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Insulin Regimens in Type 2 Diabetes

TO THE EDITOR: In the Treating to Target in Type 2 Diabetes (4-T) study, Holman et al. (Oct. 29 issue)¹ previously reported in 2007 that at 1 year there was less hypoglycemia among patients who received a basal-insulin–based regimen.² Early in 2008, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study³ signaled safety concerns with respect to hypoglycemia. With its open-label design, the 4-T study could thus have a bias against effective insulin dosing in the biphasic group, since insulin doses could be adjusted as clinically appropriate. Also, a potential legacy effect of poorer glycemic control after 1 year² might make initiating prandial or biphasic insulin favorable.⁴ Probably, few patients would have needed a second type of insulin in the biphasic group if a third biphasic injection had been an option.

After 1 year, the glycated hemoglobin level and the risk of hypoglycemia were similar in all three study groups. Hence, the cumulative risk of hypoglycemia may not be as important an outcome as the glycated hemoglobin level. The proportion of patients who had a glycated hemoglobin level of less than 6.5% could have depended on the baseline glycated hemoglobin level, which was (insignificantly) 0.2% lower in the basal group. However, baseline adjustments were defined only for subgroups. Less weight gain thus represents the main advantage of initiating detemir, an effect probably specific for detemir rather than for all types of basal insulin.⁵ Thus, we do not agree that the 4-T study convincingly suggests a more favorable outcome for a basal-insulin–based regimen than a biphasic-insulin–based regimen in patients with type 2 diabetes who have not received previous insulin therapy.

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1. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736-47.
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4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-Year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
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TO THE EDITOR: Holman et al. report that there was a significant difference in the number of deaths from cardiovascular causes among patients in the three study groups in the 4-T study. Of 14 deaths from cardiovascular causes, 4 were in the biphasic group, 9 in the prandial group, and 1 in the basal group ($P=0.002$). This result is of particular interest in light of the findings of the ACCORD trial,¹ in which there was increased cardiovascular mortality in the intensive-therapy group (target glycated hemoglobin level, <6%) than the standard-therapy group (target glycated hemoglobin level, 7.0 to 7.9%). In the ACCORD trial, the proportions of patients who received prandial insulin regimens and who had severe hypoglycemia were higher in the intensive-therapy group than in the standard-therapy group. Because patients in the ACCORD trial were randomly assigned to a therapeutic strategy rather than a specific treatment regimen, it was not possible to establish whether the increased cardiovascular mortality was related to specific drugs or drug combinations (e.g., prandial insulin and rosiglitazone), the sequelae of hypoglycemia, or other factors associated with intensive therapy. We believe that the results regarding the rate of death from cardiovascular causes in the 4-T study merit further attention and scientific discussion.

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1. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.

TO THE EDITOR: Holman et al. describe the 3-year efficacy of three types of insulin regimens in patients with type 2 diabetes. We think that the results support alternative conclusions. The proportion of patients who replaced sulfonylureas with a second type of insulin to achieve good metabolic control differed significantly among the three groups, with 67.7% in the biphasic group, 73.6% in the prandial group, and 81.6% in the basal group ($P=0.002$). These data support the conclusion that biphasic insulin maintains a good metabolic control in a higher proportion of patients than either basal or prandial insulin alone.

As stated by Roden in the accompanying editorial,¹ the regimen that was initiated with basal insulin and the regimen initiated with prandial insulin converged in a basal-plus-prandial strategy. From a clinical-practice perspective, I think that these data support the idea that a biphasic regimen is a better option than the prandial or basal insulin alone, and the basal-plus-prandial regimen would be a better option as a next step than biphasic insulin.

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1. Roden M. Optimal insulin treatment in type 2 diabetes. *N Engl J Med* 2009;361:1801-3.

THE AUTHORS REPLY: In the 4-T study, we compared three treatment strategies over 3 years, which allowed for the evaluation of the cumulative effects, rather than short-term advantages, of these regimens. We openly addressed concerns that

had been raised in the ACCORD study, and any such effect probably would have been felt in each study group equally. The addition of a midday dose of biphasic insulin as an alternative strategy to adding prandial insulin was not tested in our study but would still have required a third injection.

The disparity in the number of deaths from cardiovascular causes among the study groups is clearly a concern, but a detailed review of the individual cases is uninformative. The numbers of patients who died and who were taking a second type of insulin were 1 (25%) in the biphasic group, 3 (33%) in the prandial group, and 1 (100%) in the basal group. As compared with the cohort as a whole, the median rates of grade 2 hypoglycemia were lower in the biphasic and prandial groups but higher in the basal group, with per-patient rates of 1.7 in the biphasic group, 2.3 in the prandial group, and 4.3 in the basal group per year, with no reports of any grade 3 episodes. Median glycated hemoglobin levels were 6.9%, 7.0%, and 7.9%, respectively.

The 4-T trial used analogue insulin preparations to compare formulations with different insulin-delivery profiles in a head-to-head manner. As stated in the article, we believe that our findings may well be generalizable to other short- and long-acting insulin preparations with similar action profiles, although the costs of these may vary across health care systems.

The proportions of patients who required a second insulin formulation (with cessation of sulfonylurea therapy) per protocol because they had a glycated hemoglobin level of more than 6.5% were 88% in the biphasic group, 82% in the prandial group, and 89% in the basal group. However, only 68%, 74%, and 82% of the patients, respectively, actually made a sustained transition to a complex insulin regimen. We are exploring further the reduced take-up of insulin intensification in the biphasic group but maintain that the primary results of the 4-T trial support the initial addition of basal insulin to oral therapy, with subsequent intensification to a basal-prandial regimen.

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Since publication of their article, the authors report no further potential conflict of interest.