

Physicians' Corner

Afloat in a Rising Sea of Type 2 Diabetes: Looking for Lighthouses in the 4-T Trial

Commentary provided by Charles F. Shaefer, Jr., MD, FACP, FCCP

University Primary Care Physicians, Augusta, Georgia

My family and I are sailors. After years of heading out into oceans and bays, we have come to realize just how important the lighthouses and marker buoys are to help us navigate through tricky or unknown passages. These navigational guides are critical to maintaining a proper sense of direction and progress during a sailing trip. I have always depended on knowledge of these guides to keep from getting lost and to help me achieve safe passage. Largely, this approach has served me well. I admit I have accidentally run aground from time to time, but when I did hit bottom, I was always confident that I knew exactly where on the bottom I sat! There is comfort in knowing where you are and where you are going. Obviously, I put much emphasis on scanning for navigational markers.

GUIDANCE BUOYS IN DIABETES TREATMENT

This same search for “guidance buoys” spills over into my reading and evaluation of medical studies, particularly as they apply to diabetic treatment. It is important to know where you are and where you are going with the treatment of your type 2 diabetes patient. A specific pathway for diabetic treatment, such as the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus algorithm for the treatment of type 2 diabetes,¹ may be relatively easy to follow once that “safe passage” has been identified. However, the fact that there are so many treatment choices out there, so many different ways to turn and become lost, makes it imperative to search for evidence-based markers that give some sense of direction or confirmation that we are moving along the right pathway.

In the 4-T (Treating To Target in Type 2 Diabetes) trial, Holman and coinvestigators² contributed significantly to our sense of guidance in the delivery of therapy for patients with type 2 diabetes. While the purpose of the study was to provide information about the degree of diabetic control that could be achieved with strategies involving basal, prandial, and biphasic insulin in addition to oral antidiabetic drugs (OADs), within the study are several points that are immensely valuable to the primary care provider for guidance about the day-to-day treatment of diabetes.

The first “buoy” in the 4-T trial should help give us guidance with regard to effective titration of basal insulin. For reasons that are somewhat obscure to me, I have noticed that there is often a 30-unit barrier, or ceiling, to basal insulin titration. Many primary care providers will titrate basal insulin upward to a level of ~30 units and then come to a halt. Whether this seems like an uncomfortable amount of insulin to some providers or whether it has to do with experiences in training is totally unclear to me. What is evident, however, is that regardless of the area of the country I visit, there is a noticeable pattern of primary care providers not titrating above 30 units of basal insulin. Typically, the provider either stops titrating and remains at the 30-unit mark or switches from basal insulin to a premixed insulin product. They may believe that a premixed product may be simpler and more effective for the patient.

TITRATION ALGORITHMS

While there are a variety of forced-titration and self-titration insulin algorithms in use, none seem to provide much prospective guidance regarding how high the basal insulin dose is likely to be carried to achieve ultimate control.³⁻⁶ Obviously, in the highly insulin-resistant type 2 diabetes patient there may be a significant degree of variability in the final effective dosage; but the 4-T trial demonstrated that in 89% of participants, the actual insulin dose used corresponded to pretitration projections.² Therefore, almost 90% of patients could be armed with knowledge about their ultimate insulin requirement at the outset of treatment.

Share Insulin Titration Goals With the Patient

The impact of this finding is clear. When we embark on a titration algorithm for basal insulin, we may improve effective dosing by discussing with our patients what a reasonable basal insulin estimate for them might be. The authors of the 4-T trial used a fairly complex mathematical formula to assess ultimate insulin need. While more general estimates have not been subjected to research scrutiny, as was the 4-T trial algorithm, a commonly acknowledged estimate of 0.4–0.6 unit/kg per day of basal insulin is likely to be required. So where does this estimate come from? Forced titration studies involving patients with type 2 diabetes who were not well controlled on OADs and therefore required the addition of basal insulin

show that, in the final analysis, this level of insulin use was needed for study subjects to reach fasting glucose targets. This rough estimate has worked across a spectrum of studies—from the Treat-to-Target trial³ comparing the addition of glargine with that of neutral protamine Hagedorn (NPH) insulin to the study comparing detemir with glargine as the added basal insulin.⁷ Even the recent 4-T trial² demonstrated daily basal insulin doses in line with this estimate. Therefore, the first practical lesson from 4-T is to be sure at the time we initiate insulin treatment that we share with the patient what the ultimate titration goal is likely to be based on our estimation. This knowledge will not only empower the patient to break through that 30-unit barrier and move on to effective basal doses but also make the provider more comfortable as the dose level increases. In addition, this approach will make the insulin titration follow-up visit far more productive. All of us have experienced the follow-up visit when a patient proudly announces that he or she has added 30% to the basal insulin dose—all the way from 10 units daily to 13 units daily, when the estimated target may be closer to 50 units. The patient is disappointed that glucose control is not better, and the provider is discouraged by an unproductive office visit. Estimating and then sharing the insulin goal with the patient should help to avoid this problem.

Basal Versus Biphasic Insulin

Another valuable piece of information that comes from the 4-T trial confirms a notion that for years has been an often unreferenced teaching point. We have routinely taught that patients who continue to have glycosylated hemoglobin (A1C) levels <8.5% to 9% on 1 or 2 OADs are most likely to benefit from the addition of basal insulin. In the 4-T trial,² not only did the authors reach this same conclusion, they also shed significant light on the use of basal insulin versus biphasic insulin (premixed analogues) or prandial insulin to achieve A1C targets when starting at A1C levels \leq 8.5%. In fact, basal insulin was actually preferred over biphasic or prandial insulin. Although the A1C end points achieved with basal insulin plus OADs were similar to those achieved with biphasic or prandial insulin, the basal insulin/OAD regimen exposed patients to less risk of hypoglycemia or weight gain than did the biphasic or prandial regimens. This finding correlates well with the ADA/EASD consensus algorithm for the treatment of type 2 diabetes, which suggests that premixed insulin should not be used during dose adjustment phases.¹ The 4-T trial certainly guides us toward the use of basal insulin rather than biphasic insulin in the most commonly encountered patients who are not able to reach A1C targets on 1 or 2 oral agents. Obviously, this is another important “navigational” consideration, as it speaks directly to how to select among the insulin types used most often.

Benefits of Self-Titration Algorithms

In an excellent editorial regarding the 4-T trial, McMahon and Dluhy⁸ indicated that they were disappointed that better A1C results were not achieved in the trial. Authors and editorialists alike concluded that part of the problem was not having as effective a titration algorithm as possible. McMahon and Dluhy specifically commented that more important than the dose of insulin is an adequate titration algorithm to drive the increasing insulin dosage. They went on to reflect on the benefit of self-titration algorithms as effective and highly satisfactory tools that assist patients in going from a starting dose of basal insulin to a truly effective dose with maximum self-participation and self-control and few adverse events.⁴⁻⁶ This notion was again underscored in the 4-T trial.

Insulin Glargine Versus Insulin Detemir

Finally, the 4-T trial sheds some light on the practical use of insulin detemir. My personal observation is that most practitioners have recognized that NPH insulin probably doesn't fit into the modern collection of basal insulins. They relate to me that in their practices, NPH insulin is used only when highly restrictive formularies offer no other option. For most of us, the choice of basal insulin is either detemir or glargine. However, as McMahon and Dluhy suggest,⁸ there is clearly a difference between detemir and glargine and their basic pharmacokinetic and pharmacodynamic profiles. Obviously, an essential consideration of any basal insulin strategy is the critical question of how many times a day the patient will need to take the insulin. Although it is widely accepted that glargine is a once-daily basal insulin,⁹ I have observed that many practitioners and pharmacists do not have a firm concept of whether detemir is a once-daily or twice-daily basal insulin. In the 4-T trial,² 33.8% of patients required detemir twice daily to reach an effective dose. Whereas some of the available clamp studies disagree with regard to the pharmacokinetic and pharmacodynamic profiles of glargine and detemir,^{9,10} findings of the 4-T trial agree with those of other clinical trials^{5,7,11} and suggest that, in a number of patients, detemir will be needed twice daily. This is highly useful information for planning the direction and details of a patient's basal insulin treatment strategy.

NAVIGATIONAL MARKERS IN TYPE 2 DIABETES WATERS

It is helpful to discover any “navigational aide” that will allow us to move more confidently down a diabetes treatment path. The 4-T trial provides several such “markers” for those of us sailing around in type 2 diabetes waters. First, at

moderate levels of A1C elevation, basal insulin added to OADs should be our preferred strategy. Second, providing our patients with estimated titration end points may be a very useful piece of encouraging information. Working out this estimate may help both patients and providers reach effective basal dosing. Third, a self-administered forced-titration algorithm may be one of the more critical elements in instituting and advancing basal insulin therapy. Finally, we learn once again that it is important for practitioners to understand the basic pharmacologic properties of the various therapeutic agents, as there are subtle but distinct differences in performance that will influence the choice of agent.

Hopefully, the contents of both this issue and future issues of *Insulin* will continue to assist the primary care community in better understanding how to navigate through the myriad agents available and develop a workable strategy to help their patients reach their A1C targets.

“Fair winds and following seas”

(Navy jargon for “smooth sailing to all”)

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