Burden of Resistant Hypertension in Hypertensive Patients with Non-Dialysis Chronic Kidney Disease

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Key Words

Blood pressure control · Hypertension · Survival analysis · Chronic kidney disease

Abstract

Background/Aims: In chronic kidney disease (CKD), no data on resistant hypertension (RH) are so far available despite the high prevalence of uncontrolled hypertension. We evaluated frequency, correlates and prognosis of RH in 300 consecutive incident hypertensive CKD patients in an academic renal clinic. **Methods:** RH was defined as office blood pressure (BP) $\geq 130/80$ mm Hg despite ≥ 3 drugs at full dose including a diuretic, or as BP at goal with ≥ 4 full-dose drugs. Patients were evaluated at referral and after 6 months of nephrology management; thereafter, they were included in a renal survival analysis lasting 37.6 months. **Results:** On referral, glomerular filtration rate was 41.3 ± 16.6 ml/min/1.73 m² and BP $148 \pm 23/81 \pm 12$ mm Hg. After 6 months, BP decreased by $8 \pm 23/3 \pm 12$ mm Hg. From referral to month 6, RH detection increased from 26 to 38% due to the significant increment in full-dose antihypertensive medications (from 2.0, IQR 1.0–3.0 to 2.5, IQR 2.0–3.0). Diabetes and proteinuria predicted the incidence of RH at month 6. Presence of RH at month 6 was associated with greater risk of renal death (HR,

1.85, 95% CI, 1.13–3.03), independent of main clinical features and degree of BP control. **Conclusion:** In CKD, RH is prevalent and associated with decreased renal survival, independent of BP levels.

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Introduction

Resistant hypertension (RH) is defined as office blood pressure (BP) that remains above goal [$>140/90$ mm Hg for the overall population and $\geq 130/80$ mm Hg for those with diabetes mellitus or chronic kidney disease (CKD)] despite the use of at least 3 antihypertensive agents at full dose including a diuretic or the use of 4 or more antihypertensive agents at full dose in the setting of optimal BP control, in the absence of white coat hypertension (WCH) or poor compliance to prescribed therapy that identify the condition of pseudoresistance [1–3]. The concurrent evaluation of BP, number and dose of antihypertensive

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drugs at the individual patient level and adherence to prescription is therefore necessary to distinguish between RH and uncontrolled hypertension.

A scientific statement from the American Heart Association (AHA) has recently highlighted the need to improve awareness and knowledge of RH which remains limited despite the presumed high cardiovascular (CV) risk associated with this condition [2]. In this context, evaluation of CKD patients is highly relevant for two reasons. First, the prevalence of renal disease is rapidly rising worldwide with approximately 10% of the adult population currently affected [4]. Notably, 65–95% of CKD patients develop hypertension as the glomerular filtration rate (GFR) declines from 85 to 15 ml/min [5] and hypertension constitutes a major risk factor for the progression of renal disease [5–10], as well as to the high CV risk observed from the early stages of CKD [5, 10–13]. Second, the burden and importance of RH in CKD is currently unknown. Indeed, several surveys in CKD patients demonstrate a high incidence of uncontrolled hypertension in clinical practice [14–21]; however, the value of these surveys is limited due to the absence of information on the number/dose of antihypertensive agents utilized and the cross-sectional design of these audits which precludes any evaluation of the effects of intensification of antihypertensive therapy on BP control. Landmark hypertension trials in CKD also attest to the difficulty of achieving BP goal in as many as 50% of non-diabetic and 70% of diabetic patients despite titration of antihypertensive therapy to goal and the use of 3.5–4.5 antihypertensive agents per patient [7, 22–24]. However, also these trials do not specifically address the role of RH.

We therefore conducted a retrospective study to evaluate RH in an outpatient CKD clinic to assess its magnitude after 6 months of nephrology management, its predictors and its association with renal survival.

Methods

Patients

We considered eligible for the analysis all consecutive incident patients, referred because of CKD diagnosis by the general practitioners working in the same area of our hospital, who presented to the outpatient clinic of the Department of Nephrology, Second University of Naples, Naples, Italy, from January 1, 2002 to December 31, 2006.

Patients were included if not on dialysis and without a kidney transplant, with CKD stages 2–5, that is, either with an estimated GFR (eGFR) <60 ml/min/1.73 m² or eGFR 60–90 ml/min/1.73 m² plus proteinuria >0.3 g/24 h in two consecutive visits with an interval ≥3 months.

Exclusion criteria were: less than two visits during the first 6 months of follow-up in the renal clinic, BP on the first visit <130/80 mm Hg without antihypertensive therapy, evidence of acute kidney injury, active malignancy, severe liver or heart failure, active steroid or immunosuppressive therapy use. Patients were also excluded from analyses when adherence to prescribed therapy was poor; compliance was evaluated at each visit in the clinic by checking returned medications and using specific questions on assumption of pharmacological therapy directed not only to the patient but, more importantly, to family members. Specifically, we ask the number of times the patient has not taken the prescribed medications in the last week as well as if he/she takes medications at the indicated time. The patient is identified as poorly compliant to therapy, and therefore excluded from studies, if the missing rate is ≥20% or the indicated time is not respected in two visits. In our experience, this approach has been more efficacious than the individual pill count in identifying non-adherent patients. On the other hand, to minimize the problem poor adherence, participating nephrologists dedicated time during each visit to highlight to the patient and family members of the high cardio-renal risk associated with CKD and the major benefits of compliance with therapy. Presence of WCH was an additional exclusion criterion; specifically, patients not at goal on the first visit were asked to report home BP values obtained by electronic devices preliminarily tested in the office or underwent 24 h ambulatory BP monitoring (ABPM) to exclude this condition characterized by BP ≥130/80 mm Hg in the office with either daytime <135/80 mm Hg on ABPM or BP <135/80 mm Hg at home.

Study Design

This is a retrospective study using a database that included all consecutive patients incident in our outpatient clinic. The database provided comprehensive and detailed information on demographic, clinical, laboratory, therapeutic features and presence or absence of left ventricular hypertrophy at echocardiography (LVH) and history of CV disease, defined as hospitalization for coronary heart disease, cerebrovascular and peripheral vascular disease, or heart failure. Baseline treatment was that prescribed by the general practitioner; from then on, treatment was that prescribed by the nephrologist in the clinic.

To discriminate between patients with and without RH, we reviewed the BP level and drug regimen for each individual during the first visit in our clinic (*referral or baseline*), and at the *month 6* and *month 12 visit* in the clinic, for a total number of 900 visits. At each visit, a patient was defined as having RH if office BP was either ≥130 and/or ≥80 mm Hg in spite of the use of ≥3 antihypertensive agents at full dose including a diuretic or <130/80 mm Hg with ≥4 agents at full dose [2]. The daily doses of antihypertensive agents that were considered as ‘full dose’ according to the manufacturer’s recommendations in Italy are reported in the Appendix.

After completion of the first 6 months in the clinic, data on renal death were collected until November 30, 2009.

The study was approved by the Institutional Review Board and all patients gave informed consent to use their data.

Management of CKD in the Renal Clinic

Patients were always seen by the same nephrologists in the clinic. The frequency of visits was determined by the clinical status of the patient and K/DOQI guidelines [25, 26]. The five par-

ticipating nephrologists are all well versed and committed to the therapeutic goals recommended by K/DOQI. Specifically, the treatment of BP was aimed at reaching both a systolic BP <130 and a diastolic BP <80 mm Hg. All patients were instructed to restrict dietary salt (<6 g NaCl/day) and protein (≤ 0.8 g/kg b.w./day) by providing personalized written regimens. Antihypertensive medications were distributed from 08:00 to 22:00 h; doses of furosemide ≥ 50 mg/day were also divided in two administrations (08:00 and 20:00 h). All prescribed antihypertensive medications were commercially available and totally reimbursed.

Analyses of blood and urinary samples were performed in the central laboratory of the hospital. GFR was estimated by the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation. 24-Hour urine collection was obtained at each visit and used for measurement of proteinuria, urinary excretion of Na (UNaV) and urea. The latter two measurements were aimed at assessing the adherence to the prescribed diet. The collection was considered inadequate and repeated if the creatinine excretion was outside of the 60–140% range of the value calculated according to Dwyer and Kenler [27].

BP measurement was performed at each visit by the nephrologist in a quiet environment, in the morning, using a mercury sphygmomanometer with a cuff size of appropriate dimension and with the patient in the sitting position after 10 min of rest. The first and fifth Korotkoff sounds were used to define systolic and diastolic BP values; the mean of three consecutive readings taken 2 min apart were considered for this analysis.

The patients who did not achieve the BP goal were screened for secondary causes of hypertension other than CKD by history, physical examination and laboratory studies. Ancillary studies were obtained as needed based on the findings of the routine examinations, except for renal ultrasound which was obtained in all patients.

Statistics

Continuous variables are reported as either mean $\pm$ SD or median and interquartile range (IQR) on the basis of their distribution. Comparisons of continuous variables with normal distribution were performed using paired or unpaired Student's *t* test. For variables with non-normal distribution we used paired or unpaired Wilcoxon non-parametric test. Categorical variables are expressed as percent and analyzed by χ^2 test or by McNemar test.

Multivariable logistic regression analysis was used to identify baseline factors associated with a risk of having RH at month 6 visit. The model was built by identifying a priori the main potential determinants of RH; the model accounted for demographic (age, gender), clinical characteristics (diabetes, body mass index, LVH, previous CV events, 24-hour urinary sodium) and severity of CKD (eGFR, proteinuria). Baseline BP was not added in the final analysis because of its high correlation with the month 6 value which was being used to establish the presence or absence of RH.

For the survival analysis, the primary composite end-point was the time to renal death defined as the time from the month 6 visit to all-cause death or dialysis/renal transplantation, whichever occurred first. We analyzed the unadjusted association of RH diagnosis at month 6 with the time to renal death by using Kaplan-Meier survival curves compared by log-rank test. The multivariable Cox proportional-hazards model was used to estimate the hazard ratio (HR) and the corresponding 95% confi-

dence intervals (CI), adjusted for the effect of potentially confounding variables identified a priori (age, gender, diabetes, BP goal achievement, CV disease, eGFR, proteinuria). A two-tailed *p* value <0.05 was considered significant. Data were analyzed using SPSS 12.0 (SPSS Inc., Chicago, Ill., USA).

Results

Whole Cohort Analysis

550 patients were eligible for this study, of which 250 were excluded for various reasons (fig. 1), leaving 300 patients to be included in this analysis. In particular, 148 patients were excluded because of pseudoresistance, 28 were in fact found poorly adherent to therapy and 120 were identified as having WCH (91 by home BP and 29 by ABPM). Since diagnosis of WCH based on home BP measurements was reported in the charts as category (yes/no), no data on these measurements are available. Conversely, in the 29 WCH patients diagnosed by ABPM, mean daytime BP was $122 \pm 7/68 \pm 6$ mm Hg and nighttime was $116 \pm 16/62 \pm 8$ mm Hg. When considering out-of-office BP values in WCH patients, RH was detected in the same percentage of patients when office measurements (20.8%) were compared to ABPM/home BP (20%). By definition, RH patients of the latter subgroup were characterized by daytime/home BP at target despite treatment with ≥ 4 full-dose drugs including a diuretic. All patients were Caucasians. Enrolled patients had a high CV risk profile including advanced age, high body mass index and large prevalence of diabetes, LVH and CV disease (table 1). On referral, proteinuria was ≥ 1.0 g/24 h in 23% of the cohort (46% of stage 2 patients).

Most patients had systo-diastolic hypertension at baseline (table 2). In the first 6 months of management in clinic, BP decreased on average $8 \pm 23/3 \pm 12$ mm Hg and the prevalence of BP goal increased by 57%, from 12.3 to 19.3%. The improvement in BP control was due predominantly to the intensification of antihypertensive therapy since 24-hour sodium excretion did not change between the two visits. At the month 6 visit, 54.7% of the cohort was taking 3 or more classes of drugs while this occurred in only 16.7% on referral. Indeed, the median number of antihypertensive drugs increased from 2.0 (1.5–3.0) to 3.0 (2.0–3.0) from baseline to month 6. The use and dose of furosemide increased by 30% while prescription of thiazides did not change.

The increment in full-dose antihypertensive medications and diuretic therapy increased the diagnosis of RH from 26% on referral to 38% at month 6 (fig. 1). Specifi-

Fig. 1. Flow chart of the study. HF = Severe heart failure; LC = severe liver cirrhosis; HD = hemodialysis. Pseudoresistance: white coat hypertension, n = 120; poor adherence to therapy, n = 28.

cally, 227 (76%) patients maintained the same status in the two visits, either RH (n = 62) or Not-RH (n = 165), while 73 (24%) patients changed status from referral to month 6 visit (52 from Not-RH to RH and 21 from RH to Not-RH). Of note, no further increase in RH detection was observed at month 12 visit (42%, p = 0.401 vs. month 6).

Comparison of RH versus Not-RH Patients at Month 6

A larger prevalence of diabetes, diabetic nephropathy, LVH, lower GFR and higher levels of proteinuria and BP characterized RH patients (table 3). UNaV was the same in RH and Not-RH patients with adherence to prescribed low salt diet (UNaV ≤ 100 mmol/24 h) observed in only a minority of either group (25% in Not-RH and 28% in RH). Multivariable logistic regression analysis identified diabetes and proteinuria as baseline factors independently associated with RH status at month 6 (table 4).

The number of visits during the first 6 months of follow-up was greater in RH (4.0 ± 1.9) versus Not-RH (3.4 ± 1.6 ; p = 0.006). In both groups, BP levels decreased to a similar extent from baseline to the end of the observation; specifically, the reduction of systolic BP was 9 ± 28 and 7 ± 20 mm Hg in RH and Not-RH, respectively, whereas diastolic BP decreased by 2 ± 12 and 4 ± 12 mm Hg. We did not find any patient with renovascular hypertension, primary hyperaldosteronism, alcohol or drug abuse.

Table 1. Demographic and main features in the whole cohort of patients on referral (n = 300)

Age, years	67.3 $\pm$ 11.3
Males, %	59.3
Smokers, %	21.7
Body mass index	29.7 $\pm$ 5.6
Diabetes, %	38.0
Left ventricular hypertrophy, %	64.7
History of cardiovascular disease, %	37.7
Serum creatinine, mg/dl	1.90 $\pm$ 1.01
Causes of renal disease, %	
Hypertension	51.0
Diabetes	22.7
GN/IN/PKD	10.7
Other	15.7
Hemoglobin, g/dl	12.8 $\pm$ 2.1
Cholesterol, mg/dl	195 $\pm$ 44

Data are expressed as mean $\pm$ SD or median (IQR) or %.

GN = Glomerulonephritis; IN = interstitial nephritis; PKD = polycystic kidney disease.

Renal Survival Analysis

No renal death (dialysis/transplant or death) was observed in the first 6 months. After the month 6 visit, patients were included in a survival analysis that lasted a median of 37.6 months (IQR 24.3–52.0). During this

Table 2. Clinical, laboratory and therapeutic features of the whole cohort of patients on referral and after 6 months of follow-up in the renal clinic (n = 300)

	Referral	Month 6	p
Body weight, kg	76.4 ± 15.7	76.2 ± 15.4	0.195
eGFR, ml/min/1.73 m ²	41.3 ± 16.6	40.9 ± 16.6	0.546
SBP, mm Hg	148 ± 23	141 ± 17	<0.0001
DBP, mm Hg	81 ± 12	78 ± 11	<0.0001
BP goal achievement, %			0.015
SBP <130 and DBP <80	12.3	19.3	
SBP ≥130 and DBP <80	23.3	27.0	
SBP <130 and DBP ≥80	4.7	6.7	
SBP ≥130 and DBP ≥80	59.7	47.0	
Proteinuria, g/24 h	0.20 (0.06–0.87)	0.18 (0.06–0.70)	0.011
Urinary Na, mmol/24 h	156 ± 67	155 ± 66	0.865
Full-dose BP drugs, n	2.0 (1.0–3.0)	2.5 (2.0–3.0)	<0.0001
CEI or ARB, %	78.3	87.0	0.0004
CEI + ARB, %	7.7	12.0	0.019
CCB, %	43.0	50.7	0.002
β-Blockers, %	31.0	37.0	0.001
α-Blockers, %	7.3	15.0	<0.0001
Thiazides, %	33.7	29.7	0.207
Furosemide, %	28.0	36.3	0.002
Furosemide, mg/day	42 ± 33	56 ± 33	<0.0001

Data are expressed as mean ± SD or median (IQR) or %.

SBP = Systolic blood pressure; DBP = diastolic blood pressure; eGFR = GFR value by the 4-variable MDRD equation; CEI = converting enzyme inhibitor; ARB = angiotensin II receptor antagonist.

period, renal death occurred in 79 patients (fig. 1). Diagnosis of RH at month 6 was associated with shorter renal survival (fig. 2). This result persisted after adjustment for the effect of main determinants of renal survival and BP goal (table 5); specifically, the multivariable-adjusted risk for renal death was almost double in RH versus Not-RH patients (HR 1.85, 95% CI 1.13–3.03). The predictive role of RH did not change when in the model BP goal was substituted with either systolic (HR for RH: 1.84, 95% CI 1.14–2.99) or diastolic BP level (HR for RH: 1.98, 95% CI 1.21–3.22). That the predictive role of RH was independent from BP goal or level was also confirmed by the absence of any significant interaction of RH with BP goal ($p = 0.816$), and either systolic ($p = 0.664$) or diastolic ($p = 0.686$) BP level. Similarly, when the hemoglobin value at month 6 visit was added to the model, HR for this parameter was not significant (0.88, 0.77–1.02) and HR for RH did not change (1.86, 1.14–3.05).

Discussion

In 2008, the AHA has reinforced the concept that RH is a pathologic condition distinct from uncontrolled hypertension [2]. The concept of RH is clinically relevant even if the definition is somewhat arbitrary with regard to the number of antihypertensive medications required. The purpose of early detection and careful evaluation of patients with RH is in fact aimed at identifying individuals who have secondary causes of hypertension who may benefit from specific therapeutic considerations [1, 2]. This point is critical since prognosis of this condition is supposed to be poor. The latter concept holds particularly true in CKD, which constitutes a major cause of hypertension and it is characterized by a well-defined cardiorenal risk from stages as early as CKD 1 or 2 [4, 13].

This study is the first to provide information regarding the burden of RH in CKD patients. The CKD cohort examined was characterized by a high prevalence of advanced age, overweight, diabetes, LVH and significant history of CV events. These features are comparable to

Table 3. Demographic and main clinical and laboratory parameters in patients stratified by diagnosis of RH at month 6

	Not-RH (n = 186)	RH (n = 114)	p
Age, years	67.6 ± 11.7	68.0 ± 10.7	0.815
Male gender, %	62.4	54.4	0.172
Body mass index	29.3 ± 5.1	30.1 ± 6.7	0.187
Smokers, %	19.9	24.6	0.341
Diabetes, %	30.6	50.0	0.001
History of cardiovascular disease, %	35.5	41.2	0.319
Left ventricular hypertrophy, %	60.2	71.9	0.039
Causes of renal disease, %			<0.0001
Hypertension	55.9	43.0	
Diabetes	13.4	37.7	
GN/IN/PKD	12.9	7.0	
Other	17.7	12.3	
eGFR, ml/min/1.73 m ²	43.1 ± 16.7	37.4 ± 15.8	0.004
Hemoglobin, g/dl	13.1 ± 1.7	12.7 ± 1.8	0.073
Cholesterol, mg/dl	190 ± 39	192 ± 43	0.797
Proteinuria, g/24 h	0.14 (0.05-0.54)	0.26 (0.10-1.25)	0.001
Urinary Na, mmol/24 h	152 ± 68	151 ± 69	0.872
Systolic BP, mm Hg	137 ± 16	146 ± 17	<0.0001
Diastolic BP, mm Hg	77 ± 11	80 ± 11	0.011
BP <130/80 mm Hg, %	25.8	7.9	<0.0001
BP drugs, n	2.0 (1.0–3.0)	4.0 (3.0–4.0)	<0.0001
Full-dose BP drugs, n	2.0 (1.5–2.5)	3.5 (3.0–4.0)	<0.0001
CEI or ARB, %	84.4	91.2	0.088

Data are expressed as mean ± SD or median (IQR) or %.

GN = Glomerulonephritis; IN = interstitial nephritis; PKD = polycystic kidney disease; eGFR = GFR value by the 4-variable MDRD equation; BP = blood pressure; CEI = converting enzyme inhibitor; ARB = angiotensin II receptor antagonist.

Table 4. Multivariable logistic regression analysis of baseline predictors of RH at month 6

Parameter	OR	95% CI	p
Age, years	1.00	0.98–1.03	0.770
Male gender	0.57	0.32–1.01	0.054
Body mass index	1.01	0.96–1.05	0.881
Diabetes	1.97	1.18–3.28	0.009
History of CVD	1.21	0.71–2.07	0.477
Left ventricular hypertrophy	1.41	0.81–2.44	0.224
eGFR, ml/min/1.73 m ²	0.98	0.97–1.01	0.062
Proteinuria, g/24 h	1.29	1.07–1.56	0.009
Urinary sodium, mmol/24 h	1.00	0.99–1.01	0.369

CVD = Cardiovascular disease; eGFR = GFR value by the 4-variable MDRD equation.

Table 5. Multivariable Cox analysis of determinants of renal death occurring during the follow-up subsequent to month 6 visit

Parameter	HR	95% CI	p
Resistant hypertension	1.85	1.13–3.03	0.014
Age, years	0.99	0.97–1.01	0.144
Male gender	1.40	0.85–2.32	0.187
BP <130/80 mm Hg	0.75	0.37–1.53	0.434
Diabetes	0.69	0.42–1.12	0.133
History of CVD	1.37	0.82–2.29	0.231
eGFR, ml/min/1.73 m ²	0.92	0.90–0.93	<0.0001
Proteinuria, g/24 h	1.16	1.07–1.25	<0.001

CVD = Cardiovascular disease; eGFR = GFR value by the 4-variable MDRD equation.

Fig. 2. Time to renal death after diagnosis of RH at month 6 visit (--- = RH; — = Not-RH).

those previously reported in a recent national survey of CKD patients followed in 26 Italian renal clinics [14]. In the presence of such an unmodifiable burden of CV risk, uncontrolled hypertension was a common finding; almost 90% patients, in fact, had basal BP levels $\geq 130/80$ mm Hg on referral.

Management in the renal clinic was associated with a significant improvement in BP control over the initial 6 months with a relative increase of 57% in the prevalence of BP goal. The effectiveness of this therapeutic approach is further supported by a final control rate of about 20%, which is higher than the one observed in the recent Italian multicenter survey where only 12% of the prevalent CKD patients had BP $<130/80$ [14]. The increased use of full-dose antihypertensive medications and diuretics was critical to improve identification of resistant patients; prevalence of RH increased in fact by 46% from referral to month 6 (fig. 1).

These results add important information regarding the magnitude of RH in CKD. Indeed, no study has specifically addressed the prevalence of RH in CKD as in the general population. A high prevalence has only been hypothesized from analyses of cross-sectional and hypertension outcome studies showing that 20–50% of patients

have uncontrolled hypertension despite multiple drug therapy [2, 3].

Several risk factors have been proposed for RH in the general population including advanced age, diabetes, obesity, renal disease and LVH [1–3]. Our study suggests that RH has peculiar characteristics in CKD since diabetes and proteinuria emerged as the only significant risk factors for RH in our cohort (table 4). This finding adds further insights into the concept that diabetes and proteinuria are associated with poor BP control [14–18, 28, 29]. It is reasonable to hypothesize that a more advanced vascular damage may play a determining role in the development of RH in CKD. In this regard, endothelium dysfunction and arterial stiffness, which are typical features of diabetes, have been also identified in proteinuric patients [30, 31]. In particular, recent studies in CKD have shown that proteinuria, rather than GFR, relates to the severity of hypertension [29]. Furthermore, although low GFR is recognized as a CV risk factor [13], proteinuria in CKD patients is considered a better marker of the presence of vascular disease [32, 33].

We found no relationship between salt intake and RH in our CKD cohort (table 4). This finding only apparently contrasts with recent studies indicating the presence of volume expansion and sodium sensitivity of BP in non-CKD patients with RH [34, 35]. Indeed, these features, while being present only in a limited number of patients with essential hypertension, are common in CKD, especially when adherence to the prescribed dietary salt restriction is low [5, 14–17, 36], as was the case in our cohort where the vast majority of patients had high values of 24-hour UNaV. A determining role of salt intake is therefore hard to verify in our cohort and we cannot exclude that intensive dietary salt restriction could be effective in reducing BP in CKD patients with RH, as demonstrated in non-CKD patients [35].

Indirect evidence from population studies and clinical trials in non-CKD patients suggests that RH, being a proxy for severe vascular damage and target-organ damage, heralds unfavorable prognosis [1–3]. The current study supports this hypothesis in CKD by showing, for the first time, an association between RH and renal survival (fig. 2). In particular, risk for renal death was 85% greater in patients who were identified as resistant at month 6 independent of main clinical features. Noteworthy, the predictive role of RH was also independent of the degree of BP control; this finding demonstrates that in CKD patients diagnosis of RH has a clinical meaning distinct from achieved BP levels.

Our study provides novel information regarding the magnitude of RH in CKD patients; however, the estimation is limited by the retrospective design of our study. The study is also limited by the lack of assessment of systemic RAS activity and its contribution to the development of RH [34]. While this limitation precludes us from drawing definitive conclusions on risk profile and mechanism(s) of RH in our CKD patients, the antihypertensive polytherapy and the large use of RAS inhibitors prevent any meaningful evaluation of this system in our patients [37, 38]. A further limitation is the absence of ambulatory BP control in all RH patients; indeed, although diagnosis of RH is based on office BP, recent studies have shown a superior predictive role of ABPM versus office BP measures in RH patients [39, 40]. In this regard, we found that within the group of WCH patients, excluded a priori for being identified as pseudoresistant, 20% of the patients were characterized by normal out-of-office BP in the presence of at least 4 antihypertensive drugs. Such patients should probably be classified as having RH even though current definition does not include ABPM/home measures for RH diagnosis. Further studies are needed to gain more insights into this interesting issue.

In conclusion, in hypertensive CKD patients, intensification of antihypertensive therapy allows to properly reveal the frequency of RH; specifically, after 6 months of follow-up in a renal clinic, RH was identified in 38% of cases with increased risk in the presence of proteinuria and diabetes. Identification of RH is clinically meaningful as this condition is associated with poor renal survival independent of BP control. Our results should help the design of randomized trials aimed at assessing in CKD patients with RH the effectiveness of salt restriction and other alternative therapeutic interventions that have been proven to be efficacious in reducing the burden of RH in non-CKD patients [35, 41–43].

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Disclosure Statement

There are no conflicts of interest.

Appendix

Daily doses of antihypertensive agents considered as ‘full dose’ according to the manufacturer’s recommendations in Italy

Drug	Dose
α_2 -Adrenergic agonist	
Clonidine	300 μ g
α -Blocker	
Doxazosin	4 mg
β -Blocker	
Carvedilol	25 mg
Bisoprolol	5 mg
Metoprolol	100 mg
Atenolol	100 mg
Calcium channel blockers	
Nifedipine	60 mg
Felodipine (extended release)	10 mg
Lacipidine	6 mg
Nicardipine	40 mg
Amlodipine	10 mg
Manidipine	20 mg
Lercanidipine	20 mg
Verapamil	160 mg
Diltiazem	240 mg
Converting enzyme inhibitors	
Enalapril	20 mg
Ramipril	10 mg
Lisinopril	20 mg
Fosinopril	20 mg
Perindopril	4 mg
Zofenopril	30 mg
Delapril	30 mg
Angiotensin receptor blockers	
Irbesartan	300 mg
Valsartan	160 mg
Candesartan	16 mg
Losartan	100 mg
Telmisartan	80 mg
Eprosartan	600 mg
Olmesartan	20 mg

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