Choosing an Insulin Regimen for Patients With Type 2 Diabetes

Reviewed by Michael Pignone, MD, MPH

STUDY

Holman RR, Thorne KI, Farmer AJ, Davies MJ, Keenan JF, Paul S, Levy JC; 4-T Study Group: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* 357:1716–1730, 2007

SUMMARY

Design. A randomized controlled trial comparing three insulin regimens: biphasic insulin aspart twice daily, prandial insulin aspart three times daily, or basal insulin detemir once daily (with the option of twice daily if needed).

Subjects. Participants included 708 patients (64% male) ≥ 18 years of age (mean age 61.7 years) with type 2 diabetes, hemoglobin A_{1c} (A1C) levels of 7.0–10.0% on maximally tolerated doses of sulfonylurea and metformin, who were willing to inject insulin and perform self-monitoring of blood glucose. Patients with BMI > 40 kg/m², taking thiazolidinediones, or who had been diagnosed with retinopathy or nephropathy were excluded.

Methods. Participants were recruited from 58 clinical centers in the United Kingdom and Ireland and randomized centrally. Participants assigned to each group were managed according to a regimen-specific trial algorithm that estimated starting insulin dose. Patients were then seen at 2, 6, 12, 24, 38, and 52 weeks with interim phone contact and were managed by algorithm, based on capillary blood glucose levels obtained before each visit. Additional regimen changes between visits were encouraged if necessary. The primary outcome was A1C at 52 weeks after enrollment. Other outcomes included hypoglycemic events, weight gain, and proportion of patients achieving A1C levels < 6.5%.

Results. At 52 weeks, the mean A1C was 7.3% for biphasic insulin, 7.2% for prandial insulin, and 7.6% for basal insulin. Few patients achieved an A1C of < 6.5% (17, 24, and 8% for biphasic, prandial, and basal groups, respectively). Hypoglycemic events were more common in the biphasic (mean 5.7 events during 52 weeks) and prandial (mean 12.0 events) than in the basal insulin group (mean 2.3 events). No severe hypoglycemia occurred, and there were no differences in other severe adverse events. Weight gain was greater with the biphasic (+ 4.7 kg) and prandial (+ 5.7 kg) regimens than with the basal (+ 1.9 kg) regimen. No differences in quality of life were observed. One-third of patients on the basal regimen required twice-daily injections, and a minority of patients (biphasic 9, prandial 4, and basal 18%) required addition of a second type of insulin to control hyperglycemia.

Conclusions. Biphasic and prandial insulin regimens produced somewhat lower mean A1C levels than a basal regimen but were associated with more minor hypoglycemic events and weight gain and required more injections.

COMMENTARY

The 4T study provides important information for a challenging clinical issue: the decision about what type of insulin regimen to use in patients with type 2 diabetes who have suboptimal glycemic control on oral agents (in this case, metformin and sulfonylurea) alone. The 4T investigators compared regimens of biphasic insulin aspart (twice daily), prandial insulin aspart (three times per day), or basal insulin detemir (one or two times per day) and found that the biphasic and prandial regimens produced slightly lower mean A1C levels but more frequent nonsevere hypoglycemia and greater weight gain. The trial was not designed or powered to address other clinical endpoints, such as cardiovascular events or microvascular complications. The methodological quality of the trial was high. Randomization produced relatively balanced groups. The proportion of patients completing 52 weeks of follow-up was > 90% and did not differ significantly by group.

To determine how the results of this trial should affect clinical practice, we must weigh the potential benefits and downsides of the different regimens. Given that the prandial regimen produced only slightly lower (0.1%) A1C levels with more hypoglycemia and weight gain than the biphasic regimen, it would be difficult to recommend the prandial regimen as first-line therapy for patients initiating insulin.

Whether the biphasic regimen should be considered to be superior to the basal regimen as initial therapy is more difficult. The difference in A1C between regimens is modest (0.3–0.5%) and would translate into only modest differences in the absolute risk of microvascular events, particularly for older

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patients with no baseline nephropathy or retinopathy.[1] This benefit would come with increased weight gain and hypoglycemia. The biphasic regimen requires two injections per day, whereas the basal regimen requires either one or two shots per day. Whether the difference in the number of injections is meaningful to patients who have agreed to insulin therapy is unclear. However, the time spent on diabetes care is substantial[2] and should be factored into the decision about which initial insulin regimen to begin, recognizing that patients can be shifted to a more intensive regimen if initial control is deemed inadequate.

It is important to recognize that the management of patients' insulin regimens within this trial was guided by a well-designed algorithm and regular clinical assessments over the phone and in person. The outcomes obtained may be different in usual care, with a wider variety of patients and less structured assessment and follow-up. It is possible that such practice differences could affect both the likelihood of benefit (differences in A1C) as well as safety (differences in hypoglycemia). The direction of such effects is not certain, but one could hypothesize that differences in benefit among regimens could be effaced by a lack of organized care and that the likelihood of adverse events could increase. Given this, I plan to continue starting patients on an initial basal regimen, while reserving the option of a more intensive regimen if adequate glycemic control is not achieved.

REFERENCES

[1]CDC Diabetes Cost-Effectiveness Group: Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *JAMA* 287:2542–2551, 2002

[2]Safford MM, Russell L, Suh DC, Roman S, Pogach L: How much time do patients with diabetes spend on self-care? *J Am Board Fam Pract* 18:262–270, 2005

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