

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Long-Acting Insulin Analogues versus Human NPH Insulin for Adults with Type 2 Diabetes and Unresponsive to Non- insulin Therapies: Clinical Effectiveness, Cost- Effectiveness, and Guidelines

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Research Questions

1. What is the comparative clinical effectiveness of long-acting insulin analogues versus human NPH insulin for the treatment of adults with type 2 diabetes who are not responding to non-insulin therapies alone?
2. What is the comparative cost-effectiveness of long-acting insulin analogues versus human NPH insulin for the treatment of adults with type 2 diabetes who are not responding to non-insulin therapies alone?
3. What are the evidence-based guidelines regarding the selection of a first-line insulin therapy for the treatment of adults with type 2 diabetes who are not responding to non-insulin therapies alone?

Key Findings

Two evidence-based guidelines were identified regarding the selection of first-line insulin therapy for the treatment of adults with type 2 diabetes who are unresponsive to non-insulin therapies. No relevant studies pertaining to the comparative clinical effectiveness and cost-effectiveness of long-lasting insulin analogues versus human NPH insulin were identified.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and April 20, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer conducted an initial screening of titles and abstracts of citations, and a second reviewer confirmed selected studies based on the inclusion criteria presented in Table 1 and prepared the summary of abstracts.

Table 1: Selection Criteria

Population	Adults with type 2 diabetes who are not responding to non-insulin therapies (i.e., DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors) alone in any clinical setting
Intervention	Q1-Q2: Long-acting insulin analogues Q3: Long-acting insulin analogues; human NPH insulin

Comparator	Q1-Q2: Human NPH insulin Q3: No comparator required
Outcomes	Q1: Clinical effectiveness (e.g., quality of life, glycemic control, changes in weight) and safety (e.g., adverse effects, hypoglycemic events) Q2: Cost-effectiveness Q3: Evidence-based guidelines and recommendations
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Two evidence-based guidelines were identified regarding the selection of first-line insulin therapies for adults with type 2 diabetes who do not respond to non-insulin therapies. No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies or economic studies were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Two evidence-based guidelines^{1,2} were identified regarding the selection of first-line insulin therapies for adult patients with type 2 diabetes (T2DM) who are unresponsive to non-insulin therapies.

Diabetes Canada¹ recommends those patients with T2DM who are unresponsive to non-insulin antihyperglycemic therapies should add once-daily long-acting insulin over premixed or bolus insulin to their treatment regimen. Additionally, long-acting insulin analogues are recommended over NPH insulin for reducing nocturnal and symptomatic hypoglycemia although it wasn't stated whether this was suggested for those T2DM patients who are specifically unresponsive to non-insulin therapies.

The National Institute for Health and Care Excellence (NICE)² recommends a variety of insulin therapies depending on a patient's needs and severity of hypoglycemia (i.e. depending upon which non-insulin therapies have inadequately controlled hypoglycemia). However, the recommendations do not specifically state whether TD2M patients who are unresponsive to non-insulin therapies should consider long-acting insulin over human NPH insulin or vice versa.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Economic Evaluations

No literature identified.

Guidelines and Recommendations

1. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. *Can J Diabetes*. 2018;42(Suppl 1):S1-S325; <http://guidelines.diabetes.ca/docs/CPG-2018-full-EN.pdf>. Accessed 2019 May 3. See: Insulin Treatment for Type 2 Diabetes Recommendations, Page 115
2. National Institute for Health Care and Excellence. Type 2 diabetes in adults (*NICE guideline NG28*). 2015; <https://www.nice.org.uk/guidance/ng28/evidence/full-guideline-pdf-78671532569>. Accessed 2019 May 3. See: Recommendation 64; page 20

Appendix — Further Information

Systematic Reviews

Non-Responsive to Non-Insulin Therapies Not Specified in Patient Population

3. Freemantle N, Chou E, Frois C, et al. Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis. *BMJ Open*. 2016;6(2):e009421.
[PubMed: PM26880669](#)
4. Rys P, Wojciechowski P, Rogoz-Sitek A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. *Acta Diabetol*. 2015;52(4):649-662.
[PubMed: PM25585592](#)

Randomized Controlled Trials

Non-Responsive to Non-Insulin Therapies Not Specified in Patient Population

5. Porcellati F, Lin J, Lucidi P, Bolli GB, Fanelli CG. Impact of patient and treatment characteristics on glycemic control and hypoglycemia in patients with type 2 diabetes initiated to insulin glargine or NPH: a post hoc, pooled, patient-level analysis of 6 randomized controlled trials. *Medicine (Baltimore)*. 2017;96(5):e6022.
[PubMed: PM28151905](#)
6. Bueno E, Benitez A, Rufinelli JV, et al. Basal-bolus regimen with insulin analogues versus human insulin in medical patients with type 2 diabetes: a randomized controlled trial in Latin America. *Endocr Pract*. 2015;21(7):807-813.
[PubMed: PM26121460](#)
7. Herrera KM, Rosenn BM, Foroutan J, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. *Am J Obstet Gynecol*. 2015;213(3):426.e1-7.
[PubMed: PM26070699](#)
8. Ruiz de Adana MS, Colomo N, Maldonado-Araque C, et al. Randomized clinical trial of the efficacy and safety of insulin glargine vs. NPH insulin as basal insulin for the treatment of glucocorticoid induced hyperglycemia using continuous glucose monitoring in hospitalized patients with type 2 diabetes and respiratory disease. *Diabetes Res Clin Pract*. 2015;110(2):158-165.
[PubMed: PM26474657](#)

Non-Randomized Studies

Non-Responsive to Non-Insulin Therapies Not Specified in Patient Population

9. Curington R, Espel M, Heaton PC, Luder H, Brown B. Clinical outcomes of switching from insulin glargine to NPH insulin in indigent patients at a charitable pharmacy: the Charitable Insulin NPH: Care for the Indigent study. *J Am Pharm Assoc (2003)*. 2017;57(3s):S229-s235.
[PubMed: PM28366602](#)

10. Fiesselmann A, Wiesner T, Fleischmann H, Bramlage P. Real-world therapeutic benefits of patients on insulin glargine versus NPH insulin. *Acta Diabetol.* 2016;53(5):717-726.
[PubMed: PM27093968](#)
11. Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P. All-cause and cause-specific mortality among users of basal insulins NPH, detemir, and glargine. *PLoS One.* 2016;11(3):e0151910.
[PubMed: PM27031113](#)
12. Prentice JC, Conlin PR, Gellad WF, Edelman D, Lee TA, Pizer SD. Long-term outcomes of analogue insulin compared with NPH for patients with type 2 diabetes mellitus. *Am J Manag Care.* 2015;21(3):e235-243.
[PubMed: PM26014311](#)
13. Bellia A, Babini AC, Marchetto PE, Arsenio L, Lauro D, Lauro R. Effects of switching from NPH insulin to insulin glargine in patients with type 2 diabetes: the retrospective, observational LAUREL study in Italy. *Acta Diabetol.* 2014;51(2):269-275.
[PubMed: PM24275956](#)
14. Zdarska DJ, Kvapil M, Rusavy Z, et al. Comparison of glucose variability assessed by a continuous glucose-monitoring system in patients with type 2 diabetes mellitus switched from NPH insulin to insulin glargine: the COBIN2 study. *Wien Klin Wochenschr.* 2014;126(7-8):228-237.
[PubMed: PM24563017](#)
15. Rosenstock J, Fonseca V, Schinzel S, Dain MP, Mullins P, Riddle M. Reduced risk of hypoglycemia with once-daily glargine versus twice-daily NPH and number needed to harm with NPH to demonstrate the risk of one additional hypoglycemic event in type 2 diabetes: evidence from a long-term controlled trial. *J Diabetes Complications.* 2014;28(5):742-749.
[PubMed: PM24856612](#)

Economic Evaluations

Non-Responsive to Non-Insulin Therapies Not Specified in Patient Population

16. Alemayehu B, Speiser J, Bloudek L, Sarnes E. Costs associated with long-acting insulin analogues in patients with diabetes. *Am J Manag Care.* 2018;24(8 Spec No.):SP265-SP272.
[PubMed: PM30020738](#)
17. Idris I, Gordon J, Tilling C, Vora J. A cost comparison of long-acting insulin analogs vs NPH insulin-based treatment in patients with type 2 diabetes using routinely collected primary care data from the UK. *J Med Econ.* 2015;18(4):273-282.
[PubMed: PM25422990](#)
18. Morales C, de Luis D, de Arellano AR, Ferrario MG, Lizan L. Cost-effectiveness analysis of insulin detemir compared to neutral protamine Hagedorn (NPH) in patients with type 1 and type 2 diabetes mellitus in Spain. *Diabetes Ther.* 2015;6(4):593-610.
[PubMed: PM26589521](#)