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Lack of Longitudinal Association between Thiazolidinediones and Incidence and Progression of Diabetic Eye Disease: The ACCORD EYE Study

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Abstract

Purpose—To report the longitudinal association between use of thiazolidinediones (TZDs), visual acuity (VA) change and diabetic eye disease incidence and progression.

Design—Cohort study ancillary to a randomized clinical trial

Methods—We analyzed baseline and four-year follow up data of 2,856 ACCORD trial participants with no history of proliferative diabetic retinopathy. Based on stereoscopic fundus photographs, we evaluated diabetic macular edema (DME) progression and DR progression. We also evaluated 10- and 15-letter change on the ETDRS visual acuity chart.

Main Outcome Measures—Incidence or progression of DME or DR and change in visual acuity.

Results—TZD use was not associated with DME incidence in either the analysis of any use (adjusted odds ratio [aOR] (95% CI): 1.22 (0.72 to 2.05)) or duration of use (aOR: 1.02 (0.99 to 1.04)). Diabetic retinopathy (DR) incidence/progression was more common in patients with no or mild DR at baseline who were ever treated with TZDs (aOR: 1.68 (1.11 to 2.55)), but this

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association disappeared when adjusting for the time on TZD (aOR: 1.02 (1.00 to 1.04)). DR progression among those with moderate or worse DR at baseline was no different between TZD users and non-users. TZD usage had no effect on the ultimate visual acuity outcome.

Conclusion—In this longitudinal study of patients with type 2 diabetes, we found no association between TZD use and visual acuity outcomes or DME progression, and no consistent evidence of increased DR progression in patients ever treated with TZDs vs. those never treated with TZDs.

Introduction

Diabetic macular edema (DME) is a frequent and important component of diabetic retinopathy (DR) and an important cause of impaired vision in persons with diabetes. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) estimated that the prevalence of macular edema in persons with Type 2 diabetes of twenty-year duration is approximately 28%.[1]

Widely accepted methods to reduce visual loss from DME include intensive glycemic control as shown in the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Study of Diabetes (UKPDS),[2,3] blood pressure control as shown in the UKPDS,[4] and local therapies such as macular laser photocoagulation and intravitreal injection of anti-vascular endothelial growth factor agents.[5,6]

Thiazolidinediones (TZDs) are oral hypoglycemic agents. TZDs are selective ligands of the nuclear transcription factor peroxisome-proliferator-activator-receptor-γ (PPAR-γ) that improve glycemic control by increasing insulin sensitivity and decreasing insulin resistance. Previous research provides mixed results on the potential for cardiovascular adverse effects of TZD use, and these studies led to significant discussion among the medical community regarding the use of these medications. During this controversy, in 2008 the Food and Drug Administration issued guidance requiring that clinical trials investigating glucose-lowering medications must demonstrate no unacceptable increased in cardiovascular disease[7]. A case report and small case series have suggested an association between TZDs and DME progression.[8,9] Additionally, two retrospective cohort studies also suggested TZDs were associated with DME.[10,11] These studies prompted our team to investigate the effects of TZD in diabetic eye disease in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. We have previously reported a lack of a cross-sectional association between TZDs and DME, using baseline data from ACCORD.[12] This report examines the longitudinal association between TZDs and change in DR, DME, and visual acuity utilizing data obtained through the four-year follow up period of the ACCORD Eye Study.

Methods

The ACCORD Eye Study enrolled a subset of patients from the ACCORD trial. Details of both the primary trial and the Eye Study have been published previously.[13–15] The ACCORD trial and ACCORD-Eye are registered at clinicaltrials.gov (#NCT00000620 and NCT00542178, respectively). The National Institutes of Health research governing board for intramural research and the local institutional review board for each center approved the research. Briefly, the ACCORD trial was designed to evaluate whether intensive glycemic

control, intensive blood pressure control, and/or treatment of dyslipidemia with fenofibrate had an effect on cardiovascular disease among patients with type 2 diabetes. A substantial subset of ACCORD participants were either on TZDs at baseline or used TZD during the study. TZD use was added at the discretion of the treating physician at a study visit when additional treatment was required to attain the glycemic control goal. Those who were randomized to the intensive glycemic arm tended to have greater number of oral hypoglycemic agents, including metformin, sulfonylurea, thaizaolidinedione, and others. TZD use was determined based on what was prescribed to the participant by the study team at each study visit. Distance visual acuity was evaluated at baseline, two years, and four years using an Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity chart.

ACCORD-Eye enrolled a subset of ACCORD participants without a history of proliferative DR treated with laser photocoagulation or vitrectomy. The primary aim of the ACCORD-Eye ancillary study was to determine whether intensive glycemic, lipid, and/or blood pressure control reduce the risk of DR incidence or progression. All participants provided written informed consent. Participants in ACCORD-Eye were examined by a study ophthalmologist or optometrist, and a certified photographer took seven-field stereoscopic fundus photographs at baseline and year four. At each ACCORD annual study visit, the patient's ophthalmic history was taken, asking specifically if any treatment for diabetic eye or other ocular disease had been undertaken, and the baseline and year-4 study eye exam were performed looking for evidence of laser photocoagulation or vitrectomy since the previous visit. The Fundus Photograph Reading Center (University of Wisconsin) graded all photographs for DME and DR using disease severity scales developed from photographs and classification obtained in the Early Treatment Diabetic Retinopathy Study (ETDRS).[16,17] We calculated incidence and progression of DR separately. For each, we considered endpoint (incidence or progression) to be reached if the participant had progressed three steps or more on the ETDRS person-level scale[16] at the 4-year visit, if there was evidence of scars from laser photocoagulation and/or vitrectomy treatment for DR, or if the participant self-reported these treatments during the study. We defined DME incidence as the onset of definite DME in one or both eyes of a subject without DME at baseline or treatment for DME, and progression as an increase of two or more steps on the ETDRS scale for DME[17] based on the eye with the most significant change, as graded on stereoscopic fundus photographs. DME and DR analyses are limited to participants in the ACCORD Eye study, as only the participants in the Eye study received a comprehensive eye exam and stereoscopic color fundus photographs. Our pre-specified analysis plan defined reporting DR outcomes separately for those who were classified as none or mild non-proliferative diabetic retinopathy at baseline. Post-hoc we decided to also evaluate these two groups combined, since from a clinical perspective they would be managed similarly.

As part of the ACCORD study, each medical clinic received an ETDRS visual acuity chart, and distance acuity was taken at baseline, two years, and four years, using their own current refractive correction. For the visual acuity analyses, we included all individuals in the primary ACCORD trial who would have been eligible for screening for participation in the ACCORD-Eye study, based on their baseline ACCORD evaluation and who had visual acuity data at baseline and four years. Some of these individuals were ineligible for participation in ACCORD-Eye due to history of vitrectomy or laser or other reasons, or were

not invited to participate because their enrollment in the primary trial occurred prior to the start of ACCORD-Eye study. We analyzed visual acuity decline between the baseline and 4-year visits based on 10+ and 15+ letter decline in at least one eye in participants that had baseline presenting distance visual acuity of 30 or more letters (Snellen equivalent 20/250 or better). Similarly, we analyzed 10+ and 15+ letter gains in participants with a baseline presenting acuity of 70 or fewer letters (Snellen acuity of 20/40 or worse).

We defined TZD exposure in two ways: any time on TZD during the study period, and the duration of TZD exposure during the study period. ACCORD provided TZDs as part of the study formulary, and at study visits site investigators could alter the medications prescribed as needed in order to get their participant to study goal.

Statistical analyses

We evaluated the relationship between TZD use and three outcomes: DME development and progression, DR development and progression, and visual acuity change. For each outcome, we evaluated both any self-reported TZD use and duration of TZD use and for each, we generated two logistic regression models: 1) unadjusted and 2) adjusted for ACCORD site, glycemia intervention, blood pressure trial participation, blood pressure intervention, lipid intervention, previous cardiac event, age, sex, race (Caucasian vs. non-Caucasian), and time since diabetes diagnosis. We report Wald confidence intervals and p-values from likelihood ratio tests. No adjustments were made for multiplicity. We conducted a sensitivity analysis, using a new-user cohort design in which we excluded all individuals reporting TZD use at baseline. We repeated the aforementioned analyses using this limited cohort.

Results

Of the 10,251 individuals in the main ACCORD trial, 6,245 met the inclusion criteria for the ACCORD-Eye study based on their ACCORD baseline visit data, completed the year-four ACCORD study visit, and had visual acuity data at that visit. Baseline characteristics of these individuals are provided in Table 1, divided by exposure to TZDs (whether they used TZD) during the study period. A subset of 3,473 enrolled in the ACCORD-Eye study, and 2,856 of these had gradable fundus photographs at baseline and were assessed for outcomes at 4 years. This group is the basis for our primary analysis, and they are described in Table 2. Approximately half of ACCORD-Eye participants had some DR at baseline (Table 2), and 218 (7.8%) had DME in at least one eye. TZD exposure during the study was common, with 77% of participants reporting at least some TZD use during the four-year study period (Table 3), and more than 35% of the population reporting TZD use of more than 3 years. The average amount of time on TZD was 24.4 months and 25.9 months for those in the DR and visual acuity samples, respectively.

Macular Edema Incidence and Progression

Fifty-nine participants did not have the complete DME parameters graded at both baseline and follow-up and were excluded from all DME analyses. Among the remaining participants, at baseline 92% did not have DME in either eye. Within this group, development of DME was rare, with only 4% of those without DME at baseline having

DME evident or having undergone treatment for DME by the four-year visit. Among the 218 participants (8%) with some DME at baseline, congestive heart failure (CHF) at baseline was twice as common as it was in those without DME at baseline (6% versus 3%). A total of 34 participants experienced DME progression in at least one eye between the baseline and four-year visit (Table 4), with those having CHF at baseline no more likely to have DME progression than those without CHF at baseline (15.4% and 15.7%, respectively). Rates of progression were similar in those never using TZD, using TZD at baseline, or initiating TZD during the study period (13.9%, 17.2% and 15.1%, respectively. Among the 143 individuals with incident DME or 2-step progression, 4.2% had a CHF event between baseline and four years, compared with 1.9% of those without DME progression. For both incidence and progression, unadjusted and adjusted regression analyses showed very similar results, with no evidence of an association between TZD use and DME (Table 5; Figure 1). Sensitivity analysis utilizing the new-user cohort approach resulted in nearly identical findings.

Diabetic Retinopathy Incidence and Progression

Incident DR occurred in approximately 7% of participants (Table 4) and an additional 7% of participants with mild DR at baseline experienced progression, while 24% of those with moderate or worse disease at baseline (defined as level 6 or worse on the individual ETDRS DR Severity scale)[16,17] progressed. We did not observe a significant difference in DR incidence among those exposed to TZD compared to those not exposed. However, within the group with mild DR at baseline, we saw a borderline statistically significant association between any TZD use and increased risk of progression (Table 5; Figure 1). This association disappeared when adjusting for duration of TZD use within the study period instead of using the binary yes/no TZD variable. Among those with moderate or worse DR at baseline, we saw no evidence of an association between TZD use and diabetic retinopathy progression. Sensitivity analyses of the new user cohort generally showed similar findings; however, the association between DR progression and any TZD use among those with mild disease at baseline moved from an OR of 1.77 (0.97–3.26) to 1.99 (1.01–3.92). Further, the OR for DR incidence accounting for time on TZD moved from 1.02 (0.99 – 1.05) to 1.05 (1.01–1.09).

Visual Acuity Change

Approximately 17% of participants experienced a 10+ letter decline in visual acuity in at least one eye. Both univariate and multivariate analyses showed no association between TZD exposure and visual acuity decline of 10 or 15 letters (Table 5; Figure 2). Comparing the 539 participants with 10+ or 15+ letter acuity improvement to those without such improvement yielded similar results. Unadjusted and adjusted analyses did not show a statistically significant association between TZD use and visual acuity improvement.

Discussion

TZD and Diabetic Macular Edema

Results of this study demonstrate a lack of a longitudinal association between TZD use and DME incidence or progression. These results are consistent with our previous cross-sectional analysis of baseline data from the ACCORD Eye Study, in which we reported no association between DME prevalence and the use of TZD.[12] In the current longitudinal

analysis of the same study population, with four-year follow up using centrally-interpreted stereoscopic fundus photographs, again we saw no association between TZD use and DME incidence, progression or treatment in either the unadjusted or adjusted analyses; nor did we find a difference when limiting to people without TZD use at baseline. Our findings are in keeping with two prior cross-sectional studies of optical coherence tomography that showed no association between TZD use and increased macular thickness.[18,19] These findings are important given that TZD remains an important line of therapy.[20]

Our findings do not support previous case-series reports implicating these agents as associated with DME.[8,9] Additionally, our findings differ from those of two previous large retrospective database cohort studies.[10,11] However, our study differs significantly from these prior studies. In both retrospective studies, DME was diagnosed from a computerized review of ICD-9 diagnosis, not from fundus photography or clinical eye examination information. Fong et al[10] investigated the incidence of DME in a population of individuals with diabetes identified within the Kaiser Permanente (KP) database. After limiting the sample to patients with diabetes who had a glycosylated hemoglobin below seven, participated in the KP drug benefit, and had at least one eye exam in 2006, the analyses include approximately 41% of the diabetic population with the drug benefit. Within this sub-group, they report a 60% increased risk of developing DME (95% CI: 1.4 to 1.8) in one year among those receiving glitazones compared to those not taking a glitazone, after adjusting for age and glycemic control. Further analyses including glitazone duration suggested that cumulative dose did not alter the risk of incident DME.[10] In addition to the obvious differences between a retrospective database study and a clinical trial, our study differs from the Fong study in that our analyses were able to adjust for important confounders such as diabetes duration, concomitant medication use, and other comorbidities. Additionally, although the total duration of follow up is similar between the studies, Fong assessed DME events in a one-year time period, while our study evaluated a four-year period.

More recently, Idris et al conducted a retrospective database analysis of approximately 100,000 individuals residing in the United Kingdom. After adjusting for key confounders, findings suggest a 3.3-fold increased risk of DME at one year among TZD users compared to non-users, with similar findings for ten-year outcomes. The study did not have data on duration of TZD use and, therefore, could not adjust for variable duration. The magnitude of the findings is similar to the Fong findings;[10] however, the incidence of DME (~1%) is a bit lower than the Fong findings. Patients in the TZD group had higher hemoglobin A1c levels at baseline, were less likely to be on aspirin, fibrates, ACE inhibitors, statins and RAS blockers, and were more likely to be on insulin, which may affect risk of DME.[11]

A recent analysis of the US Food and Drug Administration reporting system database analyzed data from the two most common glitazones separately. That analysis showed 5.6-fold increased risk of DME in patients taking rosiglitazone compared to no TZD use, but no increased risk of DME in patients taking pioglitazone.[21] In our study, the vast majority of patients utilizing a TZD were taking rosiglitazone. Hence, our differential findings cannot be explained by the specific TZD being used.

TZD and DR Incidence and Progression

In our study, we found no evidence of an association between TZD use and DR incidence. Additionally, unadjusted odds ratios showed no statistically significant difference in DR progression when evaluating any TZD exposure or duration of TZD usage. Adjusted models evaluating no DR and mild DR at baseline separately did not show statistically significant differences; however, in a model combining these groups, we found that those treated with TZDs had 68% greater odds of developing DR or experiencing progression compared to participants who were never treated with TZD (95% CI: 1.11 to 2.55). This association was not present when we accounted for duration of TZD usage (aOR: 1.01; 95% CI: 1.00 to 1.03). Of note, this combined grouping was not pre-specified, but was thought to be clinically meaningful since these two groups are often assessed similarly by clinicians. In our sensitivity analysis of people without TZD use at baseline, there was some evidence of an association between any TZD use and DR progression in those with mild DR at baseline, and limited evidence of an association between duration of TZD use and DME incidence. However, it is important to note that our analyses include multiple evaluations. Hence, there is a reasonable probability that we would find at least one significant p-value due to chance. While the significance of these findings is uncertain, TZD exposure may be a surrogate for severity of the underlying diabetes and poor control. Neither TZDs nor insulin are typical first-line therapies for type 2 diabetes. In general, patients are placed on these medications when optimum control is not otherwise achieved. Idris reported an adjusted odds ratio of 2.75 for DME progression in patients on TZDs alone, but noted an OR of 4.39 for DME progression in patients taking TZDs and insulin, which may suggest that disease severity and the ability to control the disease is the driving factor instead of TZD utilization.[11] Of note, however, we found no association between TZD use and disease progression among those with CHF at baseline. Certainly the Idris population differs from ours, with statin and aspirin use much lower in the Idris population than ours.

In our prior cross-sectional analysis of the ACCORD-Eye study, DR was more common in participants taking TZDs at baseline (47% vs. 41%; p=0.008).(11) Within this group at four years, we did not see differential rates of progression based on TZD exposure; participants with moderate or worse DR at baseline with and without TZD use had similar progression rates. Prior research on the possible association between TZD use and DR is limited. Most studies have looked specifically at DME and not all forms of DR; hence, we have limited data with which to compare the current study. We look forward to future studies to see if this association is confirmed.

TZD and Visual Acuity

The association between TZD use and visual acuity change has not been evaluated extensively in previous studies. In the current analysis, we utilized the broader sample of participants enrolled in the ACCORD Trial to evaluate the possibility of clinically significant visual acuity change associated with TZD usage. We found no association between either any TZD use or duration of TZD use and clinically meaningful visual acuity change at four years. This result is consistent with our cross-sectional analysis in which we found less than a one-letter difference between the TZD and non-TZD treated participants at baseline.[12] This finding is similar to a cross-sectional study of 59 patients reporting >6 months TZD

usage and 49 without TZD in which no significant differences were seen in best-corrected visual acuity or level of DR for the TZD versus no TZD groups.[18]

The strengths of this study are its longitudinal nature, large sample size, direct link to a randomized clinical trial with pre-specified outcomes of visual acuity, and use of standardized, centrally-interpreted photographs to grade DME and DR progression. Weaknesses include method of determination of quantitative TZD usage and follow up limited to only four years. In addition, because history of TZD exposure prior to study enrollment would constitute an unmeasured exposure, a subject who was taking TZDs and then ceased prior to ACCORD would be analyzed as not having had TZD exposure. This would have the effect of attenuating any differences between TZD exposure and non-exposure as we have measured it. However, prior studies of TZD and DR incidence that showed an association were based mostly on short timeframes with similar TZD usage definitions. We assessed DME with stereo photographs because this study was started prior to the widespread availability of optical coherence tomography (OCT) at the onset of the ACCORD-Eye Study. The lack of OCT technology and the limited number of participants affected with DME are limitations of the current study. While this study is larger than most prior prospective studies, the ability to examine DME progression in detail is limited by the number of patients (n=218) with DME at baseline. Of note, however, a recent study examining the role of macular thickness and volume in patients who took TZDs compared with those who did not found no significant difference in mean central retinal thickness between the groups, and the TZD group had significantly lower macular volume.[18] Finally, clinical trials participants may be healthier than the general population, and as such, rates of progression may be lower in our sample.

In summary, we did not demonstrate an association between TZD usage and DR or DME incidence or progression, or clinically meaningful visual acuity change over a four-year period. It remains possible that exposure to TZD longer than the four years of follow up in our study could be associated with DME progression. Additionally, the possibility of rare idiosyncratic reactions in susceptible patients cannot be ruled out as a potential cause of DME progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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	No TZD Exposure	Any TZD Exposure	Adjusted Odds Ratio	P−value
Macular Edema				
Incidence	22/586=3.8%	87/1993=4.4%	1.22	0.45
Progression	8/53=15.1%	26/165=15.8%	0.90	0.84
Diabetic Reinopathy				
Incidence	17/320=5.3%	75/1050=7.1%	1.54	0.14
Progression among mild	16/262=6.1%	68/905=7.5%	1.77	0.06
Progression among moderate or worse	17/69=24.6%	60/250=24.0%	1.03	0.94

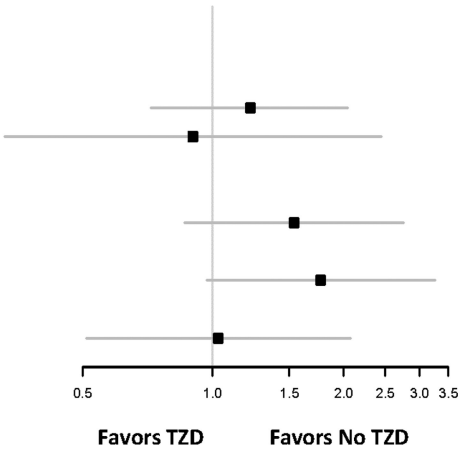

Figure 1.

Adjusted* Association between Thiazolidinedione Use and Disease Incidence and Progression

*Adjusted for age, sex, race, clinical center network, treatment group (BP vs. lipid, intensive glycemia, intensive BP, fibrate, secondary prevention), and diabetes duration.

Visual Acuity Change	No TZD Exposure	Any TZD Exposure	Adjusted Odds Ratio	P-value
10+ letter decline	234/1393=16.8%	849/4852=17.5%	1.03	0.78
15+ letter decline	127/1393=9.1%	421/4852=8.7%	0.92	0.50
10+ letter improvement	112/390=28.7%	427/1262=33.8%	1.23	0.15
15+ letter improvement	71/390=18.2%	267/1262=21.2%	1.10	0.55

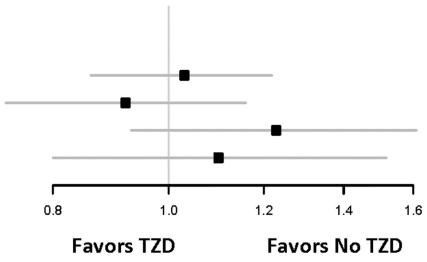

Figure 2.

Adjusted* Association between Thiazolidinedione Use and Visual Acuity Change

*Adjusted for age, sex, race, clinical center network, treatment group (BP vs. lipid, intensive glycemia, intensive BP, fibrate, secondary prevention), and diabetes duration.

Table 1

Baseline Characteristics of ACCORD Participants Who Met the Eligibility Criteria for ACCORD Eye and Had Visual Acuity Data Available at Baseline and Four Years

	Overall (N=6245)	No TZD Exposure (N=1396)	TZD Exposure (N=4849)	P-value
Age (years)	62.0 (6.6)	63.1 (6.7)	61.7 (6.6)	<0.0001
Female	37.3%	38.6%	36.9%	0.25
Nonwhite	33.1%	33.0%	33.1%	0.95
Education				0.85
< High school	13.1%	13.1%	13.1%	
High school diploma or GED	26.8%	27.4%	26.6%	
Some college or technical school	33.5%	32.6%	33.8%	
>= College diploma	26.6%	26.9%	26.5%	
Smoking status				0.51
Never	41.5%	42.1%	41.4%	
Former	45.3%	45.6%	45.2%	
Current	13.2%	12.2%	13.4%	
Diabetes duration (years)	10.6 (7.6)	10.8 (8.2)	10.6 (7.4)	0.50
Hemoglobin A1c (%)	8.2 (1.0)	8.1 (0.9)	8.3 (1.0)	<0.0001
HDL-c (mg/dl)	41.8 (11.4)	42.2 (11.6)	41.7 (11.3)	0.09
LDL-c (mg/dl)	103.9 (33.3)	104.2 (33.0)	103.8 (33.4)	0.73
Triglycerides (mg/dl)	191.6 (155.3)	178.5 (122.0)	195.4 (163.4)	0.0004
Systolic blood pressure (mm Hg)	135.6 (16.6)	136.5 (17.0)	135.4 (16.5)	0.02
Diastolic blood pressure (mm Hg)	74.8 (10.5)	74.5 (10.6)	74.9 (10.5)	0.31
Urinary albumin-creatinine ratio (mg/mg)	83.3 (322.6)	88.5 (457.2)	81.8 (271.7)	0.49
Body Mass Index (kg/m2)	32.2 (5.5)	32.2 (5.5)	32.3 (5.4)	0.60
Prior thiazolidinedione exposure	20.2%	0.43%	25.9%	<0.0001
History of cardiovascular disease	34.0%	35.0%	33.8%	0.41
Congestive heart failure	3.7%	5.4%	3.2%	0.0002
Visual acuity (number of letters)				
Worse eye	71.0 (14.3)	70.5 (14.4)	71.1 (14.2)	0.15
Better eye	78.7 (8.4)	78.3 (8.6)	78.8 (8.3)	0.05
Average of both eyes	74.8 (10.3)	74.4 (10.5)	75.0 (10.2)	0.07

Abbreviations: DR, diabetic retinopathy; ME, macular edema; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; GED, general equivalency degree Data are presented as mean (standard deviation) or percentages unless otherwise noted.

Table 2

Baseline Characteristics of ACCORD-Eye Participants with Four-year Follow up Data Available

	Overall (N=2856)	No TZD Exposure (N=651)	TZD Exposure (N=2205)	P-value
Age (years)	61.6 (6.3)	62.3 (6.5)	61.3 (6.3)	0.0007
Female	38.2%	43.0%	36.7%	0.0038
Nonwhite	30.1%	28.7%	30.5%	0.38
Education				0.71
< High school	11.8%	10.8%	12.2%	
High school diploma or GED	23.6%	23.0%	23.7%	
Some college or technical school	35.6%	36.1%	35.5%	
>= College diploma	28.9%	30.1%	28.6%	
Smoking status				0.49
Never	41.6%	43.6%	41.0%	
Former	44.8%	43.2%	45.3%	
Current	13.6%	13.2%	13.7%	
Diabetes duration (yrs)	10.0 (7.1)	10.0 (7.6)	10.0 (7.0)	0.98
Hemoglobin A1c (%)	8.2 (1.0)	8.1 (1.0)	8.3 (1.0)	0.0002
HDL-c (mg/dl)	41.9 (11.3)	42.6 (11.3)	41.8 (11.2)	0.09
LDL-c (mg/dl)	100.7 (32.7)	100.8 (32.9)	100.7 (32.7)	0.96
Triglycerides (mg/dl)	195.1 (162.6)	175.4 (104.0)	200.8 (175.8)	0.0005
Systolic blood pressure (mmHg)	134.5 (17.0)	135.4 (18.1)	134.2 (16.6)	0.11
Diastolic blood pressure (mmHg)	74.9 (10.5)	75.1 (10.5)	74.9 (10.5)	0.66
Urinary albumin-creatinine ratio (mg/mg)	71.8 (253.1)	89.6 (355.7)	66.5 (213.5)	0.04
Body Mass Index (kg/m2)	32.4 (5.5)	32.7 (5.5)	32.4 (5.4)	0.22
Prior TZD exposure	20.2%	0.77%	26.0%	<0.0001
History of cardiovascular disease	31.3%	33.0%	30.8%	0.29
Congestive heart failure	3.2%	4.3%	2.9%	0.08
Visual acuity (number of letters)				
Worse eye	72.4 (13.5)	71.8 (13.9)	72.5 (13.3)	0.27
Better eye	79.5 (8.7)	79.1 (8.8)	79.6 (8.6)	0.20
Average of both eyes	75.9 (10.2)	75.5 (10.5)	76.0 (10.1)	0.20
Diabetic Retinopathy Severity (ETDRS Person Scale Levels [*]):				0.88
No retinopathy (1)	48.0%	49.2%	47.6%	
Mild nonproliferative diabetic retinopathy (NPDR) (2–5)	40.9%	40.3%	41.1%	
Moderate NPDR (6–7)	6.2%	5.8%	6.3%	
Moderately severe NPDR or worse retinopathy (8+)	4.9%	4.6%	5.0%	
Macular edema [†]:	7.8% N=2797	8.3% N=639	7.7% N=2158	0.59
Better eye				0.42

	Overall (N=2856)	No TZD Exposure (N=651)	TZD Exposure (N=2205)	P-value
1A	97.1%	97.7%	96.9%	
1B	1.1%	0.8%	1.3%	
1C	1.4%	0.9%	1.5%	
2 or worse	0.4%	0.6%	0.4%	
Worse eye				0.34
1A	92.2%	91.7%	92.4%	
1B	1.9%	1.6%	1.9%	
1C	3.8%	3.8%	3.8%	
2 or worse	2.1%	3.0%	1.9%	

Abbreviations: TZD, Thiazolidinedione; DR, diabetic retinopathy; ME, macular edema; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; GED, general equivalency degree; ETDRS: Early Treatment of Diabetic Retinopathy Study

Data are presented as mean (SD) or percentages unless otherwise noted.

*Based on ETDRS Person scale for DR[16]; see table 2 in section 3 of the supplemental materials of Chew et al.[22]

†Based on ETDRS DME scale[21]

Table 3

Thiazolidinedione Exposure: Any Exposure and Exposure Duration

	Macular Edema Sample N=2797 %	Diabetic Retinopathy Sample N= 2856 %	Visual Acuity Sample N=6245 %
Ever on thiazolidinedione (TZD)	77.2	77.2	77.6
Duration of TZD use during the ACCORD-Eye Study:			
None	22.8	22.8	22.4
Less than 2 years	23.2	23.3	20.7
2–3 years	17.3	17.3	14.5
Greater than 3 years	36.7	36.6	42.5

Table 4

Disease Incidence and Progression Stratified by Thiazolidinedione Exposure

Characteristic	N at Risk	N with outcome (%)	TZD Exposure Among those with Outcome	
			Any N (%)	None N (%)
Macular Edema:				
Incidence	2,579	109 (4.2)	87 (4.4)	22 (3.8)
Progression	218	34 (15.6)	26 (15.8)	8 (15.1)
Diabetic Retinopathy:				
Incidence	1,370	92 (6.7)	75 (7.1)	17 (5.3)
Progression among mild at baseline	1,167	84 (7.2)	68 (7.5)	16 (6.1)
Progression among moderate or worse at baseline	319	77 (24.1)	60 (24.0)	17 (24.6)
Visual Acuity Change:				
10+ letter decline *	6,245	1,083 (17.3)	849 (17.5)	234 (16.8)
15+ letter decline *	6,245	548 (8.8)	421 (8.7)	127 (9.1)
10+ letter improvement †	1,652	539 (32.6)	427 (33.8)	112 (28.7)
15+ letter improvement †	1,652	338 (20.5)	267 (21.2)	71 (18.2)

Abbreviations: TZD, thiazolidinedione; ME, macular edema; DR, diabetic retinopathy.

* Among participants with 30+ letters at baseline.

† Among participants with 70 or fewer letters at baseline.

Table 5

Association between Thiazolidinedione (TZD) Use and Disease Incidence or Progression

	Ever on TZD		Proportion of time on TZD (per 5 percentage point increase)†	
	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio† (95% CI)
Macular Edema Incidence and Progression				
Incidence	1.17 (0.73 to 1.89) p=0.51	1.22 (0.72 to 2.05) p=0.45	1.01 (0.99 to 1.04) p=0.44	1.02 (0.99 to 1.05) p=0.18
2-step Progression among those with disease at baseline	1.05 (0.45 to 2.49) p=0.91	0.90 (0.33 to 2.45) p=0.84	0.99 (0.94 to 1.03) p=0.59	0.98 (0.93 to 1.04) p=0.46
Diabetic Retinopathy Incidence and Progression				
Baseline None	1.37 (0.80 – 2.36) p=0.24	1.54 (0.86 – 2.76) p= 0.14	1.01 (0.98 – 1.04) p=0.52	1.02 (0.99 – 1.05) p=0.26
Baseline Mild	1.25 (0.71 – 2.19) p=0.43	1.77 (0.97 – 3.26) p= 0.06	0.99 (0.97 – 1.02) p=0.66	1.02 (0.98 – 1.05) p=0.33
Baseline None or Mild Combined	1.31 (0.89 – 1.94) p=0.16	**1.68 (1.11 – 2.55) p= 0.01**	1.00 (0.98 – 1.02) p= 0.87	1.02 (1.00 – 1.04) p=0.14
Baseline Moderate or Worse	0.97 (0.52 – 1.80) p=0.91	1.03 (0.51 – 2.08) p=0.94	1.00 (0.96 – 1.03) p=0.84	1.00 (0.96 – 1.04) p=0.92
Visual Acuity				
10+ letter decline* (N=1083 with decline)	1.05 (0.90 to 1.23) p=0.52	1.03 (0.86 to 1.22) p=0.78	1.00 (0.99 to 1.01) p=0.87	1. 00 (0.99 to 1.01) p=0.64
15+ letter decline* (N=548 with decline)	0.95 (0.77 to 1.17) p=0.63	0.92 (0.73 to 1.16) p=0.50	1.00 (0.99 to 1.01) p=0.60	1. 00 (0.99 to 1.01) p=0.64
10+ letter improvement* (N=539 with improvement)	1.25 (0.95 to 1.64) p=0.11	1.23 (0.93 to 1.61) p=0.15	1.01 (1.00 to 1.02) p=0.39	1.00 (0.99 to 1.02) p=0.62
15+ letter improvement* (N=338 with improvement)	1.21 (0.90 to 1.61) p=0.21	1.10 (0.80 to 1.52) p=0.55	1.00 (0.99 to 1.02) p=0.37	1.00 (0.98 to 1.02) p=0.94

Abbreviations: TZD, thiazolidinedione; OR, odds ratio; CI, 95% confidence interval.

*in at least one eye

†The odds ratios are for each 5 percentage points of change in TZD exposure.

†Adjusted for age, sex, race, clinical center network, treatment group (BP vs. lipid, intensive glycemia, intensive BP, fibrate, secondary prevention), and diabetes duration.