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Is Chronic Kidney Disease Progression Influenced by the Type of Renin-Angiotensin-System Blocker Used?

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Keywords
Proteinuria · Chronic kidney disease · Renin angiotensin system · Angiotensin-converting enzyme inhibitor · Angiotensin receptor blocker

Abstract
Introduction: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce proteinuria and slow renal disease progression more effectively than other therapies in patients with chronic kidney disease (CKD). However, differences regarding efficacy and safety between these therapies remain controversial. ***Objectives:*** Aim of this study was to analyze the different treatment effect of ACEI, ARB, and non-ACEI/ARB in CKD progression. The primary outcome was survival to end-stage renal disease (ESRD) and/or death and to ESRD censored by all-cause death, secondary outcomes were proteinuria reduction and hyperkalemia. ***Methods:*** We analyzed data from 1,120 patients extracted from the National Renal Healthcare Program cohort, which included 17,238 CKD nondialysis subjects who were successively monitored between September 1, 2004 and August 31, 2016. Inclusion criteria were at least a 1-year follow-up, 3 clinical visits, and no previous treatment with ACEI or ARB. From the baseline visit onward, patients continued with 3 different treatment schemes: no ACEI/ARB, started on ACEI or ARB, but while avoiding both treatments in combination. Chi^2, *t* test, binary logistic regression, and multivariate regression models (Cox proportional Hazard model and competing risk Fine and Gray model were used for statistical analysis. ***Results:*** Mean age and follow-up were 67.9 (± 15) and 3.8 (± 2) years, respectively. Estimated glomerular filtration rate averaged 42.1 ± 23 mL/min/1.73 m^2 and 300 (27%) patients were diabetics. Progression to ESRD was significantly worse in the no ACEI/ARB group (hazard ratio [HR] 4.23, 95% CI 1.28–13.92) versus ACEI (reference group; $p = 0.01$). The analysis by competing-risks' regression showed significantly higher risk of ESRD in the no ACEI/ARB group (HR 3.63, 95% CI 1.34–9.85) versus ACEI ($p = 0.01$). There were no significant differences between ACEI and ARB groups (HR 1.31, 95% CI 0.37–4.66) regarding the risk of progression to ESRD. Survival was similar in all 3

On behalf of all the nephrologists that reported to the NRHP, Uruguay.

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groups (p = 0.051). Statistically significantly more patients experienced reductions in proteinuria/albuminuria in ACEI and ARB groups (together) versus no ACEI/ARB group (p = 0.016, OR 1.82, 95% CI 1.12–2.94). No difference in hyperkalemia frequency was found between them (p = 0.17). ***Conclusions:*** In patients with CKD, treatment with ACEI or ARB had a superior effect than no ACEI or ARB treatment on slowing kidney disease progression and on proteinuria reduction. Efficacy of ACEI and ARB was comparable.

Introduction

The prevalence of all stages of chronic kidney disease (CKD) varies between 7 and 12% in the different regions of the world [1]. Multiple factors linked to the progression of CKD over time have been identified (proteinuria, hypertension, and metabolic acidosis, among others). The correction of them has shown benefit in terms of CKD progression and delay in the onset of dialysis [2]. Optimization and magnification of the renin angiotensin aldosterone system blockade is a strategy that had a positive impact on the CKD progression and global survival in multiple population studies [3]. International guidelines recommend angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) to reduce proteinuria, slow CKD progression, and improve overall survival in patients with CKD [4, 5]. However, if differences among them exist, in achievement of clinical benefits or side effects (such as hyperkalemia) is not well defined [6, 7]. We conducted this trial to compare the efficacy in slow progression to end-stage renal disease (ESRD), diminish all-cause mortality, proteinuria reduction, and safety of ACEI, ARB, and no ACEI/ARB treatment in a cohort of CKD patients included in a national survey.

Methods

This is a retrospective cohort study of the Uruguayan National Renal Healthcare Program (NRHP) cohort. The NRHP Registry includes patients with an estimated glomerular filtration rate (eGFR) below 60 mL/min and/or proteinuria of 0.3 g/L or more at least 3 months who were included by a nephrologist in the CKD registry (www.fnr.gub.uy) when they agreed to it (informed consent).

We identify potentially eligible patients from the 17,238 CKD adults (83% with stages III–V non-dialysis CKD) included in the registry. Inclusion criteria were at least 3 clinical visits over 1 year follow-up before study enrolment, no previous treatment with an ACEI or ARB and no changes of ACEI or ARB treatments during the study follow-up. Patients were divided into 3 groups according to therapy: those never treated with ACEI/ARB (No ACEI/ARB), those treated only with ACEI (ACEI), and those treated only with ARB (Fig. 1).

Data were analyzed from September 1, 2004, to August 31, 2016. Age, sex, comorbidities (diabetes, ischemic heart disease, peripheral artery disease, heart failure, and stroke), systolic blood pressure (SBP) and diastolic blood pressure, proteinuria and/or albuminuria excretion, serum creatinine, serum potassium (among other analytical results), and treatment with an ACEI or an ARB or with neither of them in all registered visits and outcomes including proteinuria reduction, renal replacement therapy (RRT) or all-cause death were registered. eGFR was calculated using the CKD Epidemiology Collaboration creatinine equation [8].

The primary outcome was survival to ESRD and/or all-cause death. Secondary outcomes were proteinuria or albuminuria reduction and hiperkalemia frequency.

CKD stages were defined according to KDIGO [4] in 5 stages. Laboratory results were reliable since nationwide multidisciplinary consensus on proteinuria and creatinine laboratory tests and their standardization were held by the NHRP advisory committee [9]. Arterial hypertension was defined according to VII-NJC [10] – SBP ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. ESRD was defined by RRT (dialysis or renal transplantation) initiation. NHRP registry data were cross-referenced with the Uruguayan Registry of Dialysis, a mandatory registry that includes all patients who begin RRT in the country, and with the Uruguayan Death Index to ensure that outcome data (RRT or all-cause death) was confirmed.

Albuminuria/proteinuria was defined as albuminuria ≥30 mg/day or albuminuria/creatininuria ratio ≥30 mg/g and/or proteinuria ≥150 mg/day or proteinuria/creatininuria ratio ≥150 mg/g, in at least 2 separate urine samples. A reduction of proteinuria or albuminuria was considered achieved if at least a 30% reduction was obtained from baseline until the end of the follow-up period among individuals with albuminuria/proteinuria at study initiation [11]. Hyperkalemia was defined as serum potassium ≥5.6 mEq/L and the highest value of serum potassium for each patient were analyzed. The observation period started at patient inclusion in the NRHP Registry until RRT, death, or end of follow-up by August 31, 2016, whichever occurred first.

Statistics

Data were expressed as mean ± SD, median, and interquartile range. Chi^2, t test, and multivariate regression models were used. The Cox proportional hazard model was used to estimate the association between time to ESRD, all-cause death, or time to the composite outcome (death and ESRD) with the studied covariates. In all regression models, we adjusted for age, diabetes, cardiovascular comorbidities, BP, proteinuria, and initial eGFR. As an alternative analysis, we assessed risk of ESRD with a competing risk of all-cause death using the Fine and Gray model, which extends the Cox proportional hazards model to competing-risks data by considering the sub-distribution hazard. Chi^2 and binary logistic regression were used to analyze proteinuria reduction. The software used was Stata Statistical Software; StataCorp. 2017 Release 25, College Station, TS: StataCorp LLC and IBM® SPSS Statistics®, version 22.

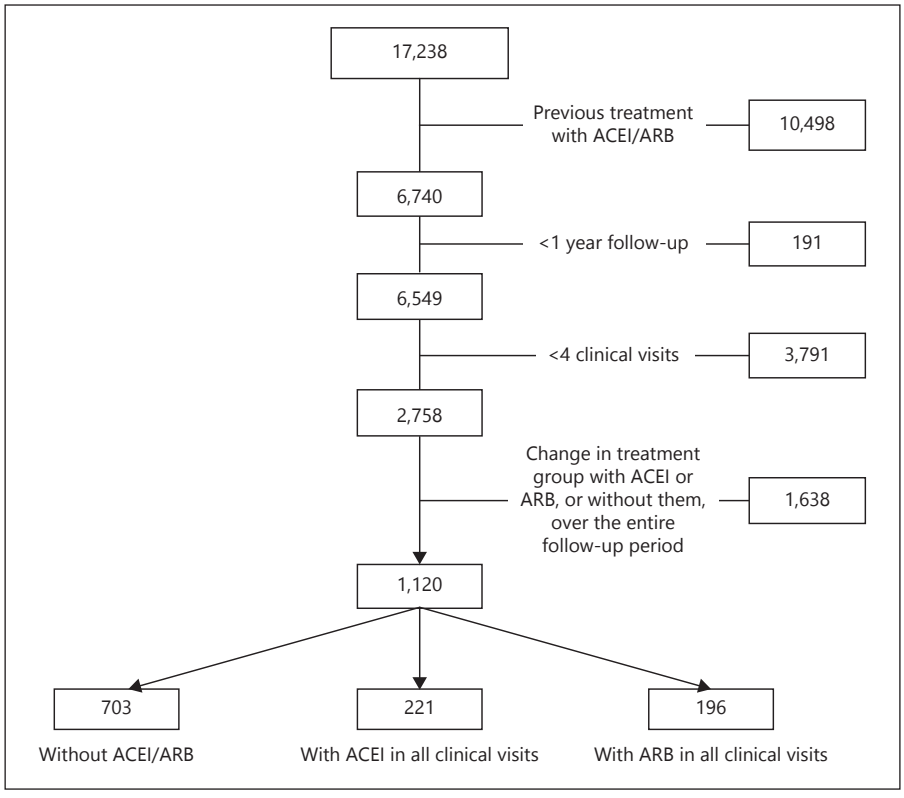


Fig. 1. Flowchart of patient selection. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Results

Global Population Characteristics

One thousand one hundred and twenty patients (Fig. 1) received treatment with an ACEI (n = 221) or an ARB (n = 196; avoiding both treatment in combination) or neither of them (n = 703) in all registered visits. There were 632 men (56.4%) with mean age 67.9 (±15) years and a mean follow-up of 3.80 (±2.01) years (range 1.01–10.07 years), total follow-up time 4,267 years (Tables 1, 2). The nephropathies were mainly vascular (444, 39.8%), tubulointerstitial (123, 10.9%), diabetic (112, 10%), glomerulopathies (46, 4.1%), others (189, 16.8%), and undiagnosed (206, 18.4%). Patients had multiple comorbidities at baseline: diabetes (300, 26.8%), hypertension (773, 69%), ischemic heart disease (217, 19.3%), peripheral artery disease (65, 5.8%), heart failure (105, 9.4%), and/or cerebrovascular disease (55, 4.9%; similar to the NRHP global population).

At the time of the first visit, 367 (32.8%) patients were undergoing treatment with diuretics, 345 (30.8%) with calcium channel blockers, 265 (23.7%) with beta-blockers, and 26 (2.3%) with alpha-blockers. Reasons for which patients did not receive an ACEI or an ARB are not available. The patients from the group with no ACEI/ARB were older, had a lower SBP, and a lower eGFR, on average (Table 1).

CKD Progression and Survival

Overall, 254 patients died (22.7%), and 85 (7.6%) patients progressed to ESRD during the studied period. The progression to ESRD was statistically significantly worse in the no ACEI/ARB group (hazard ratio [HR] 4.23, 95% CI 1.28–13.92) versus ACEI (reference group; Cox regression model p = 0.01). There were no significant differences between ARB and ACEI (HR 0.80, 95% CI 0.16–4.00, p = 0.791). The competing-risks regression analysis for ESRD censored by death (Fine and Gray) also showed statistically significantly higher risk of ESRD in the no ACEI/ARB group (HR 3.63, 95% CI 1.34–9.85) versus ACEI (p = 0.01), whereas the difference between ACEIs and ARBs was not significant after these adjustment (HR 1.31 95% CI 0.37–4.66, p = 0.681) (Table 2; Fig. 2). Survival was similar in the 3 groups (Table 2).

Changes in Proteinuria and/or Albuminuria

Overall population had a mean baseline proteinuria of 0.33 ± 1.26 g/day (Table 1). Out of 286 patients with initial proteinuria and/or albuminuria, 171 were men

Table 1. Baseline characteristics of included patients

	Overall	No ACEI/ARB	ACEI	ARB	*p* value
Number	1,120	703	221	196	
Age, years, mean ± SD	67.9±14.9	69.1±15.2^{+}	63.0±15.4^{+++}	67.2±12.2^{++}	<0.00$^{\Phi}$
Gender, male, *n* (%)	632 (56)	389 (55)	132 (59)	111 (57)	ns
CV comorbidities ≥1, *n* (%)	334 (30)	215 (30)	45 (21)***	74 (38)	<0.00*
Diabetes, *n* (%)	300 (27)	149 (21)	80 (36)	71 (36)	<0.00*
SBP, mm Hg, mean ± SD	129.7±20.6	126.9±19.3^{+}	132.9±20.9	135.7±20.8^{++}	<0.00$^{\Phi}$
DBP, mm Hg, mean ± SD	74.4±13.0	72.5±11.5^{+}	77.3±12.9	76.9±12.6^{++}	<0.00$^{\Phi}$
Urine protein, g/day, mean ± SD	0.33±1.26	0.30±1.20^{+}	0.51±1.79	0.28±0.77	ns
eGFR, mL/min/1.73 m^2, mean ± SD	42.1±23.1	36.3±19.4^{+}	55.3±26.1^{+++}	47.5±19.9^{++}	<0.00$^{\Phi}$
CKD stages III–V, *n* (%)	953 (85)	638 (91)	158 (71)	157 (80)	<0.00*
Other antihypertensive drugs, *n* (%)					
Diuretics	367 (32.8)	256 (36.4)*	43 (19.4)***	68 (34.7)	<0.00*
Beta blockers	265 (23.7)	188 (26.7)*	29 (13.1)***	48 (24.5)	<0.00*
Calcium antagonists	345 (30.8)	254(36.1)*	38 (17.1)***	53 (27.0)**	<0.00*
Alpha blockers	26 (2.3)	20 (2.8)	2 (0.9)	4 (2.0)	ns
Time of follow-up, years, mean ± SD	3.81±2.01	3.52±1.92^{+}	4.38±2.09^{+++}	4.19±2.05^{++}	<0.00$^{\Phi}$

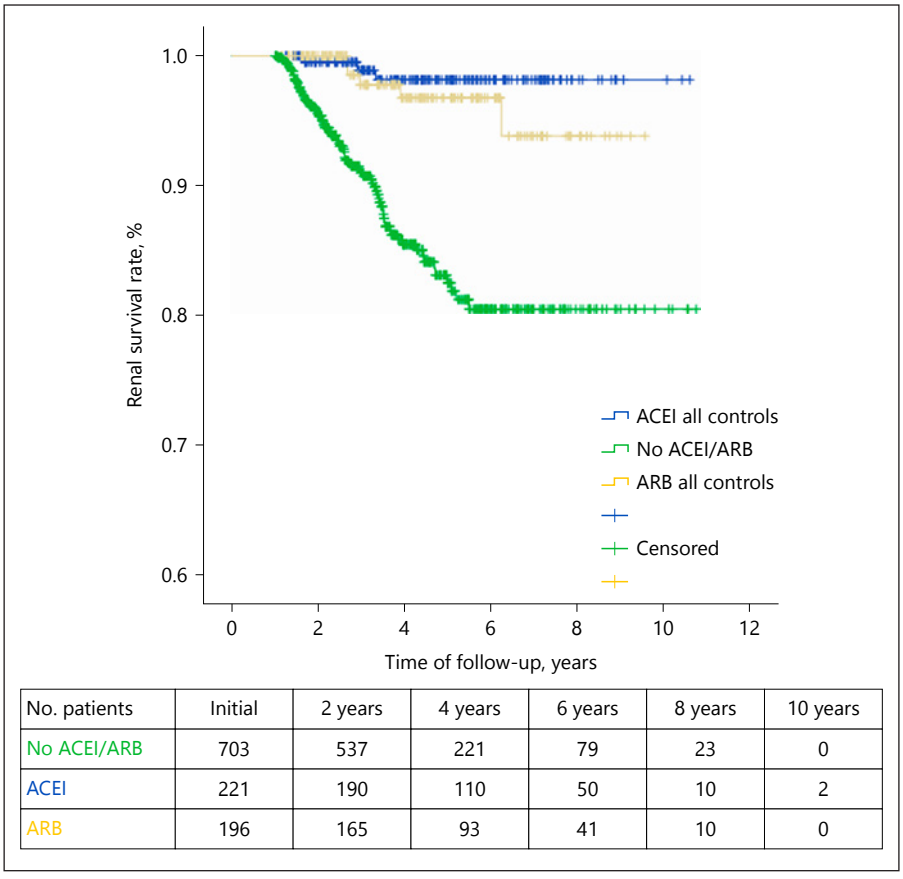
* Chi^2 $p < 0.05$.
* No ACEI/ARB vs. ACEI.
** No ACEI/ARB vs. ARB.
*** ACEI vs. ARB.
$^{\Phi}$ ANOVA posttest Bonferroni $p < 0.05$.
$^{+}$ No ACEI/ARB vs. ACEI.
$^{++}$ No ACEI/ARB vs. ARB.
$^{+++}$ ACEI vs. ARB.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ns, non significant.

Table 2. Outcome analysis. Time of exposure to risk, ESRD, and death incidence rates. Cox multivariate regression and fine and gray (competing risk) models adjusted by age, diabetes, blood pressure, CV comorbidities, proteinuria, and initial eGFR

	Overall, *n*	No ACEI/ARB, *n*	ACEI, *n*	ARB, *n*
Death	254	163	51	40
ESRD	85	77	3	5
Death + ESRD	339	240	54	45
Exposure time (years/patient)	4,267.2	2,474.5	967.9	821.2
Death rate (events/100 patient-year)	5.95	6.58	5.26	4.87
ESRD rate (events/100 patient-year)	1.99	3.11	0.30	0.60

Statistical model*	Event	Compared group	HR (95% CI)	*p* value
Cox regression	Death	No ACEI/ARB vs. ACEI (ref.)	0.68 (0.46–1.00)	0.051
		ARB vs. ACEI (ref.)	0.74 (0.46–1.18)	0.206
Cox regression	Death and ESRD	No ACEI/ARB vs. ACEI (ref.)	1.09 (0.76–1.56)	0.632
		ARB vs. ACEI (ref.)	0.80 (0.51–1.26)	0.331
Cox regression	ESRD	No ACEI/ARB vs. ACEI (ref.)	4.23 (1.28–13.92)	0.010
		ARB vs. ACEI (ref.)	0.80 (0.16–4.00)	0.791
Fine and gray (competitive risk)	ESRD censored by death	No ACEI/ARB vs. ACEI (ref.)	3.63 (1.34–9.85)	0.011
		ARB vs. ACEI (ref.)	1.31 (0.37–4.66)	0.681

* Adjusted by age, diabetes, CV comorbidity, blood pressure, proteinuria, and initial eGFR.
ACEI, angiotensin-converting enzyme inhibitors; ref., reference group; ARB, angiotensin receptor blockers; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.



No. patients	Initial	2 years	4 years	6 years	8 years	10 years
No ACEI/ARB	703	537	221	79	23	0
ACEI	221	190	110	50	10	2
ARB	196	165	93	41	10	0

Fig. 2. Global population renal survival rate (n = 1,120) censored by death. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

(59.8%) with mean age 67.9 ± 15.0 years and 113 (39.5%) were diabetics (Table 3). Furthermore, 73 patients received an ACEI (25.5%), 50 patients received an ARB (17.5%), and 163 patients were on no ACEI/ARB therapy (57%). Mean follow-up time was 3.5 (± 2.1) years (range 1.01–10.1 years). There were no differences in follow-up time between the ACEI and ARB groups. Overall, 160 patients (55.9%) obtained a proteinuria or albuminuria reduction of 30% or more between the first and last visit, 37 (12.9%) of which reached ESRD and 62 (21.7%) died. Significantly more patients with ACEI or ARB (considered altogether) experienced proteinuria/albuminuria reduction ≥30% (64.2 vs. 49.7%. Chi^2 p = 0.016, OR 1.82, 95% CI 1.12–2.94). Groups receiving an ACEI versus an ARB did not show significant differences in proteinuria/albuminuria reduction (64.4 vs. 64.0%; Table 3).

Hyperkalemia

Cases of hyperkalemia (serum potassium ≥5.6 mEq/L) were observed in all treatment groups, but their frequencies were not statistically significantly different among groups (Table 4), neither in the global population (Chi^2 p = 0.17), CKD stages I–II (p = 0.90) nor CKD III–V (p = 0.11).

Discussion

Therapy with ACEI or ARB showed superior effects on CKD progression and proteinuria versus no ACEI/ARB treatment, without significant hyperkalemia, and with no difference between ACEI and ARB in the CKD cohort studied.

ACEI/ARB is widely used in CKD because of their antihypertensive, antiproteinuric, and nephroprotective effects. However, whether differences between them exist for these results has been less studied. In the present study, 703 (4.1%) patients never received them, but the reasons were not listed in the records available (Tables 1, 3).

Despite the fact that the evidence demonstrated ACEI/ARB benefits in proteinuric [12–15] and nonproteinuric patients [16, 17] (on CKD progression and cardiovascular

Table 3. Proteinuric group: baseline characteristics

	Overall	No ACEI/ARB	ACEI	ARB	*p* value
Number	286	163	73	50	
Age, years, mean ± SD	67.9±15.0	68.4±15.4^{+}	57.8±16.7^{+++}	65.5±12.7^{++}	<0.05$^{\Phi}$
Gender, male, *n* (%)	171 (59.8)	96 (58.9)	43 (58.9)	32 (64)	ns*
CV comorbidity, *n* (%)	87 (30.4)	51 (31.3)	17 (23.3)	19 (38)	ns*
Diabetes, *n* (%)	113 (39.5)	50 (30.7)	39 (53.4)	24 (48)	<0.05*
SBP, mm Hg, mean ± SD	132.1±20	129.9±18.2	131.0±18.6^{+++}	140.7±25.3	<0.05$^{\Phi}$
DBP, mm Hg, mean ± SD	75.9±12.6	75.1±12.0	76.5±12.7	78.3±14.5	ns$^{\Phi}$
Urine protein, g/day, mean ± SD	1.17±2.15	1.16±2.13	1.34±2.69	0.99±1.16	ns$^{\Phi}$
Urine protein reduction ≥30%, *n* (%)	160 (55.9)	81 (49.7)*	47 (64.4)	32 (64)	<0.05*
eGFR, mL/min/1.73 m^2, mean ± SD	45.6±29.1	33.5±21.9^{+}	67.3±31.9^{+++}	53.3±24.3^{++}	<0.05$^{\Phi}$
CKD stages III–V, *n* (%)	215 (75.2)	145 (89)	38 (52.1)	32 (64)	<0.05*
Time of follow-up, years, mean ± SD	3.53±2.1	3.06±1.85^{+}	4.09±2.24	4.30±2.30^{++}	<0.05$^{\Phi}$

* Chi^2 $p < 0.05$.
* No ACEI/ARB vs. ACEI and vs. ARB.
*** ACEI vs. ARB.
$^{\Phi}$ ANOVA posttest Bonferroni $p < 0.05$.
$^{+}$ No ACEI/ARB vs. ACEI.
$^{++}$ No ACEI/ARB vs. ARB.
$^{+++}$ ACEI vs. ARB.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ns, non significant.

Table 4. Hyperkalemia (Kp ≥5.6 mEq/L) frequency in global population

	No ACEI/ARB	ACEI	ARB	Chi^2 test *p* value
Kp ≥5.6 mEq/L, *n* (%)				
All population	77 (10.9)	28 (12.7)	14 (7.1)	0.17
CKD stages 1–2	3 (4.6)	4 (6.3)	2 (5.1)	0.90
CKD stages 3–5	74 (11.6)	24 (15.2)	12 (7.6)	0.11

CKD, chronic kidney disease; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

mortality), there are sometimes obstacles to their prescription. There is sufficient evidence to show that most of these obstacles (such as age [18–20] and low GFR [21, 22]) should not be contraindications to treatment with ACEIs or ARBs, although treatment must be performed under appropriate supervision.

Evidence of ACEI/ARB prescription in patients with a low GFR is more contradictory [21, 23, 24]. The potential risks and benefits of ACEI/ARB use in advanced CKD are currently under investigation. The UK-based STOP-ACEI trial is a randomized, controlled, open label study of ACEI/ARB which aims at analyzing the effect of ACEI/ARB withdrawal in progressive and advanced CKD [22]. Until the results of this study are available, it will be necessary to individualize treatment based on the characteristics of the patient and to be aware of possible side effects of ACEI/ARB treatment.

In the present study, progression to ESRD was worse for nontreated patients (no ACEI/ARB; HR 4.23, 95% CI 1.28–13.92; Fig. 2) in the whole population (proteinuric and nonproteinuric groups) without differences between those groups. Also, in the proteinuric group, ACEI or ARB treatment was statistically significantly associated with proteinuria reduction without substantial differences between the ACEI and ARB groups (Table 3).

Several studies tried to establish the optimal BP target level [13, 18, 25–34], although this remains controversial and clinical trials are ongoing. In a previous study con-

ducted in the same Uruguayan CKD cohort, it was observed [31] that a SBP higher than 159 mm Hg or lower than 120 mm Hg was associated with a higher risk of a new cardiovascular event. Mallat [32] emphasized that, in patients with evidence of renal disease, guidelines recommended ACEI/ARB-based therapy due to their superior renoprotective effects compared to other antihypertensive classes.

In the present study, survival was similar for all 3 groups (Cox's regression model) in the limited follow-up (Table 2) as participants were a subpopulation (mostly with CKD stage III or higher) that had not previously received an ACEI or an ARB, which meant they were most likely diagnosed and treated late during the course of CKD. Nevertheless, there is a near significant trend in mortality (all-cause death) favoring ACEI versus no ACEI/ARB (Cox's regression, $p = 0.051$; Table 4), as it was expected.

Hyperkalemia, as well as the initial rise in serum creatinine, was well described side effects after ACEI/ARB prescription [6, 14], although severe hyperkalemia was rarely reported. Some authors described that hyperkalemia was statistically significantly associated with ARB treatment more frequently than with ACEI [6, 14]. Guidelines advise to check serum creatinine and potassium level within 2 weeks of initiating an ACEI or ARB [4, 7, 35]. In the present cohort, hyperkalemia was present in all groups, without statistically significantly differences among them (hence, it is mandatory to monitor serum potassium levels). As this was a retrospective study, no data were available regarding specific hyperkalemia treatment, which was a limitation of the present study.

There are other limitations of the study, as it was a retrospective study, but as a national cohort of almost 20,000 CKD patients with a mean follow-up of 3.8 years granted the advantage of providing "real-world" data. The population analyzed has been strictly selected to compare the effects of ACEI versus ARB without the bias of previous treatment. As a result of this strategy, the number of patients included was relatively small (Fig. 1). Additionally, 85% of patients included in the study had CKD stage III or higher and were likely a subgroup that had not received proper previous care and/or that had been diagnosed or referred to nephrologists late in the course of CKD. As a retrospective analysis from a registry, the exact drugs used and their doses were unknown. Moreover, the groups studied showed differences in baseline characteristics (Table 1).

The group studied had similar characteristics (i.e., mean age, sex distribution, BP, and biochemical data) to those of the whole NRHP population [36] from which patients were selected. Cardiovascular comorbidities were highly prevalent (Tables 1, 3) in the entire population of the study (in the proteinuric as well as in the nonproteinuric subpopulation), as it was reported in all CKD cohorts [13–16].

We found that treatment with either ACEI or ARB showed a superior effect on CKD progression and on proteinuria reduction when compared to no ACEI/ARB treatment. The positive effect of these treatments was similar for ACEI and ARB and was not associated with a significant increase in hyperkalemia frequency.

Acknowledgments

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Statement of Ethics

All patients included had signed an informed consent, pursuant to Uruguayan Law No. 18331.

Disclosure Statement

All authors declared to have no conflict of interest. All authors read and approved the final version of the manuscript.

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Author Contributions

All authors contributed to this work.

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