Effect of Linagliptin on Cognitive Performance in Patients With Type 2 Diabetes and Cardiorenal Comorbidities: The CARMELINA Randomized Trial

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OBJECTIVE

Type 2 diabetes is associated with cognitive dysfunction and an increased dementia risk, particularly in individuals with concomitant cardiovascular and/or kidney disease. Incretin therapies may modulate this risk via glycemic and nonglycemic pathways. We explored if the dipeptidyl peptidase 4 inhibitor linagliptin could prevent cognitive decline in people with type 2 diabetes with cardiorenal disease.

RESEARCH DESIGN AND METHODS

The CArdiovascular and Renal Microvascular outcomE study with LINAgliptin (CARMELINA)-COG substudy was an integral part of CARMELINA (NCT01897532) that randomized participants with cardiorenal disease to linagliptin 5 mg or placebo once daily (1:1), in addition to standard of care. The primary cognitive outcome was the occurrence of accelerated cognitive decline at the end of treatment, defined as a regression-based index score ≤16th percentile on the Mini-Mental State Examination (MMSE) or a composite measure of attention and executive functioning and analyzed in participants with a baseline MMSE ≥24. Effects across subgroups by baseline factors, as well as absolute cognitive changes, were also assessed.

RESULTS

Of the 6,979 participants in CARMELINA, CARMELINA-COG included 1,545 (mean ± SD age, 68 ± 8 years; MMSE, 28.3 ± 1.7; estimated glomerular filtration rate, 52 ± 23 mL/min/1.73 m^2; and HbA_{1c}, 7.8 ± 0.9% [61.4 ± 10.1 mmol/mol]). Over a median treatment duration of 2.5 years, accelerated cognitive decline occurred in 28.4% (linagliptin) vs. 29.3% (placebo) (odds ratio 0.96 [95% CI 0.77, 1.19]). Consistent effects were observed across subgroups by baseline characteristics. Absolute cognitive performance changes were also similar between treatment groups.

CONCLUSIONS

In a large international cardiovascular outcome trial in people with type 2 diabetes and cardiorenal disease, linagliptin did not modulate cognitive decline over 2.5 years.

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Cognitive impairment, including mild cognitive impairment (MCI) and dementia, is increasingly recognized as an important complication of type 2 diabetes (1). Indeed, decline in cognitive function is greater in people with type 2 diabetes as compared with those without (1–5), in particular in the setting of concomitant renal (6) and cardiovascular (CV) complications (7).

Subtle cognitive changes, also referred to as cognitive decrements, can be encountered in all age-groups and show only modest deterioration over time (1,3). By contrast, accelerated decline, which may evolve to MCI or dementia, principally occurs in people >60 years of age (1,3,4). Particularly, these more severe forms of cognitive dysfunction represent an independent predictor for adverse clinical outcomes like hypoglycemia, CV events, and death (8) and are posing a tremendous economic, societal, and public health burden. This is particularly worrisome given that the affected number of people with type 2 diabetes with MCI is expected to increase over the next decades (9).

Higher glucose levels have been associated with incident dementia both in people with and people without type 2 diabetes (10). Indeed, there is growing evidence for a role of glycemic control in diabetes-associated cognitive dysfunction (11), including a possible nonlinearity in which both high glucose and too tight glucose control are linked to poorer cognitive functioning (12). However, it should be noted that effect sizes of cognitive decline attributable to glycemia are small (11), and the underlying processes of cognitive dysfunction in type 2 diabetes are largely unknown (1,3). Neither pharmacological interventions (13) nor intensive glycemic control has been demonstrated to slow cognitive impairment (14).

Incretin therapies, which are increasingly used in type 2 diabetes management, have also emerged as a potential therapeutic agent for Alzheimer disease (15) as well as vascular brain injury (16). The underlying hypothesis of potential benefit relates to the variety of direct or indirect targets in the brain for glucagon-like peptide 1 (GLP-1) receptor agonists or dipeptidyl peptidase 4 (DPP-4) inhibitors, including neuronal cells, different glia cells, and stem cells (17). Animal data show that DDP-4 inhibitors may suppress blood–brain barrier disruption and attenuate cerebral oxidative stress or neuroinflammation (16,18) and may reduce brain damage following a stroke (19). In an observational study in elderly patients with type 2 diabetes, increased plasma DPP-4 activity has also been associated with elevated risk of MCI (20).

Linagliptin is a selective, once-daily DPP-4 inhibitor (21) with minimal renal excretion approved for glycemic management of type 2 diabetes. The CArdiovascular and Renal Microvascular outcomE study with LINAgliptin (CARMELINA), involving 6,979 participants, demonstrated CV safety of linagliptin; however, no incremental benefit was demonstrated over a median follow-up of 2.2 years compared with placebo, when given in addition to the usual standard of care for the primary composite outcome of CV death, nonfatal myocardial infarction (MI), nonfatal stroke (hazard ratio [HR] 1.02 [95% CI 0.89, 1.17]), and fatal/nonfatal stroke (HR 0.91 [95% CI 0.67, 1.23]) (22). CARMELINA also preplanned to assess effects on global, and domain-specific, cognitive function. In this study, we report the impact of linagliptin on accelerated cognitive decline and on global cognitive function using a validated standardized cognitive test battery sensitive to relatively mild cognitive changes.

RESEARCH DESIGN AND METHODS

Design and Sample

The CARMELINA-COG substudy was an integral part of the CARMELINA trial (22). In brief, CARMELINA was a multicenter, international, randomized, double-blind study in patients with type 2 diabetes at high cardiorenal risk. It was conducted at 605 centers in 27 countries and included adults with type 2 diabetes, HbA_{1c} 6.5–10.0%, at high CV risk (history of vascular disease and urine albumin-to-creatinine ratio [UACR] >30 mg/g [or equivalent]) or high renal risk (estimated glomerular filtration rate [eGFR] 45–75 mL/min/1.73 m^2 and UACR >200 mg/g [or equivalent] or eGFR 15–45 mL/min/1.73 m^2 regardless of UACR). Participants with end-stage kidney disease, defined as eGFR <15 mL/min/1.73 m^2 or requiring maintenance dialysis, were excluded, as were those who prior to providing informed consent had been treated (≥7 consecutive days) with GLP-1 receptor agonists, other DPP-4 inhibitors, or sodium–glucose cotransporter 2 inhibitors. The trial was event driven until a minimum of 611 participants had experienced a primary outcome event (time to first occurrence of CV death, nonfatal MI, or nonfatal stroke [three-point major adverse CV event]). To maintain glycemic equipoise, investigators were encouraged to monitor and use additional medication for glycemic control (except DPP-4 inhibitors, GLP-1 receptor agonists, and sodium–glucose cotransporter 2 inhibitors) according to applicable standard of care throughout the trial.

The cognition substudy included patients who signed a separate informed consent for the substudy and only in countries using the Latin alphabet. The primary analysis was prespecified to be conducted in participants who had *1*) a valid baseline cognitive assessment, *2*) confounder information captured (i.e., documented years of formal education), and *3*) a valid follow-up cognitive assessment within 7 days after last study medication intake. A baseline Mini-Mental State Examination (MMSE) score <24 was exclusionary from the primary analysis population because we intended to specifically target prevention of cognitive impairment.

Cognitive Testing Procedures and Confounder Assessment

The cognition substudy aimed to test if linagliptin 5 mg once daily relative to placebo once daily could prevent accelerated cognitive decline using the MMSE (23) as a measure of global cognitive functioning. In addition, we obtained a more domain-sensitive composite measure of attention and executive functioning (A&E) using two additional tests: the Trail Making Test (TMT) and the Verbal Fluency Test (VFT) (24,25).

Cognitive tests were conducted at baseline (prior to first drug intake) and at study end or at time of early discontinuation of trial medication. Follow-up cognitive assessments were only conducted if participants had a score ≥24 on the MMSE at baseline. In addition to the cognitive assessment, participants were requested to complete a depression questionnaire (26) during each of the two scheduled visits.

MMSE

The MMSE is a screening instrument developed to screen for the presence

of cognitive impairment in older adults (23) and evaluates cognitive aspects including orientation in time and place, verbal short-term memory, attention, semantic knowledge, and visuoconstruction; a maximum score of 30 can be obtained. A cutoff of <24 is considered to indicate the presence of cognitive impairment (27). Participating centers used country-specific validated versions.

TMT

The TMT is a test of scanning, visuomotor tracking, divided attention, psychomotor speed, and cognitive flexibility (24). The TMT is sensitive to cognitive decrements associated with type 2 diabetes, and in older individuals, test performance decreases with advancing age (25). The test requires an individual to connect the dots of 25 consecutive targets on a sheet of paper. There are two parts of the TMT: A, which only contains numbers (1, 2, 3, etc.), and B, which contains numbers and letters (1, A, 2, B, etc.). The aim is to complete the test as quickly as possible, and the time taken to complete the test is recorded. The maximum time available to complete version A was 300 s and version B 360 s, and these scores were also assigned to participants who exceeded these time windows. The English versions of the TMT test instructions were translated into the local languages.

VFT

The VFT is a sensitive indicator of cognitive dysfunction and is sensitive to the effects of aging and type 2 diabetes (25). The test instructs the person to verbalize as many words as possible in 60 s and involves different categories; semantic fluency requires generation of words from a certain category (e.g., animals or profession), whereas the letter version (phonemic fluency) requires verbalization of words starting with a specific letter. In CARMELINA, the category "animals" and the letters "F," "A," and "S" were used across all participating countries and languages. The number of words/animals after 15 s and after 60 s were recorded. The English versions of the test instructions were translated into the local languages. Number of words per letter was adjusted for the participants' language, because of language-specific differences in word frequencies.

Center for Epidemiologic Studies Depression Scale

Depression or depressive symptoms are a confounder to cognitive performance; hence, all participants also completed the Center for Epidemiologic Studies Depression Scale (CES-D), a widely used and validated 20-item questionnaire on depressive symptoms over the past week (26) in which a score ≥16 is indicative of depression. Whenever available in a country, the validated version of the CES-D was used, and for others, a back translation was created and verified.

Primary Cognitive Outcome

The primary outcome was the incidence of accelerated cognitive decline, treated as a dichotomous outcome measure (presence or absence) and defined as a score ≤16th percentile of the regression-based index (RBI) scores for cognitive decline in the total study population for MMSE, A&E, or both at the end of study. This cutoff was chosen because it reasonably sets an individual apart from the mean performance and corresponds to ~1 SD.

To characterize attention and executive functioning, the TMT and the VFT were combined to one composite score (the A&E score). Details on the derivation of the A&E score are provided in the Supplementary Data, section A. The RBI score was used to compare effects between treatment groups. An RBI score reflects the difference between an observed score (FUobserved) and a predicted score (FUpredicted) on a cognitive performance task at the end of follow-up (i.e., MMSE or A&E *z* score). Details of the regression methods for predicted scores are provided in the Supplementary Data, section B.

RBI scores were calculated by comparing the actual observed score to the predicted score for each individual (RBI score = [FUobserved − FUpredicted]/SD of residuals) on the MMSE or A&E *z* score. Hence, a negative RBI score reflects relatively faster cognitive decline than would be expected for a particular participant based on his or her individual characteristics at baseline.

Subgroup analysis for the primary outcome was predefined for nine baseline factors: sex (male and female), age (<70 and ≥70 years), race (black, white, Asian, and other), ethnicity (Latino/Hispanic and non-Latino/Hispanic), CES-D score (<16 and ≥16 and by median split), CV risk categories (established macrovascular disease and albuminuria without established renal disease, established renal disease without macrovascular and albuminuria disease, and established macrovascular disease and albuminuria and established renal disease), duration of type 2 diabetes (≤1 year, >1 to ≤5 years, >5 to ≤10 years, and >10 years), baseline dementia risk for patients ≥60 years of age by median score (≤5 and >5), and UACR (<30 mg/g, ≥30 to ≤300 mg/g, and >300 mg/g). Dementia risk was derived using the validated diabetes-specific dementia risk score estimate (5).

It was anticipated that 20–25% of the CARMELINA-COG population would meet the primary cognitive outcome. With 4,000 individuals anticipated to be studied over a median 3.5 years of follow-up, this would provide ~900 individuals fulfilling the definitions of accelerated cognitive decline. At a power of 0.8 and $\alpha = 0.05$, this would enable a detection of a relative risk reduction of 17% (linagliptin outcome rate 19% vs. placebo outcome rate 23%).

Sensitivity/Secondary Cognitive Outcomes and Further End Points

Prespecified and post hoc–specified sensitivity analyses of the primary end point were conducted *1*) in the cohort including participants who had their follow-up cognitive assessment >7 days after their last intake of study medication (post hoc), *2*) in the cohort that excluded participants who had psychiatric disease or history of drug abuse (predefined), and *3*) using an adjusted analysis with the following covariates for the logistic regression analysis (predefined): age at baseline (continuous), sex (male and female), years of formal education at baseline (continuous), race (black, white, Asian, and other), ethnicity (Latino/Hispanic and non-Latino/Hispanic), language, and CES-D score at baseline (<16 and ≥16).

Analyses of accelerated cognitive decline were also performed using a 10% cutoff (and not the 16th percentile) to define accelerated cognitive decline in a secondary end point (predefined) and in a further end point defining cognitive decline by an MMSE <24 or a decrease >4 points relative to baseline at end of treatment visit (predefined).

Additional end points included change from baseline in proportion of participants with prevalent depression (predefined), absolute change from baseline to end of treatment in cognitive performance (post hoc) (overall and in those with accelerated cognitive decline), change from baseline in HbA_{1c} (post hoc), and, in post hoc analysis, occurrence of all adverse events and occurrence of hypoglycemia. The two latter items were captured based on investigator-reported events and coded using the Medical Dictionary for Drug Regulatory Activities version 20.1 (22).

Statistical Analysis

For the analysis of the primary as well as secondary outcome (using other cutoffs to define accelerated cognitive decline or other definitions), the incidence of accelerated cognitive decline at end of treatment was compared between the two treatment groups using a logistic regression model including treatment and region as a factor. The odds ratio (OR) along with the 95% Wald CI and two-sided *P* value were calculated for treatment comparison. For subgroup analyses, terms for treatment, region, subgroup, and subgroup-by-treatment interaction were included in the logistic regression model.

Change from baseline in continuous cognition covariates over time were evaluated with an ANCOVA model including terms for treatment, region, and baseline value of the end point. HbA_{1c} change from baseline was evaluated post hoc with a mixed model repeated measures with terms for treatment, baseline HbA_{1c} value, week, region, treatment-by-week interaction, and baseline HbA_{1c} value-by-week interaction.

Hypoglycemic events were analyzed post hoc providing incidence rate ratios (IRRs) and 95% CIs and time to first initiation of glucose-lowering medications was analyzed using a Cox proportional hazards regression model with randomized treatment and geographical region (North America and Europe) as factors.

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Between August 2013 and August 2016, a total of 6,979 participants were included in CARMELINA. Of this population, 2,694 participants from sites in 12 countries in Europe (60.7%) and North America (39.3%) (Supplementary Data, section C) were eligible for CARMELINA-COG. Of those, confounder information and baseline cognitive assessment were missing from 28, and 338 participants had a baseline MMSE <24, restricting the baseline primary analysis population to 2,328. In total, 1,545 participants (linagliptin, 800; and placebo, 745) had an on-treatment follow-up cognitive assessment and constitute the primary CARMELINA-COG analysis data set (patient flowchart, Supplementary Data, section D).

Table 1—Select baseline characteristics by treatment group

	Linagliptin (*n* = 800)	Placebo (*n* = 745)
Male/female	503 (62.9)/297 (37.1)	501 (67.2)/244 (32.8)
Age, years	67.8 ± 8.3	67.7 ± 8.0
Medical history		
History of MI*	205 (25.6)	168 (22.6)
History of ischemic/hemorrhagic stroke*	87 (10.9)	77 (10.3)
Atrial fibrillation	101 (12.6)	115 (15.4)
Clinical diagnosis of of heart failure	133 (16.6)	119 (16.0)
Education level		
High school or less¤	517 (64.6)	481 (64.6)
College or higher¤	283 (35.4)	264 (35.4)
BMI, kg/m^2¤¤	32.5 ± 5.1	32.8 ± 5.3
MMSE score	28.3 ± 1.7	28.2 ± 1.8
10-year dementia risk, %¤¤¤	25.0 ± 15.1	25.0 ± 15.2
Clinical diagnosis of depression in previous 2 years	55 (6.9)	57 (7.7)
Depression score according to CES-D	9.9 ± 8.5	10.2 ± 8.3
<16	623 (77.9)	569 (76.4)
≥16	174 (21.8)	173 (23.2)
Missing	3 (0.4)	3 (0.4)
Renal function characteristics		
eGFR (MDRD), mL/min/1.73 m^2	52.7 ± 23.2	51.3 ± 22.8
UACR, mg/g, median (25th–75th percentile)	102.7 (27.0, 405.8)	123.9 (35.4, 522.1)
UACR, *n* (%)		
<30 mg/g	212 (26.5)	172 (23.1)
30–300 mg/g	349 (43.6)	320 (43.0)
>300 mg/g	239 (29.9)	253 (34.9)
Diabetes-related characteristics		
Type 2 diabetes duration, years	14.8 ± 9.2	15.4 ± 9.4
HbA_{1c}, % (mmol/mol)	7.8 ± 0.9 (61.5 ± 10.1)	7.8 ± 0.9 (61.3 ± 10.0)
Fasting plasma glucose, mg/dL	152.9 ± 41.2	152.0 ± 41.8
Hyper- or hypoglycemia requiring hospitalization during last 2 years	21 (2.6)	18 (2.4)
Glucose-lowering therapies		
Any glucose-lowering therapy	763 (95.4)	715 (96.0)
Metformin	367 (45.9)	353 (47.4)
Sulphonylurea	253 (31.6)	242 (32.5)
Any insulin	498 (62.3)	466 (62.6)
Insulin dose	48.8 ± 38.0	47.4 ± 30.7
CV therapies		
Antiplatelets	565 (70.6)	514 (69.0)
Statins	640 (80.0)	614 (82.4)
Antihypertensives	769 (96.1)	727 (97.6)
Systolic blood pressure, mmHg	140.6 ± 17.2	141.5 ± 17.5
Diastolic blood pressure, mmHg	77.3 ± 10.4	76.8 ± 10.5
LDL cholesterol, mmol/L (mg/dL)	2.2 ± 0.9 (85.5 ± 34.1)	2.2 ± 0.9 (85.1 ± 34.1)

Data are *n* (%) or mean ± SD unless otherwise noted. MDRD, Modification of Diet in Renal Disease study equation. *In conjunction with albuminuria. ¤Defined as less than or greater than/equal to median of years of formal education in participants ≥60 years of age. ¤¤BMI missing for 3 (0.1%) patients given placebo. ¤¤¤According to the diabetes-specific dementia risk score estimate.

Baseline clinical characteristics were well balanced between groups (Table 1 and Supplementary Data, section E), with overall (mean ± SD) age 67.8 ± 8.1 years, BMI 32.6 ± 5.2 kg/m^2, and HbA_{1c} 7.8 ± 0.9% (61.4 ± 10.1 mmol/mol). Duration of type 2 diabetes was 15.1 ± 9.3 years, eGFR 52.0 ± 23.0 mL/min/1.73 m^2, and median years of formal education was 12. MMSE and CES-D scores were 28.3 ± 1.7 and 10.1 ± 8.4, respectively, with 22.5% having a CES-D score ≥16. The estimated 10-year risk for dementia in those at least 60 years of age was 25%.

The median (minimum, maximum) time between baseline assessment and cognitive follow-up assessment was 912 (24, 1,525) days, corresponding to 2.5 (0.1, 4.2) years, with no between-group difference (linagliptin: 916 [24, 1,525] days/2.5 [0.1, 4.2] years; placebo: 911 [65, 1,438] days/2.5 [0.2, 3.9] years). Baseline characteristics of participants who dropped out of the study, or died postbaseline, are provided in the Supplementary Data, section F.

Those randomized to linagliptin had lower HbA_{1c} throughout the trial observation period (overall mean [95% CI] difference for linagliptin vs. placebo −0.34% [−0.45, −0.24]/−3.8 mmol/mol [−4.9, −2.6] based on least square means), without increase in overall hypoglycemia risk (any hypoglycemia: linagliptin 33.0% vs. placebo 37.7% [IRR (95% CI) 0.82 (0.69, 0.97)]; hypoglycemia requiring assistance or hypoglycemia with plasma glucose <54 mg/dL: linagliptin 18.5% vs. placebo 21.7% [IRR 0.81 (0.65, 1.02)]) (Supplementary Data, section G) despite a higher use of additional glucose-lowering medications in the placebo group (any new introduction of glucose-lowering medication: linagliptin 13.0% vs. placebo 18.3% (HR 0.68 [0.53, 0.88]; P = 0.003) (Supplementary Data, section G), with no between-group difference in weight (overall mean [95% CI] difference linagliptin vs. placebo −0.32 kg [−0.90, 0.26] based on least square means).

Effects on the Primary Cognitive Outcome

Of the 1,545 patients who were included in the primary cognitive analysis, 445 (28.8%) had accelerated cognitive decline, but there was no difference between treatment groups in the incidence (227 out of 800 [28.4%] in the linagliptin group and 218 out of 745 [29.3%] in the placebo group; OR 0.96 [95% CI 0.77, 1.19]; P = 0.6938) (Fig. 1*A*).

The proportion of participants with incident accelerated cognitive decline varied slightly across baseline characteristics subgroups, with larger proportions declining with advancing age (≥70 years 32.1% vs. <70 years 26.4%) and higher CES-D score (≥16: 32.9% vs. <16: 27.5%); however, there was no heterogeneity observed for the effects of the randomized treatment assignment by any baseline factors (Fig. 2).

Sensitivity/Secondary Cognitive Outcome Analyses

Analyses that included participants who had their follow-up cognitive assessment >7 days after their last dose of study medication (which expanded the analysis set by 252 participants) or excluding participants who had psychiatric disease or history of drug abuse prior to inclusion (which excluded 69 participants) showed results congruent with the primary results (Supplementary Data, section H). Similarly, when defining incidence of accelerated cognitive decline as MMSE <24 or a decline of >4 MMSE points relative to baseline, there were also no difference between the groups (linagliptin 9.1% vs. placebo 8.4%; P = 0.59) (Supplementary Data, section H). Furthermore, applying a cutoff at 10% to define accelerated cognitive decline provided similar results (OR 0.95 [0.73, 1.23]; P = 0.6816; linagliptin: 18.0%; placebo: 18.8%) (Fig. 1*B*), as did the covariate-adjusted sensitivity analyses (Supplementary Data, section H).

Absolute changes from baseline in MMSE, VFT, and TMT were similar between treatment groups (Table 2), but the 445 participants with accelerated cognitive decline had a greater reduction in MMSE and A&E (Supplementary

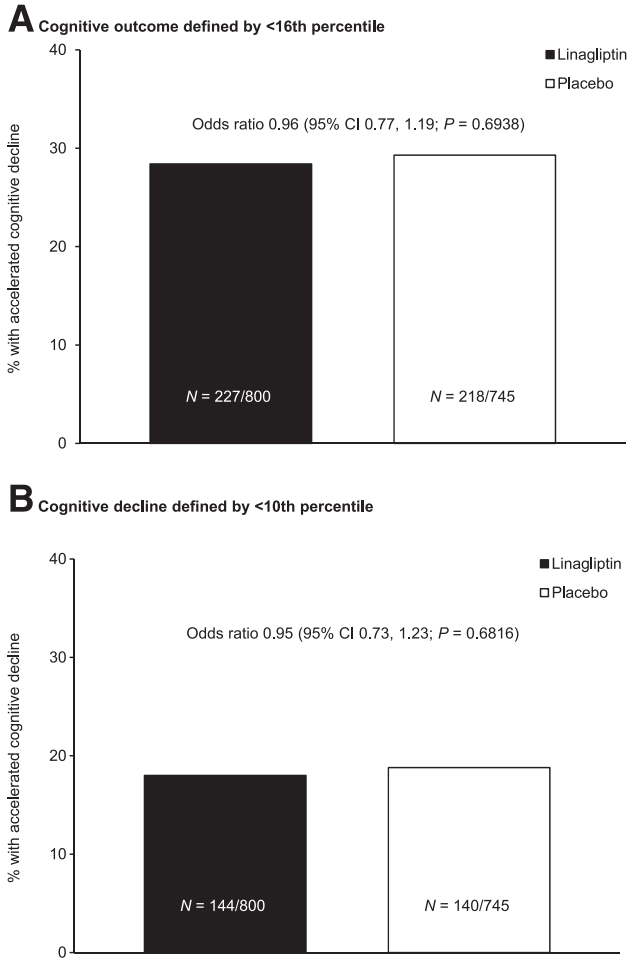

Figure 1—Proportions with and effect of linagliptin vs. placebo on accelerated cognitive decline. *A*: Cognitive decline defined by decline at the 16th percentile. *B*: Cognitive decline defined at the 10th percentile.

	Linagliptin	Placebo	OR (95% CI)	OR (95% CI)	*P*-value
	n with event / N analyzed (%)				
All patients	227/800 (28.4)	218/745 (29.3)	0.96 (0.77, 1.19)		0.6938
Age <70 years	114/460 (24.8)	121/431 (28.1)	0.84 (0.63, 1.14)		0.2149
Age ≥70 years	113/340 (33.2)	97/314 (30.9)	1.12 (0.80, 1.55)		
Male	137/503 (27.2)	145/501 (28.9)	0.92 (0.70, 1.21)		0.6733
Female	90/297 (30.3)	73/244 (29.9)	1.01 (0.70, 1.46)		
Black	15/42 (35.7)	17/41 (41.5)	0.75 (0.31, 1.83)		0.2793
White	208/739 (28.1)	191/681 (28.0)	1.00 (0.80, 1.26)		
Asian	2/13 (15.4)	9/18 (50.0)	0.16 (0.03, 0.98)		
Other	2/6 (33.3)	1/5 (20.0)	1.00 (0.05, 22.18)		
Non-Latino/non-Hispanic	205/738 (27.8)	197/667 (29.5)	0.92 (0.73, 1.16)		0.2012
Latino/Hispanic	22/62 (35.5)	21/78 (26.9)	1.45 (0.70, 3.00)		
T2D duration ≤1 year	4/25 (16.0)	3/18 (16.7)	1.77 (0.25, 12.25)		0.3334
T2D duration 1 to ≤5 years	25/87 (28.7)	26/63 (41.3)	0.64 (0.32, 1.29)		
T2D duration 5 to ≤10 years	44/161 (27.3)	47/151 (31.1)	0.83 (0.51, 1.36)		
T2D duration >10 years	154/527 (29.2)	142/513 (27.7)	1.08 (0.83, 1.42)		
CVD + albuminuria YES/Renal disease NO	79/270 (29.3)	66/230 (28.7)	1.03 (0.70, 1.51)		0.1790
CVD + albuminuria NO/Renal disease YES	108/371 (29.1)	103/374 (27.5)	1.08 (0.79, 1.49)		
CVD + albuminuria YES/Renal disease YES	39/151 (25.8)	47/131 (35.9)	0.60 (0.36, 1.01)		
Normoalbuminuria	64/212 (30.2)	44/172 (25.6)	1.26 (0.80, 1.98)		0.3755
Microalbuminuria	95/349 (27.2)	98/320 (30.6)	0.85 (0.61, 1.18)		
Macroalbuminuria	68/239 (28.5)	76/253 (30.0)	0.93 (0.63, 1.37)		
CES-D <16	169/623 (27.1)	159/569 (27.9)	0.96 (0.74, 1.24)		0.9354
CES-D ≥16	56/174 (32.2)	58/173 (33.5)	0.94 (0.60, 1.47)		
CES-D <median (8)	86/366 (23.5)	89/339 (26.3)	0.86 (0.61, 1.21)		0.4676
CES-D ≥median (8)	139/431 (32.3)	128/403 (31.8)	1.02 (0.76, 1.36)		
Dementia risk score ≤median + age ≥60	103/442 (23.3)	116/420 (27.6)	0.79 (0.58, 1.08)		0.0368
Dementia risk score >median + age ≥60	86/230 (37.4)	68/222 (30.6)	1.35 (0.91, 2.00)		

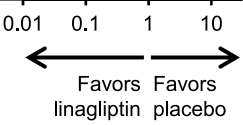

Figure 2—Effect on accelerated cognitive decline by subgroups (OR [95% CIs]). *P* values depict treatment-by-subgroup interaction. CVD, CV disease; T2D, type 2 diabetes.

Data, section I). CES-D did not change notably during the course of the trial between treatment groups, with a proportion of individuals at the final assessment with a CES-D score ≥16 of 24.5% in the linagliptin group and 25.6% in the placebo group ($P = 0.58$), as compared with 21.8% and 23.2%, respectively, at baseline.

Changes in scores for VFT, TMT, and A&E are provided in Table 2.

Adverse Events

The overall safety profile of linagliptin was consistent with previous clinical data (22), with a frequency of occurrence of adverse events, serious adverse events, and adverse events leading to study drug discontinuation for patients treated with linagliptin versus placebo in CARMELINA-COG being 83.4% vs. 87.7%, 37.5% vs. 42.1%, and 1.0% vs. 1.5%, respectively.

CONCLUSIONS

CARMELINA-COG studied a population of patients with type 2 diabetes at high risk for CV and renal events, hence also at high risk for cognitive decline, and indeed, this study showed that the baseline estimated 10-year risk for dementia in those at least 60 years of age was high (25%). Linagliptin did not modulate the risk for accelerated cognitive decline over 2.5 years, but the participants who fulfilled accelerated cognitive decline criteria had changes in cognitive function scores (e.g., MMSE) that far exceeded those in the overall population and were typically much higher than what has been observed in other studies (28–30).

The duration of CARMELINA-COG was determined by the rate of accrual of CV events, and because CARMELINA included a high CV risk population, this led to a relatively short observation period in the context of studying cognitive decline, as well as a smaller number of individuals than anticipated recruited to the trial. As cognitive decline trajectories are usually slow, and number of individuals needed to study more subtle cognitive changes are high, both of these are limitations of this study.

Yet, it should be noted that the results were consistent using the more stringent (10%) cutoff for accelerated decline. The longer-running CAROLINA trial (expected to be >5 years), which compares linagliptin with glimepiride also on cognitive outcomes, could address this limitation, although this trial is an active comparator with the sulfonylurea glimepiride (31).

CARMELINA-COG used the MMSE, TMT, and VFT as the cognitive testing battery, and it is uncertain if results would have looked different using other testing batteries, subjective cognitive complaints measures (32), or comparisons with normative data sets using different cutoffs (33). Because previous systematic reviews have shown that effect sizes of type 2 diabetes–associated cognitive decrements are quite similar across different tests of memory, speed, and A&E (34), we do not think this would have changed the results notably. In particular, in CARMELINA, the intention

Table 2—Absolute changes in MMSE, A&E, TMT, VFT, and CES-D by treatment group

	Linagliptin (n = 800)	Placebo (n = 745)
MMSE score		
Baseline	28.3 (1.7)	28.2 (1.8)
Follow-up	27.8 (2.5)	27.7 (2.6)
Change from baseline	−0.5 (2.4)	−0.5 (2.4)
A&E (z score)		
Baseline	0.0 (0.7)	0.0 (0.7)
Follow-up	0.0 (0.7)	0.0 (0.7)
Change from baseline	0.0 (0.7)	−0.1 (0.7)
VFT letter 60 (in seconds)		
Baseline	8.3 (4.2)	8.4 (4.1)
Follow-up	8.5 (4.2)	8.3 (3.9)
Change	0.0 (2.8)	−0.2 (2.6)
VFT animals 60 (in seconds)		
Baseline	15.7 (6.3)	15.7 (6.2)
Follow-up	15.0 (6.2)	14.9 (5.7)
Change	−0.8 (6.4)	−0.9 (5.4)
Overall VFT 60 z score		
Baseline	0.0 (0.9)	0.0 (0.9)
Follow-up	0.0 (0.9)	−0.1 (0.8)
Change	−0.1 (0.7)	−0.1 (0.6)
TMT-A (in seconds)		
Baseline	89.9 (71.1)	85.7 (64.9)
Follow-up	95.8 (72.8)	89.5 (67.1)
Change	4.6 (42.1)	3.0 (36.2)
TMT-B (in seconds)		
Baseline	166.1 (94.3)	161.1 (89.5)
Follow-up	171.9 (93.4)	165.9 (88.1)
Change	6.8 (67.1)	7.6 (64.6)
TMT ratio[1]		
Baseline	1.4 (1.2)	1.3 (1.1)
Follow-up	1.3 (1.0)	1.3 (1.0)
Change	0.1 (1.1)	0.1 (1.1)
CES-D score		
Baseline	9.9 (8.5)	10.2 (8.3)
Follow-up	10.6 (9.4)	11.0 (8.8)
Change	0.7 (8.7)	0.8 (8.7)

Data are means (SD). VFT animals 60, VFT score for the category animals in 60 s; VFT letter 60, averaged VFT scores for the letters F, A, and S in 60 s. [1]TMT ratio: (TMT-B − TMT-A)/TMT-A.

was to identify those individuals with accelerated decline rather than detecting very subtle cognitive changes. Moreover, elaborate cognitive testing protocols with a full diagnostic evaluation for MCI or dementia are not currently feasible in a large international trial like this.

The number of participants analyzed with both global cognitive functioning and domain-pecific function parameters was relatively large as compared with other trials that have tested for cognitive outcomes and also includes a population at much higher risk for deterioration in cognitive function. Hence, CARMELINA-COG is advancing the scientific understanding of cognitive trajectories in type 2 diabetes, an area that has been largely understudied (14). Although the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial had a larger number of participants (n = 11,132), it was not a blinded placebo-controlled trial, it was designed to assess effects of intensive glucose lowering on cognitive impairment, and it only used MMSE (28). Prior to CARMELINA-COG, there had been very few randomized controlled studies that were designed to test the nonglycemic effects of pharmacological interventions on cognition in type 2 diabetes, with most being too small or with too short a duration to adequately address this topic, as reviewed by others (13,14,35). In CARMELINA, the use of metformin and other glucose-lowering drugs at baseline was balanced across treatment groups. A higher proportion of participants in the placebo group received additional non–incretin-based glucose-lowering therapies during the course of the trial, and a difference in HbA_{1c} favoring linagliptin was observed. However, because no glucose-lowering intervention (13,35) or glucose lowering per se (14) has proven efficacious to modulate the risk of cognitive decline, we do not think this influenced the results. One further consideration is that we recruited participants who received secondary CV and kidney preventive medication according to the guideline-recommended standard of care. With suggestions of risk factor goal attainment being linked to risk for cognitive impairment (36), this could have influenced our likelihood of being able to demonstrate effects.

Linagliptin did not increase the risk for hypoglycemia, which is important because hypoglycemia, in particular severe hypoglycemia, has been correlated with cognitive impairment (37,38). The role of hypoglycemia in relation to risk of MCI and dementia is, however, debated, and several studies have not observed such a relationship (39), including in participants with type 1 diabetes with a much higher frequency of severe hypoglycemia than in type 2 diabetes (40).

It should be noted that we observed a relatively large dropout between baseline assessment and follow-up (i.e., from 2,328 participants to 1,545). The main reasons for this were that either the cognitive assessment was >7 days after end of treatment (n = 252), participants had missing or implausible values for MMSE, VFT, or TMT and were excluded (n = 308), or participants died (n = 223), which underscores the high mortality burden associated with cardiorenal disease in type 2 diabetes, with significant reduced life expectancy (41). In addition, several participants prematurely discontinued study drug (n = 263), albeit not at a rate that is unusual for a trial like this, which triggered a shortening in observation time between the two cognitive assessments. Nonetheless, despite those dropping out, and those that died were at higher risk for cognitive decline, based on the estimated 10-year dementia risk (see Supplementary Tables F1 and F2), we do not believe that this influenced the result since it was similar in the two treatment arms and because of the neutral result across a number of subgroups and in sensitivity analyses. However, the generalizability of these results does not

necessarily extend to those at highest risk for cognitive decline.

An interesting observation from this substudy was that a quarter of the population in CARMELINA-COG had subclinical depression at the end of treatment. Compared with individuals without type 2 diabetes, people with diabetes have a significant higher risk of developing depression (42), but a prevalence of >20% is higher than what is typically reported in most studies (42,43), which probably is related to the higher cardiorenal comorbidity disease burden among the participants in CARMELINA (22,43).

Conclusion

In a large international CV outcome trial in people with type 2 diabetes and cardiorenal disease, linagliptin did not modulate cognitive decline over 2.5 years.

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