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+Effect of thiazolidinediones and insulin on cognitive outcomes in ACCORD-MIND

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Abstract

Objective—To examine the relationship of cognitive performance to exposure to insulin (INS) and thiazolidinediones (TZD) in the ACCORD-MIND cohort.

Methods—Participants (55–80 yrs) with type 2 diabetes (T2D), hemoglobin A1c (HbA1c) >7.5% (>58 mmol/mol), and a high risk of cardiovascular events were randomly assigned to receive intensive control targeting HbA1c to < 6.0% (42 mmol/mol) or a standard strategy targeting HbA1c to 7.0–7.9% (53–63 mmol/mol). The Digit Symbol Substitution Test (DSST) was assessed at baseline and at 20 and 40 mo. Exposure to INS was calculated as average daily dose/kg of body weight; exposure to rosiglitazone (ROS) was calculated as days of ROS prescription in the intervals preceding the 20 and 40-mo DSSTs.

Results—At baseline, INS use was associated with reduced DSST performance, but not after controlling for co-morbidities and lab values. There was no relationship between use of a TZD and DSST performance on at baseline. ROS but not INS exposure was associated with greater decline in DSST performance over 40 mo in subjects randomized to the intensive but not the standard group.

Conclusions—Exposure to a TZD may increase cognitive decline in some patients with T2D. However, these results may be confounded by unexplained differences between participants.

Keywords

thiazolidinediones; insulin; diabetes; cognition

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Introduction

Patients with diabetes are at increased risk to develop dementia (Biessels et al., 2006). Some studies suggest that this may be because of the insulin resistance associated with type 2 diabetes (Craft, 2007). Previous studies have suggested that insulin sensitizers like thiazolidinediones (Watson et al., 2005) or even insulin itself (Plastino et al., 2009) may improve cognitive performance in patients with dementia. However, whether such drugs have a benefit on age-associated cognitive decline in community dwelling individuals with type 2 diabetes has not been tested. The ACCORD-MIND study provides a unique opportunity to address this question. In this study, cognitive function was assessed three times over 40 months in nearly 3000 participants with longstanding type 2 diabetes and at high risk for cardiovascular disease (CVD) (Williamson et al., 2007). At the time of enrollment, about 20% were on a thiazolidinedione. Over the course of the study more than 90% of ACCORD participants randomized to intensive glycemic control and almost 60% randomized to standard glycemic control were exposed to thiazolidinediones (mostly rosiglitazone) (Gerstein et al., 2008). This is likely the largest population to date of individuals with type 2 diabetes who had exposure to drugs of this class while undergoing prospective evaluation of cognitive function.

In this report we examine the relationship between exposure to insulin and drugs of the thiazolidinedione class and performance on a battery of cognitive tests. In the first analysis we tested the hypothesis that participants taking insulin or rosiglitazone/pioglitazone at entry into ACCORD will have better age-adjusted scores of cognitive function at baseline than will subjects not taking these drugs at baseline. In the second analysis, we tested the hypothesis that the rate of decline in cognitive function in ACCORD-MIND participants will be inversely related to the time of exposure to rosiglitazone or exposure to insulin (cumulative dose/kg body weight ÷ elapsed time) during the study.

Material and Methods

Research design

The rationale, study design, and entry criteria for the ACCORD trial have been described elsewhere (Gerstein et al., 2008). In brief, ACCORD was conducted at 77 clinical sites in the United States and Canada. Between January 2001 and October 2005, 10,251 participants with type 2 diabetes and a current A1c level at 7.5% to 11.0% plus either a prior CV event (35%), anatomical evidence of atherosclerosis, left ventricular hypertrophy, albuminuria, or at least two additional CV risk factors and were enrolled. Key exclusion criteria included frequent or serious hypoglycemic events, inability or unwillingness to do self-measurement of blood glucose or use injected insulin, a body-mass index (weight in kilograms divided by the square of the height in meters) more than 45, a serum creatinine higher than 1.5 mg per deciliter (133 micromole per liter), or other serious illness.

The participants were randomized to one of two therapeutic strategies for glycemic control: an intensive strategy, aiming to achieve nearly normal glycemic control with A1c less than 6.0%; or a standard strategy, aiming to maintain A1c between 7.0 and 7.9%. To reach these glycemic targets, any antihyperglycemic agents approved by regulatory authorities could be used, as considered appropriate for each individual by investigators at the clinical sites, together with lifestyle interventions. The ACCORD formulary provided, free of cost to participants, at least one agent in each of the major categories of antihyperglycemic drugs. Rosiglitazone was the drug provided in the thiazolidinedione class. Participants were permitted to use the other thiazolidinedione available in the market at the time (pioglitazone), but had to purchase the drug themselves until late in the ACCORD follow-up.

All participants were also enrolled in a double two-by-two factorial design in either a randomized blood pressure trial comparing an intensive with a standard blood-pressure treatment strategy, or a randomized lipid trial comparing treatment with fenofibrate versus placebo while maintaining good control of low-density lipoprotein cholesterol, mainly with simvastatin. The primary endpoint of all components of ACCORD was a composite of cardiovascular mortality, non-fatal myocardial infarction, or non-fatal stroke. All-cause mortality was a predefined secondary endpoint. All blood and urine measurements in this report were obtained from baseline samples analyzed in the ACCORD central laboratory. The study protocols were approved by ethics boards at all participating centers and all participants provided written informed consent.

ACCORD-MIND, described elsewhere (Williamson et al., 2007), enrolled a subset of 2977 participants from 51 ACCORD sites from August 2003 to October 2005. Participants eligible for MIND were > 55 years of age and were fluent in English or Spanish. Certified technicians administered and scored a 30-minute battery of cognitive tests (English or validated Spanish translations) performed by each participant at baseline (targeted to be performed within 45 days after randomization into ACCORD) and again after 20 and 40 months. To ensure participants were not hypoglycemic at the time of testing, tests were administered only if capillary glucose was ≥ 60 mg/dl (3.3 mmol/L) and usually after breakfast.

Cognitive Test

The ACCORD-MIND battery, described elsewhere (Williamson et al., 2007), was chosen because of its sensitivity to cognitive changes arising from both cerebrovascular and neurodegenerative etiologies. The primary cognitive measure for this study was the Digit Symbol Substitution Test (DSST), which is a subset of the Wechsler Adult Intelligence Scale (WAIS-III). It assesses a wide variety of cognitive domains, predominantly visual motor speed, learning capacity, sustained attention and working memory. It has been used in cognitively intact individuals and it has been shown to predict cognitive decline, physical disability [2% over 8.4 years for a 1-point lower score, (Rosano et al., 2005)] and mortality [0.2 to 0.7% per year for a 1-point lower score, (Pavlik et al., 2003; Rosano et al., 2005; Swan et al., 1995)]. Scores of 0 (worst) to 133 (best) are possible. Across the range of normal cognition, 6 points on the DSST is approximately equivalent to 1 point on the mini-mental status exam (MMSE) with which clinicians may be more familiar (Proust-Lima et al., 2007). The DSST is the cognitive test of greatest interest in this study since it provides a broad assessment of cognition (Proust-Lima et al., 2007).

Definition of thiazolidinediones and insulin exposure

At enrollment, participants were asked [yes/no] if they were currently taking either thiazolidinediones or insulin. After enrollment, participants taking thiazolidinedione were nearly always also using rosiglitazone that was provided by the study. Since pioglitazone was used in only 44 MIND participants prior to month 20 and in only 228 prior to month 40, a decision was made to not consider pioglitazone in these analyses. Participants that used pioglitazone were included in all analyses we present. In sensitivity analyses for longitudinal models, we exclude intervals (0-20 months or 20-40 months) for participants that used pioglitazone either during or prior to the interval. During ACCORD follow-up, doses of TZDs and other glycemic oral agents were collected for the purpose of participant management only. Consequently, we chose not to present analyses involving use of TZDs in terms of dose, but to summarize exposure to TZDs in terms of the cumulative time that the participant was prescribed the medication in the intervals preceding the 20 and 40-month cognitive tests (i.e. the number of days of prescription of rosiglitazone between baseline and the 20-month and the 20-month and 40-month measurements). For insulin, where dosage

was recorded more systematically, we defined exposure to any insulin as the average daily dose/kg of body weight in the intervals preceding the 20 and 40-month cognitive tests (i.e. the cumulative daily dose during these periods divided by the number of days of follow-up in the period).

Baseline Covariates

Baseline covariates included in the analysis were those used by Cukierman-Yaffe et al. in their previously reported baseline models of ACCORD-MIND data (Cukierman-Yaffe et al., 2009). These covariates included demographics (age, gender, education, race, language spoken, living alone), health habits (current smoker, alcohol consumption), medical comorbidities (history of depression, time since diagnosis of diabetes, history of stroke, cardiovascular disease, non-stroke cardiovascular disease, vitrectomy, neuropathy, presence of hyperlipidemia, hypertension or use of blood pressure drugs, BMI(m/kg²), and laboratory values (urine albumin-to-creatinine ratio, A1c (%), fasting plasma glucose (mg/dL).

Statistical Methods

All statistical analyses were conducted at the coordinating center with the use of SAS software, version 9.2 (SAS Institute). Means/proportions were calculated for each baseline characteristic by whether the participant was on a thiazolidinedione at baseline. Similarly, we calculated means/proportions for baseline characteristics by whether the participant was ever prescribed a thiazolidinedione.

Multiple regression analyses were used to investigate the relationship between baseline cognitive scores and thiazolidinedione use at baseline. A series of models were fit to explore how confounding between baseline covariates and use of a thiazolidinedione or insulin at baseline affects cognitive function at baseline. In model 1 the unadjusted association between baseline thiazolidinedione use and cognition was examined. In model 2 the association between thiazolidinedione use at baseline and cognition was corrected for baseline demographic characteristics. In model 3, the use of insulin at baseline was added to the variables in model 2. Model 4 examined the association between baseline thiazolidinedione use and cognition, adjusting for demographics and health habits. Model 5 consisted of model four with the addition of the use of insulin at baseline. In model 6, medical comorbidities and laboratory measurements were added to the variables in to model 4. Model 7 added baseline use of insulin use to model 6. In models 3, 5 and 7, we also added an interaction term between insulin and thiazolidinedione to understand how concomitant use of both agents affected cognitive performance at baseline.

A mixed effects model for repeatedly measured outcomes was used to investigate the association between rosiglitazone exposure and the change in cognitive function over time. For each outcome, we measured the change from baseline (follow-up value minus baseline value) and fit models to the 20 and 40-month changes as a function of the baseline covariates, the days of use of rosiglitazone and the average daily dose of insulin (units/kg). These medication variables were used as time-varying covariates in these models. The series of models that were fit were identical to Models 1-7, except that baseline thiazolidinedione and insulin (yes/no) variables were removed and replaced with days of rosiglitazone exposure and average daily dose of insulin during follow-up, respectively within glycemia groups and combined. We also added an interaction term between insulin and thiazolidinedione in models 3, 5 and 7 to understand how concomitant use of both agents affected cognitive performance over time. Finally, to determine if the observed relationships changed when controlling for glycemia control, models 6 and 7 were fit again after adding the most recent A1C level as a time dependent covariate. This is equivalent to controlling for the baseline A1C level and the change from baseline.

Results

Baseline characteristics of the ACCORD-MIND participants by use of thiazolidinediones and insulin at the time of enrollment are shown in Table 1. No difference was found between participants on thiazolidinediones at baseline as compared to those participants not taking the drug at baseline in performance on the DSST. In contrast, participants taking insulin scored lower on the DSST when compared to those participants not taking insulin at baseline.

Baseline characteristics of the ACCORD-MIND participants exposed to rosiglitazone or insulin during the trial are compared to those of participants never exposed to the drug in Table 2. The performance on the DSST was marginally better at baseline in the drug-exposed participants than in those not exposed during the trial. The performance on the DSST at baseline in the insulin-exposed participants was not different than that in those not exposed during the trial.

In Table 3, performance on the DSST at baseline was examined as a function of the variables included in the 7 models described above. In the unadjusted model, $\beta=0.739$ ($p>0.05$) for the association between TZD use and baseline DSST level. In all models, female sex, younger age, and higher levels of education were each associated with a significantly better baseline performance and Spanish as a primary language and non-white ethnicity were associated with a significantly poorer performance on the DSST at baseline. These variables continued to have a significant association with baseline DSST performance after controlling for insulin or thiazolidinedione use at baseline and for baseline health habits, medical co-morbidities, and laboratory values. The use of insulin prior to randomization was found to have a negative association with DSST performance at baseline (models 3 & 5) but this relationship disappeared after controlling for medical co-morbidities and laboratory values (model 7). These latter covariates, such as diabetes duration, are highly confounded with the use of insulin at baseline. In fact, addition of only the diabetes duration covariate causes the estimate of the insulin β to reduce from -1.650 ($p<0.001$) to -0.632 ($p>0.05$). The interaction between insulin and thiazolidinedione was not significant in any model where it was entered.

Table 4 contains mean and standard deviations of measures of medication use and change in cognition at the 20- and 40-month visits by glycemia group. Tests between glycemia groups on the cognitive outcomes have been reported elsewhere (15). In the standard group, being male ($\beta=-1.06$; $p<0.05$ in model 7) and having higher levels of baseline urine albumin/creatinine ratio ($\beta=-1.52$; $p<0.05$ in model 7) were significantly associated with greater decline in DSST at 40 months (estimates of the effect of baseline covariates on change in DSST for each model are available on request from the author). For none of the 7 models considered, neither exposure to rosiglitazone nor insulin had a significant effect on the change in DSST performance within the standard group over 20 or 40 months of follow-up (see Table 5 for medication results). The interaction between insulin and thiazolidinedione was not significant in any standard group model where it was entered.

In the intensive group, increasing age ($\beta=-1.32$; $p<0.01$ in model 7), white ethnicity ($\beta=-1.12$; $p<0.05$ in model 7) and no history of hypertension or use of BP medications ($\beta=-1.327$; $p<0.05$ in model 7) were significantly associated with greater decline in DSST at 40 months (estimates of the effect of baseline covariates on change in DSST for each model are available on request from the author). Within intensive group participants, person years of exposure to rosiglitazone did not have an effect on the change in DSST performance over 20 months of follow-up, but over 40 months a significant inverse relationship was found when controlling for baseline demographic characteristics (Table 5). This relationship between rosiglitazone exposure and the change in performance over 40

months of follow-up persisted after further adjustment for medical comorbidities, health habits, laboratory values, and insulin exposure. Insulin exposure was inversely associated with change in DSST performance over 40 months within intensively treated participants, but like the baseline models, the significance of this relationship disappeared after controlling for medical comorbidities and laboratory values (Table 5). When both glycemic groups were combined, rosiglitazone exposure was not associated with change in DSST performance over 20 or 40 months, and the relationship with insulin exposure disappeared when controlling for medical comorbidities and laboratory values (Table 5). When the most recent A1C was entered into these models, overall conclusions about either the rosiglitazone or the insulin variables did not change. Conclusions also remained the same when we excluded cognition data for intervals (0-20 months or 20-40 months) during which participants either had concurrent or prior use of pioglitazone

To further explore how the relationship between rosiglitazone exposure and the change in DSST performance over time may be related to potential confounding with other variables related to rosiglitazone exposure, participants at the extremes of the rosiglitazone distribution were identified (< 0.5 years versus ≥ 3 years of rosiglitazone exposure). Comparing participants at the two extremes for rosiglitazone exposure within the intensive group, we found that in comparison to those in the ≥ 3 years exposure group (N=501), those with < 0.5 years of exposure (N=376) were older (age=63.1 vs 61.7; $p<0.001$), had a greater use of insulin at baseline (51.6% vs 28.5%; $p<0.001$), a longer duration of diabetes (11.8 yrs vs 9.2 yrs; $p<0.001$), a more likely history of heart failure (8% versus 2.2%; $p<0.001$) and lower baseline DSST scores (51.5 versus 54.4; $p=0.006$). These differences were not quite as pronounced within the standard group, where those with <0.5 years of exposure (N=1459) were still older (age=63.3 vs 61.7; $P<0.001$), and had a greater use of insulin at baseline (38.7% vs 25.2%; $p<0.001$), but showed no statistically significant difference for duration of diabetes (10.4 yrs vs 11.3 yrs; $p=0.79$), history of heart failure (6.8% versus 4.5%; $p=0.19$) and baseline DSST scores (53.0 versus 55.0; $p=0.07$). The mean 40-month change in the DSST within these 4 groups were: Intensive (< 0.5) = -0.79, Intensive (≥ 3.0) = -2.15, Standard (< 0.5) = -1.99, Standard (≥ 3.0) = -1.31. Thus, the low exposure -- standard group experienced almost as great a decline in DSST as the high exposure intensive group.

Discussion

In this analysis, insulin use at baseline was associated with reduced performance on the DSST in participants in the ACCORD-MIND study, but the significance of this relationship disappeared after controlling for medical co-morbidities and laboratory values. No relationship was found between baseline use of a thiazolidinedione and performance on cognitive tests administered at baseline. However, rosiglitazone use was associated with significantly greater decline in DSST performance over 40 months in subjects randomized to the intensive but not the standard glycemia group, although this decline was small (0.5 DSST units over 40-months for each person year of rosiglitazone use during that time). Patients with type 2 diabetes are at increased risk for the development of all types of dementia (Biessels et al., 2006). Vascular disease, which can result in cerebral ischemia and infarction, is common in this population and is believed to contribute to their risk for cognitive dysfunction. Insulin resistance has also been hypothesized to increase dementia risk (Craft, 2007). Interestingly, cognitive performance is improved in memory-impaired humans following administration of intranasal insulin (Reger et al., 2006), a procedure that raises intracerebral insulin levels and may help overcome cerebral insulin resistance. Early studies with insulin sensitizers like rosiglitazone were associated with improvements in cognitive function (Watson et al., 2005) (Abbatecola et al., 2010), but no benefit was shown during a longer randomized trial of rosiglitazone (Gold et al.).

We found that rosiglitazone exposure was associated with an increased rate of decline in DSST performance in the group randomized to intensive glycemic control. While this association was found to be statistically significant, the clinical relevance is uncertain. A change in DSST score of 0.5 units is roughly equivalent to the difference in cognition seen between older adults who differ in age by one year (MacDonald et al., 2003). We also found that rosiglitazone exposure did not correlate with changes in DSST scores over time in the group randomized to standard control and thiazolidinedione use at baseline was not associated with DSST scores in either group. One difference noted between the intensive and standard glycemic control groups in ACCORD was the rate at which they experienced hypoglycemia; with an annualized rate of 3.1% in the intensive group and of 1.0% in the standard group (Gerstein et al., 2008). While we controlled for insulin exposure in our analysis, a variable identified to significantly relate to the risk of experiencing severe hypoglycemia (Bonds et al, 2012), it is possible that hypoglycemia in the rosiglitazone treated participants in the intensive group contributed to the increased rate of decline in DSST performance over 40 months. Future studies will need to address the impact of hypoglycemia on cognitive decline in patients with type 2 diabetes who are treated with combination therapy. Taken together, our observations provides further evidence that drugs in the thiazolidinedione class do not have a positive effect on cognitive changes over time in older adults with type 2 diabetes mellitus.

The ACCORD-MIND study examined the largest population of subjects with type 2 diabetes exposed to a thiazolidinedione while undergoing a progressive evaluation of cognitive function to date. The study also included a long period of follow-up. Despite these strengths, the report is limited by the fact that participants were not randomized to rosiglitazone therapy. Consequently, it is likely that the subjects on the drug were different than the subjects who were not given the drug. The impact of these differences on cognitive decline over time are unknown, but our examination of participants stratified by < 0.5 and > 3.0 years of exposure shows that intensive group participants at these extremes differed by age, insulin use at baseline, and heart failure history. What other confounding factors that could have influenced cognition over time are unknown. In addition, the impact of rosiglitazone on the decline in DSST over 40 months is small and of uncertain clinical significance.

In summary, we found that rosiglitazone exposure but not insulin use was associated with greater decline in DSST performance over 40 months in ACCORD-MIND participants randomized to the intensive but not the standard glycemia group. However, since subjects were not randomized to rosiglitazone therapy we cannot exclude the presence of variables that could confound our result. We conclude that drugs in this class do not appear to be of benefit in preventing cognitive decline in patients with type 2 diabetes.

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Table 1
Baseline Characteristics of ACCORD-MIND Participants By Use of TZDs or Insulin at Enrollment

Variable	Total	TZD Use at Enrollment		P-value	Insulin Use at Enrollment		P-value
		No	Yes		No	Yes	
N	2977	2353	624		1952	1025	
Female (%)	1388 (46.62)	1126 (47.85)	262 (41.99)	0.0090	882 (45.18)	506 (49.37)	0.0298
Age	62.48 +/- 5.82	62.50 +/- 5.86	62.41 +/- 5.68	0.7147	62.36 +/- 5.80	62.72 +/- 5.85	0.1066
Education:				0.1078			0.0110
Not a High School Graduate (%)	392 (13.2)	328 (13.9)	64 (10.3)		244 (12.5)	148 (14.4)	
Just High School (%)	769 (25.8)	606 (25.8)	163 (26.1)		482 (24.7)	287 (28.0)	
Some College or Technical School (%)	1027 (34.5)	800 (34.0)	227 (36.4)		675 (34.6)	352 (34.3)	
College Graduate or More (%)	789 (26.5)	619 (26.3)	170 (27.2)		551 (28.2)	238 (23.2)	
Ethnicity:				0.0008			0.0083
American Indian/Alaska Native Only (%)	65 (2.2)	45 (1.9)	20 (3.2)		46 (2.4)	19 (1.9)	
Asian Only (%)	67 (2.3)	53 (2.3)	14 (2.2)		53 (2.7)	14 (1.4)	
African American/Canadian Only (%)	478 (16.1)	402 (17.1)	76 (12.2)		284 (14.5)	194 (18.9)	
Other (%)	81 (2.7)	74 (3.1)	7 (1.1)		50 (2.6)	31 (3.0)	
Spanish (%)	212 (7.1)	169 (7.2)	43 (6.9)		141 (7.2)	71 (6.9)	
Caucasian Only (%)	2074 (69.7)	1610 (68.4)	464 (74.4)		1378 (70.6)	696 (67.9)	
Spanish as Primary Language	110 (3.69)	86 (3.65)	24 (3.85)	0.8219	80 (4.10)	30 (2.93)	0.1074
Living Alone (%)	657 (22.07)	527 (22.40)	130 (20.83)	0.4024	432 (22.13)	225 (21.95)	0.9104
Current Smoker (%)	352 (11.82)	278 (11.81)	74 (11.86)	0.9757	224 (11.48)	128 (12.49)	0.4163
> 3 Drinks/Week (%)	232 (7.79)	179 (7.61)	53 (8.49)	0.4628	159 (8.15)	73 (7.12)	0.3222
Depression or PHQ9 score 10 (%)	1026 (34.46)	821 (34.89)	205 (32.85)	0.3407	626 (32.07)	400 (39.02)	0.0001
Mean Diabetes Duration	10.39 +/- 7.35	10.24 +/- 7.61	10.95 +/- 6.24	0.0308	8.35 +/- 6.15	14.29 +/- 7.86	<.0001
Previous Cardiovascular Disease (%) ^J	869 (29.19)	692 (29.41)	177 (28.37)	0.6101	492 (25.20)	377 (36.78)	<.0001
Stroke (%)	151 (5.07)	125 (5.31)	26 (4.17)	0.2462	80 (4.10)	71 (6.93)	0.0008
Non Stroke CVD (%)	718 (24.12)	567 (24.10)	151 (24.20)	0.9578	412 (21.11)	306 (29.85)	<.0001
Vitrectomy (%)	15 (0.50)	13 (0.55)	2 (0.32)	0.4669	3 (0.15)	12 (1.17)	0.0002
Neuropathy (%) ²	1472 (49.45)	1162 (49.38)	310 (49.68)	0.8955	851 (43.60)	621 (60.59)	<.0001
Hyperlipidemia (%) ³	2426 (81.49)	1892 (80.41)	534 (85.58)	0.0031	1556 (79.71)	870 (84.88)	0.0006

Variable	TZD Use at Enrollment		P-value	Insulin Use at Enrollment		P-Value
	Total	No		Yes	No	
Previous Hypertension or Use of BP Drugs (%)	2578 (86.60)	2026 (86.10)	0.1242	552 (88.46)	1625 (83.25)	<.0001
Body Mass Index (kg/m ²)	32.98 +/- 5.36	32.76 +/- 5.34	<.0001	33.80 +/- 5.37	32.58 +/- 5.34	<.0001
Urine Albumin/Creatinine	0.09 +/- 0.40	0.09 +/- 0.43	0.6508	0.09 +/- 0.29	0.06 +/- 0.23	<.0001
HbA1c (%)	8.28 +/- 1.05	8.32 +/- 1.07	<.0001	8.11 +/- 0.96	8.19 +/- 1.06	<.0001
Fasting Plasma Glucose (SD) (mg/dL)	175.5 +/- 55.01	178.9 +/- 56.30	<.0001	162.7 +/- 47.76	178.3 +/- 50.44	0.0001
DSST	52.55 +/- 15.89	52.33 +/- 15.90	0.1553	53.35 +/- 15.83	53.45 +/- 15.94	<.0001

Data are mean ± SD or counts followed by %. BP – Blood Pressure; PHQ – physician's health questionnaire

¹ myocardial infarction, angina with ischemic changes on graded exercise test or positive imaging, coronary revascularization procedures, or stroke

² history of neuropathy or absent ankle reflexes or vibration perception at great toe for either foot

³ on lipid lowering medication or an untreated LDL-C > 130 mg/dL (3.38 mmol/L)

Table 2
Baseline Characteristics of ACCORD-MIND Participants By Use of Rosiglitazone or Insulin during ACCORD Follow-Up

Variable	On TZD During Follow-Up			P-value	On Insulin During Follow-Up			P-value
	No	Yes			No	Yes		
N	808	2169			1119	1858		
Female (%)	389 (48.14%)	999 (46.06%)		0.3104	530 (47.36%)	858 (46.18%)		0.5302
Age	63.49 $\pm$ 6.07	62.11 $\pm$ 5.68		<0.0001	62.71 $\pm$ 5.87	62.35 $\pm$ 5.79		0.0987
Education:				0.8584				0.6651
Not a High School Graduate (%)	107 (13.2%)	285 (13.1%)			145 (13.0%)	247 (13.3%)		
Just High School (%)	212 (26.2%)	557 (25.7%)			286 (25.6%)	483 (26.0%)		
Some College or Technical School (%)	269 (33.3%)	758 (34.9%)			377 (33.7%)	650 (35.0%)		
College Graduate or More (%)	220 (27.2%)	569 (26.2%)			311 (27.8%)	478 (25.7%)		
Ethnicity:				0.4023				0.0192
American Indian/Alaska Native Only (%)	18 (2.2%)	47 (2.2%)			25 (2.2%)	40 (2.2%)		
Asian Only (%)	18 (2.2%)	49 (2.3%)			32 (2.9%)	35 (1.9%)		
African American/Canadian Only (%)	128 (15.8%)	350 (16.1%)			162 (14.5%)	316 (17.0%)		
Other (%)	30 (3.7%)	51 (2.4%)			29 (2.6%)	52 (2.8%)		
Spanish (%)	63 (7.8%)	149 (6.9%)			99 (8.8%)	113 (6.1%)		
Caucasian Only (%)	551 (68.2%)	1523 (70.2%)			772 (69.0%)	1302 (70.1%)		
Spanish as Primary Language	33 (4.08%)	77 (3.55%)		0.4921	62 (5.54%)	48 (2.58%)		<0.0001
Living Alone (%)	176 (21.78%)	481 (22.18%)		0.8177	253 (22.61%)	404 (21.74%)		0.5812
Current Smoker (%)	88 (10.89%)	264 (12.17%)		0.3360	128 (11.44%)	224 (12.06%)		0.6135
> 3 Drinks/Week (%)	78 (9.65%)	154 (7.10%)		0.0208	96 (8.58%)	136 (7.32%)		0.2144
Depression or PHQ9 score $\geq$ 10 (%)	266 (32.92%)	760 (35.04%)		0.2795	338 (30.21%)	688 (37.03%)		0.0001
Mean Diabetes Duration	10.64 $\pm$ 8.23	10.29 $\pm$ 6.99		0.2458	7.90 $\pm$ 6.49	11.90 $\pm$ 7.43		<0.0001
Previous Cardiovascular Disease (%) ^f	260 (32.18%)	609 (28.08%)		0.0286	262 (23.41%)	607 (32.67%)		<0.0001
Stroke (%)	44 (5.45%)	107 (4.93%)		0.5710	48 (4.29%)	103 (5.54%)		0.1310
Non Stroke CVD (%)	216 (26.73%)	502 (23.14%)		0.0418	214 (19.12%)	504 (27.13%)		<0.0001
Vitrectomy (%)	5 (0.62%)	10 (0.46%)		0.5888	3 (0.27%)	12 (0.65%)		0.1586
Neuropathy (%) ²	410 (50.74%)	1062 (48.96%)		0.3877	481 (42.98%)	991 (53.34%)		<0.0001
Hyperlipidemia (%) ³	654 (80.94%)	1772 (81.70%)		0.6367	883 (78.91%)	1543 (83.05%)		0.0049

Variable	On TZD During Follow-Up		P-value	On Insulin During Follow-Up		P-value
	No	Yes		No	Yes	
Previous Hypertension or Use of BP Drugs (%)	710 (87.87%)	1868 (86.12%)	0.2130	921 (82.31%)	1657 (89.18%)	<.0001
Body Mass Index (kg/m ²)	32.61 +/- 5.43	33.11 +/- 5.33	0.0227	32.44 +/- 5.13	33.30 +/- 5.47	<.0001
Urine Albumin/Creatinine Ratio (mg/g)	0.12 +/- 0.63	0.08 +/- 0.28	0.0569	0.06 +/- 0.24	0.11 +/- 0.48	0.0061
HbA1c(%)	8.08 +/- 0.97	8.35 +/- 1.07	<.0001	8.02 +/- 1.00	8.43 +/- 1.05	<.0001
Fasting Plasma Glucose (SD) (mg/dl)	168.0 +/- 50.90	178.3 +/- 56.21	<.0001	171.6 +/- 49.20	177.8 +/- 58.10	0.0028
DSST	51.58 +/- 15.88	52.91 +/- 15.88	0.0429	52.69 +/- 16.09	52.47 +/- 15.78	0.7172

Data are mean ± SD or counts followed by %. BP – Blood Pressure; PHQ – physician's health questionnaire

- 1 myocardial infarction, angina with ischemic changes on graded exercise test or positive imaging, coronary revascularization procedures, or stroke
- 2 history of neuropathy or absent ankle reflexes or vibration perception at great toe for either foot
- 3 on lipid lowering medication or an untreated LDL-C > 130 mg/dL (3.38 mmol/L)

Table 3

Modeling Results for Baseline DSST Score

Variable	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Female vs Male	5.042(^c)	5.093(^c)	5.472(^c)	5.506(^c)	5.523(^c)	5.525(^c)
Age (per 1 year)	-0.716(^c)	-0.711(^c)	-0.739(^c)	-0.734(^c)	-0.709(^c)	-0.710(^c)
Education:						
Not HS Grad vs. College Grad.	-18.248(^c)	-18.107(^c)	-17.847(^c)	-17.728(^c)	-17.453(^c)	-17.442(^c)
HS Grad vs College Grad.	-10.293(^c)	-10.156(^c)	-10.090(^c)	-9.963(^c)	-9.621(^c)	-9.609(^c)
Some College vs College Grad.	-6.040(^c)	-5.963(^c)	-5.843(^c)	-5.776(^c)	-5.579(^c)	-5.574(^c)
Ethnicity: non-white vs. white	-9.907(^c)	-9.832(^c)	-9.900(^c)	-9.822(^c)	-9.340(^c)	-9.338(^c)
Spanish as Primary Language(vs Other Language)	-11.820(^c)	-12.069(^c)	-11.840(^c)	-12.074(^c)	-12.151(^c)	-12.171(^c)
Living Alone (vs With others)	-0.580	-0.603	-0.488	-0.516	-0.456	-0.456
Current Smoker (vs all others)			-1.274	-1.271	-1.370	-1.365
> 3 Drinks/Week (vs. all others)			2.793(^b)	2.789(^b)	2.397(^b)	2.404(^b)
Depression or PHQ9 score 10 (vs. all others)			-1.671(^c)	-1.553(^b)	-1.323(^b)	-1.310(^b)
Mean Diabetes Duration (per 1 year)					-0.159(^c)	-0.152(^c)
Stroke (yes vs. no)					-6.600(^c)	-6.591(^c)
Non Stroke CVD (yes vs. no)					0.015	0.028
Vitrectomy (yes vs. no)					-4.878	-4.855
Neuropathy ¹ (yes vs. no)					0.499	0.521
Hyperlipidemia ² (yes vs. no)					1.111	1.133
Hypertension or Use of BP Drugs (yes vs. no)					-1.575(^d)	-1.542(^d)
Body Mass Index (per 1 kg/m ²)					-0.030	-0.027
Urine Albumin/Creatinine (per 1 unit)					-1.145(^d)	-1.125
HbA1c (per 1%)					-0.724(^b)	-0.702(^b)
Fasting Plasma Glucose (per 1 mg/dL)					0.003	0.003

Variable	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
TZD Use At Enrollment (yes vs. no)	-0.101	-0.220	-0.101	-0.210	-0.120	-0.153
Insulin Use At Enrollment (yes vs. no)		-1.766(c)		-1.650(c)		-0.303

Data presented are the coefficient for the association between the variable and the performance on the DSST; for categorical variables (i.e. sex) the coefficient represents the mean difference in score between those with and without the characteristic; for continuous variables the coefficient represents the mean difference in score for every 1 unit difference. CVD – cardiovascular disease; BP – Blood Pressure; PHQ – physician’s health questionnaire

Model Definitions:

- 1) Baseline DSST = TZD Use (Estimated Beta Coefficient = 0.739; not significant at P<0.05)
- 2) Baseline DSST = Demographics + TZD Use
- 3) Baseline DSST = Demographics + TZD Use + Insulin Use
- 4) Baseline DSST = Demographics + Health Habits + TZD Use
- 5) Baseline DSST = Demographics + Health Habits + TZD Use + Insulin Use
- 6) Baseline DSST = Demographics + Health Habits + Medical Comorbidities/Lab Results + TZD Use
- 7) Baseline DSST = Demographics + Health Habits + Medical Comorbidities/Lab Results + TZD Use + Insulin Use

¹ history of neuropathy or absent ankle reflexes or vibration perception at great toe for either foot.

² on lipid lowering medication or an untreated LDL-C > 130 mg/dL (3.38 mmol/L)

^a p<0.05

^b p<0.01

^c p<0.001

Table 4
Summary (Mean $\pm$ SD) of Medication Use and Cognition Change at 20/40 month visits

Time-Varying Characteristic	20-Month Visit		40-Month Visit	
	Standard Glycemia	Intensive Glycemia (N=1352)	Standard Glycemia (N=1332)	Intensive Glycemia (N=1297)
Rosiglitazone Use (Person Years)	0.62 $\pm$ 0.72 (N=1413)	1.29 $\pm$ 0.58 (N=1366)	1.20 $\pm$ 1.32 (N=1326)	2.29 $\pm$ 1.11 (N=1286)
Insulin Use (Average dose/kg)	0.23 $\pm$ 0.35 (N=1413)	0.32 $\pm$ 0.38 (N=1366)	0.26 $\pm$ 0.37 (N=1345)	0.37 $\pm$ 0.40 (N=1310)
DSST Change (FU-BL)	-1.6 $\pm$ 7.97 (N=1395)	-1.1 $\pm$ 8.26 (n=1352)	-2.0 $\pm$ 8.54 (N=1332)	-1.6 $\pm$ 7.63 (N=1297)

Table 5

Summary of Medication Effects on 20/40 month change in DSST

Glycemia Group	Time-Varying Predictor	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
20-Month Change in DSST Score								
Standard	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	0.047	0.030	-0.006 -0.844	0.042	0.007 -0.813	0.021	-0.025 -0.731
Intensive	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	-0.335	-0.374	-0.434 -0.514	-0.385	-0.428 -0.392	-0.406	-0.424 -0.267
Both	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	-0.069	-0.094	-0.156 -0.624	-0.088	-0.145 -0.555	-0.106	-0.151 -0.438
40-Month Change in DSST Score								
Standard	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	0.090	0.106	0.095 -0.454	0.124	0.116 -0.344	0.160	0.159 -0.095
Intensive	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	-0.351	-0.379 ^(a)	-0.493 ^(b) -1.509 ^(b)	-0.398 ^(a)	-0.508 ^(b) -1.452 ^(b)	-0.448 ^(a)	-0.519 ^(b) -1.210
Both	Person Years of Rosiglitazone Use Average Dose/kg of Insulin	-0.111	-0.110	-0.152 -0.969 ^(a)	-0.106	-0.145 -0.876 ^(a)	-0.100	-0.129 -0.682

Data presented are the coefficient for the association between the variable and change in DSST score. This is equal to the predicted change in DSST score (FU-BL) for every additional person year of rosiglitazone use or 1 unit/kg difference in insulin.

Model Definitions:

- 1) Change in DSST = PY of TZD
- 2) Change in DSST = Demographics + PY of TZD
- 3) Change in DSST = Demographics + PY of TZD + Average Dose/kg of Insulin
- 4) Change in DSST = Demographics + Health Habits + PY of TZD
- 5) Change in DSST = Demographics + Health Habits + PY of TZD + Average Dose/kg of Insulin
- 6) Change in DSST = Demographics + Health Habits + Medical Comorbidities/Lab Results + PY of TZD
- 7) Change in DSST = Demographics + Health Habits + Medical Comorbidities/Lab Results + PY of TZD + Average Dose/kg of Insulin

^aP<0.05

^bP<0.01.