EDITORIAL

Revisiting NPH Insulin for Type 2 Diabetes
Is a Step Back the Path Forward?

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In spring 2017, the American Diabetes Association tasked a working group with examining soaring insulin list prices,[1] which had nearly tripled between 2002 and 2013.[2] Because pharmaceutical spending represents a prime contributor to the escalating costs of diabetes care in the United States,[2,3] these increases in insulin pricing warranted analysis.

In its recent report,[4] the American Diabetes Association working group detailed how a complex supply chain with only 3 suppliers and little price transparency had contributed to inflated insulin prices and a doubling of out-of-pocket costs between 2006 and 2013 for Medicare Part D enrollees, many of whom are on fixed incomes.

High insulin prices have additional adverse consequences for individuals with diabetes. These adverse consequences include nonadherence and nonpersistence (ie, premature discontinuation of prescribed therapies) and represent an important problem in need of solutions.

The basal insulin analogs glargine and detemir have largely supplanted once-popular human insulins (eg, neutral protamine Hagedorn [NPH]), for type 2 diabetes[5] at more than 10 times the price.[6] To justify their high cost, the relative clinical benefits of basal insulin analogs should be clear and compelling. Evidence from clinical trials suggests that basal insulin analogs modestly lower absolute rates of nocturnal hypoglycemia compared with NPH insulin,[7] but meta-analyses show little evidence for other benefits with basal insulin analogs such as reduction of severe hypoglycemia or improvement in glycemic control in type 2 diabetes.[7,8] Therefore, the clinical value of using basal analogs as front-line insulins for type 2 diabetes is unclear. There is a need for high-quality evidence comparing basal insulin analogs and NPH insulin for type 2 diabetes in clinical practice settings.

In this issue of *JAMA*, Lipska and colleagues[9] report findings from a retrospective cohort study that helps address this evidence gap. The authors conducted a propensity-matched analysis of data from a large integrated health care system, in which they compared time to an emergency department (ED) visit or hospital admission for hypoglycemia (primary outcome) and change in hemoglobin A_{1c} level within 1 year (secondary outcome) among patients initiating either basal insulin analogs (n = 1928) or NPH insulin (n = 23 561) between 2006 and 2015.

The overall rate of hypoglycemia-related ED visits or hospital admissions was low (11.9 events per 1000 person-years in the basal insulin analog group and 8.8 events per 1000 person-years in the NPH insulin group), and the event rates did not differ significantly between patients starting basal insulin analogs and NPH insulin in the adjusted analyses (hazard ratio, 1.16 [95% CI, 0.71 to 1.78]).

Patients starting NPH insulin experienced a modestly larger reduction in hemoglobin A_{1c} level 1 year after initiation compared with those starting basal analogs (between-group difference, −0.22% [95% CI, −0.09 to −0.37]). Based on these findings, Lipska et al[9] concluded that basal insulin analogs may not yield benefits vs NPH insulin with regard to the examined outcomes in type 2 diabetes.

This analysis had several strengths, including use of actual clinical data from a large cohort; cohort matching on a broad range of patient factors; and censoring patients for death, insulin discontinuation, addition of other insulins, and loss of prescription coverage. This analysis also had limitations that could be addressed in future comparisons of basal insulin analogs and NPH insulin. First, the authors exclusively examined hypoglycemia that resulted in ED or hospital visits, so they could not comment on hypoglycemic events that did not trigger health care use. These events could include nocturnal hypoglycemia, which basal insulin analogs reduce relative to NPH insulin in clinical trials,[7] and other symptomatic hypoglycemic events, which are clinically meaningful to patients.

Second, these results may not generalize to other health care systems because, counter to current prescribing trends in the United States favoring basal insulin analogs, the rate of NPH insulin initiation in the study population was particularly high (92%). Clinicians' greater familiarity with NPH insulin in this health care system may have reduced the likelihood of hypoglycemia among NPH insulin users, which may partly explain the low event rates.

Third, this analysis focused on initiation of basal insulin in patients with poorly controlled type 2 diabetes (mean hemoglobin A_{1c} level was 9.4% at baseline); therefore, the findings may not generalize to other populations such as patients with better-controlled type 2 diabetes, patients with type 1 diabetes, or those using complex basal-prandial insulin regimens.

Fourth, the method for matching patients in this study did not generate cohorts that were balanced on all covariates, possibly because the chosen approach was developed for genomics data of much higher dimensions than the more limited set of covariates available to these authors. As a result, residual confounding is possible, which the authors appropriately noted. Ensuring balance in all observed covariates could have further reduced residual confounding, but it

is unlikely that the findings would have meaningfully differed given the null results reported.

In its recent report, the American Diabetes Association working group on insulin pricing suggested, "Human insulin may be an appropriate alternative to more expensive analog insulins for some people with diabetes."[4] Lipska and colleagues[9] flip this formulation by proposing "it is likely that only select patients with type 2 diabetes benefit from insulin analogs vs human insulin preparations." What remains unknown is whether there is meaningful heterogeneity in how specific types of patients respond to basal insulin analogs and NPH insulin, and if such heterogeneity does exist, which factors moderate differences in patient responses.

Identifying moderating factors would allow clinicians to tailor insulin recommendations to maximize clinical benefits while minimizing costs. For example, some patient subgroups may experience better clinical and economic outcomes with NPH insulin, some subgroups may have similar outcomes, and some subgroups may experience better clinical and economic outcomes with basal insulin analogs. Future analyses with larger sample sizes should explore heterogeneity in patient responses to basal insulin analogs and NPH insulin because the current study was not powered to examine such subgroup differences.

By demonstrating that basal insulin analogs and NPH insulin were associated with rates of hypoglycemia-related ED visits or hospital admissions and glycemic control that did not differ significantly, this study corroborates findings from prior comparative trials in a clinical practice environment. Along with pursuing measures to help control increasing insulin costs,[10] reemphasizing NPH insulin as a front-line insulin option for most patients with type 2 diabetes could begin to bend the insulin cost curve for patients and insurers.

In this era of high costs of diabetes care, questions of value in insulin prescribing are unlikely to be resolved anytime soon. Newer, even higher-priced basal insulin analogs are now being promoted despite their minor absolute benefits vs current widely used analog options,[11,12] so questions about value will remain pressing into the foreseeable future.

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