

Finally, with regard to the comments of van der Spek and Sonke, the determination of progression in a nonblinded setting may be biased, but similar hazard ratios for disease progression and for death provide support for the premise that bias in removing patients from the study did not affect the results. The data from all patients may not satisfy the proportional-hazards assumption, but the stratified log-rank test was the primary comparison between the treatment groups.

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1. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-45.
2. Lenz HJ, Van Cutsem E, Khambata-Ford S, et al. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *J Clin Oncol* 2006;24:4914-21.

Addition of Insulin to Oral Therapy in Type 2 Diabetes

TO THE EDITOR: Holman et al. (Oct. 25 issue)¹ report on the Treating to Target in Type 2 Diabetes (4-T) study of the addition of insulin to oral therapy in patients with type 2 diabetes. I think it is unreasonable for the authors to conclude that better glycemic control can be obtained with the addition of biphasic or prandial insulin than with the addition of basal insulin alone. Such a conclusion should be drawn only from trials with equal “insulinization” of the study groups. Since insulin detemir has a lower affinity, the mean daily molar dose requirement for basal insulin would be expected to be higher (up to 3.8 times) for detemir than for neutral protamine Hagedorn (NPH).²

Insulin doses in the three groups at the end of the study by Holman et al. showed significant variation, with the lowest dose in the group that received basal insulin alone (insulin doses in the prandial, biphasic, and basal groups, 0.61, 0.53, and 0.49 IU per kilogram of body weight per day, respectively; $P=0.04$ for the overall comparison). Beyond the underinsulinization in all three study groups, given an expected dose of 1.2 IU per kilogram per day to overcome glucotoxicity in obese patients with type 2 diabetes for long-term therapy,³ the group that received basal insulin detemir alone seems to have been the least insulinized.¹

Thus, poorer glycemic control with basal insulin detemir alone in this trial might well be considered the result of insufficient dose titration.

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1. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biph-

asic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 2007;357:1716-30.

2. Vague P, Selam JL, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. *Diabetes Care* 2003;26:590-6.

3. Pouwels MJ, Tack CJ, Hermus AR, Lutterman JA. Treatment with intravenous insulin followed by continuous subcutaneous insulin infusion improves glycaemic control in severely resistant Type 2 diabetic patients. *Diabet Med* 2003;20:76-9.

TO THE EDITOR: In their editorial accompanying the report on the 4-T study, McMahon and Dluhy advocate initiating insulin therapy with basal insulin, describing prandial and premixed insulins as “suboptimal choices” with “an unnecessarily high risk of hypoglycemia.”¹ This recommendation is inconsistent with both the results of the 4-T study and those of studies cited by Holman et al. in their discussion, and it trivializes the approximately 80% likelihood of not reaching glycemic targets among patients with glycated hemoglobin levels exceeding 8.5% who are treated with basal insulin. Furthermore, the presumption that the risk of approximately four to eight episodes of nonsevere hypoglycemia per patient-year outweighs the benefits of an additional glycated hemoglobin reduction of approximately 0.5% is unsubstantiated, given the minimal risk of mild hypoglycemia and a concern that reported differences in hypoglycemia may reflect detection bias from increased monitoring by the prandial-insulin group.

Finally, the editorialists’ speculation that the longer half-life of glargine may have resulted in better glycemic control than that provided by detemir or NPH is not supported by prior studies.^{2,3}

We await completion of both the 4-T study and the ongoing DURABLE Trial⁴ (comparing the 2-year durability of premixed and basal insulin in maintaining glycemic goals in type 2 diabetes).

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1. McMahon GT, Dluhy RG. Intention to treat — initiating insulin and the 4-T study. *N Engl J Med* 2007;357:1759-61.
2. Rosenstock J, Davies M, Home PD, Larsen J, Tamer SC, Scherthaner G. Insulin detemir added to oral anti-diabetic drugs in type 2 diabetes provides glycemic control comparable to insulin glargine with less weight gain. *Diabetes* 2006;55: Suppl 1:A132. abstract.
3. 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.
4. ClinicalTrials.gov. The DURABLE trial: evaluating the durability of starter insulin regimens in patients with type 2 diabetes. (Accessed February 22, 2008, at <http://www.clinicaltrials.gov/ct/show/NCT00279201?order=3>.)

THE AUTHORS REPLY: Dağdelen is concerned that the three groups in the 4-T study were not equally insulinized. Insulin detemir is formulated at a higher concentration than NPH (2400 nmol per liter vs. 600 nmol per liter), since it has a lower molar potency than human insulin. This insulin-formulation dose equivalence was based largely on studies in type 1 diabetes. It is uncertain whether the detemir formulation available provides dose equivalence in type 2 diabetes, but we disagree with Dağdelen's expectation that the detemir dose requirement in the 4-T study would be as high as 1.2 IU per kilogram per day. This assumption is based on a study of just eight subjects with a mean body-mass index (the weight in kilograms divided by the square of the height in meters) of 38 and a baseline glycated hemoglobin level of 12.6%. A trial that compared insulin detemir twice a day with NPH insulin in 475 subjects with type 2 diabetes, with baseline glycated hemoglobin levels and a duration of diabetes that were similar to those in the 4-T study, showed a mean dose requirement after 6 months of 0.75 IU per kilogram per day.¹

The 4-T study aimed to achieve glycemic targets with treatment, not to achieve equivalent insulinization.² The trial compared the ability of three different insulin regimens to reach these glycemic goals, with the biphasic and prandial regi-

mens by their nature offering more opportunities each day for insulin dose titration than the basal regimen. Over the first year of the study, basal insulin doses continued to be increased, but no further reduction in the mean glycated hemoglobin level was seen after 6 months, demonstrating that studies of short-term efficacy can be misleading with respect to longer-term outcomes.

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1. Hermansen K, Davies M, Derezinski J, 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-naïve people with type 2 diabetes. *Diabetes Care* 2006;29:1269-74.
2. 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.

THE EDITORIALISTS REPLY: We concur with Ilag and colleagues on the imperative to help patients with type 2 diabetes attain their glycemic targets. In the 4-T study, only 27% of patients with type 2 diabetes reached a glycated hemoglobin level of 7% or less after 1 year of treatment with insulin detemir. In contrast, 58% of patients in the Treat-to-Target Trial with a similar starting glycated hemoglobin level who were treated with either glargine or NPH reached that target after 24 weeks of treatment. Neither prandial nor premixed insulin appears to have had additional efficacy, as compared with the results of the Treat-to-Target Trial, but both were associated with a substantially higher rate of confirmed hypoglycemia. We share the authors' anticipation of further research that will help clinicians weigh the differential benefits of introducing prandial, premixed, or basal insulin when insulin therapy is indicated. However, our interpretation of the best evidence suggests that basal insulin remains the optimal approach for initiating insulin therapy in patients with type 2 diabetes until subsequent studies demonstrate superior efficacy with a different strategy.

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