Chapter 3
Apparent Treatment-Resistant Hypertension and Chronic Kidney Disease: Another Cardiovascular–Renal Syndrome?

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Introduction

Arterial hypertension is the most frequent comorbid condition of chronic kidney disease (CKD) affecting almost 80% of CKD patients [1]. The prevalence of hypertension is higher in patients with kidney damage and preserved glomerular filtration rate and increases further as the glomerular filtration rate declines. Among the participants of the Modification of Diet in Renal Disease Study, the prevalence of hypertension increased from 66 to 95 percent as the glomerular filtration rate fell from 83 to 12 mL/min per 1.73 m^2 [2]. Apparent treatment-resistant hypertension (aTRH) is defined as an office BP $\geq$ 140/90 mmHg despite triple antihypertensive treatment including a diuretic [3] and has become an increasingly recognized subform of arterial hypertension. Among patients with aTRH, true treatment resistance must be discriminated from pseudoresistance that results from inadequate medication, inadherence, white-coat hypertension, or errors/artifacts in correct BP measurement. The prevalence of aTRH was estimated to be 11.8% among hypertensive adults with an increase from 5.5% between 1994 and 1998 to 8.5% between 1998 and 2004 [4]. Ambulatory 24-h blood pressure measurement is an important investigation to identify patients with true treatment-resistant hypertension and to rule out

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A. Covic et al. (eds.), *Resistant Hypertension in Chronic Kidney Disease*,
DOI 10.1007/978-3-319-56827-0_3

those with white-coat hypertension or incorrect BP measurements in the office setting. A large study that investigated aTRH with the use of ambulatory BP measurement found that one third of the patients had white-coat hypertension leaving a prevalence of true treatment-resistant hypertension of 7.6% [5]. The notorious problem of inadherence to antihypertensive treatment is also one key factor even in patients considered to have true treatment-resistant hypertension. In an elegant study, Jung et al. verified adherence to medical treatment in patients that were judged to have true treatment resistance by measuring antihypertensive drugs or their metabolites in the urine [6]. Surprisingly, inadherence to the prescribed drugs was found in 37% of the patients from whom 30% did not take any of the prescribed drugs.

aTRH increases the cardiovascular risk of the patients substantially as many have a high prevalence of end-organ damage [5, 7]. Particularly, the cardiovascular risk of patients is potentiated when aTRH and CKD convene [8].

Apparent Treatment-Resistant Hypertension in CKD

The prevalence of aTRH is increased among CKD patients [4], and CKD is an important risk factor for the development of treatment-resistant hypertension besides male sex, longer duration of hypertension, current smoking, and diabetes mellitus [5]. A recent population-based cross-sectional study provided more detailed data on the relationship between CKD and aTRH [9]. In that study involving 10,700 hypertensive individuals, the overall prevalence of aTRH based on in-home measurements was 17.9%, the prevalence of CKD 29.2%. Patients with aTRH were treated with an average of 3.6 classes of antihypertensive drugs, mostly diuretics (87%), angiotensin-converting enzyme inhibitors (62%) or angiotensin receptor blockers (40%), beta blockers (73%), and calcium channel antagonists (72%). The main finding of the study was that the prevalence of aTRH was gradually related to both the GFR and albuminuria stages of CKD: in individuals with a GFR ≥60, 45–59, and <45 ml/min per 1.73 m^2, aTRH was prevalent in 16%, 25%, and 33%, respectively, and in those with an albumin-to-creatinine ratio (ACR) <10, 10–29, 30–299 in 12%, 21%, 28%, and 48%, and ≥300 mg/g, respectively. Both GFR and ACR increased the prevalence of aTRH additively, and patients with a GFR <45 ml/min/1.73m^2 and an ACR ≥300 mg/g crea had an almost 60% prevalence of aTRH. The increased prevalence of aTRH in patients with lower GFR and higher ACR stages was still evident after adjustment for other variables including current smoking status, waist circumference, diabetes, history of myocardial infarction or stroke, and patients with GFR <45 ml/min/1.73m^2 and an ACR ≥300 mg/g crea had an adjusted prevalence ratio of 3.44 compared to those with GFR ≥60 and an ACR <10 mg/g crea (Fig. 3.1). Altogether, the study strongly underscored the close relationship between CKD and aTRH that was incremental with the two dimensions of CKD, namely, GFR and albuminuria that are now part of the CKD classification.

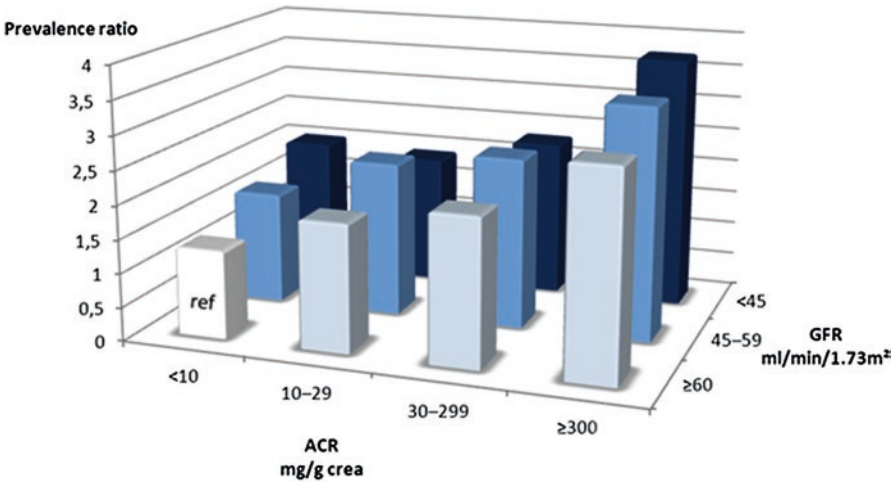

Fig. 3.1 Prevalence ratios for aTRH associated with various GFR and ACR levels after adjustment for demographic and socioeconomic factors, current smoking, alcohol use, waist circumference, diabetes, total cholesterol, HDL cholesterol, statin use, C-reactive protein, history of myocardial infarction, and history of stroke (Data from Tanner et al. [9])

Bidirectional Interaction of CKD and aTRH to Define Cardiovascular–Renal Syndrome

At the heart of the definition of cardiorenal syndrome by Ronco et al. [10] is the interdependence of the heart and the kidney that ensures adequate organ function of each other. When heart failure ensues, there is inevitably kidney dysfunction, and when there is kidney dysfunction, there is also cardiac dysfunction. The classification of Ronco et al. discriminates between cardiorenal syndromes whereby kidney dysfunction is subsequent to cardiac disease (types 1 and 2) and renocardiac syndromes whereby kidney disease comes first and leads to cardiac damage (types 3 and 4). However, in the literature and clinical jargon, the term renocardiac syndrome is not commonly used and cardiorenal syndrome is used as an umbrella term for all types.

Similar to the cardiorenal syndrome, the relationship between CKD and aTRH can also be characterized by a bidirectional interaction and interdependence. Arterial hypertension is on the one hand an important cause of CKD and determinant of CKD progression. This is particularly true for patients with aTRH. On the other hand, advanced CKD and end-stage renal disease lead almost in every instance to the development of de novo arterial hypertension or to exacerbation of preexistent arterial hypertension, possibly resulting in aTRH. Arterial hypertension and aTRH are the most important sequelae of CKD rendering CKD a systemic disease that affects vessels and various organ systems alike. From this perspective, the interaction between CKD and aTRH can be considered as another cardiovascular–renal

syndrome that in some cases makes it impossible to determine if CKD and aTRH are cause or consequence. Both diseases have a detrimental effect on each other and are linked by positive feedback loops that are characteristic for a vicious cycle (Fig. 3.2). In practice, CKD may induce aTRH that promotes CKD progression that again exacerbates aTRH. The cycle can also be constructed the other way around: aTRH induces CKD that exacerbates aTRH that in turn exacerbates CKD. It is noteworthy that the bidirectional relationship between aTRH and CKD is related to both the GFR and the albuminuria stages of CKD. Patients with either reduced GFR or high albuminuria have higher prevalence of aTRH [9], and inversely, patients with aTRH have a higher prevalence of albuminuria and lower GFR [5].

Another characteristic of a vicious cycle is that there no steady state or equilibrium unless there is an intervention that interrupts the feedback loops. With regard to the cardiovascular–renal syndrome, both CKD and aTRH have deleterious effects for the patients if left untreated or undertreated. This explains the high morbidity and mortality of CKD and aTRH patients who have extraordinarily high risk of both cardiovascular events such as sudden death, myocardial infarction, stroke, or hemorrhage and cardiovascular diseases such as coronary and peripheral artery disease and heart failure (Fig. 3.2). In a recent study on the outcome of CKD patients with aTRH, de Nicola et al. stratified 436 CKD patients into four groups using ambulatory and office blood pressure measurements [11]. Besides a control group without hypertension (27% of the cohort), patients were classified in those with pseudoresistance (normal 24 h BP, but high office BP; 7%), masked (high 24 h BP, but normal BP; 43%), and true resistant hypertension (high 24 h and office BP; 23%). After a follow-up of 57 months, patients with true hypertension had significantly increased hazard ratios for both cardiovascular and renal events including fatal ones (1.98- and 2.66-fold, respectively). Patients with masked hypertension had also an increased hazard ratio for renal events, whereas patients with pseudoresistance had a favorable outcome without a difference compared to the control group without arterial hypertension. This study again emphasizes that it is highly important to identify those patients within the group of patients with aTRH who have true resistant hypertension with the aid of 24 h ambulatory BP measurements.

Manifestations of the Cardiovascular–Renal Syndrome

Another hallmark of patients with the cardiovascular–renal syndrome is the presence of advanced target-organ damage to the vasculature, heart, and kidney. Hypertensive vasculopathy is characterized by endothelial dysfunction and remodeling of both small and large arteries with the histological findings of hyalinosis, media thickening, and plaque formation. Microangiopathy results from narrowing of the lumen in capillaries and small resistance arteries, whereas macroangiopathy leads to either narrowing of medium conduit arteries due to arterio−/atherosclerosis or aneurysms in large arteries such as the aorta. Hypertensive nephropathy shows similar features of hypertensive vasculopathy leading to ischemia of the glomerulus and tubulus, eventually sclerosis and interstitial fibrosis. Hypertensive

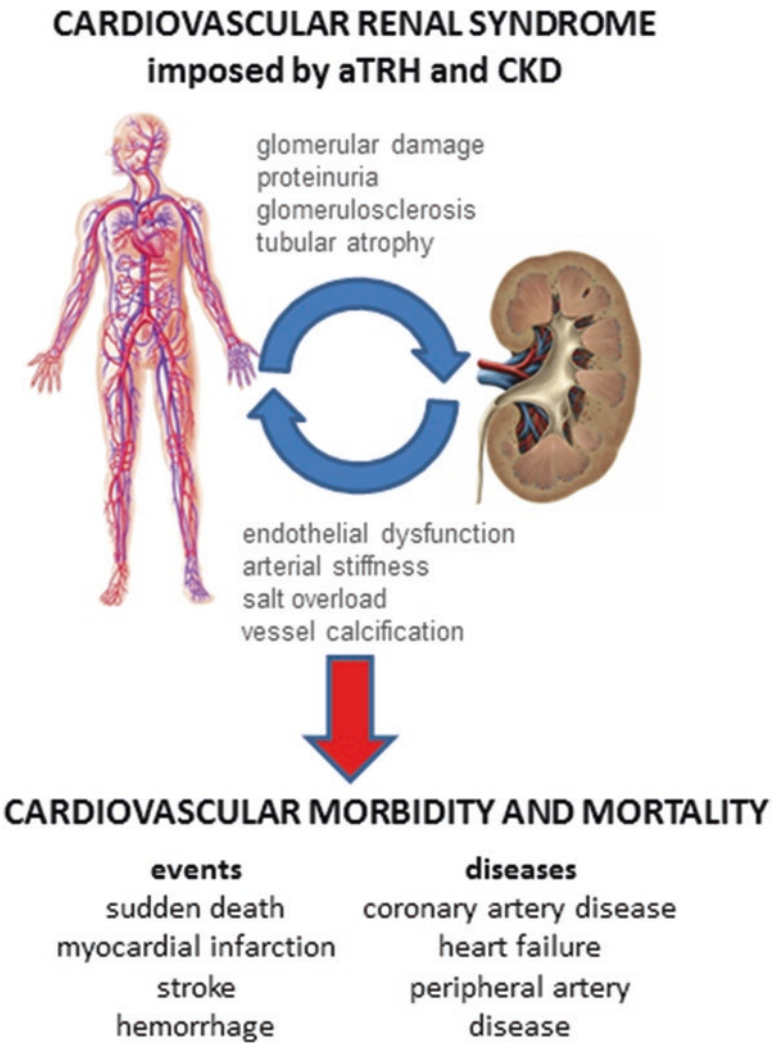

Fig. 3.2 Cardiovascular–renal syndrome imposed by apparent treatment-resistant hypertension (aTRH) and chronic kidney disease (CKD) (Note that only the most prominent interactions between aTRH and CKD are depicted)

heart disease encompasses concentric hypertrophy and diastolic, later systolic dysfunction. On the level of the coronary arteries, both macroangiopathy and microangiopathy can be encountered. Clinical correlates of hypertensive target-organ damage are arterial stiffness, albuminuria, left ventricular hypertrophy, and arterio−/atherosclerosis leading to the known cardiovascular diseases such as coronary and peripheral artery disease, stroke, and heart and renal failure. The identification of hypertension as the major driving risk factor behind these cardiovascular diseases has been, among others, a major success from 50 years of research originating from the Framingham studies [12].

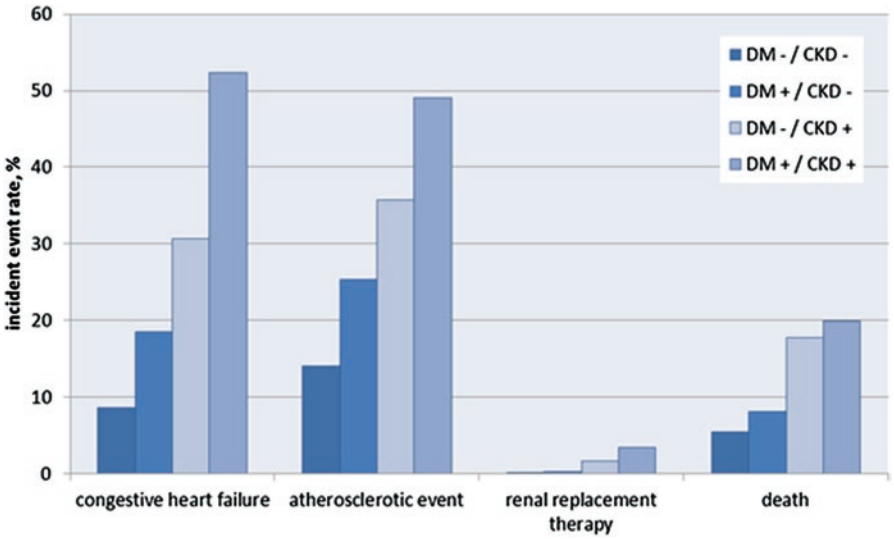

Fig. 3.3 Incident event rates of cardiovascular and renal complications during 2-year time period between 1999 and 2001 in a sample of 1 million Medicare patients. *DM* diabetes mellitus, *CKD* chronic kidney disease (Data from Keith et al. [15])

In the last decade, CKD has emerged as a new and potent cardiovascular risk factor [13, 14] in addition the so-called traditional Framingham-derived risk factors. This is highlighted by the high cardiovascular mortality of CKD patients who have a higher risk to die from cardiovascular disease than to progress to end-stage renal failure [15, 16]. Compared with diabetes mellitus that has been traditionally regarded as a major cardiovascular risk factor, CKD is even a stronger and a more consistent cardiovascular risk factor. In a Medicare sample with approximately 1 million patients, the incidence of congestive heart failure, atherosclerotic event, renal replacement therapy, or death was much higher in CKD patients compared to patients with diabetes mellitus (Fig. 3.3). The presence of CKD in a patient is on one hand a marker that reflects target-organ damage and the burden of cardiovascular disease. On the other hand, CKD and its sequelae directly interfere with the pathogenesis of cardiovascular disease and worsen cardiovascular disease burden. This is similar to the clinical significance of acute kidney injury which is at the same time a risk marker and risk factor for increased mortality among hospitalized patients.

Worsening of cardiovascular disease by CKD can be attributed to mechanisms and sequelae that are unique to advanced CKD. Among these, salt retention and volume expansion, increase of uremic toxins, and deranged calcium–phosphorus balance are major risk factors that not only strikingly aggravate cardiovascular disease but also introduce different pathophysiological pathways. Thus, CKD and its sequelae are now considered as nontraditional cardiovascular risk factors and have opened up an intensely studied area of current research.

Altered Pathophysiology of Arteriosclerosis in Cardiovascular–Renal Syndrome

The vasculopathy of CKD is characterized by media calcification that is unique to CKD patients in contrast to intimal calcification of cholesterol-rich plaques in patients with common atherosclerosis [17]. Media calcification in CKD is considered not to be merely a passive process resulting from elevated calcium x phosphorus product but also an active process involving induction of an osteoblast-like phenotype of smooth muscle cells of the media (also termed osteoblastic transdifferentiation; [18]). Key molecule triggering these events is phosphate that enters the cells via transporters such as the sodium-dependent phosphate transporter (PiT-1). The complex derangements encompassing chronic kidney disease–mineral bone disorder (CKD–MBD) include also increases in the fibroblast growth factor 23, decreases in the FGF23 coreceptor klotho, and eventually increased parathyroid hormone. CKD–MBD is associated with widespread vascular calcification (Fig. 3.4) and arterial stiffness. Clinically, this translates to increased pulse wave velocity and high blood pressure amplitude (pulse pressure). Arterial stiffness leads to pulse wave reflections that increases cardiac afterload and promotes development of left ventricular hypertrophy. The hemodynamic consequences of arterial stiffness are dramatic, and the perfusion in these stiff vessels without vasomotor function becomes dependent on cardiac output (CO) and cannot be regulated adequately, particularly when there is a drop in CO. This gives rise to sudden ischemic events

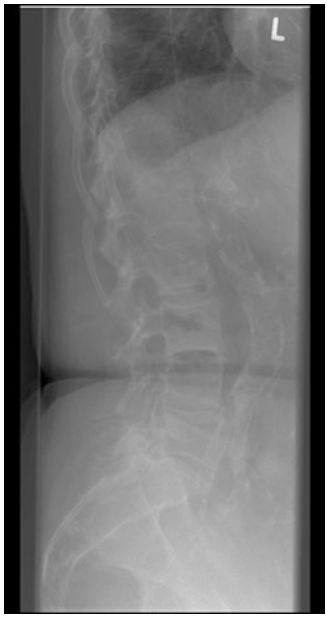

Fig. 3.4 Completely calcified aorta of a 65-year-old female patient with long-standing CKD (>20 years; current stage CKD 4 T)

and even sudden death that is the leading cause of death in patients with ESRD and thought to result from myocardial ischemia and ventricular fibrillation.

In CKD-associated vasculopathy, cholesterol-rich plaque formation seems to be less relevant and statin therapy which is undoubtedly protective in atherosclerosis of the non-CKD population is losing its efficacy as CKD progresses to ESRD. In the Study of Heart and Renal Protection (SHARP), risk reduction of cholesterol-lowering was confined to CKD patients with stages 3–4, but not observed in ESRD patients [19]. In this regard, acute myocardial infarction resulting from plaque rupture and thrombosis of a coronary artery (type I infarction according to the third universal classification [20]) is in ESRD patients less common compared to myocardial damage and infarction resulting from relative ischemia (type II) due to reduced perfusion and drop in CO. In the 4D trial that investigated the effects of 20 mg simvastatin versus placebo in ESRD patients, fatal acute myocardial infarction occurred only in 15% of the patients compared to a 50% of fatalities due to sudden death [21].

Salt Retention and Overhydration in Cardiovascular–Renal Syndrome

Another important determinant of CKD-related cardiovascular disease burden is salt retention and volume overload that is common in CKD patients. In a study using bioimpedance spectroscopy, overhydration as defined by an excess of 7% or more of the extracellular volume was found in 52% of the patients with predialysis CKD [22] and strongly correlated with systolic blood pressure. Our group similarly found that overhydration was common in CKD patients and correlated to both the GFR and albuminuria stages of CKD (Fig. 3.5; [23]). Multiple regression analysis revealed that proteinuria was the strongest independent predictor of overhydration pointing to a causative role of proteinuria in the genesis of overhydration and salt retention. In CKD patients, salt retention might occur due to the activation of the epithelial sodium channel ENaC which is an important determinant of sodium homeostasis in both health and disease. Although sodium reabsorption by ENaC accounts for only a few percent of the filtered sodium load, ENaC activity determines the final concentration of sodium in the urine. Serine proteases are powerful regulators of ENaC activity by cleaving its gamma subunit and increasing the open probability of the channel. Under physiological conditions serine proteases such as prostasin or tissue kallikreins are involved in this process; however, under the pathophysiological conditions of proteinuria, ENaC might be illicitly activated by the serine protease plasmin that is generated from aberrantly filtered plasminogen [24]. Plasminogen is a large protein (91 kDa) that is normally withheld by the intact glomerulus. However, after glomerular injury, larger amounts of plasminogen can be filtered and converted to plasmin in the tubulus lumen by the urokinase-type

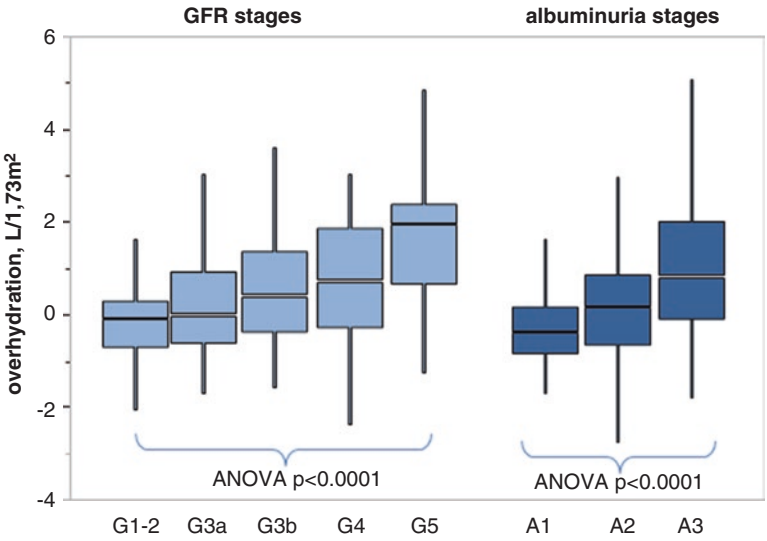

Fig. 3.5 Relationship between overhydration and GFR and albuminuria stages of CKD [23]

plasminogen activator (uPA) that is expressed in the tubular epithelium. Urinary excretion of plasmin has been found to strongly correlate with both proteinuria and albuminuria ($r > 0.8$ [23]) and more importantly with overhydration in proteinuric diabetic patients and CKD patients. The relationship between proteinuria and overhydration seems to be linear and extends to patients with proteinuria in the non-nephrotic range as well [25].

ENaC activation by proteinuria and/or plasminuria is an attractive mechanism explaining the high prevalence of overhydration and edema in CKD patients and a link to aTRH. Indeed, in the study of de la Sierra et al. [5], higher albuminuria stages were an independent factor associated with an increased prevalence of aTRH. The link between proteinuria and salt retention in CKD patients could also explain the finding that arterial hypertension of CKD patients is particularly salt-sensitive and that high salt intake exacerbates blood pressure control and associates with adverse renal outcomes in CKD patients [26]. Altogether, these findings underscore the detrimental role of salt in patients with cardiovascular–renal syndrome and the importance of a salt restriction in the diet. A number of studies have shown reductions in blood pressure during salt restriction in CKD patients. Salt restriction also improves the response to the antihypertensive effects of angiotensin-converting enzyme inhibitors. In a randomized study with proteinuric CKD patients (mean proteinuria 1.5 g/24 h) and a relatively preserved GFR (mean creatinine clearance 70 ml/min), moderate salt restriction resulting in a reduction in urinary sodium excretion from 186 mmol to 106 mmol per day markedly enhanced the blood pressure lowering effect of lisinopril [27]. Similarly, salt restriction also augmented the antiproteinuric effect of lisinopril.

Diagnostic Workup and Evaluation of Cardiovascular–Renal Syndrome

Twenty-four hours ambulatory BP measurement is the gold standard for the diagnosis of true resistant hypertension. It is an essential investigation in patients with aTRH to identify those with normal 24 h BP that corresponds to pseudoresistance or white-coat hypertension. The prognosis of this subgroup is more benign [11]; however, it is a risk factor for future development of resistant hypertension [28]. The utilization of 24 h ambulatory BP measurement differs from country to country, but in general utilization seems to be low and should be increased [29]. Obstacles to a more frequent utilization are probably related to availability, costs, patient participation, and logistical issues as the device must be returned the next day. Besides diagnosing true resistant hypertension, 24 h ambulatory BP measurement is also essential in the follow-up of patients with true resistant hypertension to ensure adequate blood pressure control and to decide if new drugs including reserve drugs such as minoxidil must be introduced. In addition, demonstration of a treatment refractory state using ambulatory BP measurement is the prerequisite to warrant interventional therapies such as renal denervation or baroreceptor stimulation. The use and interval of ambulatory BP measurement during follow-up must be decided individually and can be monthly, 6-monthly, or annually. Although the correlation of home BP measurement to ambulatory BP measurement is fair to moderate, patients with cardiovascular renal syndrome should implement home BP measurement to help the physicians in their assessment of adequate BP control at a visit.

During the initial workup of patients with cardiovascular renal syndrome, the most common secondary causes of hypertension should be ruled out. These are in descending order of frequency [30]: obstructive sleep apnea syndrome (60–70% of the patients with true resistant hypertension), hyperaldosteronism (7–20%), renal artery stenosis (2–24%), renoparenchymal disease (1–2%), drug or alcohol-induced (2–4%), and thyroid disorder (1%). These entities can be investigated in an outpatient setting by careful history taking, duplex sonography, and laboratory analyses. Polygraphy to screen for sleep apnea syndrome should be available when a patient reports daytime sleepiness or snoring. When a new patient is referred, results of the diagnostic workup should be reviewed and new tests or retests ordered when there is a gap or equivocal results. Once completely done, retesting is usually not necessary unless there is clinical suspicion of newly developed disease, e.g., arteriosclerotic renal artery stenosis after long-standing aTRH.

Another important aspect of the diagnostic workup of patients with cardiovascular–renal syndrome is the thorough evaluation of target end-organ damage to estimate the burden of disease and to identify established cardiovascular or renal disease (stroke, coronary artery disease, heart failure, peripheral artery disease, nephropathy, advanced retinopathy). From patient to patient, differences in end-organ damage may be present depending on the presence of microangiopathy or

macroangiopathy or nephropathy or cardiac disease. These lead to differences in vulnerability of the individual patient and help to stratify the future risk, e.g., development of heart failure or end-stage renal disease. After broad testing for end-organ damage initially, physicians can confine to follow those parameters reflecting the present end-organ damage more regularly than those which were negative. Established markers of end-organ damage that can be controlled during follow-up are albuminuria, estimated GFR, pulse wave velocity, pulse pressure, carotid wall thickening, ankle–brachial index, and left ventricular hypertrophy. The latter can be best investigated using echocardiography that provides further important information on cardiac status; however, the availability of echocardiography is sometimes limited, and echocardiographic parameters change only slowly so that the interval of repeat echocardiography may be two or more years unless there is clinical suspicion of newly developed cardiac disease, e.g., development of congestive heart failure.

Implications of Cardiovascular–Renal Syndrome for Treatment

To account for the bidirectional interaction of CKD and aTRH in cardiovascular–renal syndrome, it is necessary to pursue a bidirectional or multilayered treatment approach that ultimately stops the vicious cycle of the cardiovascular renal syndrome. Treating physicians must analyze the pathophysiological interaction of CKD and aTRH and identify the triggering factors individually since these are numerous and can vary from patient to patient. Some factors will be not modifiable as they represent end-organ damage such as arterial stiffness or glomerulosclerosis. However, others can be identified and are amenable to specific treatment, e.g., inadequate blood pressure control due to unidentified secondary causes of aTRH, volume expansion, or identification of renoparenchymal disease. In the next step, physicians must implement rigorous treatment goals aimed to correct for the triggering factors. This could be the rigorous correction of salt overload and volume expansion in a patient with aTRH that is triggered by proteinuric CKD using antiproteinuric and diuretic drugs. Disappearance of edema and achievement of dry weight could be taken as surrogate treatment goals to control aTRH in such a patient. Even without visible edema, saluretic medication should be considered in any patients with aTRH and CKD to guarantee salt excretion. In this context, spironolactone deserves special attention as its addition to a multiple drug regimen often dramatically improves blood pressure control in aTRH. This was first seen in the ASCOT trial [31] and most recently in the PATHWAY-2 Study [32]. The high efficacy of spironolactone as an add-on treatment challenges the current definition of aTRH that is defined by treatment resistance on a triple antihypertensive regimen

including a diuretic. According to these results, the diagnosis of true resistance should only be reserved for those patients with persistent high blood pressure after add-on treatment with spironolactone.

In another patient with aTRH, progression of hypertensive nephropathy rescue treatment with minoxidil may be warranted (after add-on treatment with spironolactone had no effect) and sometimes needed since this potent drug is often the last remedy in patients with otherwise refractory hypertension [33]. However, it has side effects that preclude its widespread use and requires experience. Generally, the physician should be familiar with the pharmacological armamentarium to treat cardiovascular–renal syndrome including second- and third-line drugs or regimens including interventional therapies such as renal denervation or baroreceptor stimulation.

Aggressive and rigorous pharmacological therapies in patients with CKD and aTRH have the high potential of side effects due to the presence of end-organ damage and organ dysfunction. Hence, many contacts and revisits are required to ensure safety while cautiously targeting the treatment goals. These serve to monitor the adequacy of treatment and to identify side effects, some of which can be serious and lead to hospitalization or patient death. During treatment with minoxidil, for example, edema formation is a serious side effect that in some cases can progress to life-threatening pericardial effusion. Monitoring of weight, the development of edema, and adjustment of concomitant diuretic therapy are of great importance with this drug. Other pharmacological treatments involving renin–angiotensin blockade and diuretics often result in deterioration of renal function and development of electrolyte derangements that can only be diagnosed in the early stages by laboratory checks. Pharmacotherapy with these substances often needs careful titration to find out tolerated doses without side effects. However, changes in salt and water balance either by seasonal variation (hot summer) or by disease (e.g., diarrhea) can quickly lead to derangements. Altogether, therapeutic rigor as much as patient motivation is needed to achieve treatment goals in patients with cardiovascular renal syndrome.

Conclusions

The coincidence of CKD and aTRH can indeed be coined as another cardiovascular renal syndrome that is characterized by a bidirectional interaction. Patients with cardiovascular renal syndrome have a high burden of end-organ damage and are at a very high risk for mortality. Multifaceted treatment adopted for the individual patients and therapeutic rigor is necessary to break the vicious cycle of cardiovascular renal syndrome and to ultimately improve patient outcome.

Disclosure There are no relationships with companies that may have a financial interest in the information contained in this manuscript.

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