COMMENTARY

A Clinical Conundrum: Intensifying Glycemic Control in the Presence of Advanced Diabetic Retinopathy

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Diabetic retinopathy (DR) is a potentially devastating complication of diabetes because of the risk of developing blindness. While therapies to prevent blindness are improving, in much of the world visual impairment continues to occur and impact on the lives of people with diabetes and the societies they live in (1,2). Glycemic control has been shown to provide protection from progression of DR (3–5), but there appear to be limits to that protection. Lowering A1C with a goal of achieving A1C <7% was no better than using a goal slightly above that (6.8% vs. 7.3%) when baseline A1C was ∼7.5% at the outset; this small decrement and small continued difference did not further protect the retina (6). Furthermore, if duration of diabetes is sufficiently long, even relatively tight control is eventually associated with development of DR (3–5), suggesting that there are other factors that mediate DR besides glycemia (7,8).

Another factor that might limit the effect of improving glycemia to prevent progression is the presence of advanced DR at the time of initiating a glycemic control trial (9). The Veterans Affairs Diabetes Trial (VADT) did not show evidence of protection against DR progression, explained by the severity level of DR at the start of the trial (9), which was greater than in other comparable large trials (3–5).

This month's issue of *Diabetes Care* contains another publication from the VADT with the major outcome focused on eye procedures that were performed subsequent to entry into the trial and during long-term follow-up (10). These included procedures targeted at retinal complications, such as laser photocoagulation, intravitreous injection of anti-VEGF, and vitrectomy. The need for eye procedures was compared for an intervention (tight glycemic control) versus a standard control group. There was no benefit to being in the intensive therapy arm over the control arm in the number of procedures performed, despite a 1.5% A1C difference in the two main groups in the trial (6.9% vs. 8.4%, respectively), with a baseline starting A1C of ∼9.4% (9). Indeed, there was a nonsignificant increase in number of procedures performed in the intervention group (10).

Important strengths of this report are the large size of the cohort, the length of follow-up, and the prospective nature of this randomized, controlled study. The report includes three periods over a total of 17 years of follow-up of VADT. Its major weakness is the post hoc nature of the analysis, which led to the limitation that the clinical rationale for the primary outcome, ocular procedures, was not determined in advance. Procedures were carried out according to the prevailing approaches used by the patients' eye care providers. Thus, this outcome depended on individual choices of practitioner and patient and availability of the procedures. Additionally, the authors included cataract surgery as one of the eye procedures, a complication more common in diabetes but not known to be affected by glycemic control or having pathogenesis similar to that of DR. However, separate analysis excluding cataract surgery revealed the same result for retina-focused procedures, suggesting that this is not a confounder.

Failure to find a reduction in ocular procedures therefore fits with the original findings of the VADT that intensive glycemic control was ineffective in impacting DR incidence or progression (9) and even raises the possibility that there may be increased risk to the retina associated with aggressive intervention to improve glycemia (10). The authors suggest lack of benefit is explained by greater severity of DR at the initiation of the trial compared with other landmark studies (3–5).

In evaluation of the results of other large studies that investigated the role of glycemic control in DR, it is clear that the results are not uniform. Earlier studies showed dramatic differences between effects of tight and usual glucose control on incidence and progression of DR (3,4). In later trials involving type 2 diabetes, only the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed

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benefit (5), also after longer-term follow-up (11). Both the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial (6) and VADT (9) failed to show significant benefit. In the case of ADVANCE this may be due to better glycemia in the entire cohort prior to study entry as well as good glycemic control in the standard therapy group during the study (6). This is the opposite of the explanation for the same negative outcome observed in the VADT, namely, advanced DR and poor diabetes control at the outset (9). These similar outcomes in disparate populations suggest that improving glycemic control will not protect against DR if one already has good glucose control, or, in contradistinction, too advanced DR at the outset.

More importantly, what does this tell us about management of diabetes in people with advanced DR that we see in practice? It is certainly not uncommon for a diabetes specialist or primary care provider to see a patient in poor control, often with longer disease duration, who already has significant DR. What can we expect will happen with DR when we initiate tight glucose control? Will we see lack of protection, or even worse, deterioration of retinal findings as glycemia improves (12–14)? The hint at an increased number of procedures with better control in the current study reinforces that concern (10). There is a dearth of information to guide us in this not uncommon situation. Should we slow down the rate of glycemic normalization? Should we ignore potential loss in visual acuity to obtain other benefits of glycemic control? How do we discuss this with our patients to give them agency in the decision, when the data are so meager?

This report advances the field by forcing us to confront these questions, raised by trials such as the VADT that unexpectedly show no benefit in response to previously well-accepted practices. In the case of the ADVANCE trial, we are cautioned that we may not get further retinal protection from additional lowering of A1C in patients with reasonable control already (6). We can live with that. But the situation is less than clear for patients who have advanced DR, who are often in poor glycemic control and can comprise 25% of primary care diabetes patients (15). Aggressive simultaneous treatment of eye disease and glucose may be the answer, especially since recent studies indicate potential utility for intraocular VEGF inhibitors at earlier stages of DR (16).

It appears that we will have no good answers to these questions without the benefit of a clinical trial to evaluate outcomes in a population specifically designed to address these issues. The results of a trial with patients selected for more advanced DR and including a variety of ethnic groups (17), that emphasizes DR outcomes and quality of life, would be enormously helpful to the practicing physician faced with the conundrum posed by these patients when we see them in the clinic.

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