



# Association of Blood Glucose Control and Lipids With Diabetic Retinopathy in the Veterans Affairs Diabetes Trial (VADT)

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## OBJECTIVE

This study examined whether lipids modify the relationship between intensive glucose control (INT) and diabetic retinopathy (DR).

## RESEARCH DESIGN AND METHODS

The incidence and progression of DR were assessed in 858 of 1,791 participants with 7-field stereoscopic fundus photographs at baseline and 5 years later.

## RESULTS

Odds of DR progression were lower by ~40% in those with baseline total cholesterol (TC)  $\geq 200$  mg/dL ( $P = 0.007$ ), LDL-C  $\geq 120$  mg/dL ( $P < 0.02$ ), or HDL-C  $\geq 40$  mg/dL ( $P < 0.007$ ) in the INT arm versus standard glycemic treatment. Odds of DR progression were reduced by ~40% in those who had TC  $\leq 140$  mg/dL ( $P \leq 0.024$ ), triglycerides (TG)  $\leq 120$  mg/dL ( $P = 0.004$ ), or HDL-C  $\geq 45$  mg/dL ( $P = 0.01$ ) at the fifth year. Odds of DR progression were lower by ~40–50% with reductions of TC by  $\geq 40$  mg/dL ( $P < 0.0001$ ), of LDL-C of  $\geq 40$  mg/dL ( $P < 0.004$ ), and of TG by  $\geq 60$  mg/dL ( $P = 0.004$ ) at the fifth year. Odds of DR progression increased by 80% with increases in TC of  $\geq 20$  mg/dL ( $P < 0.0001$ ) and by 180% with increases in LDL-C by  $\geq 60$  mg/dL ( $P < 0.004$ ). After adjusting for covariants, those with higher TC at baseline and lower TC during and at the fifth year and higher HDL-C throughout study had significantly decreased odds of DR progression in INT.

## CONCLUSIONS

INT was associated with decreased odds of progression but not with onset of retinopathy in those with worse lipid levels at baseline and more improved lipid levels during the study. Higher HDL-C was consistently associated with better response to INT throughout the study.

Diabetic retinopathy (DR) is a very common complication of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) and is an important cause of vision loss and legal blindness in working-aged adults. The annual cost of this disorder in the U.S. is ~\$500 million (1). The pathogenesis of DR is multifactorial, and previous studies have suggested an association between abnormal lipid levels and DR in subjects with T1DM and T2DM (2–5). The reports of this association have been inconsistent; nonetheless, the association between DR and abnormal lipid metabolism is biologically plausible. However, we are unaware of any previous report that has examined the possible interaction between the intensity of glucose control and blood

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lipids levels in determining retinopathy progression. In this study, we sought to determine the relationship between lipid levels (values at baseline, changes in, and at the fifth year of study) and incidence and progression of DR in the Veterans Affairs Diabetes Trial (VADT) and whether this varied in response to treatment assignment to intensive glucose control (INT) versus standard glucose control (STD).

## RESEARCH DESIGN AND METHODS

This is a post hoc analysis of data from the VADT, an open-label prospective randomized controlled trial targeting patients with poorly controlled T2DM. The details of the study design were reported previously (6,7). Briefly, 1,791 patients with T2DM with inadequate response to maximal doses of oral agents or insulin therapy were studied in an open-label, randomized study of intensive glucose lowering. The data from 858 of the 1,791 patients in the VADT who completed 7-field stereo fundus photographs at baseline and 5 years later are reported here.

### Assessment of Eye Complications

Certified photographers obtained 7-field stereoscopic color photographs of the retina at baseline and 5 years later (8,9). The fundus photographs of these subjects were examined by trained personnel at the Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison. The readers were masked to subject's characteristics, including glycemic treatment assignment. The 23-level Early Treatment Diabetic Retinopathy Study (ETDRS) was used to describe the onset and progression of DR. Each eye was individually graded for retinopathy lesions, independent of the grading of the other eye, and the eye with worse DR was used for the analysis. Onset of DR was defined by development of eye outcomes during the study in individuals with a previous report of absence of microaneurysms and other characteristics of DR using the ETDRS severity scale (level 10) at the beginning of the study. Progression of DR was defined as changes in ETDRS severity scale of two steps or more between the baseline and 5-year follow-up.

### Statistical Analysis

Multiple logistic regression analysis was used to determine baseline predictors. Among the baseline risk factors, the

most biologically relevant variables to the outcome variables, the onset and progression of DR, were selected for model inclusion and for adjustment. The relevant variables included age, HbA<sub>1c</sub>, duration of DM, cardiovascular disorders, BMI, systolic and diastolic blood pressure, estimated glomerular filtration rate, fibrinogen, plasminogen activator inhibitor 1, C-peptide, and history of eye disorders (Supplementary Table 1). Because lipid particles neither by themselves nor with interaction with INT had any effect on the onset of DR, in this analysis we are reporting the role of various lipid particles at baseline, at the end of the study, and the changes of lipid during the study on their interaction with INT on progression of DR. The model selection procedure was as follows: After univariate analyses were performed on each outcome of interest using logistic regression, each covariate with treatment interactions was tested separately in logistic regression. The predictor variables and the treatment interactions with a *P* value of  $\leq 0.2$  were selected as candidates in the multiple logistic regression models. Then, backward elimination was performed with a cutoff *P* value of  $< 0.07$  for finding an interaction effect between lipids and INT in the final model. No interaction effect between covariates was allowed to enter the model without the corresponding main treatment effects.

Furthermore, the longitudinal mixed-effects model was used to assess the lipids repeated measures for 5 years between the two treatment arms. The data analysis was generated using SAS 9.3 software (SAS Institute Inc., Cary, NC), and significance was defined as  $P \leq 0.05$ . A sensitivity analysis was performed with adjustment for baseline HbA<sub>1c</sub> and duration of diabetes.

## RESULTS

In the entire cohort of 1,791 participants, 1,352 had the first (baseline) eye photograph and 858 (48% of the entire cohort) had the first and second photograph at 5 years into the study. Among those subjects who did not complete the second retinal photograph, 130 died, 82 terminated the study earlier, and 20 had strokes. The remainder declined the second examination. Reported here are the data from 858 of 1,791 subjects in the VADT who completed 7-field

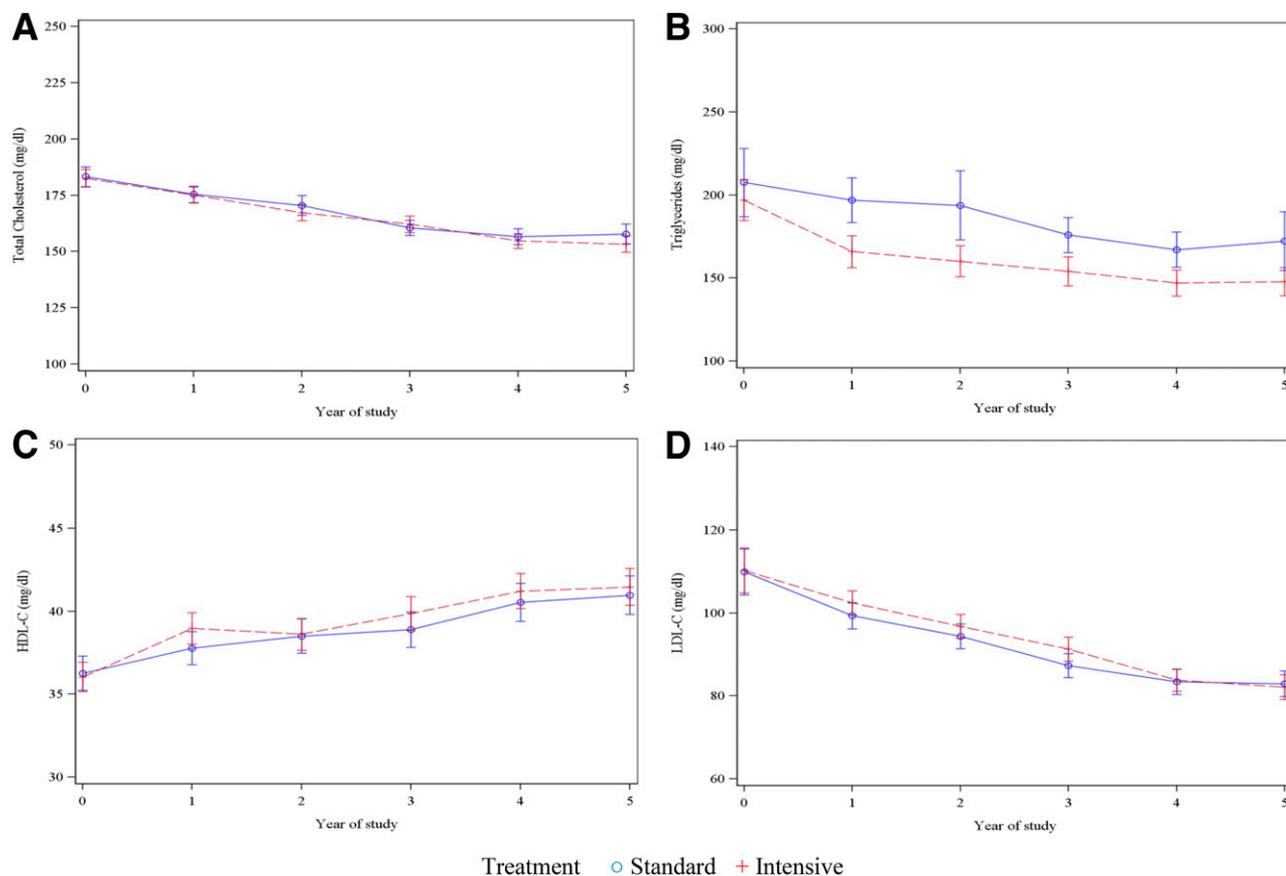
stereo fundus photographs at baseline and 5 years later. The individuals included in this study were largely representative of the VADT cohort as a whole. However, those not included because they did not have the second retinal photograph were older with longer duration of DM and with more cardiovascular events, as previously reported (Supplementary Table 1) (10).

There was excellent balance in baseline characteristics between the STD and INT arms of the trial (Supplementary Table 2) (10). Assignment to INT did not have any effect on the incidence or progression of DR in the cohort as a whole. However, significant interactions were noted between glycemic treatment assignment and lipid levels on the progression of DR. Lipid levels significantly changed within the first year of the study but were relatively stable in the last 2 years. There was no significant lipid separation between the two glycemic treatment arms during the study except in triglyceride (TG) levels. The TG levels in the INT cohort were significantly lower than those in the STD cohort (Fig. 1).

### Progression of DR

Of the 858 patients with 7-field stereo fundus photographs and all other data, 595 had baseline retinopathy (305 in INT and 290 in STD). Of these, 120 subjects (20%) (54 in INT and 66 in STD) experienced progression of DR during the study. Of subjects with baseline retinopathy, 31% had only microaneurysms, 37% had mild nonproliferative DR (NPDR), 23% had moderate to severe proliferative DR (PDR), and 9% had PDR. The rest of the cohort, 494 subjects, who had only a baseline retinal assessment, had normal retina in 27%, microaneurysm in 20%, mild NPDR in 27%, moderate to severe NPDR in 18%, and PDR in 8% of this group.

We first determined that an interaction existed between glycemic treatment assignment and baseline lipid parameters, assessed as continuous variables (Fig. 2). Models including this interaction demonstrated that the odds of progression of DR were 44% lower (odds ratio [OR], 0.56; 95% CI 0.35–0.91;  $P = 0.007$ ) in INT participants with baseline total cholesterol (TC) of  $\geq 200$  mg/dL compared with STD. If baseline LDL-C was  $\geq 120$  mg/dL, the odds of DR progression were 37% lower (OR 0.63; 95% CI 0.40–0.996;  $P < 0.02$ ) in INT individuals. In the INT subjects



**Figure 1**—A: Total cholesterol levels significantly changed within the first year of the study and remained relatively stable in the last 2 years,  $P < 0.001$ , with no separation between the study arms. B: There was only a significant separation for TG levels between glycaemic treatment arms, where TG levels for the INT cohort were significantly lower than those from STD cohort;  $P = 0.0003$ . C and D: The levels of HDL-C and LDL-C both decreased significantly during the study; however, there was no separation between the two study arms.

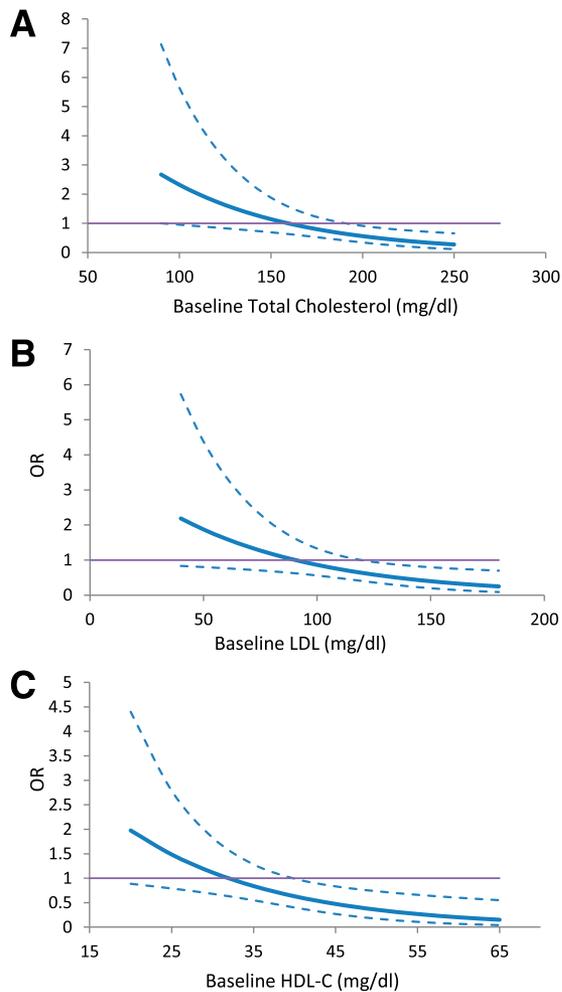
with baseline HDL-C of  $\geq 40$  mg/dL, the odds of DR progression were 37% lower (OR 0.63; 95% CI 0.40–0.99;  $P < 0.007$ ) (Fig. 2). Thus, those at higher vascular risk (higher TC and LDL-C and lower HDL-C) seemed to be those that had the most beneficial association with reduced DR progression in response to INT, an important but not completely surprising result. The particular lipid levels were not predetermined; they were levels where a significant interaction between INT and lipids was observed (Fig. 2). After the model backward selection procedure and adjusting for various covariables, we found the reduced progression of DR in INT was associated with higher baseline TC ( $P = 0.003$ ) and HDL-C ( $P = 0.05$ ).

We then determined whether final lipid levels achieved at the end of the study, assessed as continuous variables, were associated with greater benefit with INT, analogous to greater cardiovascular risk reduction occurring with LDL-C levels of  $< 70$  mg/dL after statin therapy (Fig. 3). There were significant

or borderline significant interactions between treatment assignment and final lipid levels ( $P \leq 0.05$  for TC, HDL-C, and TG and  $P = 0.07$  for LDL-C) after adjusting for each baseline lipid. If a TC of  $\leq 140$  mg/dL was achieved, the odds of DR progression were reduced by 38% (OR 0.62; 95% CI 0.39–0.97;  $P \leq 0.024$ ). In participants with a final HDL-C of  $\geq 45$  mg/dL, the odds of DR progression decreased by 38%, (OR 0.62; 95% CI 0.40–0.99;  $P = 0.01$ ). In INT participants who achieved a final TG of  $\leq 120$  mg/dL, the odds of DR progression decreased by 37%, (OR 0.63; 95% CI 0.4–0.98;  $P = 0.004$ ) (Fig. 3). The odds of an interaction between INT and LDL-C reduction were nearly significant ( $P = 0.07$ ). Thus, those with the best final lipid levels (lowest TC, LDL-C, and TG and highest HDL-C) appeared to be those with decreased DR progression if randomized to the INT but not STD. Again, the particular lipid levels were not predetermined; they were levels where a significant interaction between INT and lipids was observed

(Fig. 3). After the model backward selection procedure and adjusting for various covariables, we found that lower TC ( $P = 0.012$ ) and higher HDL-C ( $P = 0.029$ ) at the end of the study were associated with reduced DR progression in INT cohort.

In a third analysis, we studied the relationship between change in lipid parameters during the study period, assessed as continuous variables, and DR progression in INT versus STD. Participants in INT with decreases in TC, LDL-C, and TG during the study had reduced DR progression, but more DR progression was noted in those with increases in TC and LDL-C. If TC was reduced by  $\geq 40$  mg/dL, the odds of DR progression declined by 47% (OR 0.53; 95% CI 0.33–0.85;  $P < 0.0001$ ). Moreover, with an increase of TC by  $\geq 20$  mg/dL, the odds of DR progression increased by 80% (OR 1.81; 95% CI 1.02–3.21;  $P < 0.0001$ ). A decrease in LDL-C of  $\geq 40$  mg/dL during the study was associated with a 44% reduction in the odds of DR progression (OR 0.56; 95% CI 0.35–0.89;  $P < 0.004$ ),



**Figure 2**—A: The odds of progression of DR were 44% lower (OR 0.562; 95% CI 0.345–0.913;  $P = 0.007$ ) in INT participants with baseline TC of  $\geq 200$  mg/dL. B: If the baseline level of LDL-C was  $\geq 120$  mg/dL, the odds of DR progression were 37% lower (OR 0.634; 95% CI 0.403–0.996;  $P < 0.02$ ) in INT individuals. C: In the INT subjects with baseline HDL-C level of  $\geq 40$  mg/dL, the odds of DR progression were 37% lower (OR 0.630; 95% CI 0.401–0.990;  $P < 0.007$ ).

whereas an increase of LDL-C by  $\geq 60$  mg/dL was associated with a 180% increase in the odds for progression (OR 2.77; 95% CI 1.02–7.55;  $P < 0.004$ ). A decline of TG by  $\geq 60$  mg/dL was associated with a decrease in the odds of DR progression by 38% (OR 0.62; 95% CI 0.40–0.98;  $P = 0.004$ ). So, those with the greatest improvement in lipid levels were those with decreased DR progression. We also studied the data after the model backward selection procedure and adjusting for various covariables and found that more reduction in TC during the study was associated with reduced odds of DR progression during the study ( $P < 0.001$ ).

In a sensitivity analysis that adjusted for baseline HbA<sub>1c</sub> and duration of diabetes, the results were essentially the same as presented above except that

the interaction between INT and fifth year HDL-C was attenuated.

#### Incidence of DR

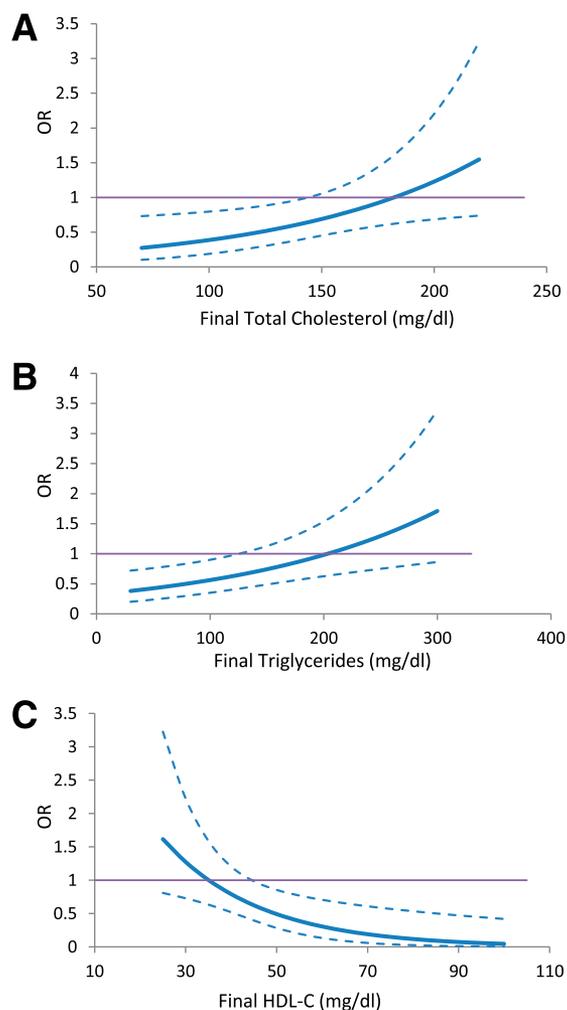
Of the remaining 263 subjects who did not have DR at the entry, there were 128 subjects (46%) in INT and 135 (54%) in STD. Of those, 114 (43%) developed DR during the study, 52 in INT and 62 in STD. However, there was no interaction between treatment assignment and lipid levels for the incidence of DR.

#### CONCLUSIONS

This study found no significant association between glycemic treatment assignment (6) or improving lipid levels during the study (Fig. 1) and DR development and/or progression in the cohort as a whole. However, there were multiple and consistent interactions between

INT and lipid parameters regarding progression of DR, indicating that the response to INT was related to the initial, change in, and final levels of several standard lipid parameters. Specifically, we identified a protective association of INT with the progression of DR in those who had higher TC and LDL-C at entry (Fig. 2) and better TC, LDL-C, and TG by the end of the study (Fig. 3). Moreover, those with the greatest improvement in the levels of TC, LDL-C, and TG during the study also appeared to have less progression of DR. Although the relationships were somewhat attenuated after adjustment for multiple covariates, the findings reported here on the influence of lipids on the response of this microvascular complication to INT are very analogous to the well-recognized effect of lipid levels on the improvement of macrovascular disease with statin therapy. For macrovascular disease, those at highest risk (i.e., worse lipid levels) benefit the most from the intervention (statin therapy). Furthermore, those with the greatest statin-induced LDL-C lowering tend to have the most cardiovascular benefit (11). Higher HDL-C levels at baseline and at the completion of the study were associated with reduced DR progression. In contrast, there was no association between lipids and incidence of DR in the whole cohort nor was there evidence of any lipid treatment interaction for new DR (11).

Observational studies have consistently shown that uncontrolled blood glucose level is a major risk factor in the pathogenesis of macrovascular and microvascular disease in subjects with DM (12). An inverse relationship between HbA<sub>1c</sub> and progression of DR and the incidence of macular edema (ME) was reported after 6 years of follow-up in the New Jersey 725 observational study in African Americans with T1DM (13). Baseline HbA<sub>1c</sub> was an independent predictor of progression of DR in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, an observational study, in people with T2DM (14). The same findings were observed in another observational study, the EURODIAB Prospective Complications Study in T1DM (15). In the UK Prospective Diabetes Study (UKPDS), the severity of retinopathy was correlated with level of blood glucose and was seen equally in both sexes. Each 1% decrease in HbA<sub>1c</sub> was associated with a 37% reduction in the



**Figure 3**—A: If a TC of  $\leq 140$  mg/dL was achieved, the odds of DR progression were reduced by 38% (OR 0.615; 95% CI 0.390–0.970;  $P \leq 0.024$ ). B: In participants with final HDL-C of  $\geq 45$  mg/dL, the odds of DR progression decreased by 38% (OR 0.624; 95% CI 0.396–0.985;  $P = 0.01$ ). C: In INT participants who achieved final TG of  $\leq 120$  mg/dL, the odds of DR progression decreased by 37% (OR 0.628; 95% CI 0.404–0.976;  $P = 0.004$ ).

microvascular end point, mainly DR (16,17). However, the effect of intensive glycemic control on microvascular outcomes in recent large, prospective interventional studies conducted in patients with T2DM of long duration has not been consistent. In the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation (ADVANCE) study, a borderline and nonsignificant reduction in ME and hard exudates and in the risk of microvascular events were observed in those in the glycemic intensive group. Importantly, the relative risk reduction for incidence and progression of DR was only 5% (18,19). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, assignment to INT was accompanied by a significant decrease in progression of DR, and the

severity of retinopathy correlated with the level of blood glucose during the study (20,21). However, the intensity of the glycemic control in ACCORD was also associated with increased all-cause and cardiovascular mortality and cannot be recommended in general practice (22). In the Diabetes Control and Complications Trial (DCCT), which included subjects with T1DM, those with better blood glucose control had decreased progression of DR during the trial (23). This beneficial effect persisted for many years after the study was completed, even in those subjects whose blood glucose increased after the trial was terminated (24,25). In contrast, in the VADT, INT had a modest and not significant effect on progression of DR (10).

It has been well established that patients with abnormal lipid parameters

have a higher incidence of macrovascular events and that the prognosis of cardiovascular disorders is worse in those with DM compared with those without DM. Although debatable, some data suggest that dyslipidemia is more atherogenic in subjects with DM and that this is probably due to different metabolic pathways of lipid particles in individuals with diabetes compared with individuals without diabetes (12,26). The association between dyslipidemia and microvascular outcomes is less clear. None of the lipid parameters in our study were independent factors associated with DR outcomes. However, some, but not all the major studies have shown an association between lipids and DR; for example, the New Jersey 725 study, after 6 years of follow-up, reported a significant progression of DR and increased incidence of ME in the participants with higher TC and LDL-C (13). The DCCT reported an association between hard exudates and clinically significant ME with higher levels of serum total cholesterol, but the association of DR and various lipid parameters was no longer significant after controlling for other covariates (27). The ETDRS showed those with an elevated level of TC and LDL-C at baseline had a twofold greater chance of having hard exudate at baseline and were also at higher risk of developing hard exudate during the study (5). The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported an association between high serum TC and presence of hard exudate and increasing progression of DR in patients with diabetes treated with insulin (28). Toth et al. (29), reported data from an observational study from Health Core Integrated Research Database (HIRD) in 72,267 patients, age 18–64 years with T2DM, monitored for more than 2 years while achieving the American Diabetes Association goals for TG, LDL-C, and non-HDL-C. They found a significant decrease in microvascular events (retinopathy, nephropathy, and neuropathy) with any lipid control, even in those who did not achieve lipid goals (29). Interestingly, a decrease in progression of retinopathy was noted in the subgroup of patients on fenofibrate (10.2%) versus placebo (6.5%) in the ACCORD lipid study (20,21). Fenofibrate caused a significant decrease in TC and TG and an increase in HDL-C levels in the study (30). However, there was no

correlation between retinopathy progression and these lipid fractions, suggesting that the fenofibrate effect was mediated by a nonlipid mechanism (20,21). This further supports the earlier report of a reduced need for retinal photocoagulation in the group on fenofibrate in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (31). However, because fenofibrate could have been acting through nonlipid pathways in both of these trials, the underlying mechanism of its action has to be examined in future studies.

Recent studies have demonstrated that standard lipid measurements may not provide a full assessment for the development of microvascular disorders in individuals with diabetes. Apolipoproteins (apo) or the particles they are carried in may be particularly relevant to DR. Higher apoA1 levels were associated with less progression of retinopathy, whereas higher apoB levels correlated with greater progression of DR. Thus, it has been suggested that apoA1 and apoB might be stronger biomarkers for DR than the traditional lipid profile (32). Moreover, the presence of apoB in the retina of human eyes with DR, demonstrated by immunostaining of apoB100 on postmortem retinal tissue of normal subjects and subjects with various degrees of DR, further supports this hypothesis (33). A clinical study of patients with T1DM and T2DM found apoA1 was inversely correlated with retinal vessel tortuosity and directly associated with increased vasomotor responsiveness to acetylcholine. These findings demonstrated functional and anatomical effects of apoA1 on retinal vessels (34). Others have demonstrated the toxicity of extravasated highly oxidized glycated LDL-C on retinal pericytes in DR postmortem studies using retinas from humans with and without diabetes and in murine models with diabetes (35). These studies support the damaging effect of various apo and modified lipoproteins on retinal vessels in individuals with diabetes.

Our finding of beneficial interactions between INT and lipid parameters on DR progression raises the mechanistic question of whether INT lowers lipid levels or converts more atherogenic lipid particles to fewer atherogenic particles. To examine this possibility, investigators used two specific methods to measure lipid particles and lipid subfractions in a

subset of patients from VADT. The first method, apo-defined lipoprotein subclasses assessment, examined lipid particles based on their apo complement; the second method used nuclear magnetic resonance to study the lipoproteins according to the particle size and found substantial differences in lipid particles in the two treatment arms of the study. Those in the INT arm had fewer atherogenic lipid particles compared with participants from STD; subjects receiving INT had lower levels of atherogenic particles, such as apoCIII, larger-diameter LDL-C, and VLDL-C, and fewer small and more medium HDL-C (36). This study clearly showed INT led to lipid particles that were less atherogenic. In addition, another VADT substudy examined blood from a subset of patients during the first year of the trial. They also reported more favorable changes in lipid fractions in the cohort of patients assigned to the INT arm (37). If one assumes that what is damaging to the macrovasculature is damaging to the microvasculature as well, the interaction between INT and lipids on DR progression may be because INT reduces the atherogenicity of lipid particles. Admittedly, such an interpretation is highly speculative; it would be interesting to study this notion further in future trials.

The main limitations of this study are that this analysis was retrospective and not prespecified and that there were only two retinal photographs (baseline and at the fifth year of the study). As such, the results reported must be regarded as hypothesis generating. In addition, because the cohort was largely an older male population with advanced diabetes, the conclusions may not be applicable to a more heterogeneous population with T2DM. The strength of this report includes the well characterized study population and the careful long-term measures of retinopathy.

### Summary

Our data show interesting interactions between INT and various lipid parameters in relationship to DR progression. Patients assigned to the INT arm with higher baseline levels of TC and LDL-C or higher HDL-C benefited the most and demonstrated lower odds of progression of DR. Those assigned to the INT arm with decreased levels of TC, TG, or LDL-C by the end of the study also had smaller odds of DR progression. Higher

HDL-C was associated with better response to INT throughout the study. Of course, these findings need to be confirmed in future trials.

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

**Author Contributions.** All authors vouch for the accuracy and completeness of the data and the analysis. N.A. and N.V.E. researched the data and wrote the manuscript. G.D.B. and L.G. conducted the statistical analysis. L.A., R.K., P.D.R., and R.H. reviewed and edited the manuscript. D.R. contributed to the design of the study and reviewed the statistical analysis. N.A. is the guarantor of this work and, as such, had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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