“Ultralong”-acting insulin for diabetes: How long is long enough?

CLINICAL QUESTION

In patients with diabetes (type 1 or 2), how does the “ultralong”-acting insulin degludec compare to long-acting or NPH insulin?

BOTTOM LINE

In both type 1 and 2 diabetes, insulin degludec reduces the risk of severe hypoglycemia compared to insulin glargine [number needed to treat (NNT)=17-59]. The risk of symptomatic hypoglycemia is either similar, or at best lower with degludec (NNT=19-29), with no other differences in clinical outcomes or hemoglobin A1c.

EVIDENCE

- Degludec versus glargine 100 units/mL:
  - Five systematic reviews\(^1-5\) compared degludec to glargine in individuals with type 1 diabetes [4 randomized controlled trials (RCTs), 1477 patients] and type 2 diabetes (10-15 RCTs, 9619-16,328 patients) with follow-up 12 weeks to 2 years:
    - Hemoglobin A1c: Differences not clinically significant (≤0.1%).\(^1-5\)
    - Hypoglycemia:
      - Severe (requiring assistance) hypoglycemia: Most showed relative risk reduction (RRR) ~30%\(^1,3,4\) with degludec, whereas another found no statistically significant difference.\(^5\)
Symptomatic hypoglycemia: Range from no statistical difference\textsuperscript{1,4} to RRR 18%.\textsuperscript{2}

- E.g., in blinded RCTs\textsuperscript{6-8} NNT=17-59 for severe hypoglycemia and NNT=19-29 for overall hypoglycemia.

  - No differences in severe adverse events, treatment discontinuation, death, cardiovascular events, or weight gain.

  - Limitations:
    - Some meta-analyses\textsuperscript{1,4} included RCTs with thrice-weekly degludec and mixed insulins. Symptomatic hypoglycemia would be statistically different without these RCTs;
    - Review of type 1 diabetes excluded hypoglycemia outcomes from largest RCT;\textsuperscript{5}
    - All RCTs industry-funded and only 3 were blinded.\textsuperscript{6-8}

- Degludec versus glargine 300 units/mL (1 RCT, 924 patients): No difference in any outcome.\textsuperscript{9}

- Degludec versus detemir:
  - Type 1 diabetes (2 RCTs, 806 patients): No differences except in 1 RCT in 1 out of 5 nocturnal hypoglycemia outcomes.\textsuperscript{5}
  - Type 2 diabetes: No RCTs.\textsuperscript{3}

- Degludec versus NPH insulin: No RCTs.\textsuperscript{1-5,10}

**CONTEXT**

- Insulin degludec’s longer half-life (24 hours versus glargine’s ~12) increases administration time flexibility,\textsuperscript{11} but takes 3-4 days to see the full effect of dose changes (versus glargine’s 1-2 days).

- Guidelines suggest degludec over detemir/glargine 100 units/mL to reduce hypoglycemia in both type 1 and 2 diabetes.\textsuperscript{11,12}

- Detemir/glargine do not consistently reduce severe hypoglycemia versus NPH insulin, with similar efficacy.\textsuperscript{13}

- Costs/15mL: Degludec $135, detemir $135, glargine (Basaglar®) $90, NPH $65.\textsuperscript{14}

**REFERENCES**


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