

EDITORIAL



Intention to Treat — Initiating Insulin and the 4-T Study

Graham T. McMahon, M.D., M.M.Sc., and Robert G. Dluhy, M.D.

The normalization of glucose levels plays an important role in protecting patients with diabetes from complications such as myocardial infarction and stroke. To accomplish this goal, most patients with type 2 diabetes will ultimately require treatment with insulin, since oral antidiabetic drugs become insufficient as insulin production declines. Many diabetologists recommend that insulin therapy be initiated if a patient has a glycated hemoglobin level of more than 7% after having received the maximal dose of two oral agents for more than a few months.¹

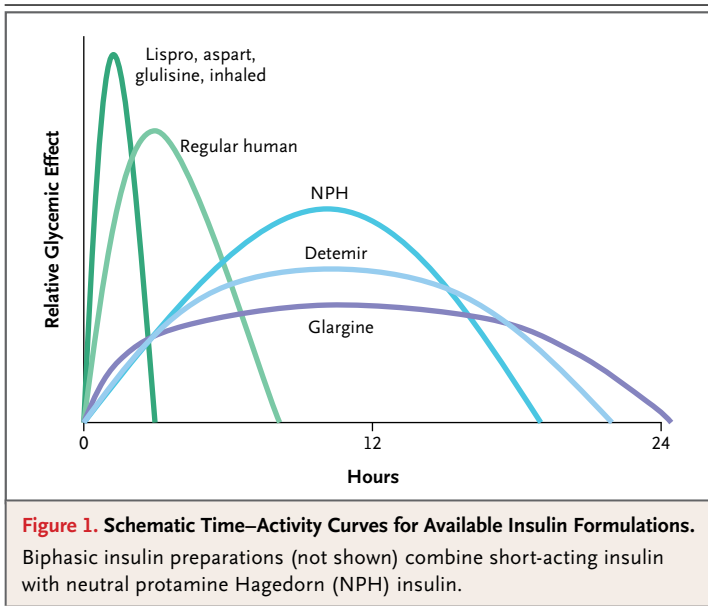
The question of how to initiate insulin therapy in patients with type 2 diabetes has become increasingly complicated as the range of insulin formulations with differing time–activity profiles has expanded. Clinicians seeking to initiate insulin often worry about insulin-induced hypoglycemia and weight gain. In this issue of the *Journal*, Holman et al.² present data from the first year of a 3-year, multicenter, open-label trial, called the Treating to Target in Type 2 Diabetes (4-T) study, that compares three of the many available strategies for combining oral antidiabetic agents and insulin. Patients were eligible for the study if they had type 2 diabetes with suboptimal glycemic control (defined as a glycated hemoglobin level of 7 to 10%) while receiving “maximally tolerated” sulfonylurea and metformin therapy. The investigators compared insulin initiation with a basal, biphasic, or prandial formulation in an attempt to clarify the relative merits of these three approaches. It is worth noting that this study was designed by the investigators but sponsored by Novo Nordisk, which manufactures all the studied types of insulin.

Glucose elevation after meals contributes more to the glycated hemoglobin level when glucose

levels are closer to target, whereas between-meal glucose levels contribute fractionally more as the mean glucose level rises.³ Consequently, basal insulin treatment is usually sufficient to bring most patients close to the glycated hemoglobin target, but attaining normal glucose levels usually necessitates the use of additional prandial insulin.

Basal formulations of insulin differ substantially in their pharmacodynamics. Glargine (Lantus, Sanofi-Aventis) is relatively peak-free and appears to have the longest and most stable duration of action among the basal insulin formulations. Detemir (Levemir, Novo Nordisk) has a half-life that increases with increasing dose. The peak and half-life of detemir insulin are intermediate between those of glargine and neutral protamine Hagedorn (NPH) insulin; the latter has a clear peak, and its pharmacokinetics can be erratic (Fig. 1). Prandial formulations of insulin include aspart (Novolog, Novo Nordisk), glulisine (Apidra, Sanofi-Aventis), lispro (Humalog, Eli Lilly), and inhaled insulin (Exubera, Pfizer). These prandial insulin formulations share broadly similar half-lives and effect; all are substantially faster in onset and clearance than regular human insulin. Biphasic insulin formulations typically combine prandial insulin with NPH.

The dosing and titration algorithm for insulin is just as important as the type of insulin chosen. The starting dose of insulin at bedtime is generally less important than a titration algorithm that targets a morning fasting glucose level of no more than 100 mg per deciliter. With appropriate instruction, many patients can titrate their own insulin doses according to simple rules with minimal oversight from practitioners.⁴ A typical starting dose is 10 units, or 0.1 to 0.2 unit per kilogram of body weight.¹ Most patients ulti-



mately require between 0.5 and 1.0 unit per kilogram.

Data from previous clinical trials indicate that the majority of patients receiving dual oral therapy who do not reach their glycemic target can achieve a glycated hemoglobin level of 7% or less with glargine or NPH at bedtime^{4,5} or detemir once or twice daily.^{6,7} As compared with NPH, the relatively peak-free basal insulin formulations (glargine and detemir) are associated with a lower risk of morning hypoglycemia after the nighttime dose.^{4,7}

The 4-T study adds to the available literature on insulin initiation. The study aimed to bring each patient's glycated hemoglobin level to 6.5% or less. The results from the first year are disappointing, since only a minority of patients achieved the target goal: 17% of those in the biphasic group, 24% in the prandial group, and 8% in the basal group. These rates are lower than those achieved in other trials of insulin initiation with different titration algorithms and different insulin formulations.^{4,5,7-9}

Why did relatively few patients achieve the target level of glycated hemoglobin in the first year of the 4-T study? Though the glycated hemoglobin level and other glucose targets are noted, the titration algorithm used in the study is not provided in detail. It is possible that part of the failure to reach the goal was that the algorithm was insufficiently proactive or was insufficiently

implemented, possibly resulting from the diversity of the 58 centers. The investigators did not appear to have a standardized approach to educating and supporting the patients and helping them maintain behavioral changes. Another possibility is that the rate of hypoglycemia in patients receiving prandial and biphasic insulins (with a respective median of eight and four symptomatic hypoglycemic events per patient per year with a glucose level of <56 mg per deciliter) constrained attempts to advance the insulin dose. In addition, previous clinical trials have indicated that the continuing administration of sulfonylureas as insulin is added, as was done in the study by Holman et al., exposes patients to additional hypoglycemic risk without providing additional benefit.¹⁰

The lower-than-expected effectiveness of detemir in the study may be attributable to the pharmacokinetics of this type of insulin — its half-life is dose dependent and shorter than that of glargine.¹¹ The reduced half-life may have resulted in inadequate insulin exposure in the second half of each day, since nearly 40% of patients required a second daily dose. The positive news from this study is its confirmation that the rate of hypoglycemia in patients treated with detemir is reassuringly low, since the majority of patients had no symptomatic events accompanied by a glucose reading of less than 56 mg per deciliter.

The 4-T study provides a clear indication that prandial and biphasic insulin formulations are suboptimal choices for insulin initiation and probably expose patients to an unnecessarily high risk of hypoglycemia without clinically important benefit. The second phase of the study should help to define the best next step for patients who do not reach their glucose target while receiving basal insulin alone, since these patients are most likely to benefit from additional prandial insulin.

For now, the recommendations for starting insulin therapy need not change as a result of this study. For patients with a glycated hemoglobin level of more than 7% on maximal doses of two oral agents, the best approach is to continue metformin and add a basal insulin; sulfonylureas are not synergistic with insulin and should generally be stopped.

Deciding among the various strategies for insulin initiation is probably less important than taking steps to start insulin in patients who need

it. Furthermore, though it is important to focus on glucose levels in patients with diabetes, clinicians should be aggressive with blood-pressure management since hypertension contributes at least as much as glucose to overall cardiovascular risk. In addition, aspirin, lipid-lowering therapies, smoking cessation, and exercise and weight-loss programs should be initiated when appropriate.¹² Patients do better when they have access to diabetes educators, understand their disease, and know how to interpret their self-monitored glucose records.¹³ Achieving these integrated goals saves lives,¹⁴ whatever insulin formulation is chosen.

No potential conflict of interest relevant to this article was reported.

Drs. McMahon and Dluhy are editors at the *Journal*.

This article (10.1056/NEJMe078196) was published at www.nejm.org on September 21, 2007.

1. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 2006;29:1963-72. [Erratum, *Diabetes Care* 2006;29:2816-8.]
2. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357. DOI: 10.1056/NEJMoa075392.
3. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 2003;26:881-5.
4. Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003;26:3080-6.
5. Yki-Järvinen H, Kauppinen-Mäkelin R, Tiikkainen M, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 2006;49:442-51.
6. Philis-Tsimikas A, Charpentier G, Clauson P, Ravn GM, Roberts VL, Thorsteinsson B. Comparison of once-daily insulin detemir with NPH insulin added to a regimen of oral antidiabetic drugs in poorly controlled type 2 diabetes. *Clin Ther* 2006;28:1569-81. [Erratum, *Clin Ther* 2006;28:1967.]
7. Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P. A 26-week, randomized, parallel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 2006;29:1269-74. [Erratum, *Diabetes Care* 2007;30:1035.]
8. Raskin P, Allen E, Hollander P, et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28:260-5.
9. Janka HU, Plewe G, Busch K. Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. *J Am Geriatr Soc* 2007;55:182-8.
10. Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1999;130:389-96.
11. Porcellati F, Rossetti P, Ricci Busciantella N, et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes mellitus: a double-blind, randomized, cross-over study. *Diabetes Care* (in press).
12. American Diabetes Association. Standards of medical care in diabetes — 2007. *Diabetes Care* 2007;30:Suppl 1:S4-S41.
13. Norris SL, Engelgau MM, Narayan KM. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomized controlled trials. *Diabetes Care* 2001;24:561-87.
14. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;348:383-93.

Copyright © 2007 Massachusetts Medical Society.