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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Non-Insulin Therapies versus Prandial Insulin for Adults with Type 2 Diabetes: Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Research Questions

1. What is the comparative clinical effectiveness of non-insulin therapies versus prandial insulin for the treatment of adults with type 2 diabetes who are receiving basal insulin?
2. What is the comparative cost-effectiveness of non-insulin therapies versus prandial insulin for the treatment of adults with type 2 diabetes who are receiving basal insulin?
3. What are the evidence-based guidelines regarding the use non-insulin therapies for the treatment of adults with type 2 diabetes who are receiving basal insulin?

Key Findings

Six systematic reviews (four with meta-analyses), five randomized controlled trials, five non-randomized studies, and nine economic evaluations were identified regarding non-insulin therapies versus prandial insulin for the treatment of adults with type 2 diabetes who are receiving basal insulin. In addition, three evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including Medline via OVID, 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. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, and guidelines. 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 11, 2019. Internet links were provided, where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with type 2 diabetes who are receiving basal insulin in any clinical setting
Intervention	Non-insulin therapies (i.e., DPP-4 inhibitors, GLP-1 receptor agonists, or SGLT2 inhibitors)
Comparator	Q1-2: Prandial insulin (i.e., meal-time insulin) Q3: No comparator
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.

Six systematic reviews (four with meta-analyses), five randomized controlled trials, five non-randomized studies, and nine economic evaluations were identified regarding non-insulin therapies versus prandial insulin for the treatment of adults with type 2 diabetes who are receiving basal insulin. In addition, three evidence-based guidelines were identified. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Tables 2, 3 and 4 detail the included systematic reviews,[1-6] randomized controlled trials,[7-11] non-randomized studies,[12-16] and economic evaluations,[17-22] respectively. Overall, Glucagon-like peptide 1-receptor agonists (GLP-1RA), dipeptidyl peptidase (DPP-4) inhibitors, and sodium-glucose transport protein 2 (SGTL-2) inhibitors as add-ons to basal insulin appear to be potentially useful treatments for type 2 diabetes.

The three identified evidence-based guidelines were focused on treatment of type 2 diabetes.[26-28] One guideline, from the Korean Diabetes Association, recommends that if A1C levels are not met on basal insulin, intensification should be considered with a GLP-1RA or prandial insulin.[26] A guideline from the National Institute for Health and Care Excellence[27] recommends to only offer a GLP-1 mimetic in combination with insulin with specialist advice and continuous support from a multidisciplinary team. Finally, a guideline from the Scottish Intercollegiate Guidelines Network[28] recommends GLP-1 receptor agonist therapy in people with a body mass index of ≥30 kg/m^2 (or ethnicity-adjusted equivalent) combined with basal insulin as a third- or fourth-line treatment. DPP-4 inhibitors should be considered as dual or triple therapy for lowering HbA_{1c}.[28] There were no recommendations regarding SGT2 inhibitors in combination with basal insulin.[28]

Table 2: Summary of Included Systematic Reviews

Author, Year	Intervention and Comparator	Results	Authors' Conclusions
Castellana, 2019[1]	• GLP-1RA+insulin combinations vs. basal-plus/basal-bolus	• Both regimens had similar HbA_{1c} reductions (P = 0.13) • GLP-1RA had greater weight loss (P<0.001) and lower incidence of hypoglycemic events (P < 0.001)	The authors concluded that treatment intensification with GLP-1RA is supported and similar in efficacy to basal-plus/basal bolus
Maiorino, 2017[2]	• GLP-1 + basal insulin vs. "other" injectable diabetes treatments	• Combination treatment was similar to basal-bolus insulin regimes	The authors concluded that GLP-1 is a promising option combined with basal insulin
Raccah, 2017[3]	• GLP-1RA + basal, DPP-4 + basal vs. rapid acting insulin	• All treatments reduced HbA_{1c} and fasting plasma glucose • Postprandial plasma glucose reduced with GLP-	"The evidence supports effectiveness of the available add-on treatments to basal insulin."[3]

Author, Year	Intervention and Comparator	Results	Authors' Conclusions
		1RA and rapid acting insulin	
Wysham, 2017[4]	• GLP-1RA + basal insulin + basal ± rapid acting insulin	• Weight loss (P < 0.0001) and reduction in glycated hemoglobin (P < 0.0001) greater in GLP-1RA	The authors concluded that GLP-1 added to basal insulin provided improved glycemic control and weight reduction, but not lower hypoglycemia
Cimmaruta, 2016[5]	• GLP-1 RA vs. short acting insulin to intensify basal insulin	• NR	The authors concluded that studies showed equal or higher efficacy of GLP-1
Eng, 2014[6]	• GLP-1 +basal vs. anti-diabetic treatments	• Mean reduction in HbA1c greater than basal-bolus • Lower relative risk of hypoglycemia and greater weight loss with GLP-1	The authors concluded that GLP-1 and basal insulin is a potential therapeutic strategy for type diabetes

GLP-1 RA = glucagon-like peptide 1 receptor agonist; NR = not reported; vs. = versus.

Table 3: Summary of Included Randomized Controlled Trials and Non-Randomized Studies

Author, Year	Population	Intervention and Comparator	Results	Authors' Conclusions
Randomized Controlled Trials				
Vellanki, 2018[7]	Patients with T2DM undergoing non-cardiac surgery treated with: • Diet • Oral agents	• Linagliptin • Basal-bolus glargine and rapid-acting insulin before meals Both groups received supplemental insulin for BG >7.8 mmol/L	• Mean daily BG was inferior with linagliptin compared to basal-bolus glargine • Significantly fewer hypoglycemic events were observed in the linagliptin group	The authors concluded that linagliptin was safe for patients with T2DM with mild to moderate hypoglycemia
Yamamato, 2018[8]	Patients with T2DM without severe insulin deficiency	• Liraglutide • BBIT	• HbA1c was reduced in the liraglutide group and remained the same in the BBIT group • Body weight was reduced in the liraglutide group and increased in the BBIT group	The authors concluded that "Lira-basal therapy is superior to BBIT for T2DM without severe insulin deficiency."[8]
Leiter, 2017[9]	Patients with T2DM	• Once-weekly glucagon-like peptide-1 receptor agonist (albiglutide) • Prandial insulin added to basal insulin	• Not reported in abstract	"We have previously reported that once-weekly albiglutide was noninferior to thrice-daily lispro for glycemic lowering, with decreased weight and risk of

Author, Year	Population	Intervention and Comparator	Results	Authors' Conclusions
				hypoglycemia, in patients inadequately controlled on basal insulin over 26 weeks. Findings after 52 weeks reveal similar responses to albiglutide as an add-on to insulin glargine."[9]
Pasquel, 2017[10]	General medicine and surgery patients with T2DM	• Sitagliptin plus basal glargine once daily • Basal-bolus regimen with glargine once daily and rapid-acting insulin lispro or aspart before meals	• LOS was similar between treatment groups • mean daily BG concentration in the sitagliptin group was not inferior to that in the basal-bolus group • Hypoglycemia occurred less frequently in the sitagliptin group • A similar number of patients in each group developed AKI	The authors concluded that the sitagliptin treatment was non-inferior to basal bolus insulin
Yoon, 2017[11]	Korean patients with T2DM inadequately controlled on metformin plus optimized insulin glargine	• Exenatide twice daily • Three times daily mealtime insulin lispro	• HbA1C was significantly reduced in both groups • Fasting glucose and weight decreased with exenatide and increased with insulin lispro • Hypoglycemic events were similar between groups	The authors "found treatment with exenatide twice daily improved glycemic control without weight gain in Korean patients with T2DM unable to achieve glycemic control on metformin plus basal insulin."[11]
Non-Randomized Studies				
Lang, 2018[12]	Adults with T2DM	Added to basal insulin • Exenatide twice daily • Mealtime insulin	• The percentage of patients reaching A1C levels was similar in both groups • Fewer hypoglycemic episodes and more weight loss were observed in the exenatide group	The authors concluded that "[exenatide] added to basal insulin was as effective in a real-world setting as mealtime insulin added to basal insulin in reducing A1C, with less weight gain and less hypoglycemia for a wide range of A1C

Author, Year	Population	Intervention and Comparator	Results	Authors' Conclusions
				attainment levels and baseline values."[12]
Perez-Belmonte, 2018[13]	Medicine department inpatients with T2DM	• Standard basal-bolus insulin regimen • A dipeptidyl peptidase-4 inhibitor (linagliptin) plus basal insulin	• No differences were observed between groups in mean daily BG concentration after admission, LOS, or complications • Patients on basal-bolus insulin received higher total insulin doses and a higher daily number of injections	"This study shows that in real-world clinical practice, the linagliptin-basal insulin regimen was as effective and safe as the standard basal-bolus regimen in non-critical patients with type 2 diabetes with mild to moderate hyperglycaemia treated at home without injectable therapies."[13]
Levin, 2017[14]	Patients with T2DM receiving basal insulin	• Addition of rapid-acting insulin • Addition of a GLP-1 RA • Increasing basal insulin dose	• HbA1C changes were similar between the GLP-1 and rapid-acting insulin groups but higher for the GLP-1 vs the increased dose group • The rate of hypoglycemia was lower for the GLP-1 group than the other two groups	The authors concluded that basal insulin in combination with GLP-1 RAs was an effective intensification strategy as compared to increasing basal insulin dose
Dalal, 2015[15]	Patients with T2DM receiving basal insulin initiating add-on therapy	• GLP-1 + basal insulin • Rapid acting insulin	• Similar numbers of hypoglycemic events • GLP-1 had fewer all cause and diabetic related hospitalizations	The authors concluded that add on therapy with a GLP-1 had fewer hospitalizations and total all cause costs
Digenio, 2014[16]	Patients with T2DM managed in a US community practice taking basal insulin	• GLP-1 RA • Prandial insulin	• Similar changes were observed between groups for HbA1C • Body weight changes were significantly different between groups at 6 months and 1 year in favor of the GLP-1 RA • Hypoglycemia was significantly greater in the prandial	The authors concluded the results "suggest an association between adding a GLP-1 receptor agonist with similar glycemic control, greater reduction in body weight, lower hypoglycemia incidence"[16] than prandial insulin

Author, Year	Population	Intervention and Comparator	Results	Authors' Conclusions
			insulin group	

AKI = acute kidney injury; BBIT = basal-bolus insulin therapy; BG = blood glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; LOS = length of stay; T2DM = type 2 diabetes mellitus; US = United States.

Table 4: Summary of Included Economic Evaluations

Author, Year , Country	Type of Analysis, Time Horizon, Discount Rate, Perspective	Intervention and Comparator	Results	Authors' Conclusions
Dempsey, 2018[17] **US**[a]	• Cost-effectiveness • NR • 3% annually • Health care payer perspective	• IDegLira (insulin degludec + liraglutide) • insulin glargine U100 plus insulin aspart	• IDegLira was associated with increased discounted life expectancy by 0.22 QALYs • Direct medical costs were less with IDegLira	"Based on clinical trial data, the present analysis suggests that IDegLira is associated with improved clinical outcomes and cost savings compared with treatment with insulin glargine U100 plus insulin aspart for patients with type 2 diabetes not achieving glycemic control on basal insulin in the US."[17]
Dempsey, 2018[18] **US**[a]	• Cost utility • 1 year • NA • Health care payer perspective	• IDegLira (insulin degludec + liraglutide • insulin glargine U100 plus insulin aspart	• IDegLira was associated with improved quality of life by 0.12 QALYs compared with insulin glargine U100 plus insulin aspart.	The authors concluded that IDegLira improved quality-adjusted life expectancy and reduced costs per patient
Drummond, 2018[19] **UK**[a]	• Cost-effectiveness • 1 year • NA • NR	• IDegLira (insulin degludec + liraglutide) • Basal-bolus therapy with insulin glargine U100 plus up to 4 times daily insulin aspart	• IDegLira was associated with a 0.05 QALY improvement • ICER of £5,924 per QALY gained	The authors concluded that IDegLira was a cost-effective alternative to BBT with insulin glargine U100 plus insulin aspart
Ericsson, 2017[20] **Sweden**[a]	• Cost-effectiveness • 40 years • NR • Societal perspective	• IDegLira (insulin degludec + liraglutide) • Insulin glargine • NPH • Insulin • Insulin aspart plus either glargine or	IDegLira was dominant over insulin aspart plus insulin glargine or NPH insulin	"IDegLira is estimated to be a cost-effective treatment in Sweden compared with commonly used intensification treatments for patients with T2DM uncontrolled with

Author, Year , Country	Type of Analysis, Time Horizon, Discount Rate, Perspective	Intervention and Comparator	Results	Authors' Conclusions
		NPH • Liraglutide plus either glargine or NPH.		basal insulin."[20]
Hunt, 2017[21] **Netherlands**	• Cost-effectiveness • Patient lifetime • NR • Health care payer perspective	• IDegLira (insulin degludec + liraglutide) • Basal-bolus therapy with insulin glargine U100 plus 3 times daily insulin aspart	• IDegLira resulted in a mean increase of 0.43 QALYs • IDegLira was associated with lower costs	"This analysis suggests that IDegLira is cost-effective versus basal-bolus therapy in patients with T2DM who are uncontrolled on basal insulin in the Netherlands."[21]
Kvapil, 2017[22] **Czech Republic**	• Cost-effectiveness • Patient lifetime • NR • Public payer perspective	• IDegLira (insulin degludec + liraglutide) • Basal insulin intensification strategies	• IDegLira was associated with an improvement of 0.31 QALYs • ICER of CZK 693,763 per QALY gained compared to basal insulin + GLP-1	"Results from this evaluation suggest that IDegLira is a cost-effective treatment option compared with basal-bolus therapy and basal insulin + GLP-1 RA for patients with T2DM in the Czech Republic whose diabetes is not optimally controlled with basal insulin."[22]

ICER = incremental cost-effectiveness ratio; NA = not applicable; NPH = neutral protamine Hagedorn; NR = not reported; QALY = quality-adjusted life-year; U = units per millilitre; UK = United Kingdom; US = United States.
[a] Based on the same clinical trial.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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Appendix — Further Information

Previous CADTH Reports

29. CADTH Canadian Drug Expert Committee (CDEC) final recommendation: lixisenatide (Adlyxine – Sanofi-Aventis Canada Inc.). Ottawa (ON): CADTH; 2017 Oct 18: https://www.cadth.ca/sites/default/files/cdr/complete/SR0520_Adlyxine_complete_Nov-23-17.pdf. Accessed 2019 Apr 22.

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Patients on Basal Therapy Not Specified

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Randomized Controlled Trials – Alternative Population (Basal Insulin and Metformin)

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Clinical Practice Guidelines – Unknown Methodology

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