Effects of Linagliptin Versus Glimepiride on Cognitive Performance in Type 2 Diabetes Mellitus: The CAROLINA® COGNITION Sub-Study

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Introduction

- Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and an increased risk of dementia, particularly in those with cardiovascular (CV) disease.[1]
- Underlying mechanisms are largely unclear and no therapies have proven efficacy in preventing cognitive decline.[2]
- Mechanistic studies postulate that incretin therapies can modulate this risk via glycaemic and non-glycaemic pathways;[3] however, in a cognition sub-study of the placebo-controlled, cardio-renal outcome trial of the dipeptidyl peptidase-4 inhibitor linagliptin (CARMELINA®; NCT01897532),[4] neutral effects on cognitive endpoints were observed over 2.5 years in patients with T2DM and multiple comorbidities.[5]

Objective

- To assess the long-term effect of linagliptin versus the sulphonylurea glimepiride on accelerated cognitive decline in patients with relatively early T2DM at increased risk of CV.

Methods

- The CAROLINA® COGNITION sub-study was an integral part of CAROLINA® (Cardiovascular Safety of Linagliptin; NCT01243424).[6]
  - A multicentre, international, randomised, parallel-group, double-blind trial to evaluate the CV safety of linagliptin versus glimepiride as once-daily oral therapies, in patients with T2DM at high CV risk.
  - T2DM and a high CV risk defined by (1 or more of the 4 below):
    1. History of macrovascular disease
    2. Evidence of vascular-related end-organ damage
    3. Age over 70 years
    4. At least 2 CV risk factors (10 years of T2DM, hypertension, smoking and/or dyslipidaemia)
  - Primary outcome: time to first CV death, non-fatal myocardial infarction, or non-fatal stroke.
- Analyses were done in patients with a baseline Mini-Mental State Examination (MMSE) ≥24 using the Latin alphabet.
- The primary cognitive outcome, analysed at the end of treatment, was the occurrence of accelerated cognitive decline, defined as a regression based index (RBI) score ≤16th percentile on either the MMSE or a composite measure of attention and executive functioning (A&E).[7]

Results

- Of 4018 eligible CAROLINA® COGNITION patients, 3163 were included in the primary analyses (**Figure 1** and **Table 1**).
- At the end of trial, after 6.2 years, accelerated cognitive decline occurred in 27.8% (449/1618, linagliptin) versus 27.6% (426/1545, glimepiride); odds ratio 1.01 (95% CI 0.86, 1.18).
- At Week 160, accelerated cognitive decline occurred in 27.6% (446/1618, linagliptin) versus 26.3% (406/1545, glimepiride); odds ratio 1.07 (95% CI 0.91, 1.25).
- The proportion of patients with accelerated cognitive decline varied slightly across baseline characteristics subgroups — larger proportions declined with advancing age (<70 years: 25.4% vs ≥70 years: 32.2%) and higher Centre for Epidemiologic Studies Depression Scale (CES-D) score (<16: 26.2% vs ≥16: 34.1%).
  - However, there was no heterogeneity observed for the treatment effects (**Figure 2**).
- Absolute cognitive changes were not different between treatment groups (**Table 2**).
- As observed in the main trial,[8] glycated haemoglobin at the end of the study did not differ between treatments (**Figure 3**); differences were observed for weight (**Figure 4**) and risk for hypoglycaemia (**Figure 5**).

Table 1. Baseline characteristics by treatment group

	Linagliptin (n=1618)	Glimepiride (n=1545)
Male/Female	1002 (61.9)/616 (38.1)	958 (62.0)/587 (38.0)
Age, years	64.4±9.1	64.4±9.3
Myocardial infarction	226 (14.0)	187 (12.1)
Cerebrovascular disease	169 (10.4)	154 (10.0)
Atrial fibrillation	86 (5.3)	74 (4.8)
Known coronary artery disease	394 (24.4)	366 (23.7)
Education level, years	10.8±3.4	10.8±3.5
MMSE	28.5±1.7	28.5±1.7
CES-D score	8.7±8.0	9.3±8.3
<16	1335 (82.5)	1242 (80.4)
≥16	250 (15.5)	278 (18.0)
Missing	33 (2.0)	25 (1.6)
T2DM duration, years	7.7±6.2	7.4±5.9
HbA1c, %	7.1±0.5	7.1±0.6
Fasting plasma glucose, mg/dl	140.2±30.0	141.1±29.3
BMI, kg/m²	30.8±5.0	30.7±4.9
Selected glucose-lowering therapy		
Metformin	1348 (83.3)	1306 (84.5)
Sulphonylurea	434 (26.8)	422 (27.3)
Glinide	13 (0.8)	13 (0.8)
α-glucosidase inhibitor	43 (2.7)	34 (2.2)
Glitazone	1 (0.1)	2 (0.1)
Selected CV therapies		
Lipid-lowering medications	1197 (74.0)	1180 (76.4)
Statins	1111 (68.7)	1113 (72.0)
Antihypertensives	1428 (88.3)	1387 (89.8)
eGFR (MDRD), ml/min/1.73 m²	75.8±19.0	76.9±18.8
Systolic blood pressure, mmHg	135.9±15.9	136.2±16.4
Diastolic blood pressure, mmHg	78.8±9.5	78.8±9.3
LDL-cholesterol, mmol/l	2.4±0.9	2.4±0.9

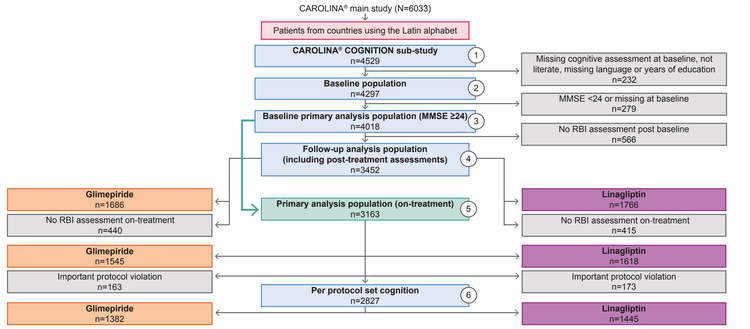
Data are n (%) or mean ± SD unless otherwise stated. BMI, body-mass index; CES-D, Centre for Epidemiologic Studies Depression Scale; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination; MDRD, Modification of Diet in Renal Disease study equation; SD, standard deviation; T2DM, type 2 diabetes.

Table 2. Absolute values and changes from baseline (means ± SD) in MMSE and A&E

	Week 160		Week 400	
	Linagliptin	Glimepiride	Linagliptin	Glimepiride
MMSE score				
Baseline	28.5±1.7	28.5±1.7	28.5±1.7	28.5±1.7
Follow-up	28.2±2.1	28.3±2.2	28.1±2.7	28.1±2.7
Change from baseline	-0.2±2.0	-0.2±2.1	-0.4±2.6	-0.4±2.6
A&E (z-score)				
Baseline	−0.006±0.7041	0.012±0.7304	−0.006±0.7041	0.012±0.7304
Follow-up	−0.059±0.7332	−0.051±0.7064	−0.099±0.7668	−0.091±0.7828
Change from baseline	−0.046±0.7485	−0.057±0.7204	−0.107±0.8083	−0.138±0.8148

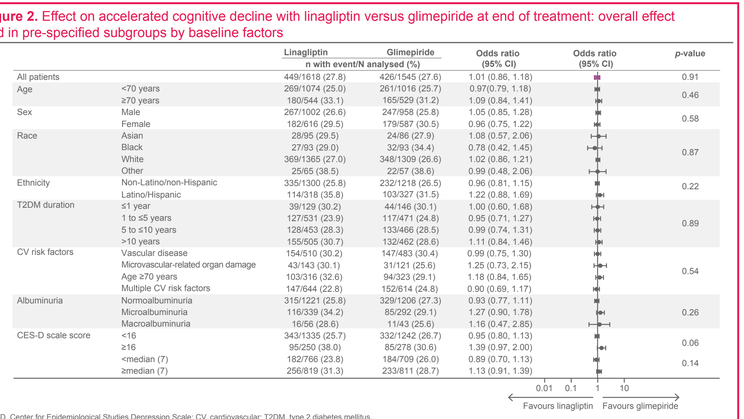
A&E, attention and executive functioning; MMSE, Mini-Mental State Examination; SD, standard deviation.

Figure 1. Flowchart for CAROLINA® COGNITION sub-study



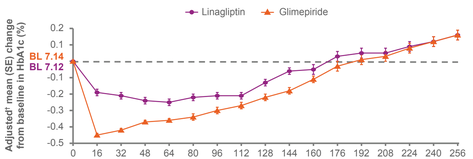
①Includes all patients who were dispensed study medication and were documented to have taken at least 1 dose of investigational treatment (treated set). ② Includes all patients in the treated set who have baseline assessment (of which at least 1 of the z-scores, A&E or MMSE can be calculated), are literate and their years of formal education are available (BL-COG). ③ All patients in BL-COG with MMSE ≥24 at baseline. This set is used for language correction and calculation of z-scores (BL-COG-ELIG). ④ Includes all patients included in the BL-COG-ELIG who have at least 1 post-baseline assessment (FAS-COG-EXT). ⑤ Includes all patients included in the BL-COG-ELIG who have at least 1 follow-up assessment (treatment stop + 7 days); this set is used for the primary analysis (FAS-COG) ⑥ Includes all patients in the FAS-COG who do not have an important protocol violation (i.e. psychiatric disease or history of alcohol/drug abuse prior to inclusion; PPS-COG). A&E, attention and executive functioning; MMSE, Mini-Mental State Examination; RBI, regression based index.

Figure 2. Effect on accelerated cognitive decline with linagliptin versus glimepiride at end of treatment: overall effect and in pre-specified subgroups by baseline factors



CES-D, Center for Epidemiological Studies Depression Scale; CV, cardiovascular; T2DM, type 2 diabetes mellitus.

Figure 3. HbA1c over time in patients in the CAROLINA® COGNITION sub-study until Week 256*

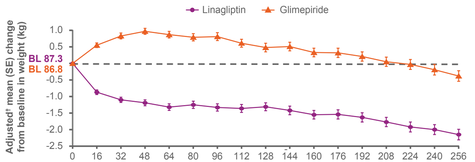


No. patients

Linagliptin	1617	1542	1395	1297	1228	1173	1128	1077	1041	1007	974	925	878	836	806	761	740
Glimepiride	1545	1507	1418	1340	1274	1211	1167	1124	1083	1040	1020	967	923	865	827	793	755

*Post hoc analysis; †Based on MMRM including treatment, week, week-by-treatment interaction, continuous baseline HbA1c and baseline HbA1c-by-week interaction. BL, baseline; HbA1c, glycated haemoglobin; MMRM, mixed model for repeated measures; SE, standard error.

Figure 4. Weight over time in patients in the CAROLINA® COGNITION sub-study until Week 256*

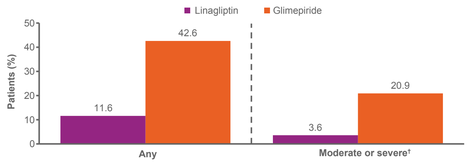


No. patients

Linagliptin	1618	1608	1571	1547	1529	1520	1499	1491	1486	1481	1484	1450	1406	1365	1360	1334	1317
Glimepiride	1544	1533	1505	1483	1476	1459	1449	1447	1442	1432	1430	1400	1366	1333	1302	1274	1254

*Post hoc analysis; †Based on MMRM including treatment, week, week-by-treatment interaction, continuous baseline weight and baseline weight-by-week interaction. BL, baseline; MMRM, mixed-model repeated measures; SE, standard error.

Figure 5. Proportion of patients in the CAROLINA® COGNITION sub-study with hypoglycaemia*



First event occurring between first study drug intake until 7 days after last permanent study drug stop. *Post hoc analysis †Moderate or severe hypoglycaemic adverse event: Symptomatic with plasma glucose ≤70 mg/dl or any severe hypoglycaemic adverse event. A severe event was defined as an event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions.

Conclusions

- In a large, international CV outcome trial in patients with relatively early T2DM at elevated CV risk, no difference in the risk for cognitive decline was observed between linagliptin and glimepiride over 6.2 years.

Disclosures

GJB has received research grants awarded to his institution from Boehringer Ingelheim. **CV**, **JJ** and **EvB** report no conflict of interest. **AP** is employed by HMS analytical software paid by Boehringer Ingelheim. **GW** and **OEJ** are employees of Boehringer Ingelheim. **BZ** has received research grants awarded to his institution from Boehringer Ingelheim, AstraZeneca and NovoNordisk honoraria from Janssen, Sanofi and Eli Lilly and Company, Boehringer Ingelheim, NovoNordisk, and Merck. **MAE** has received honoraria from Boehringer Ingelheim.

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