Observation on Renal Outcomes in the Veterans Affairs Diabetes Trial

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OBJECTIVE—The Veterans Affairs Diabetes Trial (VADT) was a randomized, prospective, controlled trial of 1,791 patients with type 2 diabetes to determine whether intensive glycemic control would reduce cardiovascular events compared with standard control. The effect of intensive glycemic control and selected baseline variables on renal outcomes is reported.

RESEARCH DESIGN AND METHODS—Baseline mean age was 60.4 years, mean duration of diabetes was 11.5 years, HbA_{1c} was 9.4%, and blood pressure was 132/76 mmHg. The renal exclusion was serum creatinine >1.6 mg/dL. Renal outcomes were sustained worsening of the urine albumin-to-creatinine ratio (ACR) and sustained worsening by one or more stages in the estimated glomerular filtration rate (eGFR).

RESULTS—Intensive glycemic control did not independently reduce ACR progression but was associated with a significant attenuation in the progression of ACR in those who had baseline photocoagulation, cataract surgery, or both. The beneficial effect of intensive glycemic control increased with increasing BMI and with decreasing diastolic blood pressure (DBP). Intensive glycemic control was associated with less worsening of eGFR with increasing baseline ACR and insulin use. Baseline systolic blood pressure, triglycerides, and photocoagulation were associated with worsening of eGFR.

CONCLUSIONS—Intensive glycemic control had no significant effect on the progression of renal disease in the whole cohort but was associated with some protection against increasing ACR in those with more advanced microvascular disease, lower baseline DBP, or higher baseline BMI and on worsening of eGFR in those with high baseline ACR.

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We explored the available data from the Veterans Affairs Diabetes Trial (VADT) to determine which of the selected baseline characteristics predicted worsening of nephropathy and to assess any variables that have interactions with intensive (INT group) versus standard (STD group) glycemic treatment. The primary goal of the VADT was to compare the effects of intensive and standard glucose control on cardiovascular events (1). Final median glycated hemoglobin levels were 8.4% in the STD group and 6.9% in the INT group. Secondary outcomes included microvascular complications, such as retinopathy, nephropathy, and neuropathy. Nephropathy is a major microvascular complication of diabetes that is characterized by persistent albuminuria, a rise in arterial blood pressure, and a decline in glomerular filtration rate leading to chronic kidney disease (CKD) and end-stage renal failure. The main VADT showed that intensive glucose control had minimal effects on the incidence of renal failure, but there was a significant reduction ($P = 0.01$) in any worsening of the urine albumin-to-creatinine ratio (ACR) in the INT group (1). This article will further explore the relationship of risk factors and treatment on renal outcomes and help generate hypotheses for future testing.

RESEARCH DESIGN AND METHODS

The design of the VADT has been reported elsewhere (2). We assigned 1,791 veterans at 20 VA medical centers who had a suboptimal response to therapy for type 2 diabetes to receive either intensive or standard glucose control. Patients with serum creatinine >1.6 mg/dL were excluded. The median follow-up was 5.6 years. The primary outcome was the time from random assignment to the first occurrence of a major cardiovascular event. Strict control of blood pressure and dyslipidemia, daily aspirin, diet, and education were uniform in both arms. Protocol and consent forms were approved by the institutional review board at each of the 20 participating sites. All patients provided written informed consent. An independent data- and safety-monitoring committee, whose members were aware of study-group assignments, monitored safety and efficacy.

Statistical analysis

As outcomes, renal disease progression was measured in two ways. First, patients' baseline ACR measures were categorized and compared with the last two available on-study ACR measures. Categories were as follows: 0–29 mg/g, no albuminuria; 30–300 mg/g, microalbuminuria; and >300 mg/g, macroalbuminuria. The progression of albuminuria was defined as an increase of albuminuria for at least two successive yearly visits without reversion to an improved level. Of 1,791 patients, 864 had no albuminuria and 448 had microalbuminuria with at least two follow-up measures after baseline, for a total of 1,312 subjects eligible for analysis.

Second, renal disease progression was measured by the estimated glomerular filtration rate (eGFR). Patients' annual

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measures of serum creatinine, age, and race were used to calculate eGFR according to the Cockcroft-Gault equation (3). Patients were categorized according to their eGFR level into one of five categories of renal function, as follows: GFR ≥90 mL/min per 1.73 m^2 = CKD stage 1; 60–89 mL/min per 1.73 m^2 = CKD stage 2; 30–59 mL/min per 1.73 m^2 = CKD stage 3; 15–29 mL/min per 1.73 m^2 = CKD stage 4; and <15 mL/min per 1.73 m^2 = CKD stage 5. Patients' baseline measures were compared with their last two recorded eGFRs, and if both were worse than their baseline eGFR, that patient was considered to have the outcome of persistent worsening of eGFR or progression of CKD. Of 1,791 patients in the study, 141 were missing baseline measures of eGFR, leaving 1,650 subjects eligible for analysis.

For both measures of renal disease progression, a multiple logistic regression model was used to determine baseline predictors of on-study renal disease progression. We took the natural log of baseline ACR + 0.1 and baseline triglycerides + 0.1 to minimize the influence of extremely large values on the model parameter estimates. The model selection procedure was as follows: after univariate analyses were performed on each outcome of interest using logistic regression, each predictor (independent) variable with treatment interactions were tested separately in logistic regression. To be more inclusive, the predictor variables and the treatment interactions with a P value ≤ 0.2 were selected as candidates in the multiple logistic regression models, and backward elimination was performed with a cutoff P value of < 0.07. No interaction effect was allowed to enter the model without the corresponding main effects. All models were estimated in SAS version 9.2 PROC LOGISTIC. Treatment was forced to remain in the model in the backward elimination procedure. In Figs. 1–4, which depict the interaction effects with intensive glycemic treatment, the solid line represents the point estimate of the treatment odds ratios (ORs) at various levels along the x-axis that ranges from the 10th to the 90th study sample percentile, whereas the dotted lines represent the 95% upper and lower CIs. In Figs. 2 and 3, in which one interaction effect is explained, another continuous interaction variable is fixed at the 50th percentile of the study sample (n = 1,791), whereas categorical interaction variables are fixed at 0 (absence of the categorical variable).

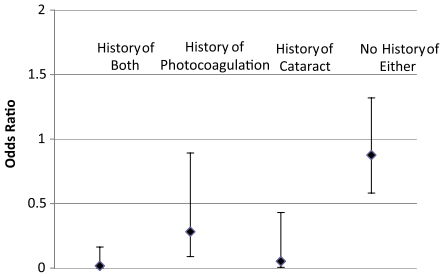

Figure 1—*ACR worsening: treatment by eye disease interaction effects. Shown are the ORs and 95% CIs for the interaction between intensive glycemic treatment and eye disease at all combinations of eye disease status, whereas baseline BMI and DBP are fixed at the median value of 31 kg/m^2 and 76.3 mmHg, respectively. Intensive glycemic treatment was associated with a reduced risk of worsening of ACR by 72% in those who had photocoagulation (OR 0.28 [95% CI 0.09–0.89]), by 95% in those who had cataract surgery (0.05 [0.01–0.43]), and by 98% in those who had both at baseline (0.02 [<0.01–0.16]).*

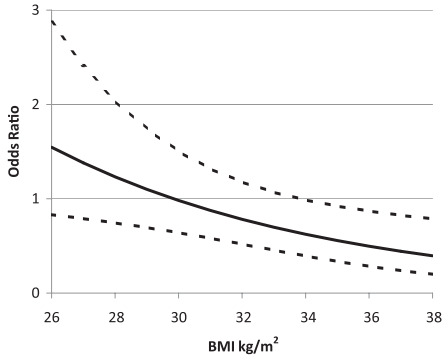

Figure 2—*ACR worsening: treatment by BMI interaction effects. Shown are the ORs and 95% CIs for the interaction between intensive glycemic treatment and BMI, with DBP fixed at the median value of 76.3 mmHg. Other variables are fixed at no history of photocoagulation or cataract surgery. In general, intensive glycemic treatment was associated with less worsening of ACR in patients with relatively higher BMIs. The modeled intensive glycemic treatment OR estimates became statistically significant at BMI >34 kg/m^2.*

RESULTS—There were 1,791 patients in the VADT. Baseline age was (means ± SD) 60.4 ± 8.7 years, duration of diabetes was 11.5 ± 7.5 years, HbA_{1c} was 9.4 ± 1.5%, systolic blood pressure (SBP) was 132 ± 17 mmHg, and diastolic blood pressure (DBP) was 76 ± 10 mmHg. The demographic characteristics of the cohort used for analysis for this article are shown in Supplementary Appendix A. To elucidate if intensive glycemic treatment affects renal disease progression, and which baseline risk factors predict progression of renal disease, we examined several variables recognized to be associated with kidney disease in those patients in whom data were available at baseline. These included assignment to intensive treatment, age at onset of diabetes, duration of diabetes, ethnicity, BMI, history of smoking, insulin treatment at baseline, blood pressure, lipid profile, glycemic control measured by HbA_{1c}, pancreatic reserve measured by C-peptide, fibrinogen, plasminogen activator inhibitor-1, previous cardiovascular events, presence of baseline diabetic retinopathy, history of photocoagulation, history of vitrectomy, history of cataract surgery, history of macular edema, ACR, and eGFR.

Univariate analysis

When each variable was observed individually, worsening of ACR over time was significantly reduced in those patients assigned to the INT group, those with higher HDL cholesterol, and those with higher GFR at baseline. Higher baseline ACR, BMI, HbA_{1c}, fibrinogen, presence of previous cardiovascular events, any degree of diabetic retinopathy, and history of retinal photocoagulation were significantly associated with worsening of the ACR ($P < 0.05$). Relative increases in SBP, fibrinogen, ACR, and history of retinal photocoagulation were significantly associated with worsening of the eGFR ($P < 0.05$) (Supplementary Appendix B and C). Assignment to the INT group did not have a significant effect on the worsening of eGFR. After analyses of treatment interaction effects, all the variables with $P \leq 0.2$ were included in the multiple logistic regression model to test which variables are significantly associated with the worsening of ACR and eGFR, while adjusting for all other variables in the final model after backward elimination.

Multiple logistic regression analysis of ACR progression

The final model for any worsening albuminuria resulted in one significant main effect and an effect of intensive treatment that depended on four variables. Natural log of baseline ACR is significantly associated with worsening ACR (OR 1.27 [95% CI 1.11–1.45]) while controlling for all other covariates in the model. The four variables, history of photocoagulation

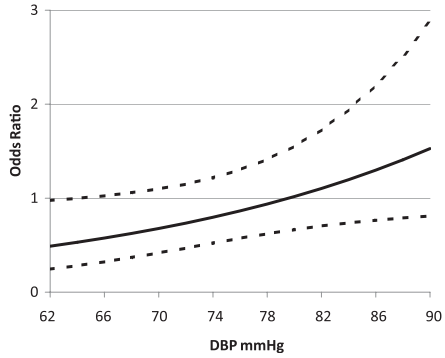

Figure 3—*ACR worsening: treatment by DBP interaction effects. Shown are the ORs and 95% CIs for the interaction between intensive glycemic treatment and DBP, with BMI fixed at the median value of 31 kg/m^2; all other variables are fixed at no history of photocoagulation or cataract surgery. In general, intensive glycemic treatment was associated with less worsening of ACR in patients with relatively lower DBP. The modeled intensive glycemic treatment OR estimates became statistically significant at DBP <64 mmHg.*

(P = 0.06), history of cataract surgery (P = 0.009), BMI (P = 0.009), and DBP (P = 0.03), have significant interactions with intensive glycemic treatment.

Figure 1 shows the ORs and 95% confidence limits for the interaction between intensive glycemic treatment and eye disease at all combinations of eye disease status, whereas baseline BMI and DBP were fixed at the median value of 31 kg/m^2 and 76.3 mmHg, respectively. Intensive glycemic treatment was associated with a reduced risk of worsening of ACR by 72% in those who had photocoagulation only (OR 0.28 [95% CI 0.09–0.89]), by 95% in those who had cataract surgery only (0.05 [0.01–0.43]), and by 98% in those who had both at baseline (0.02 [<0.01–0.16]).

Figure 2 represents the ORs and 95% confidence limits for the interaction between intensive glycemic treatment and BMI with DBP fixed at the median value of 76.3 mmHg. Other variables are fixed at no history of photocoagulation or cataract surgery. In general, intensive glycemic treatment was associated with less worsening of ACR in patients with relatively higher BMI. The OR for treatment, favoring intensive glycemic treatment, became statistically significant at BMI >34 kg/m^2.

Figure 3 represents the ORs and 95% confidence limits for the interaction between intensive glycemic treatment and DBP, with BMI fixed at the median value of 31 kg/m^2 and all other variables are fixed at no history of photocoagulation or cataract surgery. In general, intensive glycemic treatment was associated with less worsening of ACR in patients with relatively lower DBP. The OR for treatment, favoring intensive glycemic treatment, became statistically significant at DBP <64 mmHg.

Multiple logistic regression analysis of eGFR progression

The final model for any worsening of eGFR has four main effects independent of intensive glycemic treatment and one interaction effect with intensive glycemic treatment. Again, each variable is interpreted, controlling for all other variables in the model. Higher SBP was associated with a statistically significant increased risk of 8% in worsening of eGFR per 10-mmHg increase in SBP (OR 1.08 [95% CI 1.01–1.17]). A history of photocoagulation also was associated with an increased risk of worsening eGFR (1.69 [1.15–2.47]). Increasing natural log of baseline triglycerides marginally increased the risk of worsening eGFR (1.22 [0.99–1.50]). Use of insulin at baseline was associated with 21% attenuation in worsening eGFR (0.79 [0.62–1.0]). Figure 4 shows that the natural log of baseline ACR predicted subsequent worsening of eGFR. Intensive control of blood glucose was associated with an attenuation in the decline of eGFR in patients with higher ACR, suggestive of more advanced disease, more than those with lower ACR, becoming significant at ACR >665 mg/g (0.61 [0.37–1.00]; P = 0.04).

CONCLUSIONS—Several large trials have assessed the magnitude and independence of the effects of intensive glucose and blood pressure control on macro- and microvascular clinical outcomes in patients with long-standing type 2 diabetes. Although intensive glycemic control in the VADT did not show any significant differences in retinopathy, major nephropathy (defined as doubling of serum creatinine or need for renal replacement therapy), or neuropathy compared with the STD group, it seemed to significantly reduce any worsening of albumin excretion (1). Kidney dysfunction is common in older patients with type 2 diabetes and coronary artery disease (4), microalbuminuria is an early finding in diabetic nephropathy, and the presence of albuminuria predicts increased risk of coronary artery disease and peripheral vascular disease (5,6). Therefore, we thought it would be useful to see if any factors predicted the development of nephropathy in patients with diabetes and to see which patients might benefit most from intensification of therapy. Several baseline characteristics were associated with worsening of ACR or eGFR in the VADT. However, significant interactions in reduction of albuminuria with intensive glycemic treatment were only seen in those with baseline eye disease, higher BMI, and lower DBP; significant interactions in reduction of eGFR with intensive glycemic treatment were only seen in those with higher baseline ACRs.

Several other studies have addressed the question of the impact of good glycemic control on renal disease in both type 1 and type 2 diabetes. In the Diabetes Control and Complications Trial involving 1,441 individuals with type 1 diabetes, those in the INT group had markedly reduced incidence and progression of albuminuria and a delayed protective benefit on glomerular filtration (7,8). Several smaller glycemic intervention studies in type 1 diabetes preceded the Diabetes Control and Complications Trial (9–12), generally confirming the albuminuria benefit of glycemic control. There also are several earlier studies in people with type 2 diabetes showing an albuminuria benefit of better glycemic control (13–16). Recent cardiovascular trials, including the Action in Diabetes and Vascular Disease:

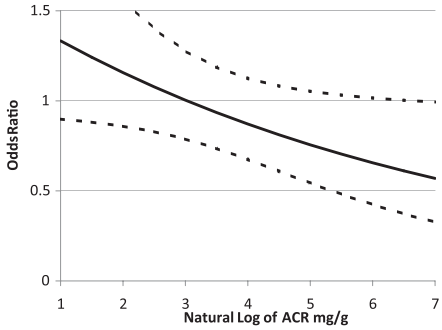

Figure 4—*eGFR worsening: interaction effect between treatment and baseline ACR. The figure shows treatment ORs and 95% CIs. The natural log of baseline ACR predicted subsequent worsening of eGFR. There was a statistically significant interaction effect in-that the beneficial effect of intensive glycemic treatment against worsening eGFR was associated with increasing values of the natural log of baseline ACR, becoming significant at ACR >665 mg/g (OR 0.61 [95% CI 0.37–1.00];* P = *0.04).*

Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD), also have reported an albuminuria benefit of glycemic control (17–19).

The epidemiologic link between the presence of retinopathy and nephropathy has long been known (20). This was also seen in baseline analyses in the VADT, where increasing baseline severity of retinopathy was significantly correlated with lower eGFR and higher levels of albuminuria (21). Our finding that intensive glycemic therapy was associated with the greatest effect in those with markers of advanced eye disease (photocoagulation and cataract surgery) supports the general idea that the intervention was most effective in those with advanced and generalized microvascular disease. However, this relationship did not occur with the eGFR end point. History of photocoagulation was a risk for worsening eGFR, but there was no interaction with intensive glycemic treatment.

The beneficial effect of intensive glycemic treatment increased with increasing BMI, becoming significant at $\geq$34 kg/m^2. There has been growing appreciation that obesity, per se, independent of diabetes, increases the risk for the initiation and progression of kidney disease and that weight loss can reduce proteinuria (22). Griffin et al. (22) have provided an excellent review of the various theories of the pathogenesis of obesity-related kidney injury, the details of which are beyond the scope of our discussion. In brief, they have postulated that the link between obesity and kidney injury is consistent with a "multi-hit" model, with reduced nephron number at birth being the initial hit and enhanced glomerular blood pressure transmission to the reduced number of nephrons being the second hit. Thus, obesity seems to put people at greater risk for nephropathy, and the interaction between intensive glycemic treatment and BMI is again consistent with the idea that people at greatest risk might be those that benefit the most from an intervention.

Our finding of an interaction between intensive glycemic treatment and baseline DBP is intriguing, especially in light of one of the findings from the ADVANCE Blood Pressure Trial suggesting such an interaction. We report that intensive glycemic treatment was associated with albuminuria benefit only in those with lower diastolic pressure. A part of the ADVANCE trial evaluating blood pressure reduction indicated that lower blood pressure among patients undergoing intensive glucose control probably explains some of the 10% reduction in primary combined outcome of major macrovascular and microvascular events, mainly as a consequence of a 21% relative reduction in nephropathy (17).

The UK Prospective Diabetes Study demonstrated that each 10-mmHg decrease in SBP was associated with average reductions in rates of diabetes-related mortality (15%), myocardial infarction (11%), and the microvascular complications of retinopathy or nephropathy (13%). The ACCORD Blood Pressure trial tested the effect of SBP $<$120 mmHg (intensive blood pressure therapy group) versus $<$140 mmHg (standard blood pressure therapy group) on major cardiovascular events among high-risk individuals with type 2 diabetes. Compared with the standard-therapy group, the group with SBP $<$120 mmHg had significantly higher rates of elevations in serum creatinine and significantly lower eGFR (23). However, the micro- and macroalbuminuria at the final visit was significantly lower in the intensive-therapy group, and there was no between-group difference in the frequency of end-stage renal disease or the need for dialysis. The significance of these findings on cardiovascular and renal outcomes is uncertain from the ACCORD study (23). We also confirmed that higher SBP was associated with worsening eGFR, but intensive glycemic control did not prevent worsening of renal function in these patients.

The finding that intensive glycemic control retarded the decline in eGFR only in those with substantial proteinuria has, to the best of our knowledge, not been previously observed. The reason for this is not clear, but it is in concert with the idea that treatment of any kind may have the greatest impact in those at highest risk. After adjusting for other factors, we did not find that the presence of previous cardiovascular events was associated with worsening of renal function at baseline or with intensive glycemic control.

In the UK Prospective Diabetes Study, patients with type 2 diabetes had elevated triglycerides, which were an independent risk factor for microalbuminuria. Elevated LDL cholesterol and triglycerides were an independent risk factor for macroalbuminuria. The level of triglycerides rises as diabetic nephropathy progresses to overt proteinuria (24). Our results suggest that higher HDL cholesterol at baseline was associated with less worsening of GFR only in univariate analyses. Higher triglyceride concentration was associated with increased worsening of eGFR, which continued despite intensification of glycemic control.

On the basis of our observations in this carefully followed cohort of older patients with diabetes, it seems that intensification of glycemic control was associated with the most benefit in reducing the progression of nephropathy in a subset of patients with worse baseline disease, especially those with microvascular eye disease, greater body weight, lower diastolic blood pressure, and higher levels of albuminuria. We were not able to show the benefit in attenuating progression of renal disease in patients with higher SBP, higher triglycerides, and previous cardiovascular events. Although this retrospective analysis generates interesting hypotheses, they cannot be used as treatment recommendations and need additional testing. Extrapolation of our findings to younger nonobese patients with diabetes and women must be done with caution.

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L.A., N.A., and N.V.E. provided clinical care during the study, designed the analysis, researched data, and wrote and edited the manuscript. G.D.B., D.G.K., and T.E.M. researched data, provided statistical analysis, and wrote and edited the manuscript. W.C.D. and C.A. designed the original study, contributed to discussion, and reviewed and edited the manuscript. All authors of this article had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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