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Lack of Glycemic Legacy Effects in the Veterans Affairs Diabetes Trial

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In randomized trials, intensive glycemic control has not resulted in lower risks of major cardiovascular events or death than standard glycemic control among patients with type 1 or type 2 diabetes during intervention periods. However, extended follow-up in some of these trials indicates that cardiovascular benefits may emerge over time. For example, follow-up in the Diabetes Control and Complications Trial (DCCT) involving patients with type 1 diabetes showed that intensive glycemic control was associated with beneficial effects with regard to cardiovascular events.¹ Similar postintervention follow-up in the United Kingdom Prospective Diabetes Study (UKPDS) showed reductions in the risks of cardiovascular events and death among patients with newly diagnosed type 2 diabetes who had been randomly assigned to intensive glycemic control,² a finding replicated in observational cohort studies.^{3,4} Such beneficial effects — termed “metabolic memory” or “legacy effects” — emerged after glycemic levels no longer differed between treatment groups.

Long-term follow-up in the Veterans Affairs Diabetes Trial (VADT) has provided the opportunity to ask whether a glycemic legacy effect exists in patients with advanced type 2 diabetes. The VADT included 1791 military veterans who had received a diagnosis of type 2 diabetes a mean of 11.5 years earlier and who had been randomly assigned to intensive or standard glucose control for a median of 5.6 years.⁵ The trial showed a between-group difference of 1.5 percentage points in the median glycosylated hemoglobin levels (6.9% in the intensive-therapy group vs. 8.4% in the standard-therapy group).⁵ At trial completion, there was no significant between-group difference in the incidence of cardiovascular events, cardiovascular mortality, or all-cause mortality.⁵ However, an interim analysis after 10 years of follow-up showed that the intensive-therapy group had a significantly lower incidence of cardiovascular events than the standard-therapy group.⁶ Because a modest difference in glycosylated hemoglobin levels (0.2 to 0.3 percentage points) between the trial groups persisted during follow-up, the existence of a legacy effect could not be fully assessed.

In this issue of the *Journal*, Reaven et al.⁷ report the results from a 15-year follow-up study in the VADT. The difference in the glycosylated hemoglobin levels between the two groups was no longer apparent after 9 years (glycosylated hemoglobin level, approximately 8% in each

group). After the present extended follow-up, the risk of the primary composite cardiovascular outcome (non-fatal heart attack, nonfatal stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or death from cardiovascular causes) was nonsignificantly lower, by 9%, in the intensive-therapy group than in the standard-therapy group (47.3 vs. 51.8 events per 1000 person-years; hazard ratio, 0.91; 95% confidence interval, 0.78 to 1.06). Likewise, no significant between-group difference in cardiovascular mortality or all-cause mortality was seen. Moreover, the association between treatment group and cardiovascular events was almost entirely explained by the glycated hemoglobin levels over the preceding 3 years rather than by earlier glycemic levels, which suggests that glycemic control does not have a prolonged effect on cardiovascular events. Consistent with these findings, follow-up in two major trials of intensive as compared with standard glycemic control in patients with advanced diabetes (ACCORD [Action to Control Cardiovascular Risk in Diabetes] and ADVANCE [Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation]) also showed no evidence of emergent cardiovascular benefits.^{8,9}

Thus, a glycemic legacy effect was observed in the post-trial follow-up in the DCCT and UKPDS but not the VADT, ACCORD, or ADVANCE trials. Several possible explanations for this difference exist. First, an attractive hypothesis for the glycemic legacy effect is that early intensive control reduces oxidative stress and advanced glycation end products, which otherwise lead to vascular damage over many years. On the basis of that hypothesis, patients with a longer duration of type 2 diabetes may have preexisting vascular injury; thus, at 15 years, benefits from intensive glycemic control no longer exist. Second, the DCCT and UKPDS were conducted three decades ago, when the use of cardioprotective strategies, such as antiplatelet agents, angiotensin-converting–enzyme inhibitors, and statins, was not standard practice. In contrast, the VADT tested the effect of intensive glycemic control during a new era in which cardiovascular risk factors are aggressively controlled.

The VADT was not designed to evaluate the effect of specific glucose-lowering agents on outcomes, and similar drug classes were used in both treatment groups. Recent cardiovascular-outcomes trials of glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors have shown benefits, as compared with placebo, regarding major cardiovascular events in patients with established cardiovascular disease. These benefits were independent of glycemic control.¹⁰ Thus, for patients with advanced diabetes, clinical focus on how glucose levels are lowered rather than on achieving intensive targets may lead to better cardiovascular outcomes.

A major implication of the VADT follow-up study is that older patients with advanced diabetes should not expect long-term cardiovascular benefits from intensive glycemic control. Instead, interventions that clearly reduce cardiovascular risk — such as smoking cessation, blood-pressure control, statin therapy, use of antiplatelet agents, and the use of glucose-lowering agents with proven cardiovascular benefits in patients with established cardiovascular disease — should be prioritized. Although a glycemic legacy effect may exist for younger patients, the current era of comprehensive cardiovascular risk-factor control may reduce, if not eliminate, legacy effects. Glycemic goals that are likely to produce both cardiovascular and microvascular benefits and minimize harms, consistent with patient

preferences and values, may be the most effective, evidence-based, and safest strategy for patients with type 2 diabetes.

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