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Improving the Management of Chronic Kidney Disease in Uruguay: A National Renal Healthcare Program

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Key Words
Chronic kidney disease · Registry · Epidemiology · Evaluation of chronic kidney disease progression · Nephrology care · Renoprotection

Abstract
Background: Uruguay has implemented a chronic kidney disease (CKD) prevention program. ***Aims:*** The objectives of the study are to assess the results of the National Renal Healthcare Program (NRHP). ***Methods:*** This study is a cohort study of nondialysis-registered patients from October 2004 to March 2008. We made a comparison between patients under nephrology care (NC) or the care of a primary care physician (PCP; prereferral). In the outcome analysis, the primary endpoint was end-stage renal disease (ESRD) and the secondary endpoints were progression of CKD, compliance with the therapeutic goals and death. ESRD/mortality predictors were determined by Cox analysis. ***Results:*** The study comprised 2,219 patients aged 67.4 ± 13.5 years, of whom 52.5% were male, 42.1% hypertensive, 16.9% had diabetic nephropathy, and 61.3 and 21.4% were in CKD stages III and IV, respectively. At baseline, NC patients showed a better control than patients under the care of a PCP: systolic blood pressure ≥160 mm Hg (22.4 vs. 31.1%); total cholesterol <5.8 mmol/l (56.6 vs. 42.5%); and low-density lipoprotein cholesterol <2.9 mmol/l (41.2 vs. 29.1%). Control improved in patients under the care of a PCP according to years of enrollment. Outcome analysis (1,188 patients) showed a significant improvement in targets, with 56% of the patients stabilizing. CKD stage IV, diabetic nephropathy, proteinuria and hypertension increased the risk of ESRD; angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and age <65 years decreased the risk. ***Conclusions:*** Our results highlight the best management of CKD patients in both groups and the impact of the NC and renin-angiotensin-aldosterone system blockers.

Chronic kidney disease (CKD) is considered a public health issue [1–3], and the strategies to delay its progression are prevention, early detection and intervention [4, 5]. A lot of patients are still referred to nephrology care (NC) close to the starting time of renal replacement therapy, and late referral is associated with a poorer outcome once in dialysis [6–10]. Nephrologists cannot care for all CKD patients, and the prevention and early detection of this disease requires a skilled, multidisciplinary primary care team and a coordinated approach [11]. In order to attain such care, different strategies have been published based on the healthcare system and the living standards of various countries [12–25].

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Uruguay is a developing country with 3.2 million inhabitants, with 13.7% over the age of 65 and a predominantly Caucasian population (97.2%) [26].

Within this context, Uruguay has implemented a National Renal Healthcare Program (NRHP). The general and specific objectives, implementation, main strategies for generalization and the preliminary results of the pilot program have recently been published [27]. The program was planned and designed by the Uruguayan Society of Nephrology [28] according to the Latin American Society of Nephrology and Hypertension [20–30] and the recommendations of the consensus workshops of the International Society of Nephrology [31], and is supported by the National Resource Fund and the Public Health Ministry.

The NRHP has an online multiple-purpose disease patient registry. After being included in the program, patients receive shared management between doctors from the primary care system (PCS) and nephrologists in a reference–counter reference system depending on stage [32] and etiology of the CKD. Patients in CKD stage IV are referred to an advanced CKD clinic with a tertiary level of care, staffed by a formal multidisciplinary team under the nephrologists' leadership. There are no records of patients assisted at the PCS at the registry.

The objectives of the study are to assess the results of the NRHP by measuring the quality of care in primary care, the impact of NC, compliance with the treatment targets, the progression of CKD and the rate and risk factors of ESRD and death.

Methods

Data Analysis and Statistics

This is an observational study of registered patients, aged 20 years and over, with CKD stages I–IV, enrolled between October 1, 2004 and March 31, 2008 from healthcare providers participating in the NRHP. Patients were referred to the NC voluntarily by a primary care physician (PCP) or directly from the laboratory in the case of urinary abnormalities or elevated serum creatinine levels. Patients under NC and those recently referred by a PCP could be included in the CKD registry only by nephrologists. The inclusion criteria were: estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, proteinuria >300 mg/day, and/or microalbuminuria between 30–300 mg/day in diabetic patients, when persistent for more than 3 months.

The Multi-Task Treatment (MTT) [33–35] approach was recommended in clinical guidelines [36] and educational courses for the management of patients with CKD in the PCS and is prescribed by PCPs and nephrologists in order to stabilize CKD. MTT involves: the administration of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) as first-line antihypertensive and antiproteinuric drugs, statins, antiplatelet agents and allopurinol, if necessary; dietary salt and protein restrictions depending on CKD stage; smoking cessation; avoidance of excessive alcohol intake, and a healthy lifestyle. The adherence of physicians to the proposed MTT was assessed by the frequency of use of the drugs previously mentioned.

The recommended treatment targets were: proteinuria <0.3 g/day, systolic blood pressure (SBP) <130 mm Hg, diastolic blood pressure (DBP) <80 mm Hg or ≤125/75 if proteinuria >1 g/day, a normal BMI (18.5–24.9), waist perimeter <102 cm in males and <88 in females, serum total cholesterol (TCh) <5.18 mmol/l, low-density lipoprotein cholesterol (LDL-C) <2.59 mmol/l, high-density lipoprotein cholesterol >1.04 mmol/l in males and >1.29 in females, triglycerides <1.69 mm/l, hemoglobin levels >11 mg/dl, HbA1c in diabetic patients lower than 7%, and normal serum uric acid (<416 μmol/l for males, <357 for females).

From the variables included at baseline and on control visit questionnaires, we selected the following for the purposes of this analysis: age, gender, race, diagnosis, date and cause of death, diabetes (serum fasting glucose ≥126 mg/dl or taking insulin/antidiabetic drugs), blood pressure (mm Hg), weight (kg), height and waist perimeters (cm), serum creatinine (mg/dl, modified Jaffé reaction), proteinuria (g/l or day) or microalbuminuria (albuminuria/creatinuria mg/g), lipid profile, and serum uric acid levels (μmol/l). The following baseline comorbid conditions were also selected: coronary heart disease (CHD; history of acute myocardial infarction, coronary bypass surgery or percutaneous transluminal coronary angioplasty), left ventricular hypertrophy (ECG or echocardiography), peripheral vascular disease (absence of lower limb pulses, surgical revascularization or color Doppler ultrasonography), congestive heart failure (CHF; clinical diagnosis), a cerebrovascular accident (clinical diagnosis, CT or MRI scan), and neoplasia.

Previous data allowed the CKD operational definition and CKD stages devised by the Kidney Disease Outcomes Quality Initiative (KDOQI) [32]. Late referral to nephrologists was defined as CKD stage IV at the 1st NC. Stabilization was defined by an eGFR reduction lower than 1 ml/min/year. Slow progression was if the rate of reduction was 1–3 ml/min/year and fast progression if the decline of eGFR >3 ml/min/year. High blood pressure was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg or the use of antihypertensive drugs. Patients were considered obese if their BMI was ≥30 and overweight if their BMI was 25–29.9. The etiology of the underlying CKD was categorized as follows: vascular nephropathy, diabetic nephropathy, obstructive nephropathy, primary glomerulonephritis, tubulointerstitial nephropathy, cystic diseases, others and unknown.

Primary data were collected from the online CKD registry, which has an alarm system to minimize the loss of follow-up. Secondary data were taken from the National Death Records and the Uruguayan Registry of Dialysis to check dates, attributed causes of death and ESRD patients.

An internal comparison of groups between patients under NC or the care of a PCP (prereferral), both at baseline and in the follow-up, was performed. Baseline characteristics were analyzed for all of the registered patients. The primary endpoint in the outcome analysis was ESRD and the secondary endpoints were progression of CKD, compliance with the therapeutic goals and death. The analysis was done with the inclusion of patients with at least 6 months of follow-up, which was computed from the date

of entry up to the date of death, dialysis, transplantation or the last control. Undocumented data were expressed as N for each variable.

The GFR was estimated by the abbreviated Modification of Diet in Renal Disease equation [32].

The change in eGFR (prereferral) was the difference in the eGFR between the first known creatinine level and the creatinine at baseline divided by the time-lag between the 2 measures. The eGFR change after enrolling into the NRHP was estimated by the difference between the first and last available eGFR divided by the time-lag between the 2 estimations in patients with at least 6 months of follow-up. Individual eGFR changes were also estimated by the linear regression model (least squares method) in patients with at least 3 creatinine values. The correlation coefficient and the regression equation between these 2 estimations were calculated.

Normally distributed variables were expressed as means ± SD (or SE) and compared with a t test or ANOVA as required. Nonparametric variables were expressed as medians and interquartile ranges, and compared either by a Mann-Whitney or Wilcoxon test.

Categorical variables were expressed as proportions and 95% CI, and compared by a χ^2 test or McNemar's test as needed. The Cox proportional hazard regression model was used to assess risk factors associated with ESRD and death.

All p values were two-tailed; $p < 0.05$ was considered significant.

At the end of the study, the number of patients without NC for more than 1 year was 268.

Results

From October 2004 to March 2008, 2,219 patients were registered: 62.4% from Montevideo and 74.1% from the public healthcare system. In total, 506 (22.8%) patients had NC for more than 6 months before entry to NRHP, with a median time of follow-up and interquartile range of 30.1 months (14.2–65.6).

The data analysis at baseline and in the follow-up was done in the 2 cohorts of patients: those under NC (prereferral) and those under the care of a PCP (prereferral). The mean time of prereferral follow-up was significantly higher in patients under previous NC versus patients under the care of a PCP: 48.1 (43.4–52.7) and 26.3 months (23.6–29.0), respectively; $p < 0.05$.

Data Analysis at Baseline

Baseline Characteristics

Baseline characteristics on admission of enrolled patients are shown in table 1. Males comprised 52.5% (age 67.4 ± 13.5 years). More than 50% were older than 60 years, without any significant differences between the groups.

The most frequent diagnoses were vascular and diabetic nephropathies. Vascular nephropathy (44.8%) was predominant in patients referred by a PCP ($p < 0.05$) and primary glomerulonephritis, systemic and cystic diseases were more frequently seen in patients under NC ($p < 0.05$).

More than 50% of the patients had dyslipidemia, and the more frequent cardiovascular comorbidities were left ventricular hypertrophy and CHD. The frequency of diabetes was significantly higher in patients under the care of a PCP (39.2 and 30.0%, respectively). There were no significant differences between the groups concerning hyperuricemia, smoking habits and NSAIDs. The frequency of patients with a family history of nephropathy was significantly higher in patients under prereferral NC ($p < 0.01$).

CHD and CHF frequency increased by CKD stage (fig. 1). The frequency of peripheral vascular disease (11.1 vs. 4.0%) and CHD (27.8 vs. 17.1%) was significantly higher in diabetic patients versus nondiabetic patients.

Medical Care Indicators

Most patients had systolic hypertension (58.6%). Only 35.5% had a DBP >90 mm Hg. The frequency of SBP ≥160 mm Hg was significantly higher in patients under prereferral PCP care ($p < 0.05$; table 2).

The majority of patients were referred in CKD stage III (61.3%), and 21.4% were referred in stage IV. The frequency of more advanced CKD was higher under prereferral NC ($p < 0.05$; table 2). The median age increased significantly from CKD stage I to IV: 51.3 ± 1.5, 61.1 ± 0.9, 69.0 ± 0.3 and 71.6 ± 0.6 years, respectively.

Proteinuria was over 300 mg/dl in 34.2% of the total registered population, and most of these patients were under prereferral NC ($p < 0.05$; table 2). Diabetic patients referred because of microalbuminuria comprised 16.7%.

The most frequent lipid abnormalities were serum elevated TCh and elevated LDL-C, being more frequent in patients under prereferral PCP care ($p < 0.05$; table 2).

Hemoglobin levels were below 11 mg/dl in only 12.8% of patients; about 50% of patients had elevated uric acid levels without significant differences between the groups.

Comparison of Patients under the Care of a PCP (Prereferral) by Years of Enrollment

Medical care in the PCS improved, as was evidenced by the significant decrease in the number of patients with SBP ≥160 mm Hg and the significant improvement in TCh and LDL-C levels, according to years of enrollment (table 3).

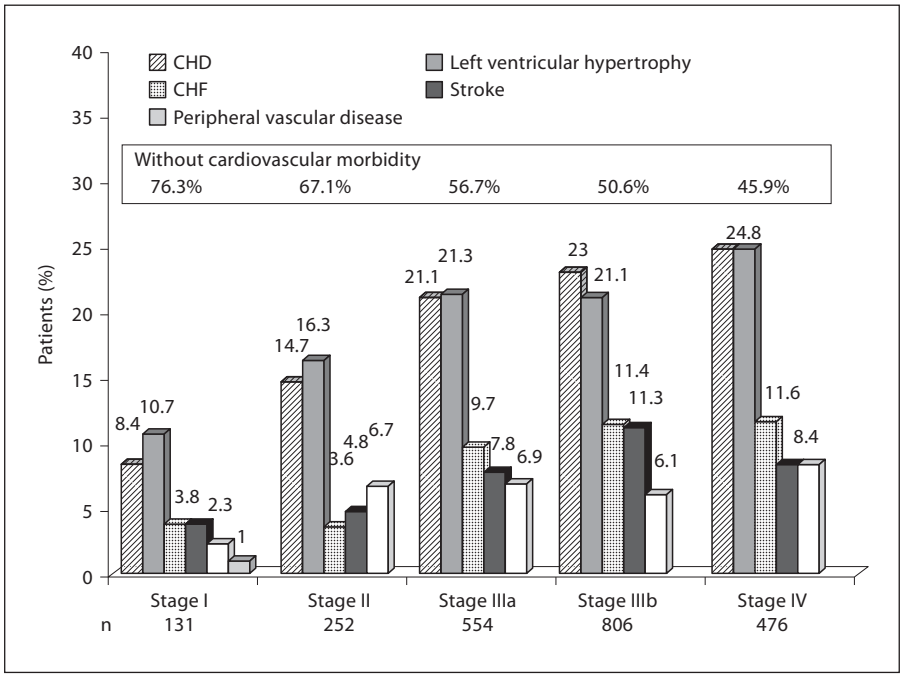

Fig. 1. Frequency of cardiovascular morbidity by CKD stage at inclusion into the NRHP.

Table 1. Baseline characteristics of patients

	Patients under prereferral NC[1]	Patients under prereferral PCP care[2]	p
Gender and age			
Male gender	53.0 (48.8–57.3)	52.4 (50.0–54.8)	NS
Age ≥65 years	61.5 (57.3–65.7)	64.2 (61.9–66.5)	NS
Diagnosis			
Vascular nephropathy (hypertensive)	33.2 (29.1–37.3)	44.8 (42.4–47.2)	<0.05
Diabetic nephropathy	14.0 (11.0–17.0)	17.7 (15.9–19.5)	NS
Obstructive nephropathy	9.5 (6.9–12.1)	7.0 (5.8–8.2)	NS
Primary glomerulonephritis	7.9 (5.5–10.3)	2.6 (1.8–3.4)	<0.05
Tubulointerstitial nephropathy	1.8 (0.6–3.0)	0.9 (0.5–1.3)	NS
Cystic diseases	2.8 (1.4–4.2)	0.6 (0.2–1.0)	<0.05
Systemic diseases	2.2 (0.9–3.5)	0.3 (0.2–0.8)	<0.05
Comorbid conditions			
CHD	20.0 (16.5–23.5)	21.4 (19.5–23.3)	NS
Left ventricular hypertrophy	25.7 (21.9–29.5)	19.3 (17.4–21.2)	<0.05
Peripheral vascular disease	5.9 (3.8–8.0)	6.8 (5.6–8.0)	NS
CHF	7.7 (5.4–10.0)	10.3 (8.9–11.7)	NS
Stroke	7.7 (5.4–10.0)	8.9 (7.6–10.2)	NS
Without cardiovascular comorbidity	54.9 (50.6–59.2)	55.2 (52.8–57.6)	NS
Diabetes	30 (26.0–34.0)	39.2 (36.9–41.5)	<0.05
Dyslipidemia	52 (47.6–56.4)	54.5 (52.1–56.9)	NS
Obesity	34.7 (30.6–38.8)	36.7 (34.4–39)	NS
Neoplasia	2.4 (1.1–3.7)	2.7 (1.9–3.5)	NS

Values are percentages (95% CI).
[1] n = 506. [2] n = 1,713.

Table 2. Medical care at baseline

	Patients under prereferral NC	Patients under prereferral PCP care	p
Blood pressure (n = 506/1,713)			
SBP			
<140 mm Hg	46.4 (42.1–50.7)	39.9 (37.0–41.6)	NS
≥160 mm Hg	22.4 (18.8–26.0)	31.1 (29.1–33.5)	0.05
DBP			
<90 mm Hg	70.2 (66.2–74.2)	62.8 (60.5–65.1)	<0.05
≥100 mm Hg	12 (9.2–14.8)	16.5 (14.7–18.3)	NS
GFR (n = 506/1,713)			
Stage I–II	15.6 (12.4–18.8)	16.4 (14.7–18.3)	NS
Stage III	55.5 (51.2–59.8)	64.1 (61.8–66.4)	<0.05
Stage IV	28.9 (25–32.8)	19.4 (17.5–21.3)	<0.05
Proteinuria (n = 371/1,394)			
<0.3 g/day	50.2 (45.1–55.3)	68.8 (66.4–71.2)	<0.05
0.3–1 g/day	32.4 (27.6–37.2)	22.6 (20.4–24.8)	<0.05
>1 g/day	17.4 (13.5–21.3)	8.6 (7.1–10.1)	<0.05
Other			
TCh <5.8 mmol/l (n = 408/1,316)	56.6 (51.8–61.4)	42.5 (39.8–45.2)	<0.05
Triglycerides <1.69 mmol/l (n = 387/1,214)	62.5 (57.7–67.3)	50.3 (47.5–53.1)	<0.05
HDL-C ≥1.04 mmol/l (M), ≥1.29 mmol/l (F) (n = 380/1,146)	72.1 (67.6–76.6)	70.7 (68.1–73.3)	NS
LDL-C <2.9 mmol/l (n = 323/1,029)	41.2 (35.8–46.6)	29.1 (26.3–31.9)	<0.05
Hemoglobin ≥11 g/dl (n = 423/1,228)	88.0 (84.9–91.1)	86.8 (84.9–88.7)	NS
Uricemia <416 μmol/l (M), <357 μmol/l (F) (n = 386/1,184)	51.0 (46.0–56.0)	43.8 (41.0–46.6)	NS

HDL-C = High-density lipoprotein cholesterol; M = male; F = female.
Values are percentages (95% CI).

Table 3. Patients under the care of a PCP (prereferral)

	1st year	2nd year	3rd year	p
Blood pressure				
SBP <130 mm Hg	21.8 (18.2–25.4)	26.1 (22.2–30.0)	26.3 (22.6–30.0)	NS
SBP ≥160 mm Hg	40.4 (36.1–44.7)	31.3 (27.2–35.4)	26.9 (23.1–30.7)	<0.05
DBP <80 mm Hg	27.3 (23.4–31.2)	32.3 (28.1–36.5)	26.8 (23.0–30.6)	NS
DBP ≥110 mm Hg	21.4 (17.8–25.0)	15.5 (12.3–18.7)	14.9 (11.9–17.9)	NS
Lipid profile				
TCh <5.8 mmol/l	31.1 (27.0–35.2)	44.0 (39.6–48.4)	44.1 (39.9–48.3)	<0.05
Triglycerides <1.69 mmol/l	44.5 (40.1–46.9)	50.5 (46.0–55.0)	51.0 (46.7–55.3)	NS
LDL-C <2.9 mmol/l	17.9 (14.5–21.3)	32.2 (28.1–36.6)	30.4 (26.5–34.3)	<0.05
Progression of CKD (prereferral)				
Stabilization	36.8 (32.6–41.9)	42.9 (38.5–47.3)	55.4 (51.2–59.6)	<0.05
Fast progression	51.1 (46.7–55.5)	48.1 (43.6–52.6)	37.1 (33.0–41.2)	<0.05
Δ eGFR ml/min/month, median (IQ range)	–0.26 (–0.16; 0.12)	–0.19 (–0.86; 0.0)	0 (–0.67; 0.0)	<0.05

Δ eGFR = Change in estimated glomerular filtration rate; IQ = interquartile.
Values are percentages (95% CI).

Table 4. Accomplishment of targets in the first and last nephrology consultation (paired samples)

	First consultation	Last consultation	p
Patients under prereferral NC			
SBP <130 mm Hg (n = 218)	25.7 (19.9–31.5)	33.0 (26.8–39.2)	NS
DBP <80 mm Hg (n = 218)	26.5 (20.6–32.4)	39.8 (33.3–46.3)	<0.05
Proteinuria <0.3 g/day (n = 107)	39.3 (30.0–48.6)	46.7 (37.2–56.2)	NS
Hemoglobin levels ≥11 g/dl (n = 171)	89.5 (84.9–94.1)	87.7 (82.8–92.6)	NS
TCh <5.8 mmol/l (n = 155)	49.7 (41.8–57.6)	60.0 (52.3–67.7)	NS
Triglycerides <1.69 mmol/l (n = 140)	56.4 (48.2–64.4)	60.0 (51.9–68.1)	NS
LDL-C <2.9 mmol/l (n = 108)	39.8 (30.6–49.0)	41.7 (32.4–51.0)	NS
Patients under prereferral PCP care			
SBP <130 mm Hg (n = 843)	24.4 (21.5–27.3)	30.4 (27.3–33.5)	<0.05
DBP <80 mm Hg (n = 843)	29.7 (26.6–32.8)	37.4 (34.1–40.7)	<0.05
Proteinuria <0.3 g/day (n = 441)	64.9 (60.4–69.4)	66.9 (62.5–71.3)	NS
Hemoglobin levels ≥11 g/dl (n = 482)	83.4 (80.1–86.7)	87.5 (84.5–90.5)	NS
TCh <5.8 mmol/l (n = 540)	33.7 (29.7–37.7)	63.5 (59.4–67.6)	<0.05
Triglycerides <1.69 mmol/l (n = 468)	46.6 (42.1–51.1)	57.5 (53.0–62.0)	<0.05
LDL-C <2.9 mmol/l (n = 391)	22.3 (18.2–26.4)	43.7 (38.8–48.6)	<0.05

Values are percentages (95% CI).

The median loss of eGFR improved significantly according to years of enrollment, with more than 55% enrolled with a stabilized CKD and a lower frequency of fast progression.

Outcome Analysis

The outcome analysis was carried out in 1,188 patients with no differences in terms of age, gender, ethnicity and diagnosis distribution with regard to the total registered population. The median time of follow-up was 13.8 months (interquartile range: 7.5–21.9).

Accomplishment of Targets and Treatment in the First and Last Nephrology Consultation

Once patients were enrolled in the program, they showed a slight improvement in the performance of targets, even those under NC (prereferral).

Comparing the first and last paired controls of patients under NC (prereferral), those who attained blood pressure targets increased significantly in the DBP control, but only a third of them were in target. The changes were not significant for SBP, proteinuria, hemoglobin and lipid levels. Most patients were in target for hemoglobin levels (87.7%), and 60% were in target for TCh and triglyceride levels (table 4).

For patients under the care of a PCP (prereferral), the changes were significant in SBP, DBP, TCh and triglyceride levels ($p < 0.05$; table 4).

There were no differences in BMI, serum fasting glucose, serum albumin and high-density lipoprotein cholesterol. The evaluation of MTT in patients under NC (prereferral) only showed a significant increase in the use of statins: 28.1 vs. 50.4% (table 5); in patients under the care of a PCP (prereferral), there was a significant increase in statins, antiplatelet drugs and allopurinol use (table 5).

The frequency of patients treated with ACEi/ARBs in the last nephrology consultation was 59.4% in patients under NC (prereferral) and 63.8% in patients under the care of a PCP (prereferral).

Disease Progression after Enrollment in the NRHP

In the 526 patients who fulfilled the requirements for evaluating the change in eGFR, the change was +0.02 (–0.48 to +0.60) ml/min/month: 55.9% of patients were stabilized and 36.5% had fast progression. Although there was no difference in the eGFR change before and after the inclusion of patients with NC (prereferral), there was an improvement in the eGFR loss in patients under the care of a PCP (prereferral): 193 paired sample patients showed a median GFR change of –0.26 (–1.04 to 0.00) ml/min/month before and +0.02 (–0.49 to +0.64) ml/min/month after inclusion (Wilcoxon test, $p < 0.001$; fig. 2).

The ESRD rate was 5.3/100 patients/year. It was higher in patients referred in CKD stage IV (14.2/100 patients/year).

Table 5. Comparison of treatment at baseline and in the last nephrology consultation (paired data)

	Baseline	Last consultation	p
Patients under prereferral NC (n = 224)			
ACEi/ARBs	52.5 (46.0–59.0)	59.4 (53.0–65.8)	NS
Statins	28.1 (22.2–34.0)	50.4 (43.9–56.9)	<0.05
β-Blockers	19.2 (14.0–24.4)	18.3 (13.2–23.4)	NS
CCB	33.0 (26.8–39.2)	26.8 (21.0–32.6)	NS
Antiplatelet drugs	21.4 (16.0–26.8)	29.0 (23.1–34.9)	NS
Allopurinol	15.6 (10.8–20.4)	23.2 (17.7–28.7)	NS
Patients under prereferral PCP care (n = 1,124)			
ACEi/ARBs	62.3 (59.5–65.1)	63.8 (61.0–66.6)	NS
Statins	24.4 (21.9–26.9)	49.5 (46.6–52.4)	<0.05
β-Blockers	22.2 (19.8–24.6)	22.5 (20.1–24.9)	NS
CCB	22.9 (20.4–25.4)	23.5 (21.0–26.0)	NS
Antiplatelet drugs	23.3 (20.8–25.8)	32.8 (30.1–35.5)	<0.05
Allopurinol	10.7 (8.9–12.5)	21.6 (19.2–24.0)	<0.05

Values are percentages (95% CI).
CCB = Calcium channel blockers.

A Cox proportional risk model showed that factors associated with ESRD were: age, CKD stage, diabetes nephropathy and renin-angiotensin aldosterone system (RAS) blockers. Increased risk was seen with CKD stage IV [RR = 4.72 (2.71–8.22)] and diabetes nephropathy [RR = 2.43 (1.25–4.74)], and risk was decreased by age [RR = 0.54 (0.32–0.92)] and RAS blockers [RR = 0.14 (0.07–0.27); table 6]. The individual and sequential introductions of proteinuria and blood pressure levels in the model were also significantly associated with ESRD. The risk of ESRD was higher in patients with proteinuria >1 g/day at baseline versus patients with proteinuria <1 g/day [RR = 6.03 (3.04–11.96), $p < 0.001$]. The risk of ESRD was also greater if we consider the average SBP throughout the follow-up, depending on whether the patients had a SBP ≥140 versus <140 mm Hg [RR = 2.53 (1.28–4.97), p = 0.007]; average DBP in the same period, depending on whether the patients had a DBP ≥90 versus <90 mm Hg [RR = 2.70 (1.39–5.25), p = 0.003]; and SBP at baseline ≥160 mm Hg [RR = 1.98 (1.20–3.25), p = 0.07]. RAS blockers remained significant after the inclusion of proteinuria and blood pressure in the Cox model.

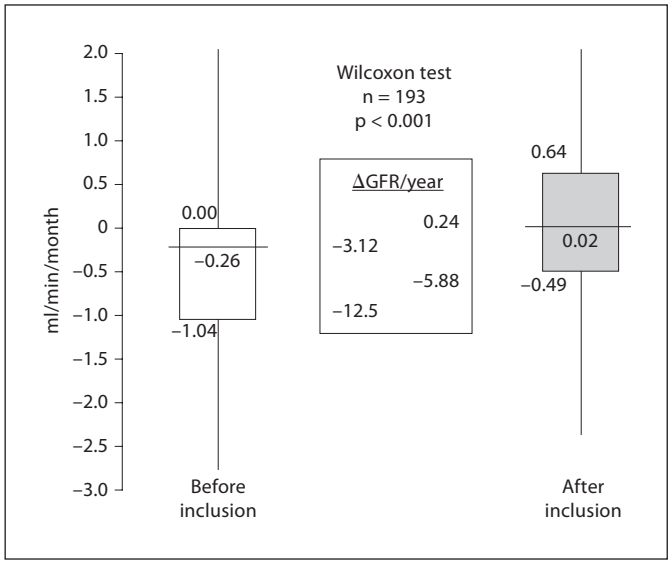

Fig. 2. GFR change per month before and after the inclusion into the NRHP. Patients without prior NC.

Death Rates, Causes of Death and Risk Factors Associated with Death

The frequency of death (13.6%) was higher than the frequency of ESRD (6.0%), independent of the stage at referral. Death frequency increased with the progressive CKD stage, from 7.0% in stages I–II to 21.0% in stage IV (fig. 3). The mortality rate also increased according to the CKD stage: 5.3/100 patients/year in stages I–II and 16.4/100 in stage IV (fig. 4). The mortality rate and the rate of new CV events were the double of the ESRD rate (10.9, 10.5 and 5.3/100 patients/year, respectively). Car-

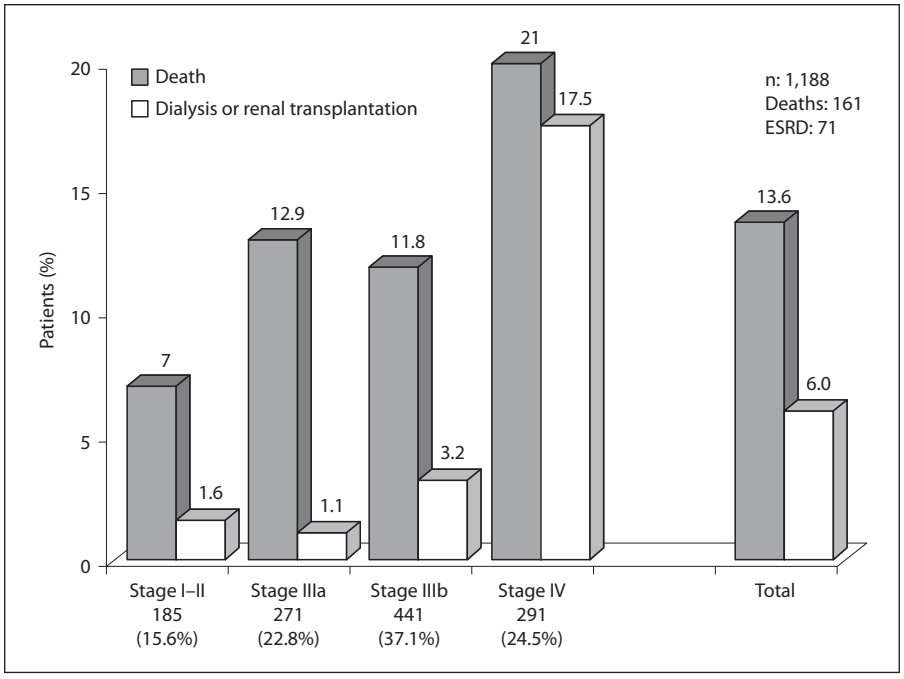

Fig. 3. Frequency of ESRD and death by CKD stage.

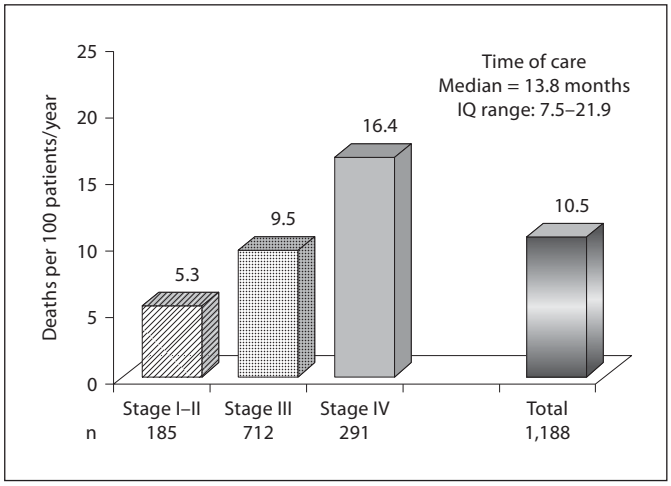

Fig. 4. Mortality per 100 patients/year by CKD stage.

diovascular disease (40.8%) and malignancy (22.5%) were the more frequent causes of death.

The Cox proportional risk model showed that factors associated with high mortality were: CKD stage IV [RR = 2.04 (1.47–2.83)], male gender [RR = 2.10 (1.48–2.91)], age >65 years [RR = 2.53 (1.69–3.81)] and CHF [RR = 1.66 (1.09–2.53)]. RAS blockers decreased the risk [RR = 0.39 (0.28–0.54); table 7].

Discussion

Until recently, early renal care in Uruguay had been unequal due to a dual healthcare system (public and private) that benefits patients enrolled in the private system. However, since renal replacement therapy became available in 1980, the care of ESRD patients has been more equitable thanks to the coverage of the National Resource Fund, becoming similar to what is observed in developed countries [37–40]. Data obtained from the dialysis registry have shown that early CKD care has been suboptimal at all periods of time without any significant improvement in recent years [41]. This continuing problem has been attributed to multiple reasons, but the lack of a structured early CKD care program could be a significant determining factor. The NRHP intends to improve renal healthcare in the total population and to make the prevention of kidney disease sustainable and tenable [42]. The prevalence of early CKD is unknown, but is estimated to affect 7.2% of the total population by extrapolation from the CKD frequency in NHANES III [43], and is adjusted to the Uruguayan prevalence of dialysis patients (0.12%). The scope of data collected is still very limited and the conclusions could not be applied to the total population.

The characteristics of the population enrolled mainly reflect the renal care in individuals under the cover-

Table 6. Risk factors of ESRD in CKD patients

Cox proportional risk model	β	RR	CI	p
CKD stage IV (Ref. I–III)	1.552	4.72	2.71–8.22	<0.001
RAS blockage (Ref. NO)	–1.983	0.14	0.07–0.27	<0.001
Age ≥65 years	–0.614	0.54	0.32–0.92	0.024
Diagnosis (Ref. vascular nephropathy)				0.004
Diabetic nephropathy	0.887	2.43	1.25–4.74	0.009
Primary glomerulonephritis	0.910	2.48	0.91–6.82	0.078
Obstructive nephropathy	–0.909	0.40	0.13–1.21	0.105
Other				0.778
Gender				0.601

n = 1,138, events = 71. RAS = Renin-angiotensin-aldosterone system.

Table 7. Risk factors of death in CKD patients

Cox proportional risk model	β	RR	CI	p
CKD stage IV (Ref. I–III)	0.713	2.04	1.47–2.83	<0.001
Male	0.743	2.10	1.48–2.91	<0.001
Age <65 years	0.929	2.53	1.69–3.81	<0.001
CHF	0.507	1.66	1.09–2.53	0.018
CHD				0.304
Left ventricular hypertrophy				0.245
Stroke				0.190
Neoplasm				0.909
Diabetes				0.322

n = 1,177, events = 161.

age of the public healthcare system (74.1%) and under the medical care of the PCS, representing a population with fewer economic resources that has difficulty accessing healthcare. As these patients are sent to the registry voluntarily, this could be a limitation to our analysis. The patients' characteristics at the entry of the CKD registry are similar to those observed in ESRD programs with a predominant inclusion of male and elderly patients, but with a greater median age than the median age of patients entering ESRD programs and a higher prevalence of hypertension and diabetes than nephropathy [44–46].

Among the CKD risk factors at enrollment, the frequency of hypertension (88.1%), overweight/obesity (70.5%) and diabetes (37.1%) were higher than what is observed in the country's general population (34, 60 and 8.2%, respectively) [47–49]. Cardiovascular morbidity was high, increased with CKD stage and was 54.1% in stage IV.

There is no general agreement on how to define late referral to regular NC, i.e., should it be according to the time before starting dialysis or CKD stage. As a timely referral is essential in delaying or stabilizing the loss of kidney function, the study chose to define early/late referral according to the stage of CKD at the first NC. In our registry, the majority of patients were referred in CKD stage III, and for patients under the care of a PCP (prereferral), 18.6% were considered late referrals.

The comparison of patients under prereferral NC and PCP care provided evidence of the advantages of NC. Patients under NC (prereferral), although they had a kidney disease over a long evolution and a more advanced CKD stage, showed similar morbidity with better control of blood pressure, lipid profile and treatment goals. We cannot, however, rule out a placebo effect of NC referral and close follow-up, because patients may feel they are more severely ill and became more compliant with treatment.

In patients under PCP control (prereferral), although there might be a bias in selection, it is possible that this improvement can also be the result of a better management of patients and awareness of CKD risk factors thanks to the multiple educational program activities and the free access to medication. Blood pressure management in the general population is a challenging issue, but in the enrolled patients, the proportion that attained blood pressure targets during follow-up improved significantly. Although still inadequate, the percentage of patients on target is vastly superior to that observed in historical surveys of hypertension carried out in the general population of the country [50]. These improvements have been highlighted by Rodríguez-Iturbe [51] in a recent editorial comment.

The outcome analysis also showed significant changes in the achievement of treatment targets. The most significant changes were observed in the lipid pattern with a high frequency of patients on target. The comparison of drug indications in the first and last medical control revealed a significant increase in patients taking statins, in line with the improvement in the lipid profile. The use of antiplatelet agents and allopurinol also increased significantly. This change was attributed to the free access to medications in patients in the public healthcare system thanks to the efforts of the program. The impact of statins on the CKD progression and cardiovascular comorbidity will be assessed in the near future.

The frequency of overweight/obesity remains an unsolved problem, as it is found throughout the country's population and deserves more attention.

RAS blockers were the drugs of choice to treat hypertension (61.8%) in this group of CKD patients. In the follow-up, the use of ACEi/ARB agents did not increase as much as was expected. The possible causes are not evident, but the age of the population and/or the advanced CKD at enrollment could have been important limitations.

The evaluation of CKD progression poses many challenges [52]. In the data analysis of the study's registry, GFR was estimated by the 4-variable Modification of Diet in Renal Disease equation that has various limitations [53, 54]. Overall, however, it is a well-accepted estimate of renal function and is used in many studies [55]. As this estimate requires accuracy in creatinine determination, the NRHP has initiated a creatinine standardization program in the country [56] based on the traceability of the creatinine measure to the reference method and standards as part of an International Society of Nephrology grant.

In this study, the progression of CKD was evaluated by the change in eGFR between 2 values taking into account the observation time. To validate this methodology, we also estimated progression by linear regression, and the correlation with the first-last eGFR change was highly significant ($r = 0.937$, $r^2 = 0.877$; $p < 0.001$).

Progression of CKD was mainly analyzed considering the changes in the eGFR over time since only a minority of patients had proteinuria at enrollment. Because of this limitation, the population was categorized according to the rate of decline in the eGFR, and the study chose to focus on CKD which was either stabilized or in progression rather than on CKD regression and remission, as was suggested [57, 58]. Stabilization of CKD was achieved in 56% of the patients that met the requirements for assessing eGFR change during follow-up, and eGFR improvement was most relevant in patients under the care of a PCP (prereferral).

Among the predictors of ESRD, the risk was significantly higher in patients with CKD stage IV, diabetic nephropathy and proteinuria >1 g/day at baseline, as well as in hypertensive patients, throughout the follow-up [59, 60].

A remarkable finding of the analysis was the impact of a RAS blockade [61–64]. Even though the percentage of patients treated with ACEi/ARB agents did not increase significantly, these were effective in reducing the risk of ESRD after adjusting for age, gender, diagnostic, comorbidity and CKD stage. Proteinuria and blood pressure were independent risk factors of ESRD.

Another important finding was that these patients were more likely to die than go on dialysis (13.6 vs. 6.0%), as was described [65, 66]. The more advanced the CKD, the higher the mortality rate. Cardiovascular disease was the most frequent cause of death (40.8%) due to the high frequency of cardiovascular comorbidity.

Factors significantly associated with a higher death rate were CKD stage IV, male gender, age >65 years and CHF. In this population, no association was found between diabetes status and the risk of dying. We have no sure explanation for this. There may be more access to healthcare for diabetic patients and a better clinical management of CHD and CHF. This is a further point to analyze in the future.

Renoprotection aims to reverse or retard the progressive deterioration of renal function and the program adopts the remission clinic's MTT and targets in order to achieve clinical stabilization, a strategy that has been effective in this population. Despite the short observation period, our results highlight the importance of the edu-

cational programs, free access to drugs in the PCS and the impact of NC with a better management of CKD patients before and after joining the program. The recommended MTT approach is bearing fruit, and the authors expect these results will encourage PCPs, nephrologists, healthcare providers and authorities to join the NRHP and the registry to improve the management of CKD patients.

This study has several limitations regarding the population that has been included and the outcome analysis. The paper is based on patients included in the CKD registry performed by nephrologists. In our country, there are no individual data regarding the healthcare provided by PCPs to allow a comparison with this population. Patients have been voluntarily included, but there has been no systematic or random selection of them. The duration and frequency of monitoring controls before and after referral is not similar, which may affect statistical analysis. For the outcome analysis, the follow-up time is short, considering a longer period could allow the analysis of other risk factors. The methodology used to estimate CKD progression has several limitations that have been previously mentioned. The MTT was strongly recommended to be applied by GPs and nephrologists, but not as a protocol. In those who followed the recommendation, the efficacy of the treatment could be assessed.

Disclosure

With the application for the International Society of Nephrology's call for a noncommunicable chronic disease prevention program in developing countries in January 2007, the NRHP has obtained a grant for a 5-year project, with special funds for the remote electronic CKD registry and the creatinine standardization program.

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