

*Canadian Agency for
Drugs and Technologies
in Health*

*Agence canadienne
des médicaments et des
technologies de la santé*

Insulin preparations: Which types for which patients? Examining the Evidence

Presenter, Title, Affiliation

Month 2009

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Do you have any affiliations (financial or otherwise) with a commercial organization that may have a direct or indirect connection to the content of the workshop?

Learning objectives

Upon completion of this workshop the participant will:

- Understand the evidence base supporting the use of human insulin and insulin analogues in the treatment of diabetes
- Identify the appropriate use of insulin preparations in:
 - The general population with diabetes
 - Special cases where insulin analogues should be considered.

Outline

Context

- Diabetes in Canada
- Physiology and pathophysiology of diabetes
- Options for insulin therapy

The evidence base for optimal therapy

- Scientific process
- Conclusions and recommendations

Where did the evidence come from?

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH is an independent, not-for-profit agency funded by 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.

Diabetes in Canada (Types 1 and 2 combined)

Prevalence

- In 2005-2006, approximately 1.9 million were diagnosed with diabetes
- One in 17 people had been diagnosed with diabetes
- The prevalence rate for both males and females was 5.9%

Incidence

- In 2005-2006, 199,471 individuals were newly diagnosed with diabetes - 6.4 per 1,000 overall

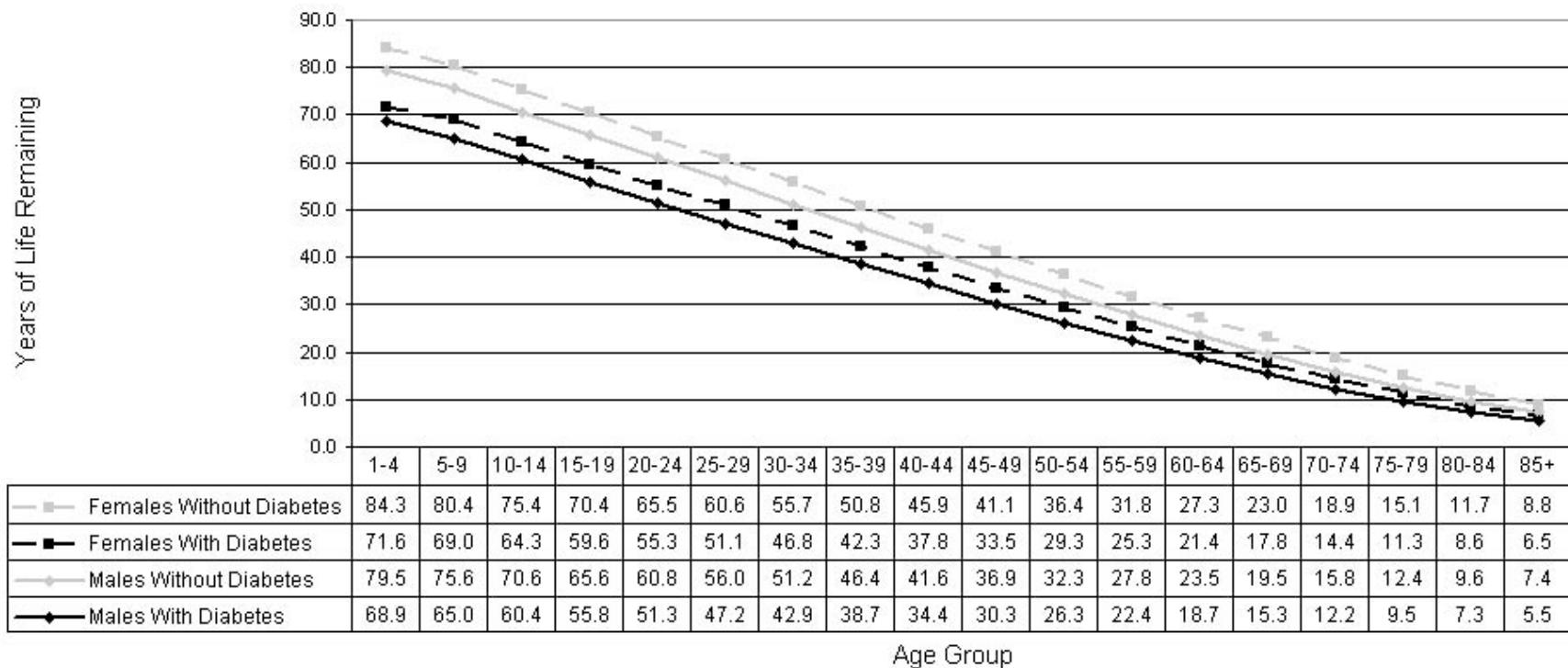
Diabetes in Canada

Disease burden

- Diabetes shortens life expectancy for all ages.
 - For example, 25 to 39-year old people with diabetes had an approximate nine year reduction in life expectancy in 2005-2006.

Years of life remaining

Figure 7. Years of Life Remaining for People With Diagnosed Diabetes
Compared to Those Without Diagnosed Diabetes, by Age Group,
Canada, 2004-2005



Source: Public Health Agency of Canada, using NDSS data files contributed by all provinces and territories; Life Table from Statistics Canada, August 2007

Source: PHAC, *Diabetes in Canada: highlights from the National Diabetes Surveillance System 2004-2005; 2008*. Reproduced with the permission of the Minister of Public Works and Government Services Canada; 2008.

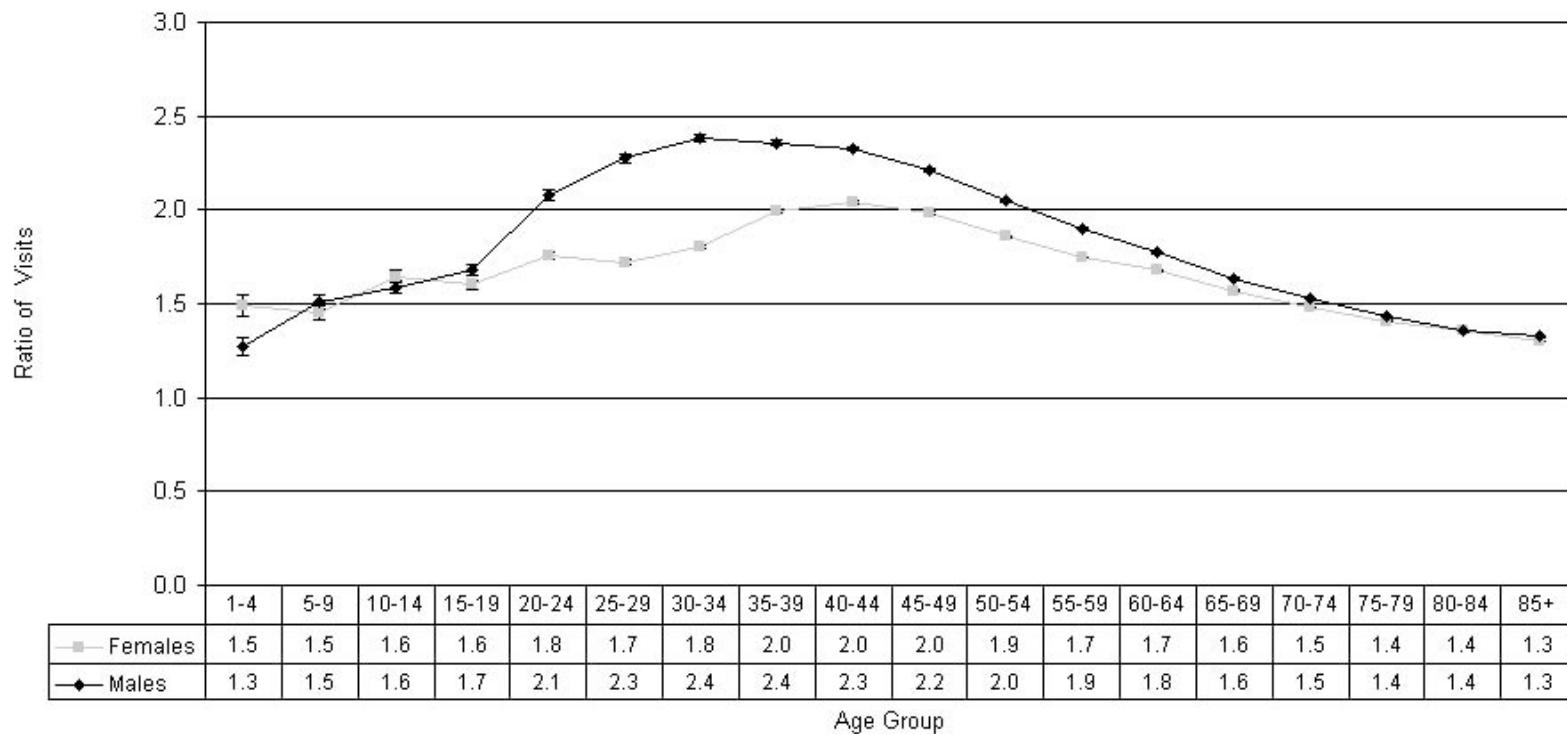
Diabetes in Canada: Disease burden

Among adults aged 20 years and older, compared to adults without diabetes, adults with diabetes were hospitalized:

- 23 times more often for lower limb amputations;
- seven times more often for chronic kidney disease;
- three times more often for hypertension or heart failure;
- three times more often for heart attack; and
- three times more often for stroke.

Ratio of visits

Figure 8. Ratio of Number of Visits to Family Physicians by People Aged 1 Year and Older With Diagnosed Diabetes Compared to Those Without Diagnosed Diabetes, Canada*, 2004-2005



Source: Public Health Agency of Canada, using NDSS data files contributed by all provinces and territories, as of October 31, 2007

†The 95% Confidence Interval shows an estimated range of values which is likely to include the true rate ratio 19 times out of 20.

*Québec and Nunavut data not included in analysis

Source: PHAC. *Diabetes in Canada: highlights from the National Diabetes Surveillance System 2004-2005*; 2008. Reproduced with the permission of the Minister of Public Works and Government Services Canada; 2008.

Physiology of insulin

Basal insulin secretion

- Background low-level continuous secretion
- Prevents keto-acidosis

Variable biphasic meal-stimulated secretion

- first phase rapid
- second phase lasts longer

Insulin-receptor binding stimulates glucose uptake by target tissues

Eaton, et al. *J Clin Endocrinol Metab* 1990;71:1508-1518.

Polonsky, et al. *J Clin Invest* 1988;81:442-448.

Kruszynska, et al. *Diabetologia* 1987;30:16-21.

Polonsky, et al. *J Clin Invest* 1986;77:98-105.

Waldhaus, et al. *Diabetologia* 1979;17:221-227.

Insulin secretion in a person without diabetes

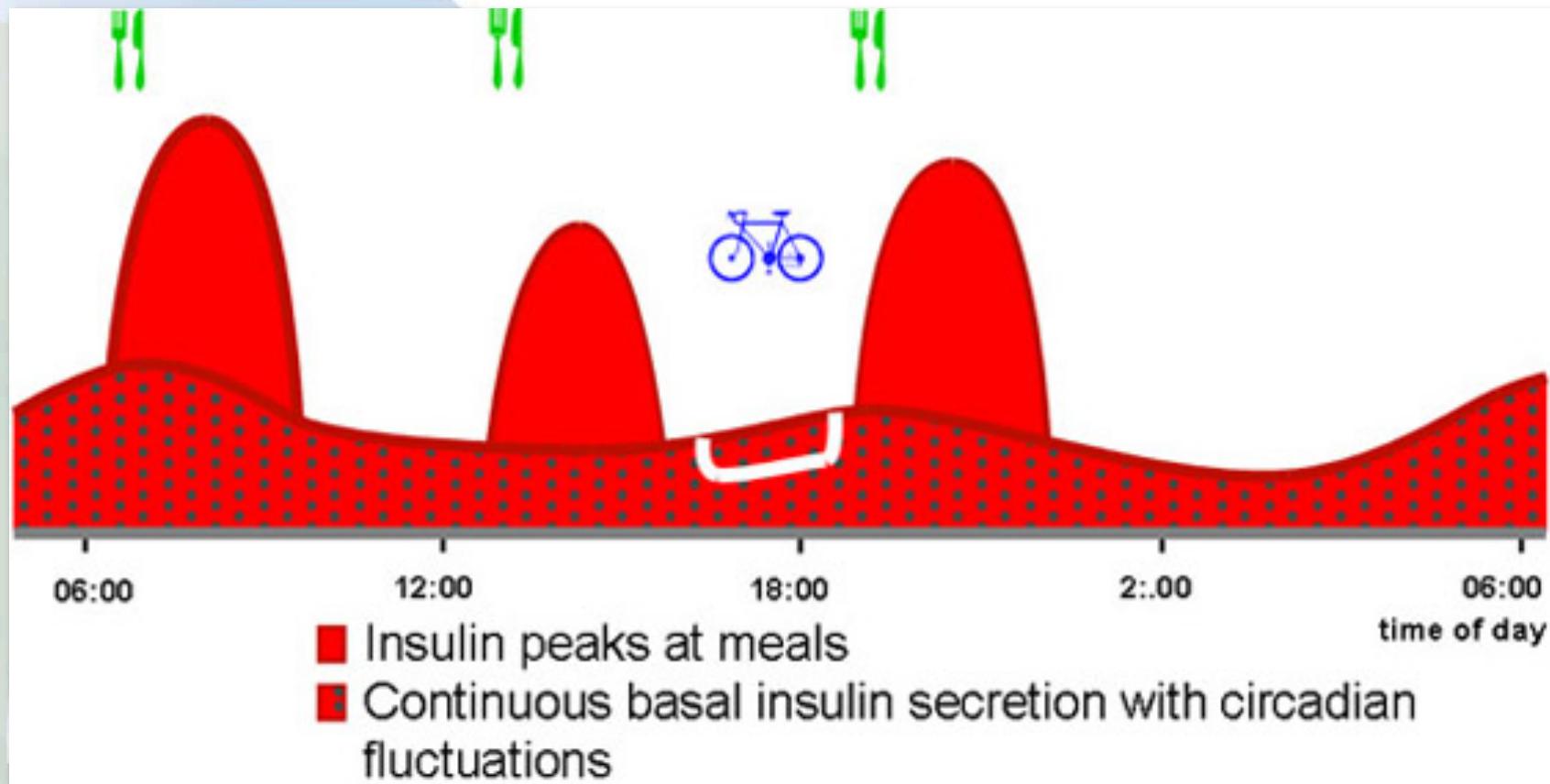


Image used with permission from: *Why use pump therapy?* Warwick (UK): Advanced Therapeutics (UK) Ltd; 2009.

Diabetes types: Insulin requirements

Type 1: autoimmune. Complete insulin deficiency

- Always requires insulin treatment

Type 2: insulin resistance and progressive loss of insulin secretory ability

- Initial pharmacologic treatment with oral agents for most patients
- Patients may require insulin at a later date

Pregnancy

- Gestational Diabetes: similar to temporary type 2 diabetes; insulin therapy initiated if glycemic targets not achieved after 2 weeks from nutrition therapy alone
- Women with type 1 and type 2 diabetes have additional management issues when pregnant

Human insulin

- **Genetically-engineered production from bacteria**
- **Different types have different pharmacokinetics due to solubility of diluent which affects absorption**
- **Brand names: “Humulin®, Novolin ®”**
- **“Prandial” or “Bolus” or Short-acting**
 - “R”, “Regular”, “Toronto”
 - Onset 30 minutes, peak 2-3 hours, duration 6.5 hours

Human insulin (cont'd)

- “Basal” or Intermediate-acting
 - “N”, “NPH”
 - Onset 1-3 hours, peak 5-8 hours, duration up to 18 hours
- Mixture of these two types:
 - 30/70 (30%R and 70%N), 50/50

Insulin analogues

Modified structures to change pharmacokinetics

- Switching sequences of amino acids (lispro, aspart)
- Addition of amino acids (glargine) or fatty acid moiety (detemir)

Rapid-acting insulin analogues: (“Bolus” insulins)

- Lispro (Humalog®) and aspart (NovoRapid®)
- Onset 10-15 min, peak 1-2 hours, duration 3-5 hours

Insulin analogues (cont'd)

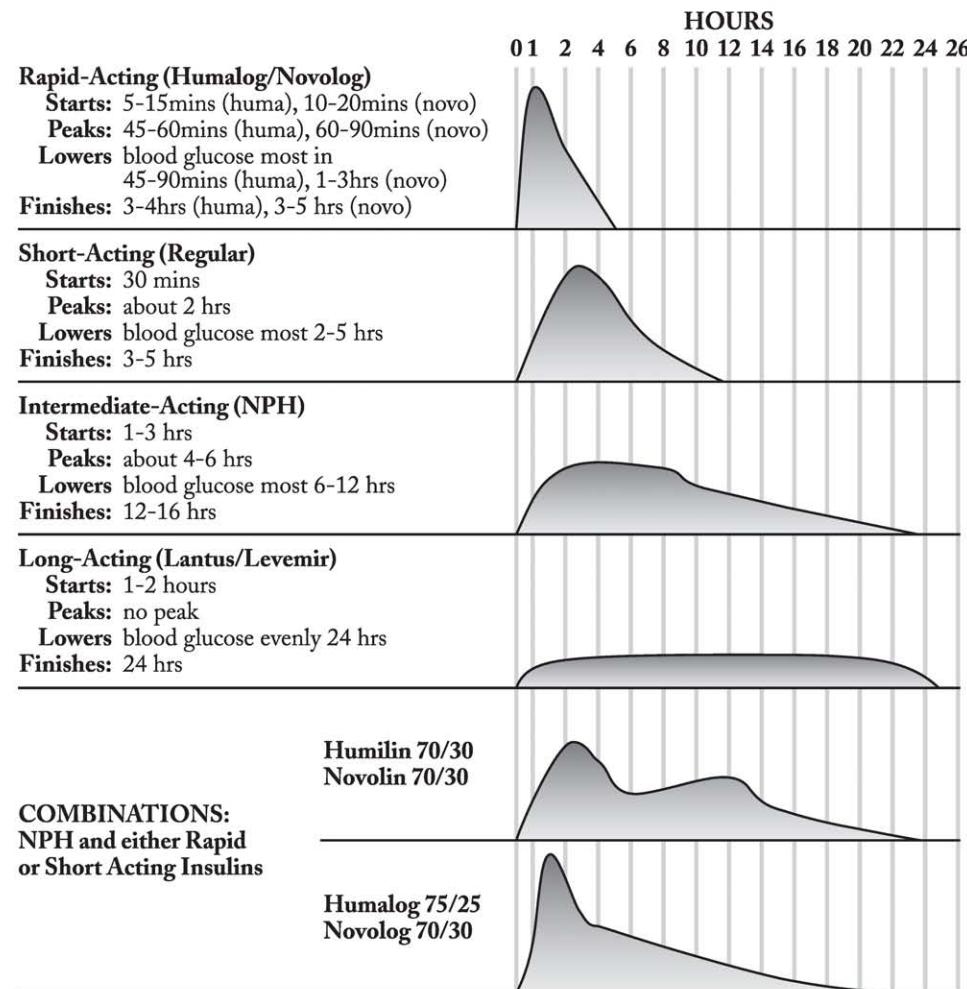
Long-acting insulin analogues: (“Basal” insulins)

- Glargine (Lantus®) and detemir (Levemir®)
- Onset 90 minutes, no peak, duration glargine 24 hours, detemir 16-24 hours

“Biphasic” mixtures containing short-acting analogues and intermediate acting insulins

- Humalog Mix 25® or Mix 50® and NovoMix 30®

Pharmacokinetics of insulins



American Diabetes Association. The term "Novolog®" is the international name for what is called "NovoRapid ®" in Canada.
Used with permission.

Developed by University of Michigan Health System from original material - American Diabetes Association; October 2008.

Approximate unit costs of basal insulins*

Vial, 1x 10 mL, 100 units/mL:

- Lantus®=\$56.80
- Humulin® N=\$18.90
- Novolin® NPH=\$19.40

Cartridge, 5x3 mL, 100 units/mL

- Lantus®=\$85.20
- Levemir®=\$109.80
- Humulin® N=\$36.90
- Novolin® NPH=\$37.95

*Costs are current as of December, 2008 and may vary between regions and over time.

Approximate unit costs of bolus insulins* (cont'd)

Vial, 1x 10 mL, 100 units/mL:

- NovoRapid®=\$26.90
- Humalog ®=\$25.80
- Humulin ® R=\$18.90
- Novolin ® ge Toronto=\$19.40

Cartridge, 5x3 mL, 100 units/mL:

- NovoRapid ®=\$53.70
- Humalog ®=\$51.60
- Humulin ®R=\$37.95
- Novolin ® Toronto=\$38.10

*Costs are current as of December, 2008 and may vary between regions and over time.

Studying the evidence: COMPUS Expert Review Committee

BC	Dr. M. Dahl	Endocrinologist
BC	Dr. E. Ur	Endocrinologist
BC	Dr. A. Virani	Pharmacist
AB	Dr. S. Klarenbach	Nephrologist/Epidemiologist
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SK	Dr. M. Caughlin	Family Physician
MB	Dr. H. Dean	Pediatric Endocrinologist
ON	Dr. L. Dolovich	Pharmacist/Health Economist
ON	Dr. M. Evans	Family Physician/Practice Support
ON	Panos Petrides	Public Member
NS	Dr. M. Allen	Family Physician/Health Education
NS	Cathy MacNutt	Public Member

Scientific process: Selection of clinical outcomes

- **Surrogate outcomes:**
 - A1C
 - Fasting plasma glucose
 - Two hour post-prandial glucose
- **Short-term complications:**
 - Severe hypoglycemia
 - Nocturnal hypoglycemia
 - Overall hypoglycemia

CADTH. *Optimal Therapy Report - COMPUS 2008;2(1)*.

CADTH. *Optimal Therapy Report - COMPUS 2008;2(2)*.

Scientific process: Selection of clinical outcomes (cont'd)

- **Long-term complications/mortality**
- **Other surrogates: weight gain, BMI, blood pressure, LDL, % of patients A1C<7.0%**
- **Health-related quality of life and patient satisfaction**
- **Health care resource use**

CADTH. *Optimal Therapy Report - COMPUS* 2008;2(1).

CADTH. *Optimal Therapy Report - COMPUS* 2008;2(2).

Scientific process: Systematic review

Systematic Review

- Search of world literature for studies of relevance
- Previous systematic reviews and meta-analyses
- Primary studies: Randomized-controlled (RCT), non-randomized controlled, and observational studies all considered
- Two independent researchers then rate studies for inclusion (e.g., excluded if target outcomes not obtainable)
- Quality of evidence depends on study design, conduct and analysis
- For this project:
 - 123 articles were included in the systematic review

CADTH. *Optimal Therapy Report - COMPUS* 2008;2(1).

CADTH. *Optimal Therapy Report - COMPUS* 2008;2(2).



Considering the evidence

Studies first analyzed for evidence of clinical benefit and harm

- Safety, effectiveness and clinically-important differences (if any)

Results then analyzed on the basis of cost for clinical benefit

Recommendations formulated

- based on efficacy, safety and pharmacoeconomic data
- “GRADE” process ranks the quality of evidence and the strength of each recommendation

Feedback sought from advocacy groups and industry

Information gaps

Human insulins and insulin analogues:

- Most studies look at surrogate outcomes (lab tests, clinical measurements such as blood pressure, weight) and short-term complications (hypoglycemia)

Virtually no studies on important long-term outcomes yet: diabetes related mortality, and microvascular and macrovascular disease

Example of scientific process

In patients with type 2 diabetes on oral antidiabetes drugs who also require a basal insulin:

Are there advantages for either NPH or glargin?

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs

Clinical Outcomes:

- A1C
- Fasting plasma glucose
- Severe hypoglycemia
- Nocturnal hypoglycemia
- Overall hypoglycemia
- Long-term complications/mortality
- Surrogates: weight gain, BMI, blood pressure, LDL, % of patients A1C<7.0
- Health-related quality of life and patient satisfaction

Cost-effectiveness

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes agents: A1C

Nine randomized-controlled studies

N= 3,397 patients

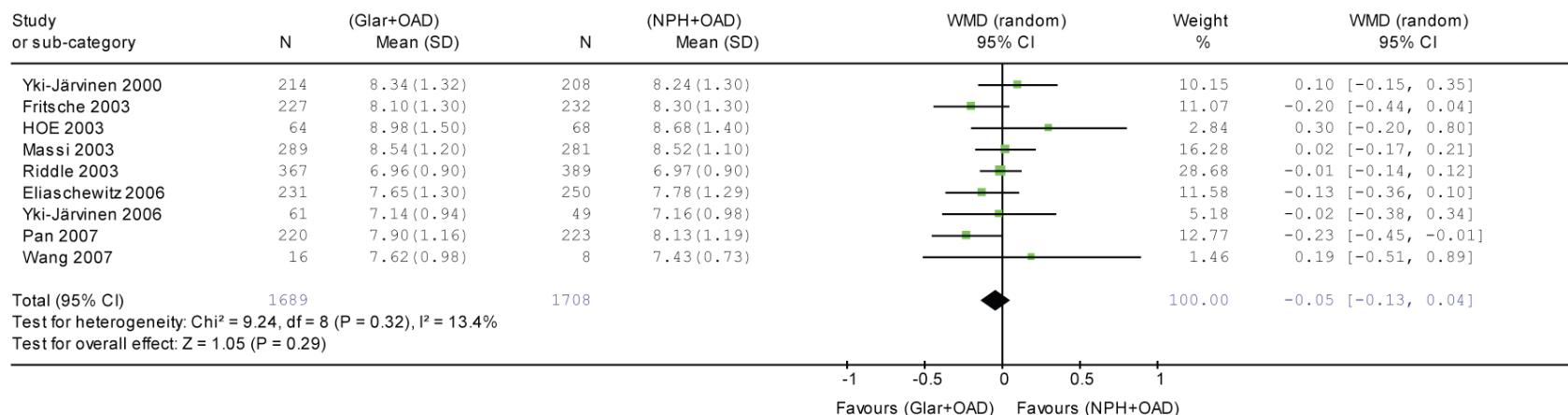
No significant difference in A1C

Pooled estimates within each of the subgroups of oral antidiabetes drugs (sulfonylurea, metformin or various) showed slight but not clinically significant differences

Forest plot of A1C from all RCTs

examining Glargine vs. NPH + in adult patients with type 2 diabetes on oral antidiabetes drugs – A1C, WMD

Review: LAIA T2 DM &T1 Pediatrics (Version 02)
 Comparison: 10 (Glar+OAD) vs (NPH+OAD) in LA Type 2 DM
 Outcome: 01 HbA1c in LA Type 2 DM patients no subcategory



A1C=Glycosylated hemoglobin; CI=Confidence interval; Glar=Insulin glargin; NPH=Neutral protamine Hagedorn; OAD=Oral antidiabetes drug; RCT=Randomized controlled trial; SD=Standard deviation; WMD=Weighted mean difference

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs

Outcome	# RCTs (Total sample size)	Effect estimate (95% CI)
A1C	9 (N=3,397)	-0.05 (-0.13 to 0.04)
Fasting Plasma Glucose	6 (N=2,406)	-0.10 (-0.28 to 0.07)
Severe hypoglycemia (relative risk)	7 (N=2,866)	0.66 (0.29 to 1.48)
Nocturnal hypoglycemia (relative risk)	7 (N=2,532)	0.56 (0.47 to 0.68)
Overall hypoglycemia (relative risk)	8 (N=2,642)	0.87 (0.81 to 0.93)
Other surrogates	Weight, BMI, blood pressure, LDL	No difference
Long-term complications: Ischemic heart disease		No difference
Long-term complications: other		Insufficient data
Health-related Quality of Life/Patient Satisfaction		Explanation: Next slides
Cost-effectiveness		Explanation: Next slides

A1C=Glycosylated hemoglobin; BMI=Body mass index; CI=Confidence interval; LDL=Low-density lipoprotein; RCT=Randomized controlled trial;

Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs (cont'd)

Health-related quality of life and patient satisfaction

- Mean improvement score in treatment satisfaction significantly favoured glargine over NPH:
 - 1 RCT, N=481, moderate quality study

Cost-effectiveness

- How is this determined?

Cost-effectiveness

Difference in treatment cost between strategies:

- \$4,945 more expensive for glargine
- Difference in Quality-Adjusted Life Years (QALY): A commonly used measure of health and life-span
 - incremental benefit of 0.008 QALY with glargine

Incremental cost-utility analysis

- Cost of glargine – cost of NPH/QALYs glargine-QALYs NPH
- There is no concrete cost-effectiveness threshold used in Canada
 - Published cost-effectiveness thresholds have ranged from \$20,000/QALY - \$100,000/QALY
- Glargine vs. NPH: \$642,994/QALY gained

CADTH. *Optimal Therapy Report - COMPUS* 2008;2(1). Laupacis, et al. *CMAJ* 1992;146(4):473-81.

Culyer, et al. *J Health Serv Res Policy* 2007;12(1):56-8. McCabe, et al. *Pharmacoeconomics* 2008;26(9):733-44.

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Rawlins, et al. *BMJ* 2004;329(7459):224-7.



Glargine vs. NPH in patients with type 2 diabetes on oral antidiabetes drugs

Recommendation:

- NPH be used in preference to glargine in most adults with type 2 diabetes taking oral antidiabetes drugs who require a basal insulin

Primary consideration:

- The incremental cost of glargine over insulin NPH outweighs its modest clinical benefit in this situation

Strength of recommendation: “Strong”

Quality of clinical evidence: “Moderate”

Glargine vs. NPH: Type 1 diabetes (adults)*

Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	8 (N=2,406)	-0.12 (-0.25 to -0.01) reduction with glargine
Severe hypoglycemia (relative risk)	6 (N=2,113)	0.81 (0.49 to 1.36)
Nocturnal Hypoglycemia (relative risk)	5 (N=1,943)	0.97 (0.87 to 1.09)
Overall Hypoglycemia (relative risk)	5 (N=1,893)	1.02 (0.97 to 1.07)
Weight	3 (N=1,138)	Favoured glargine
Long-term complications/mortality		Retinopathy no difference
HRQoL and Patient satisfaction	1 (N=517)	No difference reported for HRQoL. Patient satisfaction favoured glargine.
Cost effectiveness		\$87,932 per QALY gained

A1C=Glycosylated hemoglobin; CI=Confidence interval; HRQoL=Health-related quality of life; QALY=Quality-adjusted life year;
RCT=Randomized controlled trial;

*Common pre-meal bolus insulin in both treatment study groups

Detemir vs. NPH: Type 1 diabetes (adults)*

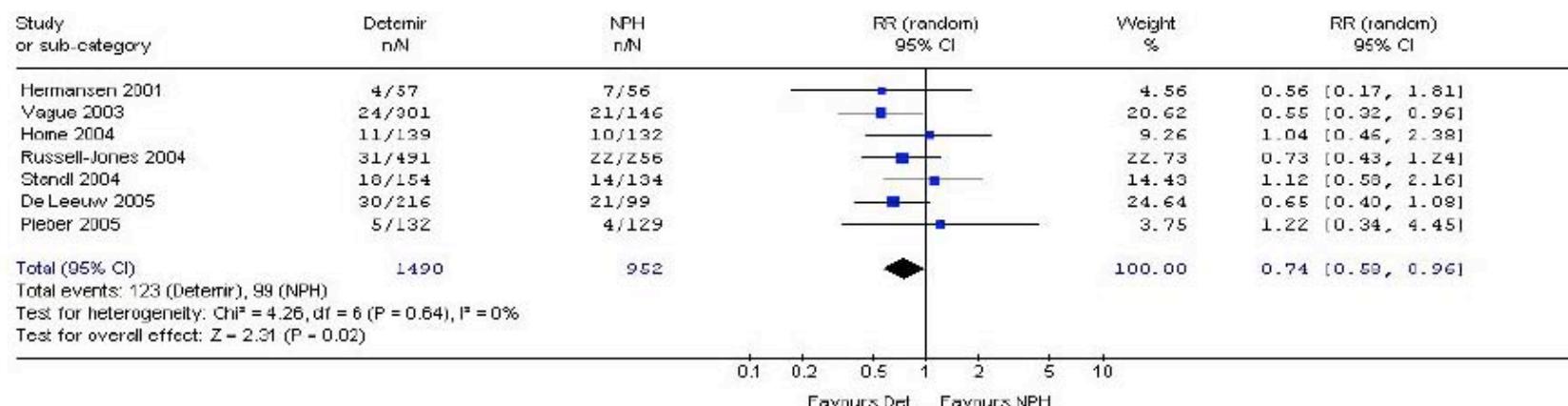
Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	7 (N=2,558)	-0.06 (-0.13, 0.02) No statistical difference
Severe hypoglycemia (relative risk)	7 (N=2,442)	Favoured detemir
Nocturnal Hypoglycemia (relative risk)	6 (N=2,311)	Favoured detemir
Overall Hypoglycemia (relative risk)	6 (N=2,110)	No difference
Weight	6 (N=2,302)	Favoured detemir
Long-term complications/all cause mortality		No difference
Patient satisfaction	No studies	Not applicable
Cost effectiveness		\$387,729 per QALY gained

A1C=Glycosylated hemoglobin; CI=Confidence interval; QALY=Quality-adjusted life year; RCT=Randomized controlled trial;

*Common pre-meal bolus insulin in both treatment study groups

Forest plot of the relative risk of severe hypoglycemia (number of patients with at least one episode) from all RCTs examining Detemir vs. NPH in adult patients with type 1 diabetes

Figure 13: Forest plot of all RCTs that examined the use of IDet versus NPH for the treatment of type 1 DM in adult patients – RR of severe hypoglycemia: Number of patients with at least one episode



DM=Diabetes mellitus; CI=Confidence interval; IDet=Insulin detemir; NPH=Neutral protamine Hagedorn; RCT=Randomized controlled trial; RR=Relative risk

Long-acting insulin analogues and hypoglycemia

Some comparative studies demonstrated a reduced risk/incidence of hypoglycemia with long-acting insulin analogues vs. NPH

- Not observed consistently across studies
- Hypoglycemia not consistently defined

Adults with type 1 diabetes with prior severe recurrent hypoglycemia actually excluded from seven of nine trials comparing detemir with NPH

Long-acting insulin analogues: Key message

In patients with type 1 diabetes or type 2 diabetes requiring basal insulin, insulin NPH should be considered first.

Although the evidence is limited and inconsistent, patients experiencing significant hypoglycemia while using insulin NPH may benefit from long-acting insulin analogues.

Bolus insulin therapy (lispro or aspart) vs. regular insulin

Type 1 diabetes: (Children, adolescents, adults and pregnancy)

- No clinically significant differences in A1C, however there was a marginal benefit
- Hypoglycemia: marginal benefits in some studies for pump users and adults and adolescents on multiple doses
- Significant increase patient satisfaction
- \$673,041 per QALY gained is only for type 1 adults using MDI (lispro vs. human insulin);
- \$104,598 per QALY gained is for type 1 adults using MDI (aspart vs. human insulin)

Key message: Bolus insulin type 1 diabetes

In patients with type 1 diabetes, either regular human insulin or rapid-acting insulin analogues can be considered as first-line therapy (except in adolescent patients).

In adolescent patients with type 1 diabetes, rapid-acting insulin analogues may be considered as first-line therapy.

Bolus insulin type 1 diabetes special considerations

Regular human insulin may be preferred when

- Affordability is an important consideration

Consider rapid-acting insulin analogues when:

- Flexibility of administration with meals is of primary importance
- Significant hypoglycemia is experienced while using regular human insulin, or in cases where hypoglycemia is a major concern

Rapid-acting insulin analogues are preferred for adolescents using multiple daily injections

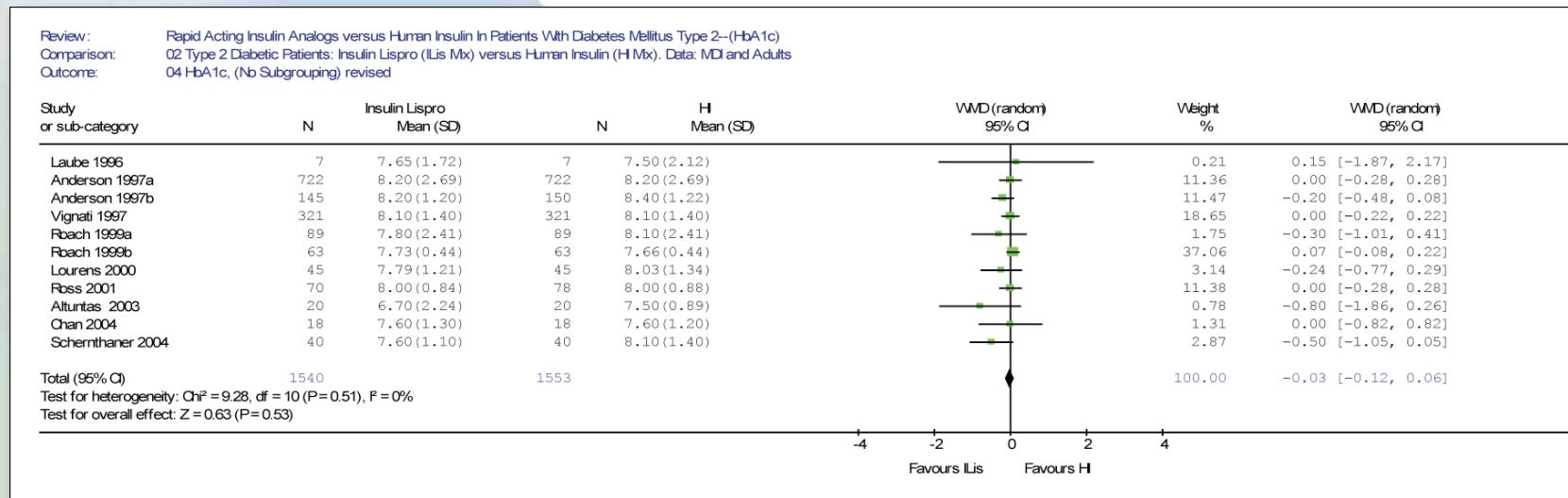
- Evidence for lispro
- A better fit for the unpredictable patterns of dietary intake and activity

Bolus insulin type 2 diabetes Lispro vs. regular insulin

Outcome	RCTs (Total sample size)	Effect estimate (95% CI)
A1C	11 (N=3,093)	No significant difference
Severe hypoglycemia (relative risk)	2 (N=1,622)	No significant difference
Nocturnal Hypoglycemia (relative risk)	1 (N=178)	No significant difference
Overall Hypoglycemia (relative risk)	3 (N=384)	No significant difference
Weight	3 (N=1,682)	No significant difference
All cause mortality	1 (N=80)	No significant difference
Patient satisfaction	1 (N=885)	No significant difference
Cost-effectiveness		\$130,865 per QALY gained

A1C=Glycosylated hemoglobin; CI=Confidence interval; QALY=Quality-adjusted life year; RCT=Randomized controlled trial;

Forest plot of A1C from all RCTs examining lispro or insulin lispro mix vs. human insulin in adult patients with type 2 diabetes – A1C, WMD



A1C=Glycosylated hemoglobin; CI=Confidence interval; DM=Diabetes mellitus; HI=Human insulin; ILis=Insulin lispro; QALY=Quality-adjusted life year; RCT=Randomized controlled trial; WMD=Weighted mean difference

Type 2 diabetes A1C, hypoglycemia and weight

No significant differences for lispro vs. human insulin as a single agent

No significant differences for A1C and overall hypoglycemia in insulin biphasic mixtures containing lispro vs. aspart

Other Evidence

Other meta-analyses suggest no general advantage of analogues over human insulins

- Institute for Quality and Efficiency in Health Care [IQWiG] (Germany) 2007

IQWiG. Rapid-acting insulin analogues in the treatment of diabetes mellitus type 1; 2007.



Key message: Bolus insulin

In patients with type 2 diabetes requiring bolus insulin, regular human insulin may be considered first.

- Although the evidence is limited and inconsistent, patients who are experiencing significant hypoglycemia while taking human insulin may benefit from rapid-acting insulin analogues.

Cases where insulin analogues should be considered

Adolescents with type 1 diabetes

- Insulin lispro is recommended as first line bolus insulin

Although the evidence is limited and inconsistent, patients with type 2 diabetes who are experiencing significant hypoglycemia while taking human insulin may benefit from rapid-acting insulin analogues

Other patient factors favoring analogue consideration:

- Flexibility of dose and meal timing for rapid-acting insulin analogues
- Increased patient satisfaction in some studies

Pregnancy

Type 1 diabetes in pregnancy

- Bolus insulin: either regular insulin or rapid-acting insulin analogues
- Basal insulin:
 - Long-acting insulin analogues not studied

Gestational diabetes

- Bolus insulin: either regular insulin or rapid-acting insulin analogues (e.g., insulin aspart)
- Basal insulin
 - Long-acting insulin analogues not studied

Learning objectives

Understand the evidence-base which supports the use of human insulins and insulin analogues in the treatment of diabetes

- Systematic review of world literature
- Pooled meta-analysis of peer-reviewed trials
- Recommendations based on clinical evidence with pharmaco-economic analysis added afterwards

Learning objectives (cont'd)

Identify the appropriate use of insulin preparations in:

- The general population with diabetes
 - First-line agents for bolus insulin:
 - Adults with type 1 diabetes: regular human insulin or rapid-acting insulin analogues
 - Adolescents with type 1 diabetes, insulin lispro or rapid-acting insulin analogues suggested over regular human insulin
 - Type 1 diabetes in pregnancy and gestational diabetes: regular human insulin or rapid-acting insulin analogues
 - Type 2 diabetes: regular human insulin
 - First-line agents for basal insulin:
 - Type 1 and type 2 diabetes: NPH insulin

Learning objectives (cont'd)

Identify special cases where insulin analogues should be considered:

- Adolescents with type 1 diabetes: lispro for bolus
- Hypoglycemia (severe episodes) in any patient: both rapid- and long-acting insulin analogues
- Patient convenience/meal flexibility: rapid-acting insulin analogue
- Patient preference

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