ONLINE EXCLUSIVE

Q/Is NPH associated with fewer adverse events than analog basal insulin for adults with T2D?

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doi: 10.12788/jfp.0191

EVIDENCE-BASED ANSWER

A/ **NO.** Insulin glargine may lead to less patient-reported, symptomatic, and nocturnal hypoglycemia, although overall, there may not be a difference in the risk for severe hypoglycemia or hypoglycemia-related emergency department (ED) visits and hospitalizations (strength of recommendation [SOR]: **B**, systematic review of randomized controlled trials [RCTs], individual RCTs, and observational study).

Evidence summary

No difference in overall hypoglycemia risk between glargine and NPH

A 2015 systematic review and meta-analysis of 28 RCTs compared efficacy and safety outcomes for insulin glargine, NPH insulin, premixed insulin preparations, and insulin detemir in 12,669 adults with type 2 diabetes (T2D) who were also taking an oral antidiabetic drug (OAD).[1] In the comparison of glargine to NPH, there was no difference in risk for hypoglycemia (5 trials; N not provided; risk ratio [RR] = 0.92; 0.84-1.001).

Symptomatic hypoglycemia (6 RCTs; RR = 0.89; 0.83-0.96) and nocturnal hypoglycemia (6 RCTs; RR = 0.63; 0.51-0.77) occurred significantly less frequently in those treated with glargine and an OAD compared to NPH and an OAD. The risk for severe hypoglycemia was not different between regimens (5 RCTs; RR = 0.76; 0.47-1.23). Weight gain was also similar (6 RCTs; weighted mean difference [WMD] = 0.36 kg [–0.12 to 0.84]). This review was limited by the fact that many of the trials were of moderate quality, the majority were funded by pharmaceutical companies, fasting glucose goals varied between trials, and some trials had a short duration (6 months).

There may be some advantages of glargine over NPH

A 2008 meta-analysis of 12 RCTs (5 of which were not included in the 2015 review) with 4385 patients with T2D compared fasting plasma glucose (FPG), A1C, hypoglycemia, and body weight for patients treated with NPH vs with glargine.[2] Researchers found a significant difference in patient-reported hypoglycemia (10 trials; N not provided; 59% vs 53%; $P < .001$), symptomatic hypoglycemia (6 trials; 51% vs 43%; $P < .0001$), and nocturnal hypoglycemia (8 trials; 33% vs 19%; $P < .001$), favoring glargine over NPH. However, there was no difference between these 2 groups in confirmed hypoglycemia (2 trials; 10% vs 6.3%; $P = .11$) or severe hypoglycemia (7 trials; 2.4% vs 1.4%; $P = .07$). Of note, there was no difference between groups in FPG or A1C and a smaller weight gain in the NPH group (6 trials; WMD = 0.33 kg; 95% CI, –0.61 to –0.06). This review did not assess potential biases in the included trials.

Other results indicate a significant benefit from glargine

A 2014 RCT (published after the systematic review search date) compared hypoglycemia risk between NPH and glargine in 1017 adults ages 30 to 70 years who'd had T2D for at least 1 year.[3] Patients were randomized to receive an OAD paired with either once-daily glargine or twice-daily NPH. Insulin doses were titrated over the first 3 years of the study to achieve standard glycemic control (described

as FPG < 120 mg/dL; this goal was changed to < 100 mg/dL after the first year).

Over 5 years, once-daily glargine resulted in a significantly lower risk for all symptomatic hypoglycemia (odds ratio [OR] = 0.71; 95% CI, 0.52-0.98) and for any severe event (OR = 0.62; 95% CI, 0.41-0.95) compared to NPH. Using a logistic regression model, the authors predicted that if 25 patients were treated with NPH instead of glargine, 1 additional patient would experience at least 1 severe hypoglycemic event. This trial was funded by a pharmaceutical company.

Hypoglycemia requiring hospital care was similar for basal insulin and NPH

A 2018 retrospective observational study (N = 25,489) analyzed the association between the initiation of basal insulin analogs vs NPH with hypoglycemia-related ED visits or hospital admissions.[4] Adults older than 19 years with clinically recognized diabetes were identified using electronic medical records; those included in the analysis had newly initiated basal insulin therapy during the prior 12 months. Data was gathered via chart review.

The difference in ED visits or hospital admissions was not different between groups (mean difference = 3.1 events per 100 person-years; 95% CI, –1.5 to 7.7). Among 4428 patients matched by propensity score, there was again no difference for hypoglycemia-related ED visits or hospital admissions with insulin analog use (adjusted hazard ratio = 1.16; 95% CI, 0.71-1.78).

Editor's takeaway

Meta-analysis of large RCTs shows the glargine insulin adverse effects profile, specifically nonsevere hypoglycemia, to be inconsistently better than NPH. These small differences, plus once-daily dosing, may encourage prescribing of analog basal insulin, but price and the need for more than once-daily dosing remain worthy considerations. JFP

References

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