Effects of Linagliptin on Cardiovascular and Kidney Outcomes in People With Normal and Reduced Kidney Function: Secondary Analysis of the CARMELINA Randomized Trial

Vlado Perkovic,[1] Robert Toto,[2] Mark E. Cooper,[3] Johannes F.E. Mann,[4,5] Julio Rosenstock,[6] Darren K. McGuire,[2] Steven E. Kahn,[7] Nikolaus Marx,[8] John H. Alexander,[9] Bernard Zinman,[10,11] Egon Pfarr,[12] Sven Schnaidt,[13] Thomas Meinicke,[13] Maximillian von Eynatten,[12] Jyothis T. George,[12] Odd Erik Johansen,[14] and Christoph Wanner,[15] on behalf of the CARMELINA investigators

[1]Faculty of Medicine, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[2]University of Texas Southwestern Medical Center, Dallas, TX
[3]Department of Diabetes, Central Clinical School, Monash University, Melbourne, Victoria, Australia
[4]Kuratorium für Dialyse Kidney Centre, Munich, Germany
[5]Department of Nephrology, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany
[6]Dallas Diabetes Research Center, Dallas, TX
[7]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA
[8]Department of Internal Medicine I, University Hospital Aachen, RWTH Aachen University, Aachen, Germany
[9]Duke Clinical Research Institute, Duke Health, Durham, NC
[10]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
[11]Division of Endocrinology, University of Toronto, Toronto, Ontario, Canada
[12]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
[13]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
[14]Boehringer Ingelheim Norway KS, Asker, Norway
[15]Division of Nephrology, Department of Medicine, Würzburg University Clinic, Würzburg, Germany

Corresponding author: Vlado Perkovic, vlado.perkovic@unsw.edu.au

Received 9 February 2020 and accepted 6 April 2020

Clinical trial reg. no. NCT01897532, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.12129993.

OBJECTIVE

Type 2 diabetes is a leading cause of kidney failure, but few outcome trials proactively enrolled individuals with chronic kidney disease (CKD). We performed secondary analyses of cardiovascular (CV) and kidney outcomes across baseline estimated glomerular filtration rate (eGFR) categories ($\geq$60, 45 to <60, 30 to <45, and <30 mL/min/1.73 m^2) in Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA), a cardiorenal placebo-controlled outcome trial of the dipeptidyl peptidase 4 inhibitor linagliptin (NCT01897532).

RESEARCH DESIGN AND METHODS

Participants with CV disease and/or CKD were included. The primary outcome was time to first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke (three-point major adverse CV event [3P-MACE]), with a secondary outcome of renal death, end-stage kidney disease, or sustained $\geq$40% decrease in eGFR from baseline. Other end points included progression of albuminuria, change in HbA$_{1c}$, and adverse events (AEs) including hypoglycemia.

RESULTS

A total of 6,979 subjects (mean age 65.9 years; eGFR 54.6 mL/min/1.73 m^2; 80.1% albuminuria) were followed for 2.2 years. Across eGFR categories, linagliptin as compared with placebo did not affect the risk for 3P-MACE (hazard ratio 1.02 [95% CI 0.89, 1.17]) or the secondary kidney outcome (1.04 [0.89, 1.22]) (interaction P values >0.05). Regardless of eGFR, albuminuria progression was reduced with linagliptin, as was HbA$_{1c}$, without increasing risk for hypoglycemia. AEs were balanced among groups overall and across eGFR categories.

CONCLUSIONS

Across all GFR categories, in participants with type 2 diabetes and CKD and/or CV disease, there was no difference in risk for linagliptin versus placebo on CV and kidney events. Significant reductions in risk for albuminuria progression and HbA$_{1c}$ and no difference in AEs were observed.

Results from recent cardiovascular (CV) outcome trials of glucose-lowering medications have helped to define the relative benefit and risks of these agents (1). This in turn has informed updated treatment guidelines and recommendations from multiple societies (2–4) with a primary focus on the CV benefits of glucose-lowering therapies rather than glycemic outcomes. Up to 40% of people with type 2 diabetes will develop chronic kidney disease (CKD) (5), and a substantial number will progress to advanced stages of CKD, including end-stage kidney disease (ESKD) (6). People with type 2 diabetes and any level of CKD have a substantially increased risk of death, CV events, heart failure (HF) events, and kidney failure (7,8), as well as a reduced quality of life (9,10). In addition, individuals with diabetes and CKD tend to be less well controlled with regards to CV risk factors and have a lower likelihood of glycemic goal attainment, while being at higher risk for hypoglycemia (11,12). This is particularly marked for those with advanced kidney disease. There is thus a substantial need to develop treatments that might preserve kidney function in diabetes and also treatments that improve safely glycemic control in this high-risk population. However, data regarding the safety and efficacy of glucose-lowering therapies in people with existing kidney disease are generally limited because the vast majority of recent CV outcome trials in type 2 diabetes did not proactively recruit those with CKD (13). Furthermore, although data from trials assessing different intensities of glucose-lowering therapy have suggested that more intensive glucose lowering reduces albuminuria, effects on major renal outcomes have been inconsistent (14–17).

Linagliptin is a dipeptidyl peptidase 4 inhibitor (DPP-4i) that undergoes enterohepatic cycling, with a large majority (85%) eliminated via biliary excretion (18), and does not need dose adjustment in people with CKD. Analyses of pooled data from previous studies have supported the hypothesis that linagliptin may lower albuminuria (19) and might also prevent progression of kidney disease (20). The Cardiovascular and Renal Microvascular Outcome Study With Linagliptin (CARMELINA) trial, for which primary results were reported previously (8,21), enrolled a population enriched for the presence of CKD, including advanced CKD. That trial confirmed the CV and kidney safety of linagliptin. In this analysis, we report effects on primary CV and secondary kidney outcomes and on a comprehensive range of further pre- and post hoc–specified kidney outcomes as well as glycemic data, overall and in subgroups defined by the presence or absence of reduced kidney function.

RESEARCH DESIGN AND METHODS

Design and Procedures

The design and primary results have been reported previously (21,22). In brief, CARMELINA was a multicenter, randomized, double-blind clinical trial in adults with type 2 diabetes (HbA$_{1c}$ 6.5–10.0% [48–86 mmol/mol]) at high risk for CV and kidney disease, defined as history of vascular disease and urinary albumin-to-creatinine ratio (UACR) >30 mg/g (or equivalent); estimated glomerular filtration rate (eGFR) 45–75 mL/min/1.73 m^2 and UACR >200 mg/g (or equivalent); or eGFR 15–45 regardless of UACR. It was conducted at 605 centers in 27 countries. Investigators were encouraged to use additional CV medications and medications for glycemic control (except DPP-4i, glucagon-like peptide 1 [GLP-1] receptor agonists, and sodium–glucose cotransporter 2 [SGLT2] inhibitors) according to applicable standard of care throughout the trial. Participants who prematurely discontinued study medication were followed for ascertainment of CV and key secondary kidney outcome events. Attempts were made to collect vital status information on every randomized patient at study completion, in compliance with local law and regulations. The protocol was approved by Institutional Review Boards or Ethics Committees for each participating site, and all participants provided written informed consent for trial participation.

Outcomes

CV and Kidney Outcomes and Adjudication of Kidney Events

The trial was event driven, and follow-up continued until a minimum of 611 participants had experienced a primary CV outcome event (time to first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke [three-point major adverse CV event (3P-MACE)]). The key secondary outcome, a kidney outcome that was part of the confirmatory testing strategy, was time to first occurrence of a composite of adjudication-confirmed kidney failure outcome (ESKD or renal death) or a sustained decrease of ≥40% in eGFR from baseline. It was anticipated that at least 432 participants would experience the key kidney outcome event during the same period needed to accrue the ≥611 3P-MACE. This would yield a power of 85% to test for superiority of linagliptin versus placebo for the key secondary kidney outcome at a one-sided α-level of 2.5%, assuming a hazard ratio (HR) of 0.75.

To ensure the highest standard of ascertainment for renal effects of linagliptin versus placebo, the following kidney outcomes were prospectively captured and centrally adjudicated by experts masked to study treatment assignment: *1*) ESKD, *2*) renal death, *3*) sustained decrease of eGFR of ≥40%, and *4*) sustained decrease of eGFR of ≥50% (for all definitions, see Supplementary Section A).

Sensitivity Analysis of Key Secondary Kidney Outcome and Further Kidney Outcomes

For the key secondary kidney outcome, prespecified sensitivity analyses were conducted for participants with a minimum treatment duration of 30 days (i.e., analyses that considered data from individuals being on investigational product for at least 30 days; on-treatment set) and by censoring at day 0 and day 30 after last dose of investigational product taken, respectively (i.e., analysis that considered data from individuals until 0 or 30 days, respectively, after last study medication intake). A robustness analysis of this outcome was also assessed using variants of eGFR (i.e., with sustained decrease of ≥50% or ≥30% in eGFR from baseline), doubling of serum creatinine from baseline (equivalent to a ≥57% reduction in eGFR), or sustained eGFR <10 mL/min/1.73 m^2.

Additional prespecified and post hoc kidney outcomes (Supplementary Table B1) include the composite of renal death or ESKD, time to first doubling of serum creatinine regardless of other renal events, effect on geometric mean (gMean) UACR, albuminuria progression and regression, and effects on eGFR as assessed by a slope analysis. Slope changes were further analyzed according to both acute change (defined as the effect over the first 12 weeks of treatment) and chronic change (defined as the effect between week 12 of

treatment and end of treatment). Post hoc sensitivity analyses were performed to assess if changes in albuminuria depended on HbA_{1c} changes.

Several outcome analyses were performed to assess the impact of requiring events to be sustained. Sustainability was fulfilled when at least two consecutive laboratory assessments met the definition of the end point. The confirmatory assessment had to be performed at least 28 days after the initial assessment that qualified for the event (i.e., assessments performed <28 days after the initial drop would not qualify for a sustained event). The outcome definition was met without a confirmatory assessment in case: 1) the decrease happened at trial end, 2) there was an occurrence of death after the initial decrease, or 3) the initial decrease happened at the last available measurement (for sustained albuminuria end points).

Efficacy and Safety

Additional outcomes were change from baseline in HbA_{1c} and occurrence of adverse events (AEs) and hypoglycemia. The latter two were captured based on investigator-reported events and coded using the Medical Dictionary for Drug Regulatory Activities version 20.1.

Subgroup Analysis

Prespecified subgroup analyses were done for participants by GFR categories according to Kidney Disease: Improving Global Outcomes (KDIGO) (23): G ≤ 2: >60; G3a: 45–60; G3b: 30–45; and G ≥ 4: <30 mL/min/1.73 m², as well as dichotomously by eGFR >60 versus ≤60 mL/min/1.73 m². Because the published evidence base is particularly scarce in those with eGFR <45 mL/min/1.73 m², post hoc analyses were also done for participants with eGFR <45 versus ≥45 mL/min/1.73 m².

Statistical Analyses

Time-to-event outcomes were analyzed using Cox proportional hazards regression models, with randomized treatment and geographical region as factors. For end points including hospitalization for HF, the factor history of HF (yes or no) was included in addition. For subgroup analyses, an additional factor for subgroup as well as a subgroup-by-treatment interaction term was included in the regression models. Censoring was applied the day a participant was last

known to be free of the specific outcome event. All analyses were performed using the intention-to-treat principle, modified to exclude randomized participants who did not take at least one dose of study medication (treated set). Handling of missing data is described in the statistical analysis plan published elsewhere (21).

A formal test of heterogeneity of the treatment effect among subgroups was performed for each subgroup analysis. A two-sided $P < 0.05$ was considered significant for all analyses with no adjustments made for multiple testing. Iteratively measured continuous parameters were analyzed using mixed-effect models for repeated measures including randomized treatment, region, week, treatment-by-week interaction, and linear covariates of baseline measurement and baseline-by-week interaction in the model. Overall safety assessments were conducted using descriptive statistics for AEs. Analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Among 6,979 randomized and treated participants, a total of 4,348 (62.3%) had a baseline eGFR <60 mL/min/1.73 m², including 3,000 (43.0%) with eGFR <45 mL/min/1.73 m². The proportions with normo-, micro-, and macroalbuminuria at baseline were 1,392 (19.9%), 2,894 (41.5%), and 2,690 (38.5%), respectively. The baseline characteristics by GFR categories (Table 1 and Supplementary Table C1) were balanced across randomized groups. Compared with participants with preserved kidney function, those with lower eGFR tended to be older, have higher HbA_{1c} and baseline blood pressure, longer duration of diabetes, and higher levels of albuminuria. Overall, the median observation time and treatment exposure in the trial were 2.2 and 1.9 years, respectively, and were consistent across groups according to GFR categories (Supplementary Table D1). Median observation time until occurrence of first component of 3P-MACE was 2.1 years for both linagliptin and placebo and for the key secondary kidney outcome was 1.9 and 1.7 years, respectively, with overall follow-up data available of 98.7% (3P-MACE) and 88.0% (key kidney outcome), respectively. Vital status was known in 99.7% at study completion and did not differ by GFR groups (Supplementary

Table D1). Premature discontinuation of study medication was 23.9% and 27.4% in the linagliptin and placebo group, respectively, with similar proportions across eGFR categories (Supplementary Table D1).

CV and Kidney Outcomes by Baseline Kidney Function

CV Outcomes

Incidence rates for the primary CV composite outcome 3P-MACE and the other CV, HF, and mortality outcomes increased with lower levels of baseline renal function (Supplementary Fig. E1). Consistent neutral effects on the primary CV outcome 3P-MACE (HR 1.02 [95% CI 0.89, 1.17]; $P = 0.7398$) as well as on further CV or HF outcomes were observed across all renal subgroups comparing linagliptin with placebo (Fig. 1A and Supplementary Fig. F1), with some evidence of heterogeneity observed for all-cause mortality (P for interaction 0.0289 and 0.0547 in the four- and two-eGFR category analyses, respectively), which likely is a play of chance given the many subgroup analyses conducted without adjustment and the lack of a consistent risk gradient by declining GFR categories.

Kidney Outcomes

The key kidney composite outcome of 40% reduction in eGFR, ESKD, or renal death was not different among the groups (HR 1.04 [95% CI 0.89, 1.22]; $P = 0.6164$) (Fig. 1B), including across all kidney function subgroups (Fig. 1B and Supplementary Fig. F1). As with the CV outcomes, higher rates of the kidney composite outcome were observed with lower kidney function (Supplementary Fig. E1). Sensitivity analyses considered minimum treatment durations or various approaches to censoring after last dose of study drug taken (Supplementary Fig. F2), as well as undertaking robustness analyses using other cutoffs of eGFR reduction other than a 40% reduction, including doubling of serum creatinine and a 30% and 50% eGFR decrease (Supplementary Fig. F3), and found no difference between linagliptin and placebo. The same was true for different definitions of various composite outcomes, including sustained ESKD or renal death (linagliptin, 136 [of which 135 were ESKD] and incidence rate 1.8/ 100 patient-years vs. placebo, 154 [of which 152 were ESKD] and incidence rate 2.0/100 patient-years) (HR 0.87

Table 1—Baseline characteristics by eGFR categories <30, 30 to <45, 45 to <60, and ≥60 mL/min/1.73 m²

	eGFR <30	eGFR 30–<45	eGFR 45–<60	eGFR ≥60	Overall
N (%)	1,062 (15.2)	1,938 (27.8)	1,348 (19.3)	2,631 (37.7)	6,979 (100)
Age, years	66.7 (9.5)	68.8 (8.6)	66.9 (8.6)	62.8 (8.6)	65.9 (9.1)
Male	568 (53.5)	1,121 (57.8)	885 (65.7)	1,816 (69.0)	4,390 (62.9)
Region					
Europe (including South Africa)	345 (32.5)	788 (40.7)	552 (40.9)	1,249 (47.5)	2,934 (42.0)
Latin America	409 (38.5)	563 (29.1)	426 (31.6)	912 (34.7)	2,310 (33.1)
North America	210 (19.8)	419 (21.6)	268 (19.9)	283 (10.8)	1,180 (16.9)
Asia	98 (9.2)	168 (8.7)	102 (7.6)	187 (7.1)	555 (8.0)
eGFR (MDRD), mL/min/1.73 m²	23.4 (4.2)	37.2 (4.1)	51.4 (4.4)	81.6 (16.7)	54.6 (25.0)
<30	1,062 (100)	0	0	0	1,062 (15.2)
<15	21 (2.0)	0	0	0	21 (0.3)
UACR, mg/g, median (25th–75th percentile)	585 (77–2,039)	125 (24–719)	223 (60–731)	126 (46–412)	162 (44–728)
UACR (mg/g)*					
<30	159 (15.0)	535 (27.6)	214 (15.9)	484 (18.4)	1,392 (19.9)
30–300	293 (27.6)	688 (35.5)	566 (42.0)	1,347 (51.2)	2,894 (41.5)
>300	609 (57.3)	714 (36.8)	568 (42.1)	799 (30.4)	2,690 (38.5)
HbA$_{1c}$, %	7.9 (1.0)	7.9 (1.0)	8.0 (1.0)	8.0 (1.0)	8.0 (1.0)
HbA$_{1c}$, mmol/mol	62.5 (10.8)	62.4 (10.7)	63.7 (11.0)	64.3 (11.2)	63.4 (11.0)
Diabetes duration, years	17.3 (9.8)	16.6 (9.7)	15.4 (9.5)	12.0 (8.4)	14.8 (9.5)
BMI, kg/m²	31.5 (5.6)	31.6 (5.4)	31.3 (5.3)	30.9 (5.1)	31.3 (5.3)
SBP/DBP, mmHg	143 (20)/76 (11)	141 (19)/76 (11)	141 (18)/78 (10)	139 (16)/79 (10)	141 (18)/78 (10)
HF	253 (23.8)	512 (26.4)	374 (27.7)	734 (27.9)	1,873 (26.8)
Insulin	823 (77.5)	1,288 (66.5)	769 (57.0)	1,171 (44.5)	4,051 (58.0)
Metformin	180 (16.9)	717 (37.0)	821 (60.9)	2,090 (79.4)	3,808 (54.6)
Sulfonylurea	231 (21.8)	543 (28.0)	438 (32.5)	1,030 (39.1)	2,242 (32.1)
Any antihypertensives	1,035 (97.5)	1,877 (96.9)	1,307 (97.0)	2,472 (94.0)	6,691 (95.9)
ACE inhibitors or ARBs	797 (75.0)	1,583 (81.7)	1,145 (84.9)	2,133 (81.1)	5,658 (81.1)
Statins	764 (71.9)	1,432 (73.9)	982 (72.8)	1,840 (69.9)	5,018 (71.9)

Data are n (%) or mean (SD) unless otherwise indicated. ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.
*Data missing for three (0.0%) participants: two (0.1%) linagliptin and one (0.0%) placebo.

[0.69, 1.10]) (Supplementary Fig. F4) and ESKD, renal death, or sustained eGFR <10 mL/min/1.73 m² (HR 0.84 [95% CI 0.67, 1.05]) (Supplementary Fig. F5).

Albuminuria burden was modestly reduced with linagliptin, as evident by significant reductions in risk of progression to albuminuria, with consistent effects (interaction P value = 0.35) across GFR categories G ≤ 2 to G ≥ 4 (Fig. 2A) by reduction in gMean changes in albuminuria from similar baseline (e.g., adjusted gMean at week 36 for linagliptin 130.36 vs. 150.19 mg/g for placebo [gMean ratio 0.87 (0.81, 0.93)] and at week 84 for linagliptin 128.81 vs. 145.76 mg/g for placebo [gMean ratio 0.88 (0.82, 0.95)]) and by reduced proportions of participants who had albuminuria progression or increased proportions with albuminuria regression (Supplementary Figs. G1 and G2 and Supplementary Table G1); however, in the sustained analysis, the

magnitude of effect was attenuated. Of note, the reduction in albuminuria progression with linagliptin was not dependent on change in HbA$_{1c}$ (Supplementary Fig. G3). No significant difference in the annual rate of change in eGFR was observed (slope difference −0.175 mL/min/1.73 m²/year [95% CI −0.472, 0.122]; P = 0.2485) (Fig. 2B), despite a small acute effect observed with linagliptin relative to placebo by week 12 (slope difference −0.22 mL/min/1.73 m²/4 weeks [95% CI −0.38, −0.07]; P = 0.0040) (Fig. 2C and Supplementary Figs. G4 and G5), driven by changes in the G ≤ 2 group. Annual rate of slope change between week 12 and end of treatment was not impacted by linagliptin treatment (0.09 mL/min/1.73 m²/year [95% CI −0.22, 0.41]; P = 0.5638, relative to placebo) (Fig. 2C).

Effects on Glycemia and Hypoglycemia
HbA$_{1c}$ was significantly reduced with linagliptin, regardless of baseline kidney

function (Fig. 3A and Supplementary Table H1) with average (95% CI) reduction in HbA$_{1c}$ of −0.35% (−0.45, −0.25)/−3.83 mmol/mol (−4.92, −2.75) in the advanced CKD subgroup with eGFR <45 mL/min/1.73 m² and −0.36% (−0.45, −0.28)/−3.99 mmol/mol (−4.92, −3.06) for those with baseline eGFR ≥45 mL/min/1.73 m². These improvements in glycemic control occurred despite reduced use of other glucose-lowering treatments during follow-up overall and across all predefined renal subgroups in the linagliptin arm (Supplementary Table H2), including by GFR groups <45 (HR 0.76 [95% CI 0.65, 0.86]) versus ≥45 mL/min/1.73 m² (0.77 [0.68, 0.88]) (Fig. 3B). Fewer participants initiated or increased insulin dose among participants randomized to linagliptin compared with placebo regardless of GFR (Supplementary Table H2), with an HR of 0.69 (95% CI 0.59, 0.81) (P < 0.0001) in those with eGFR <45 mL/min/1.73 m² and 0.76 (0.65, 0.88) (P = 0.0004)
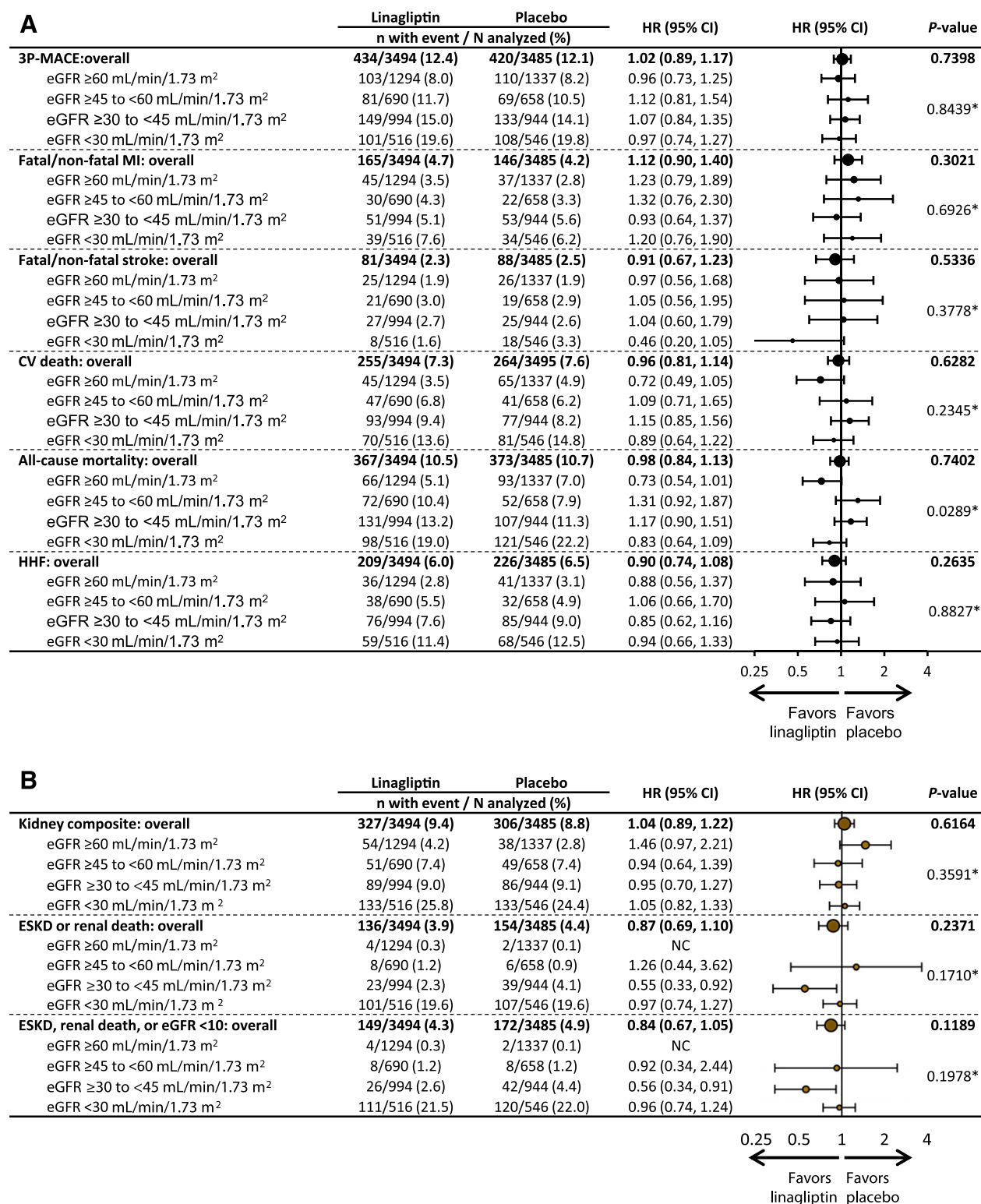
A

	Linagliptin	Placebo	HR (95% CI)	HR (95% CI)	P-value
	n with event / N analyzed (%)				
3P-MACE:overall	**434/3494 (12.4)**	**420/3485 (12.1)**	**1.02 (0.89, 1.17)**		**0.7398**
eGFR ≥60 mL/min/1.73 m²	103/1294 (8.0)	110/1337 (8.2)	0.96 (0.73, 1.25)		
eGFR ≥45 to <60 mL/min/1.73 m²	81/690 (11.7)	69/658 (10.5)	1.12 (0.81, 1.54)		0.8439*
eGFR ≥30 to <45 mL/min/1.73 m²	149/994 (15.0)	133/944 (14.1)	1.07 (0.84, 1.35)		
eGFR <30 mL/min/1.73 m²	101/516 (19.6)	108/546 (19.8)	0.97 (0.74, 1.27)		
Fatal/non-fatal MI: overall	**165/3494 (4.7)**	**146/3485 (4.2)**	**1.12 (0.90, 1.40)**		**0.3021**
eGFR ≥60 mL/min/1.73 m²	45/1294 (3.5)	37/1337 (2.8)	1.23 (0.79, 1.89)		
eGFR ≥45 to <60 mL/min/1.73 m²	30/690 (4.3)	22/658 (3.3)	1.32 (0.76, 2.30)		0.6926*
eGFR ≥30 to <45 mL/min/1.73 m²	51/994 (5.1)	53/944 (5.6)	0.93 (0.64, 1.37)		
eGFR <30 mL/min/1.73 m²	39/516 (7.6)	34/546 (6.2)	1.20 (0.76, 1.90)		
Fatal/non-fatal stroke: overall	**81/3494 (2.3)**	**88/3485 (2.5)**	**0.91 (0.67, 1.23)**		**0.5336**
eGFR ≥60 mL/min/1.73 m²	25/1294 (1.9)	26/1337 (1.9)	0.97 (0.56, 1.68)		
eGFR ≥45 to <60 mL/min/1.73 m²	21/690 (3.0)	19/658 (2.9)	1.05 (0.56, 1.95)		0.3778*
eGFR ≥30 to <45 mL/min/1.73 m²	27/994 (2.7)	25/944 (2.6)	1.04 (0.60, 1.79)		
eGFR <30 mL/min/1.73 m²	8/516 (1.6)	18/546 (3.3)	0.46 (0.20, 1.05)		
CV death: overall	**255/3494 (7.3)**	**264/3495 (7.6)**	**0.96 (0.81, 1.14)**		**0.6282**
eGFR ≥60 mL/min/1.73 m²	45/1294 (3.5)	65/1337 (4.9)	0.72 (0.49, 1.05)		
eGFR ≥45 to <60 mL/min/1.73 m²	47/690 (6.8)	41/658 (6.2)	1.09 (0.71, 1.65)		0.2345*
eGFR ≥30 to <45 mL/min/1.73 m²	93/994 (9.4)	77/944 (8.2)	1.15 (0.85, 1.56)		
eGFR <30 mL/min/1.73 m²	70/516 (13.6)	81/546 (14.8)	0.89 (0.64, 1.22)		
All-cause mortality: overall	**367/3494 (10.5)**	**373/3485 (10.7)**	**0.98 (0.84, 1.13)**		**0.7402**
eGFR ≥60 mL/min/1.73 m²	66/1294 (5.1)	93/1337 (7.0)	0.73 (0.54, 1.01)		
eGFR ≥45 to <60 mL/min/1.73 m²	72/690 (10.4)	52/658 (7.9)	1.31 (0.92, 1.87)		0.0289*
eGFR ≥30 to <45 mL/min/1.73 m²	131/994 (13.2)	107/944 (11.3)	1.17 (0.90, 1.51)		
eGFR <30 mL/min/1.73 m²	98/516 (19.0)	121/546 (22.2)	0.83 (0.64, 1.09)		
HHF: overall	**209/3494 (6.0)**	**226/3485 (6.5)**	**0.90 (0.74, 1.08)**		**0.2635**
eGFR ≥60 mL/min/1.73 m²	36/1294 (2.8)	41/1337 (3.1)	0.88 (0.56, 1.37)		
eGFR ≥45 to <60 mL/min/1.73 m²	38/690 (5.5)	32/658 (4.9)	1.06 (0.66, 1.70)		0.8827*
eGFR ≥30 to <45 mL/min/1.73 m²	76/994 (7.6)	85/944 (9.0)	0.85 (0.62, 1.16)		
eGFR <30 mL/min/1.73 m²	59/516 (11.4)	68/546 (12.5)	0.94 (0.66, 1.33)		

0.25   0.5   1   2   4

← Favors linagliptin   Favors placebo →

B

	Linagliptin	Placebo	HR (95% CI)	HR (95% CI)	P-value
	n with event / N analyzed (%)				
Kidney composite: overall	**327/3494 (9.4)**	**306/3485 (8.8)**	**1.04 (0.89, 1.22)**		**0.6164**
eGFR ≥60 mL/min/1.73 m²	54/1294 (4.2)	38/1337 (2.8)	1.46 (0.97, 2.21)		
eGFR ≥45 to <60 mL/min/1.73 m²	51/690 (7.4)	49/658 (7.4)	0.94 (0.64, 1.39)		0.3591*
eGFR ≥30 to <45 mL/min/1.73 m²	89/994 (9.0)	86/944 (9.1)	0.95 (0.70, 1.27)		
eGFR <30 mL/min/1.73 m²	133/516 (25.8)	133/546 (24.4)	1.05 (0.82, 1.33)		
ESKD or renal death: overall	**136/3494 (3.9)**	**154/3485 (4.4)**	**0.87 (0.69, 1.10)**		**0.2371**
eGFR ≥60 mL/min/1.73 m²	4/1294 (0.3)	2/1337 (0.1)	NC		
eGFR ≥45 to <60 mL/min/1.73 m²	8/690 (1.2)	6/658 (0.9)	1.26 (0.44, 3.62)		0.1710*
eGFR ≥30 to <45 mL/min/1.73 m²	23/994 (2.3)	39/944 (4.1)	0.55 (0.33, 0.92)		
eGFR <30 mL/min/1.73 m²	101/516 (19.6)	107/546 (19.6)	0.97 (0.74, 1.27)		
ESKD, renal death, or eGFR <10: overall	**149/3494 (4.3)**	**172/3485 (4.9)**	**0.84 (0.67, 1.05)**		**0.1189**
eGFR ≥60 mL/min/1.73 m²	4/1294 (0.3)	2/1337 (0.1)	NC		
eGFR ≥45 to <60 mL/min/1.73 m²	8/690 (1.2)	8/658 (1.2)	0.92 (0.34, 2.44)		0.1978*
eGFR ≥30 to <45 mL/min/1.73 m²	26/994 (2.6)	42/944 (4.4)	0.56 (0.34, 0.91)		
eGFR <30 mL/min/1.73 m²	111/516 (21.5)	120/546 (22.0)	0.96 (0.74, 1.24)		

0.25   0.5   1   2   4

← Favors linagliptin   Favors placebo →

Figure 1—Effect of linagliptin vs. placebo by renal function on CV outcomes, mortality, and hospitalization for HF (HHF) (*A*) and kidney outcomes (*B*). *P value of subgroup-by-treatment interaction test. NC, not calculated.

in those with eGFR ≥45 mL/min/1.73 m², respectively (Fig. 3C). Consistent with the overall trial results, the improvement for linagliptin in HbA$_{1c}$ across eGFR categories occurred without an increased risk for hypoglycemia (Fig. 3D and Supplementary Figs. I1 and I2), although the absolute risk for hypoglycemia increased in both groups with declining baseline eGFR. For example, in the advanced CKD subgroup with eGFR <45 mL/kg/1.73 m², any hypoglycemia, hypoglycemia with plasma glucose <54 mg/dL or severe hypoglycemia (analyzed together), or severe hypoglycemia in the placebo group occurred 1.9-, 2.3-, and
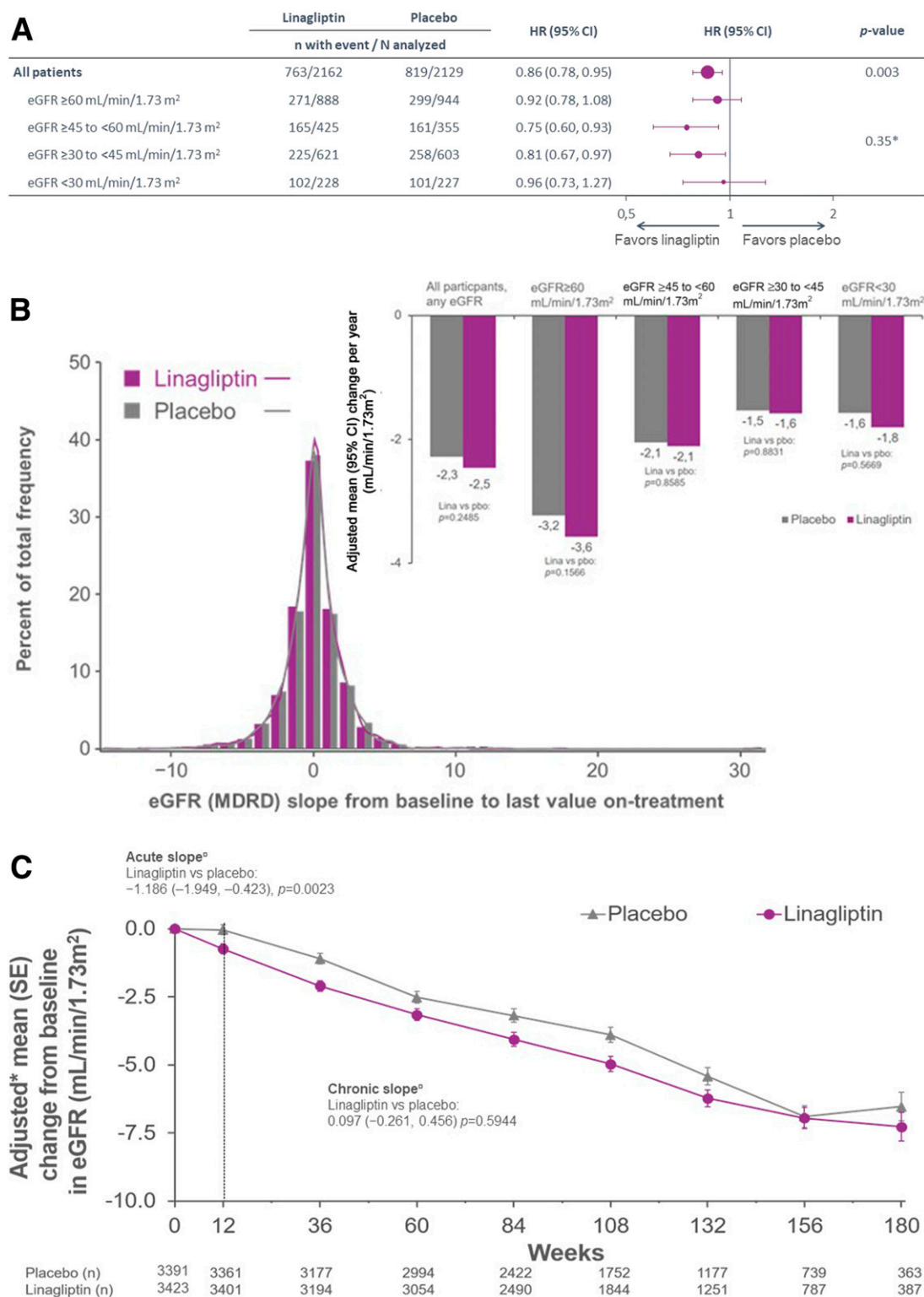
Figure 2—*A*: Time to first occurrence of albuminuria progression (change from normo- to micro- or macroalbuminuria or from micro- to macroalbuminuria) for linagliptin vs. placebo by eGFR subgroups. *P for interaction. *B*: Overall effects on eGFR (MDRD) slope from baseline to last value on treatment and by eGFR category G ≤ 2 to ≥ G4 for linagliptin (Lina) vs. placebo (pbo). *C*: Overall change from baseline in eGFR (MDRD) over time for linagliptin vs. placebo and comparison of acute vs. chronic slope differences. MMRM, mixed model for repeated measures; OC, observed case. *Adjusted mean eGFR slope based on MMRM including terms for time as a linear covariate, treatment, region, and baseline eGFR as categorical covariates, and treatment-by-time interaction, baseline eGFR-by-treatment interaction, baseline eGFR-by-time interaction, and baseline eGFR-by-treatment-by-time interaction.
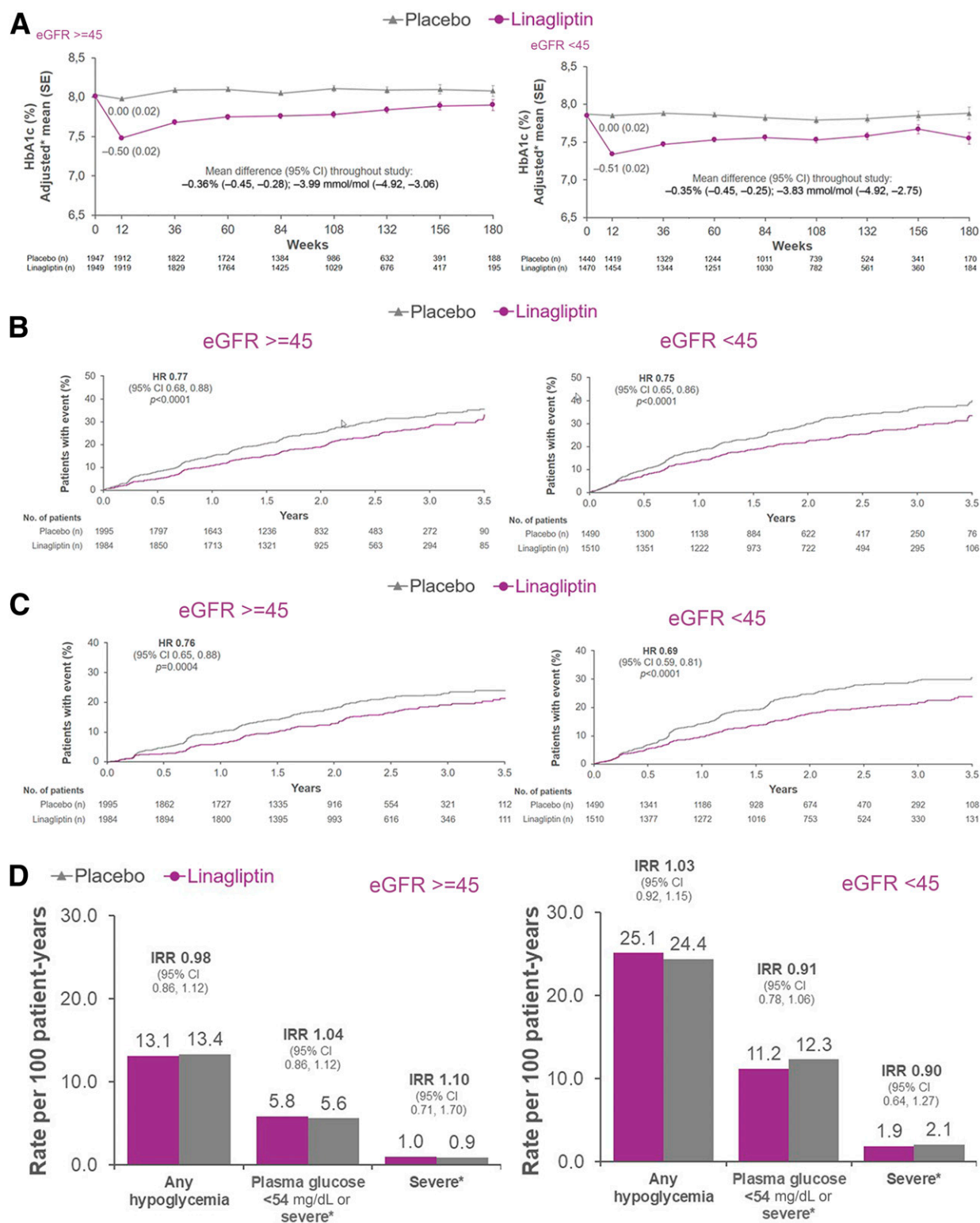
Figure 3—*A*: HbA$_{1c}$ over time by eGFR 45 mL/min/1.73 m^2 subgroups for linagliptin vs. placebo. *Baseline values are descriptive; post-baseline data from mixed model repeated measures adjusting for treatment, region, baseline HbA$_{1c}$ value, week, treatment-by-week interaction, and baseline HbA$_{1c}$ value-by-week interaction. *B*: New introduction of any glucose-lowering medications by eGFR 45 mL/min/1.73 m^2 subgroups for linagliptin vs. placebo. *C*: Time to initiation of long-term use of insulin or long-term dose increase in insulin by eGFR 45 mL/min/1.73 m^2 subgroups for linagliptin vs. placebo. *D*: Occurrence of hypoglycemia by eGFR 45 subgroups for linagliptin vs. placebo. IRR, incidence rate ratio. *Severe defined as requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

2.5-fold more frequently, respectively, relative to those with eGFR ≥45 mL/min/1.73 m^2 (Fig. 3D).

AEs

In line with the overall safety results, the frequency of occurrence of investigator-reported AEs, serious AEs, and AEs leading to study drug discontinuation for patients treated with linagliptin versus placebo in CARMELINA did not differ among treatment groups by renal function, but those with the lowest renal function generally had a higher frequency of AEs (Supplementary Table I1).

CONCLUSIONS

The CARMELINA trial was deliberately enriched for participants with reduced kidney function. As a result of this enriched population, this trial captured more renal outcomes than most CV outcome trials of glucose-lowering therapies and found no overall effect on the main composite renal outcome comprised of the composite of renal death, ESKD, or sustained ≥40% reduction in eGFR from baseline. It also demonstrated that linagliptin did not increase CV risk among people with reduced kidney function, including participants with an eGFR <45 mL/min/1.73 m^2 for whom few data have previously been collected. Finally, linagliptin treatment was associated with improvements in glycemic control, without increasing hypoglycemia risk, as well as albuminuria, across all levels of kidney function. The former led to a reduction in the need for other glucose-lowering therapies, including insulin addition and uptitration, both overall and in people with reduced kidney function.

These results from CARMELINA are important, as people with reduced kidney function have limited glucose-lowering therapy options, as a number of agents are contraindicated or require dose reduction (12,24,25). This is particularly true for those with eGFR <45 mL/min/1.73 m^2. Furthermore, people with reduced kidney function are at increased risk of drug-related adverse effects (25), so it is particularly important to obtain specific safety data in this population (12,13). Most glucose-lowering trials of DPP-4i (26–29) have included modest numbers of participants with CKD, and very few with advanced CKD, in contrast to CARMELINA, in which recruitment of people with CKD was a prespecified goal (22). In this

context, the present results expand the evidence base among DPP-4i specifically for linagliptin and demonstrate its CV safety in CKD, including those with an eGFR <45 mL/min/1.73 m^2. Of note, despite a previous trial indicating an increased risk of hospitalization for HF with another DPP-4i, saxagliptin, and suggesting that this might be particularly true for people with CKD (27,30), CARMELINA also demonstrates that linagliptin does not increase the risk of HF overall (8,22) or in the subset of participants with reduced kidney function.

In addition, the present results demonstrate that the glucose-lowering efficacy of linagliptin was preserved in participants with reduced kidney function. The glycemic benefits also translated into a reduced need for other glucose-lowering therapies, including insulin, without increasing risk for hypoglycemia. Although SGLT2 inhibitors are now advocated to be used relatively early in type 2 diabetes, because they have been shown to prevent or slow down the progression of CV and HF events and CKD (2–4,31), their glucose-lowering efficacy diminishes with reduced eGFR; in this context, linagliptin may have an important role, as it improves glycemic control and reduces the need for insulin without increasing the risk of hypoglycemia (2–4,31) and, in comparison with other DPP-4i, does not require any dose adjustment with declining renal function.

A neutral effect on the main renal composite outcome was observed, despite a significant though modest reduction in albuminuria burden. Of note, in an exploratory analysis, this reduction in albuminuria was not driven by changes in glycemic control, which is interesting and aligns with some mechanistic data suggesting that linagliptin has nonglycemic kidney effects (e.g., via attenuation of podocyte injury or inhibition of myofibroblast transformation [32] or inhibition of endothelial-to-mesenchymal transition and restoration of miRNA-29s [33]); however, this trial cannot address mechanisms potentially underlying this observation. These results, therefore, both expand and are broadly consistent with previous large trials of DPP-4i, in which modest effects on albuminuria were observed, without any clear benefits on excretory kidney function (34,35), although a modest acute reduction in GFR during the first 4 weeks in those with the least reduced renal function at baseline occurred

(i.e., in the G ≤ 2 group), which did not lead to an overall GFR difference. Similar results were observed in the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) (34) and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (28). Potential reasons for a mild acute GFR reduction in those with normal or better preserved renal function could be remission of hyperfiltration, possibly related to an early natriuretic effect mediated by stromal cell–derived factor-1α (36), or indirectly via the two- to threefold increase in GLP-1, which induces natriuresis by reducing the Na/H exchange transporter isoform 3–dependent sodium reabsorption in the proximal tubule or via modulation of ≥1 of the >40 other substrates metabolized by DPP-4, including high-mobility group protein box 1 (37), which this trial cannot provide a definitive answer for. While the data on GLP-1 receptor agonists are more mixed, with some suggestion of possible renal benefit reported (38,39), the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial observed the largest number of major renal outcomes in trials of the GLP-1 receptor agonist class and did not demonstrate clear benefit for either persistent doubling of creatinine (184 events; HR 0.89 [95% CI 0.67, 1.19]) or ESKD (120 events; HR 0.87 [95% CI 0.61, 1.24]) (38). Notably, the completed outcome trials with GLP-1 receptor agonists were not powered for kidney outcomes and did not specifically enroll patients with CKD, as CARMELINA did. Although reduction in albuminuria has been proposed as an independent surrogate for hard kidney outcomes (40), a potential reason for the lack of clear effect on major renal outcomes in CARMELINA is that the albuminuria reduction was smaller than those observed with other renoprotective therapies, specifically angiotensin receptor blockade (41) or SGLT2 inhibitors (42,43). Alternatively, it can be argued that the observation time may also have been too short to demonstrate benefit in CARMELINA, particularly in light of the modest albuminuria reduction observed.

The strengths of this analysis include the large number of participants with reduced kidney function. The trial was conducted to a high standard and achieved the planned number of CV and renal outcomes, and these renal outcomes were prospectively captured, centrally

adjudicated, and prespecified along with subgroup analyses by baseline kidney function. The trial also had some limitations. The median follow-up was only 2.2 years, with 1.9 years for the key kidney outcome, and beyond the key kidney outcome, we only report secondary analysis. In addition, the trial excluded people with a baseline eGFR <15 mL/min/1.73 m^2 and those receiving dialysis, so the generalizability of the present results to a broader population is uncertain, although smaller studies specific to these populations have been previously conducted (44). Further prospective trials designed to assess kidney effects of linagliptin should ensure sufficient follow-up and representation of people with eGFR <15 mL/min/1.73 m^2.

In conclusion, results from CARMELINA provide evidence of the potential for linagliptin having an important role in type 2 diabetes with CKD by improving glucose control, reducing albuminuria regardless of baseline eGFR, and reducing the need for other glycemic therapies including insulin, without increasing CV risk and with no significant overall effect on kidney outcomes.

References

1. McGuire DK, Marx N, Johansen OE, Inzucchi SE, Rosenstock J, George JT. FDA guidance on antihyperglyacemic therapies for type 2 diabetes: one decade later. Diabetes Obes Metab 2019;21:1073–1078
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–2701
3. Das SR, Everett BM, Birtcher KK, et al. 2018 ACC Expert Consensus Decision Pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol 2018;72:3200–3223
4. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2018;42(Suppl. 1):S1–S325
5. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol 2017;12:2032–2045
6. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet 2013;382:260–272
7. Wen CP, Chang CH, Tsai MK, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. Kidney Int 2017;92:388–396
8. McGuire DK, Alexander JH, Johansen OE, et al.; CARMELINA Investigators. Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes mellitus at high cardiovascular and renal risk in CARMELINA. Circulation 2019;139:351–361
9. Mokdad AH, Ballestros K, Echko M, et al.; US Burden of Disease Collaborators. The state of US health, 1990-2016: burden of diseases, injuries, and risk factors among US states. JAMA 2018; 319:1444–1472
10. Nguyen NTQ, Cockwell P, Maxwell AP, Griffin M, O'Brien T, O'Neill C. Chronic kidney disease, health-related quality of life and their associated economic burden among a nationally representative sample of community dwelling adults in England. PLoS One 2018;13:e0207960
11. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
12. Lo C, Toyama T, Wang Y, et al. Insulin and glucose-lowering agents for treating people with diabetes and chronic kidney disease. Cochrane Database Syst Rev 2018;9:CD011798
13. Khunti K, Gomes MB, Pocock S, et al. Therapeutic inertia in the treatment of hyperglycaemia

in patients with type 2 diabetes: a systematic review. Diabetes Obes Metab 2018;20:427–437

14. Coca SG, Ismail-Beigi F, Haq N, Krumholz HM, Parikh CR. Role of intensive glucose control in development of renal end points in type 2 diabetes mellitus: systematic review and meta-analysis intensive glucose control in type 2 diabetes. Arch Intern Med 2012;172:761–769

15. Perkovic V, Heerspink HL, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive glucose control improves kidney outcomes in patients with type 2 diabetes. Kidney Int 2013;83:517–523

16. Ruospo M, Saglimbene VM, Palmer SC, et al. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev 2017;6:CD010137

17. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898

18. Golightly LK, Drayna CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. Clin Pharmacokinet 2012;51:501–514

19. Groop PH, Cooper ME, Perkovic V, Emser A, Woerle HJ, von Eynatten M. Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction. Diabetes Care 2013;36:3460–3468

20. Cooper ME, Perkovic V, McGill JB, et al. Kidney disease end points in a pooled analysis of individual patient-level data from a large clinical trials program of the dipeptidyl peptidase 4 inhibitor linagliptin in type 2 diabetes. Am J Kidney Dis 2015;66:441–449

21. Rosenstock J, Perkovic V, Johansen OE, et al.; CARMELINA Investigators. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. JAMA 2019;321:69–79

22. Rosenstock J, Perkovic V, Alexander JH, et al.; CARMELINA® Investigators. Rationale, design, and baseline characteristics of the CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin (CARMELINA®): a randomized, double-blind, placebo-controlled clinical trial in patients with type 2 diabetes and high cardio-renal risk. Cardiovasc Diabetol. 2018;17:39

23. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [published correction appears in Kidney Int Suppl (2011) 2017;7:e1]. Kidney Int Suppl (2011) 2017;7:1–59

24. Solini A, Penno G, Bonora E, et al.; Renal Insufficiency and Cardiovascular Events Study Group. Age, renal dysfunction, cardiovascular disease, and antihyperglycemic treatment in type 2 diabetes mellitus: findings from the Renal Insufficiency and Cardiovascular Events Italian multicenter study. J Am Geriatr Soc 2013;61:1253–1261

25. Weir MR, Fink JC. Safety of medical therapy in patients with chronic kidney disease and end-stage renal disease. Curr Opin Nephrol Hypertens 2014;23:306–313

26. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–242

27. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317–1326

28. White WB, Cannon CP, Heller SR, et al.; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–1335

29. Gantz I, Chen M, Suryawanshi S, et al. A randomized, placebo-controlled study of the cardiovascular safety of the once-weekly DPP-4 inhibitor omarigliptin in patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2017;16:112

30. Scirica BM, Braunwald E, Raz I, et al.; SAVOR-TIMI 53 Steering Committee and Investigators*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial [published correction appears in Circulation 2015;132:e198]. Circulation 2014;130:1579–1588

31. Sarafidis P, Ferro CJ, Morales E, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant 2019;34:208–230

32. Sharkovska Y, Reichetzeder C, Alter M, et al. Blood pressure and glucose independent renoprotective effects of dipeptidyl peptidase-4 inhibition in a mouse model of type-2 diabetic nephropathy. J Hypertens 2014;32:2211–2223; discussion 2223

33. Kanasaki K, Shi S, Kanasaki M, et al. Linagliptin-mediated DPP-4 inhibition ameliorates kidney fibrosis in streptozotocin-induced diabetic mice by inhibiting endothelial-to-mesenchymal transition in a therapeutic regimen. Diabetes 2014;63:2120–2131

34. Cornel JH, Bakris GL, Stevens SR, et al.; TECOS Study Group. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: outcomes from TECOS. Diabetes Care 2016;39:2304–2310

35. Mosenzon O, Leibowitz G, Bhatt DL, et al. Effect of saxagliptin on renal outcomes in the SAVOR-TIMI 53 trial. Diabetes Care 2017;40:69–76

36. Lovshin JA, Rajasekeran H, Lytvyn Y, et al. Dipeptidyl peptidase 4 inhibition stimulates distal tubular natriuresis and increases in circulating SDF-$1\alpha^{1-67}$ in patients with type 2 diabetes [published correction appears in Diabetes Care 2017;40:1420–1421]. Diabetes Care 2017;40:1073–1081

37. MacIsaac RJ, Thomas MC. Effects of diabetes medications targeting the incretin system on the kidney. Clin J Am Soc Nephrol 2018;13:321–323

38. Mann JFE, Ørsted DD, Brown-Frandsen K, et al.; LEADER Steering Committee and Investigators. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med 2017;377:839–848

39. Dieter BP, Alicic RZ, Tuttle KR. GLP-1 receptor agonists in diabetic kidney disease: from the patient-side to the bench-side. Am J Physiol Renal Physiol 2019;315:F1519–F1525

40. Coresh J, Heerspink HJL, Sang Y, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol 2019;7:115–127

41. Hellemons ME, Persson F, Bakker SJ, et al. Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria: a post hoc analysis of the IRMA-2 trial. Diabetes Care 2011;34:2078–2083

42. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334

43. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306

44. Nakamura Y, Tsuji M, Hasegawa H, et al. Anti-inflammatory effects of linagliptin in hemodialysis patients with diabetes. Hemodial Int 2014;18:433–442