Chapter 4
The Importance of Ambulatory and Home Monitoring Blood Pressure in Resistant Hypertension Associated with Chronic Kidney Disease

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Introduction to Out-of-Office BP Monitoring

Out-of-office blood pressure (BP) measurements include ambulatory blood pressure monitoring (ABPM) lasting 24 h and home BP monitoring (HBPM) obtained with patient at home, seated and resting. ABPM provides a more precise assessment of BP profiles and a description of circadian rhythm of BP (dipping status), whereas HBPM only discloses abnormal BP profiles [1].

ABP monitors are compact, typically worn on a belt or in a pouch, and connected to a sphygmomanometer cuff on the upper arm by a tube. The monitors are usually programmed to obtain readings every 15–30 min throughout the day and night, and it is obtained while patients perform their normal daily activities. At the end of the recording period, the readings are downloaded into a computer for processing. Patients must fill out a diary during the monitoring period to document any symptoms, awakening and sleeping times, naps, periods of stress, timing of meals, and medication ingestion [1].

Based on the goal proposed by current guidelines [1, 2], combining clinical BP and ABPM allows disclosing four pressor profiles (Table 4.1). This assessment is not a "semantic exercise," because it optimizes refining the risk profile of hypertensive patients [3–5].

Alternatively, for the detection of white coat hypertension (WCH) and masked hypertension (MH), HBP monitoring may be suitable, by means of self-reporting of BP values. This approach for measuring BP outside of the clinic provides a great

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Table 4.1 Main information derived from ambulatory blood pressure monitoring (ABPM) and office blood pressure (BP)

	ABPM	Office BP
Recommended target[a]	24 h ABP <130/80 Daytime ABP <135/85 Nighttime ABP <120/70	≤140/90 (Ualb < 30 mg/d) ≤130/80 (Ualb 30–300 mg/d) ≤130/80 (Ualb >300 mg/d)
Pressor profiles		
Controlled hypertension	At goal	At goal
White coat hypertension	At goal	Not at goal
Masked hypertension	Not at goal	At goal
Sustained hypertension	Not at goal	Not at goal
Circadian profiles		
Dipper	Nighttime BP < daytime BP by 10–20%	–
Extreme dipper	Nighttime BP < daytime BP by >20%	–
Non-dipper	Nighttime BP < daytime BP by 0–10%	–
Inverse dipper	Nighttime BP greater than daytime BP	–

[a]Recommendations on BP targets are based on Refs. [1, 2]

advantage that is well accepted and cheaper than ABPM. In order to obtain an accurate HBPM, the measurements must be performed by the patient two times in the morning and two times in the evening. A minimum of three consecutive days and a preferred period of 7 consecutive days of HBPM is a reasonable approach for clinical practice. HBPM results are obtained by averaging all values recorded after excluding the readings obtained on the first day of HBPM [1]. The recommended BP threshold for optimal HBPM is <135/85 mmHg [1].

A major shortcoming of HBPM is the lack of data on nocturnal BP that makes this technique less accurate for an optimal evaluation of cardiovascular risk in CKD. Conversely, ABPM provides an accurate picture of circadian rhythm of BP and the detection of nocturnal hypertension. Indeed, BP is physiologically lower during sleep by 10–20% as compared to daytime values. Therefore, a night/day ratio of BP ranging between 0.8 and 0.9 is considered normal, and patients are defined as "dipper," while the lack of nighttime BP reduction by at least 10% identifies individuals as "non-dipper." In particular, as described in Table 4.1, a decline of nocturnal BP between 0 and 10% with respect to diurnal BP (night/day BP ratio: 0.9:1.0) defines the "non-dipper" condition, whereas if nocturnal BP is higher than diurnal BP (night/day BP ratio > 1.0), the patient is defined as "reverse dipper." Some patients may experience a marked reduction of night BP, greater than 20% (night/day BP ratio < 0.8); this infrequent condition is defined as "extreme dipping" [1]. This classification is relevant for prognosis of hypertensive patients since several studies and meta-analyses have reported that non-dipping status and nocturnal hypertension are associated with increased risk for cardiovascular (CV) events and all-cause mortality, independent of clinical and daytime blood pressure levels [6, 7].

Importance of Ambulatory/Home BP Monitoring in CKD Patients

ABPM and HBPM as Continuous Variables

The inconclusive results on the prognostic role of the BP target in patients with CKD [8–10] might relate to the limited ability of clinical BP readings to adequately stratify the global risk in this high-risk population [11, 12]. Three large prospective cohort studies provided clear evidence that HBPM and ABPM are superior to clinical BP readings in predicting all-cause mortality, CV events, and end-stage renal disease (ESRD) [13–16]. Agarwal and Andersen demonstrated in a cohort study of 217 veterans with CKD who were followed for a median of 3.5 years the superiority of ABPM over clinical BP for predicting a composite endpoint of death or ESRD [16]. Similar results were obtained when considering HBPM versus office BP in the same cohort [13]. Furthermore, an analysis of 617 CKD patients in the African American Study of Kidney Disease and Hypertension (AASK) study found ABPM to be superior to office BP for predicting both CV events and a composite of death, ESRD, or doubling of serum creatinine over a median follow-up of 5 years [14]. Finally, Minutolo et al. [15] reported that in a cohort study of 436 CKD patients followed for a median of 4.2 years, office BP did not predict CV events or composite of death and ESRD, while ABPM, and in particular nighttime BP, increased the risk of either adverse outcome. In that study, the cardio-renal risk increased significantly when daytime or nighttime BP exceeded 135/85 or 120/70 mmHg, respectively. These data confirmed that normality thresholds for daytime and nighttime BP proposed for essential hypertension may also confidently apply to hypertension CKD [15].

All the previous studies on ABPM have used a single set of measurements, which represents a potential source of inaccuracy in properly classifying patients with BP at goal for daytime and nighttime ABPM that potentially leads to imprecise risk estimation. To address this issue, we recently tested whether an additional assessment of ABPM after 1 year provides incremental estimate of the renal risk beyond the initial evaluation [17]. We found that patients not reaching the goal for daytime and nighttime systolic BP at the two ABPM had the worst renal prognosis, while patients not at goal at baseline but reaching the goal at second ABPM were not exposed to a greater renal risk. The use of a second ambulatory monitoring after 1 year allows to correctly reclassify risk profile in 15–22% of patients based on daytime or nighttime systolic BP [17]. Therefore, in routine clinical practice, physicians may perform ABPM in order to identify patients with nocturnal hypertension, which constitutes a major predictor of CV events and progression to ESRD. Reassessment of ABPM at 1 year further refines renal prognosis and it should specifically be considered in patients with uncontrolled BP at baseline.

Altered BP Profiles

ABPM or HBPM allows for better assessment of hypertension control by identifying patients with altered BP pattern (Table 4.1). The identification of inconsistent achievement of clinical and ambulatory BP goals is helpful at refining prognosis. Three recent meta-analyses in the setting of essential hypertension have shown that WCH does not associate with increased CV risk, whereas MH heralds a higher risk of CV events [3–5]. This assessment is particularly important in CKD because the prevalence of WCH and MH appears to differ from that reported in patients with essential hypertension where the prevalence of WCH and MH is 13% and 11%, respectively [18, 19]. Indeed, a meta-analysis, including six studies and 980 CKD patients with out-of-office BP measures, reported that WCH was more frequent in patients with CKD (18%), whereas MH seems to be less common in CKD (8%) [20]. However, these estimates were strongly influenced by the BP thresholds used for classifying WCH and MH and the use of antihypertensive drugs [20]. Of note, when considering more recent studies not included in the meta-analysis, a further source of bias emerges. Indeed, the prevalence of WCH is higher than that of MH in Caucasian patients [21–23], while the opposite was found in studies enrolling Afro-American or Asian patients [24, 25] (Table 4.2).

A critical question is when to perform an out-of-office measurement of BP to detect altered pressor profiles or, alternatively, what clinical and demographic

Table 4.2 Prevalence of white coat hypertension (WCH), masked hypertension (MH), and non-dipping status in cohorts of CKD patients

Cohort	Ethnicity	Thresholds for defining BP profiles (mmHg)		WCH (%)	MH (%)	Non-dipper definition	Non-dipper (%)
		Office BP	ABPM				
Italian cohort [23]	Caucasian 100%	<140/90	Day/night <135/85/<120/70	22.1	14.5	N/D ratio SBP > 0.9	62.4
Spanish registry [21]	Caucasian 100%	<140/90	24-h BP <130/80	28.8	7.0	NA	NA
Veterans cohort [22]	Caucasian 80%	<130/80	Awake BP <130/80	24.6	4.7	N/D ratio SBP > 0.9	80.2
AASK study [28]	Afro-American 100%	<140/90	Daytime BP <135/85	5.3	25.1	N/D change SBP <10%	80.2
JAC-CKD cohort [24]	Asian 100%	<140/90	24-h BP <130/80	5.6	30.9	N/D change SBP <10%	53.5
Chinese cohort [25]	Asian 100%	≤140/90	24-h BP ≤130/80	9.7	18.2	N/D change SBP <10%	75.5

WCH white coat hypertension, *MH* masked hypertension, *ABPM* ambulatory blood pressure monitoring, *CBP* clinical blood pressure, *BP* blood pressure, *NA* not available

conditions may predict the presence of WCH or MH and, consequently, require ABPM or HBP. Two studies addressed this issue in CKD patients, separately for WCH [26] and MH [27]. Minutolo et al. [26] reported that, among 228 CKD patients stages 2–5 with high office BP, 40% of patients had WCH, and this condition was significantly associated with proteinuria >1 g/day (odds ratio [OR], 3.12), left ventricular hypertrophy (OR, 1.94), and higher office BP (OR, 1.61 for each 10 mmHg). Agarwal et al. [27], in a cohort of 295 CKD patients (stages 2–4) with normal clinical BP (<140/90 mmHg), found that MH was a common condition whose prevalence varied from 27% (using daytime BP) to 33% (using 24 h BP) up to 56% when both daytime and nighttime BP were considered. The authors suggested that a confirmatory ABPM can be avoided in patients with office systolic BP <110 mmHg, that, however, represent the large minority of patients seen in nephrology clinics. Conversely, ABPM should be mandatory in patients with office BP values in the range of prehypertension (130–139 mmHg) by considering that two out of three of these patients have MH and also considered when office BP is in the 120–129 range, that is, a condition associated with MH in 34% of cases [27].

This more accurate estimate of hypertensive status offered by ABPM with respect to clinical BP translates into better risk stratification in CKD patients. Indeed, while the global prognosis of patients with sustained hypertension (either target not at goal) is worse than for normotensive patients (both BP targets at goal), the risk for renal death (composite of ESRD and all-cause mortality) and fatal and nonfatal CV events markedly differ between WCH and MH (Fig. 4.1). Patients with MH showed

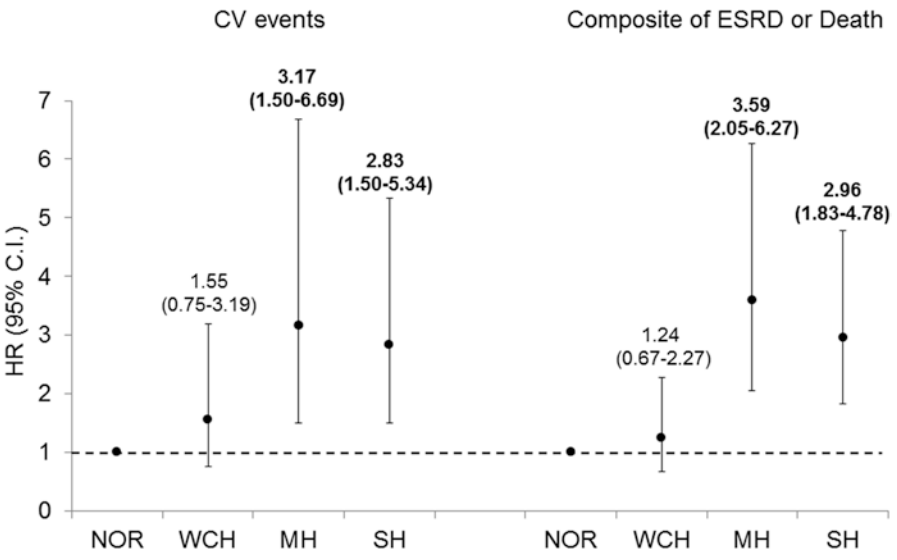

Fig. 4.1 Risk of fatal and nonfatal CV events and dialysis therapy initiation or all-cause death associated with pressor profiles identified by ABPM. In bold are indicated significant hazards. Model is adjusted for age, sex, body mass index, diabetes, history of CV disease, hemoglobin level, estimated glomerular filtration rate, 24-h proteinuria, non-dipping status, and use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and stratified for center [23]

similar cardio-renal risk as those with sustained hypertension, whereas having WCH was not associated with a higher risk for any event, therefore suggesting that the different prognosis can be ascribed reasonably to poor achievement of the ABPM target rather than office BP target [23]. Interestingly, the cardio-renal prognosis associated with WCH and MH was independent from the office and ABPM thresholds used to define BP profiles [23]. Indeed, the poor cardio-renal survival in MH patients, as well as the lack of increased risk in WCH, was consistently detected assuming the cutoff values of office BP and ABPM adopted in Spanish Registry, AASK study, Japanese study, and in a veterans cohort [15, 21, 24, 28].

It is important to note that classifying patients based on both clinical and out-of-office BP has relevant therapeutic implications by helping physicians to select the most appropriate therapeutic decision algorithm for their hypertensive patients. BP management merely driven by clinical BP may leave MH patients at higher risk due to uncontrolled ambulatory BP. On the other hand, tailoring antihypertensive treatment based only on office BP values can expose WCH patients to excessive lowering of BP, especially at night [26] and in elderly patients [29], with consequent ischemic episodes affecting renal, cerebral, and cardiac function. In this regard, it is interesting to note that in hypertensive patients with clinical BP not at goal but ambulatory BP at goal, starting antihypertensive therapy is not effective in preventing CV events compared to placebo treatment [30]. Very recently, the randomized Systolic Blood Pressure Intervention Trial (SPRINT) study has shown that lower BP (goal systolic <120 mmHg), as compared to standard control (<140 mmHg), is less effective in reducing the CV and not effective at all in preventing renal endpoints in the subgroup of patients with CKD with respect to those without CKD [31]. Indeed, driving the intensity of treatment on the basis of office BP only has led to higher rates of hypotensive episodes and acute renal injury. In this trial, it is therefore possible to hypothesize that lack of protective effect in CKD subgroup could be associated with the presence of a large prevalence of WCH, that is, a condition exposing patients at high risk of ischemic episodes. This hypothesis will be tested by the ancillary study of SPRINT trial enrolling 600 patients performing ABPM will be available [32].

Altered Circadian Profile

The distinctive characteristic of ABPM is mainly represented by the possibility of obtaining information on nighttime BP, now considered the ABPM component more strictly linked to adverse outcome [33]. Indeed, even when daytime BP is well controlled, the presence of nocturnal hypertension portends a greater risk of renal progression [15].

The lack of physiological BP decline during nighttime (non-dipping status) occurs frequently in CKD patients, being consistently above 53% in all the studies available (Table 4.2). Prevalence increases with aging [29] and in more advanced CKD stages. In a group of 459 CKD patients regularly followed in renal clinics, the risk of being non-dipper was significantly associated with older age, diabetes, left

ventricular hypertrophy, and anemia [29]. In a large Japanese cohort of CKD patients, non-dipping status was associated also with more advanced CKD, seasonal variation, and, as expected, nocturia [24].

Altered circadian profiles are strongly associated with adverse clinical outcomes in CKD [15, 16], similar to general population and essential hypertension [6, 7, 34]. In particular, in CKD patients, non-dippers and reverse dippers displayed a twofold greater CV risk and a 60–70% higher risk of renal events [15]. Agarwal and Andersen reported similar results in a cohort of veterans with CKD and highlighted that a similar risk of CV outcomes occurred by using day or night versus awake or sleep BP and that dipping status defined as the night/day ratio confers higher CV risk as compared to dipping defined as an absolute change [35]. Therefore, an adjunctive reason to perform an ABP recording in patients with CKD is to identify patients with nocturnal hypertension, which constitutes a major predictor of CV events and progression to ESRD and represents a potential target for therapy. Indeed, it has been suggested that non-dippers may benefit of antihypertensive treatment based on "chronotherapeutic" approach. This consists in the administration of one or more drugs at bedtime in order to restore the physiological nighttime BP decline. This approach has been tested in a pilot uncontrolled study, in which one antihypertensive drug was switched to bedtime in 32 CKD non-dipper patients [36]. ABPM was repeated at 8 weeks, and 28 of the 32 subjects became dippers. Noteworthy, restoring the normal nocturnal dip allowed a significant reduction of proteinuria [36]. More recently, a randomized controlled open-label crossover trial was performed in 147 former subjects from the AASK study with average GFR of 45 mL/min/1.73 m^2 with 76% patients being non-dipper. This study did not confirm a significant BP reduction at night when either one antihypertensive drug or all drugs were administered bedtime as compared with administration of therapy in the morning [37]; these results suggest that effectiveness of chronotherapy may not apply to all ethnic groups. Finally, a randomized trial tested effectiveness of chronotherapy in 661 CKD patients (66% non-dippers at baseline) and reported a surprising 65% reduction in the relative risk of the composite endpoint of death or CV events [38]. The strongly positive outcomes of this study are encouraging, but caution must be exercised. Indeed, some methodological aspects of this study (the open-label treatment for practitioners and the lack of specific algorithm used to manage BP during the follow-up) raise concerns that the positive outcomes associated with the bedtime dosing were not because of the intervention itself but because of a bias in treatment.

These issues assume greater importance in CKD with RH that represent a cluster of patients where cardio-renal risk is particularly high.

Resistant Hypertension: Definition, Cause, and Epidemiology

Hypertension is defined "resistant" (RH) when BP levels persist above the therapeutic target, despite the use of at least three antihypertensive drugs at full dose, including the diuretic, or when BP is at target, but four or more antihypertensive agents are prescribed [39, 40]. Although the exact prevalence is unknown, several

observational studies suggest that RH is a common clinical problem in general population [41–46], accounting for about 9% of hypertensive patients, and this prevalence increases to 13% when only treated patients are considered [41].

RH may be caused by biological-behavioral factors (such as smoking and obesity), drugs (NSAIDs, sympathomimetics, steroids, and cyclosporine) or exogenous substances (cocaine, amphetamines, oral contraceptive hormones, liquorice, ginseng, etc.), and secondary causes of hypertension (parenchymal and vascular renal disease, primary hyperaldosteronism, sleep apnea, pheochromocytoma, Cushing's syndrome, thyroid diseases, etc.).

Pseudoresistance

Before defining the hypertensive patient as resistant, it is mandatory to exclude the so-called pseudoresistance [39, 40]. This condition, which refers to the "apparent" failure to reach BP target despite the prescription of an appropriate antihypertensive treatment, can be dependent on factors influencing either drug therapy or BP measurement, the two essential parameters required for RH diagnosis. Poor adherence of patients to antihypertensive therapy is a critical aspect to ascertain when diagnosing RH, as suggested by several studies reporting very high discontinuation rate of drugs in hypertensive patients [47, 48]. A further critical aspect is the "therapeutic inertia," that is, the provider's failure to modify therapy despite recognition that treatment goals are unmet [49, 50]. Despite guidelines for patients with CKD having repeatedly highlighted the importance of lowering BP [2, 51, 52], control rates of hypertension remain largely unsatisfactory, in nephrology as non-nephrology setting [53–58]. Poor achievement of BP goal in CKD patients may be due to resistance to antihypertensive treatment, but it is important to underline that uncontrolled hypertension is not equivalent of RH; indeed, a patient cannot be classified as having RH if he/she is not challenged with an adequate number of drugs including a diuretic at a dose correctly up-titrated with GFR worsening. On this regard, a retrospective study in hypertensive CKD patients newly referred to one renal clinic reported that the increment in full-dose antihypertensive medications and diuretic therapy increased the diagnosis of RH from 26% on referral to 38% at month 6 [59]. Therefore, reducing clinical inertia allows to properly reveal the frequency of RH whose identification is clinically meaningful being associated with adverse outcome (see below).

Inadequate assessment of BP represents the second determinant of pseudoresistance. Improper office BP measurement technique contributes to the occurrence of pseudoresistance by producing falsely high BP readings as it occurs when some recommended rules are not followed (leave the patient in a quiet room for at least 5 min; avoid smoking, caffeine, and exercise in the 30 min before measurement; obtain 2–3 readings; use appropriate cuff size). Furthermore, the presence of arteriosclerotic and calcified arteries, usually occurring in elderly individuals, can also result in office BP overestimation leading in turn to a false diagnosis of RH [39, 40]. More important, the presence of WCH is a further cause of pseudoresistance. In the

large Spanish ABP registry, among the 68,045 patients examined, 12% were diagnosed as RH; however, after ABP monitoring, as many as 37% of RH patients were identified as pseudoresistant [60]. A multivariable analysis identified older age, female gender, shorter duration of hypertension, non-smoking, absence of diabetes, more preserved renal function, and negative history of previous CV disease as significant demographic and clinical conditions in which it is more likely to detect pseudoresistance [60]. This issue holds even more true in CKD where WCH is common [20, 21, 26, 29, 35]. With this background, we recently explored the phenomenon of pseudoresistance and true (ABPM verified) resistance in a cohort of 436 hypertensive patients with nondialysis CKD under regular nephrology care. Patients were classified according to 24-h ABP normal (<125/75 mmHg) or high (≥125 mmHg and/or ≥75 mmHg) and the absence or presence of RH (office BP ≥ 130/80 mmHg on 3 full-dose drugs including a diuretic agent or any office BP if the patient was taking four drugs) [61]. In this CKD cohort, 30% of patients (131/436) were diagnosed as resistant on the basis of only clinical BP measurements; however, combining the information derived from ABP with RH status, we found that among patients classified as RH, pseudoresistance (WCH in RH patients) involved about one patient out of four (31/131, 24%). This prevalence is lower than that reported in hypertensive patients (39%) [62].

Notably, the assessment of ABP monitoring allows disclosing a prevalence of "true" RH in about a quarter of CKD patients (100/436) that corresponds to a prevalence three times greater than that reported in essential hypertension (~8%) [60]. As illustrated in Fig. 4.2, the prevalence of true RH increased in the

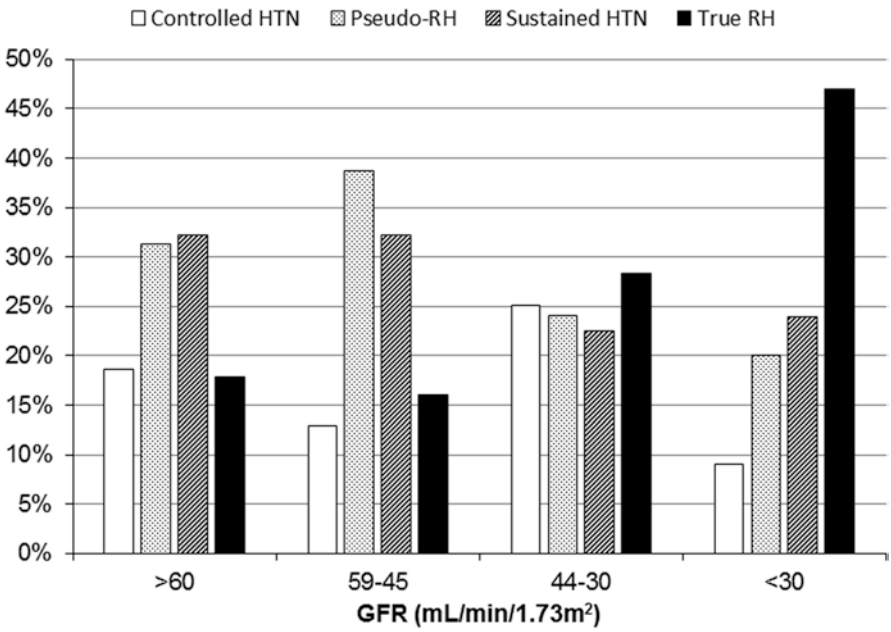

Fig. 4.2 Prevalence of pseudoresistance and true resistance in CKD patients over CKD stages [61]

more advanced CKD stages, whereas pseudoresistance is typically encountered in early stages of CKD and virtually disappeared in advanced CKD [61].

Resistant Hypertension in CKD

Keeping in mind that CKD is at the same time cause [53, 54, 63, 64] and complication [65] of poorly controlled hypertension, the evaluation of RH in CKD patients is highly relevant. In this population, in fact, RH is a common finding as testified by several studies reporting a prevalence ranging from 30% to 42% (Table 4.3) [41, 59, 61, 66–69]. Interestingly, based on these studies, we can state that CKD is one cause of RH in the general hypertensive population but, at the same time, that not all CKD patients have RH. Prevalence of RH progressively increases with worsening of renal function and with increasing urinary excretion of albumin [66]. However, these estimates are partially confounded by the phenomenon of pseudoresistance (which overestimates the prevalence of RH) and by the occurrence of clinical inertia, which underestimates the RH frequency. The large prevalence among CKD patients may be explained not only by the large burden of hypertension in this population but also by the coexistence of pathogenetic factors, such as sodium retention, overexpression of the renin-angiotensin-aldosterone system (RAAS), and enhanced activity of the sympathetic nervous system, that may explain the poor response to the treatment [70]. The main disorder in CKD is the salt and water retention, occurring in the majority of patients with low glomerular filtration rate (GFR). The resulting increase of the extracellular volume (ECV), which allows preserving the external balance of sodium, has the harmful trade-off of the development of persistent (and often refractory) hypertension. In these patients, the entity of ECV expansion is directly dependent on the degree of GFR impairment and corresponds to approximately 5–10% of body weight, even in the absence of peripheral edema [71]. Of note, the salt sensitivity of BP is not a feature limited to the advanced stages of renal disease, but begins before the development of clear hypertension and severe GFR decline [72, 73]. The fact that sodium excretion is commonly impaired in renal patients may also explain the large prevalence of nocturnal hypertension in CKD as compared to essential hypertension [74]. Furthermore, in CKD patients, systemic hypertension is also in part sustained by the RAAS, which is inappropriately activated when considering the ECV expansion. The ensuing glomerular hypertension leads to the progressive kidney damage in the long term. Therefore, RAAS inhibition is the cornerstone of the nephroprotective treatment in CKD [71]. The evaluation of clinical features associated with the presence of true RH allows physicians to identify patients who may benefit from intensive BP monitoring including out-of-office BP assessment and early therapeutic. Clinical correlates of true RH in CKD are diabetes, left ventricular hypertrophy, proteinuria, and poor adherence to low-salt diet. Each of these factors independently increases by two- to threefold the probability of having true RH [61]. Among individuals with CKD enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, higher prevalence

Table 4.3 Prevalence of apparent resistant hypertension (aRH) in CKD patients

Authors [ref.]	Data collection (years)	Patients	Participants (N)	CKD patients	aRH (%)
Persell [41]	2003–2008	General population	3710	3710 (19.9%)	24.7
Tanner [66]	2003–2009	General population	10,700	3134 (29.3%)	28.1
Hung [69]	2000–2010	Hypertensives from insurance database	111,986	2894 (2.6%)	24.8
Sim [68]	2006–2010	Hypertensives from insurance database	470,386	122,300 (26%)	22.0
De Nicola [59]	2002–2006	CKD	300	300 (100%)	38.0
De Nicola [61]	2003–2005	CKD	436	436 (100%)	30.0*
Muntner [67]	2003–2007	CKD	3612	3612 (100%)	42.3
De Beus [77]	2004–2010	CKD	788	788 (100%)	34.1

*After excluding patients with pseudoresistance by detecting white coat hypertension through ABPM, the prevalence of RH ("true RH") declined to 22.9%

of RH was detected in men, blacks, individuals with large waist circumferences, diabetes, and individuals with a history of stroke or myocardial infarction [66].

Prognostic Meaning of RH in CKD

RH increases the risk of renal damage in the general population and worsens the cardio-renal prognosis of patient with overt renal damage [68]. In the setting of essential hypertension, the presence of mild-to-moderate GFR reduction and/or microalbuminuria amplifies the cardiovascular risk correlated to RH [68, 75, 76].

In the first study exploring the prognostic role of RH in CKD patients, we reported that RH (diagnosis not verified by means of ABPM) was associated with greater risk of renal death (HR, 1.85, 95% CI, 1.13–3.03), independently from main clinical features and degree of BP control [59]. More recently, in a cohort of 788 CKD patients, de Beus et al. confirmed the increase of risk of renal and CV outcomes associated with RH [77]. However, the main limitation of these studies targeting the role of RH in CKD patients is the lack of out-of-office BP measurement, which does not allow an accurate estimate of BP load and cannot exclude the white coat effect (pseudoresistance).

This issue has been addressed in a cohort study including 436 CKD patients in which BP was assessed concurrently by ABPM and office measurement in order to correctly classify resistant patients as having pseudoresistance and true RH [61].

During 57 months of follow-up, we recorded 165 renal events (death, ESRD, or transplantation) and 109 fatal and nonfatal CV events. Patients with normal ABP had the best prognosis for either outcome independently from the RH status, whereas the highest risk for cardio-renal events was observed only in true resistance. After adjustment for confounders, true resistance predicted CV and renal risk, while sustained hypertension (ABP above the goal without RH) associated only with renal outcome (Fig. 4.3). Of note, pseudoresistant patients were not exposed to higher cardio-renal risk [61]. These findings are clinically relevant as these highlight the need to identify pseudoresistant CKD patients by ABPM to avoid aggressive and potentially harmful 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 mmHg). Under these circumstances, a tighter control of BP merely based on the detection of elevated BP in office may expose patients to ischemia-induced worsening of cardio-renal damage [78] and eventually convert their prognosis from favorable to unfavorable.

The mechanisms underlying the different prognostic value of RH are not readily apparent; however, we can hypothesize that persistence of hypertension despite optimal antihypertensive treatment specifically identifies patients with more severe vascular damage. The abovementioned correlates of true resistance (diabetes, left ventricular hypertrophy, higher proteinuria, and high salt intake) are in fact all associated with endothelial dysfunction and arterial stiffness [79–82]. In particular, proteinuria, rather than GFR, relates to the severity of hypertension [83]. Indeed,

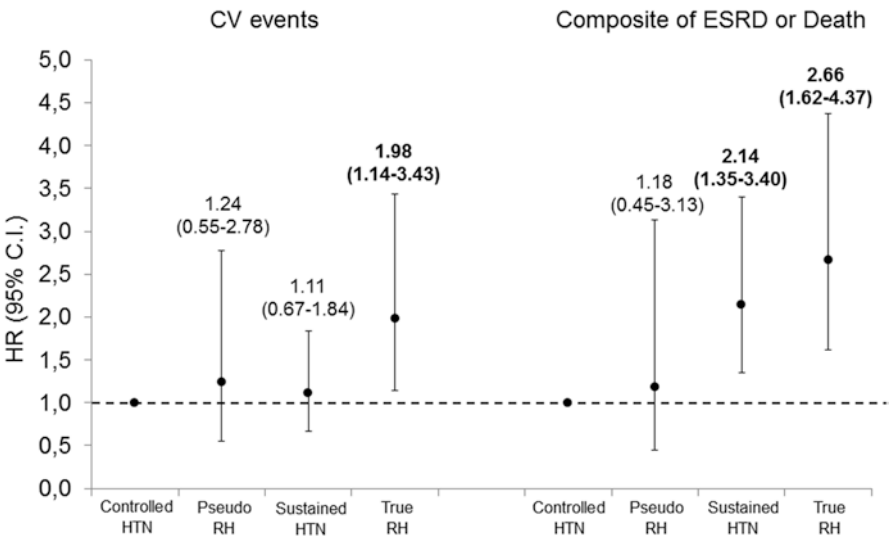

Fig. 4.3 Risk of fatal and nonfatal CV events and dialysis therapy initiation or all-cause death for each of four groups identified by ABPM and RH: true normotension (controlled HTN), pseudoresistance (pseudo RH), sustained hypertension (sustained HTN), and true resistance (true RH) [61]. Model is adjusted for age, sex, BMI, diabetes, history of cardiovascular disease, natural log-transformed 24-h proteinuria, and GFR [61]

although low GFR is recognized as a CV risk factor [84], proteinuria is considered a better marker of the presence of vascular disease in CKD patients [85].

Treatment of RH in CKD Patients

In CKD patients with RH, the cornerstone of therapy is certainly represented by the restriction of sodium intake [86]. However, this dietary measure is implemented only in about 20% of the CKD population at large regularly followed in nephrology clinics [87–89]. Interestingly, we found higher levels of sodium intake in RH patients (164 ± 68 mmol/day) compared to controls (141 ± 49 mmol/day), and consequently the adherence to low-salt diet resulted poorer in RH (14.1%) as compared to patients without RH (26.3%; $P = 0.026$) [61, 90]. This is a paradoxical condition if one considers that CKD is typically characterized by high salt sensitivity [91]. More important, a small randomized crossover trial of dietary salt restriction in patients with RH but without CKD has demonstrated that low-salt diet remarkably decreased office systolic and diastolic BP (by 23 and 9 mmHg, respectively) and 24-h BP from 150/82 to 130/72 mmHg [92]. This antihypertensive effect of dietary sodium restriction may occur directly through a correction of volume expansion and indirectly by enhancing the antihypertensive effects of RAAS inhibitors [93]. Table 4.4 reports some practical suggestions to help patients in reducing their dietary sodium intake. These recommendations should be implemented by patients over a period of 2–4 months in order to give them the time to adapt their taste receptor cells to the lower saltiness.

RH definition is based on the presence of a diuretic, while type and dose of these agents are not mentioned. While this is not a major issue in essential hypertension, selecting the class of diuretic and the correct dose becomes critical in CKD patients. Indeed, if patients with mild renal impairment (GFR >40 mL/min/1.73 m^2) may respond to thiazide diuretics, those with more advanced CKD require the use of loop diuretics and doses must be titrated to the reduced GFR [86, 94]. In a clinical

Table 4.4 Practical recommendations to restrict sodium intake

1. Look for the amount of sodium on food labels
2. Abolish salt-containing condiments (e.g., ketchup, mayonnaise, mustard, barbecue sauce)
3. Move the salt shaker away from the table
4. Cook pasta, rice, and cereals without salt (add in smaller amount directly on cooked food)
5. In cooking and at the table, increase the use of spices (e.g., herbs, lemon, vinegar, hot pepper)
6. Look for low-salt bread
7. Look for fresh or plain frozen foods
8. Avoid frozen dinners, canned soups, packaged mixes, cured meat and fish (e.g., ham, bacon, salami, anchovies, salmon)
9. Choose fresh rather than seasoned cheese
10. Rinse canned foods (e.g., tuna, legumes) to remove some sodium contained as additives
11. Abolish salty snack foods (e.g., chips, nuts, crackers)

trial performed in patients with GFR in the range 10–40 mL/min, correction of volume expansion (evidenced by body weight reduction of 2.0 kg coupled with a marked reduction in BP) was safely induced by oral administration of furosemide at doses inversely proportional to GFR level (1.0, 2.5, and 4.0 mg/kg body weight per day in patients with GFRs of 40–31, 30–20, and 19–10 mL/min, respectively) [95]. Therefore, to improve the modalities of treatment, it is helpful to start diuretic treatment with a low dose that can be progressively increased if body weight does not decrease (the goal is weight loss of 0.5 kg/day). The lack of a significant body weight reduction with increasing diuretic doses likely suggests the presence of diuretic resistance that can be overcome by adding other agents (such as metolazone) in order to limit the breaking phenomenon (sodium over-reabsorption in the distal tubule) [96]. Disappointingly enough, nephrologists are today still reluctant to use adequately loop diuretics in their hypertensive CKD patients. This erroneous attitude cannot be justified by the fear of side effects, which are infrequent, usually reversible and predictable when the patient is regularly followed [97].

A further diuretic agent successfully tested in RH patients is spironolactone based on the finding that plasma aldosterone levels are higher in patients with RH than in those with controlled hypertension [98]. Efficacy of spironolactone has been evidenced in 175 patients with true RH and normal renal function when treated with doses of 25–100 mg/day and prospectively followed for 1 year [99]. The main finding of the study was a significant and marked reduction of 24-h systolic and diastolic BP (16 and 9 mmHg, respectively) persisting up to 15 months, without difference in the entity of daytime and nighttime decline. More important, the antihypertensive effects of spironolactone have been evaluated in a randomized, controlled, double-blind study carried out in 117 patients with RH. Spironolactone was administered at doses of 25 mg/day for 8 weeks in addition to the preexisting therapy. At the end of 8 weeks of the study, systolic BP (measured in and out office) was significantly reduced in treated patients in the absence of adverse effects [100]. However, assessment of spironolactone efficacy has not been tested in patients with CKD that is a condition associated with higher risk of hyperkalemia.

Conclusions

RH is a common condition in CKD due to a combination of factors including sodium retention and enhanced neurohumoral activity. However, the higher prevalence of WCH in CKD patients likely makes mandatory out-of-office monitoring in order to distinguish between pseudoresistance and true RH. Therefore, a greater use of ABPM in CKD patients is desirable in the attempt of limiting the misclassification of hypertensive status and thus avoiding unnecessary aggressive antihypertensive medication. Catheter-based radiofrequency ablation of the renal sympathetic nerves has been proposed, but the inconclusive results provided so far and the lack of long-term data on its efficacy and safety do not recommend the use of renal denervation for treatment of RH in routine clinical practice [101]. More efforts are

required to nephrologists to improve adherence to pharmacological therapy, expand the use of low-salt diet, and correctly prescribe diuretic therapy. These strategies, being probably more effective than renal denervation [102], must be considered as the first-choice therapeutic approach for controlling RH in CKD patients.

References

1. O'Brien E, Parati G, Stergiou G, et al.; for the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. J Hypertens. 2013;31(9):1731–68.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl. 2012;2:337–414.
3. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens. 2007; 25(11):2193–8.
4. Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7030 individuals. J Hypertens. 2007;25(8):1554–64.
5. Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in initially untreated subjects: an updated meta analysis. Am J Hypertens. 2011;24(1):52–8.
6. Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, et al. International database on ambulatory blood pressure monitoring in relation to cardiovascular outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet. 2007;370:1219–29.
7. Hansen TW, Li Y, Boggia J, Thijs L, Richart T, Staessen JA. Predictive role of the nighttime blood pressure. Hypertension. 2011;57:3–10.
8. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med. 2011; 154:541–8.
9. Lv J, Ehteshami P, Sarnak MJ, et al. Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis. CMAJ. 2013;185:949–57.
10. Lv J, Neal B, Ehteshami P, Ninomiya T, Woodward M, Rodgers A, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. PLoS Med. 2012;9:e1001293.
11. Borrelli S, De Nicola L, Minutolo R, Sagliocca A, Garofalo C, Liberti ME, et al. Limitations of blood pressure target in non-dialysis chronic kidney disease: a question of method? G Ital Nefrol. 2012;29(4):418–24.
12. Lewis JB. Blood pressure control in chronic kidney disease. Is less really more? J Am Soc Nephrol. 2010;21:1086–92.
13. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69:406–11.
14. Gabbai FB, Rahman M, Hu B, Appel LJ, Charleston J, Contreras G, et al. Relationship between ambulatory BP and clinical outcomes in patients with hypertensive CKD. Clin J Am Soc Nephrol. 2012;7(11):1770–6.
15. Minutolo R, Agarwal R, Borrelli S, Chiodini P, Bellizzi V, Nappi F, et al. Prognostic role of ambulatory blood pressure monitoring in patients with nondialysis CKD. Arch Intern Med. 2011;171(12):1090–8.

16. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(7):1175–80.
17. Minutolo R, Gabbai FB, Chiodini P, Garofalo C, Stanzione G, Liberti ME, et al. Reassessment of ambulatory blood pressure improves renal risk stratification in nondialysis chronic kidney disease: long-term cohort study. Hypertension. 2015;66(3):557–62.
18. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? JAMA. 1988;259(2):225–8.
19. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension. 2002;40(6):795–6.
20. Bangash F, Agarwal R. Masked hypertension and white coat hypertension in chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol. 2009;4(3):656–64.
21. Gorostidi M, Sarafidis PA, de la Sierra A, Segura J, de la Cruz JJ, Banegas JR, et al.; for Spanish ABPM Registry Investigators. Differences between office and 24-hour blood pressure control in hypertensive patients with CKD: a 5,693-patient cross-sectional analysis from Spain. Am J Kidney Dis. 2013;62(2):285–94.
22. Andersen MJ, Khawandi W, Agarwal R. Home blood pressure monitoring in CKD. Am J Kidney Dis. 2005;45(6):994–1001.
23. Minutolo R, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, et al. Assessment of achieved clinic and ambulatory blood pressure recordings and outcomes during treatment in hypertensive patients with CKD: a multicenter prospective cohort study. Am J Kidney Dis. 2014;64(5):744–52.
24. Iimuro S, Imai E, Watanabe T, et al.; for the Chronic Kidney Disease Japan Cohort Study Group. Clinical correlates of ambulatory BP monitoring among patients with CKD. Clin J Am Soc Nephrol. 2013;8(5):721–30.
25. Wang C, Gong WY, Zhang J, Peng H, Tang H, Liu X, Ye ZC, Lou T. Disparate assessment of clinic blood pressure and ambulatory blood pressure in differently aged patients with chronic kidney disease. Int J Cardiol. 2015;183:54–62.
26. Minutolo R, Borrelli S, Scigliano R, Bellizzi V, Chiodini P, Cianciaruso B, et al. Prevalence and clinical correlates of white coat hypertension in chronic kidney disease. Nephrol Dial Transplant. 2007;22:2217–23.
27. Agarwal R, Pappas MK, Sinha AD. Masked uncontrolled hypertension in CKD. J Am Soc Nephrol. 2016;27:924–32.
28. Pogue VA, Rahman M, Lipkowitz M, et al.; for African American Study of Kidney Disease and Hypertension Collaborative Research Group. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension. 2009;53(1):20–7.
29. Minutolo R, Borrelli S, Chiodini P, Scigliano R, Bellizzi V, Cianciaruso B, et al. Effects of age on hypertensive status in patients with chronic kidney disease. J Hypertens. 2007; 11:2325–33.
30. Fagard RH, Staessen JA, Thijs L, Gasowski J, Bulpitt CJ, Clement D, et al.; for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Circulation. 2000;102(10): 1139–44.
31. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–16.
32. Effect of Intense vs. Standard Hypertension Management on Nighttime Blood Pressure – an Ancillary Study to SPRINT. ClinicalTrials.gov. Identifier: NCT01835249.
33. Sinha AD, Agarwal R. The complex relationship between CKD and ambulatory blood pressure patterns. Adv Chronic Kidney Dis. 2015;22:102–7.
34. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA, et al. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. Hypertension. 2008;51(1):55–61.
35. Agarwal R, Andersen MJ. Blood pressure recordings within and outside the clinic and cardiovascular events in chronic kidney disease. Am J Nephrol. 2006;26(5):503–10.

36. Minutolo R, Borrelli S, Chiodini P, Scigliano R, Trucillo P, Baldanza D, et al. Changing the timing of antihypertensive therapy to reduce nocturnal blood pressure in CKD: an 8-week uncontrolled trial. Am J Kidney Dis. 2007;50(6):908–17.
37. Rahman M, Greene T, Phillips RA, Agodoa LY, Bakris GL, Charleston J, et al. A trial of 2 strategies to reduce nocturnal blood pressure in blacks with chronic kidney disease. Hypertension. 2013;61(1):82–8.
38. Hermida RC, Ayala DE, Mojon A, Fernandez JR. Bedtime dosing of antihypertensive medications reduces cardiovascular risk in CKD. J Am Soc Nephrol. 2011;22(12):2313–21.
39. Calhoun DA, Jones D, Textor S, et al.; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117:510–526.
40. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol. 2008;52:1749–57.
41. Persell SD. Prevalence of resistant hypertension in the United States, 2003–08. Hypertension. 2011;57:1076–80.
42. Pimenta E, Calhoun DA. Resistant hypertension: incidence, prevalence, and prognosis. Circulation. 2012;125(13):1594–6.
43. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290:199–206.
44. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981–97.
45. Sarafidis PA, Georgianos P, Bakris GL. Resistant hypertension its identification and epidemiology. Nat Rev Nephrol. 2012;9(1):51–8.
46. Moser M, Setaro JF. Clinical practice. Resistant or difficult to control hypertension. N Engl J Med. 2006;355:385–92.
47. Mazzaglia G, Mantovani LG, Sturkenboom MC, Filippi A, Trifirò G, Cricelli C, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens. 2005;23:2093–100.
48. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336:1114–7.
49. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, Miller CD, Ziemer DC, Barnes CS. Clinical inertia. Ann Intern Med. 2001;135:825–34.
50. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, Moskowitz MA. Inadequate management of blood pressure in a hypertensive population. N Engl J Med. 1998;339:1957–63.
51. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.
52. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC task force for the Management of Arterial Hypertension. J Hypertens. 2013;31(10):1925–38.
53. De Nicola L, Chiodini P, Zoccali C, Borrelli S, Cianciaruso B, Di Iorio B, et al. Prognosis of CKD patients receiving outpatient nephrology care in Italy. Clin J Am Soc Nephrol. 2011;6(10):2421–8.
54. De Nicola L, Borrelli S, Chiodini P, Zamboli P, Iodice C, Gabbai FB, et al. Hypertension management in chronic kidney disease: translating guidelines into daily practice. J Nephrol. 2011;24(6):733–41.

55. Marín R, Fernández-Vega F, Gorostidi M, et al. COPARENAL (COntrol de la hiPertensión Arterial en Pacientes con Insuficiencia RENAL) study investigators. Blood pressure control in patients with chronic renal insufficiency in Spain: a cross-sectional study. J Hypertens. 2006;24:395–402.
56. Stevens PE, O'Donoghue DJ, de Lusignans S, Van Vlymen J, Klebe B, Middleton R, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int. 2007;72:92–9.
57. Minutolo R, De Nicola L, Zamboli P, Chiodini P, Signoriello G, Toderico C, et al. Management of hypertension in patients with CKD: differences between primary and tertiary care settings. Am J Kidney Dis. 2005;46:18–25.
58. Minutolo R, Sasso FC, Chiodini P, Cianciaruso B, Carbonara O, Zamboli P, et al. Management of cardiovascular risk factors in advanced type 2 diabetic nephropathy: a comparative analysis in nephrology, diabetology and primary care settings. J Hypertens. 2006;24:1655–61.
59. De Nicola L, Borrelli S, Gabbai FB, Chiodini P, Zamboli P, Iodice C, et al. Burden of resistant hypertension in hypertensive patients with non-dialysis chronic kidney disease. Kidney Blood Press Res. 2011;34(1):58–67.
60. de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57:898–902.
61. De Nicola L, Gabbai FB, Agarwal R, Chiodini P, Borrelli S, Bellizzi V, et al. Prevalence and prognostic role of resistant hypertension in Chronic Kidney Disease. J Am Coll Cardiol. 2013;61(24):2461–7.
62. Salles GF, Cardoso CR, Muxfeldt ES. Prognostic influence of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med. 2008;168(21):2340–6.
63. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260–72.
64. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Ford CE, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334(1):13–8.
65. Garofalo C, Borrelli S, Pacilio M, Minutolo R, Chiodini P, De Nicola L, Conte G. Hypertension and prehypertension and prediction of development of decreased estimated GFR in the general population: a meta-analysis of cohort studies. Am J Kidney Dis. 2016;67:89–97.
66. Tanner RM, Calhoun DA, Bell EK, et al. Prevalence of apparent treatment-resistant hypertension among individuals with CKD. Clin J Am Soc Nephrol. 2013;8:1583–90.
67. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, et al.; the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2010; 55:441–451.
68. Sim JJ, Bhandari SK, Shi J. Reynolds K2, Calhoun DA3, Kalantar-Zadeh K4, Jacobsen SJ. Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. Kidney Int. 2015;88(3):622–32.
69. Hung CY, Wang KY, Wu TJ, Hsieh YC, Huang JL, Loh EW, Lin CH. Resistant hypertension, patient characteristics, and risk of stroke. PLoS One. 2014;9(8):e104362.
70. Campese VM, Mitra N, Sandee D. Hypertension in renal parenchymal disease: why is it so resistant to treatment? Kidney Int. 2006;69:967–73.
71. De Nicola L, Minutolo R, Bellizzi V, Zoccali C, Cianciaruso B, Andreucci VE, et al. Investigators of the Target Blood Pressure Levels in Chronic Kidney Disease (TABLE in CKD) Study Group. Achievement of target blood pressure levels in chronic kidney disease: a salty question? Am J Kidney Dis. 2004;43:782–95.
72. Cianciaruso B, Bellizzi V, Minutolo R, Colucci G, Bisesti V, Russo D, et al. Renal adaptation to dietary sodium restriction in moderate renal failure resulting from chronic glomerular disease. J Am Soc Nephrol. 1996;7(2):306–13.
73. Konishi Y, Okada N, Okamura M, Morikawa T, Okumura M, Yoshioka K, Imanishi M. Sodium sensitivity of blood pressure appearing before hypertension and related to histological damage in IgA nephropathy. Hypertension. 2001;38(1):81–5.

74. Sachdeva A. WederAB: nocturnal sodium excretion, blood pressure dipping and sodium sensitivity. Hypertension. 2006;48:527–33.
75. Salles GF, Cardoso CR, Pereira VS, Fiszman R, Muxfeldt ES. Prognostic significance of a reduced glomerular filtration rate and interaction with microalbuminuria in resistant hypertension: a cohort study. J Hypertens. 2011;29:2014–23.
76. Salles G, Cardoso C, Fiszman R, Muxfeldt E. Prognostic importance of baseline and serial changes in microalbuminuria in patients with resistant hypertension. Atherosclerosis. 2011;216:199–204.
77. de Beus E, Bots ML, van Zuilen AD, Wetzels JF, Blankestijn PJ, MASTERPLAN Study Group. Prevalence of apparent therapy-resistant hypertension and its effect on outcome in patients with chronic kidney disease. Hypertension. 2015;66(5):998–1005.
78. Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med. 2002;347(16):1256–61.
79. Christen AI, Armentano RL, Miranda A, Graf S, Santana DB, Zócalo Y, et al. Arterial wall structure and dynamics in type 2 diabetes mellitus methodological aspects and pathophysiological findings. Curr Diabetes Rev. 2010;6:367–77.
80. Weir MR, Townsend RR, Fink JC, Teal V, Anderson C, Appel L, et al. Hemodynamic correlates of proteinuria in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2403–10.
81. Sanders PW. Vascular consequences of dietary salt intake. Am J Physiol Renal Physiol. 2009;297:F237–43.
82. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003; 42(5):1050–65.
83. Agarwal R, Light RP. GFR, proteinuria and circadian blood pressure. Nephrol Dial Transplant. 2009;24(8):2400–6.
84. De Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110(8):921–7.
85. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M. Alberta kidney disease network. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303(5):423–9.
86. De Nicola L, Minutolo R, Bellizzi V, Zoccali C, Cianciaruso B, Andreucci VE, et al. Achievement of target blood pressure levels in chronic kidney disease: a salty question? Am J Kidney Dis. 2004;43(5):782–95.
87. De Nicola L, Minutolo R, Gallo C, Zoccali C, Cianciaruso B, Conte M, et al. Management of hypertension in chronic kidney disease: the Italian multicentric study. J Nephrol. 2005; 18(4):397–404.
88. De Nicola L, Conte G, Chiodini P, D'Angiò P, Donnarumma G, Minutolo R. Interaction between phosphorus and parathyroid hormone in non-dialysis CKD patients under nephrology care. J Nephrol. 2014;27(1):57–63.
89. De Nicola L, Provenzano M, Chiodini P, Borrelli S, Garofalo C, Pacilio M, et al. Independent role of underlying kidney disease on renal prognosis of patients with chronic kidney disease under nephrology care. PLoS One. 2015;10(5):e0127071.
90. Borrelli S, De Nicola L, Stanzione G, Conte G, Minutolo R. Resistant hypertension in non-dialysis chronic kidney disease. Int J Hypertens. 2013;2013:929183.
91. Koomans HA, Roose JC, Mees EJD, Delawi IMK. Sodium balance in renal failure: a comparison with normal subjects under extremes of sodium intake. Hypertension. 1985; 7(5):714–21.
92. Pimenta E, Gaddam KK, Oparil S, Aban I, Husain S, Dell'Italia LJ, Calhoun DA. Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension. 2009;54(3):475–81.

93. Slagman MCJ, Waanders F, Hemmelder MH, Woittiez AJ, Janssen WM, Lambers Heerspink HJ, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. BMJ. 2011;343:d4366.
94. Rose BD. Diuretics. Kidney Int. 1991;39(2):336–52.
95. Dal Canton A, Fuiano G, Conte G, Terribile M, Sabbatini M, Cianciaruso B, Andreucci VE. Mechanism of increased plasma urea after diuretic therapy in uraemic patients. Clin Sci. 1985;68(3):255–61.
96. Fliser D, Schröter M, Neubeck M, Ritz E. Coadministration of thiazides increases the efficacy of loop diuretics even in patients with advanced renal failure. Kidney Int. 1994; 46(2):482–8.
97. Moser M. Why are physicians not prescribing diuretics more frequently in the management of hypertension? JAMA. 1998;279(22):1813–6.
98. Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, Pimenta E, Aban I, Oparil S, Calhoun DA. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. Arch Intern Med. 2008;168(11): 1159–64.
99. de Souza F, Muxfeldt E, Fiszman R, Salles G. Efficacy of spironolactone therapy in patients with true resistant hypertension. Hypertension. 2010;55:147–52.
100. Vaclavík J, Sedlak R, Plachy M, Navrátil K, Plásek J, Jarkovsky J, et al. Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): a randomized, double-blind, placebo-controlled trial. Hypertension. 2011;57:1069–75.
101. Lobo MD, de Belder MA, Cleveland T, Collier D, Dasgupta I, Deanfield J, et al.; British Hypertension Society; British Cardiovascular Society; British Cardiovascular Intervention Society; Renal Association. Joint UK societie' 2014 consensus statement on renal denervation for resistant hypertension. Heart. 2015;101:10–16.
102. Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension. 2014;63(5):991–9.