



Basal Insulins for Type 2 Diabetes: How Does Insulin Choice Affect the Risk of Hypoglycemia and Medication Cost?

B.C. Provincial Academic Detailing Service

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Background:

Clinical practice guidelines recommend insulin for people with type 2 diabetes characterized by metabolic decompensation, unintentional weight loss, or marked or symptomatic hyperglycemia.^{1,2} In asymptomatic patients, when glycemic targets are not achieved with combinations of non-insulin glucose-lowering medications, they also recommend intensifying therapy beginning with a basal insulin (intermediate or long acting) and potentially progressing to a basal plus bolus (prandial) regimen.^{1,2}

Compared to non-insulin glucose-lowering medications, insulin increases the risk of hypoglycemia.^{3,4} Bolus insulin and basal plus bolus combination regimens increase the risk of hypoglycemia compared to basal insulin.⁴ In community and hospital practice and during transitions of care, the Institute for Safe Medication Practices (ISMP) identifies insulin as a high-alert medication that is error prone.⁵⁻⁷ Recently this has been complicated further by the availability of high-concentration formulations of some insulins.^{8,9}

Several basal insulins and formulations are available in Canada. They include: NPH (Humulin N, Novolin ge NPH), glargine (Basaglar, Lantus, Toujeo), detemir (Levemir) and degludec (Tresiba). The primary objective of the drug approval process involves demonstrating that the new basal insulin is non-inferior for hemoglobin A1C (HbA1C) lowering when compared to a previously-approved basal insulin.¹⁰⁻¹⁴ The drug approval process does not require confirmation that differences in onset of action, time to peak effect or duration of action translate into reductions in diabetes-related morbidity, mortality or risk of hypoglycemia.¹⁰⁻¹⁴

Participants in this PAD education session will have the opportunity to discuss:

1. Evidence for the comparative hypoglycemia risk of basal insulins and medication costs for people with type 2 diabetes
2. Relevant clinical considerations when prescribing and monitoring basal insulin therapy for people with type 2 diabetes
3. How different guidelines weigh the value of intensifying glucose-lowering medications to achieve tight glycemic control in people with type 2 diabetes

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Evidence for Practice: Hypoglycemia Risk Differences for Basal Insulins

The comparative hypoglycemia risk between basal insulins cannot be confidently estimated

- ❖ Systematic reviews that examine clinical trials comparing basal insulin analogues (glargine, detemir) to NPH insulin and the more recently approved basal insulin analogues to glargine, do identify a lower relative risk for some hypoglycemia outcomes.¹⁻⁵
 - However, they do not reach firm conclusions on whether a meaningful number of people benefit from the choice of one basal insulin over another (low to very-low quality evidence).¹⁻⁵
 - Calculating absolute risk reductions and numbers needed to treat from low to very-low quality evidence introduces significant uncertainty into these summary estimates.¹⁻⁵
 - The quality of evidence of basal insulin trials is limited due to the open-label design of most trials and lack of standardized or specific hypoglycemia definitions.¹⁻¹⁵
- ❖ The U.S. Food and Drug Administration (US FDA), at the time of regulatory review, did not approve claims that any basal insulin lowers the risk of hypoglycemia compared to another.⁶⁻¹⁰
- ❖ Concurrent use of other glucose-lowering medications and bolus (prandial) insulin varies across trials, introducing important differences in the frequency of hypoglycemia.^{1,16}

Basal insulin choice is unlikely on its own to mitigate the risk of hypoglycemia for most people

- ❖ A 2018 systematic review of basal insulin analogue trials judged that the risk of bias was high for almost all of the trials reporting hypoglycemia outcomes.⁴ One trial (DEVOTE 2017) was described as low risk of bias.
- ❖ This double-blind, cardiovascular, non-inferiority trial compared degludec 100 units/mL (Tresiba) to glargine 100 units/mL (Lantus), in combination with other glucose-lowering medications in 7637 participants with type 2 diabetes.^{17,18}
 - The mean age of participants was 65 years, mean HbA1C 8.4%, mean diabetes duration 16 years, 85% had cardiovascular or moderate chronic kidney disease, 84% had previously received insulin.
 - Insulin doses were adjusted weekly aiming for an intensive fasting blood glucose goal of 4 to 5 mmol/L for most people.
 - Severe hypoglycemia* occurred in both groups: 4.9% of people in the degludec group and 6.6% of people in the glargine group (OR 0.73, 95%CI 0.60 to 0.89; median 2 years).
 - Randomization to degludec rather than glargine did not change this outcome for 98 out of 100 people.

*severe hypoglycemia: an event requiring assistance from another person to administer carbohydrate, glucagon or take other corrective actions; severe hypoglycemia is considered the most specific hypoglycemia outcome by the US FDA

Glucose targets used in basal insulin trials may limit generalizability to clinical practice

- ❖ In a 2018 systematic review of basal insulin analogues, the average trial participant was 58 years of age with a type 2 diabetes diagnosis for 11 years, an HbA1C of 8.4% and a body weight of 87 kg.⁴
- ❖ Basal insulin trials generally exclude participants with a history of severe hypoglycemia.⁶⁻¹⁰
- ❖ Basal insulin trials typically titrate basal insulin to fasting glucose levels in the range of 4 to 7 mmol/L to align with HbA1C targets of $\leq 7\%$.
 - This potentially limits the generalizability of any hypoglycemia risk differences to clinical practice if such tight control is not the goal of therapy.^{5,11,19-21}

Table 1: Guideline Recommendations – Glycemic Targets for Type 2 Diabetes

- ❖ Contemporary guidelines reach discordant conclusions on the value of intensifying glucose-lowering medications to achieve HbA1C targets $\leq 7\%$ in people with type 2 diabetes.^{1,2}

DIABETES CANADA 2018¹ <http://guidelines.diabetes.ca/>

Glycemic targets should be individualized

- **HbA1C $\leq 7\%$:** target for most people with diabetes to reduce the risk of microvascular and, if implemented early in the course of disease, cardiovascular complications
- **HbA1C $\leq 6.5\%$:** may be targeted to reduce the risk of chronic kidney disease and retinopathy, if assessed to be at low risk of hypoglycemia based on class of antihyperglycemic medication(s) utilized and the person's characteristics
- **FPG or preprandial 4 to 7 mmol/L:** to achieve an HbA1C $\leq 7\%$, people with diabetes should aim for:
 - a. FPG or preprandial target of 4 to 7 mmol/L and a 2-hour PPG target of 5 to 10 mmol/L
 - b. Further FPG lowering to 4 to 5.5 mmol/L and/or PPG lowering to 5 to 8 mmol/L may be considered, but must be balanced against the risk of hypoglycemia
- **Higher HbA1C target:** may be considered with the goals of avoiding hypoglycemia and over-treatment
 - a. Functionally dependent: 7.1 to 8%
 - b. Recurrent severe hypoglycemia, hypoglycemia unawareness; limited life expectancy; frail elderly and/or dementia: 7.1 to 8.5%
 - c. End of life: HbA1C measurement not recommended; avoid symptomatic hyperglycemia and any hypoglycemia

- **HbA1C targets and corresponding preprandial capillary blood glucose targets:³**

HbA1C $\leq 7\% \rightarrow$ 4 to 7 mmol/L

HbA1C 7.1 to 8.0% \rightarrow 5 to 8 mmol/L

HbA1C 7.1 to 8.5% \rightarrow 6 to 9 mmol/L

AMERICAN COLLEGE OF PHYSICIANS 2018² <https://www.acponline.org/clinical-information/guidelines>

Personalize goals for glycemic control on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, general health and life expectancy, treatment burden, and costs of care

- **HbA1C $< 7\%$:** studies have not consistently shown that intensive glycemic control to HbA1C $< 7\%$ reduces clinical microvascular events, such as loss or impairment of vision, end-stage renal disease, or painful neuropathy, or reduces macrovascular events and death
- **HbA1C 7% to 8%:** aim to achieve in most people with type 2 diabetes (non-pregnant adults)
- **HbA1C $< 6.5\%$:** consider de-intensifying pharmacologic therapy
- **Avoid targeting HbA1C:** treat to minimize symptoms related to hyperglycemia
 - a. life expectancy less than 10 years due to advanced age (80 years or older)
 - b. residence in a nursing home
 - c. chronic conditions (such as dementia, cancer, end-stage kidney disease, severe chronic obstructive pulmonary disease, congestive heart failure)

HbA1C hemoglobin A1C; FPG fasting plasma glucose; PPG preprandial plasma glucose

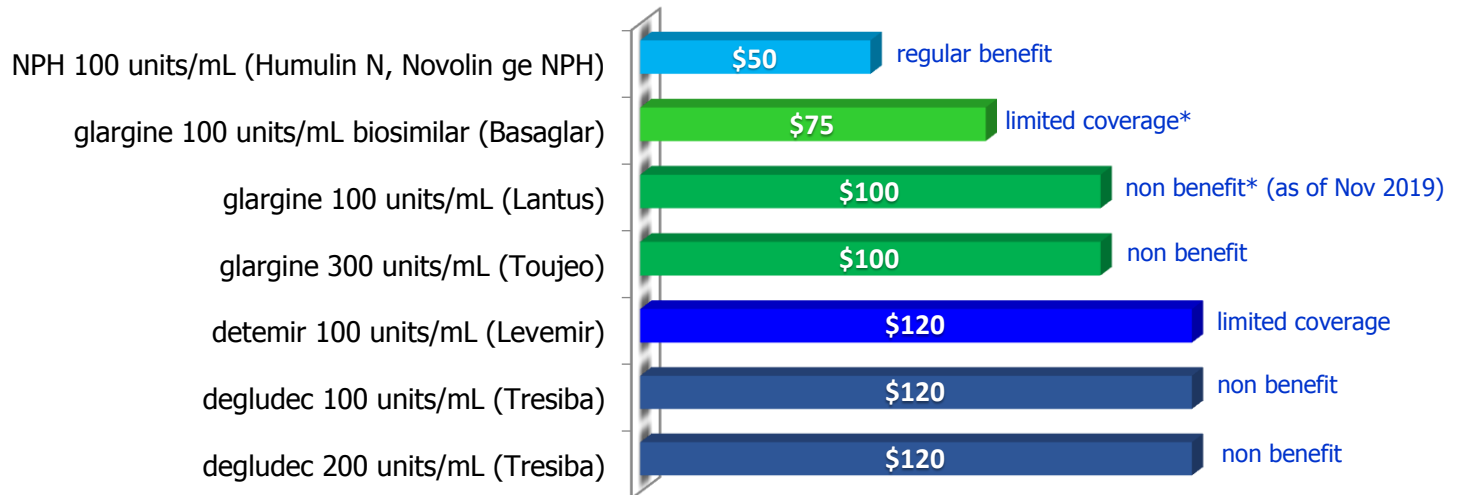
Table 2: Clinical Considerations of Basal Insulins for Type 2 Diabetes

Basal Insulin Brand Name	Clinical Considerations¹⁻¹³
NPH neutral protamine Hagedorn 100 units/mL Humulin N Novolin ge NPH	<ul style="list-style-type: none"> ▪ Once a day at bedtime or twice a day dosing (must re-suspend) ▪ Only basal insulin which can be mixed in same syringe with bolus insulin (ie, regular, aspart, lispro): draw up regular insulin first; generally not advised to mix with aspart or lispro as binding occurs rapidly, must inject immediately after mixing ▪ Prefilled pen provides 1 to 60 units per single injection
glargine 100 units/mL Basaglar (biosimilar) Lantus	<ul style="list-style-type: none"> ▪ Once a day or twice a day dosing ▪ Health Canada: biosimilar = no clinically meaningful differences in pharmacokinetics, pharmacodynamics, clinical efficacy, safety or immunogenicity ▪ Prefilled pen provides 1 to 80 units per single injection
glargine 300 units/mL <i>high concentration</i> Toujeo	<ul style="list-style-type: none"> ▪ Once a day dosing ▪ Not bioequivalent to glargine 100 units/mL ▪ Minimum time between dose increases: 3 to 4 days ▪ Prefilled pen provides 1 to 80 units per single injection; dose counter shows exact number of units, if switching from another insulin, no dose recalculation required
detemir 100 units/mL Levemir	<ul style="list-style-type: none"> ▪ Once a day or twice a day dosing ▪ Prefilled pen provides 1 to 80 units per single injection
degludec 100 units/mL 200 units/mL <i>high concentration</i> Tresiba	<ul style="list-style-type: none"> ▪ Once a day dosing ▪ Minimum time between dose increases: 3 to 4 days ▪ 100 units/mL prefilled pen provides 1 to 80 units per single injection ▪ 200 units/mL prefilled pen provides 2 to 160 units per single injection; dose counter shows exact number of insulin units, if switching from another insulin, no dose recalculation required
<p>Insulin time-action profiles (onset of action, time to peak effect, duration of action):</p> <ul style="list-style-type: none"> ❖ Typically estimated from small studies enrolling healthy volunteers or people with type 1 diabetes, thereby limiting the clinical relevance to people with type 2 diabetes.¹⁴ ❖ Rate of absorption and duration of action of basal insulins are affected by dose, injection site, blood flow, temperature and physical activity level.^{2-5,8,11,12} ❖ Approximate duration of action as reported by the Health Canada product monographs: <ul style="list-style-type: none"> ▪ NPH (Humulin N, Novolin ge NPH): up to 24 hours^{2,3} ▪ glargine 100 units/mL (Basaglar, Lantus): up to 24 hours^{4,5} ▪ glargine 300 units/mL (Toujeo): up to 36 hours⁸ ▪ detemir 100 units/mL (Levemir): 6 to 24 hrs¹¹ ▪ degludec 100 units/mL, degludec 200 units/mL (Tresiba): up to 42 hours¹² 	

Basal insulins vary in their cost

- ❖ The cost of basal insulin ranges from approximately \$50 to \$120 for a 30-day supply.¹

Figure 1: British Columbia PharmaCare Coverage and Approximate Cost of a 30-day Supply of Basal Insulin for People with Type 2 Diabetes



Cost based on 1500 units which is roughly a 30-day supply at 0.6 units/kg/day for an 87 kg person; wholesaler drug cost without markup; each test strip plus lancet adds approximately \$1.35 per glucose test [calculated from McKesson Canada <https://www.mckesson.ca/> (Accessed May 21, 2019)]

*PharmaCare coverage of Lantus will end on November 26, 2019 (exception: patients covered under Plan W First Nations Health Benefits); Basaglar is a Regular Benefit for patients covered under Plan W

Risk Factors for Hypoglycemia¹⁻³

- ❖ Intensive glycemic control
- ❖ Polypharmacy
- ❖ Treatment with insulin or sulfonylurea
- ❖ Hypoglycemia unawareness
- ❖ Alcohol use
- ❖ Advancing age or frailty
- ❖ Cognitive impairment
- ❖ Impaired renal or hepatic function
- ❖ Longer duration of diabetes
- ❖ Lower health literacy
- ❖ Lower economic status and food insecurity

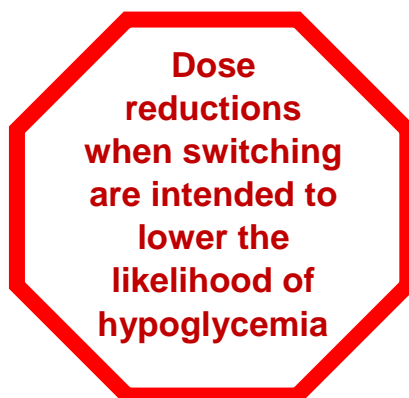
DO consider simplifying or de-intensifying glucose-lowering medications

Table 3: Initiation and Titration of Basal Insulin Based on Fasting Glucose Goals

Initiation	<ul style="list-style-type: none"> 10 units once a day or 0.1 to 0.2 units/kg once a day¹⁻³
Up Titration	<ul style="list-style-type: none"> Recommendations range from: <ul style="list-style-type: none"> Increase by 1 unit every day¹ Increase by 2 units every 3 days² Increase by 2 units every 7 days³ Note: the US FDA recommends a minimum of 3 to 4 days between dose increases of glargine 300 units/mL (Toujeo) and degludec (Tresiba)^{4,5} Reassess pharmacologic plan if basal insulin dose exceeds 0.7 to 1 unit/kg/day²
Down Titration	<ul style="list-style-type: none"> If hypoglycemia occurs, decrease basal insulin dose by 10 to 20%² See American Diabetes Association "Simplification of Complex Insulin Therapy" → http://care.diabetesjournals.org/content/42/Supplement_1/S139
Influence of other glucose-lowering medications	<ul style="list-style-type: none"> Other glucose-lowering medications should be reviewed for an opportunity for dose reduction or discontinuation to simplify the regimen and to reduce the risk of hypoglycemia (eg, sulfonylureas) Thiazolidinediones (pioglitazone, rosiglitazone): increased risk of new or worsening heart failure⁶ Sodium-glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin): sudden reduction of insulin dose or an increased requirement for insulin (illness, surgery, alcohol) are among the risk factors for SGLT2 inhibitor-associated diabetic ketoacidosis (which can be euglycemic)⁷⁻⁹

Switching Basal Insulins in Type 2 Diabetes¹⁻⁹

- ❖ Confirm insulin dose with the patient first given the medical chart and/or PharmaNet may not accurately reflect the most current insulin dosage
- ❖ Be aware of look-alike, sound-alike drug names: Lantus and levemir, glargine and glulisine, Novolin and Novolog, Humulin and Humalog

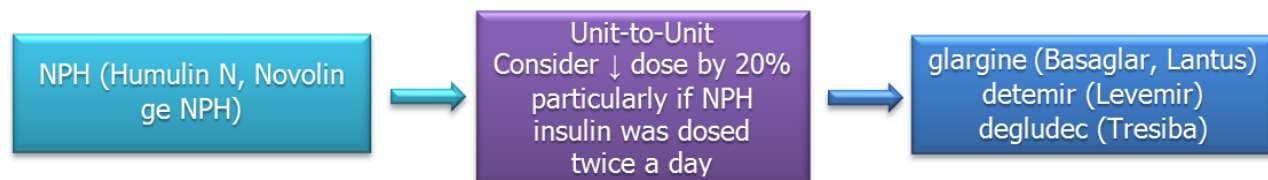
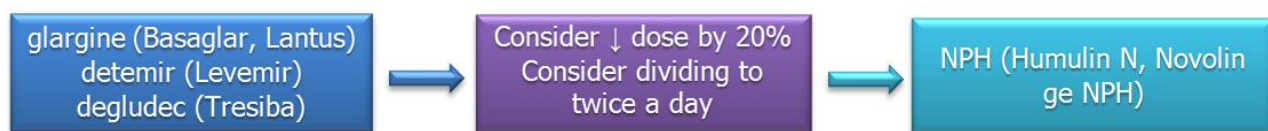
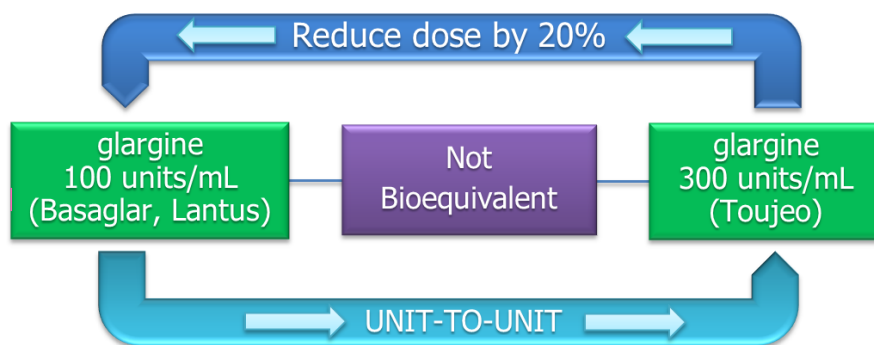


- ❖ Be aware that switching between insulins often involves switching insulin pen devices
- ❖ Be aware that there are multiple formulations and strengths of the same insulin (eg, glargine, degludec); specify units/mL on the prescription

‘When switching, think and act in units of insulin not millilitres’¹⁰
 ‘Dose counters on insulin prefilled pens correspond to units of insulin regardless of strength’¹⁰

Switching Basal Insulins in Type 2 Diabetes continued¹⁻⁹

- ❖ Some basal insulins are recommended to be switched unit-to-unit.²⁻⁶
- ❖ Other basal insulins are recommended to be switched with a 20% dose reduction to minimize the risk of hypoglycemia:
 - basal insulin dosed twice a day (NPH, Basaglar, Lantus, Levemir) to a basal insulin dosed once a day (Basaglar, Lantus, Toujeo or Tresiba)^{2,3,5-7}
 - any basal insulin dosed once a day to NPH insulin (consider also dividing the dose to twice a day)^{8,9}
 - glargine 300 units/mL (Toujeo) to a once a day 100 units/mL basal insulin (Basaglar, Lantus or Tresiba)^{2,3,5}
- ❖ Health Canada product monographs do not provide guidance on switching between all basal insulins. In these cases, consider reducing the dose by 20% to minimize the risk of hypoglycemia.⁸





Basal Insulins for Type 2 Diabetes:

How Does Insulin Choice Affect the Risk of Hypoglycemia and Medication Cost?

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Evidence to Practice

DO consider simplifying or de-intensifying glucose-lowering medications rather than switching to another basal insulin as a hypoglycemia risk reduction strategy.

- ❖ Overtreatment of type 2 diabetes in older adults with multimorbidity is common.¹⁻⁴
- ❖ Re-evaluation of the use of insulin or sulfonylureas in older adults to achieve tight glycemic control is recommended.^{5,6}

DO carefully document on the prescription: insulin type, insulin strength, starting dose, titration plan and glycemic goals.^{7,8}

- ❖ Avoid "U" as an abbreviation for the word "units".⁷
- ❖ "Subcut" is the preferred abbreviation for subcutaneous rather "SC" or "SQ".⁷
- ❖ Avoid the use of a decimal point and a zero after a whole number (eg, avoid 10.0).⁷

DO confirm that the insulin selected and the associated supplies (needles, glucose meter, strips, lancets) are **affordable and manageable** if recommending the addition of basal insulin.⁷

DO be aware that some basal insulins can be **switched unit-to-unit** while others may involve a **decrease in the dose**.

Reference list is available upon request.

Drug Costs are from McKesson Canada and are approximate without markup or professional fee:
<https://mckesson.ca/pharmaclik>

BC PharmaCare Formulary Search: <https://pharmacareformularysearch.gov.bc.ca/>

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