Intensive Glycemic Control Improves Long-term Renal Outcomes in Type 2 Diabetes in the Veterans Affairs Diabetes Trial (VADT)

Lily Agrawal,[1] Nasrin Azad,[1] Gideon D. Bahn,[2] Peter D. Reaven,[3] Rodney A. Hayward,[4] Domenic J. Reda,[5] and Nicholas V. Emanuele,[1] for the VADT Study Group

Diabetes Care 2019;42:e181–e182 | https://doi.org/10.2337/dc19-0891

Diabetes accounts for almost 50% of cases of end-stage renal disease (ESRD) in high-income countries (1). Although the impact of intensive glycemic control on macrovascular complications is relatively modest, evidence suggests that tight glucose control may reduce kidney disease progression. The role of glucose control in preventing chronic kidney disease and ESRD continues to be of significant interest.

The Veterans Affairs Diabetes Trial (VADT) was a randomized, prospective, multicenter study in 1,791 veterans with poorly controlled type 2 diabetes, primarily to determine the impact of 5.6 years of tight versus standard glycemic control on cardiovascular events; secondary outcomes included microvascular disease. After the 5.6-year interventional period, the cohort was observationally followed for an additional 10 years (median follow-up was 15 years, ending in 2017) and provided a unique view of the impact of glycemic control on important clinical outcomes. As previously reported, baseline demographics, clinical characteristics, statin and blood pressure medicine use, and mean HbA_{1c} (9.4 ± 2% [79.2 mmol/mol]) were balanced between the two groups (2). Participants received either intensive (INT) or standard (STD) glucose control for a median of 5.6 years. The median HbA_{1c} achieved was 1.5% lower in INT versus STD during the intervention phase (6.9% vs. 8.4% [52 vs. 68 mmol/mol]). Subsequent diabetes care was provided by their primary health care team, and participants were followed using the Department of Veterans Affairs (VA) medical records system and three national data registries.

Reported here is the long-term effect of intensive glycemic control on an important renal composite outcome, namely, sustained estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio >300 mg/g creatinine. We selected this composite since the relative risk for additional complications, including ESRD, cardiovascular disease, and all-cause mortality further increases once eGFR drops below 45 mL/min/1.73 m^2, and macroalbuminuria is a better risk marker for eGFR loss (3). For the outcome to be considered sustained, the last recorded value at the end of a study period had to meet the composite definition, and there should have been a previous value of eGFR <45 mL/min/1.73 m^2 or urine albumin-to-creatinine ratio >300 mg/g. An event time was assigned when either of the events of the composite outcome first occurred. Baseline eGFR or baseline albuminuria was not used to adjust the model. Kaplan-Meier survival curves generated by the product-limit method using intention-to-treat analysis are shown in Fig. 1. At the end of the VADT interventional period, there was a nonsignificant 13% reduction in time to occurrence of the composite renal outcome in the INT group (95% CI 0.70–1.074, $P = 0.19$). Three years after the intervention phase ended, the difference in HbA_{1c} between INT and STD declined to 0.2–0.3%. At the 10-year interim analysis, 445 people had reached the composite renal outcome: 22.7% in INT and 27.0% in STD groups, with a 20% reduction in the time to composite renal outcome in the INT group (95% CI 0.66–0.96, $P = 0.02$). By the end of the final VADT follow-up in 2017, 496 people had reached the composite outcome: 25.7% in INT and 29.7% in STD groups, for a 19% reduction in the INT group (95% CI 0.68–0.97, $P = 0.02$).

In this extended follow-up of the VADT cohort for 15 years, we found that 5.6 years of intensive glucose lowering reduced a composite renal outcome of development of persistent stage 3b chronic

[1]*Endocrinology Section, Medical Service, Edward Hines Jr. VA Hospital, Hines, IL*
[2]*Research, Edward Hines Jr. VA Hospital, Hines, IL*
[3]*Carl T. Hayden VA Medical Center, Phoenix, AZ*
[4]*Department of Internal Medicine, VA Ann Arbor Healthcare System, Ann Arbor, MI*
[5]*Cooperative Studies Program Coordinating Center, Edward Hines Jr. VA Hospital, Hines, IL*

Corresponding author: Lily Agrawal, lily.agrawal@va.gov

Received 2 May 2019 and accepted 23 August 2019

Clinical trial reg. no. NCT00032487, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0891/-/DC1.

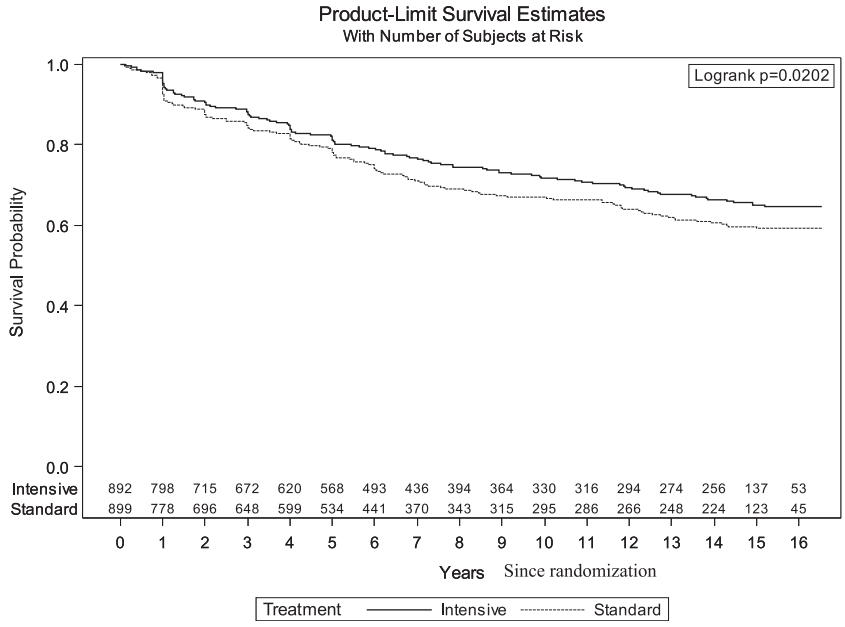

Figure 1—Kaplan-Meier analysis of time to renal composite from randomization in the VADT to end of 15 years (15 November 2000–30 June 2017). The *x*-axis shows "subjects at risk" at each year since randomization in the INT and STD cohorts. HR 0.81, 95% CI 0.68, 0.97; $P = 0.02$.

kidney disease or severe albuminuria. Consistent with other trials, there was a lag time for the effects of intensive glucose control to manifest (4). Of great interest is that the beneficial renal effect was sustained even after the separation of 1.5% in HbA_{1c} had disappeared. This benefit from glucose lowering does not appear to be explained by simultaneous improvements in other key risk factors, since use of medicines for treating diabetes, blood pressure, and lipid control were similar in both groups. Recent studies with glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors have shown lower rates of development and progression of diabetic kidney disease despite relatively modest decline in HbA_{1c} (5). These agents were not frequently used in the VADT, and it will be interesting to see if their use, on a background of good blood glucose control, could further reduce progression of kidney disease.

These VADT findings are important from a clinical perspective since they demonstrate that about 6 years of intensive glycemic control provided sustained reductions in renal outcomes at 15-year follow-up, even when using older and less expensive medicines, suggesting a possible beneficial legacy effect. Whether the reduction in the end points reported here translates into reduced dialysis, transplant, and renal death remains an important clinical question.

Funding. This work is supported by the Veterans Affairs Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development (VA CSP #465 and #465-F), National Institute of Diabetes and Digestive and Kidney Diseases grant P30DK092926, and grants from the National Institutes of Health (R01HL067690 and R01HL094775). Support for obtaining data from the VA system or the Centers for Medicare & Medicaid Services was provided by the Information Resource Center of VA Health Services Research and Development Service (Service Directed Research numbers 02-237 and 98-004). R.A.H. is supported, in part, by National Institute of Diabetes and Digestive and Kidney Diseases grant P30DK092926 (Michigan Center for Diabetes Translational Research).

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs or the U.S. Government.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. L.A. reviewed and researched data and wrote the manuscript. N.A., R.A.H., and D.J.R. contributed to the editing. G.D.B. analyzed data and reviewed and edited the manuscript. P.D.R. edited the manuscript. N.V.E. reviewed data and edited the manuscript. G.D.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

References

1. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016; 316:602–610

2. Reaven PD, Emanuele NV, Wiitala WL, et al.; VADT Investigators. Intensive glucose control in patients with type 2 diabetes - 15-year follow-up. N Engl J Med 2019;380:2215–2224

3. Astor BC, Matsushita K, Gansevoort RT, et al.; Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int 2011;79:1331–1340

4. Agrawal L, Azad N, Bahn GD, et al.; VADT Study Group. Long-term follow-up of intensive glycaemic control on renal outcomes in the Veterans Affairs Diabetes Trial (VADT). Diabetologia 2018; 61:295–299

5. Lawrence L, Menon V, Kashyap S. Cardiovascular and renal outcomes of newer anti-diabetic medications in high-risk patients. Curr Cardiol Rep 2018;20:65