Chapter 6
Risk Stratification of Resistant Hypertension in Chronic Kidney Disease

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Introduction

Resistant hypertension (RHTN) is an important clinical issue which may arise due to many etiological risk factors and host various comorbidities and is increasing gradually. Due to its negative effect on cardiovascular morbidity and mortality, ultimate care has to be taken as regard to its diagnosis, and it has to be contemplated and treated effectively.

However, sometimes ambiguity may occur in the terminology: According to the American Heart Association (AHA), the definition of treatment-resistant hypertension (TRH) is the arterial blood pressure (BP) values which, pursuant to office measurements, ideally also include diuretic treatment and which are higher than the target value despite three antihypertensive applied at optimal doses or which may be taken (or sometimes may not be taken) under control by means of four or more antihypertensive. In order to be able to make this diagnosis, pseudoresistance (including white coat hypertension) has to be excluded, since while in true resistant hypertension there is a high cardiovascular risk, the risk rate in pseudoresistant hypertension (PRH) is low. Because real distinction cannot be made in the majority of studies, we will use the term "apparent-treatment resistant hypertension (aTRH)". aTRH is defined as arterial blood pressure (ABP) that remains above goal, despite concurrent use of three or more antihypertensive medications from different classes or use of four or more antihypertensive medication classes regardless of ABP level [1, 2] The definitions which maybe classified under RHTN terminology and their potential risks are presented in Table 6.1.

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Table 6.1 Risk factors apart from BP

Type of Hypertension	Definition	Implicated risks
Resistant hypertension (RH)	BP that remains above the target value despite the concurrent use of three antihypertensive agents of different classes [1, 2]. Consequently, patients with a BP that is controlled with four or more drugs should be diagnosed to have RH	The application of ABPM identified a high rate (43% in Nicola's study) of subjects for whom BP control was considered adequate by office measurement but whose conditions were actually suboptimal [3]. ABPM may prevent undertreatment which may be omitted in routine surveillance
Apparent resistant hypertension (aTRH)	Uncontrolled clinic BP (i.e., equal to or greater than 140/90 mmHg) which prevails in spite of the prescription of three or more antihypertensive drugs or which requires the prescription of four or more drugs to be controlled	These patients have higher risks for cardiorenal events. aTRH causes a 1.5 times higher risk (95% CI, 0.8–3.0) of a cardiovascular endpoint in comparison to controlled hypertensives [4]. aTRH also increases the ESRD risk by 2.3 times (95% CI 1.4–3.7) [4]. Following the adjustment of multiple variables: man gender, black race, large waist circumference, diabetes mellitus, history of myocardial infarction or stroke, statin use, and lower eGFR and higher albumin-to-creatinine ratio levels were found to be associated with aTRH among individuals with CKD [5]
True resistant hypertension (TRH)	Uncontrolled clinic BP in spite of being compliant with an antihypertensive regimen which consists of three or more drugs (including a diuretic), each at optimal doses; also uncontrolled BP confirmed by 24-h ABPM	Prevalent in about one-fourth of CKD patients. Very high cardiorenal risk. Presence of mild-to-advanced GFR reduction and/or microalbuminuria amplifies the cardiovascular risk. The combination of ABPM with the diagnosis of RH enables a better risk stratification, especially in CKD patients. TRH may blunt the prognostic value of DM, high proteinuria, or low GFR. TRH is characterized by high sodium sensitivity of BP. Recommended to be surveyed in tertiary care centers and treated aggressively

(continued)

Table 6.1 (continued)

Type of Hypertension	Definition	Implicated risks
Pseudoresistant hypertension	Pseudoresistance refers to poorly controlled hypertension that seems to be treatment resistant but is, in fact, attributable to other factors (e.g., inaccurate measurement of BP, poor adherence to antihypertensive therapy, suboptimal antihypertensive therapy, poor adherence to lifestyle and dietary approaches to lower BP, white coat hypertension)	Pseudoresistant patients are similar to control based on ABPM profiles, target organ damage (prevalence of LVH and severity of renal disease), and long-term prognosis. Pseudoresistant CKD patients should be identified to provide correct prognostic information and, more importantly, to avoid aggressive antihypertensive therapy. A tighter control of BP merely on the basis of the detection of elevated BP in the office might cause patients to be exposed to ischemia-induced worsening of cardiorenal damage [6–8] and eventually convert their prognosis from favorable to unfavorable. In the Spanish ABPM registry, 12% of the 68,045 patients examined were diagnosed as RH; however, after ABPM, as many as 37% of them were identified as pseudoresistant [9]. In clinical practice, lack of adherence is frequently seen. As a matter of fact, about half of the patients with hypertension withdraw from the therapy within the first year following the diagnosis
White coat hypertension	Hypertension in patients with office readings indicating an average of more than 140/90 mmHg and with reliable out-of-office readings indicating an average of less than 140/90 mmHg. Having the BP in the office taken by a nurse or technician, rather than the clinician, may minimize the white coat effect	Cardiovascular risk is not increased or slightly increased compared with normal population. However it poses increased risk for developing persistent HT [7, 8]

Renal and Cardiovascular Risk of RHTN

There is very close correlation between hypertension (HT) and kidney diseases. While HT can lead to kidney disease, it may also become a result of renal disease. Almost all end-stage renal disease (ESRD) patients are hypertensive. In the US, the HT frequency in CKD is around 85% [10]. In Europe, hypertensive nephrosclerosis is one of the most common reasons of ESRD, and its rate in ESRD patients is 17% [11]. On the other hand, the control rate of HT in CKD patients is at quite low levels [12]. There are not enough studies on the TRH frequency in chronic kidney disease (CKD) patients or on its effects on patient survival. According to the US Renal Data

System, the aTRH rate among treated ESRD patients is 24% [13]. In the MASTERPLAN study performed in the Netherlands on 788 CKD patients, the aTRH frequency was demonstrated as 34% according to the office measurements and as 32% according to the ambulatory blood pressure monitoring (ABPM). The study has demonstrated, on a surveillance of an average of 5.3 years, the development of cardiovascular disease (CVD) endpoint in 17% and ESRD in 27% of the aTRH patients [4]. Based on these findings, it may be reported that the kidneys of patients that could not be treated well or that have resistant hypertension are a highly affected end organ. In the Framingham study, the 10-year coronary risk in the aTRH group, which comprises also obesity and CKD, is above 20% [14]. One of the most important studies made on this issue in CKD patients is a study performed by De Nicola et al. [3]. In this study, in which 436 CKD patients from four centers were included, the cardiovascular risk (hazard ratio [95% confidence interval (CI)]) was 1.24 (0.55–2.78) in pseudoresistance, 1.11 (0.67–1.84) in sustained hypertension, and 1.98 (1.14–3.43) in true resistance, compared with control subjects. Corresponding hazards for renal events were 1.18 (0.45–3.13), 2.14 (1.35–3.40), and 2.66 (1.62–4.37), respectively. The authors stated that in CKD, pseudoresistance is not associated with an increased cardiorenal risk, and sustained hypertension predicts only renal outcome and that true resistance is prevalent and identifies patients carrying the highest cardiovascular risk [3]. Moreover, in case of dialysis patients, 45% of the mortality cases result from cardiac events [15]. In the meta-analysis performed by Heerspink et al. [16], the reduction of systolic BP in dialysis patients by 4–5 mmHg and the diastolic BP by 2–3 mmHg significantly reduced mortality. In this regard, the ALLHAT study has been significantly indicative [17]. The patient population of the study was evaluated as a result of an average surveillance time of 4.9 years between the years 1998 and 2002, whereby 33.357 persons were admitted to the study and 14.687 persons concluded it. In the study, aTRH was determined to be in correlation with CVD, coronary heart disease (CHD), peripheral arterial disease, heart failure (HF), and ESRD. In the US National Health and Nutrition Examination Survey, Egan et al. [14] have reported the aTRH rate in hypertensive patients as 11.8%. The problem in the aTRH studies made is that there are quite less findings regarding the real relation between RHTN and CVD as already stated at the beginning. Whereas in the ALLHAT study, these findings were demonstrated clearer. aTRH was found to be in correlation with the study's outcome points, i.e., CHD, stroke, CVD, all-cause mortality, HF, and ESRD. The relationship between aTRH and outcome points are independent from other two important risk factors that are smoking and the estimated filtration rate. Moreover, aTRH also leads to increased risk in the diabetes mellitus (DM) and CHD patients groups.

In some HT studies, true determination of aTRH is quite important as well. In the REACH registry [18], the aTRH systolic/diastolic blood pressure value was taken as ≥140/90 mmHg, whereas in case of DM or chronic renal failure (CKD) as ≥130/80 mmHg. One of the important findings of ALLHAT is that aTRH gives similar results in black and white patients. However, the aTRH rate was found to be higher in black persons in all studies. aTRH was found to be directly associated especially with CVD and renal disease in all studies [17, 18].

Risk Stratification

In the determination of aTRH, it is also important in terms of risk stratification to exclude white coat hypertension in the office measurements. In the study performed by De Nicola et al. [3], ABPM has been made on patients with an office BP of 130/80 mmHg in order to exclude PRH, whereby BP 127/75 mmHg was considered as limit value. As a result of the study, the TRH rate was found to be 23%.

Although the studies focusing prognosis of RHTN in CKD patients are scarce, some new indirect evidence have emerged. In the recently published study, SPRINT study, 28% of the participants were CKD patients; it has been shown that lower systolic BP target (≤120 mmHg) has better cardiovascular outcomes compared with higher systolic blood pressure target (≤140 mmHg) [19]. In this study, renal and composite outcomes were similar between both BP arms, but in non-CKD group, lower BP arm showed significant worse renal outcomes than in the standard-treatment group (defined by a decrease in the eGFR of 30% or more to a value of less than 60 mL/min/1.73 m^2; 1.21% per year vs. 0.35% per year; hazard ratio, 3.49; 95% CI, 2.44–5.10; $P < 0.001$). Although some of resistant HT might be excluded because of the design of the study (patients using too many drugs or with extreme BP were not included), the further analyses of CKD subgroup this study will give invaluable information for both BP goals and the risk management of this CKD group. In their prospective study of 531 RHTN patients, Salles et al. [20] investigated the associations between reduced GFR and endpoints and interaction with microalbuminuria. After a median follow-up of 4.9 years, reduced GFR was an independent predictor of increased cardiovascular morbidity and mortality in these RHTN patients. Moreover, the presence of both reduced eGFR and microalbuminuria significantly increased cardiovascular risk in relation to one or another isolated, with hazard ratios of 3.0 (1.7–5.3), 2.9 (1.5–5.5), and 4.6 (2.2–10.0), respectively, for the composite endpoint, all-cause, and cardiovascular mortality.

In the 2013 ESH/ESC Guidelines for the management of arterial hypertension [21], risk stratification according to BP values was made as shown in Table 6.2. The most remarkable finding here is that in case of CKD prevalence, the patients are included in the high-risk group already from grade 1 hypertension level. The risk factors of this guideline apart from BP were specified as shown in Table 6.3. Here, subjects with an eGFR below 30 ml/min/1.73 m^2 and proteinuria above 300 mg/day, seem to have critical risk. In the JNC-7, published in 2003, cardiovascular risk factors were specified as follows: Major risk factors: target organ damage, hypertension, cigarette smoking, obesity (body mass index ≥30 kg/m^2), physical inactivity, dyslipidemia, diabetes mellitus, microalbuminuria or estimated GFR <60 mL/min, age (older than 55 for men, 65 for women), and family history of premature cardiovascular disease (men under age 55 or women under age 65) [22]. On the other hand, in the NKF K/DOQI guidelines [23], it is recommended to adjust antihypertensive treatment doses according to the systolic BP, GFR, and serum potassium follow-up in CKD patients with hypertension, and risk stratification is attempted to be made accordingly (Table 6.4). For CKD patients, ABPM becomes more important

Table 6.2 Stratification of total CV risk in categories of low, moderate, high, and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage, or symptomatic CVD

Other risk factors, asymptomatic organ damage or disease	High normal SBP 130–139 or DBP 85–89 mmHg	Grade 1 HT SBP 140–159 or DBP 90–99 mmHg	Grade 2 HT SBP 160–179 or DBP 100–109 mmHg	Grade 3 HT SBP ≥180 or DBP ≥110 mmHg
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥ 3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

Subjects with a high normal office but a raised out-of-office BP (masked hypertension) have a CV risk in the hypertension range. Subjects with a high office BP but normal out-of-office BP (white-coat hypertension), particularly if there is no diabetes, OD, CVD, or CKD, have lower risk than sustained hypertension for the same office BP

BP blood pressure, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *HT* hypertension, *OD* organ damage, *RF* risk factor, *SBP* systolic blood pressure

day by day in terms of risk stratification. The main issue is how to implement this application in practice, because there are also other points to be determined such as TRH. In the ABPM of a group of patients, for whom TRH was not identified and whose office BP was found to be normal, HTN and a CVD increase was determined in them as well. It was demonstrated that masked HTN also constitutes an important risk factor [24]. Hence this circumstance increases the importance of ABPM. One of the important functions of ABPM is that it allows to detect the patients' dipper or non-dipper distinctions. In non-dippers the CVD rate is two times higher [24].

Evaluation of Other Possible Factors

Apart from these, there are many other factors in the development of resistance in CKD. Renal artery stenosis is mostly a result of atherosclerosis, and its rate in CKD is around 5.5%. Since it is mostly asymptomatic, it is hard to know its real rate, and it is a significant RHTN and CVD risk factor. Increased arterial stiffness is a significant risk factor that is frequently seen in CKD patients and that is accompanied by RHTN. In CKD, increased arterial stiffness depends on many pathological

Table 6.3 Definitions and implicated risks related to resistant hypertension

Risk Factors
Male sex
Age (men ≥55 years, women ≥65 years)
Smoking
Dyslipidemia
Total cholesterol >4.9 mmol/L (190 mg/dL)
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL)
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL)
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity (BMI ≥30 kg/m^2)
Abdominal obesity (waist circumference: men ≥102 cm, women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years, women aged <65 years)
Asymptomatic Organ Damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV.ms)
Echocardiographic LVH (LVM index: men >115 g/m^2, women >95 g/m^2 [BSA])[a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle brachial index <0.9
Microalbuminuria (30–300 mg/24 h) or albumin–creatinine ratio (30–300 mg/g, 3.4–34 mg/mmol) (preferentially on morning spot urine)
Diabetes Mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements
HbA1c >7% (53 mmol/mol)
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or Renal Disease
Cerebrovascular disease: ischemic stroke, cerebral hemorrhage, transient ischemic attack
CHD: myocardial infarction, angina, myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73 m^2 (BSA); proteinuria (> 300 mg/24 h)
Advanced retinopathy: hemorrhages or exudates, papilloedema

Abbreviations: *BMI* body mass index, *BP* blood pressure, *BSA* body surface area, *CABG* coronary artery bypass graft, *CHD* coronary heart disease, *CKD* chronic kidney disease, *CV* cardiovascular, *CVD* cardiovascular disease, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *IMT* intima-media thickness, *LVH* left ventricular hypertrophy, *LVM* left ventricular mass, *PCI* percutaneous coronary intervention, *PWV* pulse wave velocity

[a]Risk maximal for concentric LVH: increased LVM index with a wall thickness/radius ratio of 0.42

Table 6.4 Follow-Up evaluation intervals in CKD recommended by NKF K/DOQI Guidelines (23)

Clinical condition	After initiation or increase in dose of antihypertensive therapy	
	4–12 weeks	<4 Weeks
SBP (mmHg)	120–139*	≥140 or <120
GFR (mL/min/1.73 m^2)	≥60	<60
Early GFR decline (70)	<15	≥15
Serum potassium (meq/L)	>4,5[a] or ≤4,5[b]	≤4,5[a] or >4,5[b]
	After blood pressure is at goal and dose is stable	
	6–12 months	*1–6 months*
GFR (mL/min/1.73 m^2)	≥60	<60
GFR decline (mL/min/1.73 m^2 per year)	<4 (slow)	≥4 (fast)
Risk factors for faster progression of CKD	No	Yes
Risk factors for acute GFR decline	No	Yes
Comorbid conditions	No	Yes

Clinicians are advised to evaluate each parameter and select the follow-up interval for the parameter that requires the earliest follow-up

[a]For thiazide of loop diuretic therapy

[b]For ACE inhibitor or ARB therapy

*120–129 mmHg to monitor for hypertension;130–139 mmHg to reach blood pressure goal

mechanisms. Vascular calcification, chronic volume loading, inflammation, endothelial dysfunction, oxidative stress, and activation of the renin angiotensin aldosterone system are the known mechanisms. Obesity and obstructive sleep apnea (OSA) are other risk factors. The relation between RHTN and OSA is known and has also been shown in the studies made with dialysis patients [25].

The inaccuracy and insufficiencies in the use of antihypertensive medicine or the uncontrolled use of other drugs effecting BP are significant reasons of RHTN. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors are drugs that are used very commonly and affect BP control easily. Sympathomimetic agents (including decongestants, diet pills, and cocaine), glucocorticoids, and corticosteroids are further significant drug groups that lead to RHTN. Other agents include oral contraceptives, erythropoietin, cyclosporine, herbal compounds, and natural licorice [26]. Obesity (BMI ≥30), age above 55 for men and 65 for women, and smoking (especially 20 cigarettes/day and above), and alcohol consumption of more than three portions a day may be stated as the other risk factors [21, 26].

A subject that should not be disregarded in CKD patients is the resistance caused by secondary diseases. There are prospective and retrospective studies which demonstrate that primary hyperaldosteronism is prevalent in 11–20% of resistant hypertension patients [27, 28]. Endocrinological diseases such as pheochromocytoma, Cushing syndrome, and hyperparathyroidism are further secondary reasons for resistance [27, 28].

Apart from all these, in about 10% of the RTHN patients, there cannot be identified any risk factor, considering them to be associated with genetic and environmental factors [29].

It should not be disregarded that in CKD patients, DM is an important risk factor and that it shall cause the disease to progress rapidly particularly when combined with uncontrolled hypertension [30]. Likewise dyslipidemia, which is often accompanying hypertension, is a frequently seen cardiac risk factor in CKD patients [30, 26].

Along with all these risk factors, the extension of resistant hypertension duration in CKD patients increases CVD and mortality significantly [5, 31, 32]. Particularly, in patients with a low glomerular filtration rate and high urinary albumin creatinine ratio, RHTN is higher. The use of these laboratory findings in risk assessment shall be useful for the treatment approach [32, 33].

An algorithmic approach to the RHTN for stratification of the renal and cardiovascular risk was presented in Fig. 6.1.

Conclusions

RHTN is a significant reason for morbidity and mortality in CKD patients. A major part of the patients die due to cardiac reasons. First of all, it should be identified whether these patients are true RTHN, and risk stratification should be determined well by taking into consideration all risks explained. Every successful treatment approach to be made towards risk factors shall reduce morbidity and mortality significantly.

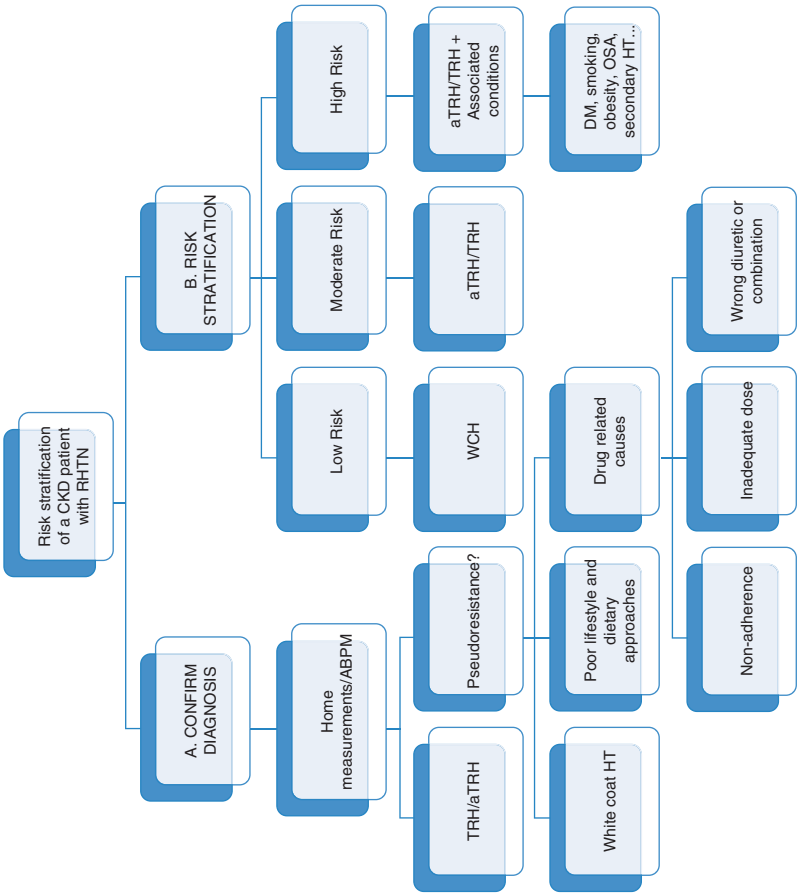

Fig. 6.1 Algorithmic approach to RHTN for renal and cardiovascular risk stratification

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