ORIGINAL ARTICLE

Effect of linagliptin versus placebo on cardiovascular and kidney outcomes in nephrotic-range proteinuria and type 2 diabetes: the CARMELINA randomized controlled trial

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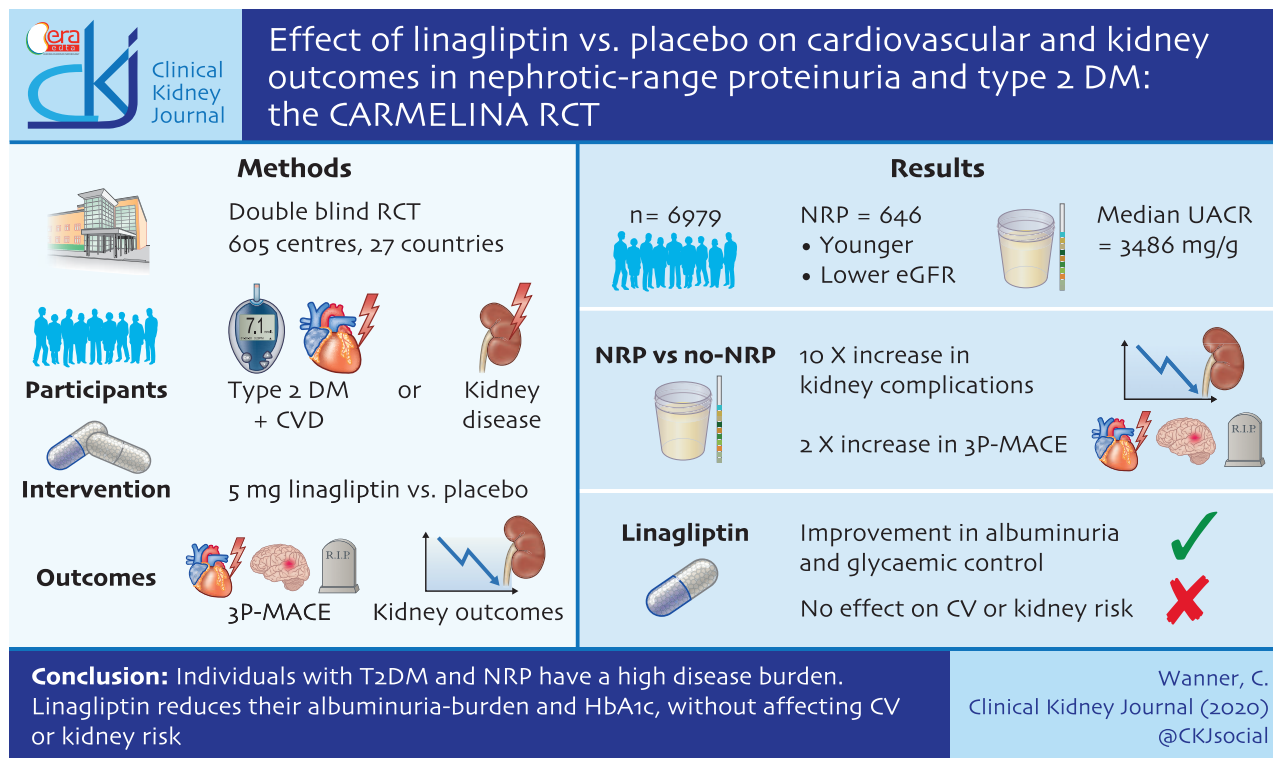University of New South Wales, Sydney, Australia

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GRAPHICAL ABSTRACT

Effect of linagliptin vs. placebo on cardiovascular and kidney outcomes in nephrotic-range proteinuria and type 2 DM: the CARMELINA RCT

Methods

Double blind RCT
605 centres, 27 countries

Participants — Type 2 DM + CVD or Kidney disease

Intervention — 5 mg linagliptin vs. placebo

Outcomes — 3P-MACE Kidney outcomes

Results

n = 6979

NRP = 646
• Younger
• Lower eGFR

Median UACR = 3486 mg/g

NRP vs no-NRP — 10 X increase in kidney complications

2 X increase in 3P-MACE

Linagliptin — Improvement in albuminuria and glycaemic control ✓

No effect on CV or kidney risk ✗

Conclusion: Individuals with T2DM and NRP have a high disease burden. Linagliptin reduces their albuminuria-burden and HbA1c, without affecting CV or kidney risk

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ABSTRACT

Background. Nephrotic-range proteinuria (NRP) is associated with rapid kidney function loss and increased cardiovascular (CV) disease risk. We assessed the effects of linagliptin (LINA) on CV and kidney outcomes in people with Type 2 diabetes (T2D) with or without NRP.

Methods. Cardiovascular and renal microvascular outcome study with LINA randomized participants with T2D and CV disease and/or kidney disease to LINA 5 mg or placebo (PBO). The primary endpoint [time to first occurrence of 3-point major adverse cardiac events (3P-MACE)], and kidney outcomes, were evaluated by NRP status [urinary albumin:creatinine ratio (UACR) ≥2200 mg/g] at baseline (BL) in participants treated with one or more dose of study medication.

Results. NRP was present in 646/6979 [9.3% (LINA/PBO $n = 317$/$n = 329$); median UACR 3486 (Q1: 2746/Q3: 4941) mg/g] participants, who compared with no-NRP were younger (62.3/66.1 years) and had lower estimated glomerular filtration rate (eGFR) (39.9/56.1 mL/min/1.73 m^2). Over a median of 2.2 years, 3P-MACE occurred with a 2.0-fold higher rate in NRP versus no-NRP (PBO group), with a neutral LINA effect, regardless of NRP. The composite of time to renal death, end-stage kidney disease (ESKD) or decrease of ≥40 or ≥50% in eGFR, occurred with 12.3- and 13.6-fold higher rate with NRP (PBO group); evidence of heterogeneity of effects with LINA was observed for the former [NRP yes/no: hazard ratio 0.80 (0.63–1.01)/1.25 (1.02–1.54); P-interaction 0.005], but not the latter [0.83 (0.64–1.09)/1.17 (0.91–1.51), P-interaction 0.07]. No heterogeneity was observed for renal death or ESKD [0.88 (0.64–1.21)/0.94 (0.67–1.31), P-interaction 0.79]. Glycated haemoglobin A1c (HbA1c) was significantly reduced regardless of NRP, without increasing hypoglycaemia risk. Regression to normoalbuminuria [1.20 (1.07–1.34)] and reduction of UACR ≥50% [1.15 (1.07–1.25)] from BL, occurred more frequently with LINA, regardless of NRP status (P-interactions >0.05).

Conclusions. Individuals with T2D and NRP have a high disease burden. LINA reduces their albuminuria burden and HbA1c, without affecting CV or kidney risk.

Keywords: albuminuria, DPP-4 inhibitor, HbA1c, kidney disease, linagliptin, renal impairment, Type 2 diabetes

INTRODUCTION

The study of glucose-lowering medications for Type 2 diabetes (T2D) has evolved from prioritizing glycaemic control to also assessing the relative cardiovascular (CV) risks and benefits in people with T2D and established CV disease [1]. As a result, there have been important updates to treatment guidelines and recommendations globally [2–4]. Yet, despite a clear advancement in CV risk management, few studies have assessed the use of glucose-lowering medications in those with T2D who suffer chronic kidney disease (CKD), although over the last few years some dedicated studies have been reported [5]. Up to 40% of people with T2D will develop CKD [6], which is associated with reduced quality of life [7, 8] and lower glycaemic goal attainment [9, 10]. A substantial number of people develop nephrotic-range proteinuria (NRP) or the nephrotic syndrome [11], and these people are at particularly high risk of progression to end-stage kidney disease (ESKD) [12].

T2D is a common cause of NRP in adults. People with T2D and NRP represent an understudied group [12, 13] with a particular clinical challenge, given the graded increase in risk for most complications with higher albuminuria categories [14]. The risk is further accentuated for accelerated loss of kidney function and increased risk for hospitalizations, and many die with NRP before reaching ESKD requiring kidney replacement therapy [15–18].

The choice of glucose-lowering therapies is limited in lower ranges of kidney function due to drug accumulation and side effects, as are the data on the safety and efficacy of glucose-lowering therapies in people with T2D and NRP, since the majority of recent CV outcome trials in T2D do not include people with NRP [5]. Management of these concomitant comorbidities focuses on controlling traditional risk factors for further progression of kidney disease [e.g. blood pressure (BP), weight and glucose] [19], and use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs) [20] for additional nephroprotection and/or control of albuminuria. There have been no new nephroprotective treatments to manage proteinuria in NRP since the introduction of ARBs in the early 2000s, although mineralocorticoid-receptor antagonists appear to be promising in NRP, with the caveat of potassium increase [21], as well as sodium–glucose co-transporter-2 (SGLT-2) inhibitors, owing to their kidney-targeted mechanism of action and demonstrated benefits in individuals with T2D [22–25].

Linagliptin (LINA), a dipeptidyl-peptidase 4 inhibitor (DPP-4i) approved for glycaemic management of T2D, does not require dose adjustment in people with CKD as it is 85% eliminated via biliary excretion [26]. Its CV and kidney safety were confirmed in the CArdiovascular and Renal Microvascular outcomE study with LINA (CARMELINA) trial [20, 27], in which 6979 individuals with CKD [3000 with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2; 2690 with urinary albumin creatinine ratio (UACR) >300 mg/g] were studied. In this trial, LINA also reduced albuminuria progression and glycated haemoglobin A1c (HbA1c), regardless of eGFR at baseline (BL), including in those with eGFR <30 mL/min/1.73 m^2 [28]. As there was no upper limit for UACR for inclusion in CARMELINA, it is also well positioned to study people with NRP and T2D, and to evaluate the safety and efficacy of LINA in this understudied group.

MATERIALS AND METHODS

Study design and procedures

The study design and primary results have been reported previously [27, 29]. In brief, CARMELINA (NCT01897532) was a multicentre, randomized, double-blind clinical outcome trial in adults with T2D [HbA1c 6.5–10.0% (48–86 mmol/mol)] at high risk for CV and kidney disease defined as history of CV disease and UACR >30 mg/g (or equivalent) or 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. It was conducted at 605 centres in 27 countries. Investigators were encouraged to use additional CV medications (e.g. statins and antihypertensive therapies) and medications for glycaemic control [except DPP-4i, glucagon-like peptide (GLP)-1 receptor agonists and SGLT-2 inhibitors] according to applicable standards of care throughout the trial. Participants who prematurely discontinued study medication were followed for ascertainment of CV and key secondary kidney outcome events, as previously described [28]. 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.

Classification of NRP

UACR was measured by a central laboratory on a first-morning void specimen, at screening; randomization (BL); at Weeks 36 and 84; then every year until the end of study visit; at the end of study visit; and 30 days after the end of study visit. Albuminuria categorization at BL was predefined based on KDIGO definitions as <30, 30–300 and >300 mg/g [16]. Additionally, NRP was defined as UACR >2200 mg/g creatinine with any GFR [29], a definition also used elsewhere [11].

Outcomes

CV and kidney outcomes. We compared the treatment effects of LINA versus placebo (PBO) in participants with NRP versus without NRP (no NRP) with a time to first event analysis of the primary outcome of the trial [CV death, non-fatal myocardial infarction or non-fatal stroke (3-point major adverse cardiac event, 3P-MACE)], CV death, all-cause mortality, hospitalization for heart failure and all-cause hospitalization and the following kidney outcomes: (i) the composite of renal death, sustained ESKD or sustained decrease of ≥40% eGFR from BL (key secondary kidney outcome); (ii) the composite of renal death, sustained ESKD or sustained decrease of 50% or more in eGFR from BL; (iii) the composite of renal death or ESKD; (iv) the composite of renal death, ESKD or sustained eGFR <10 mL/min/1.73 m^2; and (v) the composite of renal death, ESKD or doubling of serum creatinine. Effects on eGFR were assessed by an eGFR [Modification of Diet in Renal Disease (MDRD)] slope analysis (change per year) from BL to last value on-treatment (LVOT) by NRP at BL, and from BL to Week 12 (change/4 weeks) and Week 12 to LVOT (change/year). All data available for eGFR were used to calculate the slope.

Albuminuria endpoints. Albuminuria endpoints were predefined and *post hoc* defined (Supplementary data, Table S1) and analysed as time to new onset of albuminuria regression, and improvement in albuminuria status relative to BL (reduction ≥50% or ≥30% from BL UACR, respectively). In addition, in those with NRP at BL, regression to no NRP was analysed. Analysis was also conducted by applying a sustained criterion, i.e. requirement of having results confirmed in two or more consecutive measurements that were ≥28 days apart.

Efficacy and safety endpoints. Additional endpoints by NRP at BL were change from BL in HbA1c, and occurrence of adverse

events (AEs) in general and specifically hypoglycaemia. The latter two were captured based on investigator reported events and coded using the Medical Dictionary for Drug Regulatory Activities version 20.1.

Statistical analyses

P-values for association of BL characteristics between NRP groups were obtained from Chi-square test for categorical variables and from t-test for continuous variables (after log transformation for UACR). Time-to-event outcomes were analysed using Cox proportional hazards regression models, with randomized treatment and geographical region as factors. For NRP subgroup analyses, an additional factor for NRP subgroup as well as NRP 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 any dose of study medication (treated set). Handling of missing data is described in the statistical analysis plan published elsewhere [27].

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. The iteratively measured continuous parameter HbA1c was analysed using mixed-effect models for repeated measures including randomized treatment, region, week, treatment by week interaction, linear covariates of BL measurement and BL 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, USA).

RESULTS

Of 6979 randomized and treated participants followed for median of 2.2 years, 646 (9.3%) had NRP at BL (Table 1). People with

Table 1. BL characteristics [n (%), mean (standard deviation) unless otherwise stated] of participants with and without NRP

	NRP	No NRP	Overall	P-value NRP versus no NRP
n (%)	646 (100)	6330 (100)	6979 (100)	
Age, years	62.3 (9.3)	66.1 (9.0)	65.9 (9.10)	<0.001
Men, n (%)	387 (59.9)	4001 (63.2)	4390 (62.9)	0.098
Women, n (%)	259 (40.1)	2329 (36.8)	2588 (37.1)	
Region, n (%)				
Europe (including South Africa)	207 (32.0)	2724 (43.0)	2934 (42.0)	<0.001
Latin America	273 (42.3)	2037 (32.2)	2310 (33.1)	
North America	95 (14.7)	1085 (17.1)	1180 (16.9)	
Asia	71 (11.0)	484 (7.6)	555 (8.0)	
Smoking status				
Never smoked	349 (54.0)	3402 (53.7)	3751 (53.8)	0.53
Ex-smoker	223 (34.5)	2284 (36.1)	2507 (35.9)	
Currently smokes	73 (11.3)	638 (10.1)	711 (10.2)	
Missing	1 (0.2)	6 (0.1)	7 (0.1)	
eGFR (MDRD), mL/min/1.73 m^2	39.9 (21.6)	56.1 (24.8)	54.6 (25.0)	<0.001
≥90	25 (3.9)	703 (11.1)	728 (10.4)	<0.001
≥60 to <90	82 (12.7)	1820 (28.8)	1902 (27.3)	
≥45 to <60	92 (14.2)	1256 (19.8)	1348 (19.3)	
≥30 to <45	197 (30.5)	1740 (27.5)	1937 (27.8)	
≥15 to <30	242 (37.5)	798 (12.6)	1040 (14.9)	
<15	8 (1.2)	13 (0.2)	21 (0.3)	
UACR, median (25th to 75th percentile), mg/g	3486 (2746, 4941)	129 (38, 461)	162 (44–728)	<0.001
UACR, n (%)				
<30 mg/g	0	1392 (22.0)	1392 (19.9)	<0.001
30–300 mg/g	0	2894 (45.7)	2894 (41.5)	
>300 mg/g	646 (100)	2044 (32.3)	2690 (38.5)	
HbA1c, %	8.1 (1.0)	7.9 (1.0)	7.95 (1.0)	<0.001
Diabetes duration, years	16.2 (8.9)	14.6 (9.5)	14.8 (9.5)	<0.001
Body mass index, kg/m^2	30.9 (5.5)	31.3 (5.3)	31.2 (5.3)	0.06
Systolic BP/diastolic BP, mmHg	150.7 (19.7)/	139.5 (17.3)/	140.5 (17.9)/	<0.001/<0.001
	81.3 (10.9)	77.5 (10.4)	77.8 (10.5)	
Insulin	459 (71.1)	3490 (55.1)	3950 (56.6)	<0.001
Metformin	236 (36.5)	3569 (56.4)	3808 (54.6)	<0.001
SU	151 (23.4)	2090 (33.0)	2242 (32.1)	<0.001
Any antihypertensives, n (%)	627 (97.1)	6061 (95.8)	6691 (95.9)	0.11
ACE inhibitors or ARBs	530 (82.0)	5125 (81.0)	5658 (81.1)	0.50
Statins, n (%)	450 (69.7)	4566 (72.1)	5018 (71.9)	0.18
Total cholesterol, mg/dL	204.2 (61.9)	168.5 (45.4)	171.8 (48.3)	<0.001
LDL-cholesterol, mg/dL	112.8 (50.8)	88.9 (37.6)	91.1 (39.6)	<0.001
HDL-cholesterol, mg/dL	47.4 (15.2)	44.2 (12.7)	44.5 (12.9)	<0.001

Missing albuminuria data from three participants, therefore overall not always identical to the sum of subgroups (NRP + no NRP). P-values obtained from Chi-square test for categorical variables and from t-test for continuous variables (after log transformation for UACR). LDL, low-density lipoprotein; HDL, high-density lipoprotein.

NRP versus those without (Table 1) tended to be younger, had lower mean eGFR, higher UACR, higher HbA1c and longer duration of T2D, had more often insulin therapy, and had a higher systolic BP and low-density lipoprotein cholesterol. Despite no stratification by NRP, randomization to either LINA or PBO was balanced (Supplementary data, Table S2).

CV and kidney outcomes

Incidence rates for all outcomes were consistently higher in patients with NRP at BL. Specifically, those with NRP in the PBO group (Figure 1) showed a >2-fold higher rate for CV events, and 10- to 14-fold higher rates for kidney events. The incidence rates did not appear to be influenced by sex (Supplementary data, Figure S1A and B).

Overall, regardless of NRP status, there was no difference between LINA versus PBO with respect to 3P-MACE [hazard ratio (HR) 1.02 (95% confidence interval, CI 0.89–1.17)], CV mortality [0.96 (0.81–1.14)], all-cause mortality [0.98 (0.84–1.13)], all-cause hospitalization [0.93 (0.85–1.00)] or hospitalization for heart failure [0.90 (0.74–1.08)]; the corresponding results do not indicate that NRP is an effect modifier (all interaction P > 0.05) (Figure 2). Overall, there was also no difference between the key secondary endpoint [renal death, sustained ESKD or sustained decrease of ≥40% in eGFR from BL; 1.04 (0.89–1.22)], renal death, sustained ESKD or sustained decrease of ≥50% in eGFR from BL [0.98 (0.82–1.18)], renal death or sustained ESKD [0.87 (0.69–1.10)], the composite renal endpoint of renal death, ESKD or eGFR <10 mL/min/1.73 m^2 [0.84 (0.67–1.05)] or the composite renal endpoint of renal death, ESKD or doubling of creatinine [0.92 (0.77–1.11)], for LINA versus PBO. When assessed by NRP status (Figure 2), some heterogeneity was observed for LINA versus PBO for the key secondary outcome of renal death, sustained ESKD or sustained decrease of ≥40% in eGFR [NRP yes/no: 0.80 (0.63–1.01)/1.25 (1.02–1.54); P for interaction 0.005], but not for the other kidney outcomes, including the analysis using a 50% eGFR reduction or doubling of creatinine, in a corresponding composite endpoint [NRP yes/no: 0.83 (0.64–1.09)/1.17 (0.91–1.51), P for interaction
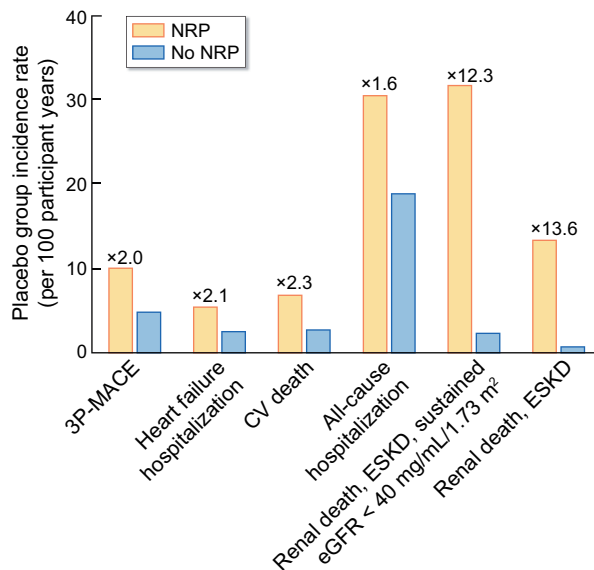
0.07 and NRP yes/no: 0.81 (0.62–1.06)/1.09 (0.84–1.41), P for interaction 0.13]. Also no heterogeneity of the effect was observed for the composite renal death or ESKD [NRP yes/no: 0.88 (0.64–1.21)/0.94 (0.67–1.31), P for interaction 0.79].

A 3-fold greater decline in eGFR per year was seen in those with NRP (NRP eGFR slopes: LINA −6.51 mL/min/1.73 m^2 versus PBO −7.07 mL/min/1.73 m^2) relative to those without NRP (no NRP slopes: LINA −2.10 mL/min/1.73 m^2 versus PBO −1.84 mL/min/1.73 m^2), but the loss in eGFR over time was not different between the treatment groups (Figure 3A). However, considering only the first 12 weeks (Figure 3B), a significant modest relative slope reduction was observed with LINA versus PBO in those without NRP at BL (−0.25 ± 0.08/4 weeks; P = 0.002), that was attenuated for the period Week 12 to LVOT (0.04 ± 0.17/year; P = 0.81). No significant effects on eGFR slopes was observed for those with NRP in either of these time windows.

Effect on albuminuria

Overall, in participants randomized to LINA, a significantly higher proportion regressed to normoalbuminuria [1.20 (1.07–1.34)], as well manifesting an UACR reduction of ≥30% from BL [1.14 (1.06–1.22)] or UACR reduction of ≥50% from BL [1.15 (1.07–1.25)], with consistent treatment effects independent of NRP (all interaction P > 0.05). Attenuated effects for all albuminuria regression endpoints were seen when analysis applied the sustained reduction of UACR criterion, both overall and by NRP, e.g. HR for UACR reduction of ≥50% from BL was 1.10 (1.00–1.21) with interaction P = 0.43 (Figure 4).

Considering participants with NRP at BL, a numerically higher proportion regressed to no NRP range [1.22 (0.98–1.52)], also in the sustained analysis [1.18 (0.92–1.51)], but neither met the statistical significance criterion (P-values 0.08 and 0.19, respectively).

Effect on HbA1c, hypoglycaemia and AEs. Difference in HbA1c over the full study duration based on least square means favoured LINA [−0.36 (−0.42 to −0.29)%], not indicating a different effect by NRP [−0.41 (−0.63 to −0.19)] and no NRP [−0.35 (−0.42 to −0.29)], without an increase in hypoglycaemia (Table 2). The proportion of participants with hypoglycaemia was, however, higher in the NRP versus no NRP in both treatment groups. Severe hypoglycaemic AEs were observed in low numbers in those with NRP (Supplementary data, Figure S1), with numerically more events in the LINA [20 (6.3%)] than the PBO group [10 (3.0%)]; IRR 2.03 (0.95–4.35).

AEs. Generally, AEs occurred more frequently in patients with NRP compared with no NRP participants. However, the frequency of any AEs, serious AEs and AEs leading to study drug discontinuation was similar between the treatment groups, independent of NRP at BL (Table 2).

DISCUSSION

This analysis of 646 individuals with NRP and T2D represents one of the largest cohorts of individuals with these conditions studied to date. The results underscore the clinical challenge faced by T2D complicated with NRP; younger age, longer T2D duration and poorer glycaemic control, where when metformin use is restricted leading to increased insulin use. Furthermore, those with NRP had more poorly controlled systolic BP, a 2-fold higher rate of CV complications and a 10-fold higher rate of

FIGURE 1: PBO group incidence rates for CV events, heart failure and all-cause hospitalization and renal outcomes in participants with NRP at BL or without NRP (no NRP) at BL. '×' denotes the relative higher event rate in NRP relative to no NRP.

	Linagliptin (N=3494)		Placebo (N=3485)		HR (95% CI)	HR (95% CI)	p-value
	n (%)	Rate/100 PY	n (%)	Rate/100 PY			
3P-MACE							
All patients	434 (12.4)	4.69	420 (12.1)	5.63	1.02 (0.89, 1.17)		**0.74**
NRP (n=646)	79 (24.9)	12.49	69 (21.0)	10.31	1.21 (0.88, 1.67)		0.28
No NRP (n=6330)	354 (11.1)	5.14	350 (11.1)	5.16	1.00 (0.86, 1.15)		
CV mortality							
All patients	255 (7.3)	3.26	264 (7.6)	3.40	0.96 (0.81, 1.14)		**0.63**
NRP (n=646)	55 (17.4)	8.11	50 (15.2)	7.06	1.17 (0.80, 1.72)		0.27
No NRP (n=6330)	199 (6.3)	2.79	213 (6.8)	3.01	0.92 (0.76, 1.12)		
All-cause mortality							
All patients	367 (10.5)	4.69	373 (10.7)	4.80	0.98 (0.84, 1.13)		**0.74**
NRP (n=646)	74 (23.3)	10.9	66 (20.1)	9.32	1.19 (0.86, 1.66)		0.21
No NRP (n=6330)	292 (9.2)	14.09	306 (9.7)	4.33	0.94 (0.80, 1.10)		
All-cause hospitalization							
All patients	1157 (33.1)	18.50	1213 (34.8)	20.07	0.93 (0.85, 1.00)		**0.06**
NRP (n=646)	148 (46.7)	29.96	154 (46.8)	30.72	0.99 (0.79, 1.24)		0.57
No NRP (n=6330)	1009 (31.8)	17.54	1058 (33.5)	19.09	0.92 (0.85, 1.00)		
Hospitalized heart failure							
All patients	209 (6.0)	2.77	226 (6.5)	3.04	0.90 (0.74, 1.08)		**0.26**
NRP (n=646)	40 (12.6)	6.41	37 (11.2)	5.70	1.31 (0.84, 2.06)		0.09
No NRP (n=6330)	169 (5.3)	2.45	188 (6.0)	2.78	0.86 (0.69, 1.05)		
Key secondary kidney endpoint							
All patients	327 (9.4)	4.89	306 (8.8)	4.66	1.04 (0.89, 1.22)		**0.62**
NRP (n=646)	125 (39.4)	26.70	148 (45.0)	31.86	0.80 (0.63, 1.01)		0.0049
No NRP (n=6330)	202 (6.4)	3.25	157 (5.0)	2.58	1.25 (1.02, 1.54)		
Renal death or sustained ESKD							
All patients	136 (3.9)	1.78	154 (4.4)	2.04	0.87 (0.69, 1.10)		**0.24**
NRP (n=646)	70 (22.1)	11.79	84 (25.5)	13.61	0.88 (0.64, 1.21)		0.79
No NRP (n=6330)	66 (2.1)	0.94	69 (2.2)	1.00	0.94 (0.67, 1.31)		
Renal death, sustained ESKD, or sustained eGFR (MDRD) < 10 ml/min/1.73 m²							
All patients	149 (4.3)	2.17	172 (4.9)	2.57	0.84 (0.67, 1.05)		**0.12**
NRP (n=646)	73 (23.0)	13.83	94 (28.6)	17.54	0.78 (0.57, 1.06)		0.36
No NRP (n=6330)	76 (2.4)	1.20	77 (2.4)	1.25	0.95 (0.70, 1.31)		
Renal death, sustained ESKD, or ≥ two-fold increase in serum creatinine‡							
All patients	219 (6.3)	3.21	229 (6.6)	3.43	0.92 (0.77, 1.11)		**0.40**
NRP (n=646)	97 (30.6)	19.13	120 (36.5)	23.18	0.81 (0.62, 1.06)		0.13
No NRP (n=6330)	122 (3.8)	1.94	108 (3.4)	1.76	1.09 (0.84, 1.41)		
Renal death, sustained ESKD, sustained decrease of ≥ 50% in eGFR							
All patients	230 (6.6)	3.39	226 (6.5)	3.42	0.98 (0.82, 1.18)		**0.87**
NRP (n=646)	101 (31.9)	20.35	119 (36.2)	23.62	0.83 (0.64, 1.09)		0.07
No NRP (n=6330)	129 (4.1)	2.05	107 (3.4)	1.74	1.17 (0.91, 1.51)		

Non-bold p-values are for interaction

0.5   1   1.5   2
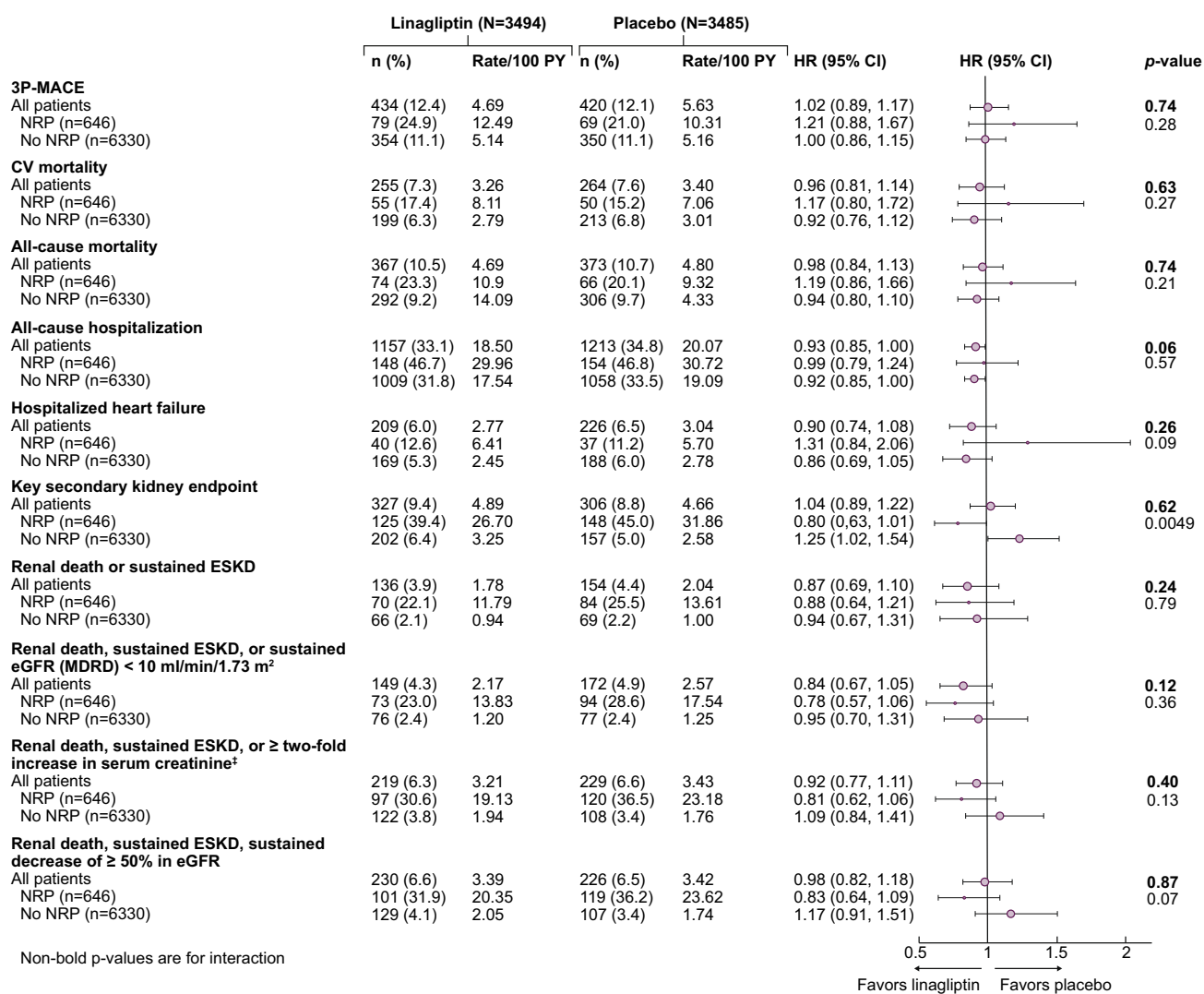
Favors linagliptin ← → Favors placebo

FIGURE 2: CV, hospitalization and kidney outcomes for LINA versus PBO, overall and by NRP at BL. Renal death, sustained ESKD or sustained decrease of ≥40% in eGFR from BL were predefined analysis, whereas the others were *post hoc* defined analysis. Point estimates on the left side of the curve indicate a positive effect for LINA. Events and HR (95% CI). Key secondary kidney endpoints: renal death, sustained ESKD or sustained decrease of ≥40% in eGFR from BL. PY, patient-year. ‡Accompanied by eGFR (MDRD) <60 mL/min/1.73 m².

kidney complications, including a 3-fold faster decline in eGFR. The trial also demonstrated that LINA treatment was associated with improvements in albuminuria and glycaemic control, without increasing hypoglycaemia risk, but did not affect CV or kidney risk among people with NRP, for whom few data have previously been published.

As remission of proteinuria may lead to symptomatic improvement, as well as being a marker of risk reduction in people with NRP [30], the observation of a significant, yet modest, increased proportion with regression to normoalbuminuria, as well as reduction of UACR ≥50% from BL, including in individuals with NRP, is interesting, and important. A previous smaller trial indicated that regression of NRP, defined as a reduction in albuminuria from NRP (defined as persisting albuminuria >2500 mg/24 h) to <600 mg/24 h, sustained for at least 1 year, was associated with both a reduction in the risk of progressing to ESKD, and improved survival [15].

The reduction in albuminuria burden aligns with some other results involving DPP-4i in T2D without NRP [31], but none has previously examined individuals with severe albuminuria.

Mechanistically, it has been suggested that these effects are not related to changes in glycaemic control [28], but rather alternate mechanism, e.g. via attenuation of podocyte injury or inhibition of myofibroblast transformation [32], or inhibition of endothelial-to-mesenchymal transition and restoration of microRNA-29s [33]. The observations of neutral effects on CV outcomes and kidney composite outcomes, despite a significant reduction in albuminuria burden, probably suggests that changes in albuminuria are not strong effect-modifier for CV disease [34] and that the magnitude of effect is too modest to modulate risk for kidney outcome [35, 36]. Alternatively, it could be argued that a median duration of 2.2 years is too short a time period to be able to modulate the risk for kidney events. The potential heterogeneity of effect for the key kidney outcome we consider is a play of chance, as this was not observed for harder kidney outcomes excluding the eGFR component, or when using other creatinine-based measures in the same composite outcome (like doubling of creatinine or other eGFR cut-offs).

The observation of a modest subacute effect on eGFR in those without NRP, i.e. in participants with a better preserved
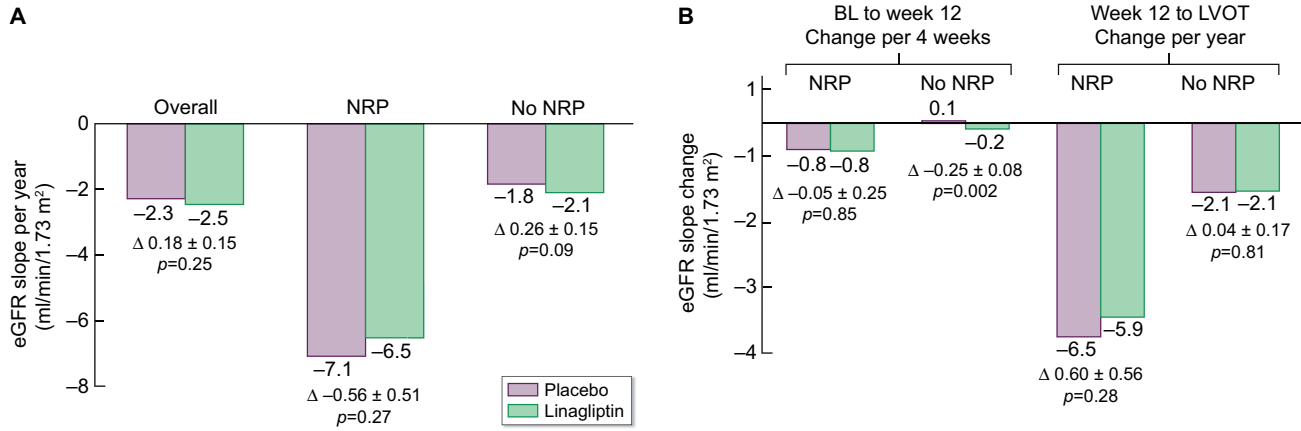
A

B

FIGURE 3: (**A**) eGFR slopes (MDRD) from BL to LVOT by NRP at BL. Δ, between-group difference ± standard error in slope. (**B**) eGFR slopes (MDRD) from BL to Week 12, and from Week 12 to LVOT by NRP at BL. Δ, between-group difference ± standard error in slope.

	Linagliptin		Placebo				
	n (%)	Rate/100 PY	n (%)	Rate/100 PY	HR (95% CI)	HR (95% CI)	*p*-value
First regression to normoalbuminuria							
All patients	631 (22.6)	11.52	538 (19.3)	9.71	1.20 (1.07, 1.34)		**0.0021**
NRP	18 (5.7)	2.80	17 (5.2)	2.51	1.15 (0.59, 2.23)		
No NRP	613 (24.7)	12.68	521 (21.2)	10.72	1.19 (1.06, 1.34)		0.91
Sustained regression to normoalbuminuria							
All patients	445 (15.9)	8.88	391 (14.0)	7.97	1.12 (0.98, 1.28)		**0.10**
NRP	13 (4.1)	2.48	14 (4.3)	2.59	0.99 (0.46, 2.10)		
No NRP	432 (17.4)	9.63	377 (15.4)	8.64	1.12 (0.97, 1.28)		0.75
First regression to normo- or microalbuminuria							
All patients	467 (35.1)	19.84	433 (31.9)	17.53	1.14 (1.00, 1.30)		**0.05**
NRP	43 (13.6)	6.95	38 (11.6)	5.74	1.25 (0.81, 1.93)		
No NRP	424 (41.7)	24.44	395 (38.5)	21.84	1.12 (0.97, 1.28)		0.64
Sustained regression to normo- or microalbuminuria							
All patients	365 (27.4)	17.03	348 (25.7)	15.93	1.08 (0.93, 1.25)		**0.31**
NRP	30 (9.5)	5.86	28 (8.5)	5.26	1.15 (0.69, 1.92)		
No NRP	335 (33.0)	20.54	320 (31.2)	19.37	1.06 (0.91, 1.24)		0.77
Time to first UACR reduction ≥ 30% from BL							
All patients	1594 (57.0)	38.71	1460 (52.5)	33.94	1.14 (1.06, 1.22)		**0.0003**
NRP	171 (54.1)	38.92	179 (54.4)	37.34	1.06 (0.86, 1.31)		
No NRP	1423 (57.4)	38.69	1281 (52.2)	33.52	1.15 (1.07, 1.24)		0.46
Sustained UACR reduction of ≥ 30% from BL							
All patients	1231 (44.0)	42.08	1161 (41.7)	41.58	1.05 (0.97, 1.14)		**0.21**
NRP	142 (44.9)	35.18	142 (43.2)	33.16	1.07 (0.85, 1.36)		
No NRP	1089 (43.9)	28.63	1019 (41.5)	27.32	1.05 (0.97, 1.15)		0.87
Time to first UACR reduction of ≥ 50% from BL							
All patients	1279 (45.8)	27.43	1145 (41.1)	23.84	1.15 (1.07, 1.25)		**0.0004**
NRP	132 (41.8)	26.25	126 (38.3)	22.67	1.17 (0.92, 1.50)		
No NRP	1147 (46.3)	27.57	1019 (41.5)	23.99	1.15 (1.06, 1.25)		0.88
Sustained UACR reduction of ≥ 50% from BL							
All patients	949 (34.0)	18.25	872 (31.3)	16.67	1.10 (1.00, 1.21)		**0.04**
NRP	104 (32.9)	18.95	94 (28.6)	15.80	1.23 (0.93, 1.62)		
No NRP	845 (34.1)	18.17	778 (31.7)	16.79	1.09 (0.99, 1.20)		0.43
Regression to non-NRP for patients with NRP at BL	160 (50.6)	34.99	156 (47.4)	29.84	1.22 (0.98, 1.52)		**0.08**
Sustained regression to non-NRP for patients with NRP at BL	128 (40.5)	25.08	123 (37.4)	21.65	1.18 (0.92, 1.51)		**0.19**

Non-bold p-values are for interaction

0.4 0.8 1.2 1.6 2.0 2.4

Favors linagliptin   Favors placebo

FIGURE 4: Effects on regression of albuminuria overall and by NRP at BL. HR based on Cox regression analyses in patients treated with one or more dose of study medication. Sustained regression to normoalbuminuria and sustained regression to normoalbuminuria or microalbuminuria were predefined analysis, whereas the others were *post hoc* defined analysis. Point estimates on the right side of the curve indicate a positive effect for LINA. Events and HR (95% CI). PY, patient-year.

Table 2. AEs occurring until 7 days after treatment discontinuation in CARMELINA by NRP at BL and overall by treatment groups

n (%)	NRP		No NRP		Overall	
	646 (100)		6330 (100)		6979 (100)	
	LINA (317)	PBO (329)	LINA (3175)	PBO (3155)	LINA (3494)	PBO (3485)
One or more AE	266 (83.9)	287 (87.2)	2429 (76.5)	2435 (77.2)	2695 (77.6)	2722 (78.1)
One or more serious AEs	174 (54.9)	180 (54.7)	1119 (35.2)	1162 (36.8)	1293 (37.2)	1342 (38.5)
AE leading to discontinuation	69 (21.8)	62 (18.8)	289 (9.1)	339 (10.7)	358 (10.3)	401 (11.5)
Aggregated SOC or single preferred terms within category 'any adverse events'						
Infections and infestations[a]	99 (31.2)	119 (36.2)	894 (28.2)	988 (31.1)	993 (28.6)	1107 (31.8)
Injury, poisoning and procedural complication[a]: includes fractures	31 (9.8)	29 (8.8)	315 (9.9)	302 (9.6)	346 (10.0)	331 (9.5)
Hypotension	2 (0.6)	0 (0)	44 (1.4)	35 (1.1)	46 (1.3)	35 (1.0)
Peripheral oedema	23 (7.3)	28 (8.5)	107 (3.4)	144 (4.6)	130 (3.7)	172 (4.9)
Hyperkalaemia	10 (3.2)	24 (7.3)	75 (2.4)	74 (2.3)	85 (2.4)	98 (2.8)
Acute kidney injury	19 (6.0)	19 (5.8)	77 (2.4)	83 (2.6)	96 (2.8)	102 (2.9)
Renal impairment	18 (5.7)	26 (7.9)	68 (2.1)	67 (2.1)	86 (2.5)	93 (2.7)
ESKD	22 (6.9)	26 (7.9)	16 (0.5)	19 (0.9)	38 (1.1)	45 (1.3)
Hypoglycaemia						
Any hypoglycaemia	108 (34.1)	110 (33.4)	926 (29.2)	914 (29.0)	1034 (29.8)	1024 (29.4)
PG <54 mg/dL or severe hypoglycaemia[b]	60 (18.9)	68 (20.7)	495 (15.6)	504 (16.0)	555 (16.0)	572 (16.4)
Severe hypoglycaemia[b]	20 (6.3)	10 (3.0)	86 (2.7)	98 (3.1)	106 (3.1)	108 (3.1)

Missing albuminuria data from three participants, therefore overall not always identical to the sum of subgroups (NRP + no NRP). [a]Based on the totality of events within the SOC. [b]Severe = requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative action.
PG, plasma glucose; SOC, system organ class.

renal function, is consistent with previous reports of DPP-4i [28, 37, 38]. This effect might be related to remission of hyperfiltration, due to an early natriuretic effect mediated by stromal cell-derived factor-1α [39] or indirectly via the 2- to 3-fold increase in GLP-1 levels. The increase in GLP-1 levels induces natriuresis by reducing the Na/H exchange transporter isoform three-dependent sodium reabsorption in the proximal tubule and/or via modulation of more than one of the >40 other substrates metabolized by DPP-4, including high-mobility group protein box 1 [40]. In toto, this did not translate into a long-term kidney benefit, but could potentially explain in part the heterogeneity of effects when evaluating composite kidney outcomes that include renal haemodynamic components.

These results from CARMELINA are important, as people with NRP have limited glucose-lowering therapy options, given a number of agents are contraindicated or require dose reduction [11, 41, 42]. This is particularly true for those with eGFR <45 mL/min/1.73 m^2. Furthermore, people with T2D and NRP could have non-diabetic renal disease, e.g. membranous nephropathy or immunoglobulin A nephropathy [6, 43], which we were not able to further characterize in this analysis, as well as being at particularly increased risk of drug-related adverse effects [38]. It is therefore particularly important to obtain specific safety data in this population [5, 10]. Most glucose-lowering trials of DPP-4i [37, 44–46] have included modest numbers of participants with CKD, with very few subjects with NRP [13, 29]. In this context, the results presented here not only demonstrate CV and kidney safety for LINA in NRP and T2D, but also demonstrate that LINA modestly reduces progression of albuminuria and increases regression to normoalbuminuria. We also did not observe an increase in risk for HF in those with NRP and T2D, which differs from a previous trial with another DPP-4i that indicated an increased risk of hospitalization for HF [47]. In this

particularly frail population, LINA was well tolerated and its safety profile was comparable to that of PBO.

SGLT-2 inhibitors are now recommended for use relatively early in T2D, since they have been shown to prevent or slow the progression of CV and HF events, as well as CKD [2–4, 48]. They may also have an important role in those with NRP as indicated in the first dedicated study in a larger proteinuric population [24] in which 503 of 4401 participants with T2D and CKD had UACR >3000 mg/g, and in whom the CV and kidney benefits were consistent with the overall study population. However, they are still mostly licensed for use in moderate-to-good renal function, and their glucose-lowering efficacy typically diminishes with reduced eGFR. Other commonly used medications for those with NRP and T2D, such as sulphonylureas, which are associated with hypoglycaemia and are contraindicated in severe renal function disorders, also require particular monitoring. In this context, LINA may have an important role as it improves glycaemic control without increasing the risk of hypoglycaemia [2–4, 45] even in the presence of reduced GFR and NRP. Thus, an agent such as LINA, which also might delay insulin initiation [28], might be used to meet the KDIGO recommendation of an individualized HbA1c target, ranging from <6.5% to <8.0% in those with T2D and non-dialysis-dependent CKD [16, 49].

The strengths of this analysis include the large number of participants with NRP and a pre-specified analysis by NRP at BL. The trial itself also prospectively captured and centrally adjudicated kidney outcomes. The trial also had some limitations. The median follow-up was only 2.2 years, many of the other analyses were defined *post hoc*, and the trial excluded people with BL eGFR <15 mL/min/1.73 m^2 and those receiving dialysis. In addition, due to the relatively low number of women with events, in particular in the NRP group, we were unable to perform a reliable outcome analysis by sex.

In conclusion, results from CARMELINA support the view that LINA has a role in treating patients with T2D and CKD, including in those complicated by the presence of NRP, by improving glucose control and modestly reducing albuminuria burden, without increasing CV, kidney risk or AEs, including hypoglycaemia.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

C.W., M.E.C., O.E.J., R.T., J.R., D.K.M., S.E.K., E.P., M.v.E., N.M., J.H.A., B.Z. and V.P. made contributions to the concept and design of the study. C.W., M.E.C., O.E.J., R.T., J.R., D.K.M., S.E.K., E.P., S.S., M.v.E., J.T.G., N.M., J.H.A., B.Z. and V.P supervised the conduct of the study. E.P. and S.S. analysed the data, following analysis-plans developed by all authors. All authors contributed to the interpretation of the data. C.W. and O.E.J. wrote the first draft of the manuscript and the revision, which was subsequently reviewed and approved by all the authors.

DATA AVAILABILITY STATEMENT

The sponsor of CARMELINA (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents and patient-level clinical study data. Researchers are invited to submit inquiries via the Vivli website (https://vivli.org/).

CONFLICT OF INTEREST STATEMENT

C.W. has received grant support, fees for advisory services and lecturing from Boehringer Ingelheim. Advisory services fees came from Bayer, MSD and MundiPharma, as well as fees for lecturing from Eli Lilly and AstraZeneca. M.E.C. has received research support from the Australian National Health and Medical Research Council (Project and Investigator Grants), and advisory boards or speaking at scientific meetings (or both) for Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, MSD, MundiPharma, Novartis, Novo Nordisk, Reata, Sanofi and Servier. O.E.J. was an employee of Boehringer Ingelheim at the time of writing of this manuscript, but is now an employee of Nestlé Health Science. R.T. is a consultant to Amgen, Boehringer Ingelheim, ZS Pharma, Relypsa, Novo Nordisk, Reata, AstraZeneca, Bayer and receives grant support from the NIH. J.R. has served on scientific advisory boards and received honoraria or consulting fees from Eli Lilly, Sanofi, Novo Nordisk, Janssen, Oramed, Boehringer Ingelheim and Intarcia; he has also received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, Oramed and Intarcia. D.K.M. has received personal fees from Afimmune, Boehringer-Ingelheim, Janssen Research and Development LLC, Sanofi-Aventis Group, Merck Sharp and Dohme, Merck & Co., Lilly USA, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai Inc., Pfizer, Metavant, Applied Therapeutics, Esperion. S.E.K. has received personal fees from Boehringer Ingelheim, Eli Lilly, Intarcia, Merck, Novo Nordisk and Pfizer. N.M. has given lectures for Amgen, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly, NovoNordisk; has received unrestricted research grants from Boehringer Ingelheim; and has served as an advisor for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca and NovoNordisk. In addition, he has served in trial leadership for Boehringer Ingelheim and Novo Nordisk. All personal compensation from pharma or device companies are declined. J.H.A. has received personal fees from Abbvie, Bayer, Bristol-Myers Squibb, CryoLife, CSL Behring, Novo Nordisk, Pfizer, Portola, Quantum Genomics, XaTek and Zafgen, and institutional research support from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cryolife, CSL Behring, Ferring, Glaxosmithkline and XaTek. B.Z. has received consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi Aventis. E.P., S.S., J.T.G. and N.D.G. are employed by Boehringer Ingelheim. M.v.E. was employed by Boehringer Ingelheim at the time of conduct of the study, but is now an employee of Nestlé Health Science. V.P. has received research support from the Australian National Health and Medical Research Council (Project and Programme Grant); steering committees for trials supported by AbbVie, Boehringer Ingelheim, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Novo Nordisk, Pfizer, Retrophin and Tricida; advisory boards or speaking at scientific meetings (or both) for AbbVie, Astellas Pharma, Astra Zeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect Corporation, Eli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen, Merck & Co, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier and Vitae. He has a policy of having honoraria paid to his employer. Parts of these data were presented during a late-breaking oral presentation at ERA-EDTA 14 June 2019, Budapest, Hungary.

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