Original Investigation

Cognitive Function and Brain Structure in Persons With Type 2 Diabetes Mellitus After Intensive Lowering of Blood Pressure and Lipid Levels
A Randomized Clinical Trial

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IMPORTANCE Persons with type 2 diabetes mellitus (T2DM) are at increased risk for decline in cognitive function, reduced brain volume, and increased white matter lesions in the brain. Poor control of blood pressure (BP) and lipid levels are risk factors for T2DM-related cognitive decline, but the effect of intensive treatment on brain function and structure is unknown.

OBJECTIVE To examine whether intensive therapy for hypertension and combination therapy with a statin plus a fibrate reduces the risk of decline in cognitive function and total brain volume (TBV) in patients with T2DM.

DESIGN, SETTING, AND PARTICIPANTS A North American multicenter clinical trial including 2977 participants without baseline clinical evidence of cognitive impairment or dementia and with hemoglobin A_{1c} (HbA_{1c}) levels less than 7.5% randomized to a systolic BP goal of less than 120 vs less than 140 mm Hg (n = 1439) or to a fibrate vs placebo in patients with low-density lipoprotein cholesterol levels less than 100 mg/dL (n = 1538). Participants were recruited from August 1, 2003, through October 31, 2005, with the final follow-up visit by June 30, 2009.

MAIN OUTCOME MEASURES Cognition was assessed at baseline and 20 and 40 months. A subset of 503 participants underwent baseline and 40-month brain magnetic resonance imaging to assess for change in TBV and other structural measures of brain health.

RESULTS Baseline mean HbA_{1c} level was 8.3%; mean age, 62 years; and mean duration of T2DM, 10 years. At 40 months, no differences in cognitive function were found in the intensive BP-lowering trial or in the fibrate trial. At 40 months, TBV had declined more in the intensive vs standard BP-lowering group (difference, −4.4 [95% CI, −7.8 to −1.1] cm^3; $P = .01$). Fibrate therapy had no effect on TBV compared with placebo.

CONCLUSIONS AND RELEVANCE In participants with long-standing T2DM and at high risk for cardiovascular events, intensive BP control and fibrate therapy in the presence of controlled low-density lipoprotein cholesterol levels did not produce a measurable effect on cognitive decline at 40 months of follow-up. Intensive BP control was associated with lower decline in TBV at 40 months relative to standard therapy.

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Invited Commentary

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The prevalence of type 2 diabetes mellitus (T2DM) in older adults has risen in recent decades.[1] Older persons with T2DM plus hypertension or, to a lesser extent, dyslipidemia have an increased likelihood of cognitive impairment and dementia compared with persons without T2DM or with T2DM alone.[2] Type 2 diabetes mellitus in combination with these comorbidities is also associated with morphologic changes in the brain structure, including brain atrophy,[3] increases in white matter lesions[4,5] due to small-vessel and microvessel damage, and stroke due to larger-vessel occlusion and hemorrhage. These morphologic changes are also important predictors of impairment in older adults.[6,7]

No accepted prevention strategies exist at present to slow the effect of hypertension or dyslipidemia on cognitive decline in T2DM. Preliminary studies have suggested hypotheses that intensive therapy to lower blood pressure (BP) and lipid levels may be effective means of preventing T2DM-related cognitive decline.[8,9] These hypotheses were tested using measures of cognitive function and magnetic resonance imaging (MRI)-based brain structure in the Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[10-12] The glycemia results for the MIND aspect of the trial have been published.[12]

Methods

The ACCORD and ACCORD MIND trial designs have been described previously.[10-12] Briefly, ACCORD was a randomized, multicenter, double 2 × 2 factorial trial of 10 251 middle-aged and older participants with T2DM at high risk for cardiovascular events because of prevalent cardiovascular disease (CVD) or additional cardiovascular risk factors. All participants in the main ACCORD trial were enrolled in the glycemia trial to compare a therapeutic strategy targeted to a hemoglobin A_{1c} (HbA_{1c}) level of less than 6.0% (intensive therapy arm) vs a strategy that targeted HbA_{1c} levels of 7.0% to 7.9% (standard therapy arm). The lipid trial (53.8% of the total sample) compared masked administration of placebo or fenofibrate in persons with low-density lipoprotein cholesterol (LDL-C) levels of less than 100 mg/dL (to convert to millimoles per liter, multiply by 0.0259) achieved through study-supplied simvastatin. The BP trial included the other 46.2% of participants and compared a therapeutic strategy targeted to systolic BP (SBP) of less than 120 mm Hg (intensive therapy) to one targeting SBP of less than 140 mm Hg (standard therapy). Participants meeting inclusion/exclusion criteria with SBP ranging from 130 to 180 mm Hg and taking 3 or fewer antihypertensives were eligible for the BP trial. All others were assigned to the lipid trial. Unique randomization sequences for ACCORD were computer generated centrally at the coordinating center using permuted blocks of 4, 8, or 12 participants. A physical examination was performed, and event data and blood samples were collected at annual visits. In February 2008, the intensive glycemic intervention was stopped because increased risk for mortality was detected in that group.[13] All participants in the intervention for intensive glycemic control were transitioned to the standard glycemic intervention protocol. The lipid and BP trials continued to the planned completion date in June 2009.

The MIND substudy within the ACCORD trial (target sample size, 2800 participants) was approved by the institutional review boards of the sponsors and each clinical site to collect additional cognitive and MRI outcomes beginning in August 2003. Immediately after randomization to an ACCORD treatment group, participants were asked to participate in the MIND substudy. Willing participants signed informed consent for collection of additional ACCORD MIND outcomes.

Cognitive Function

Cognitive function was assessed at baseline and 20 and 40 months after randomization using a test battery targeting cognitive functions typically affected in T2DM.[10] The cognitive battery assessed verbal memory, processing speed, and executive function.[14,15] The primary cognitive outcome was the number of correctly completed symbols in 120 seconds on the Digit Symbol Substitution Test (DSST), an omnibus test of psychomotor function and speed that includes aspects of learning and working memory.[16] Secondary cognitive outcomes were verbal memory and executive function. Verbal memory was measured with the Rey Auditory Verbal Learning Test[17] and reported as the sum of the number of words recalled (0-15) during the immediate-, short-, and delayed-recall trials. Executive functioning was measured with the modified Stroop Color-Word Test[18] and is reported as the interference score; a higher score indicates worse function. To assess global cognitive function and to provide a metric to compare the MIND cohort with other study groups, the Mini-Mental State Examination[19] was also administered. In addition to the cognitive tests, the Physician's Health Questionnaire[20] was administered to screen for depression, a frequent comorbidity in T2DM and a potential confounder.

Magnetic Resonance Imaging

For the MRI substudy, total brain volume (TBV) (measured in cubic centimeters), an integrated measure of neurodegenerative processes, was the primary outcome. Substantial evidence suggests that brain volume in nondemented individuals predicts future cognitive disorders.[3]

Scans were targeted within 45 days after randomization and at 40 months. The standardized MRI scan protocol and image analysis were previously described.[21,22] Monthly MRI quality control procedures followed the American College of Radiology's MRI QC Program (http://www.acr.org/quality-safety/accreditation/mri). Performance of the MRI scanner was stable across MRI sites and throughout the duration of the study as reflected by the stability of intracranial volumes (ICVs) over time (baseline mean ICV, 1132.34 cm^3; follow-up mean ICV, 1132.32 cm^3; $P = .47$ by paired t test).

Sample Size

Using unpublished data from participants in the Cardiovascular Health Study aged 65 to 75 years,[23] we anticipated a 3-point, 40-month decline in the mean DSST score among participants randomized to standard glycemia, standard BP, or placebo fibrate therapy. For comparison of cognitive function between

the intensive and standard BP therapy groups (or the fibrate and placebo lipid therapy groups) using a .05 two-sided type I error rate, a sample size of 600 participants per group (300 per cell) provided approximately 80% power to detect a 3% (1.2 DSST units) difference in 40-month means, assuming an underlying 2.5% difference in 40-month means for those participants in the intensive vs standard glycemia therapy groups (Supplement [eAppendix]). Recruitment was targeted at 350 participants per cell to account for an anticipated nonresponse rate of 15%. We ultimately recruited 2977 randomized ACCORD participants from 51 clinics throughout 6 clinical center networks (CCNs) (745 in the intensive BP therapy group, 694 in the standard BP therapy group, 782 in the fibrate therapy group, and 756 in the placebo group). The Veterans Administration CCN opted not to enroll MIND participants.

For the MRI substudy, assuming 200 participants were recruited to each BP intervention, we had 70% power to detect a 40-month difference in mean TBV of 3.3 cm^3 under the same dropout and type I error assumptions. Post hoc power calculations for the lipid trial indicated that 100 participants with evaluable data per group would provide 70% power to detect a 40-month difference of 4.1 cm^3 in mean TBV.

Statistical Analysis

All analyses were conducted at the ACCORD Coordinating Center, Wake Forest School of Medicine, using commercially available software (SAS, version 9.2; SAS Institute, Inc). All *P* values are reported as 2-sided tests. Participant characteristics are summarized with means (standard deviations) and percentages. Owing to the requirement to recruit ACCORD MIND participants and obtain consent 1 month after ACCORD randomization, which allowed some randomized participants to choose not to participate in MIND, baseline characteristics were compared (using 2-sided *t* tests and χ^2 tests) between intervention groups within each 2 × 2 factorial trial. Characteristics that differed between groups at baseline were adjusted for in post hoc analyses to explore whether conclusions from unadjusted analyses resulted from baseline imbalances.

Within the BP and lipid trials, to test the effect of the interventions on cognitive function, we used a mixed-effects analysis of covariance model appropriate for 2 × 2 factorial studies that incorporated the 20- and 40-month outcome measures and used an unstructured covariance matrix.[24] Each 2 × 2 trial was analyzed separately. Within each trial, the basic model included main-effect terms for the glycemia and BP (or lipid) interventions, a visit effect, a glycemia × visit interaction, a BP (or lipid) × visit interaction, the baseline value of the outcome, and other factors used to stratify randomization (CCN and history of CVD). Contrasts were used to test the primary hypothesis of no difference between BP (or lipid) groups at the 40-month visit.

We investigated the BP and lipid intervention effect on 40-month TBV using analysis of covariance. We analyzed each 2 × 2 trial separately. The model included main-effect terms for glycemia and BP (or lipid) interventions, baseline TBV, ICV (to adjust for head size), and previously described stratification factors.

Within the BP trial, we investigated the sensitivity of the TBV results to missing 40-month observations (including deaths) using multiple-imputation regression methods. The multiple-imputation regression models imputed missing 40-month TBV using baseline TBV, glycemia group assignment, history of CVD, CCN, and ICV. After recommendations for exploring the sensitivity of results to different missing data models,[24] we estimated 2 regression-based imputation models. In model 1, the imputation of missing 40-month outcomes was based on fitting the same regression coefficients in both BP groups; in model 2, the imputation was based on allowing the regression coefficients to be estimated within each BP group.

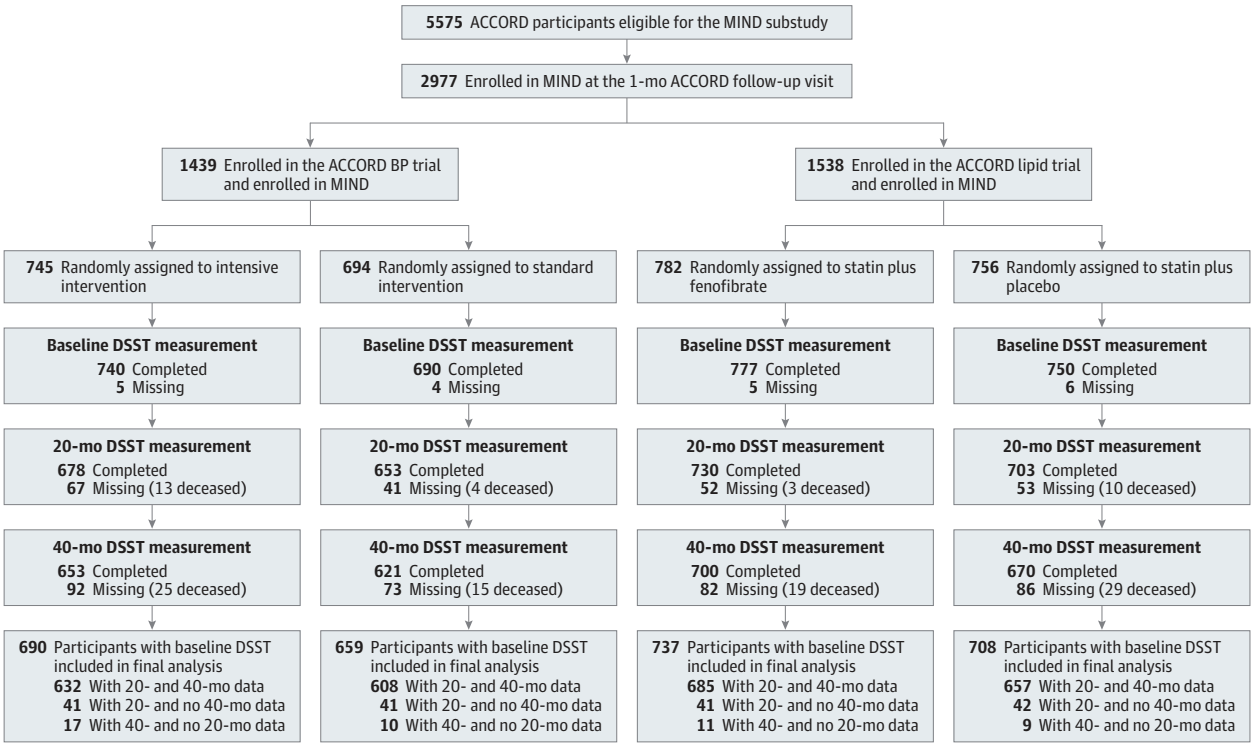
For cognition and MRI outcomes, prespecified subgroup analyses were conducted for sex, history of CVD, glycemia arm in the BP (or lipid) trial, and baseline CCN. We also conducted post hoc exploratory subgroup analyses for baseline age (<60, 60-69, and ≥70 years), T2DM duration (<5, 6-10, 11-15, and ≥16 years), and baseline DSST score (<47, 47-59, and ≥60). As prespecified, the main treatment effects on the primary cognitive (DSST) and MRI (TBV) outcomes were each tested at the .05 significance level. All other hypothesis tests (interactions, subgroup analyses, and analyses of secondary outcomes) were considered to be hypothesis generating and conducted at the .05 level. Because we report 73 tests of secondary hypotheses each at the .05 level, a 98% chance (ie, $1 - [1 - .05]^{73}$) that at least 1 test would be significant at an .05 level, assuming independence between tests.[25]

Results

Participants

Among the 10 251 participants randomized to the ACCORD trial, 5575 were eligible to participate in the MIND substudy. Of the remaining 4676, the major reasons for ineligibility included enrollment during the vanguard period of the ACCORD trial (an initial 12-month period when investigators assessed the feasibility of recruiting and treating participants according to the protocol) or before site institutional review board approval for the ACCORD MIND substudy (79.4%), being younger than 55 years (13.4%), and enrollment in the lipid trial after MIND enrollment from the lipid trial had closed (7.2%). Participants enrolled in the ACCORD MIND substudy were similar to eligible participants who did not enroll (Supplement [eTable 1]). At baseline, 46.6% of participants were female and 30.3% were nonwhite; the mean age was 62 years. The mean HbA_{1c} level was 8.3%, and mean (SD) duration of T2DM was 10.4 (7.4) years (Supplement [eTable 2]). Baseline characteristics of participants in the cognitive (n = 2977) and MRI (n = 614) portions of the ACCORD MIND substudy are presented by intervention group in the Supplement (eTables 3-6). Baseline characteristics were similar in both arms of the BP (or lipid) trial as illustrated by our comparison of baseline characteristics that identified significant (at α = .05) differences in 4 of 84 baseline comparisons (Supplement [eTables 3 and 4]). This result illustrates that despite the opportunity to opt out of the ACCORD MIND substudy after randomization, intervention group differences were consistent with chance alone. Similar results were found for comparisons between groups in the MIND MRI substudy (Supplement [eTables 5 and 6]).

Figure 1. Cohort Participation in the Primary Cognitive Outcome of the Blood Pressure (BP) and Lipid Trials



Participants were enrolled in the Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. DSST indicates Digit Symbol Substitution Test.

As in the main trial, the interventions achieved substantial separations in treatment targets in the MIND component (Supplement [eTable 7] lists unadjusted means). At 40 months, the mean SBP was 119.0 (14.7) vs 133.2 (14.8) mm Hg and mean diastolic BP was 64.0 (10.1) vs 70.2 (9.9) mm Hg in the intensive vs standard BP therapy groups, respectively. At 3 years, mean lipid levels were 156.8 (38.4) vs 152.2 (31.5) mg/dL for total cholesterol level, 82.3 (26.9) vs 82.8 (25.6) mg/dL for LDL-C level, and 43.7 (10.0) vs 45.5 (10.8) mg/dL for high-density lipoprotein cholesterol levels in women and 37.0 (8.0) vs 37.9 (9.5) mg/dL in men for the placebo vs fibrate groups, respectively. Median triglyceride levels were 150 vs 122 mg/dL (to convert to millimoles per liter, multiply by 0.0113). Adverse effects associated with each intervention have been reported previously.[13,26-28]

Cognitive Function Outcomes

Baseline cognitive function scores were similar for participants in the intensive vs standard BP and fibrate vs placebo lipid trial groups (Supplement [eTables 3 and 4]). Overall, 2957 of the 2977 ACCORD MIND participants (99.3%) had a baseline DSST (**Figure 1**) and 2794 (93.9%) had at least 1 (20- or 40-month) follow-up measure. In the BP and lipid trials, 1274 and 1370 participants, respectively, completed the 40-month cognitive assessment (Figure 1). For both trials, slight differences existed for baseline characteristics (Supplement [eTables 3 and 4]) between those with and without follow-up data (data not shown). Those participants missing follow-up data were older (mean age, 64.2 vs 62.4 years; $P < .001$), had higher SBP (mean, 140.2 vs 135.3 mm Hg; $P < .001$), and had lower DSST scores (mean, 46.7 vs 52.9; $P < .001$) compared with participants with follow-up data.

The primary outcome, DSST score, declined in the BP and lipid intervention groups (**Table 1**). However, we found no significant difference in the adjusted 40-month DSST mean scores between intensive vs standard BP therapy (BP difference between means, −0.26 [95% CI, −1.11 to 0.59]; $P = .55$) or between the fibrate vs placebo lipid groups (lipid difference between means, −0.08 [−0.92 to 0.76]; $P = .85$). Mean 40-month cognitive function did not differ between intervention groups in the BP or the lipid trial for any of the other 3 cognitive tests.

We conducted several participant subgroup analyses for the DSST, Rey Auditory Verbal Learning Test, and Stroop Color-Word Test. For the BP and lipid trials, we found no consistent differences in intervention effects on cognition within the subgroups examined (Supplement [eFigures 1-6]), including BP (or lipid) intervention effects within glycemia intervention groups.

MRI Outcomes

Six hundred thirty-two participants enrolled in the MRI substudy and 614 (378 BP and 236 lipid) had baseline scans usable for analysis (**Figure 2**). Participants were similar to the

Table 1. Cognitive Primary and Secondary Outcomes of the BP and Lipid Trials

End Point[a]	Time	BP Trial, Adjusted Mean (95% CI)				Lipid Trial, Adjusted Mean (95% CI)			
		INT Intervention	STD Intervention	Difference in Means	*P* Value[b]	Fenofibrate[c]	Placebo[c]	Difference in Means	*P* Value[b]
DSST[d]	Baseline[e]	52.28	52.28			52.79	52.79		
	20 mo	50.94 (50.36 to 51.53)	51.00 (50.41 to 51.60)	−0.06 (−0.90 to 0.78)	.89	51.39 (50.82 to 51.97)	51.59 (51.00 to 52.18)	−0.20 (−1.02 to 0.63)	.64
	40 mo	50.42 (49.82 to 51.01)	50.67 (50.07 to 51.28)	−0.26 (−1.11 to 0.59)	.55[c]	50.94 (50.35 to 51.53)	51.02 (50.42 to 51.62)	−0.08 (−0.92 to 0.76)	.85[c]
	40-mo change	−1.86 (−2.46 to −1.27)	−1.61 (−2.21 to −1.00)			−1.85 (−2.44 to −1.26)	−1.77 (−2.37 to −1.17)		
RAVLT[f]	Baseline[e]	7.51	7.51			7.51	7.51		
	20 mo	7.77 (7.64 to 7.91)	7.89 (7.75 to 8.02)	−0.12 (−0.31 to 0.08)	.23	7.91 (7.78 to 8.04)	7.86 (7.73 to 7.99)	0.05 (−0.13 to 0.23)	.58
	40 mo	7.98 (7.85 to 8.12)	8.04 (7.89 to 8.18)	−0.05 (−0.26 to 0.15)	.58	7.98 (7.86 to 8.11)	7.94 (7.80 to 8.07)	0.05 (−0.14 to 0.23)	.61
	40-mo change	0.47 (0.34 to 0.61)	0.53 (0.39 to 0.67)			0.47 (0.35 to 0.60)	0.43 (0.29 to 0.56)		
Stroop[g]	Baseline[e]	32.60	32.60			31.46	31.46		
	20 mo	31.50 (30.51 to 32.48)	31.35 (30.35 to 32.36)	0.15 (−1.26 to 1.55)	.84	31.18 (30.20 to 32.16)	30.69 (29.70 to 31.68)	0.48 (−0.91 to 1.88)	.50
	40 mo	31.10 (30.08 to 32.12)	32.14 (31.09 to 33.19)	−1.04 (−2.51 to 0.42)	.16	31.62 (30.63 to 32.62)	32.21 (31.19 to 33.22)	−0.59 (−2.01 to 0.84)	.42
	40-mo change	−1.50 (−2.52 to −0.48)	−0.46 (−1.51 to 0.59)			0.16 (−0.83 to 1.16)	0.75 (−0.27 to 1.76)		
MMSE[h]	Baseline[e]	27.25	27.25			27.53	27.53		
	20 mo	27.06 (26.89 to 27.23)	27.17 (27.00 to 27.35)	−0.11 (−0.35 to 0.13)	.35	27.35 (27.18 to 27.52)	27.47 (27.30 to 27.64)	−0.12 (−0.36 to 0.11)	.31
	40 mo	27.00 (26.83 to 27.17)	26.95 (26.77 to 27.11)	0.05 (−0.20 to 0.29)	.70	27.17 (27.00 to 27.34)	27.10 (26.93 to 27.27)	0.07 (−0.17 to 0.31)	.58
	40-mo change	−0.25 (−0.42 to −0.08)	−0.30 (−0.48 to −0.13)			−0.36 (−0.53 to −0.19)	−0.43 (−0.60 to −0.26)		

Abbreviations: BP, blood pressure; DSST, Digit Symbol Substitution Test; INT, intensive; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; STD, standard.

[a] For the DSST, RAVLT, and MMSE, higher values indicate better cognition; a negative change value, a decline in cognitive score. For the Stroop test, lower values indicate better cognition and a positive change value represents a decline in cognitive score.

[b] Calculated as tests of differences between intervention group means at each follow-up visit, adjusted for the baseline level of the outcome. The *P* value for a comparison of the 40-month change between intervention groups is left blank because, when controlling for the baseline level, it will be identical to that provided for the comparison between means at the 40-month visit.

[c] Calculated as result of test of prespecified primary outcome.

[d] Indicates number of correct cells (possible range, 0-90).

[e] Baseline mean indicates the overall mean for both groups combined as measured before randomization. This value is used to obtain the adjusted mean estimates at follow-up.

[f] Indicates the total number of words recalled (possible range, 0-15).

[g] Measured as the interference score.

[h] Possible range, 0 to 30.

ACCORD MIND participants not in the MRI substudy (Supplement [eTable 2]). At 40 months, 503 of the 614 original participants with an acceptable baseline scan (81.9%) also had an acceptable repeated MRI for the final analysis (Figure 2). Participants unable to undergo repeated scanning included 18 (16.2%) who died, 16 (14.4%) who refused, and 27 (24.3%) with new MRI-related reasons (eg, pacemaker, poor image quality). The remainder had a variety of other reasons (Supplement [eTable 8]). Unadjusted means for TBV are listed in the Supplement (eTable 9).

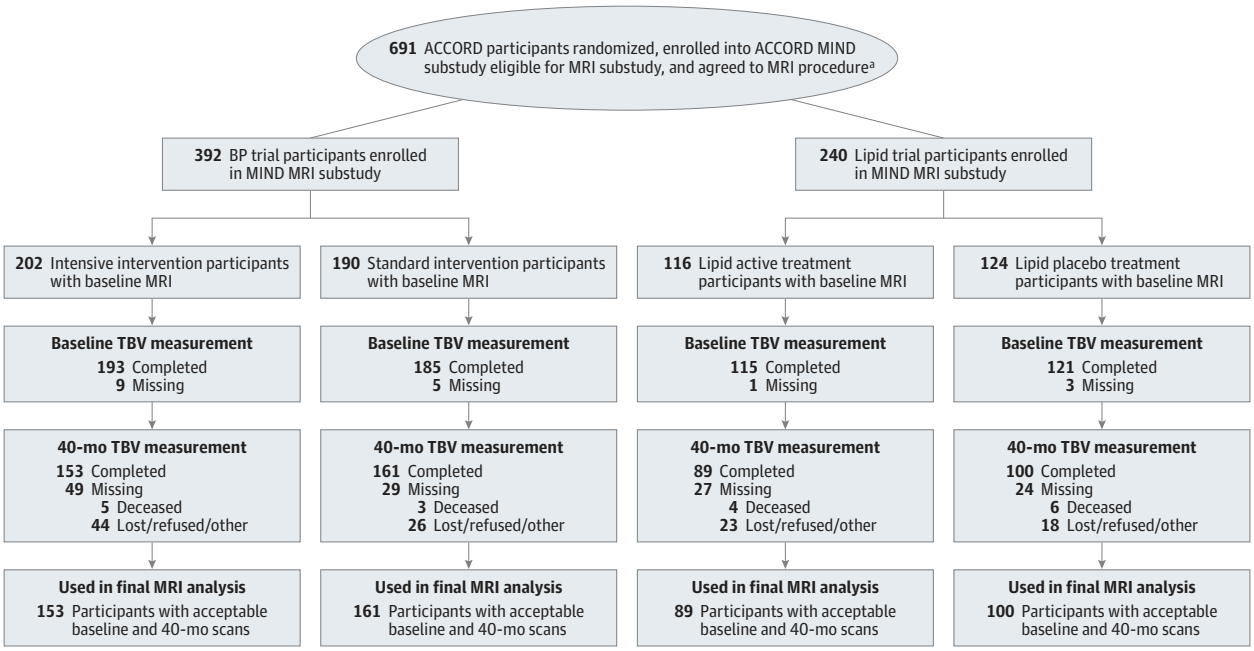
At 40 months, the intensive BP intervention group had a statistically significant lower TBV compared with the standard BP intervention group (difference between adjusted means, −4.4 [95% CI, −7.8 to −1.1] cm^3; $P = .01$) (**Table 2**). The fibrate and placebo groups did not differ in TBV (difference between adjusted means, 1.2 [95% CI, −3.1 to 5.5] cm^3) (Table 2).

Analysis of subgroups identified a significant interaction between BP and glycemia effects on TBV ($P = .009$). **Figure 3** confirms the earlier finding of the glycemic intervention in the ACCORD MIND substudy[12] that the strategy of intensive glycemia control preserved TBV across the BP and lipid trials. Figure 3 also illustrates that participants receiving the combination of standard antihypertensive therapy and intensive glycemic control experienced approximately 50% of the decline in TBV observed in the other BP trial groups. This interaction *P* value remained significant or approached significance under both imputation models (model 1, $P = .07$; model 2, $P = .03$) and when controlling for baseline covariates that differed between groups (Supplement [eTables 5 and 6]). Tests for different BP (or lipid) effects on TBV within predefined participant subgroups showed no differences (sex, CCN, baseline CVD, or cognitive function).

Discussion

The previous ACCORD MIND glycemia results[12] showed that intensive glycemia control does not preserve cognitive func-

Figure 2. Cohort Participation in the Primary Magnetic Resonance Imaging (MRI) Outcome of the Blood Pressure (BP) and Lipid Trials



Participants were enrolled in the Memory in Diabetes (MIND) substudy of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Standard and intensive BP interventions and active and placebo lipid treatments are described in the legend to Figure 1. TBV indicates total brain volume.

[a]Agreeing to the MRI procedure indicates that participants signed a consent for MRI. Enrolled in the MIND MRI substudy indicates that they underwent a baseline MRI.

Table 2. Adjusted Means for 40-Month TBV by Blood Pressure and Lipid Trials

Trial	Therapy Group	No. of Participants	Baseline Mean TBV, cm^3[a]	TBV, Mean (95% CI), cm^3[b]		*P* Value[c]
				40 mo	Change From Baseline	
Blood pressure	INT	153	921.5	902.6 (900.2 to 905.0)	−18.9 (−21.3 to −16.5)	
	STD	161	921.5	907.0 (904.7 to 909.4)	−14.5 (−16.8 to −12.2)	
	40-mo difference			−4.4 (−7.8 to −1.1)		.01
Lipid	Fenofibrate	89	937.0	924.1 (920.9 to 927.2)	−12.9 (−16.1 to −9.8)	
	Placebo	100	937.0	922.9 (919.9 to 925.9)	−14.1 (−17.1 to −11.1)	
	40-mo difference			1.2 (−3.1 to 5.5)		.59

Abbreviations: INT, intensive; STD, standard; TBV, total brain volume.

[a] Baseline mean is the overall mean for both groups combined as measured before randomization. This value is used to obtain the adjusted mean estimates at follow-up.

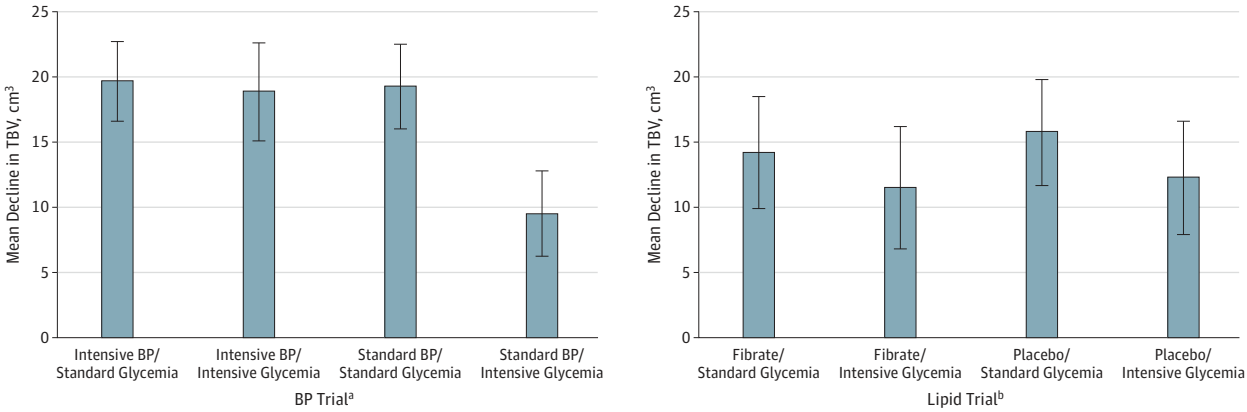
[b] Indicates adjusted mean obtained from analysis of covariance.

[c] Calculated as a test of difference between the intervention group means at the 40-month visit, adjusted for the baseline level of the outcome. When controlling for the baseline value of the outcome, the *P* value for a comparison of the 40-month means between intervention groups will be identical to the *P* value for a comparison of change from baseline (controlling for the baseline level as a covariate) to the 40-month visit.

tion as measured by the same battery used in the present study. The present results extend these findings to show that intensive BP management to a target SBP of less than 120 mm Hg and fibrate therapy in the context of LDL-C level control are not effective in reducing cognitive decline in persons with poorly controlled T2DM at high risk for CVD. Memory loss and its most dire consequence, dementia, are proven complications of T2DM. We implemented the MIND substudy within the ACCORD trial because effective treatments for prevention of cognitive decline in persons with T2DM are lacking, and recent studies suggested potential benefit from intensive BP and lipid therapy on cognitive decline.[29-31]

The previous report[12] found that maintaining TBV is best achieved in patients with T2DM by applying a strategy of intensive glycemia therapy with an Hb_{A1c} treatment goal of less than 6.0%. These results add to the previous findings by showing that preservation of TBV is greatest when used in combination with treatment to current recommended SBP targets of 135 to 140 mm Hg. Although a greater decline in TBV is associated with early cognitive impairment, a precursor to dementia,[31] the long-term implications of the imaging findings in the ACCORD MIND substudy are unknown and remain a focus of ongoing investigation and analyses. The ACCORD MIND substudy was designed with 2 primary outcomes, cog-

Figure 3. 40-Month Decline in Total Brain Volume (TBV) in the Blood Pressure (BP) and Lipid Trials



Whiskers mark 95% confidence intervals. Intensive and standard glycemia therapy groups are described in the Supplement (eAppendix). Standard and intensive BP interventions and active and placebo lipid treatments are described in the legend to Figure 1.

[a] $P < .001$ for heterogeneity of glycemia effect.

[b] $P = .86$ for heterogeneity of glycemia effect.

nition and TBV, and not to test whether MRI measures were adequate "surrogate markers" for treatment-related preservation of cognitive function. Our finding, however, suggests that TBV and white matter lesion burden alone cannot, to date, be used as surrogate markers for cognitive outcomes.

Strengths of this study include its prospective design within a randomized clinical trial. This design allows for balance between randomized groups of factors such as genetics. Other strengths include the high degree of data capture, attainment of substantial BP separation between the treatment groups, and the ability to capture functional and anatomic brain outcomes. The study also has several limitations. First, cognitive decline is a slow process, and 40 months of follow-up may be an inadequate time to ascertain subtle differences in cognitive function.[32] A 5-year extension of the ACCORD MIND substudy with MRI scanning is under way. Second, our findings are generalizable only to people with long-term T2DM at high risk of CVD and with relatively poorly controlled HbA_{1c} levels (minimal level, 7.5%). These results do not apply to persons with newly diagnosed T2DM or to individuals with longstanding glycemic control to an HbA_{1c} level of less than 7.5%. Third, the ACCORD trial tested overall strategies for achieving treatment goals. Dosages and medications used to achieve goals differed within interventions; thus, attempts to attribute effects to individual medications or doses are hampered by confounding between patient characteristics and medication choice.[28-30] Fourth, some of the advantages of randomization may have been lost because of the necessity to obtain consent from participants in the ACCORD MIND substudy immediately after randomization, thus allowing some participants to opt out of participation. Last, we acknowledge that with the large number of hypothesis tests that were performed, these results could result from chance alone.

Conclusions

During the past 2 decades, the belief that more intensive treatment strategies for controlling T2DM-related comorbidities, such as hyperglycemia, hyperlipidemia, and hypertension, would reduce clinical complications has driven large investment in new medications for this disease syndrome. However, these results from the ACCORD MIND substudy, along with the other recent ACCORD results, make clear the decreasing returns of intensive medication-based therapy for advanced T2DM and add further evidence to the need for increased investment in disease prevention and early intervention.

These results do not negate other evidence that intensive strategies to control BP and lipid levels may be indicated for other conditions such as stroke or coronary heart disease. However, this randomized clinical trial in 2977 older adults with a mean baseline Mini-Mental State Examination score higher than 27, a mean HbA_{1c} level of 8.3%, and long-term T2DM shows no overall reduction of the rate of T2DM-related cognitive decline through intensive BP therapy or adding a fibrate to well-controlled LDL-C levels.

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