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Hypertension

Prevalence and Prognostic Role of Resistant Hypertension in Chronic Kidney Disease Patients

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Objectives This study sought to evaluate in chronic kidney disease (CKD) prevalence and prognosis of true resistant hypertension (RH) (i.e., confirmed by ambulatory blood pressure [ABP] monitoring).

Background In CKD, uncontrolled hypertension is a major risk factor, but no study has properly investigated the role of RH.

Methods We prospectively studied 436 hypertensive CKD patients under nephrology care. Four groups were constituted by combining 24-h ABP with diagnosis of RH (office blood pressure ≥130/80 mm Hg, despite adherence to ≥3 full-dose antihypertensive drugs including a diuretic agent or ≥4 drugs): control (ABP <125/75 mm Hg without RH); pseudoresistance (ABP <125/75 mm Hg with RH); sustained hypertension (ABP ≥125/75 mm Hg without RH); and true resistance (ABP ≥125/75 mm Hg with RH). Endpoints of survival analysis were renal (end-stage renal disease or death) and cardiovascular events (fatal and nonfatal cardiovascular event).

Results Age was 65 ± 14 years, men 58%, diabetes 36%, cardiovascular disease 30%, median proteinuria 0.24 (interquartile range 0.09 to 0.83) g/day, estimated glomerular filtration rate 43 ± 20 ml/min/1.73 m^2, office blood pressure 146 ± 19/82 ± 12 mm Hg, and 24-h ABP 129 ± 17/72 ± 10 mm Hg. True resistant patients were 22.9%, and pseudoresistant patients were 7.1%, whereas patients with sustained hypertension were 42.9%, and control subjects were 27.1%. Over 57 months of follow-up, 109 cardiovascular events and 165 renal events occurred. Cardiovascular risk (hazard ratio [95% confidence interval]) was 1.24 (0.55 to 2.78) in pseudoresistance, 1.11 (0.67 to 1.84) in sustained hypertension, and 1.98 (1.14 to 3.43) in true resistance, compared with control subjects. Corresponding hazards for renal events were 1.18 (0.45 to 3.13), 2.14 (1.35 to 3.40), and 2.66 (1.62 to 4.37).

Conclusions In CKD, pseudoresistance is not associated with an increased cardio-renal risk, and sustained hypertension predicts only renal outcome. True resistance is prevalent and identifies patients carrying the highest cardiovascular risk. (J Am Coll Cardiol 2013;61:2461–7) © 2013 by the American College of Cardiology Foundation

Poorly controlled hypertension is a major risk factor in non-dialysis chronic kidney disease (CKD). Current guidelines for CKD patients recommend an office blood pressure (BP) target <130/80 mm Hg (1–3). These recommendations, largely extrapolated from post hoc analysis of renal trials, are being debated (4–6). Recent trials and cohort studies have in fact disclosed a lack of association between more aggressive treatment or achieved BP and prognosis (7–10). The absence of a predictive role of office BP in treated CKD might relate, at least in part, to the high prevalence of white coat hypertension (i.e., high office BP and normal ambulatory blood pressure [ABP]) (3,11,12), which might also explain why ABP better predicts mortality and end-stage renal disease (ESRD) than office BP (13,14).

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More importantly, the common observation that many patients with essential hypertension remain hypertensive despite polytherapy has led to an increased interest in the independent role of resistant hypertension (RH). Resistant hypertension is estimated to affect 15% to 30% of patients

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Abbreviations and Acronyms

ABP = ambulatory blood pressure
BMI = body mass index
BP = blood pressure
CI = confidence interval
CKD = chronic kidney disease
ESRD = end-stage renal disease
GFR = glomerular filtration rate
HR = hazard ratio
IQR = interquartile range
LVH = left ventricular hypertrophy
OR = odds ratio
RH = resistant hypertension

with essential hypertension and be associated with higher cardiovascular morbidity and mortality (15–17); therefore, it has been defined as a priority area of research by the American Heart Association (15). Resistant hypertension is diagnosed when office BP is not at goal in patients who are adhering to full doses of at least 3 different antihypertensive drugs—including a diuretic agent—or normal or elevated BP in the setting of 4 or more antihypertensive agents (15). Diagnosis of RH requires the exclusion of white coat hypertension, which identifies pseudoresistance (15–18). In the general RH population, pseudoresistance is frequent and heralds a lower cardiovascular risk as compared with true RH (19).

To date, RH has not been properly evaluated in CKD patients. Indeed, CKD is currently recognized as a frequent cause of RH in the general hypertensive population, but no study has adequately addressed the burden of RH in the specific setting of hypertensive CKD patients. Preliminary observations suggest that diagnosis of RH increases after the first 6 months of nephrology care, due to intensification of therapy by the nephrologist (20). However, that exploratory analysis is limited by the retrospective design and inconsistent ABP assessment.

On the basis of the information available in essential hypertension (15–17), we can hypothesize that CKD patients would be at higher risk of RH and that RH would be associated with poor prognosis. Therefore, we evaluated prevalence, correlates, and long-term prognosis (up to 9 years) of true RH (i.e., confirmed by ambulatory BP monitoring as recommended by the American Heart Association) (15) in a large cohort of hypertensive patients with nondialysis CKD under regular nephrology care.

Methods

This is a multicenter prospective cohort study of consecutive patients attending 4 outpatient nephrology clinics in Italy between 2003 and 2005. The participating institutions share standardized protocols for the management of CKD, including ABP monitoring in patients with hypertension, defined as office systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg or antihypertensive treatment. Patients were always seen by the same nephrologist in the clinic. Participating nephrologists are all well-versed and committed to the recommended goal of office BP <130/80 mm Hg (2). Patients were instructed to restrict dietary salt (<6 g/day). Antihypertensive agents were titrated to maximal tolerated dose, used in combination when the BP goal was not reached, and distributed from 8:00 AM to 10:00 PM. At each visit, compliance with pharmacological therapy was also evaluated; physicians asked the number of times the patient had not taken the prescribed medications in the last 2 weeks. The patient was identified as poorly compliant and excluded if the missing rate was ≥20%.

As previously described (14), hypertensive patients were included if they had CKD Stages II to V (not receiving dialysis/transplant), ≥6 months of follow-up, and ≥2 visits in the renal clinic before the initiation of study. Exclusion criteria included office BP <130/80 mm Hg without antihypertensive therapy, changes in glomerular filtration rate (GFR) >30% in the previous 3 months, changes in antihypertensive therapy 2 weeks before baseline visit, atrial fibrillation, or inadequate ABP reading. Institutional review boards of the participating centers approved the protocol, and informed consent was obtained from all patients before study enrollment.

Medical, laboratory, and medication information were collected at baseline, including history of previous cardiovascular events and left ventricular hypertrophy (LVH) diagnosed by echocardiography (yes/no). During the physician visit (8:00 AM to 11:00 AM), office BP was measured by a nephrologist according to standard methods (21). Office BP values were the mean of the 6 values recorded in the 2 consecutive days in which ABP device was placed and removed.

Participating centers shared similar ABP protocols: Spacelabs 90207 monitors (Spacelabs, Snoqualmie, Washington) were used, cuff-size was chosen on the basis of patient arm circumference and fixed to the nondominant arm, and 3 BP readings were taken concomitantly with sphygmomanometric measurements to ensure a difference <5 mm Hg between the 2 sets of values. The monitor recorded BP every 15 min between 7:00 AM and 10:00 PM and every 30 min between 11:00 PM and 7:00 AM. Daytime and nighttime periods were derived from the diaries recorded by the patients. The ABP was always obtained on a workday and under regular antihypertensive treatment. Patients had no access to the ABP values. Accuracy of 24-h urine collection was assessed as previously described (10).

Classification of patients. For the purpose of this study, patients were classified according to 24-h ABP normal (<125/75 mm Hg) or high (≥125 mm Hg and/or ≥75 mm Hg) and absence or presence of RH (office BP ≥130/80 mm Hg on ≥3 full-dose drugs including a diuretic agent or any office BP if the patient was taking ≥4 drugs). We chose 24-h ABP, because it includes both activity and resting BPs. Indeed, nocturnal BP is a main prognostic indicator of the cardiovascular outcome in CKD patients (13,14). The cutoff of 125/75 mm Hg was selected, because it is the lower threshold of normality indicated in large population-based studies (22). Therefore, patients were included into 4 groups: control (normal ABP without RH); pseudoresistance (normal ABP with RH); sustained

hypertension (high ABP without RH); and true resistance (high ABP with RH).

Outcomes. Renal outcome was defined a priori as a composite endpoint of ESRD or death, whichever occurred first. The endpoint of ESRD was reached on the day of the first dialysis session. Death certificates and autopsy reports were used to establish the underlying cause of death and to adjudicate cardiovascular deaths on the basis of the International Classification of Diseases-Ninth Revision-Clinical Modification. Cardiovascular outcomes included a composite of cardiovascular death or nonfatal cardiovascular event that required hospital stay (myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and nontraumatic amputation), whichever occurred first. Hospital records were obtained to establish diagnosis (23,24). Patients were followed-up until January 31, 2012, death, or ESRD and censored on the date of the last clinic visit.

Statistical analysis. Continuous variables are expressed as mean ± SD or as median (interquartile range [IQR]) according to their distribution. Categorical variables were reported as percentages. Differences in characteristics of patients among the 4 groups were tested by means of 1-way analysis of variance or Kruskal-Wallis (according to their distribution) and chi-square test for continuous and categorical variables, respectively.

Multivariable logistic regression analysis was used to identify the predictors of true resistance. The model accounted for demographic data (age, sex), clinical characteristics (body mass index [BMI], diabetes, history of cardiovascular disease, LVH, poor adherence to low sodium diet defined as urinary sodium excretion >100 mmol/day), and severity of CKD (GFR, log–24-h proteinuria).

A multivariable Cox proportional hazards model, stratified by center, was used to estimate hazard ratio (HR) and corresponding 95% confidence interval (CI). Cox models were adjusted for the effect of potentially confounding variables that were identified a priori, being recognized as determinants of renal and cardiovascular outcome (age, sex, BMI, diabetes, history of cardiovascular disease, natural log-transformed 24-h proteinuria, and GFR). We tested the association of renal and cardiovascular endpoint in the 4 groups with patients with normal ABP and without RH as the reference group.

Data were analyzed with SPSS (version 12.0, SPSS, Inc., Chicago, Illinois). All statistical tests were 2-tailed, and $p < 0.05$ was considered significant.

Results

Basal characteristics. Of 472 eligible Caucasian patients, 436 were included in the cohort. Reasons for exclusion have been reported in detail previously (14). Median follow-up in the renal clinic before the study start was 8.2 (IQR: 6.7 to 21.6) months and similar in the 4 groups ($p = 0.985$).

One hundred eighteen patients (27.1%) were classified as control subjects, 31 (7.1%) were classified as pseudoresistant, 187 (42.9%) were classified as having sustained hypertension, and 100 (22.9%) were classified as true resistant. The vast majority of RH patients (126 of 131, 96%) had BP ≥130/80 mm Hg in the office. Demographic, clinical, and treatment information are presented in Tables 1 and 2. Patients exhibited a high-risk profile as evidenced by advanced age, high BMI, and large prevalence of diabetes, LVH, and cardiovascular disease (Table 1). These features were remarkable in true resistant patients, which were also characterized by more severe renal disease with the lowest estimated GFR and the highest 24-h proteinuria. Multivariable logistic regression analysis showed that significant baseline correlates of true RH were diabetes (odds ratio [OR]: 2.84, 95% CI: 1.68 to 4.77), LVH (OR: 2.32, 95% CI: 1.23 to 4.38), higher proteinuria levels (OR: 2.31, 95% CI: 1.49 to 3.58), and poor adherence to low salt diet (OR: 2.15, 95% CI: 1.06 to 4.38).

The BP pattern resembled the risk profile observed in demographic and clinical characteristics (Table 2). True resistant patients had significantly higher BP levels and prevalence of nondipping status. No difference was detected in therapeutic regimens in the 4 participating centers. Seventy-four percent of patients received ≥2 agents, with inhibitors of renin-angiotensin system being the most frequent in the vast majority of the cohort (80%). Diuretic agents were the second most frequent agent, and all RH patients received at least 1 diuretic agent by definition. Furosemide was represented to a greater extent in the true resistant group in terms of frequency of use and dose, whereas other diuretic agents (thiazide drugs in most cases) were predominant in the pseudoresistant group. Adherence to the prescribed low salt diet was poor, in contrast to antihypertensive medication; only 21% of patients showed urinary sodium excretion ≤100 mEq/day ($p = 0.110$ for inter-group comparison). We found 84 of 187 patients with sustained hypertension treated with 0 to 1 drugs; of this subgroup, 26 had normal BP in office, and 34 were on a low-sodium diet regimen.

Survival analysis. Patients were prospectively followed for 52 months, on average (median 57 months, IQR: 36 to 68 months). During this period, 165 renal events and 109 fatal and nonfatal cardiovascular events were documented. Specifically, 88 patients progressed to ESRD, and 77 died. We recorded 63 nonfatal cardiovascular events and 61 cardiovascular deaths (15 occurring after a first nonfatal cardiovascular event); in particular, we registered: 67 acute myocardial infarctions (39 fatal); 25 strokes (15 fatal); 16 peripheral vascular accidents (2 fatal); and 16 acute heart failures (5 fatal). Figure 1 depicts unadjusted renal and cardiovascular event-free survival in the 4 groups. Patients with normal ABP had the best prognosis for either outcome, independent of their RH status, whereas the highest risk for cardio-renal events was observed in true resistance.

Cox analysis (Table 3) confirmed the results of unadjusted analysis. Pseudoresistant patients did not show a different cardio-renal risk versus control subjects. Patients with high ABP had a worse prognosis. However, for these patients,

Table 1 Demographic and Clinical Characteristics of Patients at Baseline

	Control (n = 118)	Pseudoresistance (n = 31)	Sustained Hypertension (n = 187)	True Resistance (n = 100)	p Value
Age (yrs)	65.9 ± 13.6	68.7 ± 8.8	62.3 ± 15.1	68.2 ± 10.9	0.001
Male	63 (53.4)	16 (51.6)	118 (63.1)	57 (57.0)	0.310
Diabetes	34 (28.8)	14 (45.2)	47 (25.1)	64 (64.0)	<0.0001
Active smoking	20 (16.9)	4 (12.9)	50 (26.7)	26 (26.0)	0.101
BMI (kg/m^2)	28.7 ± 5.1	31.4 ± 6.2	28.2 ± 4.8	30.2 ± 5.9	0.001
LVH	64 (54.2)	17 (54.8)	111 (59.4)	83 (83.0)	<0.0001
Prior CV disease	59 (24.6)	14 (45.2)	46 (24.6)	44 (44.0)	0.001
CHD	15 (12.7)	8 (25.8)	30 (16.0)	25 (25.0)	
TIA/stroke	11 (9.3)	4 (12.9)	9 (4.8)	11 (11.0)	
PVD	5 (4.2)	1 (3.2)	7 (3.7)	14 (14.0)	
Heart failure	2 (1.7)	2 (6.5)	6 (3.2)	6 (6.0)	
Renal disease					<0.0001
Hypertension	61 (51.7)	15 (48.4)	65 (34.8)	44 (44.0)	
DN	15 (12.7)	8 (25.8)	24 (12.8)	39 (39.0)	
Glomerulonephritis	9 (7.6)	—	17 (9.1)	8 (8.0)	
TIN/ADPKD/other	23 (19.5)	3 (9.7)	57 (30.5)	4 (4.0)	
Unknown	10 (8.5)	5 (16.1)	24 (12.8)	5 (5.0)	
GFR (ml/min/1.73 m^2)	46.0 ± 17.1	45.1 ± 13.8	44.8 ± 21.8	35.0 ± 18.1	<0.0001
Calcium (mg/dl)*	9.5 ± 0.6	9.3 ± 0.5	9.5 ± 0.6	9.3 ± 0.6	0.191
Phosphorus (mg/dl)*	3.8 ± 0.8	3.7 ± 0.9	3.9 ± 0.9	4.0 ± 0.9	0.241
Hemoglobin (g/dl)	13.0 ± 1.8	13.2 ± 1.3	13.1 ± 1.9	12.4 ± 1.7	0.004
Cholesterol (mg/dl)	186 ± 39	197 ± 38	191 ± 36	192 ± 39	0.467
Proteinuria (g/day)	0.2 (0.1–0.6)	0.2 (0.1–0.3)	0.2 (0.1–0.8)	0.7 (0.2–2.3)	<0.0001
UNaV (mEq/day)	141 ± 49	150 ± 54	153 ± 65	164 ± 68	0.048

Values are mean ± SD, n (%), or median (interquartile range). Definition of groups: Control (normal ambulatory blood pressure [ABP] without resistant hypertension [RH]); Pseudoresistance (normal ABP with RH); Sustained Hypertension (high ABP without RH); True Resistance (high ABP with RH). *Data are available in 251 patients.

ADPKD = autosomal polycystic kidney disease; BMI = body mass index; CHD = coronary heart disease; CV = cardiovascular; DN = diabetic nephropathy; GFR = glomerular filtration rate value by the 4-variable Modification of Diet in Renal Disease equation; LVH = left ventricular hypertrophy; TIN = tubulo-interstitial nephritis; UNaV = urinary sodium excretion.

adding information with regard to presence of RH allowed a better risk definition. Indeed, high ABP predicted both endpoints only if RH was present (true resistance); by contrast, in nonresistant patients, high ABP (sustained hypertension) predicted renal but not cardiovascular outcome. This held true also when considering only ESRD as renal endpoint (HR: 2.59, 95% CI: 1.23 to 5.44; and HR: 3.46, 95% CI: 1.57 to 7.64, in sustained hypertension and true resistance, respectively), whereas the risk of all-cause death increased only in true resistance (HR: 2.59, 95% CI: 1.34 to 5.03). Findings were further confirmed with the same Cox model after exclusion of control subjects and pseudoresistant patients; indeed, in comparison with sustained hypertension, true resistance predicted cardiovascular risk (HR: 2.05, 95% CI: 1.23 to 3.43) but not renal risk (HR: 1.23, 95% CI: 0.83 to 1.82).

No significant interaction in predicting either endpoint was found between ABP ≥125/75 mm Hg and diagnosis of RH when included separately in the Cox model ($p = 0.303$ and $p = 0.730$, for cardiovascular and renal endpoint, respectively). Finally, no interaction was found between RH and proteinuria ($p = 0.546$ and $p = 0.558$, for cardiovascular and renal endpoint, respectively) and between RH and GFR ($p = 0.060$ and $p = 0.336$, for cardiovascular and renal endpoint, respectively).

Discussion

This study provides new and important insights into the cardiovascular and renal risk assessment in hypertensive CKD patients. We demonstrate that two-thirds of our population had either true resistance (23%) or sustained hypertension without RH (43%), conditions undetectable by office BP alone, and that these conditions have a different prognostic value—true resistance is better at predicting cardiovascular endpoint, whereas sustained hypertension is more useful for predicting renal outcome. Combining these 2 diagnoses better identifies patients carrying the highest risk for cardiovascular and renal events.

Our analyses also provide important information with regard to CKD patients with pseudoresistance that are characterized by concomitant RH and normal ABP. Indeed, pseudoresistant patients were similar to control subjects, on the basis of ABP profiles, target organ damage (prevalence of LVH and severity of renal disease), and long-term prognosis. This finding is relevant, because pseudoresistant

Table 2 Office BP and ABP and Antihypertensive Therapy at Baseline

	Control (n = 118)	Pseudoresistance (n = 31)	Sustained Hypertension (n = 187)	True Resistance (n = 100)
Office systolic BP	139 ± 17	148 ± 14	146 ± 18	154 ± 20
Office diastolic BP	79 ± 10	82 ± 8	84 ± 12	82 ± 12
Office systolic BP ≥130 mm Hg	80 (67.8)	28 (90.3)	153 (81.8)	94 (94.0)
Office diastolic BP ≥80 mm Hg	63 (53.4)	20 (64.5)	133 (71.1)	68 (68.0)
Daytime systolic BP	116 ± 9	115 ± 8	138 ± 13	144 ± 16
Daytime diastolic BP	68 ± 7	65 ± 6	81 ± 10	76 ± 10
Nighttime systolic BP	106 ± 9	106 ± 9	127 ± 17	138 ± 19
Nighttime diastolic BP	60 ± 6	57 ± 7	70 ± 9	70 ± 10
Nondippers	75 (63.6)	19 (61.3)	102 (54.5)	74 (74.0)
BP-lowering drugs	1.9 ± 1.0	3.8 ± 0.9	1.8 ± 1.2	4.2 ± 1.1
0 drug	9	—	32	—
1 drug	40	—	48	—
2 drugs	45	—	57	—
3 drugs	22	19	48	37
>3 drugs	2	12	2	63
ACEI and/or ARB	96 (81.4)	31 (100)	127 (67.9)	94 (94.0)
CCB	31 (26.3)	16 (51.6)	69 (36.9)	73 (73.0)
Beta-blocker drugs	33 (28.0)	17 (54.8)	54 (28.9)	48 (48.0)
Other drug classes	9 (7.6)	8 (25.8)	18 (9.6)	45 (45.0)
Furosemide use	20 (16.9)	13 (41.9)	34 (18.2)	72 (72.0)
Furosemide dose (mg/day)	35 ± 57	19 ± 16	40 ± 40	56 ± 55
Other diuretic agents	25 (21.2)	21 (67.7)	22 (11.8)	47 (47.0)

Values are mean ± SD or n (%). Definition of groups: Control (normal ambulatory blood pressure [ABP] without resistant hypertension [RH]); Pseudoresistance (normal ABP with RH); Sustained Hypertension (high ABP without RH); True Resistance (high ABP with RH). Nondippers: night/day ratio of systolic ambulatory blood pressure (BP) (mm Hg) ≥0.9.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; CCB = calcium channel blockers.

patients accounted for 24% of the whole RH group. Similar data have been observed in the general hypertensive population. In the Spanish ABP registry, in fact, 12% of the 8,295 patients examined had RH; however, as many as 37% of them were classified as having pseudoresistance after ABP monitoring (19). Our results provide first-time observation in CKD patients that pseudoresistance is frequent and does not increase the cardio-renal risk as reported in non-CKD cohorts (18). Pseudoresistant CKD patients should be identified to provide correct prognostic information and, more importantly, to avoid aggressive antihypertensive therapy. Indeed, these patients were characterized by systolic BP levels during daytime and, especially at nighttime, close to the threshold limit of hypoperfusion (100 mm Hg) (Table 2). Under these circumstances, a tighter control of BP merely on the basis of the detection of elevated BP in the office might expose patients to ischemia-induced worsening of cardio-renal damage (6,25) and eventually convert their prognosis from favorable to unfavorable.

A major finding of our study is the very high cardio-renal risk of patients with true resistance (Fig. 1), a group that represented 35% of patients with high 24-h ABP. The finding of such an ominous prognosis is novel but certainly not surprising, on the basis of the well-established relationship between RH and cardiovascular risk in essential hypertension (17,18). Furthermore, studies have shown that presence of mild-to-moderate GFR reduction and/or microalbuminuria amplifies the cardiovascular risk correlated to RH in the general hypertensive population (26,27). The present study adds novel evidence of the poor cardio-renal prognosis of RH and extends its prognostic role to the patients with established CKD and more-advanced renal damage.

We observed a different predictive value of true resistance for the 2 endpoints (Table 3). We found that cardiovascular outcome was exclusively predicted by true resistance. Conversely, when analyzing renal survival, true resistance did not offer any additional predictive value, as compared with the status of sustained hypertension (HR: 2.66 and 2.14, respectively). Additional Cox models built with sustained hypertension included as reference group further supported the role of true resistance in predicting only cardiovascular outcome (see Results). Therefore, combining ABP and diagnosis of RH allows better risk stratification. This finding is critical in CKD patients, if one considers that in this setting the prevalence of true resistance (23%) is higher as compared with essential hypertension (17,18,28). Of interest, in the setting of RH, the presence of diabetes, higher proteinuria, and low GFR—which are all predictors of RH status—do not further increase the cardiovascular risk. In particular, although proteinuria is now well-established as an independent risk factor for cardiovascular events, our results show that cardiovascular risk did not increase in RH patients with higher levels of proteinuria.

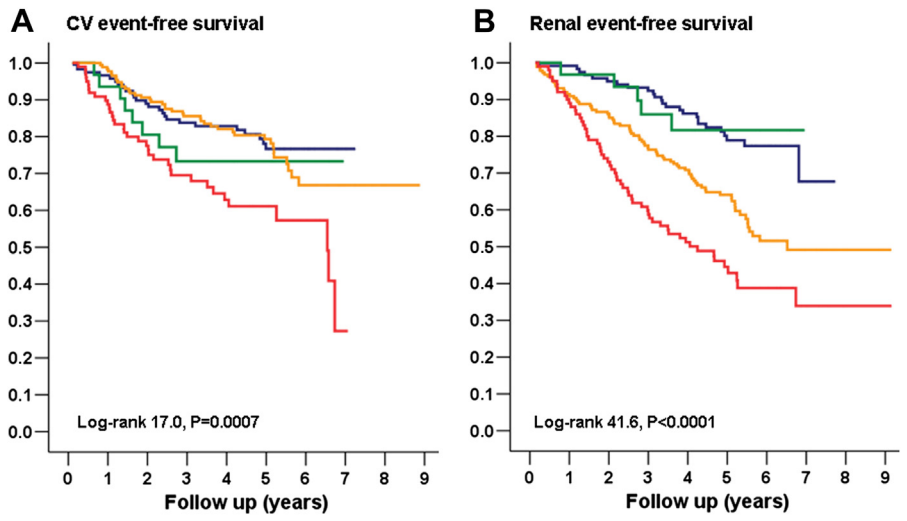

Figure 1 CV and Renal Survival

Cardiovascular (CV) **(A)** and renal **(B)** survival by hypertensive status. Control subjects are in **green**, pseudoresistance in **blue**, sustained hypertension in **orange**, and true resistance are in **red**. Cardiovascular events occurred in 25 (21.2%), 8 (25.8%), 40 (21.4%), and 36 (36.0%) patients in control, pseudoresistance, sustained hypertension, and true resistance groups, respectively. Renal events (end-stage renal disease or death) occurred in 25 (21.2%), 5 (16.1%), 78 (41.7%), and 57 (57%) patients in control, pseudoresistance, sustained hypertension, and true resistance groups, respectively.

The mechanism of such dissociation is not readily apparent; however, one can speculate that the risk associated with RH is so pronounced that proteinuria or the other factors examined do not further enhance it. The pathophysiological mechanisms underlying the different prognostic value of RH are beyond the scope of this study; however, we can hypothesize that persistence of hypertension, despite optimal antihypertensive treatment, specifically identifies patients with more severe vascular damage. Diabetes, left ventricular hypertrophy, higher proteinuria, and high salt intake—variables we found independently associated with true resistance—are in fact all associated with endothelial dysfunction and arterial stiffness (29–32).

Table 3 Multivariable Cox Models for CV and Renal Outcomes

	CV Outcome	Renal Outcome
Age (1-yr)	1.06 (1.04–1.08)*	1.00 (0.99–1.02)
Male	2.32 (1.49–3.61)*	1.46 (1.05–2.05)*
BMI (1-kg/m^2)	0.98 (0.94–1.02)	0.99 (0.96–1.02)
Diabetes (yes vs. no)	1.32 (0.87–2.01)	0.89 (0.62–1.26)
History of CV events (yes vs. no)	2.04 (1.37–3.03)*	1.11 (0.78–1.59)
Log-proteinuria	0.99 (0.72–1.36)	1.35 (1.04–1.75)*
GFR (ml/min/1.73 m^2)	0.98 (0.97–0.99)*	0.93 (0.92–0.95)*
Groups		
Control	Reference	Reference
Pseudoresistance	1.24 (0.55–2.78)	1.18 (0.45–3.13)
Sustained hypertension	1.11 (0.67–1.84)	2.14 (1.35–3.40)*
True resistance	1.98 (1.14–3.43)*	2.66 (1.62–4.37)*

Values are hazard ratio (95% confidence interval). Definition of groups: Control (normal ABP without RH); Pseudoresistance (normal ABP with RH); Sustained Hypertension (high ABP without RH); True Resistance (high ABP with RH). *Significant hazard ratio.
Abbreviations as in Table 1.

Interestingly, dietary sodium restriction improves BP control in patients with normal renal function and RH (33). This nonpharmacological intervention is pivotal in CKD, because this condition is characterized by high sodium sensitivity of BP (34). Our finding of an inverse correlation between adherence to low-salt diet and true resistance supports this hypothesis. This finding is not affected by the extensive use of diuretic agents, because their prescription was, according to protocol, unchanged for at least 2 weeks before enrollment, thus excluding diuretic influence of external sodium balance at that time (35).

Study limitations. Only Caucasian patients were enrolled, precluding extrapolation to other ethnic groups. Moreover, our results apply only to CKD patients under regular tertiary care. By contrast, the prolonged management in the renal clinic before baseline might attenuate the imprecision on the prognostic value of risk factors evaluated as single-time data. Furthermore, we cannot exclude that prevalence estimates of RH might be modified by intensifying therapy (20) or prolonging ABP monitoring (36). Finally, the observational nature of this study precludes interpretation of the results in terms of causality.

Conclusions

Our findings demonstrate that, in hypertensive CKD patients treated in renal clinic: 1) true RH is common, being present in approximately one-fourth of the overall cases and in 35% of patients with sustained hypertension; and 2) combining the clinical diagnosis of RH with ABP allows better risk stratification: pseudoresistance is not associated

with a significant increase of the cardio-renal risk; sustained hypertension without RH predicts only renal outcome, whereas the concomitance of RH and high ABP (true resistance) specifically identifies patients carrying the highest cardiovascular risk.

Therefore, we suggest concurrent evaluation of RH status and ABP in all hypertensive CKD patients followed in tertiary care centers. Not only should these patients be identified and followed for cardiovascular events, but their BP should be treated aggressively, and they might also benefit from alternative therapeutic strategies (37). However, whether aggressive treatment alters cardiovascular outcome in this subset of patients remains to be verified.

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