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Editorial

Preventing Diabetic Retinopathy Progression

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The recent report from the Action to Control Cardiovascular Risk in Diabetes Follow-on (ACCORDION) Research Group has important implications for ophthalmologists observing patients with diabetes.[1] The ACCORDION study has shown once again that intensive glycemic control has long-lasting effects in reducing the risk of retinopathy progression. Although the role of achieving so-called tight blood glucose control was controversial many decades ago, there has been consensus on its importance for more than 2 decades. So why is this recent article important?

The Diabetes Control and Complications Trial (DCCT) published the results of its 10-year clinical trial in 1993. The DCCT studied 1441 patients with type 1 diabetes, randomly assigned either to conventional or intensive therapy that achieved glycated hemoglobin (HbA1c) levels of approximately 9% versus 7%, respectively. The DCCT conclusively demonstrated the importance of intensive blood glucose control in slowing the microvascular complications of diabetes, including retinopathy, nephropathy, and neuropathy.[2] Nearly all of the DCCT participants were followed up subsequently in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study.[3] During the EDIC study, the mean HbA1c levels equalized rapidly between the 2 originally randomized groups, with that of the original intense treatment group rising to approximately 8% and that of the standard group falling to the same level. Despite this equalization of glycemic control in the 2 groups, there continued to be an approximately 50% risk reduction of further retinopathy progression in the original intensive control group, a phenomenon termed *metabolic memory*.[4] Even 3 decades after the original randomization, the relative benefits from being assigned to the intensive treatment group continue to accrue, with an almost 50% reduction in the risk of advanced retinal complications and of having ocular surgery (primarily cataract, vitrectomy, and retinal detachment surgery) in the original intensive treatment group.[5] Lest one think this is important only in persons with type 1 diabetes, the 10-year posttrial follow-up of participants with type 2 diabetes in the United Kingdom Prospective Diabetes Project (UKPDS), who initially were randomly assigned to intensive glucose therapy, also showed a reduction in risk for microvascular complications compared with those initially assigned to conventional care.[6] The continued effect of the original treatment assignment persisted, although the HbA1c levels equalized over the first year after the trial was completed, similar to the findings in the DCCT and EDIC.[4]

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The long-term beneficial results of intensive therapy in type 2 diabetes have been demonstrated again in the recent publication from the ACCORDION research group.[1] The ACCORDION study resembled the long-term follow-up of the DCCT and UKPDS as it carried out an observational follow-up of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study cohort, after the randomized treatment allocation ended. With a double 2×2 factorial design, ACCORD evaluated intensive therapy compared with standard therapy for the control of glycemia and blood pressure and evaluated the effect of fenofibrate compared with placebo in persons with type 2 diabetes with established cardiovascular disease (CVD) or who at high risk for CVD.[7] In the glycemia control arm of the ACCORD study, participants started with a mean HbA1c of approximately 8.1% and were assigned randomly to receive either intensive glycemic control (target HbA1c level, <6.0%) or standard control (target HbA1c level, 7.0%–7.9%). During the trial, the HbA1c levels decreased to a mean of 6.4% in the intensive group and to 7.5% in the standard group. After a mean 3.5 years of follow-up, the glycemia control arm of the study was discontinued because of a statistically significant increase in all-cause mortality in the intensive therapy group compared with the standard group (5.0% and 4.0%, respectively; hazard ratio, 1.22; 95% confidence interval, 1.01–1.46; $P = 0.04$).[7] The risk for CVD mortality was increased by 35% ($P = 0.02$). Although there was an increased risk of mortality in the intensive therapy group, there was a statistically significant approximately one-third reduction in risk of progression of retinopathy for various definitions of retinopathy progression in the intensive therapy group compared with the standard therapy group at the end of the ACCORD study.[8] As with the EDIC study, although the HbA1c levels quickly became equivalent in the 2 randomly assigned groups after that arm of the study was discontinued, those participants originally assigned to the intensive therapy group continued to have reduced rates of retinopathy. In the 4 years after the conclusion of the ACCORD trial, retinopathy progressed by 3 steps or more in the Early Treatment Diabetic Retinopathy scale in 5.8% of the original intensive treatment group versus 12.7% in the standard treatment group (adjusted

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odds ratio, 0.42; 95% confidence interval, 0.28−0.63; $P < 0.0001$).[1]

How can we reconcile the apparently adverse effects of intensive therapy on cardiovascular mortality in the ACCORD study and the repeatedly demonstrated benefits of intensive therapy on retinopathy and other microvascular complications? What should we tell our patients?

First, it is clear in type 1 and type 2 diabetes that intensive therapy achieving a mean HbA1c of approximately 7% results in substantial benefits in preventing and delaying the progression of retinopathy, nephropathy, and neuropathy. The ACCORD and ACCORDION findings support an additional benefit with HbA1c levels that are even lower than 7%, as has been suggested by the DCCT.[9] However, whether the costs and risks, especially with regard to hypoglycemia, of achieving HbA1c levels are much lower than 7% with current day therapies are balanced by the additional benefits is unclear. Therefore, the current goal of aiming for an HbA1c level of less than 7%, but not less than 6%, for most patients seems justified. The glycemic goals need to be individualized based on expected longevity, comorbidities, and other factors.

Second, the role of intensive therapy on the less diabetes-specific CVD complications is less clear. Both the DCCT and UKPDS, which remain the iconic, driving studies supporting intensive therapy, demonstrated beneficial effects of intensive therapy on CVD outcomes.[6,10] The specific medications used in the UKPDS and DCCT, both of which included patients with little if any CVD at baseline, included insulin, metformin and sulfonylureas and insulin, respectively. The main consideration should be what was different in the ACCORD study, especially compared with the UKPDS, which may have resulted in an adverse effect of intensive therapy on CVD. In truth, we do not know; however, notably, the ACCORD study included patients with a longer duration of type 2 diabetes than those in the UKPDS and with a far higher prevalence of CVD at baseline than in either DCCT or UKPDS.[6,10] The ACCORD study included only 3 years of follow-up compared with approximately 20 years for DCCT and UKPDS. The ACCORD study therefore was more of a short-term secondary intervention study, and its results may have little to do with the results when intensive therapy is applied earlier in the course of diabetes, which is recommended widely based on its salutary effects on microvascular disease. Secondary analyses have suggested that the intensively treated patients who were adversely affected had high HbA1c levels, that is, they were exposed to the potential adverse effects of the intensive regimen without the benefits that accrue with lower HbA1c levels.[11] Finally, intensive therapy in the ACCORD study required as many as 5 glucose-lowering medications, with most patients using at least 3. This multidrug treatment is in stark contrast with the number of drugs used in the UKPDS and in practice, which is usually no more than 2.

Based on the balance of demonstrated benefits and risks shown in the EDIC study, UKPDS, and the ACCORD study and taking into account the increased risk for mortality shown in the ACCORD study, aiming for an HbA1c level of less than 7% and avoiding diabetes polypharmacy in patients with CVD seems to be a sensible goal. The options to achieve this metabolic goal have continued to expand. In type 1 diabetes, the use of continuous glucose monitoring may prove to be useful, especially as a safeguard against hypoglycemia in those with hypoglycemia unawareness and as an essential component in the development of the artificial pancreas.[12] In type 2 diabetes, a panoply of new medications have been introduced since the end of the UKPDS. Although their relative roles are still being defined,[13] the expanded menu of glucose-lowering drugs provides many new options for achieving the glycemic goals that have been shown to reduce the long-term complications of diabetes mellitus.

The results of numerous well-designed clinical trials and long-term follow-up studies have demonstrated the benefits of controlling glycemia. The increasing options for patients both to monitor and control their blood glucose levels should improve our ability to reach the currently recommended HbA1c level goal of less than 7% safely and cost effectively. Although intravitreal anti-VEGF treatment has been demonstrated to slow the progression of, and in some cases even reverse, retinopathy severity in eyes with diabetic macular edema or proliferative diabetic retinopathy, it is apparent that intervening early to prevent or slow retinopathy development by controlling glycemia, blood pressure, and serum lipidemia is the first-line public health approach.[14,15]

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