SUPPLEMENTARY DATA

Biessels GJ, et al. Effect of Linagliptin on Cognitive Performance in Patients with Type 2 Diabetes and Cardio-Renal Comorbidities: the CARMELINA Randomized Trial

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A. A&E derivation

1) The VFT scores for the letters F, A and S in 60 s are averaged to one VFT letter fluency score.
2) Because of word-frequency differences between different Latin-based languages the letters FAS will not yield identical performance in different languages. However, FAS-equivalent letter combinations were available in a minority of languages only. Therefore, we chose to calculate a language-specific correction score. The VFT is corrected for language influences by calculating least square (LS) means in an analysis of covariance (ANCOVA) model including age, gender, years of formal education, race and language as independent variables and this was applied to patients with a MMSE score of ≥24 at baseline. The LS means for language are derived and then compared to one reference language (English), i.e. correction factors are calculated for each language separately (LSmean language/ LSmean English). Correction factors will be calculated for the three letters F, A and S taken together, and for the category fluency (i.e. animals) separately. The VFT scores of each participant are then corrected by multiplying the score with the corresponding correction factor. After correction, the scores are converted into z-scores. Z-scores are used to standardize raw test scores and make them directly comparable. Z-scores are calculated as follows: (individual raw test score – mean baseline test score study population)/ baseline standard deviation.
3) The corrected VFT letter fluency and the VFT category fluency z-scores (both after 60 seconds) are averaged to one VFT overall z-score, where the letter fluency and the category fluency each account for 50%.
4) The TMT ratio is calculated, providing an index for executive functioning: (TMT B –TMT A) / TMT A and converted into a z-score.
5) The mean of the negated TMT ratio and VFT overall z-scores is used to generate one composite score for attention and executive functioning. In secondary analysis the TMT (The TMT ratio z-score is inverted, since higher scores mean lower performance) and VFT will be analyzed separately to control for potential test-specific effects.

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B. Description of the regression methods used to develop predicted scores

Predicted follow-up scores were calculated for each individual by means of an ANCOVA model.The following covariates (predictors) were added to the model: baseline performance, age, education, gender, race and test-retest interval.

To derive the individual predicted follow-up scores, regression coefficients obtained from the ANCOVA model is multiplied by individual values on each predictor using the equation:

FU predict = $\beta 1 \times P1 + \beta 2 \times P2 + \ldots + \beta n \times Pn + a$, where $\beta 1$ is the regression coefficient (slope) for predictor P1, $\beta 2$ for predictor P2 and βn for predictor Pn and a is the intercept.

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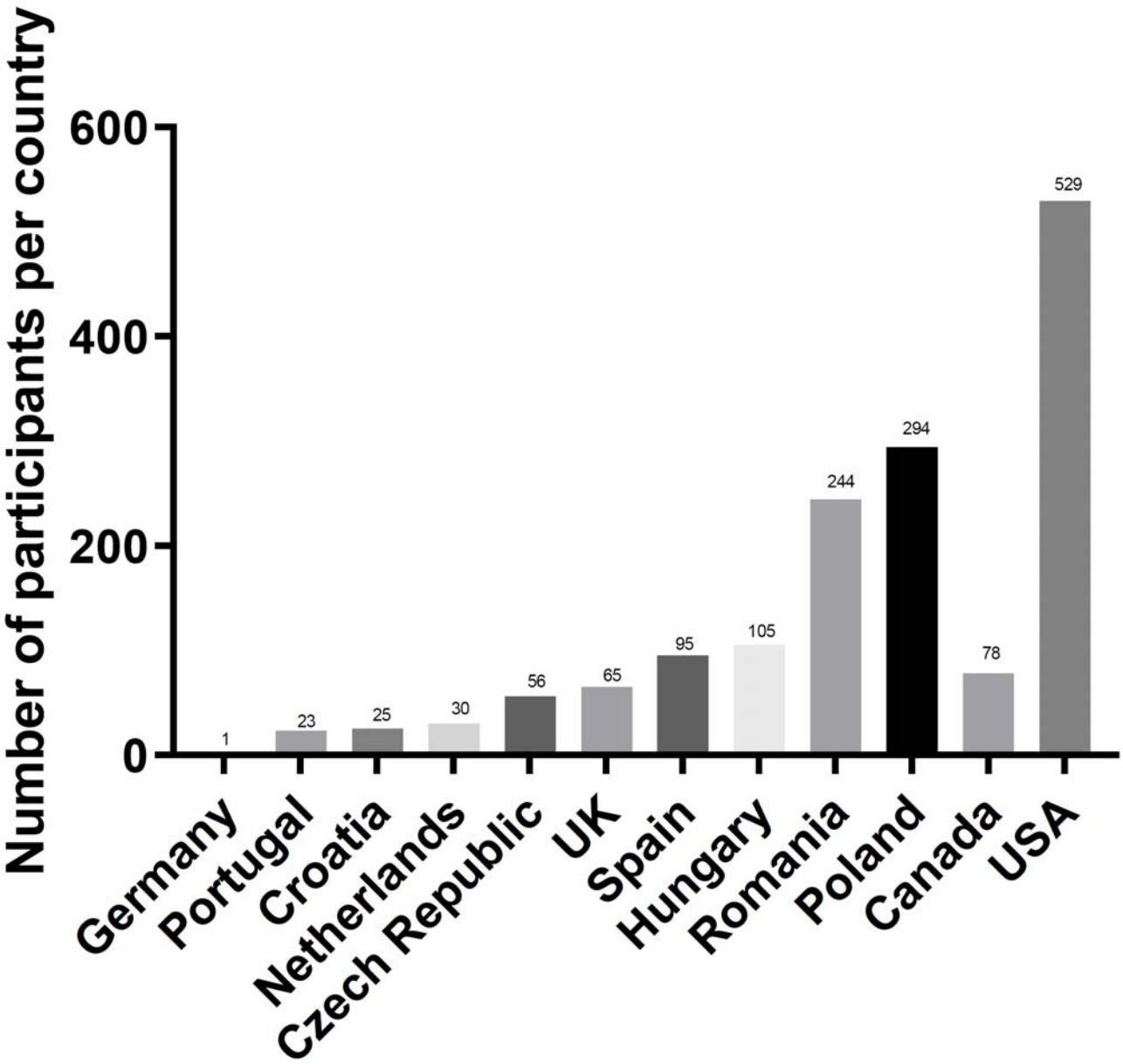
C. Participating countries and number of particpants per country in the CARMELINA-COG substudy



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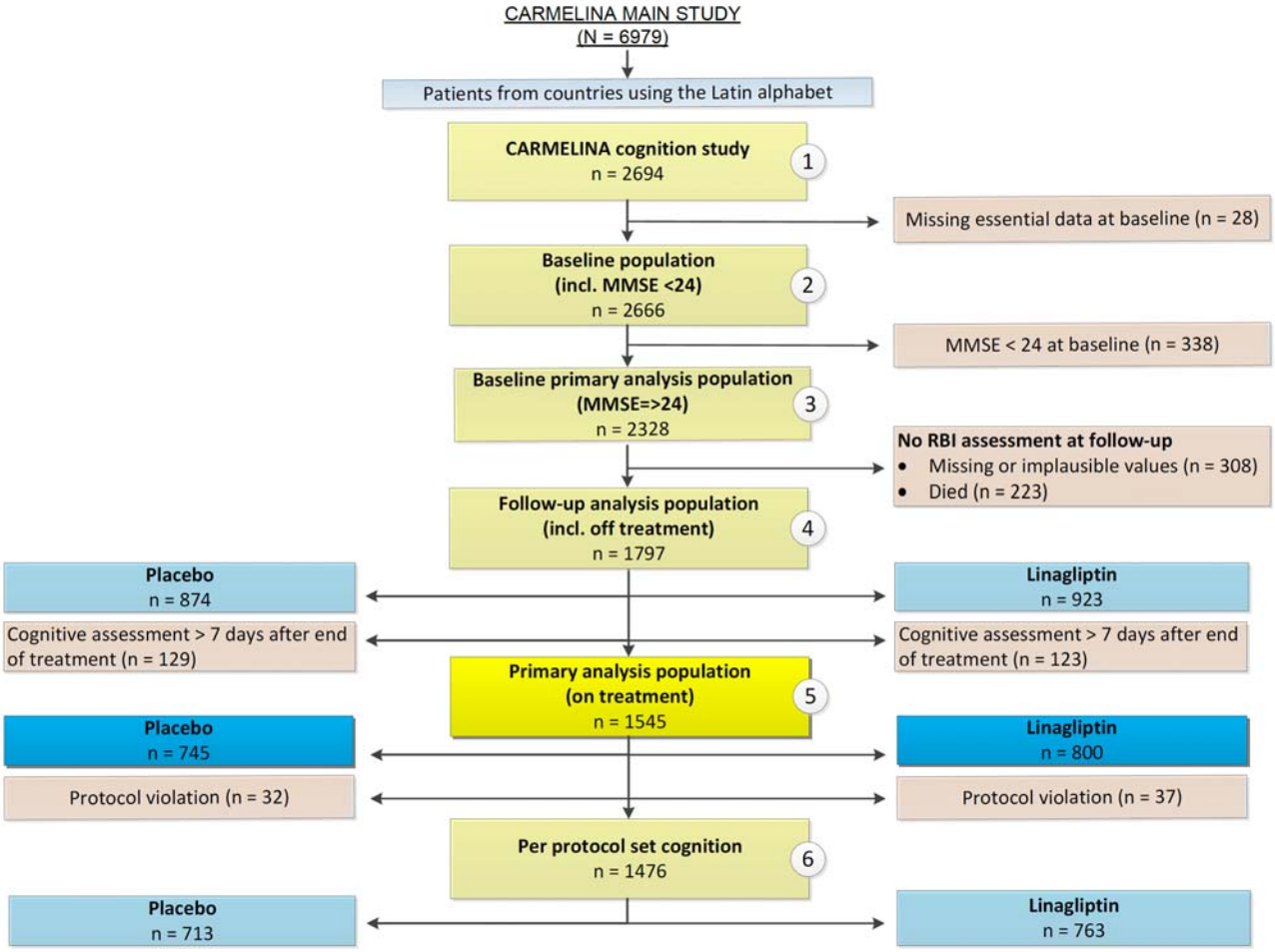
D. Flow-chart for CARMELINA-COG substudy. The primary analysis dataset encompassed the 1545 participants with valid baseline and follow-up cognitive assessments < 7 days since treatment stop and available confounder information. Sensitivity analysis was conducted in a) those without important protocol violations (n=1476) and b) in those who had two cognitive assessments regardless of time since treatment discontinuation (n=1797).



1. Population set used in CARMELINA main study without participants not recruited from countries using the Latin alphabet.
2. Population set without participants missing essential data at baseline (i.e. confounder information [education, language] and/or missing baseline cognitive assessment).
3. Population set without participants with MMSE <24 at baseline. This set is used for language correction and calculation of z-scores.
4. Population set without participants that do not have a RBI assessment at follow-up, and with participants who had their follow-up cognitive assessment more than 7 days after their last dose of study-medication.
5. Population set without participants who had their follow-up cognitive assessment more than 7 days after their last dose of study-medication; this set is used for the primary analysis.
6. Population set without participants that have important protocol violations (i.e. psychiatric disease or history of drug abuse prior to inclusion).

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E. Baseline characteristics by treatment group. Data are n (%) or mean±SD unless otherwise specified.

	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
Age, years		
<60	128 (16.0)	103 (13.8)
≥ 60 to < 65	137 (17.1)	137 (18.4)
≥ 65 to <70	195 (24.4)	191 (25.6)
≥ 70 to 75	174 (21.8)	165 (22.1
≥75 to < 85	156 (19.5)	139 (18.7)
≥85	10 (1.3)	10 (1.3)
Region		
Europe	490 (61.3)	448 (60.1)
North America	310 (38.8)	297 (39.9)
Race, n (%)		
White	739 (92.4)	681 (91.4)
Asian	13 (1.6)	18 (2.4)
Black/African American	42 (5.3)	41 (5.5)
Other¤	6 (0.8)	5 (0.7)
Ethnicity, n (%)		
Hispanic/Latino	62 (7.8)	78 (10.5)
Not Hispanic/Latino	738 (92.3)	667 (89.5)
Medical history		
History of myocardial infarction	152 (19.0)	131 (17.6)
History of ischemic/hemorrhagic stroke	74 (9.3)/8 (1.0)	67 (9.0)/9 (1.2)
Atrial fibrillation	101 (12.6)	115 (15.4)
History of heart failure	133 (16.6)	119 (16.0)
Smoking status¤¤		
Never smoked	399 (49.9)	337 (45.2)
Ex-smoker	313 (39.1)	310 (41.6)
Current smoker	87 (10.9)	98 (13.2)
Alcohol consumption		
No consumption	570 (71.3)	489 (65.6)
Any consumption	230 (28.7)	254 (34.1)
Education level¤¤¤		
High school or less	517 (64.6)	481 (64.6)
College or higher	283 (35.4)	264 (35.4)
Weight, kg	92.2±17.5	93.4±18.2
Waist circumference, cm	110.2±13.9	111.3±13.6
BMI, kg/m^2	32.5±5.1	32.8±5.3
BMI, kg/m^2 ¤¤¤¤		
<25 kg/m^2	48 (6.0)	44 (5.9)
≥25 to < 30 kg/m^2	221 (27.6)	206 (27.7)
≥30 to <35 kg/m^2	291 (36.4)	238 (31.9)
≥35 to <40 kg/m^2	175 (21.9)	181 (24.3)
≥40 to <45 kg/m^2	64 (8.0)	76 (10.2)

≥ 45 kg/m^2	1 (0.1)	0 (0.0)
Mini mental state examination 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 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
eGFR (MDRD)		
≥ 90 ml/min/1.73 m^2	71 (8.9)	59 (7.9)
≥60 - <90 ml/min/1.73 m^2	191 (23.9)	158 (21.2)
≥ 30 - <60 ml/min/1.73 m^2	434 (54.3)	427 (57.3)
≥ 15 − <30 ml/min/1.73 m^2	104 (13.0)	99 (13.3)
< 15 ml/min/1.73 m^2	0 (0.0)	2 (0.3)
UACR, mg/g, median (25th–75th percentile)	102.7 (27.0, 405.8)	123.9 (35.4, 522.1)
UACR		
< 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
≤ 5 years	112 (14.0)	81 (10.9)
> 5–≤10 years	161 (20.1)	151 (20.3)
> 10 years	527 (65.9)	513 (68.9)
HbA1c, % [mmol/mol]	7.8±0.9 [61.5±10.1]	7.8±0.9 [61.3±10.0]
HbA1c, n (%)		
< 7% [< 53.0 mmol/mol]	175 (21.9)	153 (20.5)
7 − <8% [53.0 - < 63.9 mmol/mol]	313 (39.1)	303 (40.7)
8 − <9% [63.9 - <74.9 mmol/mol]	203 (25.4)	195 (26.2)
≥ 9% [≥ 74.9 mmol/mol]	109 (13.7)	94 (12.6)
Fasting plasma glucose, mg/dl	152.9±41.2	152.0±41.8
Hyper- or hypoglycaemia requiring hospitalization last 2 years	21 (2.6)	18 (2.4)
Glucose lowering therapies		
Metformin	367 (45.8)	353 (47.2)
Sulphonylurea	253 (31.6)	242 (32.3)
Any insulin	481 (60.1)	453 (60.8)
Insulin dose	48.8±38.0	47.4±30.7
Cardiovascular therapies		
Antiplatelets	565 (69.4)	514 (67.9)
Statins	640 (78.8)	614 (81.3)
Antihypertensives, n (%)	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
Total cholesterol, mmol/L [mg/dL]	4.3±1.1 [166.9±44.4]	4.3±1.1 [165.1±41.1]
LDL cholesterol, mmol/L [mg/dL]	2.2±0.9 [85.5±34.1]	2.2±0.9 [85.1±34.1]
HDL cholesterol, mmol/L [mg/dL]	1.2±0.3 [45.1±12.9]	1.2±0.3 [44.7±13.2]
Triglycerides, mmol/L [mg/dL]	2.10±1.62 [185.1±143.3]	2.02±1.21 [177.5±106.7]

¤:American Indian/Alaska Native or Native Hawaiian/other Pacific Islander; ¤¤: smoking status missing for 1 linagliptin patient; ¤¤¤: defined by < or ≥ median of years formal education in participants with age ≥ 60 years ¤¤¤¤:BMI missing for 3 (0.1%) placebo patients; ¤¤¤¤¤: according the diabetes-specific dementia risk score estimate. *CES-D:* Centre for Epidemiologic Studies Depression Scale ; *BMI* body-mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MDRD* Modification of Diet in Renal Disease study equation, *UACR* urinary albumin-to-creatinine ratio.

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Section F. Baseline characteristics for the main analysis population contrasted with baseline characteristics of F1) those who dropped out of the study post-baseline and F2) those who died between first and second cognitive assessment.

Table F1. Select baseline characteristics by treatment group for the main analysis population contrasted with those who dropped out of the study post-baseline. Data are n (%) or mean±standard deviation unless otherwise stated.

	Primary analysis population		**Population dropping out**	
	Linagliptin (n=800)	**Placebo (n=745)**	**Linagliptin (n=371)**	**Placebo (n=412)**
Male/Female	503 (62.9)/ 297 (37.1)	501 (67.2)/ 244 (32.8)	240 (64.7)/ 131 (35.3	285 (69.2)/ 127 (30.8)
Age, years	67.8±8.25	67.7±7.99	68.4±9.82	66.6±9.39
Medical history				
History of myocardial infarction*	205 (25.6)	168 (22.6)	67 (18.1)	89 (21.6)
History of stroke*	87 (10.9)	77 (10.3)	33 (8.9)	45 (10.9)
Atrial fibrillation	101 (12.6)	115 (15.4)	44 (11.9)	60 (14.6)
Clinical diagnosis of of heart failure	133 (16.6)	119 (16.0)	92 (24.8)	100 (24.3)
Education level				
High school or less¤	517 (64.6)	481 (64.6)	235 (63.3)	269 (65.3)
College or higher¤	283 (35.4)	264 (35.4)	136 (36.7)	143 (34.7)
BMI, kg/m^2	32.5±5.1	32.8±5.3	32.9±5.6	33.0±5.5
Mini mental state examination score	28.3±1.7	28.2±1.8	28.1±1.8	28.1±1.8
10-year dementia risk¤¤, %	25.0±15.1	25.0±15.2	29.5±17.1	26.6±15.7
Clinical diagnosis of depression previous 2 years	55 (6.9)	57 (7.7)	50 (13.5)	48 (11.7)
Depression score according to CES-D	9.9±8.5	10.2±8.3	12.1±8.8	11.5±9.5
< 16	623 (77.9)	569 (76.4)	250 (67.4)	304 (73.8)
≥ 16	174 (21.8)	173 (23.2)	118 (31.8)	106 (25.7)
Missing	3 (0.4)	3 (0.4)	3 (0.8)	2 (0.5)
Renal function characteristics				
eGFR (MDRD), ml/min/1.73 m^2	52.7±23.2	51.3±22.8	44.9±18.6	47.0±21.9
UACR, mg/g, median (25th–75th percentile)	102.7 (27.0, 405.8)	123.9 (35.4, 522.1)	214.2 (44.2-882.3)	198.2 (52.7-893.8)
UACR, n (%)				
< 30 mg/g	212 (26.5)	172 (23.1)	69 (18.6)	66 (16.0)

30−300 mg/g	349 (43.6)	320 (43.0)	143 (38.5)	170 (41.3)
> 300 mg/g	239 (29.9)	253 (34.9)	158 (42.6)	176 (42.7)
Diabetes related characteristics				
Type 2 diabetes duration, years	14.8±9.2	15.4±9.4	17.6±10.6	15.2±9.2
HbA1c, % [mmol/mol]	7.8±0.9 [61.5±10.1]	7.8±0.9 [61.3±10.0]	7.9±0.9 [62.5±10.1]	8.0±1.0 [63.7±11.0]
Fasting plasma glucose, mg/dl	152.9±41.2	152.0±41.8	153.9±43.7	157.2±50.1
Hyper- or hypoglycaemia requiring hospitalization last 2 years	21 (2.6)	18 (2.4)	12 (3.2)	15 (3.6)
Glucose lowering therapies				
Any glucose-lowering therapy	763 (95.4)	715 (96.0)	362 (97.6)	403 (97.8)
Metformin	367 (45.9)	353 (47.4)	134 (36.1)	159 (38.6)
Sulphonylurea	253 (31.6)	242 (32.5)	102 (27.5)	122 (29.6)
Any insulin	498 (62.3)	466 (62.6)	267 (72.0)	290 (70.4)
Insulin dose	48.8±38.0	47.4±30.7	47.2±34.2	57.3(43.2)
Cardiovascular therapies				
Antiplatelets	565 (70.6)	514 (69.0)	250 (67.4)	276 (67.0)
Statins	640 (80.0)	614 (82.4)	293 (79.0)	321 (78.6)
Antihypertensives	769 (96.1)	727 (97.6)	360 (97.0)	397 (96.4)
Systolic blood pressure, mmHg	140.6±17.2	141.5±17.5	140.9±18.1	141.2±18.2
Diastolic blood pressure, mmHg	77.3±10.4	76.8±10.5	76.2±10.8	76.6±10.7
LDL cholesterol, mmol/L [mg/dL]	2.2±0.9 [85.5±34.1]	2.2±0.9 [85.1±34.1]	2.3±0.9 [86.9±33.2]	2.3±1.1 [87.8±40.6]

*: in conjunction with albuminuria. ¤: defined as < or ≥ median of years formal education in participants with age ≥ 60 years, ¤¤: according the diabetes-specific dementia risk score estimate. *CES-D*: Centre for Epidemiologic Studies Depression Scale. *BMI* body-mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MDRD* Modification of Diet in Renal Disease study equation, *UACR* urinary albumin-to-creatinine ratio.

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Table F2. Select baseline characteristics for the overall main analysis population contrasted with those who died post baseline before second cognitive assessment. Data are n (%) or mean±standard deviation unless otherwise stated.

	Primary analysis population (n=1545)	**Participants who died before second cognitive assessment (n=223)**
Male/Female	1004 (65.0)/ 541 (35.0)	162 (72.6)/ 61 (27.4)
Age, years	67.8±8.1	69.0±9.5
Medical history		
History of myocardial infarction*	373 (24.1)	49 (22.0)
History of stroke*	164 (10.6)	23 (10.3)
Atrial fibrillation	216 (14.0)	52 (23.3)
Clinical diagnosis of of heart failure	252 (16.3)	71 (31.8)
Education level		
High school or less¤	998 (64.6)	148 (66.4)
College or higher¤	547 (35.4)	75 (33.6)
BMI, kg/m^2	32.6±5.2	32.6±5.8
Mini mental state examination score	28.3±1.7	28.0±1.8
10-year dementia risk¤¤, %	25.0±15.1	29.7±16.9
Clinical diagnosis of depression previous 2 years	112 (7.2)	20 (9.0)
Depression score according to CES-D	10.1±8.4	12.8±9.4
< 16	1192 (77.2)	150 (67.3)
≥ 16	347 (22.5)	72 (32.3)
Missing	6 (0.4)	1 (0.4)
Renal function characteristics		
eGFR (MDRD), ml/min/1.73 m^2	52.0±23.0	42.8±20.0
UACR, mg/g, median (25th–75th percentile)	113.3 (30.1-474.3)	231.9 (67.3-941.6)
UACR, n (%)		
< 30 mg/g	384 (24.9)	35 (15.7)
30−300 mg/g	669 (43.3)	90 (40.4)
> 300 mg/g	492 (31.8)	98 (43.9)
Diabetes related characteristics		

Type 2 diabetes duration, years	15.1±9.3	17.5±10.1
HbA1c, % [mmol/mol]	7.8±0.9 [61.4±10.1]	7.9±0.9 [62.9±9.9]
Fasting plasma glucose, mg/dl	152.5±41.5	153.3±47.5
Hyper- or hypoglycaemia requiring hospitalization last 2 years	39 (2.5)	11 (4.9)
Glucose lowering therapies		
Any glucose-lowering therapy	1478 (95.7)	218 (97.8)
Metformin	720 (46.6)	67 (30.0)
Sulphonylurea	495 (32.0)	51 (22.9)
Any insulin	964 (62.4)	175 (78.5)
Insulin dose	48.1±34.7	50.6±44.0
Cardiovascular therapies		
Antiplatelets	1079 (69.8)	154 (69.1)
Statins	1254 (81.2)	173 (77.6)
Antihypertensives	1496 (96.8)	219 (98.2)
Systolic blood pressure, mmHg	141.0±17.4	139.7 ± 19.9
Diastolic blood pressure, mmHg	77.1±17.4	74.9 ± 10.7
LDL cholesterol, mmol/L [mg/dL]	2.2±0.9 [85.3±34.1]	2.2±0.9 [86.5±33.6]

*: in conjunction with albuminuria. ¤: defined as < or ≥ median of years formal education in participants with age ≥ 60 years, ¤¤: according the diabetes-specific dementia risk score estimate. *CES-D*: Centre for Epidemiologic Studies Depression Scale. *BMI* body-mass index, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MDRD* Modification of Diet in Renal Disease study equation, *UACR* urinary albumin-to-creatinine ratio.

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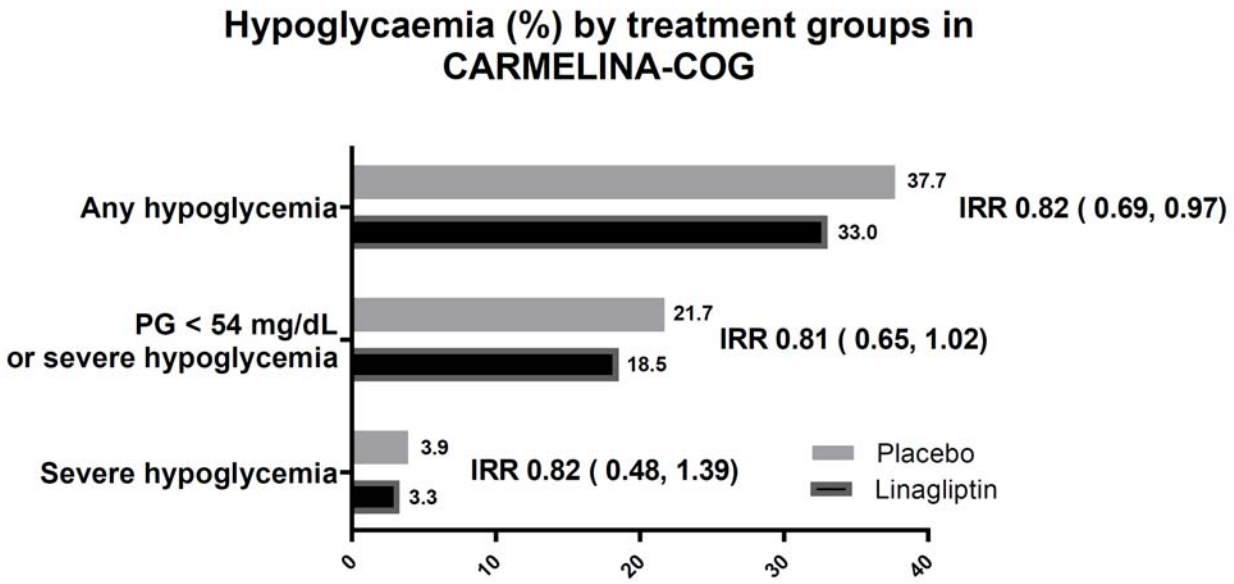
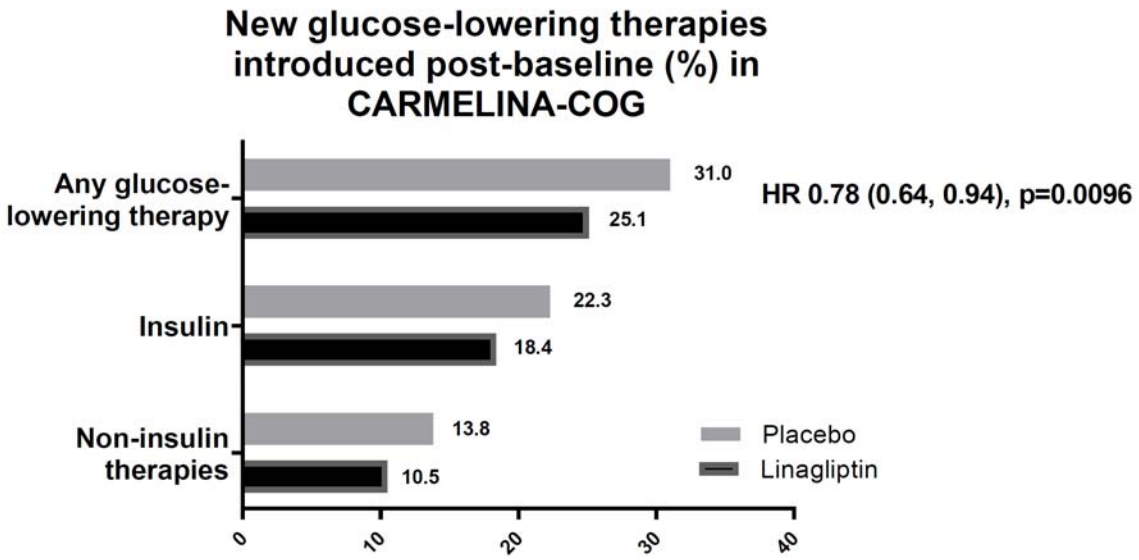
G. Hypoglycemia (A) and new-onset glucose lowering therapies (B) per treatment group. HR – hazard ratio, IRR – incidence rate ratio.

A



B



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H. Primary and secondary endpoints for accelerated cognitive decline (ACD)

	Linagliptin (n = 800)	Placebo (n = 745)		
	N (%)	N (%)	Comparison OR [95% CI] 1)	*p*- value
Primary endpoint:				
Incidence of ACD at EOT based on 16th percentile of RBI score	227 (28.4)	218 (29.3)	0.96 [0.77, 1.19]	0.69
Secondary and further endpoints :				
Incidence of ACD based on z-score at EOT[1]	273 (34.1)	274 (36.8)	0.89 [0.72, 1.10]	0.28
Incidence of ACD at EOT based on 10th percentile of RBI score[2]	144 (18.0)	140 (18.8)	0.95 [0.73, 1.23]	0.68
Incidence of ACD at EOT based on MMSE[3]	73 (9.1)	62 (8.4)	1.10 [0.77, 1.57]	0.59
Further endpoints:				
Incidence of depression based on the CES-D[4]	194 (24.5)	189 (25.6)	0.94 [0.74, 1.18]	0.58
Changes (Δ) from baseline in z-scores at EOT [5]	Mean (SE) 2)	Mean (SE) 2)	Difference linagliptin−placebo, adjusted mean (SE) [95% CI] 2)	
Δ z-score MMSE	-0.26 (0.05)	-0.28 (0.05)	0.02 (0.07)[-0.11, 0.14]	0.82
Δ z-score A&E	-0.02 (0.02)	-0.05 (0.02)	0.03 (0.03) [-0.03, 0.09]	0.29
Δ z-score TMT A	0.05 (0.02)	0.01 (0.02)	0.03 (0.03) [-0.03, 0.10]	0.28
Δ z-score TMT B	0.06 (0.03)	0.05 (0.03)	0.01 (0.04) [-0.06, 0.08]	0.81
Δ z-score TMT ratio	0.07 (0.03)	0.08 (0.03)	-0.01 (0.05) [-0.09, 0.08]	0.90
Δ z-score VFT animals -15 seconds	-0.10 (0.03)	-0.07 (0.03)	-0.03 (0.05) [-0.12, 0.06]	0.53
Δ z-score VFT FAS -15 seconds	0.04 (0.02)	0.02 (0.02)	0.02 (0.03) [-0.05, 0.08]	0.58
Δ z-score VFT animals - 60 seconds	-0.13 (0.03)	-0.13 (0.03)	<0.01 (0.04) [-0.08, 0.09]	0.94
Δ z-score VFT FAS - 60 seconds	0.02 (0.02)	-0.03 (0.02)	0.05 (0.03) [-0.02, 0.11]	0.15
Δ z-score VFT overall - 15 seconds	-0.03 (0.02)	-0.03 (0.03)	-0.01 (0.03) [-0.07, 0.06]	0.88
Δ z-score VFT overall - 60 seconds	-0.06 (0.02)	-0.09 (0.02)	0.03 (0.03) [-0.03, 0.10]	0.31
Δ z-score CES-D score	0.07 (0.03)	0.10 (0.03)	-0.03 (0.05) [-0.12, 0.06]	0.54
	N (%)	N (%)	Comparison OR [95% CI] 1)	
Incidence of ACD adjusted for hypoglycemic events[5]	227 (28.4)	218 (29.3)	0.95 [0.76 – 1.19]	0.66
Incidence of ACD adjusted for cardiovascular events[6]	227 (28.4)	218 (29.3)	0.96 [0.77-1.19]	0.69

For comparison: 1) Odds Ratio (OR) along with the 95% Profile Likelihood Confidence Interval (CI) and the two-sided p-value using a logistic regression including treatment and region as a factors , or 2) adjusted means (SD) along with the 95% Confidence Interval (CI) and the two-sided p-value are shown using an ANCOVA model with treatment, region and baseline score as factors. [1]Incidence of accelerated cognitive decline based on 16th percentile of z-score for MMSE and/or A&E at EOT. [2] Incidence of accelerated cognitive decline at EOT based on 10th percentile of RBI score. [3]Incidence of accelerated cognitive decline at EOT based on MMSE score of < 24 or a decline of > 4 points in MMSE score at EOT relative to baseline. [4]Incidence of depression based on the Center for Epidemiological Studies Depression Scale (CES-D) at baseline and EOT, where depression is defined as a score of at least (≥) 16. [5]Changes (Δ) from baseline in z-scores at EOT. [5,6]Hypoglycemic events and cardiovascular events are added as covariates in two separate models to the logistic regression model as used for the primary analysis.

MMSE: Mini-Mental State Examination VFT: Verbal Fluency Test TMT: Trail Making Test TMT ratio:(TMT-B – TMT-A) / TMT-A CES-D: Centre for Epidemiologic Studies Depression Scale, ACD = cognitive accelerated decline

SUPPLEMENTARY DATA

I. Changes in MMSE, TMT scores and VFT scores by accelerated cognitive decline in primary analysis population regardless of treatment group

	Accelerated cognitive decline: Yes (n=445)	**Accelerated cognitive decline: No (n=1100)**
	Mean (SD)	Mean (SD)
MMSE score		
Baseline	27.8 (1.9)	28.4 (1.6)
Follow-up	25.6 (3.2)	28.6 (1.5)
Change from baseline	-2.2 (3.2)	0.2 (1.5)
VFT letter 60 (in seconds)		
Baseline	7.5 (4.0)	8.6 (4.2)
Follow-up	6.7 (3.4)	9.0 (4.1)
change	-0.9 (3.0)	0.3 (2.6)
VFT animals 60 (in seconds)		
Baseline	14.6 (6.3)	16.1 (6.2)
Follow-up	12.4 (5.4)	15.9 (5.9)
change	-2.5 (5.8)	-0.2 (5.9)
TMT A (in seconds)		
Baseline	87.7 (62.2)	88.0 (70.5)
Follow-up	93.3 (70.6)	92.6 (70.0)
change	6.1 (51.70)	3.0 (33.9)
TMT B (in seconds)		
Baseline	168.2 (91.0)	161.9 (92.4)
Follow-up	197.7 (95.2)	158.9 (87.2)
change	34.6 (74.9)	-2.1 (59.8)
TMT ratio[1]		
Baseline	1.4 (1.2)	1.3 (1.1)
Follow-up	2.1 (1.3)	1.0(0.7)
change	0.87 (1.4)	-0.2 (0.9)
CES-D score		
Baseline	11.1 (8.6)	9.6 (8.3)
Follow-up	13.1 (9.7)	9.9 (8.7)
change	2.0 (9.5)	0.3 (8.3)

Results shown in Mean (SD); MMSE: Mini-Mental State Examination, VFT: Verbal Fluency Test, VFT letter 60: averaged VFT scores for the letters F, A and S in 60 seconds , VFT animals 60: VFT score for the category animals in 60 seconds, TMT: Trail Making Test. [1]TMT ratio:(TMT-B – TMT-A) / TMT-A CES-D: Centre for Epidemiologic Studies Depression Scale