



Strategies for initiating insulin in type 2 diabetes

CLINICAL QUESTION

What is the optimal initial insulin for patients with type 2 diabetes?

BOTTOM LINE

For type 2 diabetes poorly controlled with oral agents, initiating biphasic insulin reduces HbA1C by ~0.1-0.2% more than basal insulin, but results in more weight gain and symptomatic hypoglycemia. It is unclear whether this is due to insulin type or total dose administered. Basal insulin is the simplest and likely best initial approach. No insulin has been shown to reduce cardiovascular events in randomized controlled trials (RCTs).

EVIDENCE

- Results statistically significant unless indicated.
- 3 systematic reviews in the past 15 years (14-22 RCTs, 4,379-9,548 participants), comparing initiating basal insulin once daily (mostly glargine) versus biphasic (premix short and long acting) insulin twice-daily.¹⁻³ Largest (4 months–3 years):¹
 - HbA1c reduction from baseline (7 RCTs, 3,472 participants): Biphasic 0.19% greater reduction versus basal.¹
 - If small RCT removed: 0.11% difference.¹
 - Other systematic reviews showed larger difference;^{2,3} metagraphs may have incorrect numbers; 2 largest RCT not included.³

- Weight gain (4 RCTs, 2,600 patients): Biphasic 1.25kg greater increase versus basal.¹
- Total hypoglycemia (6 RCTs, 3,548 patients): Biphasic more than basal, absolute events not provided (basal Odds Ratio 0.72).¹
 - Severe/nocturnal hypoglycemia: Not different.
- Largest RCT: 2,091 participants, baseline HbA1C ~9%, glargine once-daily (basal) versus premix (25% lispro, 75% lispro protamine suspension) twice-daily (biphasic). At 24 weeks:⁴
 - HbA1c reduction from baseline: -1.7% basal versus -1.8% biphasic.
 - % patients reaching HbA1C < 7%: 40% basal versus 48% biphasic. Number Needed to Treat=13.
 - Insulin dose: Average ~36 Units basal versus ~44 Units biphasic [PEER calculation].
 - Weight gain: 2.5kg basal versus 3.6kg biphasic.
 - Symptomatic hypoglycemia (blood glucose ≤3.9): 34% basal versus 44% biphasic. Number Needed to Harm=10.
 - Severe hypoglycemia rare.
- Limitations: RCTs open label; different insulin combinations/doses, sulfonylurea common co-intervention, now rarely used with insulin.

CONTEXT

- Effects may be driven by total insulin dose, rather than type: one systematic review found when adjusted for total insulin dose, basal and biphasic HbA1c difference no longer significant.²
- RCTs (with limitations) show that insulin does not reduce mortality/cardiovascular outcomes.⁵
- Sample patient instructions online.⁶ Example: Start 10 units basal daily, titrate 1 unit/day until fasting glucose 4-7.

REFERENCES

1. Bi Y, Li X, Yang D, *et al.* J Diabetes Investig. 2012 Jun 6; 3(3):283-93.
2. Yki-Jarvinen H and Kotronen A. Diabetes Care. 2013 Aug; 36 Suppl 2(Suppl 2):S205-11.
3. Lasserson DS, Glasziou P, Perera R, *et al.* Diabetologia. 2009 Oct; 52(10):1990-2000.
4. Buse JB, Wolffenbuttel BH, Herman WH, *et al.* Diabetes Care. 2009 Jun; 32(6):1007-13.
5. Mannucci E, Targher G, Nreu B, *et al.* Nutr Metab Cardiovasc Dis. 2022 Jun; 32(6):1353-1360.
6. Diabetes Canada Clinical Practice Guidelines Expert Committee. Can J Diabetes. 2018; 42(Suppl 1):S1-S325. Appendix 9, available at <https://guidelines.diabetes.ca/appendices/appendix9>. Accessed April 28, 2024

AUTHORS

Émélie Braschi MD CCFP PhD,
Jennifer Young MD CCFP-EM

Authors do not have any conflicts of interest to declare.

IN PARTNERSHIP WITH



Tools for Practice are peer reviewed and summarize practice-changing medical evidence for primary care. Coordinated by **Dr. G. Michael Allan** and **Dr. Adrienne Lindblad**, they are developed by the Patients, Experience, Evidence, Research (PEER) team, and supported by the College of Family Physicians of Canada, and the Alberta, Ontario, and Saskatchewan Colleges of Family Physicians. Feedback is welcome and can be sent to toolsforpractice@cfpc.ca. Archived articles can be found at www.toolsforpractice.ca

This communication reflects the opinion of the authors and does not necessarily mirror the perspective and policy of the College of Family Physicians of Canada.