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CADTH Reference List

Basal Insulin Formulations for the Management of Type 2 Diabetes

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Summary of Abstracts

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Key Message

- Four systematic reviews (2 with meta-analyses and 2 with network meta-analyses), 22 randomized controlled trials, and 10 non-randomized studies were identified regarding the comparative risk of hypoglycemia in patients receiving various basal insulin formulations for the management of type 2 diabetes.

Research Question

What is the comparative risk of hypoglycemia in patients receiving various basal insulin formulations for the management of type 2 diabetes?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were basal insulin and type 2 diabetes. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses or network meta-analyses, randomized controlled trials, controlled clinical trials, or any other type of clinical trial. Comments, newspaper articles, editorials, and letters were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2016 and January 19, 2021. Internet links were provided, where available.

Selection Criteria and Summary Methods

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. The Overall Summary of Findings section was based on information available in the abstracts of selected publications. Due to the large volume of literature found, single-arm switching studies were excluded from the report.

Results

Four systematic reviews (2 with meta-analyses[1,2] and 2 with network meta-analyses[3,4]), 22 randomized controlled trials,[5-26] and 10 non-randomized studies[27-36] were identified regarding the comparative risk of hypoglycemia in patients receiving various basal insulin formulations

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients with type 2 diabetes
Intervention	Basal insulin formulations (e.g., NPH, NPL, degludec U-100, degludec U-200, determir, glargine U-100, glargine U-300, insulin glargine)
Comparator	Other basal insulin formulations (e.g., NPH, NPL, degludec U-100, degludec U-200, determir, glargine U-100, glargine U-300, insulin glargine)
Outcomes	Hypoglycemia (e.g., overall, severe, serious, nocturnal, emergency visits due to hypoglycemia)
Study Designs	HTAs, SRs, RCTs, non-randomized studies

HTAs = health technology assessments; NPH = neutral protamine Hagedorn, NPL = neutral protamine lispro; RCT =- randomized controlled trial; SR = systematic review.

for the management of type 2 diabetes. No relevant health technology assessments were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Overall Summary of Findings

Four systematic reviews (2 with meta-analyses[1,2] and 2 with network meta-analyses[3,4]), 22 randomized controlled trials,[5-26] and 10 non-randomized studies[27-36] were identified regarding the comparative risk of hypoglycemia in patients receiving various basal insulin formulations for the management of type 2 diabetes. Detailed study characteristics are provided in Table 2.

Two systematic reviews (1 with meta-analysis[2] and 1 with network meta-analysis[3]), 11 randomized controlled trials,[6,10,13-15,17,18,20,22-24] and 3 non-randomized studies[31,32,36] compared the clinical effectiveness of insulin degludec to other basal formulations and found mixed results. Authors of 1 of the randomized controlled trials[6] performed a subgroup analysis on patients with reduced renal function (i.e., estimated glomerular filtration rate < 60 mL/min/1.73m^2) and found that there were no differences in the rate or incidence of hypoglycemia compared to other patient subgroups. Authors of another randomized control trial[13] reported outcomes for older adults and found that the rate of hypoglycemia was lower among patients who received insulin degludec versus insulin glargine U-100.

Two systematic reviews (1 with meta-analysis[1] and 1 with network meta-analysis[4]), 1 randomized controlled trial,[12] and 3 non-randomized studies[33-35] compared the clinical effectiveness of neutral protamine Hagedorn (NPH) insulin to other basal formulations. Authors of 1 randomized controlled trial[12] found that, among patients with chronic kidney disease stages 3 and 4, the incidence of hypoglycemia was lower in those receiving insulin glargine versus NPH insulin.

Eight randomized controlled trials[5,7-9,16,19,21,25] and 3 non-randomized studies[27,28,30] compared the clinical effectiveness of insulin glargine U-300 to insulin glargine U-100. Authors of 1 randomized controlled trial[16] found that the rate of symptomatic hypoglycemia was lower among older adults administered insulin glargine U-300 versus insulin glargine U-100.

One systematic review[1] with meta-analysis, 2 randomized controlled trials[8,26] and 1 non-randomized study[29] compared the clinical effectiveness of insulin detemir to other basal formulations and found mixed results. The authors of 1 randomized controlled trial[11] compared the clinical effectiveness of insulin icodec to insulin glargine U-100 and found that the rate of hypoglycemia was greater in the insulin icodec group versus the insulin glargine U-100 group; however, this was not a statistically significant difference. The authors of 1 systematic review[3] with meta-analysis found that neutral protamine lispro insulin is associated with an increased risk of severe hypoglycemia compared to various other basal formulations.

Table 2: Summary of Included Studies

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Systematic reviews and meta-analyses						
Semlitsch et al. (2020)[1]	SR with MA 24 RCTs 4,740 patients with T2DM	Ultra–long-acting insulin analogues • Insulin glargine • insulin detemir	NPH insulin	Hypoglycemia	Treatment with insulin detemir compared to NPH insulin found an RR for severe hypoglycemia of 0.45 (95% CI, 0.17 to 1.20; P = 0.11; **ARR −0.9%, 95% CI, −1.4 to 0.4**; very low-certainty evidence); POR for serious hypoglycemia was 0.16 (95% CI, 0.04 to 0.61; P = 0.007; **ARR −0.9%, 95% CI, −1.1 to −0.4**; 5 trials, 1,777 participants; low-certainty evidence)	Intervention associated with lower incidence of hypoglycemia and severe hypoglycemia (insulin detemir) compared to NPH
Zhou et al. (2019)[2]	SR with MA 15 studies 16,694 patients with T2DM	Insulin degludec	Insulin glargine	Hypoglycemia	Intervention yielded a lower ratio of participants experiencing 1 or more severe hypoglycemic event (RR 0.68; 95% CI, 0.50 to 0.93, P = 0.01) and nocturnal hypoglycemia (RR 0.81; 95% CI, 0.75 to 0.88, P < 0.0001)	Intervention resulted in lower risk of hypoglycemia compared to insulin glargine
Madenidou et al. (2018)[3]	SR with NMA 39 RCTs 26,195 patients with T2DM	Insulin degludec U-100 Insulin degludec U-200 Insulin glargine U-300	Insulin detemir Insulin glargine U-100 Insulin LY2963016 Neutral protamine lispro insulin	Hypoglycemia	Specific results NR	Intervention associated with lower incidence of hypoglycemia No difference in incidence of severe hypoglycemia, except NPL (increased risk)

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Freemantle et al. (2016)[4]	SR with NMA 41 RCTs Patients on basal insulin-supported oral therapy	Insulin glargine U-300	NPH insulin Premixed insulin	Hypoglycemia	Intervention associated with significantly lower nocturnal hypoglycemia rate vs. NPH (RR 0.18; 95% CI, 0.05 to 0.55) and premixed insulin (RR 0.36; 0.14 to 0.94)	Lower rate of nocturnal hypoglycemia compared to NPH and premixed insulin
Randomized controlled trials						
Bolli et al. (2020)[5]	N = 867 insulin-naive patients with T2DM across different baseline FCP levels	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Specific results NR	Lower incidence of hypoglycemia for glargine 300 vs. glargine 100 Glargine 300 may offer an advantage for those with higher risk of hypoglycemia
Haluzik et al. (2020)[6]	N = 466 glargine N = 463 degludec Insulin-naive patients with T2DM	Insulin degludec U-100	Insulin glargine U-300	Hypoglycemia	Specific results NR	Lower incidence of hypoglycemia with glargine U-300 vs. degludec -100
Ji et al. (2020)[7]	N = 570 insulin-naive patients with T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Specific results NR	Incidence of hypoglycemia was lower in the intervention vs. comparator group
Meneghini et al. (2020)[8]	Multi-centre N = 1,653 insulin-naive patients with T2DM	Insulin glargine U-300	First-generation basal analogues • Insulin glargine U-100 • Insulin detemir	Hypoglycemia	78.4% and 75.3% of intervention and comparator groups had no documented symptomatic or severe hypoglycemia (OR 1.19; 95% CI, 1.01 to 1.41)	Lower incidence of hypoglycemia among the intervention group vs. the comparator group
Pasquel et al. (2020)[9]	N = 176 inpatients with poorly controlled T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Significantly lower rates of clinically significant hypoglycemia (0% vs. 6.0%, P = 0.023) in intervention group	Lower incidence of clinically significant hypoglycemia among the intervention group

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Philis-Tsimikas et al. (2020)[10]	N = 1,609 insulin-naive patients with T2DM	Insulin degludec U-200	Insulin glargine U-300	Hypoglycemia	Lower rate of nocturnal symptomatic hypoglycemia (RR 0.63; 95% CI, 0.48 to 0.84) and severe hypoglycemia (RR 0.20; 95% CI, 0.07 to 0.57) in intervention group	Nocturnal and severe hypoglycemia significantly lower in intervention group No significant difference for symptomatic hypoglycemia
Rosenstock et al. (2020)[11]	Double blind N = 247 insulin-naive patients with T2DM	Insulin icodec	Insulin glargine U-100	Hypoglycemia Safety	Observed rates of hypoglycemia with severity of level 2 or level 3 were low (icodec group, 0.53 events per patient-year; glargine group, 0.46 events per patient-year; estimated RR 1.09; 95% CI, 0.45 to 2.65)	Intervention provided once daily was associated with lower glucose No difference in AEs
Betonico et al. (2019)[12]	Crossover design N = 34 patients with T2DM and CKD stages 3 and 4	Insulin glargine U-100	NPH insulin	Hypoglycemia	Incidence of nocturnal hypoglycemia was 3 times lower in intervention group (P = 0.047)	Incidence of nocturnal hypoglycemia was lower with glargine vs. NPH
Heller et al. (2019)[13]	Crossover design N = 720 patients with T2DM (older and younger than 65 years)	Insulin degludec	Insulin glargine U-100	Hypoglycemia	Lowered rates of hypoglycemia in individuals 65 or under (31% vs. 43%) and over 65 (30% vs. 41%) years in intervention group	Frequency of hypoglycemia was comparatively lower in the intervention group for younger and older T2DM patients
Kawaguchi et al. (2019)[14]	Crossover design N = 30 patients with T2DM	Insulin degludec	Insulin glargine U-300	Hypoglycemia	Mean percentage of time of hypoglycemia was significantly lower in comparator group (1.3 ± 2.7 vs. 5.5 ± 6.4%, P = 0.002); mean percentage of time of severe or nocturnal hypoglycemia was significantly lower in comparator group	Significantly lower incidence of nocturnal, severe, and symptomatic hypoglycemia in insulin glargine group
Yamabe et al. (2019)[15]	Crossover design N = 24 Japanese patients with T2DM	Insulin degludec	Insulin glargine U-300	Hypoglycemia	Percentage of time with nocturnal hypoglycemia significantly lower in intervention group (P = 0.021)	Incidence of nocturnal hypoglycemia was lower with insulin glargine 300

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Ritzel et al. (2018)[16]	N = 1,014 patients ≥ 65 years old with T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Incidence and rates of confirmed or severe hypoglycemia events were low and similar between both treatment groups, with lower rates of documented symptomatic hypoglycemia with insulin glargine U-300	Similar outcomes overall; however, significantly lower risk of hypoglycemia for patients aged ≥ 75 years using glargine U-300
Rosenstock et al. (2018)[17]	N = 929 insulin-naive patients with T2DM	Insulin degludec U-100	Insulin glargine U-300	Hypoglycemia	Specific results NR	Similar outcomes overall, but lower risk of hypoglycemia incidence using insulin glargine U-300 during the titration period
Aso et al. (2017)[18]	N = 43 insulin-naive patients with T2DM 3:1 randomization	Insulin degludec	Insulin glargine	Hypoglycemia	Specific results NR	No significant difference
Bolli et al. (2017)[19]	N = 878 insulin-naive patients with T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	RR of experiencing 1 or more confirmed or severe hypoglycemic event with Gla-300 vs. Gla-100 was 0.86 (95% CI, 0.69 to 1.07) at night and 0.92 (0.82 to 1.03) at any time of day	Lower risk of hypoglycemia associated with insulin glargine U-300
Marso et al. (2017)[20]	Double blind N = 7,637 patients with T2DM	Insulin degludec	Insulin glargine U-100	Severe hypoglycemia	Severe hypoglycemia occurred in 187 patients (4.9%) in the degludec group and in 252 (6.6%) in the glargine group, for an **absolute difference of 1.7 percentage points** (rate ratio, 0.60; P < 0.001 for superiority; OR 0.73; P < 0.001 for superiority)	Lower incidence of severe hypoglycemia in the intervention group

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Terauchi et al. (2017)[21]	Japanese adult patients with uncontrolled T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Annualized rates of confirmed or severe hypoglycemia were lower in intervention group (nocturnal: RR 0.41; 95% CI, 0.18 to 0.92; anytime: RR 0.64; 95% CI, 0.44 to 0.94); cumulative number of hypoglycemic events was lower in intervention group	Lower hypoglycemic events with insulin glargine U-300
Wysham et al. (2017)[22]	Switching design N = 721 patients with T2DM at risk of hypoglycemia	Insulin degludec followed by insulin glargine U-100	Insulin glargine U-100 followed by insulin degludec	Hypoglycemia	Proportions of patients experiencing severe hypoglycemia during the maintenance period were 1.6% (95% CI, 0.6% to 2.7%) for insulin degludec vs. 2.4% (95% CI, 1.1% to 3.7%) for insulin glargine U-100 (McNemar test P = 0.35; **risk difference, −0.8% [95% CI −2.2% to 0.5%])**	Significant reduction in overall and nocturnal symptomatic hypoglycemia for insulin degludec vs. insulin glargine U-100
Osonoi et al. (2016)[23]	Multi-national N = 133 Japanese insulin-naive patients with T2DM 2:1 randomization	Insulin degludec as an add-on to existing orally administered antidiabetic drugs	Insulin glargine as an add-on to existing orally administered antidiabetic drugs	Hypoglycemia	Confirmed hypoglycemia reported in 53.4% and 61.4% of patients in intervention and comparator groups (RR 0.87; 95% CI 0.51 to 1.48) Confirmed nocturnal hypoglycemia reported in 17.0% and 22.7% of patients in intervention and comparator groups (RR 0.50; 95% CI, 0.19 to 1.32)	No significant difference
Pan et al. (2016)[24]	Multi-national N = 833 insulin-naive patients with T2DM 2:1 randomization	Insulin degludec with metformin	Insulin glargine with metformin	Hypoglycemia	Lower rates of overall (estimated RR: 0.80; 95% CI, 0.59 to 1.10) and nocturnal (estimated RR 0.77; 95% CI, 0.43 to 1.37) confirmed hypoglycemia in intervention group	No significant difference but the intervention group had a lower rate of hypoglycemia

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Terauchi et al. (2016)[25]	N = 241 Japanese patients with T2DM	Insulin glargine U-300 plus OAD	Insulin glargine U-100 plus OAD	Hypoglycemia	Nocturnal confirmed or severe hypoglycemia risk was 38% lower in intervention group (RR 0.62; 95% CI, 0.44 to 0.88); annualized rates were 55% lower at night (RR 0.45; 95% CI, 0.21 to 0.96) and 36% lower at any time (RR 0.64; 95% CI, 0.43 to 0.96)	Relative risk of nocturnal confirmed and severe hypoglycemia was lower among the intervention group
Zhang et al. (2016)[26]	Crossover design N = 42 hospitalized patients with T2DM	Insulin detemir	Insulin glargine	Hypoglycemia	Some patients had hypoglycemia events when switching from insulin glargine to detemir	No significant difference
Non-randomized studies						
Escalada et al. (2020)[27]	Retrospective chart review Switching study Multi-national Adult patients with T2DM and insulin-naive patients with T2DM	Basal insulin analogues switched to insulin glargine U-300	Basal insulin analogues switched to insulin glargine U-100 or initiating insulin glargine U-100	Hypoglycemia Hospitalizations related to hypoglycemia	Those switched to Gla-300 vs. Gla-100 had significantly greater mean reduction in hypoglycemic events (−1.29 vs. −0.81 events during 6 months; P = 0.012)	Significantly lower hypoglycemic events for insulin glargine U-300 compared to U-100
Roussel et al. (2020)[28]	Retrospective cohort N = 181,623 Patients with T2DM	Insulin glargine U300	Insulin glargine U100	Hypoglycemia ER visits and hospitalizations related to hypoglycemia	Patients in comparator group had higher crude hospitalization rates for hypoglycemia (1.4 for 100 patient-years; OR 0.67; 95% CI, 0.55-0.81); not statistically significant after adjustment for patient characteristics	ER visits were significantly lower among patients receiving insulin glargine U-300 Frequencies of hospitalizations for hypoglycemia were lower for insulin glargine U-300

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Bailey et al. (2019)[29]	Retrospective matched cohort Switching study N = 1,176 older adults with T2DM	Switching to insulin glargine U-300 from basal insulin	Switching to insulin glargine U-100 or insulin detemir from basal insulin	Hypoglycemia; ER visits and hospitalizations related to hypoglycemia	Insulin glargine U-300 was associated with less hypoglycemia [event rate: adjusted RR 0.63; 95% CI, 0.53 to 0.75; P < 0.001] and inpatient/ER-associated hypoglycemia (adjusted HR 0.58; 95% CI, 0.37-0.90; P = 0.016; adjusted RR 0.43; 95% CI, 0.31 to 0.60; P < 0.001)	Switching to insulin glargine 300 was associated with lower hypoglycemic events, and associated hospitalization and ER visits compared to first-generation basal insulins
Bailey et al. (2019)[30]	Retrospective matched cohort Switching study N = 3,012 insulin-naive adult patients with T2DM	Insulin glargine U-300	Insulin glargine U-100	Hypoglycemia	Patients in intervention group similarly or less likely to have any or inpatient/ ER-associated hypoglycemia (e.g., any hypoglycemia to 6 months: 9.7% vs. 12.5%; adjusted OR 0.61; P = 0.057)	Patients receiving glargine U-300 had similar or improved hypoglycemic outcomes than patients receiving glargine U-100
Sullivan et al. (2019)[31]	Retrospective matched cohort N = 1,276 insulin-naive adult patients with T2DM	Insulin degludec	Insulin glargine U-300	Hypoglycemia	Specific results NR	No significant difference
Tibaldi et al. (2019)[32]	Retrospective matched cohort N = 4,056 insulin-naive adult patients with T2DM	Insulin degludec	Insulin glargine U-300	Hypoglycemia	Greater reductions in change in the likelihood of hypoglycemia (OR 0.64; P < 0.01]) in intervention group	Significantly lower risk of hypoglycemic events and treatment discontinuation were demonstrated with degludec vs. glargine U-300
Lipska et al. (2018)[33]	Retrospective cohort study N = 25,489 patients with T2DM	Long-acting basal insulin analogues	NPH insulin	Hypoglycemia ER visits and hospitalizations related to hypoglycemia	Adjusted HR was 1.16 (95% CI, 0.71 to 1.78) for hypoglycemia-related ER visits or hospital admissions associated with insulin analogue use	No significant difference

First author, year	Study characteristics	Intervention(s)	Comparator(s)	Outcomes	Results	Conclusions
Ji et al. (2017)[34]	Multi-centre prospective study N = 25,343 patients with T2DM uncontrolled by OAD	Insulin glargine, insulin detemir	NPH insulin	Hypoglycemia	Specific results NR	Glargine group had the lowest incidence of minor hypoglycemic events Long-acting insulin analogues were superior to NPH No difference between groups regarding severe hypoglycemia
Fiesselmann et al. (2016)[35]	Multi-centre prospective matched study N = 2,629 patients with T2DM uncontrolled by OAD	Insulin glargine with OAD	NPH insulin with OAD	Hypoglycemia	Specific results NR	Insulin glargine with OAD was associated with lower risk of hypoglycemia than NPH insulin
Ghosal et al. (2016)[36]	Retrospective cohort study N = NR Insulin-naive patients with T2DM failing OAD	Insulin degludec	Insulin glargine	Hypoglycemia	12 vs. 40 hypoglycemic episodes in intervention vs. comparator group	Significantly less reported hypoglycemic episodes in patients receiving insulin degludec vs. insulin glargine

AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; ER = emergency room; FCP = fasting C-peptide; HR = hazard ratio; MA = meta-analyses; NMA = network meta-analyses; NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro; NR = not reported; OAD = oral antihyperglycemic drug; OR = odds ratio; POR = Peto odds ratio; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; T2DM = type 2 diabetes mellitus; vs. = versus.

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Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-Analyses

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Unclear Results

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