Eye Outcomes in Veteran Affairs Diabetes Trial (VADT) After 17 Years

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OBJECTIVE

The objective of this study was to assess the long-term role of intensive glycemic control (INT) compared with standard glycemic control in accumulated eye procedures in patients with advanced diabetes.

RESEARCH DESIGN AND METHODS

We compared the effect of treatment assignment on the accumulated number of eye procedures during the intervention period of the Veteran Affairs Diabetes Trial (VADT) (2000–2008) (median follow-up 5.6 years), the interim VADT follow-up study (2000–2013), and the full 17 years of VADT follow-up (2000–2017). We further analyzed data using various cardiovascular markers in two models. Model I included total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, and BMI. Model II included these covariates plus age and diabetic retinopathy (DR) severity score at baseline of the original trial.

RESULTS

The final analysis of the data showed a mild but nonsignificant increase in number of procedures and in retinal or retinal plus cataract surgery during the three periods of the study.

CONCLUSIONS

We found no significant benefit of INT during the original trial period in eye-related procedures, such as various procedures for DR, or during the 17 years of follow-up in cataract surgery. However, after adjusting data for some known vascular markers, the increase in the number of eye procedures with INT becomes more prevalent. This finding indicates that INT might not have a protective role in events requiring surgery in individuals with advanced diabetes.

Diabetic retinopathy (DR) is a major microvascular complication in both type 1 and type 2 diabetes mellitus (T1DM and T2DM, respectively), and it is the leading cause of blindness in individuals with diabetes. Many studies have shown the beneficial effect of intensive glucose control on diabetes-related eye complications in patients with T1DM and T2DM (1–4). During the intervention phase of the Veterans Affairs Diabetes Trial (VADT) (Cooperative Studies Program no. 465), assignment to intensive glycemic control (INT) did not have any effect on either incidence or progression of DR in the entire cohort, as assessed by centrally read seven-field stereo fundus photographs. However, poor glucose control, worse total cholesterol and

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**A complete list of the VADT Study Group can be found in the supplementary material online.*

See accompanying article, p. 2192.

LDL cholesterol at baseline, hypercoagulability, and advanced age were associated with increased risk of progression of DR. Higher C-peptide and HDL cholesterol at baseline and improvement in lipid levels during the study were accompanied by reduced incidence of DR during the intervention phase of the trial (5–8).

In this report, we present data on the long-term (median 5.6 years) effect of INT compared with standard glycemic control (STD) on the accumulated number of composite eye procedures during 13 years of follow-up (2000–2013) and the entire 17 years of VADT follow-up (2000–2017). The composite eye procedures were chosen because of data availability and the important impact of these procedures on the quality of life of individuals with diabetes.

RESEARCH DESIGN AND METHODS

VADT was an open-label prospective randomized controlled study. Briefly, VADT enrolled 1,791 individuals with advanced T2DM and assigned participants to either INT or STD. Both arms received similar training and treatment for intensive blood pressure and lipid control and healthy lifestyle. The main goal of VADT was to determine the impact of a reduction in HbA_{1c} by 1.5% in the INT arm compared with the STD arm on cardiovascular events. DR was a secondary end point of VADT. The details of eye assessment during the intervention phase of the study have been previously published (8). At the end of the intervention phase, 1,578 of the original 1,791 participants were alive, and 1,033 agreed to participate in the VADT follow-up study (VADT-F) (Cooperative Studies Program no. 465-F). In this report, we compare the effect of treatment assignment on the number of accumulated eye procedures during the original trial (2000–2008) (median follow-up 5.6 years) as well as during VADT-F (interim) (2000–2013) and the total 17-year follow-up period (2000–2017).

For statistical analysis, we used every eye event that required some procedural intervention over the course of the VADT and VADT-F periods. The procedural interventions for retinal events included laser photocoagulation, intravitreous injection of anti–vascular endothelial growth factor (e.g., Eylea, Avastin, Lucentis), retinal cryotherapy, pneumatic retinopexy, and vitrectomy. For cataract surgery, the first two cataract surgical procedures in each participant were included in this analysis. The total eye events are the combination of retinal events plus cataract surgery. The source of data collection included examination of medical records (VA, Medicare, and Medicaid) and a yearly health survey. During the original trial, we used the questionnaires in an annual survey, and during the follow-up periods, we used The CPT and HCPSC codes obtained from database searches, including VA database, Medicare, and Medicaid, and VA electronic medical record review. The available data from 1,033 participants were analyzed for this report.

Means, SDs, and *P* values are displayed for the continuous variables, and frequency tables are shown for dichotomous variables. Group differences were tested by the Student *t* test for continuous variables with normal distribution and by the Wilcoxon rank sum test for continuous variables with nonnormal distributions; for categorical variables, the χ^2 or Fisher exact test was used. For the treatment effect, we counted all accumulated retinal eye events and the first two cataract surgeries of each participant. Generalized linear models with zero-inflated Poisson distribution were used. Odds ratios (ORs), 95% CIs, and *P* values are reported. A sensitivity analysis was performed to assess the consistency of the treatment effect after adjusting for blood pressure, lipid profile, and BMI; another sensitivity analysis was then performed, including age and DR severity score at baseline in addition to these covariates. The baseline values for these factors were similar between the two arms. In addition, the time of the first eye incident was analyzed using Cox proportional hazards regression models for 1,791 participants. All statistical tests used a significance level of 0.05 and were

Table 1—Baseline characteristics of patients who originally received STD or INT at the beginning of VADT (*n* = 1,033)

Characteristic	STD (*n* = 505)	INT (*n* = 528)	*P*
Age, years	60.1 ± 8.4	59.5 ± 8.0	0.31
BMI, kg/m^2	31.1 ± 4.3	31.4 ± 4.2	0.23
Duration of diabetes, years	11.3 ± 7.1	11.7 ± 8.0	0.44
HbA_{1c}, %	9.4 ± 1.5	9.4 ± 1.4	0.69
Systolic BP, mmHg	131.8 ± 16.4	130.7 ± 15.8	0.28
Diastolic BP, mmHg	76.6 ± 10.4	76.3 ± 9.7	0.71
eGFR	82.4 ± 20.8	83.8 ± 23.4	0.34
Baseline DR score	4.10 ± 3.5	4.34 ± 3.7	0.28

Data are mean ± SD. For BMI, to convert values for weight from pounds to kilograms, multiply by 0.45. BP, blood pressure.

Table 2—Baseline characteristics of patients who originally received STD or INT at the beginning of VADT (*n* = 1,578)

Characteristic	Included (*n* = 1,033)	Not included (*n* = 545)	*P*
Age, years	59.8 ± 8.2	59.4 ± 8.9	0.36
BMI, kg/m^2	31.3 ± 4.2	31.2 ± 4.5	0.95
Duration of diabetes, years	11.5 ± 7.6	11.1 ± 7.1	0.35
HbA_{1c}, %	9.4 ± 1.4	9.5 ± 1.7	0.09
Systolic BP, mmHg	131.3 ± 16.1	131.7 ± 16.9	0.57
Diastolic BP, mmHg	76.5 ± 10.1	76.3 ± 10.3	0.73
eGFR	83.1 ± 22.2	84.1 ± 21.3	0.4
Baseline DR score	4.10 ± 3.5	3.97 ± 3.15	0.58

Data are mean ± SD. Participants who received STD, *n* = 505; participants who received INT, *n* = 528. For BMI, to convert the values weight from pounds to kilograms, multiply by 0.45. BP, blood pressure.

performed in SAS 9.4 for Windows (SAS Institute, Cary, NC). The baseline characteristics of the study cohorts are shown in Tables 1 and 2 .

RESULTS

We first studied the effect of INT on the number of total composite retinal eye procedures for accumulated retinal events in participants during each period of this study. There were no significant differences between the two study arms in any period of this trial during the 17 years of follow-up. We then adjusted the data using pertinent cardiovascular markers in the two models. In model I, the data were adjusted with total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic and systolic blood pressure, and BMI. We found that the total accumulated retinal events requiring some procedure in the INT arm did not change during the original VADT period (OR 0.983 [95% CI 0.816–1.183]; $P = 0.853$), increased by 7% in participants in the INT versus STD arm during the interim period (2000–2013) (OR 1.068 [95% CI 0.922–1.234]; $P = 0.385$), and increased by 11% during the total period (2000–2017) (OR 1.106 [95% CI 0.980–1.251]; $P = 0.112$) (Table 3). After adjusting the data using model I, there were no changes in the accumulated retinal events during VADT (OR 0.997 [95% CI 0.821–1.213]; $P = 0.980$), but the accumulated events increased by 4% during the interim period (OR 1.042 [95% CI 0.896–1.213]; $P = 0.54$) and by 10% in the INT versus STD arm (OR 1.104 [95% CI 0.971–1.256]; $P = 0.132$), although without significance (Table 3). In model II, we included baseline DR severity score and age along with the model II covariates. We found that the total accumulated retinal events requiring some procedure in the INT arm did not significantly change during the original VADT period (OR 1.048 [95% CI 0.835–1.314]; $P = 0.688$), increased by 5% during the interim period (2000–2013) (OR 1.132 [95% CI 0.951–1.348]; $P = 0.162$), and increased by 13% during the total follow-up period (2000–2017) (OR 1.133 [95% CI 0.977–1.314]; $P = 0.099$) (Table 3).

We acknowledge that cataract is not an eye complication related only to diabetes; however, it is widely accepted that the incidence of cataract is higher in individuals with diabetes. Therefore, in the next sets of analysis, we included cataract surgery in the accumulated retinal events requiring procedures and labeled these eye events or total eye events. We first studied the effect of INT on the number of total composite eye procedures for accumulated eye events in participants in each period of this trial. We then adjusted the data using the pertinent covariates in the two models as noted before.

After adjusting the data using model I, during the intervention period of VADT (2000–2008) (median 5.6 years), the total accumulated eye events increased by 8% in participants in the INT versus STD arm (OR 1.081 [95% CI 0.933–1.252]; $P = 0.302$); during the interim period (2000–2013), total accumulated eye events increased nonsignificantly by 9% in the INT versus STD arm (OR 1.089 [95% CI 0.976–1.215]; $P = 0.129$), and during the total VADT and follow-up period (2000–2017), the total accumulated eye events increased by 8% in the INT versus STD arm (OR 1.085 [95% CI 0.985–1.194]; $P = 0.098$) (Table 4).

We then adjusted the data with the covariates in model I. During the intervention period of VADT (2000–2008), the total accumulated eye events increased by 9% in the INT versus STD group (OR 1.091 [95% CI 0.938–1.270]; $P = 0.256$); during the interim period (2000–2013), the total accumulated eye events increased by 11% in the INT versus STD group (OR 1.107 [95% CI 0.954–1.197]; $P = 0.254$); and during the total follow-up period (2000–2017), the total accumulated eye events increased by 7% in the INT versus STD group (OR 1.069 [95% CI 0.967–1.181]; $P = 0.193$) (Table 4). After adjusting the total eye events with covariates using model II, during the main trial, they increased by 12% (OR 1.119 [95% CI 0.945–0.1325]; $P = 0.191$); during the interim period, they increased by 14% (OR 1.140 [95% CI 1.005–1.293]; $P = 0.042$); and during the 17-year follow-up period, they also increased by 10% (OR 1.103 [95% CI 0.986–1.234]; $P = 0.087$) (Table 4).

Additionally, using the Cox proportional hazards regression models for the time to the first eye event, we found that the average HbA_{1c} during the study and assignment to study arm did not have any significant effect on eye events during any period of the study. Moreover, there was no difference in patient self-assessment of visual acuity during the original trial and follow-up (15.9 vs. 14.6% reported poor visual acuity in the INT vs. STD arm, respectively; $P = 0.43$).

CONCLUSIONS

We previously reported that in VADT, assignment to the INT arm did not change the incidence or progression of DR (5,8). Now, we report the long-term impact of glucose control during VADT on a number of eye outcomes requiring procedures, such as any retinal treatment and/or cataract surgery, during the 17-year follow-up period. We found the total cumulative number of eye procedures either did not change or nonsignificantly increased during each period of the trial, but there were no significant differences between the two study arms (Tables 3 and 4). Furthermore, after adjusting for

Table 3—Effect of assignment to INT on retina requiring any procedures during the various study periods: 2000–2008, 2000–2013, and 2000–2017

	Before adjustment	*P*	After adjustment (model I)	*P*	After adjustment (model II)	*P*
2000–2008	0.983 (0.816–1.183)	0.853	0.998 (0.821–1.213)	0.98	1.048 (0.835–1.314)	0.688
2000–2013	1.068 (0.922–1.234)	0.385	1.042 (0.896–1.213)	0.593	1.132 (0.951–1.348)	0.162
2000–2017	1.106 (0.980–1.251)	0.112	1.104 (0.971–1.256)	0.132	1.133 (0.977–1.314)	0.099

Data are OR (95% CI). Before and after adjusting data for various covariates in two models: model I, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, and BMI; model II, same covariates plus age and DR score at baseline.

Table 4—Effect of assignment to INT on total eye events including cataract requiring any procedures during the various study periods: 2000–2008, 2000–2013, and 2000–2017

	Before adjustment	*P*	After adjustment (model I)	*P*	After adjustment (model II)	*P*
2000–2008	1.081 (0.933–1.252)	0.302	1.091 (0.938–1.270)	0.256	1.119 (0.945–0.1325)	0.191
2000–2013	1.09 (0.976–1.215)	0.129	1.107 (0.954–1.197)	0.254	1.140 (1.005–1.293)	0.042
2000–2017	1.085 (0.985–1.194)	0.098	1.069 (0.967–1.181)	0.193	1.103 (0.986–1.234)	0.087

Data are OR (95% CI). Before and after adjusting data for various covariates in two models: model I, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, systolic and diastolic blood pressure, and BMI; model II, same covariates plus age and DR score at baseline.

important cardiovascular-related covariates, such as total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, diastolic and systolic blood pressure, and BMI (model I) and the combination of these covariates plus age and DR severity score at baseline (model II), we found a trend toward an increase in eye events requiring some procedures in the INT arm of the trial compared with the STD arm during the various periods of the study (Tables 3 and 4). These data support our previous VADT findings that intensive glucose control alone in patients with advanced diabetes may not have a significant protective impact on DR or cataract requiring surgery. Moreover, advanced age or severity of DR at baseline did not have a significant role in the future trends of retinal procedures or cataract surgery in INT participants. However, higher systolic blood pressure at baseline may have been a contributing factor in increasing the eye events during the prolonged follow-up period (data not shown).

It is notable that compared with participants in other landmark diabetes clinical trials in T2DM (e.g., Steno, UK Prospective Diabetes Study [UKPDS], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Action to Control Cardiovascular Risk in Diabetes [ACCORD]), participants in VADT had a longer duration of diabetes, higher entry HbA_{1c} ($HbA_{1c} \leq 7.5\%$ was among exclusion criteria), and greater use of insulin at baseline (Table 5). These are well-known risk factors for the development and progression of retinopathy; therefore, it is not surprising that VADT participants had more retinopathy at entry than participants in the other T2DM clinical trials (Table 5). This was also true in the Diabetes Control and Complications Trial (DCCT), involving people with T1DM (Table 4). These differences may account for the sharp difference in outcome, with no glycemic benefit in VADT regarding ocular events.

In VADT, 858 participants had eye photographs at baseline. Of these, 65% had DR, and 48.1% of those with DR had moderate to severe DR; in addition, 10.7% had undergone cataract surgery, 9% had undergone photocoagulation, 1.9% had undergone vitrectomy, and 11.1% had macular edema (5). All participants were taking multiple antidiabetic medications, including insulin in >50% (8) (Table 5).

In the Steno 2 study, 160 participants with T2DM with persistent microalbuminuria were assigned to either standard or intensive diabetes treatment for a mean duration of 7.8 years. Progression of retinopathy was defined as at least one level of progression on the EURODIAB grading scale. At baseline, no DR was noted in 73% of participants, and only 6% had advanced proliferative DR. Participants were taking multiple oral hypoglycemic agents, and insulin was used in 10% of the STD group and 5% of INT group at baseline (Table 4). At completion of the main trial, DR progression was seen in 19 versus 33 participants in the INT versus STD group, respectively (OR 0.45 [95% CI 021–0.95]; $P = 0.04$) (9). After completion of the main trial, participants agreed to observation for an additional 5.5 years. After 13.3 years of follow-up (7.8 years of trial and 5.5 years of follow-up), the study showed a significant reduction in incidence of retinal photocoagulation in the INT group compared with the STD group (OR 0.45 [95% CI 0.23–0.86]; $P = 0.02$). In addition, DR progression was also reduced in the intensively treated group compared with the standard group (OR 0.57 [95%

Table 5—Comparison of clinical trials in diabetes

	VADT	Steno 2	UKPDS	ADVANCE	ACCORD	DCCT
Age, years	60.4 ± 6.3	55 ± 7.2	53.3 ± 8.6	66 ± 6	61.6 ± 6.3	13–39
Duration of diabetes, years	11.5 ± 7	5.5–6	Newly diagnosed diabetes	8	10 ± 7	2.9–9
HbA_{1c}, %	9.4 ± 0.7	8.4–8.8	7.08 ± 1.5	7.5 ± 1.6	8.2 ± 1	7.2–9
No DR, %	35	73	63	NR	50.80	NR
Any DR, %	65	27	37	3	NR	100*
Minimum/mild DR, %	NR	NR	NR	NR	18	18*
Moderate/advanced DR, %	48	NR	Men, 8 Women, 4	NR	28.70	15*
Advanced DR, %	NR	6	NR	NR	1.5	NR
Taking insulin at baseline, %	>50	6 vs. 14†	None	1.50	35	10

Data are mean ± SD, range, or %. NR, not reported. *Secondary intervention cohort. †STD vs. INT.

CI 0.37–0.88]; $P = 0.01$) (10). Furthermore, at 21.2 years of follow-up, DR progression had decreased by 33% in the INT group compared with the STD group (OR 0.67 [95% CI 0.51–0.89]; $P = 0.005$) (11). However, compared with VADT participants, the Steno cohort was younger, with a shorter duration of T2DM, less DR at baseline, and less use of insulin therapy.

In UKPDS, 1,919 of 3,867 participants had fundus photographs at baseline. Of these, 63% had no DR, and 39% of men and 35% of women had one or just a few microaneurysms in one eye (12). Of interest, individuals with DR who required or previously had photocoagulation were excluded from the trial. More advanced DR with cotton wool spots was noted only in 8% of men and 4% of women (Table 4). Development of DR was defined as one or more microaneurysms in at least one eye, and progression was defined as advancement of two or more steps on Early Treatment Diabetic Retinopathy Study (ETDRS) scale (12). At the end of the UKPDS main trial, patients assigned to the intensive treatment group had a 25% risk reduction for eye events compared with the standard group ($P = 0.0099$), mainly manifesting as less photocoagulation in the intensive arm (1). Risk reduction was also seen in DR progression (OR 0.71 [95% CI 0.53–0.98]; $P = 0.003$) and cataract extraction (OR 0.76 [95% CI 0.53–1.08]; $P = 0.046$) in the INT group (13). After the termination of the UKPDS main trial, participants were followed either by yearly visits in UKPDS follow-up clinics for 5 years or by questionnaire for an additional 5 years. In those who were originally assigned to intensive sulfonylureas insulin treatment, the significant risk reduction of 25% in microvascular events, mainly reduced photocoagulation, during the main trial continued through the 10 years of follow-up, with risk reduction of 24% (OR 0.76 [95% CI 0.64–0.89]; $P = 0.001$) (14). However, there was a nonsignificant risk reduction of 29% in microvascular disorders during the original trial and 26% during the 5 years of follow-up in those treated with metformin in the metformin and obese arm (14). Compared with participants in VADT, UKPDS participants, like the Steno cohort, were younger, with a shorter duration of diabetes (they were newly diagnosed), less DR at baseline, and less use of insulin therapy.

ADVANCE enrolled 11,140 participants with T2DM. The participants were first divided into intensive and standard blood pressure control arms. Each arm was then further divided into INT and STD glucose control (Table 4). After the completion of the study, new or worse DR occurred in 6 vs. 6.3% of those in the intensive versus standard treatment group, respectively, and the difference was not significant (3). After a median of 5 years in the original trial, participants were followed for a posttrial period of a median of 5.9 years (ADVANCE Post Trial Observational Study [ADVANCE-ON]). No significant changes in DR or blindness were noted during either period of the study (15).

The ACCORD Eye Study included the data from 2,856 participants in the original larger cohort. At entry, 50.8% of participants did not have any DR, 18% had mild DR, and 29.7% had moderate DR. Only 1.5% had advanced DR, and none had undergone laser photocoagulation or vitrectomy for proliferative DR before the study. The study had data at baseline and for 4 years of the trial with seven-field stereoscopic fundus photographs (Table 4). DR progression was reported when there were changes of three or more steps on the ETDRS scale. There was a beneficial effect of intensive glucose control during the trial (7.3 vs. 10.4% in the intensive vs. standard arm, respectively; OR 0.67 [95% CI 0.51–0.87;] $P = 0.003$) (2). In the follow-up of ACCORD (ACCORD Follow-on [ACCORDION]), data were collected for 4 years after the completion of the original intervention period. DR progression at 8 years from baseline was 5.8 vs. 12.7% for the intensive versus standard arm, respectively (OR 0.42 [95% CI 0.28–0.63]; $P \leq 0.0001$). This finding indicates that the beneficial effect of intensive therapy during the study had continued during the follow-up period (16). However, these participants did not have DR significant enough to require treatment at entry; only 49% of the cohort had minimal DR, and 35% were taking insulin. The INT protocol with which ocular benefit was achieved was very rigorous and associated with increased total and cardiovascular mortality.

In DCCT, a total of 1,441 patients with T1DM were randomly assigned to receive either intensive or conventional therapy intended to prevent hyperglycemic symptoms for almost 6.5 years. At entry, participants were 13–39 years of age, with 2.9–9 years' duration of T1DM and HbA_{1c} ranging from 7.2 to 9%. The primary prevention cohort (726 participants) at entry had 1–5 years' diabetes duration and did not have any DR. However, in the secondary intervention cohort (715 participants) with diabetes duration ranging from 1 to 15 years, microaneurysms occurred in only 58% of participants assigned to the standard arm and 68% of those in the intensive arm (4). A change of three steps on fundus photograph was considered progression of DR. At the end of the main trial, patients who formed the primary prevention cohort assigned to INT had a 76% lower adjusted risk for development of DR, and the secondary intervention cohort had a 54% lower DR progression rate compared with those assigned to the STD group (16) (Table 5). After the completion of the original DCCT period, 1,375 participants were followed in an observational study, DCCT/EDIC, for a median of 23 years. Data for ocular surgery were collected based on a self-reported annual questionnaire (4). Over a median follow-up of 23 years, those in the intensive glucose control group (whole cohorts; both the primary prevention and the secondary intervention cohorts) during the original trial had a risk reduction in total ocular surgery (8.9 vs. 13.4% in the INT vs. STD group, respectively; $P < 0.001$) (17). More risk reduction of 57–58% in DR progression was noted in the INT group 10 years after the end of the main trial (9). Of note, at entry, participants were 13–39 years of age, with 2.9–9 years' duration of T1DM and HbA_{1c} ranging from 7.2 to 9%. Therefore, participants were much younger, with a shorter duration of diabetes and significantly less DR at entry compared with participants in VADT.

The main strength of this VADT report is that it includes long-term cdata from a landmark prospective trial with well-characterized cohorts. However, we acknowledge that the decision to perform any eye procedure is not totally objective, and it is partially dependent on a provider's judgment and expertise and the accessibility of the procedure.

Based on the review of several landmark studies, the effects of intensive glucose control on DR were mixed. There was benefit with intensive glycemic control in UKPDS, ACCORD, and DCCT. There was no benefit in ADVANCE. There was no benefit and possible harm in VADT. The VADT cohort was much advanced compared with the others in terms of vascular disease, including markers of retinopathy. Therefore, retinal damage may have been too advanced for glycemic control to show benefit. This would seem to underscore the need for early intervention. A minor contributor to the difference might have been variation in clinical judgment between physicians regarding when to intervene.

In summary, we found that the number of procedures for DR and cataract surgery increased during various periods of the 17-year VADT follow-up. However, assignment to INT played no protective role, even after event adjustment with pertinent cardiovascular markers. This finding is probably due to the level of advancement of DR, in addition to the long duration and severity of diabetes in the VADT cohort.

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