Chapter 5
Resistant Hypertension in Chronic Kidney Disease

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Introduction

Resistant hypertension was first formally defined in the seventh report of the US Joint National Committee on Prevention, Detection, Evaluation of High Blood Pressure (JNC-7) as failure to achieve goal blood pressure (BP) <140/90 mmHg [or <130/80 mmHg for patients with chronic kidney disease (CKD) and diabetes] in patients who are adherent to maximal tolerated doses of ≥3 antihypertensive medications, including a diuretic [1]. Following this definition, those who are able to reach goal BP on treatment with ≥4 antihypertensive drugs are commonly classified as having controlled resistant hypertension [1]. In addition, the term "refractory hypertension" was introduced for patients who meet the definition of resistant hypertension, but their BP remains uncontrolled despite the use of ≥4 antihypertensive medications at maximally tolerated doses [2–4].

Prior to these definitions, the prevalence of resistant hypertension in the general population was poorly defined, since relevant data on the epidemiology of resistant hypertension were obtained from indirect sources, such as cross-sectional studies on hypertension control, large retrospective studies from tertiary referral centers, and hypertension outcome trials [5]. In recent years, large-scaled population studies including detailed records of the prescribed antihypertensive medication, although suffering from inherent limitations related to common causes of pseudo-resistance, provided more direct estimates of the burden of resistant hypertension, offering insight into an important issue [6]. Resistant hypertension is currently estimated to

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affect about 9–12 % of hypertensives in the general population. Furthermore, recent studies on large cohorts of patients with CKD showed that resistant hypertension affects about 20–35 % of people with CKD depending on the stage of the disease [6]. This higher burden of resistant hypertension in the CKD setting may be relevant to specific factors associated with kidney damage per se, such as impaired sodium handling leading to volume overload, excessive activation of the sympathetic nervous system (SNS), accelerated arterial stiffness, and endothelial dysfunction [6–8]. Importantly, a growing body of evidence from prospective observational studies started to shed light on the prognostic implications of resistant hypertension, showing that this entity is a strong and independent predictor of adverse cardiovascular outcomes and progression to end-stage renal disease (ESRD) [9, 10].

This chapter discusses the currently available evidence on the prevalence, incidence, and prognosis of resistant hypertension, offering also insights into factors associated with pseudo-resistance and true resistance to antihypertensive treatment among patients with CKD.

Pseudoresistant Hypertension

Before discussing in detail the pathogenesis and epidemiology of resistant hypertension, it is crucial to distinguish true resistance to therapy from the phenomenon of pseudo-resistance [3]. Pseudo-resistance relates to the appearance of uncontrolled BP under appropriate therapy with at least three antihypertensive agents in patients who have well-controlled hypertension. An important step in diagnostic evaluation of a patient with suspected resistant hypertension is the investigation and exclusion of specific factors giving falsely the impression of drug resistance, such as improper BP measurement technique, heavily calcified arteries that are difficult to compress, inappropriate doses of drugs or prescription of drug classes that are not synergistic in reducing BP, and, most importantly, poor compliance to the prescribed antihypertensive regimen and white-coat hypertension [3].

Non-Adherence to Therapy

Poor compliance to the prescribed antihypertensive therapy is a major factor contributing to pseudo-resistance. It is estimated that approximately 50 % of patients with newly diagnosed hypertension who initiate drug therapy stop following the regimen within the first year of diagnosis [11, 12]. Other studies show significant reductions in the percentage of patients who remain compliant with their antihypertensive regimen in the long-term; 5–10 years after the onset of antihypertensive treatment, only 10–15 % of the originally treated patients are still adherent to their regimen [13]. Prevalence of non-adherence among patients presenting with resistant hypertension is likely to be much higher than originally reported, since recent

clinical studies using urinary therapeutic drug monitoring to evaluate drug intake without patients' awareness of the test have shown that the majority of resistant patients were either poorly adherent or totally non-adherent to their drug therapies [14]. Potential factors contributing to poor compliance include drug-related side effects, complicated dosing schedules, poor relationship between physicians and patients, failure to educate the patient on the significance of achieving adequate hypertension control, and high costs of therapy [3].

Drug adherence should be addressed during every follow-up visit, with specific questions that emphasize on the importance of long-term compliance with therapy [15]. Drug adherence monitoring is suggested to be a beneficial approach to distinguish patients with uncontrolled BP who exhibit perfect compliance to the prescribed regimen and are possibly in need of additional diagnostic evaluations and therapeutic interventions from patients who are non-adherent and require interventions aiming to improve long-term acceptance of the need to receive antihypertensive treatment. In an observational study including 41 patients with hypertension resistant to a triple-drug regimen, Burnier and co-workers showed that electronic compliance monitoring over a 2-month period was associated with significant reductions in ambulatory BP by 11 mmHg in systolic and 9 mmHg in diastolic BP. After the 2-month monitoring period, about one third of patients on monitoring adherence normalized their BP, whereas another third of patients improved their BP control without any modification in the background antihypertensive treatment throughout the study [16]. Single-pill antihypertensive combinations were shown to improve patient compliance and can be of particular help to overcome the problem of polypharmacy [17, 18].

White-Coat Effect

The white-coat effect [i.e., an elevation in BP that occurs during clinic visits with normal out-of-office BP recordings obtained either with home or with ambulatory BP monitoring (ABPM)] is another important component of pseudo-resistance [3, 19]. Earlier studies using ABPM in order to confirm the diagnosis of resistant hypertension suggested that approximately 30 % of patients classified as resistant hypertensives on the basis of office BP measurements indeed had normal ambulatory BP values [20, 21]. A more recent analysis of the Spanish Ambulatory Blood Pressure Monitoring Registry incorporating office and ambulatory BP data from 68,045 patients receiving drug treatment for hypertension aimed to clarify the influence of white-coat phenomenon on identification of true drug resistance [22]. In this study, a total of 8295 patients met the definition of resistant hypertension on the basis of conventional office BP recordings (i.e., uncontrolled office BP >140/90 mmHg under treatment with ≥3 antihypertensive drugs, including a diuretic). However, when resistant hypertension status was determined according to the ambulatory BP values, only 5182 of these patients (62.5 %) had truly resistant hypertension, whereas the remaining 3113 patients (37.5 %) had normal ambulatory BP and were classified

as white-coat resistant hypertensives [22]. A subsequent analysis from the Spanish ABPM registry showed that the prevalence of white-coat hypertension among patients with CKD is as high as 28.8 %, suggesting that the white-coat phenomenon is also quite common in these patients and should not be neglected in diagnostic approach of a patient with suspected resistant hypertension [23].

Apart from its usefulness in confirmation of the diagnosis of resistant hypertension, performance of ABPM offers several additional advantages in improving cardiovascular risk stratification of the patients [24], particularly in the setting of CKD. In this regard, ABPM provides the ability to record BP during the night-time period and to identify the presence of a "non-dipping" pattern, which is the diminution or reversal of the normal 10–20 % nocturnal fall in BP [24]. A growing body of evidence suggests that elevated night-time BP is stronger predictor of all-cause and cardiovascular mortality than day-time BP, whereas a non-dipping status has been shown to confer a twofold higher risk for cardiovascular morbidity and mortality in comparison with a normal dipping pattern, independently from the presence of hypertension [25–27]. In addition, ABPM enables the identification of masked hypertension, which is defined as abnormally elevated out-of-office BP while BP measurements during clinic visits remain within the normal range [24]. Notably, in a recent observational study, in which 489 outpatients treated for hypertension with stage 2–4 CKD were prospectively followed for a median period of 5.2 years, masked hypertension was associated with 3.17 times higher risk for the occurrence of a composite cardiovascular endpoint consisting of fatal and nonfatal myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and non-traumatic amputation relative to controlled office and ambulatory BP [28]. Masked hypertension was also associated with a threefold greater risk for the combined renal endpoint of initiating dialysis or death. The overall cardio-renal risk attributable to masked hypertension was comparable with that of uncontrolled hypertension [28].

Truly Resistant Hypertension and Its Potential Causes in Chronic Kidney Disease

Renal parenchymal disease is considered as one of the most common medical causes of resistant hypertension. Multiple pathways associated with impaired renal function are likely to contribute to the development of resistance to antihypertensive drug treatment. These mechanistic factors are summarized in Table 5.1 and are discussed in detail below.

Sodium and Volume Overload

A key factor responsible for many cases of resistant hypertension is excessive dietary salt intake leading to chronic volume overload [29]. This is supported by several studies showing that the vast majority of patients with resistant hypertension

Table 5.1 Factors contributing to antihypertensive drug resistance in CKD

Sodium and volume excess
Sympathetic nervous system overactivity
Overactivity of the renin–angiotensin–aldosterone-system
Increased endothelium-derived vasoconstrictors
Decreased endothelium-derived vasodilators
Arterial stiffness
Pre-existing hypertension
Specific medications (cyclosporine, tacrolimus, steroids, erythropoietin)

have expanded plasma volume, which is causally related to a higher salt intake in comparison with the general population [30]. In a pilot, randomized, cross-over study including 12 patients with uncontrolled hypertension despite receiving therapy with an average of 3.4 antihypertensive agents, Pimenta et al. compared the effects of a low (50 mmol/24 h) versus a high (250 mmol/24 h) sodium-containing diet on office and 24-hour ambulatory BP [31]. The mean urinary sodium excretion was significantly lower during the low-sodium than during the high-sodium intake period (46.1 ± 26.8 vs 252.2 ± 64.6 mmol/24 h). Dietary sodium restriction was associated with remarkable reductions in office BP, by 22.7 and 9.1 mmHg in systolic and diastolic BP, respectively. These BP-lowering effects were consistent during the whole 24-hour period [31]. Thus, sodium restrictive diet should be considered as an important part of the therapeutic approach of patients with resistant hypertension, particularly when CKD is present.

The major factor contributing to salt and fluid accumulation in patients with CKD is impaired renal sodium handling and reduced capacity of the kidney to excrete daily sodium intake. Reduced nephron number and the potential excess of multiple sodium-retaining hormones such as aldosterone and endothelin create a sizable barrier to efficient urinary sodium excretion [31–33]. Overactivity of the SNS, particularly when CKD is accompanied by other co-morbid conditions such as diabetes and heart failure, is another factor that may promote sodium retention [34, 35]. Failure to use diuretic agents in appropriate doses adjusted to the level of renal function is another major issue affecting efficient sodium excretion, resulting in antihypertensive drug resistance. In patients with an estimated glomerular filtration rate (eGFR) <40 ml/min/1.73 m^2, thiazide diuretics are unlikely to be effective, with a possible exception of metolazone, which is probably active down to an eGFR of 20 ml/min/1.73 m^2, but is not available in many countries. Preliminary data suggest that chlorthalidone may also be effective in advanced renal failure. However, for eGFR of <30 ml/min/1.73 m^2, loop diuretics are often needed. Use of combinations of loop diuretics with other diuretic compounds may be necessary in selected cases to enhance natriuresis [36].

Sympathetic Overactivity

Activation of the SNS is suggested to play a pivotal role in pathogenesis of hypertension in CKD [8]. The kidney is a richly innervated organ and experimental studies suggest that the kidneys may be modulators of the SNS overactivity; this regulation is mediated through renal afferent nerves connected with integrative nuclei of the SNS in the central nervous system [37]. In animal studies, acute stimulation of these afferent nerves in response to renal ischemia and reperfusion injury was shown to induce a reflex elevation in efferent SNS activity and in BP levels [38, 39]. In experimental models of 5/6 nephrectomized rats, the turnover rate and release of norepinephrine from the posterior hypothalamic nuclei were higher in CKD than in control rats; bilateral dorsal rhizotomy down-regulated the SNS activity and preserved the BP levels within the normal range [40]. In addition, muscle sympathetic nerve activity (MSNA) studies in hemodialysis patients showed that the rate of sympathetic discharge was twice the normal and correlated strongly with the rise in plasma catecholamine levels. In contrast, patients with bilateral nephrectomy manifested lower MSNA, BP, and peripheral vascular resistance as compared with patients with retained native kidneys [41]. Taken together, the studies in animals and in humans support the notion that increased renal sensory impulses originating from the affected kidney and transmitted to the central nervous system activate brain regions involved in the noradrenergic control of BP, resulting in vasoconstriction, sodium retention, and hypertension. However, the exact mechanisms mediating the development of the excessive sympathetic activation within the kidney parenchyma still remain unclear. Other mechanisms potentially responsible for the increase in SNS activity in the CKD setting include decreased central dopaminergic tone, lower baroreceptor sensitivity, elevated plasma β-endorphin and β-lipotropin, increased serum leptin levels, and reduced renalase availability [8, 42].

Overactivity of the Renin–Angiotensin–Aldosterone-System

Excessive activation of the renin–angiotensin–aldosterone-system (RAAS) is suggested to be another major pathway for sustained BP elevation, promotion of end-organ damage, and development of antihypertensive drug resistance, particularly in the setting of CKD. One clear mechanism through which aldosterone excess promotes drug resistance, identified shortly after the discovery of the hormone itself, is its action on the distal nephron of the kidney to regulate intravascular volume and promote sodium reabsorption [43]. The original belief that aldosterone acts solely on specific receptors in epithelial tissues and modulates electrolyte and water balance via a genomic mechanism has been challenged by the identification of mineralocorticoid receptors in non-epithelial tissues, such as heart, vasculature, and the brain, suggesting that aldosterone mediates target-organ damage through non-genomic mechanisms of action [44, 45]. This notion is supported by a number of animal and human studies showing that aldosterone exerts hypertrophic, proliferative,

proinflammatory, prothrombotic, and profibrotic actions in target organs beyond the kidney, inducing endothelial dysfunction, vascular inflammation, fibrosis, and necrosis [44, 45]. This pathologic process leads to functional and structural alterations of small and large arteries, leading to sustained BP elevation. Blocking the adverse actions of aldosterone on the vasculature through selective mineralocorticoid receptor antagonists (MRAs), such as spironolactone and eplerenone, has gained renewed interest as a novel therapeutic approach of resistant hypertension in patients with or without CKD. This notion is strongly supported by the results of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) [46], in which fourth-line add-on therapy with spironolactone administered at a starting dose of 25 mg/day was accompanied by a mean BP reduction of 21.9/9.5 mmHg over a median treatment duration of 1.3 years. With close monitoring of serum potassium levels, add-on MRA therapy could be an effective and safe therapeutic approach of resistant hypertension even in the CKD setting [47, 48].

Arterial Stiffness

A typical feature of arterial remodeling in CKD is long-term structural alterations in intrinsic elastic properties of the arterial wall. These alterations include fibroelastic intimal thickening, calcification of elastic lamellae, increased extracellular matrix deposition, elastinolysis and elevated collagen along with reduced elastic fiber content [49]. This arteriosclerotic process affects mainly the central arteries, such as the aorta and the carotid artery, where cushioning the stroke volume ejected by the left ventricle is essential in order to transform the pulsatile blood flow oscillations into the continuous flow pattern required for perfusion of organs and tissues [49]. The principal mechanism through which arterial stiffness contributes to BP elevation is that higher arterial stiffness (in other words, the higher velocity of pulse wave transfer across the arterial tree) results in premature arrival of reflected wave from the periphery back to the ascending aorta during the systolic phase of the cardiac cycle [50]. Thus, the forward- and backward-traveling pulse waves are in phase and their overlap during systole rather than diastole generates an amplification effect on systolic and pulse pressures in the aorta [49, 50].

The notion that arterial stiffness makes hypertension more resistant to antihypertensive therapy is strongly supported by a post-hoc analysis of the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind (REASON) study [51]. In this study, 375 patients with essential hypertension were treated with either perindopril/indapamide combination (20/0.625 mg daily) or atenolol (50 mg daily) for 12 months. The study found that higher baseline aortic PWV was associated with smaller in extent reductions in office BP levels and that baseline aortic PWV was an independent predictor of achievement of BP control after 12 months of therapy [51]. In addition, a prospective analysis from the Framingham cohort study showed that reduced arterial compliance is a strong and independent predictor of a future diagnosis of hypertension over approximately 8 years of follow-up [52].

The reverse phenomenon was not true, since higher BP levels were unable to predict greater changes in arterial stiffness over time. The role of arterial stiffness as predictor of BP response to the antihypertensive therapy was evaluated in a post-hoc analysis of the Hypertension in Hemodialysis patients treated with Atenolol or Lisinopril (HDPAL) trial. In contrast to the observations in the general population, among hypertensive hemodialysis patients, aortic PWV at baseline was not predictor of the treatment-induced improvement in 44-hour interdialytic ambulatory BP over the course of the trial [53].

Endothelial Dysfunction

An imbalance between endothelium-derived vasoconstrictors and vasodilators in favor of the former may be another mechanistic pathway of resistant hypertension in CKD [8]. This is supported by animal studies showing down-regulation of the endothelial and inducible nitric oxide synthase activity in 5/6 nephrectomized rats, an alteration that resulted in sustained BP elevation [54]. Endothelial dysfunction is suggested to be the result of several mechanisms at play when renal function is impaired. One of these mechanisms is the higher circulating levels of asymmetric dimethylarginine (ADMA) in CKD; ADMA is an endogenous nitric oxide synthase inhibitor and its accumulation results in reduced generation of nitric oxide. The higher levels of ADMA result from both a diminished intracellular degradation by desamino-D-argininehydrolase and by reduced renal clearance of ADMA, since this molecule is mainly excreted by the kidney [55]. Apart from promoting endothelial dysfunction, ADMA also acts as a stimulus for increased generation of proinflammatory mediators, such as interleukin-6 and profibrotic molecules such as transforming growth factor-β [56]. Increased production of the potent endogenous vasoconstrictor endothelin-1 in patients with CKD is proposed to be another important player in pathogenesis of resistant hypertension [57]. The pathologic effects of endothelin-1, including vasoconstriction, inflammation, cellular injury and fibrosis, are mainly mediated by the endothelin-A receptors, which have recently become promising targets of therapy in preclinical and clinical studies [58]. Endothelin receptor blockers have been shown to produce significant reduction in BP among patients with resistant hypertension, but their role in treating this entity in patients with CKD has not been specifically investigated.

Epidemiology of Resistant Hypertension

Prevalence

In the past, the exact prevalence of resistant hypertension in the general hypertensive population was not established, since information on the epidemiology of resistant hypertension was derived from indirect sources (i.e., observations on

hypertension control from population-based studies, retrospective studies from tertiary hypertension centers, and sub-analyses of large randomized clinical trials in hypertension) [59–63]. Identification of the exact burden of resistant hypertension would ideally require properly designed prospective studies using forced titration of BP-lowering therapy up to maximally tolerated doses of ≥3 agents, including a diuretic; ideally, relevant studies should exclude common causes of pseudo-resistance [3]. Population-based studies with detailed record of the prescribed antihypertensive medications would also advance our knowledge; however, such studies would unavoidably suffer from inherent methodological limitations related to common causes of pseudo-resistance (e.g., white-coat effect, non-adherence to therapy, etc.) [3]. More recently, epidemiological studies have been performed to ascertain the prevalence of resistant hypertension. They are summarized in Table 5.2 and discussed in some detail below.

An early retrospective, observational study using electronic medical records of the years 2002–2005 provided the first direct estimate of the prevalence of resistant hypertension in the US hypertensive population [64]. In this analysis, 9.1 % of 29,474 hypertensive participants from an ambulatory care setting (or 12.1 % of drug-treated patients) were classified as having resistant hypertension, according to the definition of uncontrolled BP >140/90 mmHg despite the use of ≥3 antihypertensive medications. Another 6 % of study participants had uncontrolled BP despite receiving ≥4 antihypertensive agents, but not a diuretic. Furthermore, around 29.5 % of participants had uncontrolled BP, without receiving therapy; of these, 10–15 % had resistant hypertension [64].

A subsequent study [65] aimed to determine the prevalence of resistant hypertension in the USA using the 2003–2008 National Health and Nutrition Examination Survey (NHANES) dataset. Resistant hypertension in this survey was defined as BP >140/90 mmHg and reported use of >3 different antihypertensive medications within the previous month or use of ≥4 antihypertensive agents regardless of measured BP. In this analysis, 8.9 % of 5230 participants (or 12.8 % of drug-treated hypertensive participants) met the criteria of resistant hypertension according to the aforementioned definition [65]. Again, another 30.7 % of patients had uncontrolled BP without receiving antihypertensive treatment. Assuming that 10 % of these patients might have had resistant hypertension, the actual prevalence of resistant hypertension might have been another 3 % higher.

Trends in prevalence of uncontrolled hypertension and resistant hypertension during 1988–2008 in the USA were explored in another analysis of 13,375 hypertensive adults participating in the 3 NHANES surveys (1988–1994, 1999–2004, 2005–2008) [66]. Uncontrolled hypertension was defined as BP >140/90 mmHg among drug-treated hypertensives and resistant hypertension was defined as uncontrolled hypertension among treated patients despite the reported use of ≥3 antihypertensive drugs during the previous month. Rates of uncontrolled hypertension declined from 73.2 % in 1988–1994 to 52.5 % in 1999–2004. In contrast, the prevalence of resistant hypertension (expressed as percentage of drug-treated hypertensives) exhibited an increasing trend from 15.9 % in 1988–1994 to 28.0 % in 2005–2008 [66]. When patients with controlled BP treated with ≥4 antihypertensive drugs were also considered as resistant hypertensives, the prevalence of resis-

Table 5.2 Prevalence of resistant hypertension in the general hypertensive population

Study ID	Population characteristics	Definition of resistant hypertension	Prevalence estimates
McAdam-Marx et al. [64] Clin Ther 2009	29,474 US adults with a diagnosis of hypertension in the General Electric Centricity Medical Record	Uncontrolled BP >140/90 mmHg (or >130/80 mmHg for those with diabetes or CKD) with ≥3 antihypertensive drugs, including a thiazide	A total of 2640 out of 29,474 hypertensive patients (9.1 %) were classified as having resistant hypertension
Pershell et al. [65] Hypertension 2011	5230 hypertensive US adults participating in the 2003–2008 NHANES dataset	Uncontrolled BP >140/90 mmHg with ≥3 antihypertensive drugs in the previous month or reported use of ≥4 antihypertensive drugs regardless of BP	A total of 539 out of 5230 hypertensive patients (8.9 %) met the criteria of resistant hypertension
Egan et al. [66] Circulation 2011	13,375 hypertensive US adults from the NHANES datasets in the 3 time-periods (1988–1994, 1999–2004, 2005–08)	Uncontrolled BP >140/90 mmHg with ≥3 antihypertensive drugs in the previous month or reported use of ≥4 antihypertensive drugs regardless of BP	5.5 % of all hypertensives in 1988–1994, 8.5 % of all hypertensives in 1999–2004, and 11.8 % of all hypertensives in 2005–08 had resistant hypertension
Brambilla et al. [68] J Hypertens 2013	1312 drug-treated hypertensive participants of the BP-CARE study	Uncontrolled BP >140/90 mmHg despite the concurrent use of ≥3 antihypertensive medications or use of ≥4 antihypertensive drugs regardless of BP	A total of 255 patients (19.4 % of drug-treated hypertensive patients) were classified as resistant hypertensives
Sim et al. [67] Mayo Clin Proc 2013	470,386 hypertensives participating in the Kaiser Permanente Southern California health system during 2006–2007	Uncontrolled BP >140/90 mmHg despite triple antihypertensive therapy or current use of ≥4 antihypertensive drugs irrespective of BP control	A total of 60,327 participants (12.8 % of all hypertensives) or 15.3 % of those receiving antihypertensive medications fulfilled the diagnostic criteria of resistant hypertension
Weitzman et al. [69] Hypertension 2014	172,432 hypertensive patients belonging to the Maccabi Healthcare System in Israel	Uncontrolled BP >140/90 mmHg despite the treatment with ≥3 antihypertensive drugs at maximally tolerated doses, including a diuretic	0.86 % of the entire hypertensive population (or 2.26 % of hypertensives with uncontrolled BP) had resistant hypertension

US United States, *NAHANES* National Health and Nutrition Examination Survey, *BP* blood pressure, *CKD* chronic kidney disease, *BP-CARE* Blood Pressure control rate and CArdiovascular Risk profilE (BP-CARE) study

tant hypertension among all adult US NHANES hypertensive participants was 5.5 % in 1988–2004, increased to 8.5 % in 1999–2004 and reached 11.8 % in the 2005–2008.

The largest cross-sectional survey so far aiming to estimate the burden of resistant hypertension in the USA [67] used data obtained from 470,386 hypertensive patients participating in the Kaiser Permanente Southern California health system during 2006–2007. By defining resistant hypertension as BP >140/90 mmHg despite triple antihypertensive therapy or current use of ≥4 antihypertensive drugs irrespective of BP control, study investigators observed that 12.8 % of all hypertensives (or 15.3 % of those receiving antihypertensive medications) fulfilled the diagnostic criteria of resistant hypertension [67]. Black race, older age, male gender, obesity, impaired renal function, presence of diabetes, and history of previous cardiovascular disease were the main factors associated with higher risk of resistant hypertension. Paradoxically, rates of adherence to the prescribed antihypertensive regimen were higher among resistant hypertensives than in those with controlled hypertension.

Data on the prevalence of resistant hypertension in Europe were provided by the Blood Pressure control rate and CArdiovascular Risk profilE (BP-CARE) study [68]. Among 1312 drug-treated hypertensive participants, 255 (19.4 % of the study cohort) were classified as suffering from resistant hypertension according to the definition of uncontrolled BP >140/90 mmHg despite the concurrent use of ≥3 antihypertensive medications or use of ≥4 antihypertensive drugs regardless of BP levels [68]. Another recent survey in Israel incorporating data from 172,432 hypertensive patients followed in the Maccabi Healthcare System showed that 0.86 % of the entire hypertensive population (or 2.26 % of hypertensives with uncontrolled BP) had resistant hypertension [69]. Resistant hypertension was defined as uncontrolled BP >140/90 mmHg despite the treatment with ≥3 antihypertensive drugs at maximally tolerated doses, including a diuretic, over the previous month of BP measurement. When analysis was performed taking into account the prescribed antihypertensive medications during the 2 previous months before the BP measurement, instead of the last month, estimated prevalence of resistant hypertension increased to 1.24 % of the entire hypertensive population (or to 3.24 % of those with uncontrolled BP) [69]. These estimates of the prevalence of resistant hypertension are far lower than previously reported. This may be explained by the fact that patients with controlled hypertension under treatment with ≥4 agents were not classified as resistant hypertensives in this survey. Other factors, such as improved patient compliance, reduced physician inertia or even yearly higher average temperatures in the country of the last study compared to the USA, or North Europe may also apply.

Overt or incipient CKD is long considered as common cause of truly resistant hypertension [6]. As discussed above, several factors closely related to impaired renal function (such as greater difficulty of excreting daily salt intake, increased SNS activity, endothelial dysfunction, higher levels of proinflammatory markers, and arterial stiffness) are likely to contribute to antihypertensive drug resistance in the CKD setting [8]. The phenomenon of resistant hypertension in patients CKD is also increasingly studied in recent years. Large epidemiological studies conducted

in the general hypertensive population showed that resistant hypertensives are more likely to have reduced kidney function and micro- or macro-albuminuria, suggesting a higher burden of resistant hypertension in CKD. For example, in the NHANES 2003–2008 dataset, 33.7 % of resistant hypertensives had eGFR <60 ml/min/1.73 m^2 and 12.8 % had albumin-to-creatinine ratio (ACR) >300 mg/g relative to 16.5 and 1.9 % of patients with controlled hypertension, respectively [65]. A retrospective study of 300 patients with hypertension and CKD referred to a nephrology clinic in Italy showed that prevalence of resistant hypertension increased from 26 to 38 % after the first 6 months of standard nephrology care [70]. This observation should not be considered causally related, since simply intensification of antihypertensive therapy may qualify the identification of resistant hypertension, even when BP may be poorly controlled.

Two recent studies with more accurate methodology advanced our knowledge on the prevalence of resistant hypertension in the CKD population (see Table 5.3). The first was an analysis from a population-based sample of US hypertensive adults participating in the Geographic and Racial Differences in Stroke (REGARDS) study during 2003–2007 [71]. Resistant hypertension was defined as uncontrolled BP >140/90 mmHg, despite the current use of >3 antihypertensive drugs or therapy with ≥4 agents regardless of measured BP. Antihypertensive drug use was assessed via pill bottle review of all medications participants reported taking during the previous 2 weeks and BP was measured in the home setting. The original REGARDS study was designed to include 15,277 participants with history of hypertension under treatment with ≥1 antihypertensive drug. In the final cohort of 10,700 patients eligible for determination of their resistant hypertension status, prevalence of resistant hypertension was 15.8 % among those with eGFR ≥60 ml/min/1.73 m^2, but 24.9 % among those with eGFR 45–59 ml/min/1.73 m^2 (Stage 3A CKD) and 33.4 % among those with eGFR <45 ml/min/1.73 m^2 (Stage 3B or more advanced CKD). When participants were classified according to the levels of albuminuria, the prevalence of resistant hypertension was 12.1, 20.8, 27.7, and 48.3 % for ACR <10, 10–29, 30–299, and ≥300 mg/g, respectively [71]. It has to be noted that although the study provided important information, the reported rates of resistant hypertension, even when notably higher than the other reports, may still be an underestimation of the exact prevalence for two reasons: first, at the time of the study, the recommended threshold for BP lowering in CKD was at 130/80 mmHg in the office; second, this study used home BP readings, for which the proposed thresholds for assessment of BP control are lower than the office [72].

Another prospective observational study including 436 patients with hypertension and CKD attending four outpatient nephrology clinics in Italy during 2003–2005 used simultaneously office BP readings and ABPM in order to determine the influence of the white-coat effect on estimation of the prevalence of resistant hypertension [10]. At baseline, study participants were classified into four different categories on the basis of a normal or high ambulatory BP, according to the 125/75 mmHg threshold for mean 24-hour ambulatory BP, and absence or presence of resistant hypertension, defined as office BP >130/80 mmHg despite using ≥3 full-dose antihypertensive drugs, including a diuretic. This study showed that 100 out of 436

Table 5.3 Prevalence of resistant hypertension among patients with chronic kidney disease

Study ID	Population characteristics	Definition of resistant hypertension	Prevalence estimates
Tanner et al. [71] cJASN 2013	10,700 hypertensive US adults participating in the REGARDS study	Uncontrolled BP >140/90 mmHg with ≥3 antihypertensive drugs or use of >4 antihypertensive drugs regardless of BP	15.8 % for eGFR ≥60 ml/min/1.73 m^2; 24.9 % for eGFR 45–59 ml/min/1.73 m^2; 33.4 % for eGFR ≤45 ml/min/1.73 m^2
De Nicola et al. [10] JACC 2013	436 hypertensive CKD patients, defined as office BP >130/80 mmHg and eGFR <60 ml/min/1.73 m^2 or eGFR between 60–90 ml/min/1.73 m^2 and albuminuria >300 mg/day	Uncontrolled office BP >130/80 mmHg with ≥3 antihypertensive drugs, including a diuretic, or >4 drugs and ABP >125/75 mmHg	A total of 100 out of 436 patients (22.9 %) were classified as resistant hypertensives

REGARDS Geographic and Racial Differences in Stroke Study, *BP* blood pressure, *CKD* chronic kidney disease, *ABP* ambulatory blood pressure, *eGFR* estimated glomerular filtration rate

study participants (22.9 %) had true resistant hypertension with high ambulatory BP and 31 participants had white-coat pseudoresistant hypertension (7.1 %). Another 187 participants (42.9 %) had sustained hypertension (i.e., high ambulatory BP without resistant hypertension according to the office readings) and 118 patients (27.1 %) had controlled hypertension (i.e., normal office and ambulatory BP) [10]. Presence of diabetes, left ventricular hypertrophy, higher levels of proteinuria, and poor adherence to a sodium restrictive diet were significant determinants of true resistant hypertension in multivariate analysis. Since publication of the Italian study, the threshold of diagnosis of hypertension in CKD has been changed to 140/90 mmHg. Thus, the estimates provided may well be lower if the new thresholds are utilized.

Incidence of Resistant Hypertension

A recent retrospective cohort study aiming to evaluate the incidence of resistant hypertension in people adequately treated studied 205,750 subjects with newly diagnosed hypertension who participated in two health plan programs within the Cardiovascular Health Network registry in USA during 2002–2006 [9]. Over a 1.5-year follow-up, a total of 42,474 patients (20.6 % of the original study cohort) were receiving ≥3 antihypertensive agents for at least 1-month. After excluding those who were non-adherent, on the basis of a >80 % pharmacy refill rate for all prescribed antihypertensive medications, the investigators showed that 1.5 years after treatment initiation, 1 in 50 patients became resistant to therapy on the basis of the American Heart Association (AHA) definition of having uncontrolled BP >140/90 mmHg on three medications or controlled BP on at least four antihypertensive medications.

This accounts to an incidence rate for resistant hypertension of 1.9 % with a median follow-up of 1.5 years (0.7 cases per person-year of follow-up) [9]. With more extended follow-up, it is likely that the incidence would have been even higher, as the medications were further titrated for the remaining uncontrolled patients; further, on an even longer observational period, the increasing age and worsening obesity would further aggravate the risk of developing resistance to multiple drug therapy. In the presence of CKD, it could be hypothesized that the incidence rate of resistant hypertension might be even higher. However, there is no study to assess the incidence of resistant hypertension in the CKD setting until now.

A post-hoc analysis of data from 3666 previously untreated hypertensive patients participating in the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) provided additional evidence on incidence and possible predictors of resistant hypertension [73]. In ASCOT study, 19,257 hypertensive patients with ≥3 other cardiovascular risk factors were randomly assigned to receive atenolol adding a thiazide diuretic or to amlodipine adding perindopril. ASCOT had a 2×2 factorial design and a subgroup of 10,305 patients was further randomized to atorvastatin or placebo in a lipid-lowering study-arm. Definition of uncontrolled BP (>140/90 mmHg) on treatment with ≥3 antihypertensive drugs was used for identification of resistant hypertension. Among previously untreated hypertensive patients, 33 % (and among all participants 50 %) developed resistant hypertension during a median follow-up of 5.3 and 4.8 years, respectively (incidence rates of 75.2 and 129.7 cases per 1000 person-years, respectively) [73]. Multivariate analysis showed that independent predictors of incident resistant hypertension were raised systolic BP at baseline, diabetes, left ventricular hypertrophy, male gender, obesity, and high alcohol intake. Importantly, patients randomized to receive amlodipine relative to atenolol, those previously administered aspirin and those randomized to atorvastatin relative to placebo were less likely to develop resistant hypertension over the course of the trial [73], suggesting that the initial therapeutic approach after the diagnosis of hypertension may be of relevance for the risk of developing antihypertensive drug resistance.

Prognosis of Resistant Hypertension

In comparison with patients achieving adequate BP control with fewer than three antihypertensive drugs, whether resistant hypertension per se signifies an independent prognostic association with cardiovascular and renal outcomes is an issue that remained unclear until recently. In addition to the cardio-renal risk attributable to the degree of BP elevation [1, 74], several lines of evidence suggest that resistant hypertension is also associated with a combination of other risk factors, which may further aggravate the risk of cardiovascular morbidity and mortality. In this regard, several epidemiological studies provided evidence that more patients with resistant hypertension have target-organ damage, higher number of comorbidities, and higher rates of documented cardiovascular disease than those with controlled hypertension [75–77]. Another source of data supporting the prognostic association of resistant

hypertension with cardiovascular and renal outcomes are clinical studies evaluating the patterns of ambulatory BP profile in patients with resistant hypertension; these studies showed that resistant hypertension is associated with higher ambulatory BP values, a non-dipping night-time BP pattern and higher ambulatory arterial stiffness index [26, 78, 79], factors directly linked with increased risk for cardiovascular morbidity and mortality.

Over the past few years, a number of prospective observational studies evaluating "hard" cardiovascular and renal endpoints have provided additional evidence supporting the strong and independent association of resistant hypertension with adverse outcomes. In the aforementioned study of Daugherty et al. [9], after excluding patients with known history of cardiovascular disease, patients who developed resistant hypertension were more likely to reach the prespecified combined outcome of all-cause mortality, myocardial infraction, congestive heart failure or CKD during a mean follow-up of 3.8 years [unadjusted hazard ratio (HR): 1.54; 95 % confidence intervals (CI): 1.40–1.69] [9]. After adjustment for several risk factors, resistant hypertension remained significantly associated with elevated risk of adverse cardiovascular outcomes (adjusted HR: 1.47; 95 % CI: 1.33–1.62). When patients with pre-existing cardiovascular disease were included in a secondary analysis, patients who developed antihypertensive drug resistance were again more likely to experience an adverse cardiovascular outcome at any time-point of follow-up relative to those without incident resistant hypertension (HR: 2.49; 95 % CI: 1.96, 3.15) [9].

The association of resistant hypertension with cardiovascular outcomes was explored in a prospective study of 53,530 hypertensive patients with subclinical or established atherothrombotic disease enrolled in the international Reduction of Atherothrombosis for Continued Health (REACH) registry [80]. In this analysis, patients with resistant hypertension at baseline exhibited an 11 % higher risk of reaching the composite endpoint of cardiovascular death, myocardial infarction, or stroke at 4 years of follow-up (HR: 1.11, 95 % CI: 1.02–1.20; $P=0.017$). Hospitalizations due to congestive heart failure were also higher among resistant hypertensives as compared to those with controlled hypertension [80]. The potential role of resistant hypertension as predictor of kidney injury progression was investigated in a prospective analysis of 9974 hypertensive patients participating in the REGARDS study [81]. During a median follow-up of 6.4 years, the cumulative incidence of ESRD per 1000 person-years for hypertensive participants with and without treatment-resistant hypertension was 8.86 (95 % CI: 7.35–10.68) and 0.88 (95 % CI: 0.65–1.19), respectively. After adjustment for several risk factors, patients with resistant hypertension had 6.3 times higher risk of incident ESRD throughout the study (HR: 6.32; 95 % CI, 4.30–9.30) [81].

Subsequently, the prognostic significance of resistant hypertension on cardiovascular and renal outcomes was investigated in post-hoc analyses of two large-scaled randomized trials in hypertension. The first incorporated data from 14,867 hypertensive patients participating in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study [82]. Study participants not at goal BP while taking ≥3 classes of antihypertensive medications or taking ≥4 classes of antihypertensive medications with controlled BP during the Year 2 ALLHAT study

visit were classified as resistant hypertensives for the purposes of this analysis. After adjustment for several risk factors, patients with resistant hypertension versus those with controlled hypertension had 30 % higher risk of all-cause mortality (HR: 1.30; 95 % CI: 1.11–1.52), 44 % higher risk of coronary heart disease (HR: 1.44; 95 % CI: 1.18–1.76), 57 % higher risk of stroke (HR: 1.57; 95 % CI: 1.18–2.08), 88 % higher risk of congestive heart failure (HR: 1.88; 95 % CI: 1.52–2.34), and 95 % higher risk of developing ESRD (HR: 1.95; 95 % CI: 1.11–3.41) until the study completion [82]. In the second, 17,190 hypertensive patients with coronary artery disease participating in the INternational VErapamil SR-Trandolapril STudy (INVEST) trial were classified as having controlled, uncontrolled, or resistant hypertension according to the in-treatment BP levels achieved at the visit immediately prior to an event or censoring [83]. Resistant hypertension was defined as uncontrolled BP >140/90 mmHg on triple antihypertensive therapy or in any patient receiving at least four antihypertensive medications regardless of BP control. Compared with controlled hypertension, resistant hypertension was independently associated with 27 % higher risk of the composite endpoint of first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke (HR: 1.27; 95 % CI: 1.13–1.43) [83]. In contrast, occurrence of adverse outcomes, with the exception of nonfatal stroke, was no different between patients with resistant and uncontrolled hypertension.

The long-term prognosis of resistant hypertension in CKD was investigated during a prospective study of 436 hypertensive patients with non-dialysis requiring CKD under standard nephrology care over a mean follow-up period of 52 months [10]. The study had a composite cardiovascular outcome of cardiovascular death or nonfatal cardiovascular event requiring hospitalization (myocardial infarction, congestive heart failure, stroke, revascularization, peripheral vascular disease, and nontraumatic amputation) and a composite renal endpoint of progression to ESRD requiring dialysis or death. Given the fact that elevated BP is a strong mediator of kidney injury progression in CKD, it was no surprise that patients with resistant hypertension had an adjusted twofold increased risk of reaching the composite cardiovascular endpoint (HR: 1.98; 95 % CI: 1.14, 3.13) and an adjusted 2.6 times higher risk of reaching the renal endpoint during follow-up (HR: 2.66; 95 % CI: 1.62, 4.37) in comparison with controlled hypertensives [10]. In contrast to true resistant hypertension, which predicted both cardiovascular and renal endpoints, patients with uncontrolled hypertension shared an adjusted 2.1-fold higher risk of reaching the composite renal outcome (HR: 2.14; 95 % CI: 1.35, 3.40), but had no additional cardiovascular risk as compared to patients who had their BP adequately controlled (adjusted HR: 1.11; 95 % CI: 0.67, 1.84) [10].

Conclusion

Resistant hypertension is a growing clinical problem that based on office readings is estimated to affect about 9–12 % of hypertensives in the general population. Although CKD is for long considered as a major medical cause of resistance to

antihypertensive treatment, the epidemiology and pathogenesis of this phenomenon in the CKD was poorly studied until recently. Over the past few years, epidemiological studies highlighted that the prevalence of resistant hypertension is much higher in the CKD than in the general hypertensive population, affecting approximately 20–35 % of people with CKD depending on the stage of the disease. Specific mechanisms associated with impaired renal function, such as greater difficulty in excreting daily sodium intake, excessive SNS and RAAS activation, arterial stiffness and endothelial dysfunction, are proposed to be prominent players in pathogenesis of resistant hypertension in CKD. Furthermore, prospective observational studies over the past few years have demonstrated that resistant hypertension signifies an independent prognostic association with adverse cardiovascular outcomes and kidney injury progression to ESRD. Of importance, before labeling the diagnosis of resistant hypertension, a careful examination for and exclusion of factors related to pseudo-resistance, mainly non-adherence to therapy and white-coat phenomenon, is required. Epidemiologic studies that account for pseudo-resistance are warranted in order to fully elucidate the exact prevalence, incidence, and prognostic significance of truly resistant hypertension in CKD.

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