1C, body mass index, chronic illness, and disability payment system and ethnicity were similar between the two groups.

#### Summary of Findings for Hypoglycemia From RCTs Comparing SMBG Versus No SMBG in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of Studies (Sample Size)</th>
<th>Effect Estimate (95% CI)</th>
<th>I² (%)</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hypoglycemia</td>
<td>3 RCTs&lt;sup&gt;53,54,57-59&lt;/sup&gt; (n = 1,752)</td>
<td>RR: 1.99 (1.37, 2.89)</td>
<td>33.8</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>2 RCTs&lt;sup&gt;53,57&lt;/sup&gt; (n = 794)</td>
<td>Rate ratio: 0.73 (0.55, 0.98)</td>
<td>0</td>
<td>High</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>3 RCTs&lt;sup&gt;53,54,57-59&lt;/sup&gt; (n = 1,752)</td>
<td>RR: 0.17* (0.01, 4.12)</td>
<td>N/A</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>1 RCT&lt;sup&gt;59&lt;/sup&gt; (n = 610)</td>
<td>RR: 0.41 (0.11, 1.58)</td>
<td>N/A</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence intervals; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMBG = self-monitoring of blood glucose

*Since no events occurred in Guerci et al. (2003) or Barnett et al. (2008), only the RR from Farmer et al. (2007) contributed to the pooled estimate.
# Summary of A1c Findings for Studies Comparing Different SMBG Frequencies in Adults With Type 2 Diabetes Treated With Oral Antidiabetes Drugs or No Antidiabetes Drugs

<table>
<thead>
<tr>
<th>SMBG Frequency</th>
<th>Number of Studies (Sample Size)</th>
<th>Effect Size (95% CI or P value)</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence from RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMBG once per week versus SMBG four times per week</td>
<td>1 RCT(^6) (n = 178)</td>
<td>MD: -0.08% (-0.41, 0.25)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Evidence from retrospective cohort studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average daily SMBG: once per day versus less than once per day</td>
<td>1 R. cohort(^6) (n = 6,594)</td>
<td>MD: -0.47% (-0.57, -0.37)(^7)</td>
<td>Very low</td>
</tr>
<tr>
<td>SMBG increased by one strip per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients using OADs</td>
<td>1 R. cohort(^6) (n = 1,795)</td>
<td>0.09% (P = 0.5392)(^6)</td>
<td>Very low</td>
</tr>
<tr>
<td>Patients using sulfonylureas</td>
<td>1 R. cohort(^6) (n = 216)</td>
<td>0.02% (P &gt; 0.50)(^6)</td>
<td>Very low</td>
</tr>
<tr>
<td>New users of SMBG</td>
<td>1 R. cohort(^7) (n = 5,546)</td>
<td>-0.42% (P &lt; 0.0001)(^5)</td>
<td>Very low</td>
</tr>
<tr>
<td>Prevalent users of SMBG</td>
<td>1 R. cohort(^7) (n = 7,409)</td>
<td>-0.16% (P &lt; 0.0001)(^7)</td>
<td>Very low</td>
</tr>
<tr>
<td>SMBG increased by 10 test strips per week</td>
<td>1 R. cohort(^8) (n = 5962)</td>
<td>-0.06 (0.01)(^**) (P = 0.38)</td>
<td>Very low</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval; MD = mean difference; OADs = oral antidiabetes drugs; R. cohort = retrospective cohort; RCT = randomized controlled trial; SMBG = self-monitoring of blood glucose.

\(^6\) Data adjusted for age, sex, ethnicity, educational attainment, block group attainment, block group annual income and occupation class, years since diabetes diagnosis, diabetes therapy refill adherence, clinic appointment “no show” rate, annual eye exam attendance, self-reported exercise and diet as diabetes therapy, smoking status, alcohol consumption, and hospitalization and emergency room visits during the baseline year.

\(^7\) Adjusted for age, sex, region, body mass index, months since initiation of oral antidiabetes drugs and A1c test, number of oral medications received in six months prior to A1c test.

\(^8\) Adjusted for age, daily glyburide dose, serum creatinine concentration, urine protein content, hospital admissions, number of providers, number of ophthalmology visits, number of diabetes clinic visits.

\(^5\) Data adjusted for pre-baseline A1c (last A1c prior to baseline), sex, age, inpatient comorbidity score, diabetes refill medication adherence, diabetes therapies, appointment “no show” rate, performance of annual ophthalmology exams, prebaseline rates of hospital, emergency room, primary care and specialty visits, primary care provider type, smoking status, neighbourhood level, median family income, residence in a poorly educated neighbourhood, residence in a predominately working-class neighbourhood, and the length of time between pre- and post-A1c tests.

\(^4\) Data adjusted as in footnote \(^4\), but also for SMBG, daily insulin injection frequency, appointment “no show” rate, inpatient comorbidity score, and inpatient/outpatient utilization.

\(^**\) Coefficient (standard error) represents change in A1c for every ten glucose test strips used each week. Coefficients are derived for each outcome stratum using separate multivariate linear regression models adjusting for initial doses of glyburide and metformin and the number of oral antidiabetes drugs.
Summary of Findings for Outcomes From Studies Comparing of SMBG Versus No SMBG for Adults With Type 2 Diabetes in Adults Using No Antidiabetes Drugs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Studies (Sample Size)</th>
<th>Effect Estimate MD (95% CI)</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%) change from baseline</td>
<td>1 RCT(^\d) (n = 124)</td>
<td>-0.05 (-0.33, 0.23)</td>
<td>Moderate</td>
</tr>
<tr>
<td>A1C (%) at end</td>
<td>SMBG at least once per day versus no SMBG</td>
<td>1 R. cohort(^\d) (n = 3445)</td>
<td>-0.64* (-0.81, -0.47)</td>
</tr>
<tr>
<td></td>
<td>SMBG less than once per day versus no SMBG</td>
<td>1 R. cohort(^\d) (n = 4198)</td>
<td>-0.34(^\d) (-0.47, -0.21)</td>
</tr>
</tbody>
</table>

**Economic Information**

Unit cost: C$0.73 per test strip
ICUR — diet only, RCT data\(^\d\): C$292,144 per QALY gained (\(\Delta C = C$1,372; \Delta QALYs = 0.00470\))

A1C—hemoglobin A1C; CI—confidence interval; ICUR—incremental cost-utility ratio; MD—mean difference; QALY—quality-adjusted life-year; RCT—randomized controlled trial; R. cohort — retrospective cohort; \(\Delta C\)—difference in costs between strategies; \(\Delta QALYs\)—difference in QALYs gained between strategies

* Adjusted for age, sex, ethnicity, educational attainment, block group annual income, occupational class, years since diabetes diagnosis, diabetes therapy refill adherence, number of daily insulin injections (insulin users only), clinic appointment “no show” rate, annual eye exam attendance, self-reported exercise and diet as diabetes treatment, smoking status, alcohol consumption, and hospitalization and emergency room visit during the baseline year.

\(^\d\) Initiating once-daily monitoring resulted in lowering of A1C concentration by 0.35\% (P < 0.0001). Models were adjusted for pre-baseline A1C, sex, age, inpatient comorbidity score, diabetes refill medication adherence, diabetes therapies (therapeutic class), appointment “no show” rate, performance of annual ophthalmology exams, prebaseline rates of hospital, emergency room, primary care and specialty visits, primary care provider type, smoking status, neighborhood level, median family income, residence in a poorly educated neighborhood, residence in a predominately working-class neighborhood, and the length of time between pre- and post-A1C tests.

\(^\d\) Baseline A1C=7.48\%; mean age = 66 years; duration of diabetes = three years; frequency = 0.71 test strips per day; WMD= -0.05 (-0.33, 0.23); time horizon=40 years.
Appendix 3  Blood glucose testing recommendations for various occupations

Canadian Diabetes Association’s Clinical Practice Guidelines for Diabetes and Private and Commercial Driving
http://www.diabetes.ca/about-diabetes/living/guidelines/commercial-driving/

See also Canadian Medical Association Driver’s Guide 2006
http://www.cma.ca/index.cfm/ci_id/3422/la_id/1.htm

All drivers with diabetes

- Fitness of persons with diabetes to drive must be assessed on a case-by-case basis. [Grade D, consensus]
- Persons with diabetes should take an active role in assessing their ability to drive by maintaining medical records, accurate BG monitoring logs and a well-calibrated BG meter. [Grade D, consensus]
- Drivers should take an active role in obtaining current information concerning avoidance, recognition, and appropriate therapeutic intervention for hypoglycemia. Their long-term goal should be to maintain optimal diabetes control without the development of hypoglycemia unawareness. [Grade D, consensus]
- Drivers should measure their BG level immediately before and at least every 4 hours (more often in cases of hypoglycemia unawareness) during long drives. They should always carry BG monitoring equipment and supplies of rapidly absorbable carbohydrate within easy reach (e.g. attached to the visor). [Grade D, consensus]
- Persons should not drive when their BG level is <4.0 mmol/L. They should not begin to drive without prophylactic carbohydrate treatment when their BG level is in the 4.0 to 5.0 mmol/L range. [Grade D, consensus]
- Drivers should stop and treat themselves as soon as hypoglycemia and/or impaired driving is suspected. [Grade D, consensus]
- Persons should not drive until at least 45 to 60 minutes after effective treatment of mild to moderate hypoglycemia (BG level 2.5 to 4.0 mmol/L). [Grade D, consensus]
- The following drivers should be informed that they are at high risk of experiencing severe hypoglycemia when driving. They should make efforts to minimize the risk, including by measuring BG levels before and periodically during every driving exposure:
  - History of severe hypoglycemia during the past year
  - Hypoglycemia unawareness
  - Recurrent previous hypoglycemic reactions
  - Recent marked reduction in HbA1C or
  - HbA1C within the normal range

[Grade D, consensus]
Private and commercial drivers with type 2 diabetes treated with diet or oral antihyperglycemic agents

- The annual medical examination of a driver with diabetes should always include an assessment of the severity of retinopathy, neuropathy, nephropathy, and CVD, and a decision on whether or not the severity of any of these complications could increase the risk of an accident. [Grade D, consensus]
- Persons with diabetes who are well controlled by diet alone or by a combination of diet and oral antihyperglycemic medication are at minimal risk of a severe hypoglycemic reaction and can usually drive all types of motor vehicles with relative safety provided they remain under regular medical supervision (minimum of 2 clinic visits during the last year). [Grade D, consensus]

Insulin-treated private drivers

- Persons who require insulin to control BG can drive private vehicles if they are under regular medical supervision (minimum of 2 clinic visits during the last year). [Grade D, consensus]

Initial application for a commercial license

- Questionnaire (sample questionnaire available from the CDA upon request) to be completed by the person with diabetes, with emphasis on the risk (work schedule, insulin regimen, symptoms of hypoglycemia) and occurrence of hypoglycemia (frequency of mild and severe hypoglycemia in last 6 months). [Grade D, consensus]
- An internist or endocrinologist, or a family physician trained in diabetes care, must perform an initial complete assessment. [Grade D, consensus]
- The applicant must supply evidence of attendance at a diabetes education program. [Grade D, consensus]
- The applicant should present medical records for the preceding 24 months and an HbA1C measurement within the past 3 months. [Grade D, consensus]
- The applicant should have a full eye examination performed by an ophthalmologist or optometrist. [Grade D, consensus]
- The applicant must have a log of BG measurements performed at least twice daily during the last 6 months or since the diagnosis of diabetes if onset occurred within the last 6 months. A downloaded log from a memory equipped BG meter is preferred. [Grade D, consensus]

Exclusion criteria for maintenance of a commercial license

- Hypoglycemia within the previous 6 months of sufficient severity to require corrective intervention by an outsider or producing loss of consciousness even if spontaneous recovery occurred. [Grade D, consensus]
- Hypoglycemia appearing in the absence of warning symptoms (hypoglycemia unawareness) unless there is documentation of recovery of warning symptoms at a later date. [Grade D, consensus]
- Uncontrolled diabetes:
  - HbA1C ≥12%; or
  - ≥10% of BG levels <4.0 mmol/L. [Grade D, consensus]
• A significant change in insulin regimen (i.e. a change in the type of insulin, number of insulin injections or the introduction of insulin). In these circumstances, persons should be assessed frequently by daily or weekly telephone consults or visits with respect to the occurrence of any hypoglycemic episodes, and be permitted to drive provided the variation in BG levels indicates minimal risk. [Grade D, consensus]

• Visual impairment. The minimum standard for visual acuity is 20/40 in the better-seeing eye (20/50 in Quebec). [Grade D, consensus]

• High-risk proliferative retinopathy. [Grade D, consensus]

• Peripheral neuropathy or CVD with the potential to affect driving. [Grade D, consensus]

• Inadequate record of self-monitoring of blood glucose (SMBG) (i.e. unreliable or absent capillary BG measurements). [Grade D, consensus]

• Inadequate knowledge of the causes, symptoms, and treatment of hypoglycemic reactions. [Grade D, consensus]

**Annual medical recertification of insulin-treated commercial drivers**

• All insulin-treated commercial drivers are required to have an annual medical examination and recertification. The following should be obtained:
  
  • Medical records for the last 12 months; questionnaire to be completed by the person with diabetes (see recommendation above)
  
  • Complete physical examination
  
  • Complete eye examination by an ophthalmologist or optometrist
  
  • One A1C value during the last 3 to 4 months
  
  • Log of BG measurements during the last 6 months from a memory-equipped BG meter. [Grade D, consensus]

**Prevention of hypoglycemia for insulin-treated commercial drivers**

• The supplies required to be carried at all times while driving include:
  
  • SMBG equipment and
  
  • Source of rapidly absorbable carbohydrate within easy reach in the vehicle. [Grade D, consensus]

• BG level must be tested within 1 hour before driving and approximately every 4 hours while driving. Driving should be stopped if the BG level falls below 6.0 mmol/L and not resumed until the BG level has risen to ≥6.0 mmol/L after food ingestion. [Grade D, consensus]
**Pilots**

Civil Aviation Medicine branch of Transport Canada. Canadian guidelines for the assessment of medical fitness in pilots, flight engineers, and air traffic controllers with diabetes mellitus.  

- BG must be tested prior to flight and be greater than **6.0 mmol/L**. BG must be monitored every 30 minutes during flight.
- If, for operational reasons, the in-flight 30-minute BG measurement cannot be done, then 10 gm carbohydrate must be ingested. This, however, shall not be done on two consecutive 30-minute occasions without a BG measurement.
- The BG should be measured 30 minutes prior to landing.
- If the BG falls below **6.0 mmol/L** then 10 gm carbohydrate must be ingested.
- If the BG exceeds **15 mmol/L** then the individual should land as soon as possible and take corrective therapeutic measures.

**Air Traffic Controllers treated with insulin**

- Blood glucose levels will be tested  
  - 30 minutes prior to shift commencement  
  - Every 2 hours during shift  
- If, because of operational requirements, the 2 hourly BG cannot be done then the individual must consume at least 10 gm glucose as a snack or drink  
- No two consecutive BG estimations may be substituted by a snack.  
- If the BG falls below **3.5 mmol/L**, the individual should stop work, take at least 10 gm of readily absorbable glucose and recheck BG within 30 minutes until BG is **5.5 mmol/L** or greater.  
- If the BG is between **16.5 and 22 mmol/L**, the individual should take appropriate action to lower BG (i.e. with insulin and/or exercise) and recheck BG in 30 minutes.  
- If BG > **22 mmol/L**, the individual should stop work and take corrective action (insulin), and then recheck BG every 30 minutes until BG <22 mmol/L before resuming work.  
- If the controller experiences blurring of vision, the individual should cease work and check BG.
Train operators or controllers treated with diet and insulin or insulin secretagogues (sulfonylureas and meglitinides)


- BG monitoring is required as: Glucose readings performed at least 8 times per week. The measurements must cover the whole day, by including measurements before or after each meal, and at bedtime. At least half the measurements must be done during a working shift.
- Glucose values must be maintained above 4 mmol/L, with additional food being taken when glucose is less than 4 mmol/L.
- The individual must maintain a record of down-loaded glucose meter logs from the previous six months.
- The previous 3 month down-loaded glucose meter logs should be reviewed and commented on by a treating physician annually for individuals treated with OAD, while by a treating physician at the 6 month point of each year and by a specialist in diabetes at the 12 month point for individuals treated with insulin.
Appendix 4 Oral Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin Secretagogues (Sulfonylureas)</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Generics</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Diamicron, generics</td>
</tr>
<tr>
<td>Gliclazide, long acting</td>
<td>Diamicron MR</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl, generics</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Diabet, generics</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Generics</td>
</tr>
<tr>
<td><strong>Insulin Secretagogues, Meglitinides</strong></td>
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<tr>
<td>Nateglinide</td>
<td>Starlix</td>
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<tr>
<td>Repaglinide</td>
<td>GlucoNorm</td>
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<tr>
<td><strong>Biguanides</strong></td>
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<tr>
<td>Metformin</td>
<td>Glucophage, Glumetza, generics</td>
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<tr>
<td><strong>Alpha-glucosidase Inhibitors</strong></td>
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</tr>
<tr>
<td>Acarbose</td>
<td>Glucobay</td>
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<tr>
<td><strong>Thiazolidinediones (TZDs)</strong></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Actos, generics</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Avandia</td>
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<tr>
<td><strong>Dipeptidyl peptidase-4 Inhibitors (DPP-4s)</strong></td>
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</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td><strong>Combination Products</strong></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone/ glimepiride</td>
<td>Avandaryl</td>
</tr>
<tr>
<td>Rosiglitazone/metformin</td>
<td>Avandamet</td>
</tr>
<tr>
<td>Sitagliptin/metformin</td>
<td>Janumet</td>
</tr>
</tbody>
</table>

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References


