JAMA Internal Medicine | Original Investigation

Glucose-Lowering Medications, Glycemia, and Cognitive Outcomes
The GRADE Randomized Clinical Trial

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IMPORTANCE Type 2 diabetes (T2D) is a risk factor for cognitive impairment. Whether the choice of the second-line glucose-lowering treatment added to metformin or glycemic control affects cognitive performance in T2D of relatively short duration (<10 years) is not known.

OBJECTIVE To compare the relative effect of 4 classes of glucose-lowering medications that were randomly added to metformin on cognitive performance and to examine the association of longitudinal glycemic levels with cognitive performance.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial (the GRADE study) was conducted at 36 clinical centers in the US and included 3721 participants with T2D with baseline and follow-up cognitive performance data. GRADE was implemented 2013 to 2021, and data for this study were analyzed from February 2024 to February 2025.

INTERVENTIONS For the primary objective, the exposure was randomization of metformin-treated participants to receive long-acting insulin (insulin glargine U-100), sulfonylurea (glimepiride), glucagon-like peptide-1 receptor agonist (liraglutide), or dipeptidyl peptidase-4 inhibitor (sitagliptin). The secondary objective assessed time-weighted hemoglobin A_{1c} levels over the follow-up period.

MAIN OUTCOMES AND MEASURES The primary cognitive outcome was the Digit Symbol Substitution Test score; the secondary cognitive outcomes were the immediate and delayed recall in the Spanish English Verbal Learning Test and letter and category fluency test scores.

RESULTS At baseline, the mean (SD) duration of T2D was 4.3 (2.7) years, and the mean (SD) age was 57.1 (9.8) years. Most participants were male (2320 [62.3%]; 1401 female individuals [37.7%]) and non-Hispanic (3015 [81.6%]; 681 Hispanic individuals [18.4%]); 712 (19.1%) were Black and 2452 (65.9%) were White; 777 (20.9%) were recruited from Veterans Affairs medical centers. There were no statistically significant differences between treatment groups in the cognitive outcomes at follow-up. However, a 1-unit increase in time-weighted hemoglobin A_{1c} levels was associated with modestly lower Digit Symbol Substitution Test scores (−0.94 points; 95% CI, −1.30 to −0.57), Spanish English Verbal Learning Test scores (immediate recall, −0.27 points; 95% CI, −0.49 to −0.06), and category fluency test scores (animal fluency, −0.28 points; 95% CI, −0.47 to −0.09) over the mean (SD) of 4.1 (0.1) years of follow-up. Severe hypoglycemia requiring assistance was uncommon in all 4 groups (34 participants [0.9%]).

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial suggest that choice of second-line glucose-lowering medication class added to metformin is not associated with change in cognitive performance in persons with early T2D. Worse glycemic control is associated with modestly worse cognitive performance.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01794143

Visual Abstract
Editor's Note
Supplemental content

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JAMA Intern Med. doi:10.1001/jamainternmed.2025.1189
Published online May 19, 2025.

Cognitive impairment is a complication of type 2 diabetes (T2D).[1] To our knowledge, strategies for preventing cognitive impairment among persons with T2D have not been established,[2] although some glucose-lowering medications may have cognitive benefits.[3] The effect of different classes of glucose-lowering medications on cognitive performance among persons with T2D has not been well examined. Moreover, the effects of achieving recommended glycemic targets on cognitive performance in persons with T2D of short duration is uncertain. Few randomized clinical trials (RCTs) can answer these questions. We leveraged the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study (GRADE) to address these questions.

GRADE compared the durability of glycemic control between 4 classes of glucose-lowering medications: long-acting insulin (insulin glargine U-100), sulfonylurea (glimepiride), glucagon-like peptide receptor agonist (GLP-1ra [liraglutide]), and dipeptidyl peptidase-4 inhibitor (DPP-4i [sitagliptin]). These medications were added to metformin for more than 1250 study participants per treatment group who were followed up for approximately 5 years.[4] Glargine and liraglutide were significantly, albeit modestly, more effective in achieving and maintaining the primary target hemoglobin A_{1c} (HbA_{1c}) level (HbA_{1c} <7% [for the proportion of total hemoglobin, multiply by 0.01]; 53.0 mmol/mol) in the study cohort.[4] Cognitive performance was measured as a secondary outcome in GRADE at baseline and follow-up, providing an opportunity to examine the effects of glucose-lowering medication classes and glycemic control on cognitive outcomes in an RCT.

Our primary question was whether the glucose-lowering medications in GRADE had differential effects on cognitive performance. The secondary question was whether glycemic exposure in GRADE was related to cognitive performance. We hypothesized that participants randomly assigned to receive glargine and liraglutide, and those with better glycemic control, would have better cognitive outcomes.

Key Points

Question Does the choice of second-line glucose-lowering treatment or longitudinal glycemic control affect cognitive performance in type 2 diabetes (T2D) of short duration (<10 years)?

Findings In this randomized clinical trial of 3721 individuals with T2D, cognitive performance at 4 years of follow-up was similar in participants randomized to receive long-acting insulin, sulfonylurea, glucagon-like peptide-1 receptor agonist, or dipeptidyl peptidase-4 inhibitor added to metformin. Higher glycemic levels were associated with worse cognitive performance.

Meaning The trial results suggest that lower glycemic levels, but not the choice of second-line glucose-lowering treatment, are associated with modestly better cognitive performance after approximately 4 years in persons with T2D of short duration.

Methods

Design, Setting, and Participants

GRADE was a randomized, unmasked, open-label, parallel-arm, multicenter RCT. All participants provided written informed consent. The study was approved by each center's institutional review board. Details of the study design have been published.[4,5] This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

The GRADE protocol and statistical analysis plan are available in Supplement 1. Participants were eligible to participate if they had a T2D diagnosis of less than 10 years at the time of screening and were 30 years or older (age ≥20 years if they were American Indian or Alaska Native) at the time of diagnosis, with HbA_{1c} levels of 6.8% to 8.5% (51-69 mmol/mol) and taking at least 1000 mg of metformin daily after the run-in period, with a maximum target dose of 2000 mg daily. At randomization, participants were assigned to receive 1 of 4 glucose-lowering medications (glargine, glimepiride, liraglutide, or sitagliptin) in combination with metformin. HbA_{1c} levels were measured quarterly. The primary metabolic outcome was an HbA_{1c} level of 7% or greater (53.0 mmol/mol) on follow-up, as confirmed by repeated HbA_{1c} measurement. The secondary metabolic outcome was reaching a confirmed HbA_{1c} level greater than 7.5% (58.5 mmol/mol). After secondary outcome confirmation, insulin glargine was added in the glimepiride, liraglutide, and sitagliptin treatment groups, and insulin aspart was initiated in the glargine treatment group.[4,5]

Cognitive assessments were performed at baseline, year 4, and year 6. The full GRADE randomized cohort included 5047 participants; the main cognition analysis included 3721 participants (73.7%) with cognitive assessments at baseline and year 4 (**Figure 1**). As a sensitivity analysis, we included the additional 1125 cognitive assessments at year 6 (eFigure 1 in Supplement 2).

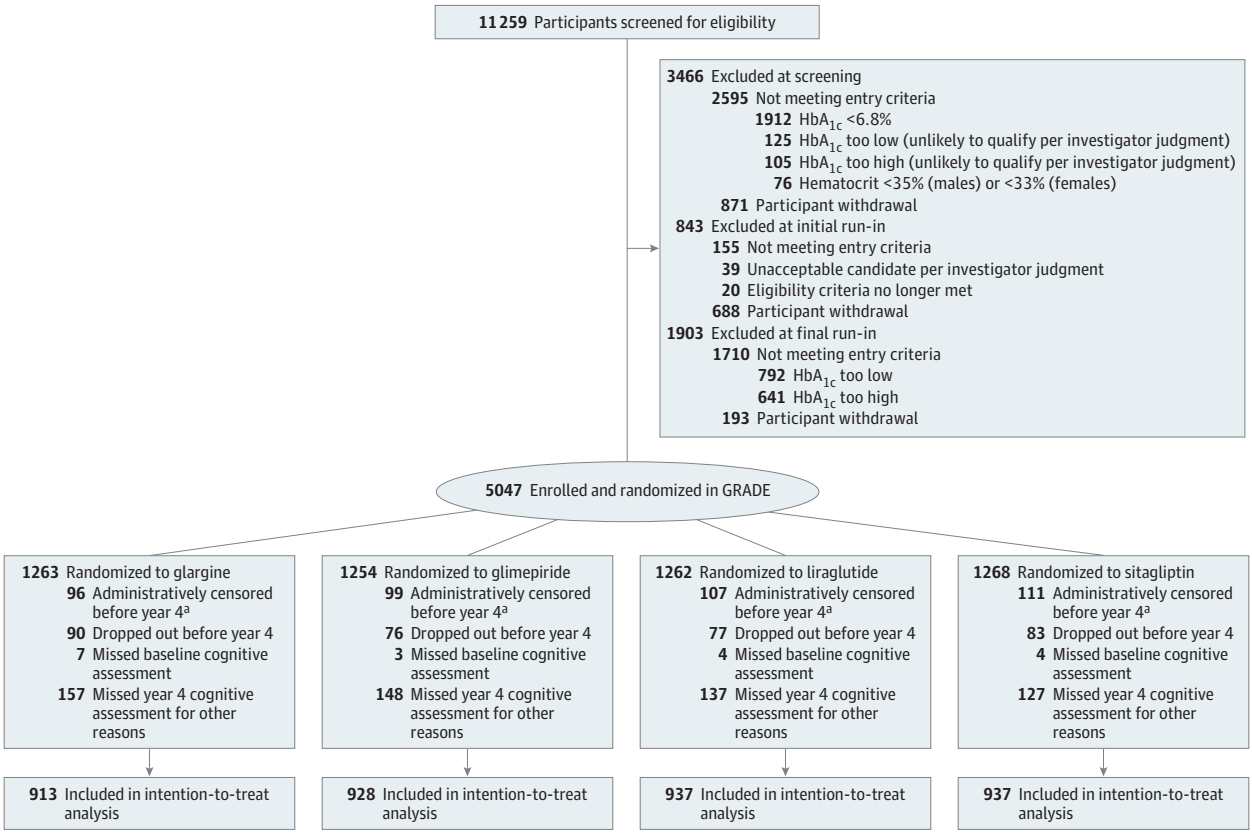
Exposures

The primary exposure was the GRADE randomized treatment assignment. The secondary exposure was glycemic control assessed as time-weighted HbA_{1c} levels. Time-weighted HbA_{1c} levels are the best predictor of T2D complications, as they capture glycemic control longitudinally.[6] Time-weighted HbA_{1c} levels were computed as the HbA_{1c} area under the curve between baseline and year 4 divided by the time between baseline and year 4. This calculation considers uneven time intervals between visits and is nearly identical to the simple average of HbA_{1c} measured at evenly spaced intervals. The mean (SD) number of HbA_{1c} observations used for this estimate was 16.5 (1.3). We examined the GRADE primary (HbA_{1c} level ≥7%; 53.0 mmol/mol) and secondary (HbA_{1c} level >7.5%; 58.5 mmol/mol) metabolic outcomes as exposures in sensitivity analyses. HbA_{1c} levels were measured in ethylenediaminetetraacetic acid whole blood on the Automated Glycohemoglobin Analyzer HLC-723G8 (Tosoh Medics, Inc) using an automated high-performance liquid chromatography method. Calibration of this method was evaluated using standard values provided by the National Glycohemoglobin Standardization Program.[7]

Cognitive Measures

Our primary cognitive outcome was within-individual change in total score of the Digit Symbol Substitution Test (DSST),[8] a

Figure 1. CONSORT Flow Diagram



[a]Denotes participants who, by the end date of the Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness Study (GRADE), had been followed up for fewer than 4 years. HbA_{1c} indicates hemoglobin A_{1c}.

measure of frontal executive abilities. Frontal executive abilities are those necessary for planning and executing complex tasks.[9] We chose the DSST as the primary outcome because it is sensitive to the cerebrovascular damage present in T2D and was the primary cognitive outcome in other T2D studies, including the Memory in Diabetes (MIND) ancillary study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.[10] In the DSST, participants try to match numbers to symbols in 90 seconds. The total number of correct answers is reported, with a maximum possible score of 133. The age-adjusted mean DSST score for US adults with T2D from the 2011 to 2014 National Health and Nutrition Examinations Survey was 45.8 (95% CI, 43.9-47.8).[11]

Our secondary cognitive outcomes were changes in performance in the Spanish English Verbal Learning Test (SEVLT)[12] and in animal[13] and letter[12,14] fluency tests (FTs). The SEVLT is a measure of memory (verbal learning), ie, the ability to recollect information.[15] The SEVLT consists of recalling a list of 15 words in 3 trials of immediate recall and 1 trial after a distractor list. For the SEVLT, we examined 2 outcomes: the sum of the number of words recalled during the first 3 trials (immediate recall) and the score of the fourth trial after the distractor list (delayed recall). The mean (SD) score in a mixed Spanish/English-speaking diabetic cohort of Hispanic or Latino adults with a mean age of 57 years was 22.3 (6.9) for immediate recall and 8.0 (3.6) for delayed recall, respectively.[16]

The animal FT asks participants to name as many animals as they can in 1 minute. The 2011 to 2014 National Health and Nutrition Examinations Survey age-adjusted mean value for this test among US adults was 16.9 (95% CI, 16.3-17.4).[11] The letter FT asks participants for as many words as possible that begin with the letter F in English (P in Spanish) in 1 minute. The total number of correct words is reported for the FT. The mean (SD) value in a sample of adults aged 18 to 55 years with T2D was 21.4 (7.4).[17] For all cognitive tests, a higher score indicates better performance.

Covariates

Demographic covariates included continuous and grouped age (<45 years, 45-59 years, and ≥60 years); self-reported male or female sex and ethnic (Hispanic or non-Hispanic) and racial groups (Black, White, and other [which included self-reported American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other race, unknown, or not reported]); education (less than high school, high school, some college, college, and graduate school); and Veterans Administration medical center site affiliation. Clinical covariates included systolic blood pressure (BP) tertiles (<121.5, 121.5 to <134,

and ≥134 mm Hg), diastolic BP tertiles (<73.5, 73.5 to <81.5, ≥81.5 mm Hg), low-density lipoprotein tertiles (<75, 75 to <101, ≥101 mg/dL [to convert to mmol/L, multiply by 0.0259]), waist circumference, weight, HbA_{1c} levels, and insulin resistance/sensitivity (homeostatic model assessment-2S, 1/mU × mmol/L^2).

Statistical Analysis

The statistical analysis plan is given in Supplement 1. The distribution of each cognitive outcome with histograms and density plots, at baseline and year 4, showed no strong deviations from normality. To compare longitudinal cognitive performance between the GRADE randomization groups, separate multivariable linear regression models for each cognitive outcome at year 4 were fit as functions of treatment and baseline cognitive outcomes (ie, 5 models that corresponded to the 1 primary cognitive outcome and the 4 secondary cognitive outcomes). This model was algebraically equivalent to modeling the change in cognitive score between baseline and year 4 as the outcome (also adjusted for baseline cognitive outcome). For each cognitive outcome, a Wald test for treatment heterogeneity was performed, and the 5 *P* values were adjusted for multiplicity using false discovery rate control. The marginal mean (ie, least-squares mean)[18] of each year-4 cognitive outcome was estimated in each treatment group. These analyses were conducted with an intention-to-treat approach. We also performed a sensitivity analysis with a per-protocol approach, analyzing the subset of 2035 participants who did not add any glucose-lowering medication to the randomized treatment and/or protocol-prescribed treatment (ie, the addition of insulin glargine or insulin aspart on reaching the GRADE secondary glycemic outcome).

To assess the association of glycemic control with cognition, for each of the 5 cognitive outcomes, multivariable linear regression models of time-weighted HbA_{1c} levels on the cognitive outcome at year 4, adjusting for the baseline cognitive outcome and for age (years), sex, race, ethnicity, education, and duration of diabetes (years) as possible confounders, were fit. For sensitivity analysis, the models were refit replacing time-weighted HbA_{1c} levels with the GRADE primary (HbA_{1c} level ≥7%) and secondary metabolic outcomes (HbA_{1c} level >7.5%) by year 4. To assess the association of demographic variables with cognition for each of the 5 cognitive outcomes, we fit a multivariable linear regression of a demographic variable and the baseline cognitive outcome on the year-4 cognitive outcome. Wald tests of the hypothesis that regression coefficients equaled 0 were adjusted for multiple testing using the false discovery rate control.

Two sensitivity analyses were performed. In the first, the change in cognitive scores between baseline and year 4 was the outcome variable (and the baseline cognitive score was not adjusted for). In the second, we included year-6 data by fitting linear mixed effects models with random intercept terms and fixed-effect terms for visit year, baseline cognitive score, and demographic variables. For glycemia analyses, time-weighted HbA_{1c} levels and the GRADE primary and secondary metabolic outcomes were treated as time-varying covariates (ie, participants who had cognitive measurements at year 4 had covariate values based on measurements from baseline to year 4, and other participants had covariate values based on measurements from baseline to year 6).

Statistical analysis was performed using R, version 4.2.1 (R Foundation) from February 2024 to February 2025. Tests were 2-tailed and statistical significance was $P = .05$.

Results

Most participants were male (2320 [62.3%]; 1401 female individuals [37.7%]) and non-Hispanic (3015 [81.6%]; 681 Hispanic individuals [18.4%]); 712 (19.1%) were Black and 2452 (65.9%) were White; 777 (20.9%) were recruited from Veterans Affairs medical centers. There were no significant differences in cognitive scores, demographic characteristics, or clinical characteristics between treatment groups at baseline in the analytic cohort with baseline and year-4 data (**Table 1**). The mean (SD) diabetes duration at randomization was 4.3 (2.7) years, and the mean (SD) follow-up duration was 4.1 (0.1) years. Cognitive scores resembled a normal distribution (eFigure 2 in Supplement 2).

Table 2 and **Figure 2** compare mean scores of the primary and secondary cognitive outcomes between the treatment groups 4 years after randomization, adjusting for baseline scores. The adjusted mean scores were nearly identical across treatment groups. However, cognition scores at year 4 differed relative to baseline demographic variables (eTable 1 in Supplement 2). Older age was associated with lower scores in all cognitive outcomes. Compared with female individuals, male individuals had lower scores in the SEVLT immediate and delayed recall. Those with higher education levels had better performance in all cognitive tests relative to lower academic attainment. Longer duration of diabetes was related to lower scores in the DSST, although there were no significant differences in other test results. Results from the change in cognitive score (eFigure 3 in Supplement 2), per-protocol, and year-6 sensitivity analyses were similar to the main intention-to-treat analyses.

Table 3 shows estimated coefficients and 95% CIs from linear regression models relating time-weighted HbA_{1c} levels with the primary and secondary cognitive outcomes that were initially adjusted only for baseline cognitive test scores. There were no significant associations between time-weighted HbA_{1c} levels and cognitive outcomes. However, in models that additionally adjusted for age, and in models adjusting for age, sex, race, ethnicity, education, and duration of diabetes, higher time-weighted HbA_{1c} levels were significantly and consistently related to lower scores in the DSST, SEVLT immediate and delayed recall, and animal FT.

We conducted sensitivity analyses examining the association of the GRADE primary metabolic outcome (HbA_{1c} level ≥7%) and secondary outcome (HbA_{1c} level >7.5%) at year 4 with the primary and secondary cognitive outcomes (eTables 2-3 in Supplement 2). The primary metabolic outcome was related to lower performance in the DSST (regression coefficient [β] = −0.6; 95% CI, −1.1 to −0; $P = .03$) and animal FT (β = −0.3; 95% CI, −0.6 to 0; $P = .03$). The secondary metabolic

Table 1. Descriptive Characteristics at the Baseline Study Visit for All Participants and by Randomized Treatment Group

Characteristic	No. (%)				
	All	Glargine	Glimepiride	Liraglutide	Sitagliptin
Total participants, No.	3721	913	928	937	943
Demographic					
Age, mean (SD), y	57.1 (9.8)	56.9 (9.7)	57.2 (9.8)	57.3 (9.8)	57.1 (10.0)
Age group, y					
<45	441 (11.9)	107 (11.7)	111 (12.0)	113 (12.1)	110 (11.7)
45-59	1754 (47.1)	444 (48.6)	423 (45.6)	426 (45.5)	461 (48.9)
≥60	1526 (41.0)	362 (39.6)	394 (42.5)	398 (42.5)	372 (39.4)
Sex					
Female	1401 (37.7)	354 (38.8)	348 (37.5)	342 (36.5)	357 (37.9)
Male	2320 (62.3)	559 (61.2)	580 (62.5)	595 (63.5)	586 (62.1)
Race					
Black	712 (19.1)	175 (19.2)	197 (21.2)	181 (19.3)	159 (16.9)
White	2452 (65.9)	614 (67.3)	588 (63.4)	617 (65.8)	633 (67.1)
Other[a]	557 (15.0)	124 (13.6)	143 (15.4)	139 (14.8)	151 (16.0)
Ethnicity					
Hispanic	681 (18.4)	162 (17.9)	171 (18.6)	171 (18.3)	177 (18.9)
Non-Hispanic	3015 (81.6)	745 (82.1)	748 (81.4)	763 (81.7)	759 (81.1)
Education					
Less than high school	275 (7.4)	71 (7.8)	76 (8.2)	57 (6.1)	71 (7.5)
High school/GED	752 (20.2)	171 (18.7)	183 (19.7)	196 (20.9)	202 (21.4)
Some college	1033 (27.8)	270 (29.6)	252 (27.2)	275 (29.3)	236 (25.0)
College	997 (26.8)	246 (26.9)	241 (26.0)	231 (24.7)	279 (29.6)
Graduate school	664 (17.8)	155 (17.0)	176 (19.0)	178 (19.0)	155 (16.4)
VA affiliate					
Not a VA site	2944 (79.1)	720 (78.9)	734 (79.1)	751 (80.1)	739 (78.4)
VA	777 (20.9)	193 (21.1)	194 (20.9)	186 (19.9)	204 (21.6)
Duration of diabetes, mean (SD), y	4.3 (2.7)	4.3 (2.7)	4.3 (2.8)	4.4 (2.7)	4.2 (2.7)
Biomarkers					
LDL, mg/dL					
0.5 - <75	1236 (34.4)	286 (32.8)	328 (36.3)	305 (33.9)	317 (34.6)
75 - <101	1714 (32.7)	281 (33.2)	297 (32.9)	289 (32.1)	307 (33.6)
101-329	1181 (32.9)	306 (35.1)	279 (30.9)	305 (33.9)	291 (31.8)
SBP, mm Hg					
76.5-121.5	1259 (33.9)	31 (34.1)	309 (33.3)	318 (33.9)	321 (34.1)
121.5-134	1246 (33.5)	311 (34.1)	305 (32.9)	328 (35.0)	302 (32.1)
134.0-208	1214 (32.6)	291 (31.9)	313 (33.8)	291 (31.1)	319 (33.9)
DBP, mm Hg					
45.5-73.5	1308 (35.2)	317 (34.7)	313 (33.8)	337 (36.0)	341 (36.2)
73.5-81.5	1192 (32.1)	305 (33.4)	307 (33.1)	291 (31.1)	289 (30.7)
81.5-131.5	1219 (32.8)	291 (31.9)	307 (33.1)	309 (33.0)	312 (33.1)
HbA_{1c}, mean (SD), %	7.5 (0.5)	7.5 (0.5)	7.5 (0.5)	7.5 (0.5)	7.5 (0.5)
Weight, mean (SD), kg	99.6 (22.4)	100.3 (22.3)	99.3 (22.8)	99.7 (22.7)	99.0 (21.7)
Waist circumference, mean (SD), cm	112.3 (15.7)	112.6 (15.5)	112.2 (16.1)	112.4 (16.0)	111.9 (15.1)
HOMA2-S, $1/(mU \times mmol/L^2)$[b]	34.4 (15.8)	33.8 (15.3)	34.4 (15.6)	35.0 (16.7)	34.5 (15.6)
Cognition test scores, mean (SD)					
DSST	46.6 (13.6)	47.1 (13.3)	45.8 (13.7)	46.9 (13.8)	46.8 (13.5)
SEVLT immediate	25.5 (5.8)	25.5 (5.6)	25.5 (5.9)	25.5 (5.9)	25.5 (5.9)
SEVLT delayed	9.4 (2.7)	9.4 (2.7)	9.4 (2.7)	9.4 (2.6)	9.4 (2.7)
WFT letter	12.5 (4.4)	12.5 (4.5)	12.6 (4.3)	12.5 (4.3)	12.4 (4.5)
WFT animal	19.3 (5.3)	19.5 (5.4)	19.1 (5.3)	19.4 (5.3)	19.4 (5.1)

Abbreviations: DBP, diastolic blood pressure; DSST, Digit Symbol Substitution Test; GED, General Educational Development; HbA_{1c}, hemoglobin A_{1c}; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; SBP, systolic blood pressure; SEVLT, Spanish English Verbal Learning Test; VA, Veterans Affairs; WFT, the letter and animal word fluency tests.

[a] Included self-reported American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, other race, unknown, or not reported.

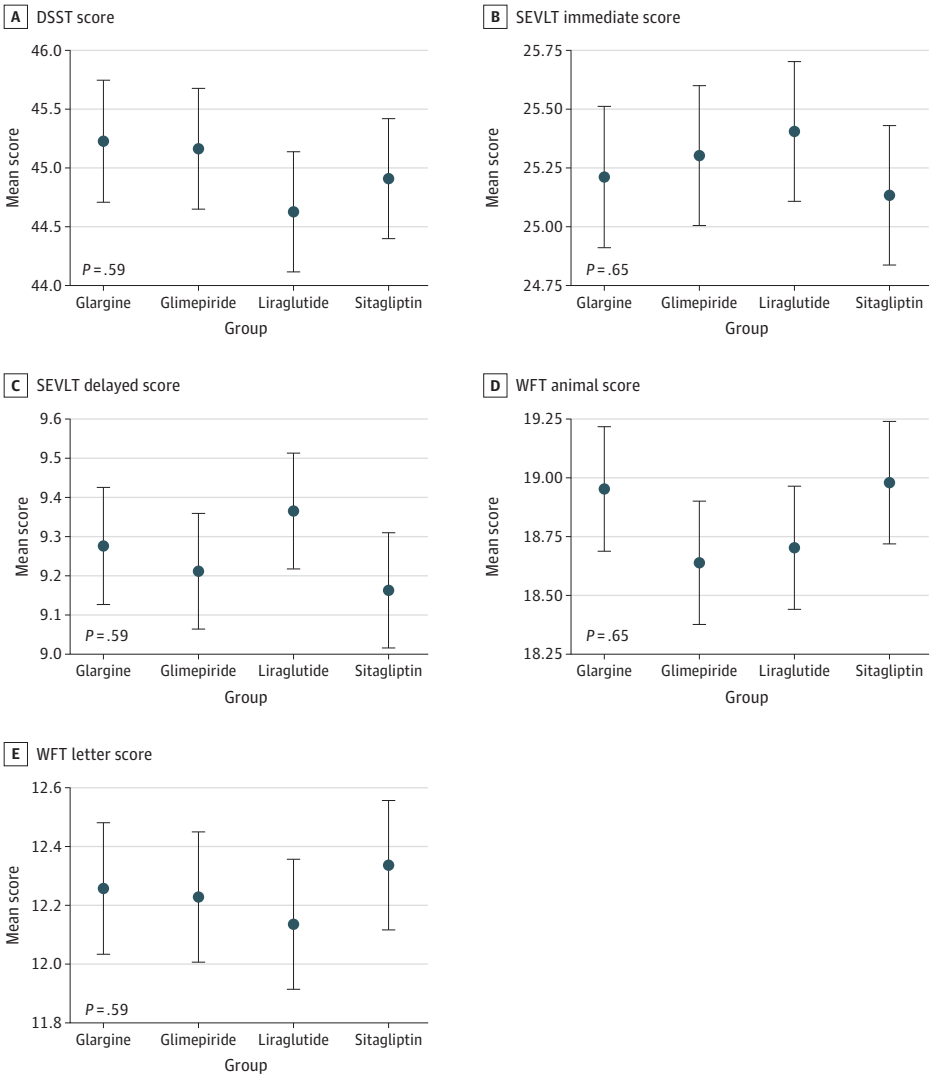
[b] The HOMA2-S of steady state insulin sensitivity was calculated using the HOMA 2 Calculator, version 2.2.3 (Diabetes Trials Unit, University of Oxford).

Table 2. Comparison of Mean Cognitive Outcome Scores at Year 4 by Randomized Treatment Group Adjusted for Baseline Cognitive Outcome Scores

Test	Score (95% CI)				*P* value
	Glargine	Glimepiride	Liraglutide	Sitagliptin	
DSST	45.2 (44.7-45.7)	45.1 (44.6-45.7)	44.6 (44.1-45.1)	44.9 (44.4-45.4)	.59
SEVLT-IR	25.2 (24.9-25.5)	25.3 (25.0-25.6)	25.4 (25.1-25.7)	25.1 (24.8-25.4)	.65
SEVLT-DR	9.3 (9.1-9.4)	9.2 (9.1-9.4)	9.4 (9.2-9.5)	9.2 (9.0-9.3)	.59
WFTL	12.3 (12.0-12.5)	12.2 (12.0-12.4)	12.1 (11.9-12.4)	12.3 (12.1-12.6)	.59
WFTA	19.0 (18.7-19.2)	18.6 (18.4-18.9)	18.7 (18.4-19.0)	19.0 (18.7-19.2)	.65

Abbreviations: DR, delayed recall; DSST, Digit Symbol Substitution Test; IR, immediate recall; SEVLT, Spanish English Verbal Learning Test; WFTA, animal word fluency test; WFTL, letter word fluency test.

Figure 2. Model-Estimated Year 4 Cognitive Outcomes by Treatment Group



The 95% CIs are shown as error bars. False discovery rate-adjusted *P* values are from joint Wald tests for treatment effects from separate linear models as adjusted for the baseline cognitive outcome. Cognitive outcomes included the Digit Symbol Substitution Test (DSST), Spanish English Verbal Learning Test (SEVLT) immediate recall and delayed recall, and the letter and animal word fluency tests (WFTs).

outcome was related to lower performance in the DSST (β = −0.8; 95% CI, −1.3 to −0.2; *P* = .004) and animal FT (β = −0.4; 95% CI, −0.6 to −0.1; *P* = .01). Sensitivity analyses that used the change in cognitive score outcome at year 4 (eTables 4-6 in Supplement 2) and year-6 data using linear mixed-effects models (eTables 7-9 in Supplement 2) found generally similar associations between glycemia and cognition.

Discussion

To our knowledge, this was the first RCT to compare the effects of 4 glucose-lowering medication classes that were added to metformin on cognitive performance among persons with early T2D. Cognitive outcomes did not differ by treatment

Table 3. Linear Regression Coefficients From Models of Time-Weighted Hemoglobin A_{1c} (HbA_{1c}) Levels on Year 4 Cognitive Outcomes

Cognitive outcome	Unadjusted (crude), β (95% CI)[a,b]	Adjusted, β (95% CI)[a,b]	
		For age	For age, sex, race, ethnicity, education, and duration of diabetes
DSST			
Time-weighted HbA_{1c}	−0.35 (−0.72 to 0.02)	−1.02 (−1.39 to −0.65)	−0.94 (−1.30 to −0.57)
P value[c]	.06	<.001	<.001
SEVLT-IR			
Time-weighted HbA_{1c}	0.05 (−0.17 to 0.26)	−0.31 (−0.52 to −0.10)	−0.27 (−0.49 to −0.06)
P value[c]	.67	.005	.01
SEVLT-DR			
Time-weighted HbA_{1c}	0.04 (−0.07 to 0.15)	−0.13 (−0.24 to −0.03)	−0.11 (−0.22 to −0.01)
P value[c]	.46	.01	.04
WFTL			
Time-weighted HbA_{1c}	−0.04 (−0.20 to 0.11)	−0.15 (−0.31 to 0.01)	−0.11 (−0.27 to 0.06)
P value[c]	.58	.07	.20
WFTA			
Time-weighted HbA_{1c}	−0.15 (−0.33 to 0.04)	−0.35 (−0.54 to −0.15)	−0.28 (−0.47 to −0.09)
P value[c]	.12	<.001	.004

Abbreviations: DR, delayed recall; DSST, Digit Symbol Substitution Test; IR, immediate recall; SEVLT, Spanish English Verbal Learning Test; WFTA, animal word fluency test; WFTL, letter word fluency test.

[a] Unadjusted refers to the lack of adjustment for demographic covariates (age, sex, race, ethnicity, education, and duration of diabetes). All models, including those that are labeled as unadjusted, control/adjust for the baseline value of the respective cognitive outcome score under analysis.

[b] Estimated regression coefficients (β) with 95% CIs represent the change in cognitive outcome score associated with a 1-percentage point increase in time-weighted HbA_{1c} levels (eg, 7% vs 6%).

[c] False discovery rate–adjusted *P* values from Wald tests of hypotheses that the regression coefficient for time-weighted HbA_{1c} levels equals 0.

group 4 years after randomization. However, worse glycemic control during the 4 years between baseline and follow-up cognitive assessments was associated with lower performance for the primary cognitive outcome and most of the secondary cognitive outcomes. Potential mechanisms that may link hyperglycemia to cognitive impairment in T2D include vascular endothelial dysfunction, inflammation and blood-brain barrier injury, cerebrovascular disease, and axonal demyelination and axonal loss.[19] The association between glycemia and cognitive performance was modest. On average, a 1-percentage point higher time-weighted HbA_{1c} level (eg, 7% vs 6%) was associated with a DSST score that was approximately 0.9 points lower, which is about 0.1 SDs of the DSST distribution among GRADE participants. The clinical significance of this difference is unclear. Although the glargine and liraglutide groups in GRADE showed better glycemic outcomes, the differences were modest[4] and may not have been sufficient to affect cognitive performance.

Repurposing of T2D medications, such as GLP-1ra[20] and DPP-4i,[21,22] has been proposed for treating and preventing cognitive impairment in persons without T2D.[23] Liraglutide is currently being tested in a phase 2 study for treating Alzheimer disease (AD) (NCT01843075). A recent observational study reported that persons with AD and T2D who were exposed to DPP-4i had lower AD neuropathology compared with those not exposed to DPP-4i.[24] Our study was conducted in a relatively young sample of adults with T2D who were unlikely to have AD; thus, they represented a different risk group compared with the ongoing RCT with liraglutide and the observational study with DPP-4i.

Worse glycemic control has been associated with a higher risk of cognitive impairment in observational studies.[25] Our results supported this hypothesis in a relatively young cohort with T2D of short duration. RCTs of persons with T2D have also examined this question with varied results. The ACCORD-MIND study in 2977 participants with a mean age of 62 years and T2D duration of less than 10 years reported no differences in cognition between participants randomized to 3.5 years of intensive (HbA_{1c} level <6%) vs standard glycemic control (HbA_{1c} level, 7.0%-7.9%).[10] An additional approximately 3-year observational follow-up after the termination of the study continued to show no differences between the groups.[26] However, an RCT comparing telemedicine vs usual care in 2169 persons with T2D of 10 years' duration with a mean age of 70 years reported better global cognition in the telemedicine arm after 4 years, and this effect was mediated by improved HbA_{1c} levels.[27] A matched cohort study with more than 8 years of follow-up evaluated the effects of receiving a multidisciplinary diabetes management program for people with T2D with a mean age of 62 years who were treated with primary care vs standard of care (the Risk Assessment and Management Program–Diabetes Mellitus) on incident dementia risk and the association of dementia with glycemic control. Among the 55 618 matched participants, those randomized to the diabetes management program had a lower risk for dementia and its major subtypes.[28] In addition, a moderate HbA_{1c} target between 6.5% and 7.5% was associated with lower dementia incidence.

The main difference between ACCORD-MIND, which had null cognitive results, and other studies that found that

better glycemic control was associated with better cognitive outcomes was that the target HbA_{1c} level in ACCORD was less than 6.0%, whereas the other studies targeted a HbA_{1c} level of less than 7.0%, as recommended by existing guidelines.[29] The strict glycemic target in ACCORD was associated with a higher rate of severe hypoglycemia that could have nullified any beneficial cognitive effects.[30] The rates of severe hypoglycemia in GRADE were low studywide.[4]

Strengths and Limitations

Our study had several limitations. The association of glycemic control with cognition demonstrated in this article was the result of an observational analysis. Thus, we must be careful in making inferences about causality. Potential sources of bias and confounding deserve further discussion. The association of time-weighted HbA_{1c} levels became apparent only when the analyses were adjusted for age. This is likely owing to negative confounding by age, the strongest predictor of cognitive performance. In GRADE, younger persons, who have better cognitive performance, were more likely to have worse glycemic control and meet the metabolic outcomes.[31]

Compared with the general population, the GRADE study excluded people with poor glycemic control (HbA_{1c} level >8.5%) and had enhanced treatment adherence due to expert team care and medications provided free of cost during the trial. These factors may limit generalizability. We could not evaluate the effects of insulin, sulfonylureas, GLP-1ra, and DPP-4i independent of metformin. We lacked brain imaging and subclinical markers of brain health. Thus, we could not evaluate effects on subclinical measures that change before cognitive performance. GRADE was initiated before the approval of sodium-glucose cotransporter-2 inhibitors, and they were not included; whether these inhibitors affect cognition is currently being investigated.[32]

Advantages of this study included a large, well-phenotyped cohort with a homogenous duration of T2D. It was multiethnic and reflected the racial and sex distribution of T2D in the US. Cognitive performance was evaluated in almost all participants at baseline, with modest attrition at follow-up. Our comparison of participants between randomization groups at baseline showed that confounders were balanced, allowing for intention-to-treat analyses for cognitive outcomes as presented. The per-protocol sensitivity analyses supported the findings of the intention-to-treat analyses.

This study examined the effects of 4 glucose-lowering medications on cognition in general. It would be of interest in the future to examine whether certain subgroups of people (eg, by age, sex, and waist circumference) benefited more from 1 medication vs another.

Conclusions

This RCT found that, in persons with early T2D, the choice of second-line glucose-lowering therapy added to metformin did not affect cognitive outcomes over 4 years of follow-up. Worse glycemic control was associated with modestly lower cognitive outcomes.

ARTICLE INFORMATION

Accepted for Publication: March 3, 2025.

Published Online: May 19, 2025. doi:10.1001/jamainternmed.2025.1189

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Conflict of Interest Disclosures: Dr Luchsinger reported consulting fees from Merck and Novo Nordisk during the conduct of the study as well as a stipend from Wolters Kluwer and royalties from Springer outside the submitted work. Dr Younes reported grants from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) during the conduct of the study. Dr Florez reported grants from the Medical University of South Carolina during the conduct of the study. Dr Martens reported grants from Abbott, Dexcom, Insulet, Lilly, Medtronic, Novo Nordisk, Sanofi, and Tandem during the conduct of the study as well as grants from Medscape, a patent for an ambulatory glucose profile CGM visualization format pending, and a salary from the HealthPartners Institute outside the submitted work. Dr Pop-Busui reported grants and personal fees from Novo Nordisk and Lexicon Pharma, grants from Bayer, and personal fees from Roche, Nevro, and Averitas outside the submitted work. Dr Seaquist reported personal fees from Lilly and nonfinancial support from Zucara outside the submitted work. Dr Barzilay reported grants from the National Institutes of Health (NIH)/NIDDK outside the submitted work. No other disclosures were reported.

Funding Support: The GRADE study was supported by a grant from the NIH/NIDDK under award number U01DK098246. The planning of GRADE was supported by a U34 planning grant from the NIDDK (U34-DK-088043). The American Diabetes Association supported the initial planning meeting for the U34 proposal. The National Heart, Lung, and Blood Institute and the US Centers for Disease Control and Prevention also provided funding support. The Department of Veterans Affairs provided resources and facilities. Additional support was provided by grant numbers P30 DK017047, P30 DK020541-44, P30 DK020572, P30 DK072476, P30 DK079626, P30 DK092926, U54 GM104940, UL1 TR000439, UL1 TR000445, UL1 TR001108, UL1 TR001409, UL1 TR001449, UL1 TR002243, UL1 TR002345, UL1 TR002378, UL1 TR002489, UL1 TR002529, UL1 TR002535, UL1 TR002537, and UL1 TR002548. Educational materials were provided by the National Diabetes Education Program. Material support in the form of donated medications and supplies were provided by Becton, Dickinson and Company, Bristol Myers Squibb, Merck, Novo Nordisk, Roche Diagnostics, and Sanofi.

Role of the Funder/Sponsor: GRADE was a parallel-group comparative effectiveness clinical trial with funding provided by the NIH/NIDDK, which had a role in the design, conduct, analysis, and publication of the study. Medications used in the trial were donated by pharmaceutical companies who had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Group Information: The GRADE Study Research Group members are listed in Supplement 3.

Data Sharing Statement: See Supplement 4.

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