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CLINICAL RESEARCH
Epidemiology and prevention

Aldosterone in chronic kidney disease and renal outcomes

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Abstract

Aims Randomized controlled trials have demonstrated the efficacy of mineralocorticoid receptor (MR) antagonism in delaying chronic kidney disease (CKD) progression in diabetes; however, they have not investigated the role of aldosterone or whether these beneficial effects could be achieved in individuals without diabetes.

Methods and results The association between serum aldosterone concentrations and kidney disease progression was investigated among 3680 participants in the Chronic Renal Insufficiency Cohort. The primary outcome was CKD progression [defined as the composite of 50% decline in estimated glomerular filtration rate (eGFR) or end-stage kidney disease, whichever occurred first]. The associations between serum aldosterone and kidney disease outcomes were assessed using Cox proportional hazard models. At baseline, higher aldosterone concentrations were associated with a lower eGFR, lower serum potassium, greater urinary potassium, and protein excretion. Over a median follow-up of 9.6 years, 1412 participants developed CKD progression. In adjusted models, each doubling of serum aldosterone was associated with a 11% increased risk of CKD progression [hazard ratio (HR) 1.11, 95% confidence interval (CI) 1.04–1.18]. Individuals with the highest quartile of serum aldosterone had a 45% increased risk of CKD progression (HR 1.45, 95% CI 1.22–1.73) compared with the lowest quartile. The risk for CKD progression was similar regardless of whether patients had concomitant diabetes (*P*-interaction = 0.10).

Conclusion Higher serum aldosterone levels among individuals with CKD are independently associated with an increased risk for kidney disease progression, irrespective of concomitant diabetes. These findings provide mechanistic support for MR antagonists in delaying CKD progression and suggest that they may also have a role in those without diabetes.

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Structured Graphical Abstract

Key Question

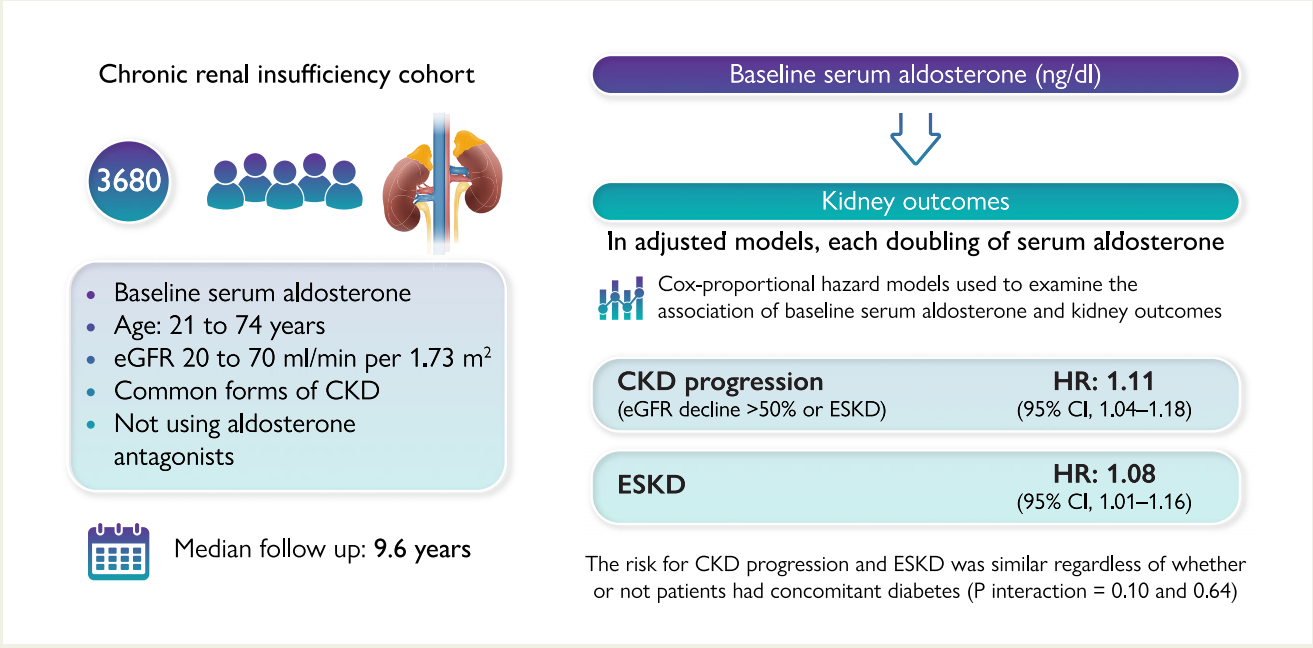
What is the association between serum aldosterone and chronic kidney disease (CKD) progression in individuals with CKD?

Key Finding

- Higher aldosterone concentrations among individuals with CKD were independently associated with increased risk for kidney disease progression.
- This risk for CKD progression was similar regardless of whether patients had concomitant diabetes.

Take Home Message

These observational data suggest that pathogenic aldosteronism may play a role in CKD progression. The data also provide mechanistic support for investigating the value of MR antagonist therapy as a method to delay CKD progression in those without diabetes.



Aldosterone in chronic kidney disease and renal outcomes: study design and summary results. CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; MR, mineralocorticoid receptor.

Keywords Aldosterone • Chronic kidney disease • End-stage kidney disease • CRIC • Diabetes

Introduction

Aldosterone is known to contribute to the development of hypertension, cardiovascular disease, and kidney disease.[1] Aldosterone activates the mineralocorticoid receptor (MR) in principal cells and plays a vital role in regulating extracellular volume homeostasis and blood pressure by inducing sodium reabsorption and potassium excretion.[2] The MR is also expressed in cardiovascular tissue and other kidney cell types, where MR activation can induce cardiac fibrosis, hypertension, left ventricular hypertrophy, podocytopathy, tubulointerstitial inflammation, and tubulointerstitial fibrosis.[3–6]

Primary aldosteronism has been shown to be a highly prevalent but under-recognized syndrome.[7,8] Patients with primary aldosteronism have a higher risk for developing cardiovascular disease[9,10] and kidney disease[11,12] and these adverse outcomes can be mitigated by MR antagonist therapy.[9] Even among patients without primary aldosteronism, MR antagonists have been shown to reduce albuminuria in individuals with chronic kidney disease (CKD) irrespective of concomitant diabetes.[13] Most recently, the FIDELIO-DKD and FIGARO-DKD trials showed that in patients with CKD and diabetes, treatment with the non-steroidal MR antagonist finerenone decreased the risk of CKD progression and cardiovascular events when compared with placebo.[14,15] These landmark findings led to the regulatory approval of finerenone for preventing the progression of CKD in diabetes.

The FIDELIO-DKD and FIGARO-DKD trials provide high-level evidence of the value of MR antagonism, but did not fully investigate the putative mechanism of action underlying the key findings. The

trials did not directly measure plasma aldosterone levels, and thus could not analyse whether aldosteronism may have been the underlying mediator accounting for the benefit of finerenone. These studies also focused on populations with diabetes, and therefore whether MR antagonism may also decrease the risk for kidney disease progression in individuals without diabetes was not evaluated.

In this study, we hypothesized that higher serum aldosterone would be associated with a higher risk for kidney disease progression irrespective of concomitant diabetes. We investigated this hypothesis among participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, a prospective observational cohort study of patients with CKD.

Methods

Study population

The CRIC study is a multicentre, prospective, observational cohort study designed to investigate the risk factors for death, cardiovascular disease, and CKD progression in participants with known CKD.[16] From 8 April 2003, through 3 September 2008 (Phase 1), 3939 participants, 21–74 years old, were enrolled across seven clinical centres in the USA, with an estimated glomerular filtration rate (eGFR) ranging from 20 to 70 mL/min/1.73 m^2.[17] Exclusion criteria for this cohort were: inability to provide written consent, institutionalization, pregnancy, enrolment in other research studies, New York Heart Association Classes III–IV heart failure, multiple myeloma, cirrhosis, human immunodeficiency virus infection, polycystic kidney disease, renal cancer, recent chemotherapy, immunosuppressive therapy, and prior treatment with dialysis for at least 1 month of organ transplant.[16,17] The institutional review board approved the study protocol at each recruiting site with written informed consent from all participants. Data and documentation files for these analyses were obtained from the National Institute of Diabetes and Digestive and Kidney Disease Central Repository in December 2019.

Main exposure and determination of population eligible for analysis

The main exposure of interest for this study was serum aldosterone concentrations. Serum aldosterone measurements were available in 3866 participants at their first study visit. Of these 3866 with available baseline aldosterone measurements, 158 participants who were on MR antagonists and 28 participants with no information on the use of MR antagonists were excluded from these analyses since this medication class can increase aldosterone levels and potentially modify the relationship between aldosterone and the main outcome. The final study population included 3860 participants.

Laboratory measurement of exposure

Aldosterone was measured using an ELISA kit (Biovendor, www.biovendor.com) from baseline plasma Ethylenediaminetetraaceticacid specimens as previously described.[18] Samples were collected in the fasting state and stored at −70°C until 2010. All measurements were conducted after a single thaw. The estimates of the intra-assay and intra-assay coefficients of variation ranged from 6.5 to 8.7%.[18]

Ascertainment of covariates

Self-reported socio-demographic characteristics, medications, height, and weight were obtained at the Year 1 study visit at the time of measurement of serum aldosterone. All baseline laboratory measurements were performed on the Year 1 visit samples using standard assays. Diabetes was defined as a fasting plasma glucose level of 126 mg/dL or random blood glucose of 200 mg/dL or higher or self-reported use of anti-diabetic medications. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[19]

Main outcome measures

Chronic Renal Insufficiency Cohort study participants were followed annually at clinic visits and via telephone contact every 6 months. The primary outcome was CKD progression, defined as the composite of 50% decline in eGFR or incident end-stage kidney disease (ESKD), whichever came first. The secondary outcomes were incident ESKD alone, defined as the initiation of chronic dialysis or kidney transplant, all-cause mortality, and major adverse cardiovascular events (MACE). Major adverse cardiovascular events comprised of incident heart failure, stroke, and myocardial infarction. End-stage kidney disease was defined based on information from clinic follow-up visits, interim telephone contact, dialysis unit record review, and information from the US Renal data system.[16] Estimated glomerular filtration rate was measured annually at every study visit, and eGFR values between annual study visits were imputed, as previously described.[20]

Statistical analysis

Continuous variables were expressed as means [standard deviation (SD)] or medians [interquartile range (IQR)], and categorical variables as count with percentages. The distribution of continuous variables was examined using the Shapiro–Wilk test. Continuous variables with non-normal distribution were log transformed. Comparison of baseline characteristics across serum aldosterone quartiles was done using the χ^2 test for categorical variables and analysis of variance and the Kruskal–Wallis test for variables with parametric and non-parametric distributions as appropriate. *P*-values for trend were calculated for eGFR, serum potassium, 24 h urine potassium, and 24 h urine sodium using Jonckheere's trend test. The association between baseline serum aldosterone and eGFR was examined using Pearson correlation.

Cox proportional hazard regression models were used to examine the multivariable-adjusted risk of outcomes according to serum aldosterone as a continuous variable (log base 2) and quartiles. Participant follow-up was censored at the time of death, loss to follow-up, or end of follow-up period, whichever occurred first. Proportional hazard assumption was confirmed using the function 'cox. zph' in 'survival' R package.[21] The Fine–Gray competing risk regression models were used to study the association of serum aldosterone and CKD progression using death as a competing event. The competing risk regression was done using 'cmprsk' package in R software.[22] The linearity assumption was checked using restricted cubic splines using 'rms' package in R software.[23]

The multivariable adjustment strategy for the Cox proportional hazard and Fine–Gray regression models was based on covariates' biological and clinical plausibility as potential confounders of the association between serum aldosterone and kidney disease outcomes. Model 1 was adjusted for age, sex, self-reported race (black vs. non-black), stratified by clinical sites, and body mass index. Model 2 included covariates in Model 1 and further adjusted for diabetes mellitus status (yes/no), systolic blood pressure, history of cardiovascular disease (yes/no), serum albumin, serum potassium, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (yes/no), history of hypercholesterolaemia (yes/no), haemoglobin A1C, loop diuretic use (yes/no), statin use (yes/no), smoking status (current), brain natriuretic peptide levels, 24 h urinary sodium, and potassium excretion. Model 3 included covariates in Model 3 and baseline eGFR, Model 4 included

Table 1 Characteristics of Chronic Renal Insufficiency Cohort study participants by serum aldosterone

N	Overall 3680	Quartile 1 920	Quartile 2 920	Quartile 3 920	Quartile 4 920	*P*-value
Serum aldosterone, ng/dL (IQR)	10.0 (7.1–14.8)	5.6 (4.6, 6.3)	8.5 (7.8, 9.2)	11.9 (10.9, 13.2)	20.6 (17.1, 29.3)	<0.001
Age, years [mean (SD)]	58.1 (11.1)	58.9 (10.5)	58.21 (10.9)	57.87 (11.0)	57.42 (11.7)	0.027
Female sex, no (%)	1645 (44.7)	474 (51.5)	420 (45.7)	360 (39.1)	391 (42.5)	<0.001
Race						
White, no (%)	1723 (46.8)	425 (46.2)	407 (44.2)	431 (46.8)	460 (50.0)	0.106
Black, no (%)	1518 (41.2)	382 (41.5)	393 (42.7)	395 (42.9)	348 (37.8)	
Other, no (%)	439 (11.9)	113 (12.3)	120 (13.0)	94 (10.2)	112 (12.2)	
Current smoker, no (%)	483 (13.1)	121 (13.2)	118 (12.8)	126 (13.7)	118 (12.8)	0.939
BMI, kg/m^2 [mean (SD)]	31.9 (7.8)	32.10 (7.7)	32.23 (7.7)	32.03 (7.6)	31.61 (7.9)	0.36
Drinker (≥once/week), no (%)	750 (20.4)	176 (19.1)	186 (20.2)	204 (22.2)	184 (20.0)	0.42
History of cardiovascular disease, no (%)	1187 (32.3)	314 (34.1)	298 (32.4)	291 (31.6)	284 (30.9)	0.48
Diabetes, yes (%)	1769 (48.1)	457 (49.7)	458 (49.8)	442 (48.0)	412 (44.8)	0.11
Calcium channel blockers, yes (%)	1487 (40.4)	314 (34.1)	348 (37.8)	409 (44.5)	416 (45.2)	<0.001
Beta-blockers, yes (%)	1792 (48.7)	430 (46.7)	442 (48.0)	469 (51.0)	451 (49.0)	0.318
Alpha-blockers, yes (%)	502 (13.6)	102 (11.1)	109 (11.8)	142 (15.4)	149 (16.2)	0.002
Alpha2 agonists, yes (%)	312 (8.5)	45 (4.9)	66 (7.2)	104 (11.3)	97 (10.5)	<0.001
Vasodilators, yes (%)	500 (13.6)	109 (11.8)	118 (12.8)	145 (15.8)	128 (13.9)	0.085
ACEi/ARB, yes (%)	2526 (68.6)	658 (71.5)	666 (72.4)	625 (67.9)	577 (62.7)	<0.001
Hypertension, yes (%)	3165 (86.0)	784 (85.2)	791 (86.0)	791 (86.0)	799 (86.8)	0.79
Diastolic blood pressure, mmHg [mean (SD)]	71.6 (12.7)	70.7 (12.3)	71.3 (12.4)	72.4 (13.4)	71.9 (12.9)	0.03
Systolic blood pressure, mmHg [mean (SD)]	128.7 (22.0)	128.9 (22.5)	128.5 (21.8)	129.3 (21.5)	128.1 (22.4)	0.70
24 h urine sodium [mean, mmol/24 h (SD)]	161.2 (77.0)	163.5 (75.0)	166.4 (80.5)	163.9 (77.3)	150.9 (74.6)	<0.01*
24 h urine potassium, mmol/24 h [median (IQR)]	51.0 (37.1, 68.1)	48.5 (35.6, 65.7)	50.7 (37.0, 67.6)	52.0 (37.7, 69.9)	53.7 (38.1, 70.2)	<0.01*
Peripheral vascular disease, yes (%)	247 (6.7)	55 (6.0)	72 (7.8)	67 (7.3)	53 (5.8)	0.22
Serum potassium, mmol/L [mean (SD)]	4.3 (0.5)	4.3 (0.4)	4.3 (0.5)	4.3 (0.5)	4.2 (0.5)	<0.01*
Brain natriuretic peptide, pg/mL [median (IQR)]	40.6 (16.9, 95.2)	41.8 (17.8, 96.3)	41.6 (15.5, 97.9)	39.8 (16.3, 94.2)	39.0 (18.5, 87.9)	0.93
Loop diuretic, yes (%)	1354 (36.8)	286 (31.1)	316 (34.3)	381 (41.4)	371 (40.3)	<0.01
Potassium-sparing diuretics, yes (%)	222 (6)	25 (2.7)	47 (5.1)	65 (7.1)	85 (9.2)	<0.001
eGFR, mL/min per 1.73 m^2 [mean (SD)]	44.3 (15.0)	48.5 (14.7)	44.9 (14.6)	42.4 (14.7)	41.3 (15.0)	<0.01*
Serum albumin, g/dL [mean (SD)]	3.9 (0.5)	3.88 (0.5)	3.92 (0.9)	3.95 (0.5)	3.96 (0.5)	<0.01
24 h urine protein, g/24 h [median (IQR)]	0.2 (0.07, 0.9)	0.13 (0.07, 0.7)	0.18 (0.07, 1.0)	0.23 (0.08, 1.0)	0.22 (0.07, 0.9)	<0.01
Haemoglobin A1C (%)	6.6 (1.5)	6.75 (1.6)	6.67 (1.5)	6.63 (1.6)	6.49 (1.5)	<0.01
History of hypercholesterolaemia (%)	3017 (82.0)	766 (83.3)	759 (82.5)	758 (82.4)	734 (79.8)	0.23
Statins (%)	2009 (54.6)	525 (57.1)	526 (57.2)	496 (53.9)	462 (50.2)	<0.01

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

*P-value reported for 24 h urine potassium, 24 h urine sodium, serum potassium, and eGFR is for trend.

covariates in Model 3 and further adjusted for baseline 24 h urine protein.

Sensitivity analyses were performed by excluding participants taking potassium-sparing diuretics and with serum aldosterone values ≥50 ng/dL. We used completed case analyses as there was <7.7% missing data on variables for time to event analyses. Interaction analyses were conducted to examine the effect of other variables on the association of serum aldosterone and kidney disease outcomes. All statistical tests were two-sided, and a *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software, version 3.5 (R Project for Statistical Computing).

Results

Baseline characteristics

The mean age of the study population was 58.1 (SD 11.1) years, of which 44.7% were women and 46.8% identified as white. The baseline characteristics of the study population are shown in *Table 1* by quartiles of serum aldosterone. The distribution of serum aldosterone concentrations is shown in *Figure 1*. Median serum aldosterone concentration was 10 ng/dL (IQR, 7.1–14.9 ng/dL). Median serum aldosterone concentration was higher in men to women (10.5 vs. 9.4 ng/dL; $P < 0.001$), in participants without vs. with diabetes (10.3 vs. 9.8 ng/dL; $P = 0.03$), and in participants using vs. not using loop diuretics (10.8 vs. 9.5 ng/dL; $P < 0.001$). Higher serum aldosterone concentrations were inversely associated with baseline eGFR and serum potassium, and positively associated with urinary potassium excretion (*Table 1*).

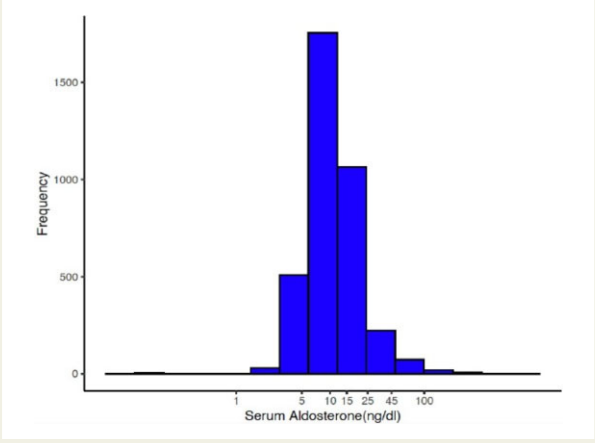


Figure 1 Distribution of serum aldosterone among participants of the Chronic Renal Insufficiency Cohort.

These trends persisted after excluding participants taking loop diuretics (data not shown). Higher serum aldosterone concentrations were significantly associated with higher urinary protein excretion at baseline; this association persisted every year until Year 5 (*Table 2*). The inverse correlation between serum aldosterone and eGFR is shown as a continuous relationship ($r = -0.15$, $P < 0.001$) (*Figure 2A*) and dichotomoized by an eGFR of 45 mL/min per 1.73 m^2 (*Figure 2B*).

Association of serum aldosterone with kidney disease outcomes

Over a median follow-up of 9.6 years, 1412 individuals developed the composite outcome CKD progression and 1129 individuals developed ESKD. Median baseline serum aldosterone concentration was significantly higher in participants who developed the composite outcome (10.6 ng/dL) when compared with those who either did not develop the composite outcome or who were censored for loss to follow-up or death (9.6 ng/dL) ($P < 0.001$). The results for the association between baseline serum aldosterone and risk for developing CKD progression are shown in *Table 3*. In a fully adjusted model, those in the highest quartile of serum aldosterone had a 45% increased risk of CKD progression {hazard ratio (HR) 1.45 [95% confidence interval (CI) 1.22–1.73]} compared with the lowest quartile. Expressing aldosterone as a continuous variable, there was an 11% higher risk for CKD progression [HR 1.11 (95% CI 1.04–

Table 2 Follow-up proteinuria in participants of chronic renal insufficiency cohort by serum aldosterone

Variables	*n*	Overall	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*-value
Aldosterone, ng/dL (IQR)	3680	20.6 (17.0–29.3)	5.57 (4.5, 6.3)	8.46 (7.8, 9.1)	11.9 (10.9, 13.1)	20.6 (17.0, 29.2)	<0.001
Baseline 24 h urine protein, g/24 h [median (IQR)]	3510	0.19 (0.07–0.95)	0.13 (0.07, 0.73)	0.18 (0.07, 1.02)	0.23 (0.08, 1.09)	0.22 (0.07, 0.97)	0.003
Year 1 24 h urine protein, g/24 h [median (IQR)]	2968	0.17 (0.07–0.90)	0.12 (0.06, 0.61)	0.17 (0.07, 0.91)	0.21 (0.08, 1.08)	0.20 (0.07, 0.99)	<0.001
Year 2 24 h urine protein, g/24 h [median (IQR)]	2494	0.18 (0.07–0.81)	0.13 (0.06, 0.60)	0.17 (0.07, 0.81)	0.22 (0.08, 0.89)	0.20 (0.07, 1.02)	<0.001
Year 3 24 h urine protein, g/24 h [median (IQR)]	1960	0.20 (0.08–0.88)	0.15 (0.07, 0.66)	0.20 (0.07, 0.87)	0.21 (0.08, 0.91)	0.23 (0.09, 1.02)	0.003
Year 4 24 h urine protein, g/24 h [median (IQR)]	1357	0.22 (0.08–0.90)	0.17 (0.07, 0.81)	0.19 (0.08, 0.90)	0.28 (0.09, 0.97)	0.26 (0.10, 0.90)	0.024
Year 5 24 h urine protein, g/24 h [median (IQR)]	638	0.25 (0.09–0.98)	0.18 (0.08, 1.07)	0.27 (0.10, 1.19)	0.24 (0.10, 1.00)	0.25 (0.10, 0.81)	0.405

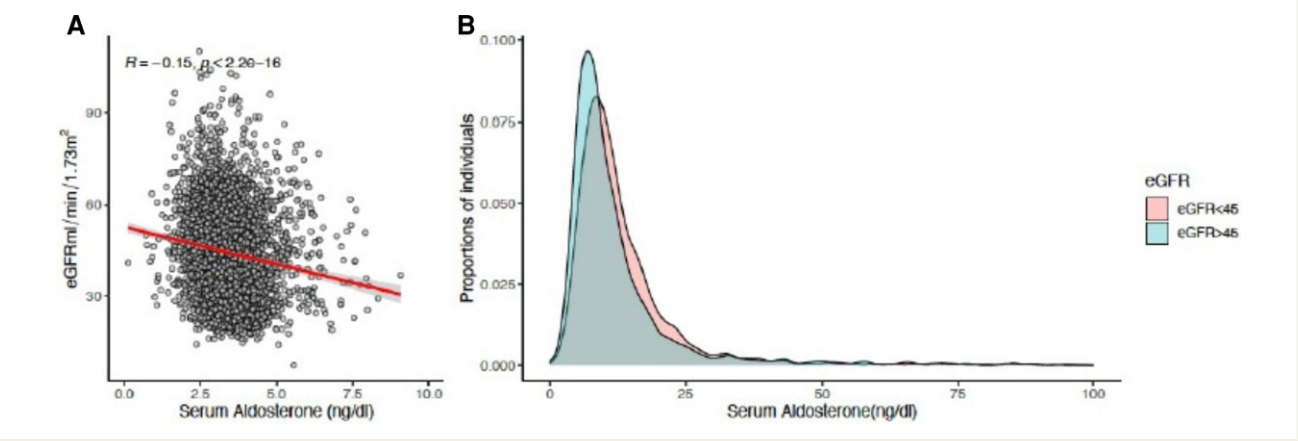


Figure 2 Correlation between serum aldosterone and estimated glomerular filtration rate. (*A*) A scatterplot between estimated glomerular filtration rate and serum aldosterone. (*B*) A density plot according to baseline estimated glomerular filtration rate.

1.18)] per doubling of serum aldosterone. *Figure 3A* shows the continuous association using restricted cubic splines in the fully adjusted model. Serum aldosterone met the linearity assumption using the wald statistics (*P*-value for linearity < 0.001). The association between serum aldosterone and CKD progression remained qualitatively similar even after excluding participants with very high serum aldosterone levels (>50 ng/dL, $n = 98$) (Supplementary material online, *Table S1*) and participants taking potassium-sparing diuretics (Supplementary material online, *Table S2*).

The results for the association between baseline serum aldosterone and risk for developing ESKD are shown in *Table 3*. Those in the highest quartile of serum aldosterone had a 46% increased risk of developing ESKD [HR 1.46 (95% CI 1.19–1.78)] compared with the lowest quartile. As a continuous variable, there was 8% higher risk for ESKD [HR 1.08 (95% CI 1.01–1.16)]. *Figure 3B* shows the continuous association using restricted cubic splines in the fully adjusted model.

Using the Fine–Gray competing risk regression the results for the association between baseline serum aldosterone and risk for developing CKD progression and ESKD alone using death as a competing event are shown in *Table 4*. The strength of association between baseline serum aldosterone and kidney outcomes was slightly attenuated but remained statistically significant.

Association of serum aldosterone and all-cause mortality and major adverse cardiovascular events

Over a median follow-up of 11.5 years, 1293 individuals reached death as an outcome and over a median follow-up of 9.1 years, 1088 individuals developed the composite outcome MACE. The results for the association of serum aldosterone and all-cause mortality are shown in *Table 3*. Those in the highest quartile of serum aldosterone had a 22% higher risk for all-cause mortality [HR 1.22 (95% CI 1.02–1.45)] compared with the lowest quartile. As a continuous variable, the association between serum aldosterone and all-cause mortality was statistically non- significant [HR 1.05 (95% CI 0.99–1.12)]. *Figure 4* shows the continuous association using restricted cubic splines in the fully adjusted model. As a continuous and in form of quartile, the association between serum aldosterone and MACE showed trends towards higher hazards but was statistically non-significant (Supplementary material online, *Table S3*).

We explored potential differences across subgroups through interaction analyses. We found that baseline eGFR ($P = 0.01$) modified the association between serum aldosterone and CKD progression alone, and that age ($P = 0.01$ and $P = 0.03$) modified the association between serum aldosterone and both kidney outcomes (*Table 5*). We found no evidence of interaction of diabetes mellitus with CKD progression ($P = 0.10$) or ESKD ($P = 0.64$) as outcomes nor any interaction between the use of ACE inhibitors and angiotensin receptor blockers and outcomes. Using 5-year follow-up data, the result for the association of baseline serum aldosterone and 50% increase in proteinuria from baseline are shown in Supplementary material online, *Table S4*.

Discussion

Pathologic aldosteronism has been postulated to be a mediator in the development CKD,[11,12] and aldosterone has garnered increased interest as a potential therapeutic target in diabetic kidney disease. In this prospective study, we observed that higher serum aldosterone levels were independently associated with a greater risk for CKD progression and ESKD in individuals with baseline CKD, independent of major confounders including baseline kidney function and urinary protein excretion (*Structured Graphical Abstract*). In addition, our study provides information about the factors associated with serum aldosterone levels in a large cohort of individuals across a spectrum of CKD severity. We found higher aldosterone levels in those with more advanced CKD, a finding that has been reported previously in small studies.[24,25] The reasons for this inverse relationship between serum aldosterone levels and advanced CKD cannot be determined with certainty. One of the factors that increase aldosterone synthesis is higher serum potassium concentration; an increase in

Table 3 Association of serum aldosterone with chronic kidney disease progression, end-stage kidney disease, and all-cause mortality

Serum aldosterone	Continuous	*P*-value	Quartile 1	Quartile 2	Quartile 3	Quartile 4
No. of events	1412	—	285	361	390	376
Association of serum aldosterone and CKD progression (ESKD or 50% eGFR decline)						
Crude	1.11 (1.06–1.17)	0.001	Reference	1.31 (1.12–1.53)	1.47 (1.26–1.71)	1.44 (1.23–1.68)
Multivariable Model 1[a]	1.14 (1.08–1.20)	0.001	Reference	1.27 (1.08–1.48)	1.37 (1.17–1.60)	1.48 (1.27–1.73)
Multivariable Model 2[b]	1.18 (1.10–1.26)	0.001	Reference	1.34 (1.14–1.59)	1.58 (1.33–1.86)	1.71 (1.44–2.03)
Multivariable Model 3[c]	1.08 (1.02–1.15)	0.007	Reference	1.27 (1.07–1.50)	1.30 (1.10–1.54)	1.38 (1.16–1.64)
Multivariable Model 4[d]	1.11 (1.04–1.18)	0.001	Reference	1.24 (1.05–1.48)	1.38 (1.16–1.64)	1.45 (1.22–1.73)
No. of events	1129	—	225	273	314	317
Association of serum aldosterone and ESKD						
Crude	1.14 (1.07–1.20)	0.001	Reference	1.26 (1.06–1.51)	1.50 (1.26–1.78)	1.56 (1.32–1.86)
Multivariable Model 1[a]	1.16 (1.09–1.23)	0.001	Reference	1.22 (1.02–1.46)	1.39 (1.17–1.65)	1.59 (1.34–1.90)
Multivariable Model 2[b]	1.19 (1.11–1.26)	0.001	Reference	1.26 (1.04–1.52)	1.62 (1.35–1.95)	1.83 (1.51–2.21)
Multivariable Model 3[c]	1.04 (0.97–1.12)	0.17	Reference	1.14 (0.94–1.38)	1.15 (0.95–1.39)	1.32 (1.09–1.61)
Multivariable Model 4[d]	1.08 (1.01–1.16)	0.02	Reference	1.16 (0.95–1.40)	1.27 (1.05–1.55)	1.46 (1.19–1.78)
No. of events	1293	—	298	310	338	347
Association of serum aldosterone and all-cause mortality						
Crude	1.04 (0.99–1.10)	0.09	Reference	1.05 (0.89–1.23)	1.16 (1.00–1.36)	1.19 (1.02–1.40)
Multivariable Model 1[a]	1.05 (0.99–1.11)	0.06	Reference	1.08 (0.92–1.27)	1.11 (0.94–1.30)	1.25 (1.07–1.46)
Multivariable Model 2[b]	1.08 (1.01–1.15)	0.01	Reference	1.13 (0.95–1.34)	1.21 (1.02–1.44)	1.34 (1.13–1.59)
Multivariable Model 3[c]	1.03 (0.97–1.10)	0.22	Reference	1.05 (0.88–1.25)	1.12 (0.94–1.33)	1.19 (1.00–1.43)
Multivariable Model 4[d]	1.05 (0.99–1.12)	0.07	Reference	1.06 (0.89–1.26)	1.13 (0.95–1.34)	1.22 (1.02–1.45)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; BMI, body mass index.
[a]Multivariable Model 1: age, sex, race, clinical centre, BMI.
[b]Multivariable Model 2: Model 1 + diabetes mellitus, systolic blood pressure, history of cardiovascular disease, haemoglobin A1c, history of hypercholesterolaemia, serum albumin, serum potassium, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, loop diuretic use, statin, smoking, BNP, 24 h urine sodium, and 24 h urine potassium.
[c]Multivariable Model 3: Model 2 + baseline eGFR.
[d]Multivariable Model 4: Model 3 + baseline 24 h urine protein.

serum potassium with worsening kidney function would plausibly stimulate aldosterone secretion. However, this is contrary to what we observed. Higher baseline serum aldosterone concentrations in this study were associated with lower rather than higher serum potassium, and higher rather than lower urinary potassium excretion; collectively, this constellation of findings supports pathologic aldosterone production and MR activation, despite lower serum potassium which should physiologically lower aldosterone production, as the driver for urinary potassium excretion. In this study, higher aldosterone levels were associated with increased baseline 24 h urine protein excretion. Previous studies had shown similar findings in patients with primary aldosteronism.[25,26] In combination with longitudinal analyses confirming baseline aldosterone concentrations as an independent predictor for CKD progression, these findings underscore prior studies linking aldosteronism with CKD,[11,12] and provide supportive evidence for the use of MR antagonists for preventing CKD progression.[14] Further, a recent observational study extends the FIDELIO findings by showing that treatment with any MR antagonist (other than finerenone) was associated with decreased progression to ESKD in CKD patients irrespective of diabetes status.[27] These findings provide a strong replication linking aldosterone as the mechanistic factor for the renoprotective role of MR antagonists in CKD, and underscore the value of our current findings wherein aldosterone was directly measured and found to be an independent predictor of adverse renal outcomes.

While much of the recent focus for MR antagonism in preventing CKD has been among patients with diabetes,[14,28] our observation that higher serum aldosterone levels are associated with CKD progression irrespective of diabetes status points to new indications for future studies.

Our results must be interpreted within the context of the study design. We were able to conduct multiple analyses to ensure the physiologic robustness of the associations. For example, the association between higher baseline aldosterone concentrations, lower

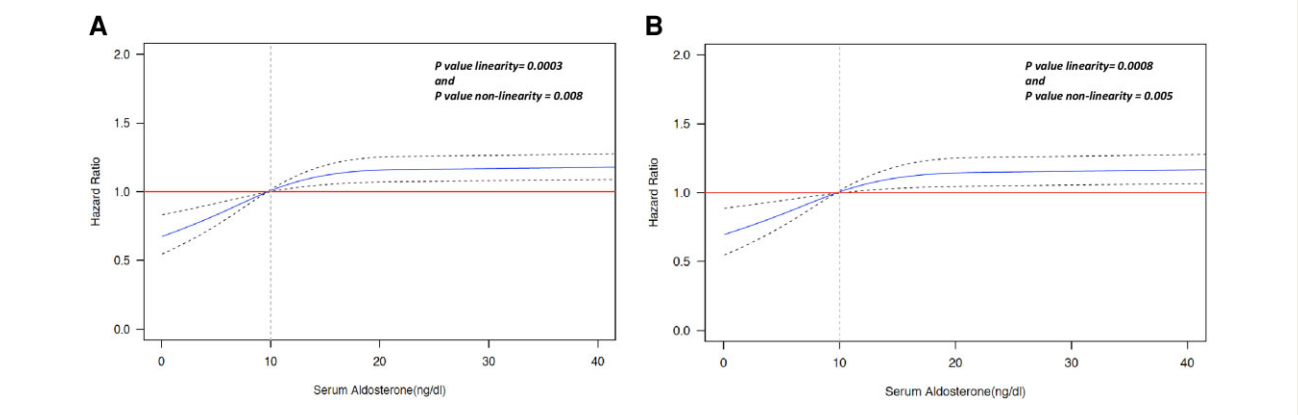


Figure 3 Association of serum aldosterone with chronic kidney disease progression (50% estimated glomerular filtration rate decline or end-stage kidney disease) (Panel A) and end-stage kidney disease (Panel B).

Table 4 Association of serum aldosterone and chronic kidney disease progression (50% estimated glomerular filtration rate decline or end-stage kidney disease) and end-stage kidney disease alone using death as a competing event

Serum aldosterone	Continuous	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Association of serum aldosterone and CKD progression (50% eGFR decline or ESKD) using death as a competing event					
Events	1412	285	361	390	376
Crude	1.11 (1.05–1.17)	Reference	1.31 (1.11–1.54)	1.47 (1.25–1.73)	1.42 (1.20–1.67)
Multivariable Model 1[a]	1.11 (1.05–1.17)	Reference	1.24 (1.05–1.46)	1.41 (1.20–1.66)	1.38 (1.17–1.62)
Multivariable Model 2[b]	1.14 (1.07–1.21)	Reference	1.25 (1.05–1.50)	1.51 (1.26–1.81)	1.55 (1.30–1.86)
Multivariable Model 3[c]	1.04 (0.97–1.11)	Reference	1.10 (0.92–1.32)	1.15 (0.95–1.39)	1.16 (0.96–1.40)
Multivariable Model 4[d]	1.09 (1.01–1.16)	Reference	1.03 (0.85–1.26)	1.17 (0.96–1.42)	1.23 (1.03–1.48)
Association of serum aldosterone and ESKD using death as a competing event					
Events	1129	225	273	314	317
Crude	1.13 (1.07–1.20)	Reference	1.24 (1.03–1.49)	1.51 (1.26–1.80)	1.55 (1.29–1.85)
Multivariable Model 1[a]	1.13 (1.06–1.21)	Reference	1.18 (0.98–1.43)	1.44 (1.20–1.72)	1.52 (1.26–1.82)
Multivariable Model 2[b]	1.17 (1.10–1.26)	Reference	1.18 (0.97–1.45)	1.56 (1.28–1.90)	1.73 (1.42–2.10)
Multivariable Model 3[c]	1.04 (0.96–1.12)	Reference	1.01 (0.82–1.25)	1.07 (0.86–1.33)	1.17 (0.94–1.45)
Multivariable Model 4[d]	1.09 (1.01–1.18)	Reference	0.95 (0.75–1.20)	1.07 (0.85–1.35)	1.25 (1.00–1.55)

ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; BMI, body mass index.
[a]Multivariable Model 1: age, sex, race, clinical centre, BMI.
[b]Multivariable Model 2: Model 1 + diabetes mellitus, systolic blood pressure, history of cardiovascular disease, haemoglobin A1c, history of hypercholesterolaemia, serum albumin, serum potassium, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, loop diuretic use, statin, smoking, BNP, 24 h urine sodium, and 24 h urine potassium.
[c]Multivariable Model 3: Model 2 + baseline eGFR.
[d]Multivariable Model 4: Model 3 + baseline 24 h urine protein.

eGFR, lower serum potassium, and higher urinary potassium excretion persisted even among patients not taking loop diuretics. Similarly, the findings were observed despite the fact that the majority of patients were using ACE inhibitors or angiotensin receptor blockers. These agents that should lower aldosterone and raise potassium in normal physiology, thus the observation of persistent hyperaldosteronism in association with lower serum potassium and eGFR provides further evidence for pathologic aldosteronism. We excluded participants who used MR antagonists since these medications are known to increase aldosterone levels and confound the relationship between the exposure and the main outcome. In contrast, an important limitation of our study was the absence of

renin measurements to indicate whether the observed aldosteronism was renin-independent (and therefore consistent with a primary aldoseronism-like phenotype[7,8]) or renin-dependent. However, as described above, the triad of higher aldosterone, lower serum potassium, and higher urinary potassium excretion argues in favour of a pathologic aldosteronism, irrespective of renin phenotype.

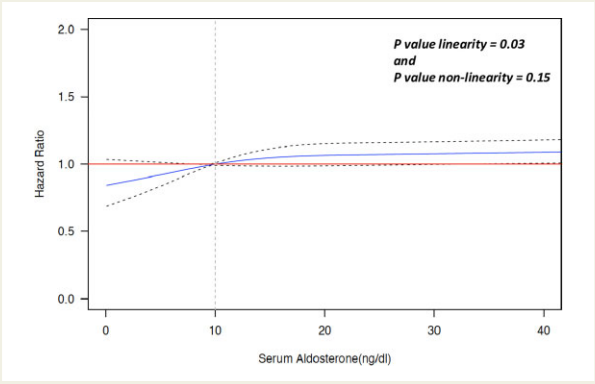


Figure 4 Association of serum aldosterone with all-cause mortality.

Few studies have examined the association between aldosterone with CKD incidence or progression. Deo *et al.*[18] presented preliminary findings from the CRIC cohort in an earlier publication focused on both cardiac and kidney outcomes; we have updated those results and focused on kidney disease outcomes including eGFR decline. Using ESKD as the outcome, they reported a non-significant association between aldosterone and ESKD risk. Our current analyses included a broader definition of CKD progression that is more comparable with current standards of clinical care and research, investigated cross-sectional and longitudinal relationships between aldosterone and eGFR, included a longer follow-up time with a greater number of outcomes, and excluded the use of MR antagonists to minimize confounding and specifically investigate the relationship between aldosterone and CKD progression. The only other study to our knowledge that has examined angiotensin II or aldosterone as a risk factor for CKD progression was published by Walker *et al.*,[29] who did not provide details on aldosterone levels or conduct adjusted analyses.

The majority of prior studies has focused on patients with primary aldosteronism. Hundemer *et al.*[11] showed that patients with primary aldosteronism had a higher risk for incident CKD when compared with patients with essential hypertension. A recent meta-analysis showed greater eGFR decline and more severe albuminuria in patients with primary aldosteronism compared with patients with

Table 5 Subgroup analysis using serum aldosterone (ng/dL) as a predictor and chronic kidney disease progression (end-stage kidney disease or 50% estimated glomerular filtration rate decline) and end-stage kidney disease as an outcome[a]

	CKD progression		ESKD	
	***P*-value for interaction**	**HR (95% CI)**	***P*-value for interaction**	**HR (95% CI)**
eGFR (mL/min/1.73 m^2)	0.01		0.06	
eGFR < 45		1.20 (1.12–1.28)		1.20 (1.12–1.29)
eGFR ≥ 45		0.99 (0.87–1.12)		0.96 (0.82–1.14)
BMI (kg/m^2)	$P = 0.25$		0.28	
BMI < 30		1.14 (1.03–1.26)		1.10 (0.98–1.24)
BMI ≥ 30		1.07 (0.98–1.15)		1.04 (0.95–1.14)
Diabetes	0.10		0.64	
Yes		1.07 (0.99–1.16)		1.07 (0.99–1.17)
No		1.16 (1.05–1.29)		1.08 (0.95–1.23)
Age (years)	0.01		0.03	
Age < 61		1.15 (1.06–1.24)		1.12 (1.03–1.22)
Age ≥ 61		1.08 (0.98–1.19)		1.04 (0.93–1.17)
Use of ACEi/ARB	0.40		0.60	
Yes		1.10 (1.02–1.18)		1.09 (1.00–1.18)
No		1.07 (0.95–1.21)		1.01 (0.88–1.16)

CKD, chronic kidney disease; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; BMI, body mass index; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

[a]Subgroup analysis was adjusted for: age, sex, race, clinical centre, BMI, diabetes mellitus, systolic blood pressure, history of cardiovascular disease, haemoglobin A1c, history of hypercholesterolaemia, serum albumin, serum potassium, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) use, loop diuretic use, statin, smoking, BNP, 24 h urine sodium, and 24 h urine potassium, baseline eGFR, and baseline 24 h urine protein.

essential hypertension.[12] In this regard, our current study extends the relationship between pathogenic aldosteronism and CKD progression beyond overt cases of primary aldosteronism, and beyond the development of CKD to progression of CKD, and beyond only those with diabetes.

There are other limitations of the current study. Serum aldosterone was measured only at a single time point at baseline and not during a period of controlled sodium intake. Aldosterone production is variable; a single aldosterone measurement does not correlate well with total daily production.[30,31] However, despite this variability, on a large population level, the correlation between aldosterone concentrations and physiologic and clinical outcomes was still robustly evident in this analysis, as well as priors.[8,32,33] Repeated measures over time, more structured blood collections, and renin levels may have provided more granular information on the activity of the renin–angiotensin–aldosterone system. Data on the duration of ACE inhibitor and angiotensin receptor blocker use were not available and may have been an important variable to consider since these medications can impact aldosterone levels and modify the risk for CKD progression.[34–36] Finally, this study is an observational cohort analysis and therefore is susceptible to residual confounding and a variety of biases; however, the main findings support observations from patients with overt primary aldosteronism and recent randomized controlled trials that used MR antagonists to delay CKD progression. In this regard, the current findings demonstrate the association of aldosterone levels with CKD progression irrespective of concomitant diabetes. In accordance with the current findings of this study there, an ongoing clinical trial (NCT05047263) is investigating the efficacy and safety of finerenone in patients with non-diabetic CKD.

In summary, we show that serum aldosterone concentrations are inversely correlated with eGFR and positively associated with 24 h urine protein at baseline, and independently associated with progression of CKD and incident ESKD. Importantly, this association between aldosteronism and CKD progression was evident in participants with and without diabetes. Given recent landmark clinical trials establishing MR antagonism as a therapy to delay the progression of CKD, the current findings provide a mechanistic explanation for the biological basis for MR antagonists in CKD. Further, these findings suggest that pathogenic aldosteronism may have a role in CKD progression in patients without diabetes, and that MR antagonist therapy should also be investigated as a method to delay CKD progression in those without diabetes.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

Data is available through NIH repository (https://repository.niddk.nih.gov/studies/cric/.

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