ORIGINAL RESEARCH

Extracellular Fluid Volume Is an Independent Determinant of Uncontrolled and Resistant Hypertension in Chronic Kidney Disease: A NephroTest Cohort Study

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***Background*—**Hypertension is highly prevalent during chronic kidney disease (CKD) and, in turn, worsens CKD prognosis. We aimed to describe the determinants of uncontrolled and resistant hypertension during CKD.

***Methods and Results*—**We analyzed baseline data from patients with CKD stage 1 to 5 (NephroTest cohort) who underwent thorough renal explorations, including measurements of glomerular filtration rate (clearance of ^{51}Cr-EDTA) and of extracellular water (volume of distribution of the tracer). Hypertension was defined as blood pressure (BP; average of 3 office measurements) ≥140/90 mm Hg or the use of antihypertensive drugs. In 2015 patients (mean age, 58.7±15.3 years; 67% men; mean glomerular filtration rate, 42±15 mL/min per 1.73 m^2), prevalence of hypertension was 88%. Among hypertensive patients, 44% and 32% had uncontrolled (≥140/90 mm Hg) and resistant (uncontrolled BP despite 3 drugs, including a diuretic, or ≥4 drugs, including a diuretic, regardless of BP level) hypertension, respectively. In multivariable analysis, extracellular water, older age, higher albuminuria, diabetic nephropathy, and the absence of aldosterone blockers were independently associated with uncontrolled BP. Extracellular water, older age, lower glomerular filtration rate, higher albuminuria and body mass index, male sex, African origin, diabetes mellitus, and diabetic and glomerular nephropathies were associated with resistant hypertension.

***Conclusions*—**In this large population of patients with CKD, a lower glomerular filtration rate, a higher body mass index, diabetic status, and African origin were associated with hypertension severity but not with BP control. Higher extracellular water, older age, and higher albuminuria were independent determinants of both resistant and uncontrolled hypertension during CKD. Our results advocate for the large use of diuretics in this population. **(*J Am Heart Assoc*. 2018;7:e010278. DOI: 10.1161/JAHA.118.010278.)**

Key Words: chronic kidney disease • extracellular water • hypertension • resistant hypertension • uncontrolled hypertension

High rates of uncontrolled hypertension and resistant hypertension, both associated with a poor cardiovascular and renal prognosis,[1–5] have been reported in patients with chronic kidney disease (CKD).[6–8] Most epidemiological studies on treatment and control of hypertension were conducted in cohorts meant to be representative of the general population, such as the National Health and Nutrition Examination Surveys (NHANESs).[9,10] Few data on the factors associated with hypertension control and resistance were obtained specifically in patients with CKD.[7] Several

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Accompanying Data S1 and Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010278

*A complete list of the NephroTest Study Group investigators can be found in the Appendix at the end of the article.

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Received July 10, 2018; accepted August 16, 2018.

Clinical Perspective

What Is New?

- In this large cohort of patients with chronic kidney disease, a lower glomerular filtration rate was a risk factor for resistant hypertension, but was not independently associated with uncontrolled hypertension, whereas a higher extracellular water rate appeared to be independently associated with both uncontrolled hypertension and resistant hypertension.

What Are the Clinical Implications?

- Our results suggest that chronic kidney disease does not prevent blood pressure control, provided adequate treatment, including a tight control of fluid overload, is administered.

small-scaled studies have suggested that volume overload plays a key role for hypertension control during CKD,[11,12] but extracellular water (ECW) was estimated, using multifrequency bioimpedance, as the most direct and accurate method to measure extracellular fluid volume and isotope dilution; however, this measurement is cumbersome and not routinely available.

The aim of the study was to define the rates and the determinants of hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension in a population of patients with CKD who underwent thorough renal explorations, including gold standard measurement of glomerular filtration rate (GFR) and ECW.

Methods

Study Design and Participants

The NephroTest study is a prospective hospital-based tricentric cohort (Physiology Departments of Tenon, Bichat, and Georges Pompidou Hospitals, Paris, France), which enrolled 2084 adult patients with CKD of various causes, stages 1 to 5, from January 2000 to December 2012. Pregnancy, a history of renal transplantation, and dialysis were exclusion criteria. Data from the baseline visit were used in this cross-sectional study. Drug treatment and blood pressure (BP) values were missing for 2 and 67 patients, respectively, so that 2015 patients were included in this study (Figure 1). All patients signed informed consent before inclusion in the cohort. The NephroTest study was approved by an ethics committee (Direction Générale de la Recherche et de l'Innovation; Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé; reference, DGRI Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé MG/CP09.503; July 9, 2009). The database, analytic methods, and study materials will not be made available to other researchers for purposes of replicating the procedure, because of restrictions on data sharing for the NephroTest study from the National Commission for Data Protection and Liberties.

Procedures

Patients were referred by their nephrologist to 1 of the 3 renal physiology units for extensive workup during a 5-hour in-person visit, including GFR measurement. Patients were asked to collect 24-hour urine the day before admission, with indications given by a trained nurse and detailed in a written information document. Medical history, treatment, anthropometric data, and a large set of clinical and laboratory variables were collected.

GFR and ECW Measurements

Measured GFR (mGFR) was determined by renal clearance of ^{51}Cr-EDTA (GE Healthcare, Vélizy, France), as previously described.[13] Briefly, a single dose of 1.8 to 3.5 MBq of ^{51}Cr-EDTA was injected intravenously. After allowing 1.5 hours for equilibration of the tracer in the extracellular fluid, urine was collected and discarded. Average renal ^{51}Cr-EDTA clearance was then determined from the average of 6 consecutive 30-minute clearance periods. Blood was drawn at the midpoint of each clearance period. ECW was calculated after the equilibrium period, as the remaining quantity of the tracer divided by the serum concentration of the tracer, and expressed in liters. To take into account the expected ECW for a given sex and weight, ECW was expressed as a ratio of measured over theoretical ECW; the latter was calculated as follows: theoretical ECW=a+b×body weight (a=7.35, b=0.135 in men and a=5.27, b=0.134 in women).[14] ECW was treated in ratio over theoretical ECW in the main analysis and in liters in a secondary analysis.

To consider potentially excessive or incomplete 24-hour urine collections, 24-hour urinary parameters were corrected by dividing the measured value by the ratio of creatinine clearance in the collection versus the fractionated urinary clearance of creatinine in the 6 timed periods of GFR measurement, as previously described.[15]

BP Measurement and Definitions

BP was calculated as the average of 3 measurements taken with an automated device by a trained observer, after 5 minutes of rest in a seated patient. Hypertension was defined as a systolic BP ≥140 mm Hg and/or a diastolic BP

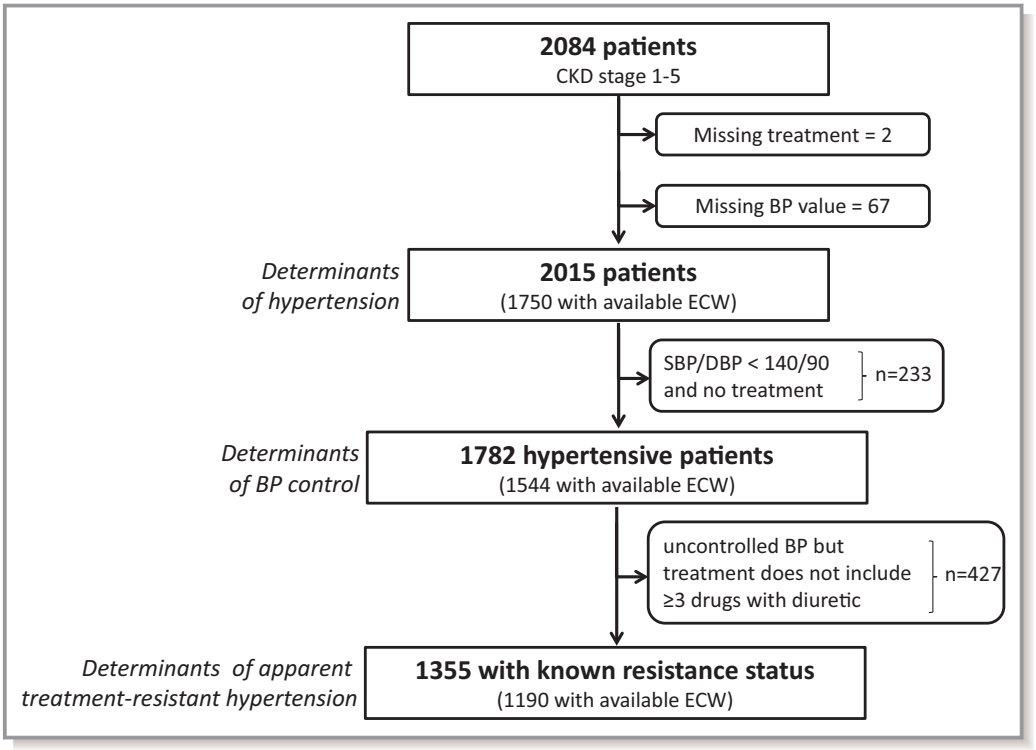


Figure 1. Flow diagram of study population. BP indicates blood pressure; CKD, chronic kidney disease; DBP, diastolic BP; ECW, extracellular water; SBP, systolic BP.

≥90 mm Hg, and/or the current use of antihypertensive drugs. β Blockers, diuretics, and blockers of the renin-angiotensin system prescribed for cardiovascular reasons or proteinuria in an otherwise normotensive patient with no history of hypertension (n=64 patients) were not considered as antihypertensive drugs so as to avoid an upwardly biased hypertension prevalence rate. BP was controlled if systolic BP was <140 mm Hg and diastolic BP was <90 mm Hg. Apparent treatment-resistant hypertension was defined as uncontrolled BP despite at least 3 drugs, including a diuretic, or controlled BP under ≥4 drugs, including a diuretic.

Statistical Analysis

Prevalence of hypertension was described in 2015 patients, and prevalences of uncontrolled and apparent treatment-resistant hypertension were described in 1782 hypertensive patients. For each condition, prevalence was calculated in the whole population, as well as according to mGFR level (≥60, 45–59, 30–44, 15–29, and <15 mL/min per 1.73 m^2). Characteristics of the patients were analyzed in the whole population as well as by hypertension, hypertension control, and hypertension resistance status. Groups were compared using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Number and types of antihypertensive drugs were analyzed in the whole population and by GFR subgroups. Cochran-Armitage tests for trend by GFR level were performed for each drug type.

Crude and fully-adjusted odds ratios (ORs) with 95% confidence intervals (95% CIs) were estimated from logistic regression models for hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension, according to ECW (in L or in ratio over theoretical ECW) and other patient characteristics (details about the choice of covariates for each dependent variable are given in Data S1). Because of technical issues or irregular urine voiding, ECW measurement was missing at random in 265 of the 2015 patients (Figure 1). Logistic regression models for hypertension, uncontrolled BP, and apparent treatment-resistant hypertension were first treated by complete case analysis for ECW, and missing values for other covariates were replaced by median for continuous variables and by the most frequent classes for categorical variables. Accordingly, determinants of hypertension were analyzed in 1750 patients with available ECW measurement, and determinants of uncontrolled hypertension were analyzed in 1544 hypertensive patients among them (Figure 1). Determinants of apparent treatment-resistant hypertension among hypertensive patients were analyzed in 1355 patients who also had a known resistance status (ie, after exclusion of patients with uncontrolled hypertension and <3 drugs or at least 3 drugs without a diuretic, because these could not

be classified as resistant or not). A secondary analysis of the determinants of resistant hypertension was performed in the total population of hypertensive patients. Finally, in sensitivity analyses, we performed multiple imputations of our data set (n=5 imputed data set; fully conditional specification using all covariates, including outcomes; maximum, 100 iterations) using all covariates in Table 1 and dependent variables, performed final models on each complete data set, and finally combined the estimated ORs using Rubin's rules.[16] All analyses were conducted using SAS 9.4 or R 3.3 (https://www.R-project.org/).

Results

Demographic data and baseline characteristics of the patients are given in Table 1 for the total population and in Table 2 by hypertension, hypertension control, and hypertension resistance status. Mean age was 58.7±15.3 years, 67% were men, 14% were of African origin, and 27% had diabetes mellitus. Mean systolic BP was 136±20 mm Hg, and mean diastolic BP was 75±12 mm Hg. Mean mGFR was 42.0±20.0 mL/min per 1.73 m^2, and mean ECW was 16.2±3.8 L. Type of nephropathies were diabetic, glomerular, vascular, polycystic, and interstitial nephropathies in 10%, 14%, 27%, 6%, and 9% of the patients, respectively. Median sodium intake, estimated from sodium excretion in the 24-hour urine collection, was 3.4 g/d, corresponding to an 8.5-g salt intake (Table 1). Prevalence of hypertension was 88% in the total population, but increased from 75% to 96% for an mGFR ≥60 to an mGFR <15 mL/min per 1.73 m^2 (Figure 2A and 2C).

Antihypertensive drugs in the population of hypertensive patients (n=1782), and by GFR subgroup, are indicated in Table 3. A diuretic was part of the treatment in 54% of hypertensive patients. Prevalence of uncontrolled hypertension was 44% (34% in patients with mGFR ≥60 mL/min per 1.73 m^2, with a progressive increase, up to 52% in patients with mGFR <15 mL/min per 1.73 m^2, as illustrated in Figure 2A and 2C). Among patients with uncontrolled BP, 46% were taking at least 3 drugs, including a diuretic, and 44% were taking ≤2 antihypertensive drugs. Most patients (73.6%) with uncontrolled hypertension had isolated systolic hypertension, 23.6% had systolodiastolic hypertension, and 2.7% had isolated diastolic hypertension. Apparent treatment-resistant hypertension (uncontrolled BP despite at least 3 drugs, including a diuretic, or controlled BP with ≥4 drugs, including a diuretic) was found in 32% of all hypertensive patients, with a progressive increase from 23% for an mGFR ≥60 mL/min per 1.73 m^2 to 49% in patients with an mGFR <15 mL/min per 1.73 m^2 (Figure 2B and 2C).

In multivariable analysis, a higher ECW was an independent determinant of hypertension, with an OR of 1.19 (95% CI, 1.05–1.35) per 10% increase when expressed as a ratio of theoretical ECW, and an OR of 1.10 (95% CI, 1.03–1.18) per 1-L increase of absolute ECW (Table 4, Table S1). Other independent determinants of hypertension included older age, higher body mass index (BMI), African origin, diabetes mellitus, previous cardiovascular event, lower mGFR, and higher albuminuria (Table 4). The association between BMI and hypertension

Table 1. Characteristics of the Patients (n=2015)

Characteristic	Value	Missing, N
Age, y	58.7±15.3	0
Men	67	0
Sub-Saharan African origin	14	108
BMI, kg/m^2	26.6±5.2	0
Previous cardiovascular event	18	39
Smoking status (current/former/never)	14/31/55	0
Diabetes mellitus	27	0
SBP, mm Hg	136±20	0
DBP, mm Hg	75±12	0
mGFR, mL/min per 1.73 m^2	42.0±20.0	0
eGFR (CKD-EPI), mL/min per 1.73 m^2	44.4±22.9	0
Extracellular water, L	16.2±3.8	265
ECW ratio over theoretical ECW	0.97±0.15	265
Type of nephropathy		0
Diabetic	10	
Glomerular	14	
Vascular	27	
Polycystic	6	
Interstitial	9	
Other or unknown	34	
Natriuresis, mmol/24 h*	146 (107–192)	258
Kaliuresis, mmol/24 h*	61.5 (45.9–78.5)	258
24-h Urinary Na/K ratio	2.37 (1.71–3.25)	120
Albuminuria, mg/mmol creatinine	8.9 (1.6–51.0)	64
[Na], mmol/L	140±3	1
[K], mmol/L	4.3±0.5	3
Plasma uric acid, μmol/L	422±110	7
[HCO_{3-}], mmol/L	25.8±3.2	12

Data are given as mean±SD, percentage, or median (interquartile range). BMI indicates body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DBP, diastolic blood pressure; ECW, extracellular water; mGFR, measured glomerular filtration rate; SBP, systolic blood pressure.
*Values corrected for inaccurate 24-hour urine collection using the ratio of 24-hour creatinine clearance over fractionated creatinine clearance, as detailed in the Methods section.

DOI: 10.1161/JAHA.118.010278

Table 2. Characteristics of the Patients by Hypertension, Hypertension Control, and Hypertension Resistance Status

	Total Population (N=2015)			Hypertensive Patients (N=1782)					
	Hypertension			Uncontrolled Hypertension			Apparent Treatment-Resistant Hypertension		
Characteristic	No (N=233)	Yes (N=1782)	*P* Value	No (N=996)	Yes (N=786)	*P* Value	No (N=1204)	Yes (N=578)	*P* Value
Age, y	47.6±16.3	60.2±14.5	<0.0001	57.2±15.1	64.1±12.6	<0.0001	58.9±15.1	62.9±12.9	<0.0001
Men	55.4 (129)	68.2 (1215)	<0.0001	65.8 (655)	71.2 (560)	0.014	65.1 (784)	74.6 (431)	<0.0001
Sub-Saharan African origin	10.7 (24)	14.4 (243)	0.13	15.4 (144)	13.2 (99)	0.20	11.9 (135)	19.7 (108)	<0.0001
BMI, kg/m^2	24.0±4.5	27.0±5.2	<0.0001	26.6±5.2	27.4±5.1	0.0001	26.1±4.9	28.8±5.3	<0.0001
Previous cardiovascular event	3.0 (7)	19.9 (347)	<0.0001	18.2 (176)	22.0 (171)	0.044	15.6 (183)	28.7 (164)	<0.0001
Smoking status									
Former	17.2 (40)	33.0 (588)	<0.0001	29.4 (293)	37.5 (295)	0.001	31.3 (377)	36.5 (211)	0.028
Current	15.5 (36)	13.5 (241)		14.7 (146)	12.1 (95)		14.7 (177)	11.1 (64)	
Diabetes mellitus	7.7 (18)	30.0 (535)	<0.0001	24.4 (243)	37.2 (292)	<0.0001	21.8 (262)	47.2 (273)	<0.0001
mGFR, mL/min per 1.73 m^2	53.3 (38.9–70.1)	37.4 (26.5–51.6)	<0.0001	38.2 (27.3–53.5)	36.2 (24.5–49.8)	0.0008	39.1 (28.1–53.7)	33.8 (22.4–46.6)	<0.0001
Extracellular water, L	14.4±3.4	16.4±3.8	<0.0001	15.9±3.7	17.0±3.8	<0.0001	15.9±3.5	17.5±4.0	<0.0001
ECW ratio over theoretical ECW	0.93±0.14	0.97±0.15	0.0015	0.95±0.14	0.99±0.16	<0.0001	0.96±0.15	0.99±0.16	0.0065
Type of nephropathy									
Diabetic	1.7 (4)	11.5 (205)	<0.0001	7.3 (73)	16.8 (132)	<0.0001	6.4 (77)	22.1 (128)	<0.0001
Glomerular	18.0 (42)	13.9 (247)		17.1 (170)	9.8 (77)		15.5 (187)	10.4 (60)	
Vascular	1.3 (3)	29.9 (532)		27.1 (270)	33.3 (262)		26.2 (316)	37.4 (216)	
Polycystic	3.0 (7)	5.9 (106)		7.2 (72)	4.3 (34)		7.6 (91)	2.6 (15)	
Interstitial	21.5 (50)	7.5 (133)		8.4 (84)	6.2 (49)		10.1 (122)	1.9 (11)	
Other or unknown	54.5 (127)	31.4 (559)		32.8 (327)	29.5 (232)		34.1 (411)	25.6 (148)	
Natriuresis, mmol/24 h	132 (103–183)	147 (108–193)	0.028	145 (106–191)	151 (109–195)	0.033	143 (107–188)	156 (114–202)	0.001
Kaliuresis, mmol/24 h	59 (44–75)	62 (46–79)	0.14	61 (46–78)	63 (47–80)	0.12	61 (46–79)	63 (45–78)	0.56
24-h Urinary Na/K ratio	2.32 (1.70–3.11)	2.37 (1.72–3.26)	0.37	2.36 (1.72–3.21)	2.38 (1.71–3.33)	0.56	2.33 (1.68–3.20)	2.48 (1.84–3.36)	0.007
ACR, mg/mmol creatinine	4.98 (0.91–25.2)	9.64 (1.78–56.4)	<0.0001	6.47 (1.52–35.0)	18.46 (2.42–87.5)	<0.0001	7.25 (1.53–41.7)	20.0 (2.90–86.3)	<0.0001
[Na], mmol/L	140±2	140±3	0.76	140±3	140±3	0.17	140±3	140±3	0.82
[K], mmol/L	4.09±0.38	4.29±0.51	<0.0001	4.30±0.51	4.28±0.51	0.49	4.30±0.50	4.26±0.55	0.22
Plasma uric acid, μmoL/L	369±100	429±109	<0.0001	432±111	426±107	0.20	419±102	450±120	<0.0001
[HCO_{3-}], mmol/L	26.4 (24.4–28.0)	26.0 (23.8–28.0)	0.11	26.0 (23.7–27.8)	26.0 (24.0–28.0)	0.44	26.0 (23.8–27.8)	26.2 (23.9–28.1)	0.25

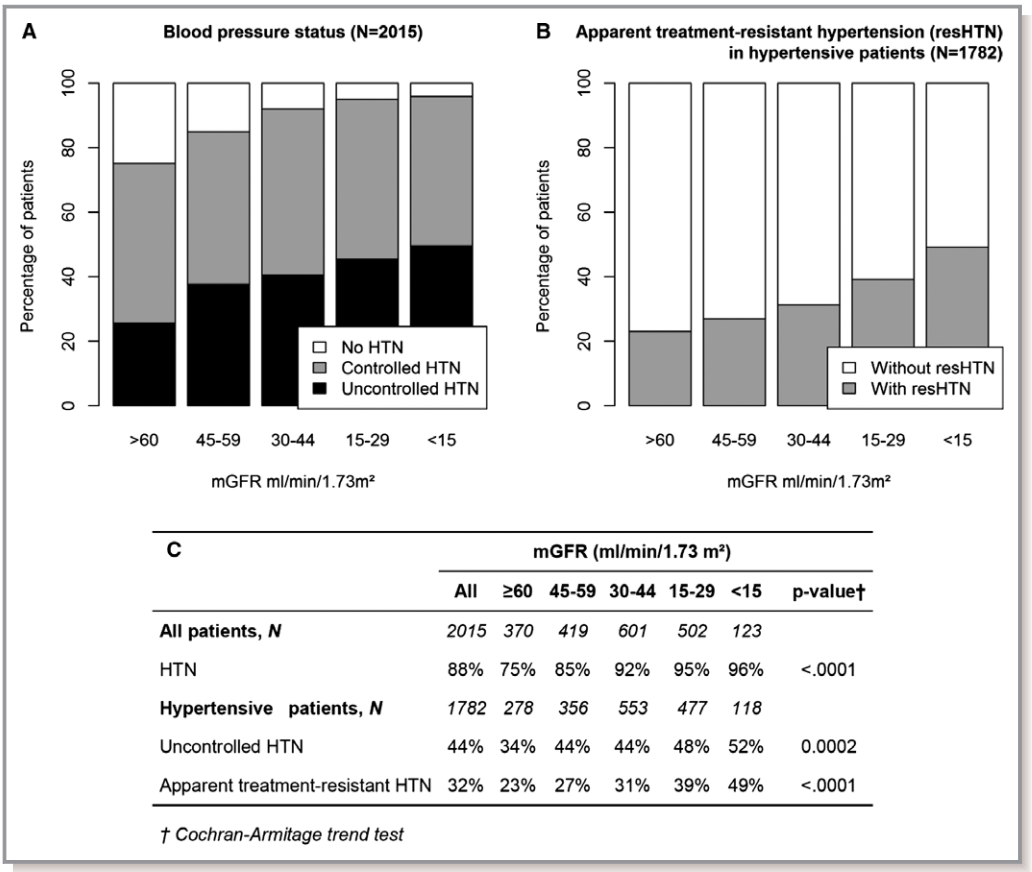
Continuous data are expressed as mean±SD or median (interquartile range), and groups were compared using Kruskal-Wallis test. Categorical data are expressed as percentage (number), and groups were compared using χ^2 test. ACR indicates albumin/creatinine ratio; BMI, body mass index; ECW, extracellular water; mGFR, measured glomerular filtration rate.

disappeared when absolute ECW value (in liters) was entered in the model, instead of its ratio over theoretical ECW (Table S1).

In the population of hypertensive patients, multivariable analysis for the determinants of uncontrolled hypertension showed that older age, higher albuminuria, diabetic nephropathy, and higher ECW (OR per 10% as a ratio over theoretical ECW, 1.11 [95% CI, 1.02–1.20]; and OR per 1 L, 1.07 [95% CI, 1.02–1.11]) were significantly associated with an increased risk of uncontrolled hypertension, whereas the use of aldosterone blockers was significantly associated with a decreased risk of uncontrolled hypertension (Table 5, Table S2). mGFR was not independently associated with hypertension control (OR per −10 mL/min per 1.73 m^2, 1.00 [95% CI, 0.99–1.00]; P=0.4).

Multivariable analysis for the determinants of apparent treatment-resistant hypertension was conducted in the population of hypertensive patients, with the exclusion of patients with uncontrolled hypertension despite no treatment (n=50) and 1 (n=116), 2 (n=182), or ≥3 drugs with no diuretics (n=79) because these patients may or may not be resistant would they be properly treated (Table 6, Table S3). Thus, resistant hypertension status defined a more severe status than nonresistant hypertension in this analysis. Older age, higher BMI, albuminuria, ECW (OR per 10% as a ratio over theoretical ECW, 1.12 [95% CI, 1.01–1.23]; and OR per 1 L, 1.08 [95% CI, 1.03–1.14]), lower mGFR, male sex, African origin, and diabetes mellitus were significantly associated with an increased risk of apparent treatment-resistant hypertension (Table 6). Compared with interstitial nephropathy, the type of nephropathy with the strongest association with apparent treatment-resistant hypertension was diabetic nephropathy (OR, 9.03; 95% CI, 3.84–21.21). A secondary analysis performed in the total population of 1782 hypertensive patients yielded similar results (Table S4).

In all analyses, similar results were obtained when 24-hour sodium and potassium excretions (instead of their ratio) were entered in the model separately (Table S5).



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	mGFR (ml/min/1.73 m²)						
	All	≥60	45-59	30-44	15-29	<15	p-value†
All patients, *N*	*2015*	*370*	*419*	*601*	*502*	*123*	
HTN	88%	75%	85%	92%	95%	96%	<.0001
Hypertensive patients, *N*	*1782*	*278*	*356*	*553*	*477*	*118*	
Uncontrolled HTN	44%	34%	44%	44%	48%	52%	0.0002
Apparent treatment-resistant HTN	32%	23%	27%	31%	39%	49%	<.0001

† Cochran-Armitage trend test

Figure 2. Prevalence of hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension by glomerular filtration rate (GFR) subgroups. A, Blood pressure status in the total population (n=2015). B, Apparent treatment-resistant hypertension in hypertensive patients (n=1782). C, Hypertension in all participants and uncontrolled hypertension and apparent treatment-resistant hypertension in hypertensive patients (n=1782). mGFR indicates measured GFR.

Table 3. Antihypertensive Treatments in NephroTest Hypertensive Patients (n=1782)

Variable	All	mGFR, mL/min per 1.73 m^2					*P* Value
		≥60 (N=278)	45–59 (N=356)	30–44 (N=553)	15–29 (N=477)	<15 (N=118)	
No. of antihypertensive drugs							<0.0001*
0	2.8 (50)	4.3 (12)	3.7 (13)	2.2 (12)	2.5 (12)	0.8 (1)	
1	19.3 (344)	26.6 (74)	26.1 (93)	19.0 (105)	13.0 (62)	8.5 (10)	
2	26.2 (467)	30.2 (84)	25.6 (91)	24.8 (137)	27.0 (129)	22.0 (26)	
3	24.6 (439)	20.9 (58)	24.4 (87)	26.8 (148)	23.5 (112)	28.8 (34)	
≥4	27.0 (482)	18.0 (50)	20.2 (72)	27.3 (151)	34.0 (162)	39.8 (47)	
Any diuretic	54.3 (967)	48.2 (134)	47.5 (169)	55.0 (304)	58.1 (277)	70.3 (83)	<0.0001†
Loop diuretic	33.6 (599)	16.5 (46)	22.5 (80)	32.9 (182)	45.5 (217)	62.7 (74)	<0.0001†
Thiazide diuretic	22.3 (398)	29.9 (83)	27.0 (96)	24.8 (137)	14.7 (70)	10.2 (12)	<0.0001†
Aldosterone blocker	2.8 (50)	4.3 (12)	2.8 (10)	2.5 (14)	2.7 (13)	0.8 (1)	0.096†
Converting enzyme inhibitor	51.6 (919)	46.8 (130)	45.8 (163)	53.3 (295)	55.1 (263)	57.6 (68)	0.001†
Angiotensin II receptor antagonist	43.9 (782)	44.2 (123)	43.0 (153)	44.3 (245)	42.3 (202)	50.0 (59)	0.73†
Calcium channel blocker	49.8 (887)	41.0 (114)	44.4 (158)	50.1 (277)	55.8 (266)	61.0 (72)	<0.0001†

Data are given as percentage (number). mGFR indicates measured glomerular filtration rate.
*χ^2 Test.
†Cochran-Armitage test for trend.

Results from sensitivity analyses showed that complete case analysis for ECW and multiple imputations give similar ORs of hypertension, uncontrolled BP, and apparent treatment-resistant hypertension analysis, according to ECW and their other determinants (Tables S1 through S4).

Table 4. Determinants of Hypertension in the Population With ECW Measurement (n=1750)

Variable	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
ECW, L	1.18 (1.13–1.24)	<0.0001	…	…
ECW ratio over theoretical ECW	1.22 (1.09–1.36)	0.0005	1.19 (1.05–1.35)	0.008
Age, y	1.06 (1.05–1.07)	<0.0001	1.04 (1.03–1.06)	<0.0001
Sex (women vs men)	0.54 (0.41–0.73)	<0.0001	0.82 (0.57–1.17)	0.2710
BMI 25–30 vs <25 kg/m^2	2.42 (1.74–3.37)	<0.0001	1.58 (1.07–2.32)	0.021
BMI ≥30 vs <25 kg/m^2	4.54 (2.73–7.56)	<0.0001	2.15 (1.20–3.83)	0.010
Ethnicity (African origin vs other)	1.41 (0.90–2.23)	0.14	2.28 (1.33–3.89)	0.003
Diabetes mellitus	6.40 (3.61–11.3)	<0.0001	2.16 (1.16–4.03)	0.015
Previous cardiovascular event	10.1 (4.11–24.6)	<0.0001	3.96 (1.56–10.0)	0.004
Smoking status (past vs none)	2.69 (1.80–4.01)	<0.0001	1.43 (0.91–2.24)	0.12
Smoking status (active vs none)	1.06 (0.70–1.60)	0.78	1.40 (0.86–2.28)	0.18
mGFR, per −10 mL/min per 1.73 m^2	1.40 (1.30–1.50)	<0.0001	1.22 (1.10–1.35)	0.0002
Log albuminuria, mg/mmol creatinine	1.17 (1.09–1.27)	<0.0001	1.19 (1.08–1.31)	0.0006
[Na], /mmol/L	0.99 (0.94–1.04)	0.73	0.98 (0.92–1.05)	0.60
[K], /mmol/L	2.29 (1.66–3.16)	<0.0001	1.77 (1.16–2.71)	0.008
[HCO_{3-}], /mmol/L	0.98 (0.93–1.02)	0.34	1.11 (1.04–1.18)	0.003
Plasma uric acid, /10 μmol/L	1.06 (1.05–1.08)	<0.0001	1.03 (1.01–1.05)	0.0008
Ratio Na/K 24-h urine	1.01 (1.00–1.02)	0.28	1.00 (0.99–1.01)	0.83

Crude and adjusted ORs (95% CIs) of hypertension are indicated, as well as *P* values. ORs were adjusted for all covariates and recruitment site. Fully adjusted ORs for ECW expressed in L are shown in Table S2. BMI indicates body mass index; CI, confidence interval; ECW, extracellular water; mGFR, measured glomerular filtration rate; OR, odds ratio.

Table 5. Determinants of Uncontrolled Hypertension in the Patients With Hypertension and ECW Measurement (n=1544)

Variable	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
ECW, L	1.08 (1.05–1.11)	<0.0001	…	…
ECW ratio over theoretical ECW	1.20 (1.12–1.29)	<0.0001	1.11 (1.02–1.20)	0.013
Age, y	1.03 (1.03–1.04)	<0.0001	1.03 (1.02–1.04)	<0.0001
Sex (women vs men)	0.76 (0.61–0.95)	0.014	0.81 (0.63–1.06)	0.12
BMI 25–30 vs <25 kg/m^2	1.24 (0.99–1.57)	0.064	1.23 (0.88–1.72)	0.22
BMI ≥30 vs <25 kg/m^2	1.39 (1.07–1.81)	0.015	1.07 (0.83–1.39)	0.60
Ethnicity (African origin vs other)	0.89 (0.67–1.18)	0.43	1.13 (0.83–1.55)	0.44
Diabetes mellitus	1.74 (1.40–2.17)	<0.0001	1.02 (0.76–1.38)	0.90
Previous cardiovascular event	1.19 (0.93–1.53)	0.17	0.82 (0.62–1.09)	0.18
Smoking status (past vs none)	1.39 (1.11–1.73)	0.004	1.16 (0.90–1.50)	0.25
Smoking status (active vs none)	0.89 (0.65–1.22)	0.46	0.94 (0.66–1.33)	0.73
mGFR, per −10 mL/min per 1.73 m^2	1.08 (1.03–1.14)	0.0042	1.00 (0.99–1.00)	0.39
Log albuminuria, mg/mmol creatinine	1.19 (1.13–1.26)	<0.0001	1.27 (1.19–1.36)	<0.0001
Type of nephropathy				
Diabetic	2.58 (1.81–3.69)	<0.0001	2.13 (1.19–3.83)	0.011
Glomerular	0.66 (0.46–0.93)	0.018	0.77 (0.45–1.31)	0.33
Vascular	1.41 (1.09–1.82)	0.009	1.40 (0.88–2.23)	0.15
Polycystic	0.76 (0.48–1.20)	0.25	1.11 (0.61–2.03)	0.73
Interstitial	1 (Reference)	…	1 (Reference)	…
Other or unknown	0.87 (0.58–1.31)	0.51	0.99 (0.62–1.57)	0.96
No. of antihypertensive treatments	1.08 (1.00–1.16)	0.039	0.93 (0.84–1.04)	0.19
Diuretic	0.90 (0.74–1.11)	0.33	1.01 (0.75–1.35)	0.97
Aldosterone blocker	2.64 (1.30–5.39)	0.008	0.45 (0.21–0.98)	0.046
[Na], /mmol/L	1.02 (0.98–1.06)	0.27	1.32 (0.88–1.99)	0.18
[K], /mmol/L	0.92 (0.75–1.12)	0.41	0.78 (0.60–1.00)	0.049
[HCO_{3-}], /mmol/L	1.02 (0.98–1.05)	0.36	1.03 (0.99–1.07)	0.20
Plasma uric acid, /10 μmol/L	0.99 (0.99–1.00)	0.26	0.99 (0.98–1.00)	0.26
Ratio Na/K 24-h urine	1.00 (1.00–1.01)	0.627	1.00 (0.99–1.01)	0.77

Crude and adjusted ORs (95% CIs) of uncontrolled hypertension are indicated, as well as *P* values. ORs were adjusted for all covariates and recruitment site. Fully adjusted ORs for ECW expressed in L are shown in Table S3. BMI indicates body mass index; CI, confidence interval; ECW, extracellular water; mGFR, measured glomerular filtration rate; OR, odds ratio.

Discussion

In this analysis conducted in 2015 patients with CKD, stage 1 to 5, who underwent gold standard GFR and ECW measurements, we showed that ECW was an independent determinant of hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension. In addition, we identified that mGFR, BMI, ethnicity, male sex, and diabetes mellitus were significantly associated with apparent treatment-resistant hypertension but not uncontrolled hypertension, whereas age, albuminuria, and diabetic nephropathy were associated with both uncontrolled and resistant hypertension.

The prevalences of hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension are in the same range orders as in previous studies conducted in patients with CKD. In the CRIC (Chronic Renal Insufficiency Cohort) study conducted in 3612 outpatients recruited between 2003 and 2007, with an estimated GFR between 20 and 70 mL/min per 1.73 m^2,[6] prevalence of hypertension was 86% (versus 88% in our study); and in hypertensive patients, BP was controlled in 67% (versus 56% in our study). Likewise, in a primary care cohort of 10 040 patients with CKD, stage 3 to 5, conducted in Kent (UK) between 2004 and 2008, prevalence of hypertension was 84%, half of which were controlled[17]; and in

Table 6. Determinants of Apparent Treatment-Resistant Hypertension in the Patients With Hypertension and ECW Measurement (n=1190)

Variable	Crude OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
ECW, L	1.16 (1.12–1.20)	<0.0001	…	…
ECW ratio over theoretical ECW	1.19 (1.09–1.29)	<0.0001	1.12 (1.01–1.23)	0.026
Age, y	1.03 (1.02–1.04)	<0.0001	1.02 (1.01–1.03)	0.003
Sex (women vs men)	0.59 (0.46–0.75)	<0.0001	0.68 (0.50–0.93)	0.017
Ethnicity (African origin vs other)	1.79 (1.31–2.45)	0.0003	2.56 (1.74–3.76)	<0.0001
BMI 25–30 vs <25 kg/m^2	2.31 (1.74–3.06)	<0.0001	1.70 (1.23–2.35)	0.001
BMI ≥30 vs <25 kg/m^2	4.02 (2.93–5.51)	<0.0001	2.64 (1.83–3.81)	<0.0001
Diabetes mellitus	3.39 (2.63–4.38)	<0.0001	1.52 (1.07–2.16)	0.018
Previous cardiovascular event	2.14 (1.61–2.83)	<0.0001	1.29 (0.93–1.80)	0.12
Smoking status (past vs none)	1.31 (1.02–1.69)	0.038	0.97 (0.71–1.33)	0.86
Smoking status (active vs none)	0.83 (0.58–1.19)	0.31	0.74 (0.48–1.15)	0.18
mGFR, per −10 mL/min per 1.73 m^2	1.22 (1.14–1.30)	<0.0001	1.19 (1.10–1.29)	<0.0001
Log albuminuria, mg/mmol creatinine	1.24 (1.16–1.31)	<0.0001	1.19 (1.10–1.28)	<0.0001
Type of nephropathy		<0.0001		
Diabetic	23.8 (11.0–51.2)	<0.0001	9.03 (3.84–21.21)	<0.0001
Glomerular	3.10 (1.49–6.47)	0.003	3.01 (1.37–6.64)	0.006
Vascular	9.06 (4.52–18.1)	<0.0001	6.09 (2.90–12.77)	<0.0001
Polycystic	1.68 (0.70–4.05)	0.25	2.14 (0.84–5.46)	0.11
Interstitial	1 (Reference)	…	1 (Reference)	…
Other or unknown	3.97 (1.98–7.95)	0.0001	2.74 (1.30–5.81)	0.008
Ratio Na/K 24-h urine	1.01 (1.00–1.02)	0.025	1.00 (1.00–1.01)	0.40

Patients with unknown resistance status (uncontrolled hypertension and <3 drugs or at least 3 drugs without a diuretic) were excluded from this analysis. Crude and adjusted ORs (95% CIs) of apparent treatment-resistant hypertension are indicated, as well as *P* values. ORs were adjusted for all covariates and recruitment site. Fully adjusted ORs for ECW expressed in L are shown in Table S4. The secondary analysis conducted in all hypertensive patients is shown in Table S5. BMI indicates body mass index; CI, confidence interval; ECW, extracellular water; mGFR, measured glomerular filtration rate; OR, odds ratio.

participants with CKD from NHANES IV, hypertension was controlled (<140/90 mm Hg) in 56% of the subjects.[18]

Two definitions are encountered for resistant hypertension.[7] One definition is uncontrolled BP despite the use of at least 3 drugs, including a diuretic. Because we aimed for resistant hypertension to be a marker of severity, and not of hypertension control, we did the following: (1) chose the second definition of resistant hypertension (uncontrolled BP despite 3 drugs, including a diuretic, or the use of ≥4 drugs, including a diuretic, regardless of BP level); and (2) excluded patients with uncontrolled BP but inappropriate treatment from the main analysis. Among US adults from NHANES, 8.9% of hypertensive participants (12.8% of treated hypertensive participants) had resistant hypertension (defined as uncontrolled BP despite 3 different drug classes or the use of at least 4 antihypertensive drug classes regardless of BP, with no requirement for the use of a diuretic, although 86% of patients with resistant hypertension used a diuretic).[9] In 470 386 hypertensive individuals in the Kaiser Permanente Southern California health system, 12.8% (15.3% of those receiving medication) have resistant hypertension. The prevalence of resistant hypertension was much higher in our study (32% of hypertensive patients), as expected in patients with CKD. Indeed, studies conducted in patients with CKD found prevalences of resistant hypertension ranging from 11%[19] to 40%,[20] with an increasing prevalence as GFR decreases.[21] In the CRIC study, factors associated with resistant hypertension were age, male sex, black race, diabetes mellitus, higher BMI, lower GFR, and higher proteinuria, all also identified to be independent predictors of resistant hypertension in our study.

Comparison of the determinants associated with uncontrolled and resistant hypertension allowed us to define factors independently associated with the severity of hypertension (as assessed by the apparent treatment-resistant hypertension status), but not uncontrolled hypertension. Indeed, determinants of a more severe hypertension do not necessarily predict a poorer control, provided appropriate treatment is prescribed. This was the case for a more advanced kidney disease (lower mGFR), a higher BMI, African origin, male sex, and diabetes mellitus, all independently associated with

resistant hypertension, but not uncontrolled hypertension. Noteworthy, the lack of an association between GFR and BP control had previously been shown in the CRIC study[6] of patients with CKD as well as in NHANES.[18] As previously shown in the CRIC study cohort,[6] this likely reflects a more aggressive treatment in patients with a lower GFR, because 58% of the patients with mGFR between 15 and 30 mL/min per 1.73 m^2 received at least 3 antihypertensive drugs versus 39% of the patients with a GFR >60 mL/min per 1.73 m^2.

Therapeutic inertia (both for nutritional and pharmacological treatment) might be a cause of poorly controlled BP. Sodium intake, estimated from 24-hour urinary sodium excretion, was 3.4 g/d, hence above the recommended intake of 1.5 to 2 g/d,[22,23] despite the well-described salt sensitivity of BP in patients with CKD.[24–26] In addition, 44% of the patients with uncontrolled BP received <3 drugs, suggesting that therapeutic inertia might be a more common cause of poorly controlled BP than resistant hypertension, as previously highlighted in NHANES.[9]

Increased sympathetic and renin-angiotensin system activities, endothelial dysfunction, and increased arterial stiffness are among the multiple mechanisms that contribute to the pathogenesis of hypertension during CKD.[27] Another key pathophysiological factor is altered renal sodium excretion, leading to fluid retention.[27] ECW has been shown to increase during CKD, even in the early stage of the disease,[11,28,29] and is thought to play a crucial role in the development of hypertension in this population.[30–32] However, no large study on the factors associated with hypertension in CKD ever relied on gold standard measurement of ECW, based on isotope dilution, because this technique is not routinely available. In our large cohort of patients with CKD, ECW, measured as the volume of distribution of ^{51}Cr-EDTA, was independently associated with hypertension, uncontrolled hypertension, and apparent treatment-resistant hypertension, after adjustment for multiple potentially confounding variables, including BMI, albuminuria, urinary sodium excretion, and plasma sodium concentration. Interestingly, BMI was not independently associated with hypertension when absolute ECW, instead of its ratio over theoretical ECW, was entered in the model. Similar findings were reported in 40 patients with CKD who underwent 24-hour ambulatory BP measurement and total body water assessment with bioelectrical impedance, suggesting that BMI was less involved in BP control when body water imbalance was entered in the model.[12] Likewise, male sex was no longer associated with resistant hypertension when absolute ECW was entered in the model, suggesting that increased ECW in men may contribute to the severity of hypertension. The ratio of ECW over theoretical ECW was chosen for the main analysis because the absolute value of ECW is strongly correlated with anthropometric parameters. In addition, although one ought to be careful when interpreting these observational data, it is of interest to note the aldosterone blockers were significantly associated with hypertension control, although the rate of antialdosterone treatment was low because of a cohort recruited since 2000. Previous reports have shown the beneficial effect of aldosterone antagonists in patients with CKD.[33–35] Likewise, a randomized trial conducted in patients with resistant hypertension[36] showed that an approach based on combined diuretics was more efficient in controlling BP than an approach based on sequential blockade of the renin-angiotensin system, and the recent randomized studies, PATHWAY-2 (Prevention and Treatment of Hypertension With Algorithm based Therapy-2) and ReHOT (Resistant Hypertension Optimal Treatment), demonstrated that spironolactone was the most efficient fourth-line treatment in resistant hypertension.[37,38] The key role of ECW reduction through sodium restriction[25,39] or diuretic treatment[31,40] for hypertension control in CKD has been shown by previous studies. Altogether, these data suggest the need for a larger use of diuretics, including aldosterone antagonists, in hypertensive patients with CKD.

Strengths of our study include the quality of GFR and ECW assessment, measured with renal clearance of ^{51}Cr-EDTA and determination of the volume of distribution of the tracer, respectively; hence, these are gold standard methods rarely available in large cohorts. In addition, analyses were adjusted for multiple confounding factors, including plasma sodium and potassium, which are often overlooked, although they are highly linked with ECW and should be considered when studying the association between ECW and BP.[41]

Our study has several limitations. First, it is an observational study with no predefined guidelines about patient care and antihypertensive treatment. On the other hand, information obtained in real-life conditions is complementary to data obtained in the controlled and standardized conditions of a randomized trial. Furthermore, our analysis was based on office BP measurement during a single visit. Repeated office measurements or, ideally, out-of- office measurements, such as ambulatory BP measurements, would have provided a higher diagnosis accuracy, and in particular would have helped identifying patients with pseudoresistant hypertension. Finally, because of the initial recruitment of this cohort (ie, patients with CKD referred by their nephrologist for an extensive workup), we can only study factors associated with prevalence, not incidence, of hypertension, uncontrolled BP, and resistant hypertension in patients with CKD.

Appendix

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Sources of Funding

The NephroTest chronic kidney disease cohort study is supported by the following grants: INSERM GIS-IReSP AO 8113LS TGIR, French Ministry of Health AOM 09114, INSERM AO 8022LS, Agence de la Biomédecine R0 8156LL, AURA and Roche 2009-152-447G. Hôpitaux Paris Nord Val de Seine provided financial support for publication fees.

Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Logistic regression models for the analyses of hypertension, uncontrolled blood pressure, and apparent treatment-resistant hypertension determinants.

Adjusted Odds Ratios (OR) with 95% confidence interval (95% CI) according to patients characteristics were estimated from three nested logistic regression models for hypertension (models 1, 2a, 3a), for uncontrolled hypertension (models 1, 2b, 3b), and for apparent treatment resistant hypertension (models 1, 2c, 3c). Predictors for model 1 were site of recruitment, age, sex, body mass index (BMI <25, 25-29, ≥ 30), ethnicity (Sub-saharian African origin versus other origins), diabetes, previous cardiovascular event, smoking status (none, past, active). In model 2a, additional predictors were mGFR and albuminuria (in mg/mmol, expressed on a logarithmic scale). In model 3a, covariates were those of model 2a, plus ECW, plasma sodium, potassium, bicarbonate and uric acid concentrations, and the ratio of sodium over potassium concentrations in the 24-hour urine collection. Models 2b and 3b included the covariates of models 2a and 3a, as well as the type of nephropathy (diabetic, glomerular, vascular, polycystic, other or unknown, and interstitial nephropathy used as reference), number of treatment, use of diuretic and use of aldosterone blocker. These covariates were not used analysis of the determinants of hypertension, as normotensive patients never had vascular nephropathy, and received no anti-hypertensive treatment. In a separate analysis, 24-hour urinary sodium and potassium excretions were tested instead of their ratio. We also tested BMI continuously instead of in classes. For the determinants of resistant hypertension, covariates were similar to those of models 2b and 3b, except that treatment-related covariates were excluded from models 2c and 3c, as the number and type of treatment were part of the definition of resistant hypertension, and blood biochemistry was also excluded from model 3c as it is influenced by diuretic treatment, itself mandatory in the definition of resistant hypertension.

Table S1. Multivariable analysis of hypertension determinants using logistic regression.

	Patients with ECW measurements N=2015								Patients N=2015	
	Model 1		Model 2		Model 3		Model 3		Model 3 MI*	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age (years)	1.04(1.03,1.05)	<.0001	1.04(1.03,1.06)	<.0001	1.04(1.03,1.06)	<.0001	1.04(1.03,1.06)	<.0001	1.04(1.03-1.05)	<.001
Sex (women vs men)	0.73(0.53,1.02)	0.062	0.67(0.48,0.95)	0.023	0.82(0.57,1.17)	0.2710	1.15(0.76,1.74)	0.50	0.90(0.64-1.26)	0.54
Ethnicity (African origin vs other)	2.26(1.38,3.68)	0.001	2.45(1.47,4.08)	0.0006	2.28(1.33,3.89)	0.003	2.22(1.30,3.78)	0.003	2.25(1.34-3.80)	0.002
BMI 25-30 vs < 25	1.57(1.09,2.26)	0.015	1.59(1.09,2.31)	0.017	1.58(1.07,2.32)	0.021	1.30(0.87,1.95)	0.21	1.65(1.15-2.36)	0.006
BMI ≥ 30 vs < 25	2.39(1.39,4.14)	0.002	2.31(1.33,4.03)	0.003	2.15(1.20,3.83)	0.010	1.43(0.76,2.70)	0.27	2.33(1.36-3.99)	0.002
Diabetes	2.93(1.60,5.34)	0.0005	2.52(1.37,4.65)	0.003	2.16(1.16,4.03)	0.015	2.16(1.16,4.02)	0.016	1.82(1.06-3.13)	0.03
Previous CV event	4.53(1.81,11.4)	0.001	4.00(1.59,10.1)	0.003	3.96(1.56,10.0)	0.004	4.10(1.62,10.4)	0.003	3.29(1.49-7.30)	0.003
Smoking status (past vs none)	1.49(0.96,2.30)	0.075	1.48(0.95,2.31)	0.084	1.43(0.91,2.24)	0.12	1.41(0.90,2.21)	0.14	1.42(0.94-2.13)	0.094
Smoking status (active vs none)	1.28(0.81,2.02)	0.29	1.43(0.89,2.30)	0.14	1.40(0.86,2.28)	0.18	1.39(0.85,2.26)	0.19	1.37(0.87-2.14)	0.18
mGFR (per -10 mL/min/1.73m²)			0.98(0.97,0.99)	<.0001	1.22(1.10,1.35)	0.0002	1.21(1.10,1.34)	0.0002	1.19(1.09-1.31)	<.001
Log albuminuria (mg/mmol creat)			1.18(1.08,1.30)	0.0005	1.19(1.08,1.31)	0.0006	1.19(1.08,1.32)	0.0006	1.16(1.06-1.27)	0.002
ECW ratio over th-ECW					**1.19(1.05,1.35)**	**0.008**			**1.16(1.02-1.31)**	**0.019**
ECW (in L)							**1.10(1.03,1.18)**	**0.007**		
[Na] (/mM)					0.98(0.92,1.05)	0.60	0.98(0.91,1.05)	0.56	0.98(0.92-1.05)	0.55
[K] (/mM)					1.77(1.16,2.71)	0.008	1.74(1.14,2.66)	0.010	1.92(1.30-2.83)	0.001
[HCO3-](/mM)					1.11(1.04,1.18)	0.003	1.10(1.03,1.18)	0.003	1.10(1.04-1.17)	0.002
Plasma uric acid (/10µM/L)					1.03(1.01,1.05)	0.0008	1.03(1.01,1.05)	0.001	1.03(1.01-1.05)	0.001
Ratio Na/K 24H-urine					1.00(0.99,1.01)	0.83	1.00(0.99,1.01)	0.81	1.00(0.99-1.01)	0.59

* sensitivity analysis using multiple imputation (MI). Model 1, 2 and 3 also adjusted for recruitment site.

BMI: body mass index; CV: cardiovascular; mGFR: measured glomerular filtration rate; ECW: extracellular water; th-ECW: theoretical extracellular water.

Table S2. Multivariable analysis of uncontrolled hypertension determinants using logistic regression.

	Patients with hypertension and ECW measurements N=1544								Patients with hypertension N=1782*	
	Model 1		Model 2b		Model 3b		Model 3b		Model 3c MI	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age (years)	1.03(1.02,1.04)	<.0001	1.04(1.03,1.05)	<.0001	1.03(1.02,1.04)	<.0001	1.03(1.02,1.04)	<.0001	1.04(1.03-1.05)	<.001
Sex (women vs men)	0.85(0.67,1.07)	0.17	0.89(0.70,1.15)	0.37	0.81(0.63,1.06)	0.12	1.03(0.77,1.37)	0.87	0.85(0.67-1.09)	0.20
Ethnicity (African origin vs other)	1.21(0.89,1.64)	0.22	1.24(0.90,1.70)	0.20	1.23(0.88,1.72)	0.22	1.21(0.87,1.70)	0.26	1.21(0.88-1.66)	0.25
BMI 25-30 vs < 25	1.00(0.78,1.28)	0.99	1.01(0.79,1.31)	0.91	1.07(0.83,1.39)	0.60	0.95(0.73,1.25)	0.73	1.16(0.91-1.48)	0.22
BMI ≥ 30 vs < 25	1.10(0.83,1.47)	0.51	1.03(0.77,1.39)	0.83	1.13(0.83,1.55)	0.44	0.87(0.61,1.23)	0.43	1.19(0.89-1.60)	0.24
Diabetes	1.51(1.19,1.91)	0.0008	0.99(0.74,1.33)	0.99	1.02(0.76,1.38)	0.90	1.01(0.75,1.37)	0.95	1.03(0.78-1.36)	0.85
Previous CV event	0.85(0.65,1.11)	0.23	0.79(0.60,1.05)	0.10	0.82(0.62,1.09)	0.18	0.83(0.62,1.10)	0.19	0.86(0.66-1.13)	0.28
Smoking status (past vs none)	1.12(0.88,1.43)	0.37	1.16(0.90,1.50)	0.24	1.16(0.90,1.50)	0.25	1.15(0.89,1.49)	0.28	1.23(0.97-1.56)	0.09
Smoking status (active vs none)	0.99(0.71,1.38)	0.94	0.92(0.65,1.30)	0.65	0.94(0.66,1.33)	0.73	0.93(0.65,1.32)	0.69	0.99(0.72-1.37)	0.95
mGFR (per -10 mL/min/1.73m²)			1.00(1.00,1.01)	0.16	1.00(0.99,1.00)	0.39	1.00(0.99,1.00)	0.36	1.03(0.96-1.10)	0.45
Log albuminuria (mg/mmol creat)			1.29(1.21,1.37)	<.0001	1.27(1.19,1.36)	<.0001	1.27(1.19,1.36)	<.0001	1.27(1.19-1.35)	<.001
Type of nephropathy				0.002		0.001		0.001		
Diabetic			1.89(1.08,3.32)	0.026	2.13(1.19,3.83)	0.011	2.12(1.18,3.80)	0.012	2.37(1.37-4.12)	0.002
Glomerular			0.68(0.41,1.14)	0.15	0.77(0.45,1.31)	0.33	0.77(0.45,1.30)	0.33	0.89(0.54-1.46)	0.64
Vascular			1.25(0.80,1.95)	0.33	1.40(0.88,2.23)	0.15	1.41(0.89,2.25)	0.14	1.57(1.01-2.43)	0.044
Polycystic			1.08(0.60,1.96)	0.79	1.11(0.61,2.03)	0.73	1.08(0.59,1.97)	0.81	1.18(0.66-2.11)	0.58
Interstitial			1(ref)		1(ref)		1(ref)		1(ref)	
Other or unknown			0.90(0.58,1.42)	0.66	0.99(0.62,1.57)	0.96	0.98(0.62,1.55)	0.93	1.16(0.75-1.79)	0.50
Number of antihypertensive treatments					0.93(0.84,1.04)	0.19	0.93(0.83,1.03)	0.17	0.90(0.82-1.00)	0.049
Diuretic					1.01(0.75,1.35)	0.97	1.01(0.76,1.36)	0.92	1.00(0.76-1.30)	0.98
Aldosterone blocker					0.45(0.21,0.98)	0.046	0.44(0.20,0.96)	0.040	0.53(0.26-1.07)	0.076
ECW ratio over th-ECW					**1.11(1.02,1.20)**	**0.013**			**1.10(1.02-1.19)**	**0.01**
ECW (in L)							**1.07(1.02,1.11)**	**0.0018**		
[Na] (/mM)					1.32(0.88,1.99)	0.18	1.31(0.87,1.97)	0.19	1.03(0.99-1.07)	0.17
[K] (/mM)					0.78(0.60,1.00)	0.049	0.78(0.60,1.00)	0.052	0.78(0.62-0.99)	0.045
[HCO3-](/mM)					1.03(0.99,1.07)	0.20	1.03(0.99,1.07)	0.20	1.02(0.99-1.06)	0.22
Plasma uric acid (/10µM/L)					0.99(0.98,1.00)	0.26	0.99(0.98,1.00)	0.22	0.99(0.98-1.00)	0.20
Ratio Na/K 24H-urine					1.00(0.99,1.01)	0.77	1.00(0.99,1.01)	0.71	1.00(1.00-1.01)	0.12

* sensitivity analysis using multiple imputation (MI). Model 1, 2 and 3 also adjusted for recruitment site.

BMI: body mass index; CV: cardiovascular; mGFR: measured glomerular filtration rate; ECW: extracellular water; th-ECW: theoretical extracellular water.

Table S3. Multivariable analysis of apparent treatment-resistant hypertension determinants using logistic regression, after exclusion of patients with unknown resistance status (uncontrolled hypertension and less than 3 drugs, or at least 3 drugs without a diuretic).

	Patients with hypertension and ECW measurements N=1190								Patients with hypertension N=1355*	
	Model 1		Model 2c		Model 3c		Model 3c		Model 3c MI	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age (years)	1.02(1.01,1.03)	<.0001	1.02(1.01,1.03)	0.0006	1.02(1.01,1.03)	0.003	1.02(1.01,1.03)	0.001	1.02(1.01-1.03)	<.001
Sex (women vs men)	0.70(0.53,0.94)	0.019	0.69(0.50,0.95)	0.022	0.68(0.50,0.93)	0.017	0.90(0.63,1.29)	0.57	0.70(0.52-0.95)	0.02
Ethnicity (African origin vs other)	2.61(1.83,3.72)	<.0001	2.58(1.76,3.79)	<.0001	2.56(1.74,3.76)	<.0001	2.51(1.71,3.69)	<.0001	2.78(1.89-4.09)	<.001
BMI 25-30 vs < 25	1.68(1.24,2.28)	0.0008	1.67(1.21,2.30)	0.002	1.70(1.23,2.35)	0.001	1.48(1.06,2.05)	0.021	1.73(1.27-2.34)	<.001
BMI ≥ 30 vs < 25	2.76(1.96,3.90)	<.0001	2.63(1.82,3.78)	<.0001	2.64(1.83,3.81)	<.0001	1.90(1.26,2.88)	0.002	2.67(1.89-3.77)	<.001
Diabetes	2.50(1.89,3.31)	<.0001	1.56(1.10,2.21)	0.012	1.52(1.07,2.16)	0.018	1.51(1.06,2.14)	0.021	1.56(1.13-2.18)	0.008
Previous CV event	1.50(1.10,2.04)	0.011	1.30(0.93,1.80)	0.12	1.29(0.93,1.80)	0.12	1.30(0.93,1.80)	0.12	1.27(0.93-1.74)	0.13
Smoking status (past vs none)	0.96(0.71,1.29)	0.78	0.98(0.71,1.34)	0.88	0.97(0.71,1.33)	0.86	0.96(0.70,1.32)	0.81	1.04(0.77-1.40)	0.82
Smoking status (active vs none)	0.94(0.63,1.41)	0.76	0.74(0.48,1.15)	0.18	0.74(0.48,1.15)	0.18	0.74(0.48,1.14)	0.17	0.69(0.46-1.04)	0.08
mGFR (per -10 mL/min/1.73m²)			1.17(1.08,1.27)	0.0001	1.19(1.10,1.29)	<.0001	1.20(1.10,1.31)	<.0001	1.17(1.08-1.26)	<.001
Log albuminuria (mg/mmol creat)			1.20(1.12,1.30)	<.0001	1.19(1.10,1.28)	<.0001	1.19(1.10,1.28)	<.0001	1.19(1.11-1.28)	<.001
Type of nephropathy				<.0001		<.0001		0.010		
Diabetic			9.18(3.94,21.39)	<.0001	9.03(3.84,21.21)	<.0001	8.82(3.75,20.74)	<.0001	9.87(4.37-22.25)	<.001
Glomerular			2.82(1.29,6.15)	0.009	3.01(1.37,6.64)	0.006	2.98(1.35,6.55)	0.007	3.29(1.55-6.99)	0.002
Vascular			5.83(2.80,12.13)	<.0001	6.09(2.90,12.77)	<.0001	6.03(2.87,12.64)	<.0001	5.92(2.93-11.99)	<.001
Polycystic			2.10(0.83,5.32)	0.12	2.14(0.84,5.46)	0.11	2.00(0.78,5.13)	0.15	2.30(0.93-5.64)	0.07
Interstitial			1(ref)		1(ref)		1(ref)		1(ref)	
Other or unknown			2.69(1.28,5.64)	0.009	2.74(1.30,5.81)	0.008	2.69(1.27,5.68)	0.010	2.98(1.46-6.09)	0.003
ECW ratio over th-ECW					**1.12(1.01,1.23)**	**0.026**			**1.10(1.00-1.21)**	**0.051**
ECW (in L)							**1.08(1.03,1.14)**	**0.002**		
Ratio Na/K 24H-urine					1.00(1.00,1.01)	0.40	1.00(1.00,1.01)	0.36	1.01(1.00-1.01)	0.14

* sensitivity analysis using multiple imputation (MI). Model 1, 2c and 3c were also adjusted for recruitment site.

BMI: body mass index; CV: cardiovascular; mGFR: measured glomerular filtration rate; ECW: extracellular water; th-ECW: theoretical extracellular water.

Table S4. Multivariable analysis of apparent treatment-resistant hypertension determinants using logistic regression, in all hypertensive patients.

	Patients with hypertension and ECW measurements N=1544								Patients with hypertension N=1782*	
	Model 1		Model 2c		Model 3c		Model 3c		Model 3c MI	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age (years)	1.01(1.00,1.02)	0.01	1.01(1.00,1.02)	0.15	1.01(1.00,1.02)	0.24	1.01(1.00,1.02)	0.19	1.01(1.00-1.02)	0.058
Sex (women vs men)	0.72(0.55,0.95)	0.018	0.73(0.55,0.96)	0.027	0.71(0.53,0.95)	0.020	0.86(0.63,1.18)	0.35	0.72(0.55-0.94)	0.016
Ethnicity (African origin vs other)	2.42(1.76,3.32)	<.0001	2.37(1.69,3.32)	<.0001	2.35(1.67,3.29)	<.0001	2.32(1.65,3.25)	<.0001	2.57(1.81-3.64)	<.001
BMI 25-30 vs < 25	1.74(1.32,2.30)	0.0001	1.74(1.30,2.32)	0.0002	1.77(1.32,2.36)	0.0001	1.60(1.19,2.16)	0.002	1.73(1.32-2.27)	<.001
BMI ≥ 30 vs < 25	2.91(2.13,3.98)	<.0001	2.86(2.06,3.96)	<.0001	2.87(2.07,3.98)	<.0001	2.29(1.59,3.32)	<.0001	2.76(2.03-3.74)	<.001
Diabetes	2.31(1.80,2.96)	<.0001	1.69(1.24,2.30)	0.0009	1.66(1.22,2.26)	0.001	1.65(1.21,2.25)	0.002	1.68(1.26-2.25)	<.001
Previous CV event	1.63(1.23,2.15)	0.0006	1.43(1.07,1.91)	0.016	1.42(1.06,1.90)	0.017	1.42(1.07,1.91)	0.017	1.43(1.08-1.88)	0.011
Smoking status (past vs none)	0.95(0.73,1.24)	0.70	0.97(0.74,1.28)	0.84	0.97(0.73,1.28)	0.82	0.96(0.73,1.27)	0.78	1.00(0.77-1.30)	0.99
Smoking status (active vs none)	0.95(0.66,1.38)	0.79	0.83(0.56,1.23)	0.35	0.82(0.56,1.21)	0.33	0.82(0.55,1.21)	0.31	0.72(0.50-1.04)	0.08
mGFR (per -10 mL/min/1.73m²)			1.20(1.11,1.29)	<.0001	1.21(1.12,1.30)	<.0001	1.21(1.13,1.31)	<.0001	1.18(1.10-1.27)	<.001
Log albuminuria (mg/mmol creat)			1.11(1.04,1.18)	0.003	1.10(1.02,1.17)	0.007	1.10(1.03,1.17)	0.007	1.09(1.02-1.16)	0.007
Type of nephropathy				<.0001		<.0001		<.0001		
Diabetic			8.18(3.78,17.71)	<.0001	7.95(3.66,17.27)	<.0001	7.90(3.64,17.15)	<.0001	8.06(3.87-16.79)	<.001
Glomerular			3.63(1.71,7.72)	0.0008	3.76(1.76,8.02)	0.0006	3.76(1.76,8.01)	0.0006	3.82(1.86-7.82)	<.001
Vascular			6.07(3.02,12.23)	<.0001	6.20(3.07,12.51)	<.0001	6.22(3.08,12.54)	<.0001	5.80(2.98-11.28)	<.001
Polycystic			2.24(0.92,5.49)	0.076	2.25(0.92,5.52)	0.077	2.17(0.88,5.34)	0.090	2.40(1.02-5.68)	0.046
Interstitial			1(ref)		1(ref)		1(ref)		1(ref)	
Other or unknown			3.02(1.48,6.14)	0.002	3.03(1.48,6.17)	0.002	2.99(1.47,6.11)	0.003	3.15(1.60-6.19)	<.001
ECW ratio over th-ECW					**1.08(0.99,1.18)**	**0.066**			**1.06(0.96-1.17)**	**0.22**
ECW (in L)							**1.05(1.01,1.10)**	**0.015**		
Ratio Na/K 24H-urine					1.00(1.00,1.01)	0.43	1.00(1.00,1.01)	0.40	1.01(1.00-1.01)	0.10

* sensitivity analysis using multiple imputation (MI). Model 1, 2c and 3c also adjusted for recruitment site.

BMI: body mass index; CV: cardiovascular; mGFR: measured glomerular filtration rate; ECW: extracellular water; th-ECW: theoretical extracellular water.

Table S5. Multivariable analysis of hypertension, uncontrolled hypertension and apparent treatment resistant hypertension determinants using logistic regression.

	Hypertension (N=2015)		Uncontrolled hypertension (N=1544)		Apparent treatment resistant hypertension (N=1190)	
	Adjusted OR (95%CI)	**p-value**	**Adjusted OR (95%CI)**	**p-value**	**Adjusted OR (95%CI)**	**p-value**
Age (years)	1.04(1.03,1.06)	<.0001	1.03(1.02,1.04)	<.0001	1.02(1.01,1.03)	0.002
Sex (women vs men)	0.86(0.59,1.25)	0.43	0.83(0.64,1.08)	0.16	0.69(0.50,0.95)	0.024
Ethnicity (African origin vs other)	2.30(1.35,3.94)	0.002	1.23(0.88,1.72)	0.23	2.54(1.73,3.74)	<.0001
BMI 25-30 vs < 25	1.54(1.05,2.27)	0.029	1.07(0.82,1.38)	0.63	1.70(1.23,2.35)	0.001
BMI ≥ 30 vs < 25	2.03(1.13,3.64)	0.018	1.12(0.81,1.53)	0.50	2.61(1.80,3.78)	<.0001
Diabetes	2.11(1.13,3.94)	0.020	1.01(0.75,1.37)	0.93	1.51(1.06,2.14)	0.021
Previous CV event	3.95(1.56,9.99)	0.004	0.82(0.62,1.10)	0.18	1.30(0.93,1.80)	0.12
Smoking status (past vs none)	1.41(0.90,2.22)	0.13	1.16(0.90,1.50)	0.26	0.97(0.71,1.33)	0.85
Smoking status (active vs none)	1.42(0.87,2.31)	0.16	0.93(0.65,1.32)	0.68	0.74(0.48,1.14)	0.17
mGFR (per -10 mL/min/1.73m²)	1.22(1.10,1.36)	0.0001	1.00(0.99,1.00)	0.36	1.19(1.10,1.30)	<.0001
Log albuminuria (mg/mmol creat)	1.19(1.07,1.31)	0.0008	1.27(1.19,1.35)	<.0001	1.19(1.10,1.28)	<.0001
Type of nephropathy						
Diabetic			2.15(1.20,3.87)	0.01	9.10(3.87,21.4)	<.0001
Glomerular			0.78(0.46,1.33)	0.37	3.06(1.38,6.75)	0.006
Vascular			1.42(0.89,2.25)	0.14	6.16(2.93,12.9)	<.0001
Polycystic			1.13(0.62,2.06)	0.69	2.17(0.85,5.54)	0.11
Interstitial			1(ref)		1(ref)	
Other or unknown			1.00(0.63,1.58)	0.99	2.78(1.31,5.89)	0.008
Number of antihypertensive treatments			0.93(0.84,1.04)	0.19		
Diuretic			1.00(0.75,1.34)	0.98		
Aldosterone blocker			0.46(0.21,0.99)	0.046		
ECW ratio over th-ECW[(a)]	**1.18(1.04,1.35)**	**0.010**	**1.11(1.02,1.20)**	**0.013**	**1.12(1.01,1.23)**	**0.025**
[Na] (/mM)	0.98(0.91,1.05)	0.54	1.30(0.86,1.95)	0.21		
[K] (/mM)	1.73(1.13,2.65)	0.012	0.77(0.59,0.99)	0.042		
[HCO3-](/mM)	1.10(1.03,1.18)	0.003	1.03(0.99,1.07)	0.20		
Plasma uric acid (/10µM/L)	1.03(1.01,1.05)	0.0007	0.99(0.98,1.00)	0.28		
24-hour urine sodium (/ 10 mmol/24h)	**1.01(0.98,1.05)**	**0.36**	**1.01(0.99,1.03)**	**0.40**	**1.01(0.99,1.03)**	**0.25**
24-hour urine potassium (mmol/24h)	**1.00(0.99,1.01)**	**0.58**	**1.00(0.99,1.00)**	**0.89**	**1.00(0.99,1.00)**	**0.48**

All models also adjusted for recruitment site. In these models, 24-hour urine sodium and potassium, instead of their ratio, were analyzed as covariates.
BMI: body mass index; CV: cardiovascular; mGFR: measured glomerular filtration rate; ECW: extracellular water; th-ECW: theoretical extracellular water.