CHAPTER

40 Hypertension in Chronic Kidney Disease

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INTRODUCTION

The prevalence of hypertension in patients with chronic kidney disease (CKD) exceeds that of the general population. Although hypertension is believed to be the etiology of kidney disease in many of these patients, hypertension is often the consequence of kidney disease stemming from any etiology. The pathophysiology of hypertension in CKD is related to multiple factors, including expanded extracellular volume from sodium retention, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), and imbalances in vasoconstrictor and vasodilator substances that regulate peripheral vascular resistance. Untreated or poorly controlled hypertension in CKD patients is associated with adverse outcomes including deterioration of renal function, development of left ventricular hypertrophy (LVH), and increased mortality. Recent clinical trials have investigated the role of various antihypertensive treatments and blood pressure targets in preventing these outcomes. The purpose of this chapter is to review the epidemiology, pathophysiology, and management of hypertension in patients with CKD. Because diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in the United States, the unique aspects of its pathophysiology and the treatment of hypertension in this setting warrant a separate discussion. Although mentioned briefly herein, the reader is referred to a recent extensive review of this topic.[1]

EPIDEMIOLOGY

Chronic Kidney Disease

Hypertension is a prevalent comorbidity associated with CKD. The prevalence of hypertension in the overall U.S. population, according to the National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2008, is 29%.[2] Data published by the United States Renal Data System (USRDS) according to NHANES data collected from 1999 to 2006 indicate that the prevalence of hypertension in the non-CKD population is 23.3%.[3] In contrast, the prevalence of hypertension in the CKD population is much higher. The prevalence of hypertension increases with each stage of CKD and is estimated to be 35.8%, 48.1%, 59.9%, and 84.1% in patients with stage I, II, III, and IV/V CKD, respectively. Although the awareness of hypertension among patients with stage III and IV CKD was similar to that in the non-CKD population, the failure to control hypertension (defined as blood pressure [BP] 130/80 mm Hg for those with CKD and 140/90 mm Hg for those without CKD) is higher among the CKD patients.

The Chronic Renal Insufficiency Cohort (CRIC) is a National Institutes of Health (NIH) sponsored prospective observational study among 3,612 patients with an estimated glomerular filtration rate (GFR) of 20 to 70 mL per minute designed to better understand factors responsible for CKD progression and cardiovascular disease.[4] Although the sample population for CRIC is smaller than NHANES, the detailed ascertainment of individual demographics, comorbidities, medication use, and laboratory analysis provides useful information for understanding the relationship between CKD and hypertension control in a population that is established in the health care system. In this population, 85.7% of patients are hypertensive based on the definition of a BP >140/90 mm Hg or with the use of an antihypertensive medication. The percentage of patients from CRIC that are aware of their diagnosis of hypertension (98.9%) and who are treated for hypertension (98.3%) is higher than in the NHANES data. However, the control of hypertension in CRIC patients is still suboptimal, with 67.1% having BP >130/80 mm Hg and 46.7% having BP >140/90 mm Hg. The CRIC data indicate that older age, African American race, and a greater amount of proteinuria are risk factors for a failure to control BP to either 140/90 or 130/80 mm Hg.[5] Overall, the epidemiologic evidence from NHANES and CRIC identifies that hypertension is a significant burden for patients with CKD and the health care providers responsible for managing these patients.

The long-term consequences of uncontrolled hypertension highlight the significance of this disease in CKD patients. Studies have reported that elevated systolic BP increases the incidence of CKD,[6,7] the progression of CKD,[8] and the incidence of ESRD.[9] Furthermore, hypertension is reported to be the second leading cause of ESRD in the

United States based on USRDS data.[10] However, it has been difficult to establish the independent effect of BP in CKD from effects related to the degree of baseline proteinuria.[11]

Elevated BP is also a risk factor for cardiovascular events, including stroke and myocardial infarction among CKD patients; however, the exact relationship between BP and outcomes is not consistent among studies. A J-shaped relationship between cardiovascular morbidity and BP has been shown,[12] suggesting that the highest risk for an outcome occurs at the highest and lowest BP, whereas the lowest risk for an outcome occurs at an intermediate BP. In one longitudinal study of patients with stage III and IV CKD, systolic BP >130 mm Hg was a predictor for an incident stroke; however, those with systolic BP <120 mm Hg had a greater risk than those with a systolic BP between 120 and 129 mm Hg.[12] In contrast, a post hoc analysis of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), a prospective randomized placebo controlled trial of the effects of perindopril on stroke among patients with a prior history of cerebrovascular disease, CKD patients had a reduced risk for a recurrent stroke across all strata of systolic BP. Moreover, there was no increase in the risk for recurrent stroke in those who achieved a systolic BP <120 mm Hg compared to higher achieved BP levels.[13]

When considering mortality as an outcome, some observational data confirm the association with low BP and events.[14,15] One study showed an increased mortality risk in subjects with baseline systolic BP in the lowest quartile (<133 mm Hg) compared to the other quartiles, and another study showed the highest mortality risk with a systolic BP <110 mm Hg and >180 mm Hg in a cohort of CKD patients inclusive of both diabetic and nondiabetic CKD. The effect from the latter study was strongest in older patients with advanced CKD and without proteinuria, thus limiting the generalizability of this finding.

In summary, observational studies demonstrate an increased risk for cardiovascular morbidity and mortality at BP levels considered hypertensive for the general population. However, it is unclear if an aggressive reduction of BP translates into decreased cardiovascular morbidity and mortality in the CKD population. The evidence from randomized clinical trials on specific BP targets is discussed in the treatment section of the chapter.

Ambulatory Blood Pressure Measurements and Chronic Kidney Disease

Although CKD patients frequently have BP measured in an office setting, it is important to recognize some of the limitations that can arise in this context. Of utmost importance to the topic of hypertension is the relationship between home and clinic BP measurements. Home and ambulatory measurements better predict the presence of end organ damage such as proteinuria compared to clinic measurements.[16] Ambulatory BP measurements also predict which CKD patients with an elevated clinic BP have a greater risk for progression to ESRD or reaching the composite outcome of ESRD or death.[17] Thus, a comprehensive ascertainment of BP burden requires the consideration of more than measurements obtained in the office.

Hemodialysis Patients

ESRD patients on hemodialysis (HD) have an annual mortality rate close to 20%, with cardiovascular disease and infections accounting for the highest percentage of deaths.[18] Although the prevalence of hypertension in the HD population is near 90%,[19] a target BP to improve outcomes has yet to be identified. Early epidemiologic studies showed that for BP measurements obtained in the HD unit, low systolic BP and systolic BP in excess of 200 mm Hg were associated with the highest mortality, particularly in older patients and diabetics.[20,21] However, it has also been shown that uncontrolled hypertension with systolic BP in excess of 140 mm Hg results in the increased incidence of LVH, de novo ischemic heart disease, and de novo cardiac failure.[22] It must be considered that low systolic BP can be a manifestation of decreased cardiac output, resulting from the structural and functional consequences of long-standing uncontrolled hypertension, which would explain its association with increased mortality.

Similar to pre-ESRD CKD patients, the timing and location of BP measurements are also important considerations in HD patients. Home and ambulatory BP measurements during the interdialytic time period, in comparison to individual HD-unit measurements, are better predictors of mortality.[23] The significance of BP changes during HD treatments has also been recently investigated. Intradialytic hypertension, increases in BP from pre- to post-HD, has been associated with increased short-term (6 month) morbidity and mortality in prevalent HD patients and decreased 2-year survival in incident HD patients.[24,25] There is evidence that mechanisms responsible for the phenomenon include extracellular volume overload[26] or increased vasoconstriction related to intradialytic endothelin-1 surges as a manifestation of endothelial cell dysfunction.[27–29] Patients with intradialytic hypertension have also been shown to have increased ambulatory blood pressure and greater impairment in underlying endothelial cell function during the interdialytic time period.[30,31] Additional mechanisms that have been proposed, but that have yet to be confirmed, include increased activity of the RAAS and SNS, changes in electrolytes during HD, and removal of antihypertensive medications during the course of HD.[32]

PATHOPHYSIOLOGY

The etiology of hypertension in CKD is multifactorial and related to both increases in cardiac output and increased peripheral vascular resistance (Table 40.1). Positive sodium balance can affect either component (Fig. 40.1), and achieving sodium balance remains a primary target of managing hypertension in patients with CKD. Multiple other mechanisms, including activation of the SNS and RAAS, endothelial cell dysfunction related to imbalances in vasodilator and vasoconstrictor substances, and increased oxidative stress, can modify the effects of each other and result in hypertension, particularly when these systems are disrupted in the context of CKD. A comprehensive summary of these processes is outlined in Figure 40.2.

40.1 Etiology of Hypertension in Chronic Kidney Disease

Extracellular volume overload
Increased renin-angiotensin-aldosterone system activity
Increased sympathetic nervous system activity
Endothelial cell dysfunction
    Increased endothelin-1 release
    Accumulation of asymmetric dimethylarginine
    Decreased production of nitric oxide
Oxidative stress
Increased vasopressin release
Hypertensinogenic drugs (erythropoietin)

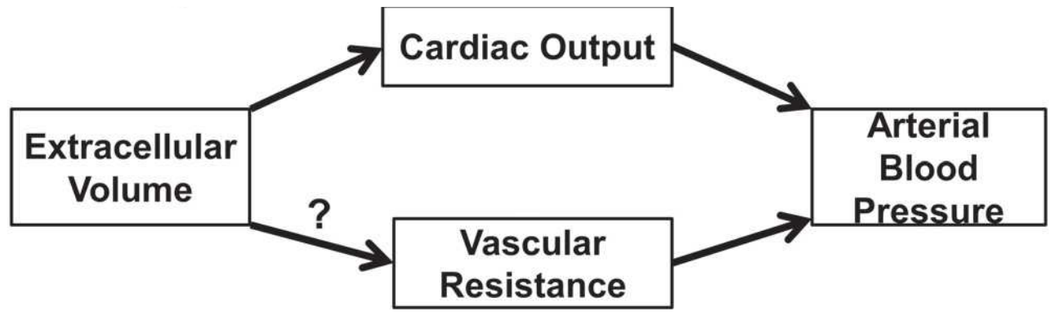


FIGURE 40.1 Blood pressure is directly related to cardiac output and vascular resistance. Extracellular volume increases cardiac output and, potentially, vascular resistance in patients with chronic kidney disease and end-stage renal disease. The achievement of euvolemia and a reduction in vascular resistance remain the primary target of blood pressure reduction in these patient populations.

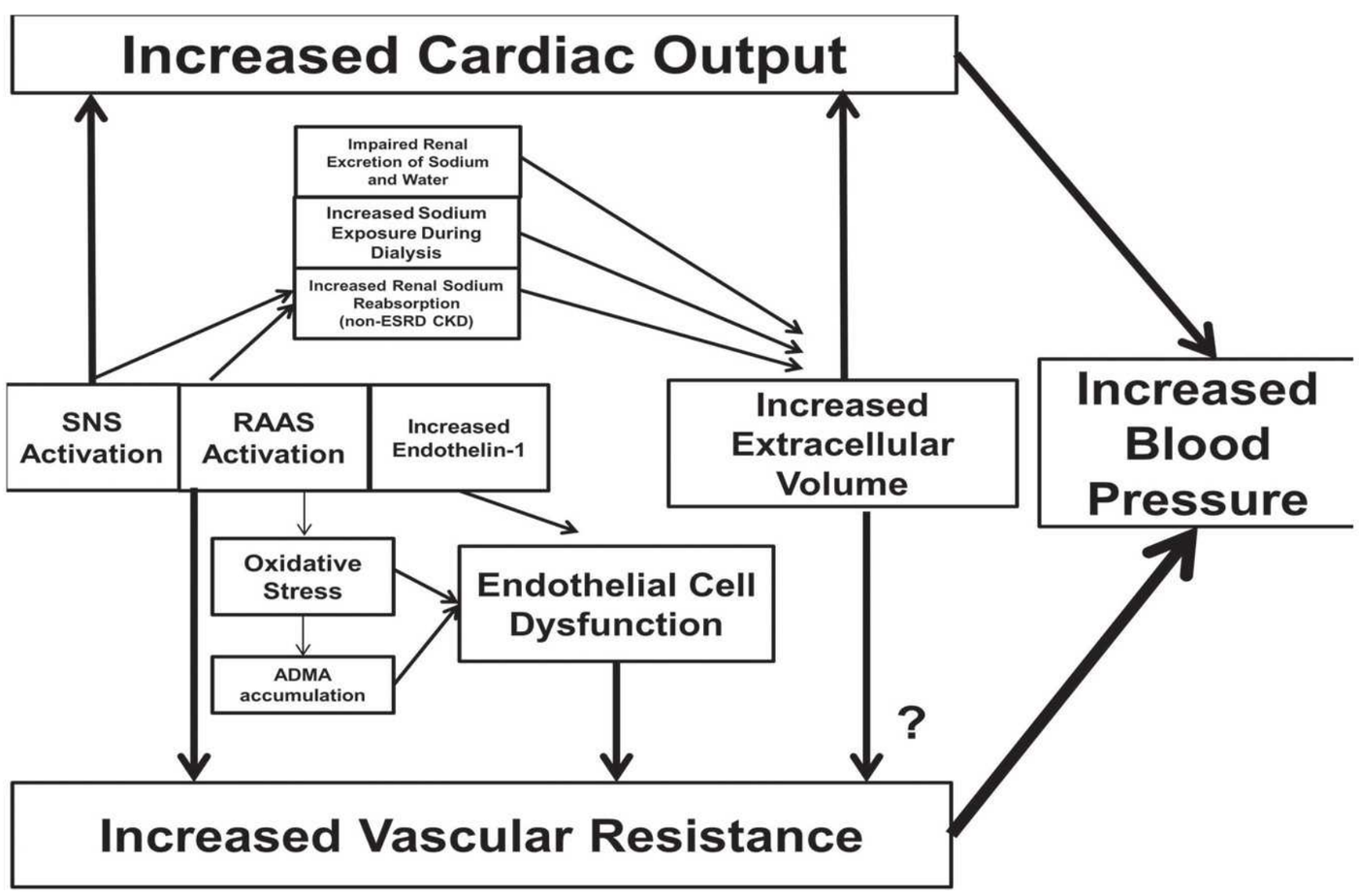


FIGURE 40.2 Both increased cardiac output and increased vascular resistance contribute to increased blood pressure in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). Increased cardiac output results primarily from increased extracellular volume. Activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) contributes to renal sodium reabsorption in non-ESRD CKD patients. In both CKD and ESRD patients, the decreased renal excretion of sodium and water from the decreased glomerular filtration rate also contributes to increased extracellular volume. Finally, in ESRD patients on hemodialysis, the transfer of sodium from the dialysate to the plasma can promote thirst and interdialytic weight gain.

Vascular resistance can be increased by the activation of the SNS and the RAAS, as well as by enhanced vasoconstriction caused by endothelial cell dysfunction. Increased RAAS activity increases angiotensin (Ang) II, which binds to receptors on vascular smooth muscle cells and causes vasoconstriction. Ang II also activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increases oxidative stress, which is believed to be responsible for the increase in the inhibitor of endothelial nitric oxide synthase, asymmetric dimethylarginine. Endothelial cell dysfunction refers to an imbalance in mediators released from the endothelial cells of which one of the results is increased vasoconstriction. An increase in asymmetric dimethylarginine (ADMA) interferes with the production of the vasodilator nitric oxide (NO). Reactive oxidative species also combine with NO to form peroxynitrite and to prevent NO that has already been produced from binding to its receptor. In the context of impaired production and function of NO, there is less opposition to the vasoconstrictive effects of endothelin (ET)-1. Extracellular volume overload has varying effects on vascular resistance, but there is evidence that there is a delayed increase in vascular resistance that follows volume-induced increases in blood pressure and acts to sustain hypertension.

Basic Concepts

BP in humans is determined both by the cardiac output and by peripheral vascular resistance. Cardiac output is dependent on the intravascular component of the extracellular space as well as the heart rate; and peripheral resistance is dependent on functions of the vascular endothelial and smooth muscle cells in response to the actions of various vasoactive mediators (both vasoconstrictors and vasodilators). Although alteration of either cardiac output or vascular resistance would initially be expected to affect BP in a concordant direction, a healthy kidney can adapt to short-term changes in BP to restore normotension. An increase in renal sodium excretion is the expected response to increased BP in healthy individuals. This pressure natriuresis allows for the restoration of extracellular volume and BP following an increase in cardiac output. However, in CKD, this homeostatic mechanism is impaired, and the kidney fails to sufficiently excrete sodium loads. In CKD and ESRD, it is hypothesized that an increase in cardiac output initiates the increase in BP, but ultimately, an increase in vascular resistance sustains the BP elevation.[33,34] Accordingly, addressing both volume status and the degree of peripheral vasoconstriction are necessary to control BP in these patient populations.

Sodium Balance and Volume Overload

Sodium balance is an important aspect in BP control in CKD and ESRD. Because of the kidney's ability to excrete sodium, healthy individuals can tolerate large amounts of sodium intake without significant increases in BP.[35] However, in the presence of kidney disease, BP is highly dependent on extracellular volume. Rats that have undergone 70% renal ablation develop severe hypertension on a high sodium diet, but hypertension is completely prevented in these animals while on a low sodium diet.[36] A lower hematocrit found in the animals on a high sodium diet suggested that extracellular volume overload was present and likely the mechanism responsible for the increased BP. Another experiment with a renal ablation model demonstrated that increased cardiac output is responsible for the initial increase in BP during acute salt loading, but increased peripheral resistance (which occurs after BP has already become increased) is responsible for the maintenance of elevated BP even after cardiac output has returned to normal.[37]

Chronic Kidney Disease Patients Not on Hemodialysis

Because CKD patients are limited in the amount of renal sodium excretion, BP and sodium balance are interrelated. Among CKD patients, those with more severe renal impairment experience greater increases in BP in response to a sodium load. Although the pressure natriuresis curve serves to maintain sodium balance in healthy individuals, CKD patients require much higher BP increases than healthy individuals to augment their renal sodium excretion. Similarly, the degree of blood volume expansion required to induce a natriuresis is higher in patients with severe renal impairment compared to those with moderate renal impairment. Overall, these findings show that the effects on BP related to sodium intake ("salt sensitivity") are augmented with the progression of renal disease.[38] During the early stages of CKD, despite suboptimal renal sodium excretion, some patients remain normotensive despite an increase in cardiac output because of a reduction in peripheral resistance.[33] Although BP is sustained in the normotensive range, these patients, who are already limited in their sodium excretion because of reductions in GFR, fail to induce the necessary pressure natriuresis to re-establish sodium balance. Consequently, further increases in sodium loading result in increased cardiac output, peripheral resistance, and BP.

When subjects with CKD increase dietary sodium ingestion from 20 to 120 mEq per day, they experience an increase in BP that is not seen even in healthy subjects who increase their dietary sodium ingestion to levels as high as 1200 mEq per day.[39] Although both groups have a similar suppression of RAAS at moderate amounts of sodium ingestion, plasma renin activity (PRA) and angiotensin (Ang) II decreased drastically in healthy subjects during periods of high sodium ingestion (1200 mEq per day).[39] Although vascular resistance could not be measured directly in this study, increased vasoconstriction in the CKD subjects appeared to be the likely mechanism responsible for the increased BP and the reduced distribution of fluid into the interstitial space. Even under clinical conditions of pharmacologic RAAS blockade, salt balance has an important role in BP. In nondiabetic proteinuric subjects with creatinine clearance ranging from 33 to 110 mL per minute ingesting a low sodium diet, a reduction in BP and proteinuria during the chronic administration of fixed doses of angiotensin converting enzyme (ACE) inhibitors is reversed during periods of increased dietary sodium ingestion.[40] As further evidence of the importance of sodium intake in relation to BP and proteinuria in CKD patients, the coadministration of hydrochlorothiazide during a high salt intake period reduces both BP and proteinuria back to values seen during the low sodium diet.

Chronic Kidney Disease On Hemodialysis

In ESRD patients with little or no renal sodium excretion, sodium removal through ultrafiltration during HD is the primary means to maintain extracellular volume status because a pressure natriuresis is not possible. Consequently, compared to healthy controls, HD patients have a significantly higher cardiac output.[41] However, the presence of hypertension among HD patients is also highly dependent on elevations in vascular resistance.[41] Extracellular volume potentially impacts both of these parameters to influence BP. When subjected to sodium loading, HD patients typically respond with an increase in both BP and cardiac output. The pattern of vascular resistance following sodium loading is more variable, but increases typically do not occur until after the elevated cardiac output has already led to an

increase in BP.[34,42] In between HD treatments, during the interdialytic period, HD patients gradually gain weight with their routine dietary intake of sodium and water. The BP patterns during a typical interdialytic period show rhythmic oscillations superimposed on a general linear increase in BP over time.[43] This pattern is modified by interdialytic weight gain such that greater weight gain is associated with an increase in the slope of BP rise.[44] Subsequently, greater increases in interdialytic weight gain have been associated with increased pre-HD systolic BP at the next HD treatment.[45] However, that increased interdialytic weight gain is also associated with a greater reduction in BP during the course of that treatment (likely as a response to the ultrafiltration required to remove the interdialytic fluid gain).[45] Such evidence supports the hypothesis that extracellular volume (through either increases in cardiac output or vascular resistance) is primarily responsible for hypertension in this population. Consequently, one HD center has described a 98% success rate in withdrawing antihypertensive medications while using the ultrafiltration that can be achieved during a cumulative weekly dialysis time of 24 hours.[46] Thus, recognition and successful attainment of a patient's dry weight can facilitate the initial BP management in most, but not all, HD patients.

Therefore, HD treatment with adequate ultrafiltration should normalize BP in many HD patients. However, the basis for this practice assumes that interdialytic sodium and fluid intake is not excessive. An insufficient time on HD needed to completely restore normal extracellular fluid volume and achieve dry weight without inducing symptomatic hypotension limits this practice. A cross-sectional study found that major differences between ultrafiltration-sensitive and ultrafiltration-resistant HD patients were the pre- and post-HD atrial natriuretic peptide (ANP) levels between groups.[47] The ultrafiltration-sensitive group had reductions in ANP during HD (as well as lower pre-HD ANP), whereas the higher pre-HD ANP levels in the ultrafiltration-resistant group persisted despite similar amounts of ultrafiltration, suggesting that this group had remaining extracellular volume contributing to the elevated BP. It should be recognized, however, that extracellular volume overload may not always manifest itself overtly. In some cases, patients may have additional extracellular volume despite appearing euvolemic on clinical exam. The Dry Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) study was a randomized clinical trial in which hypertensive HD subjects were randomized to either continue their current HD and ultrafiltration prescription or have their dry weight challenged during each HD treatment over several weeks by 0.1 kg per 10 kg dry weight until symptoms developed. The subjects randomized to additional ultrafiltration demonstrated significant decreases in ambulatory systolic BP after 4 weeks and 8 weeks.[48]

The dialysate used during HD is another important factor that may contribute to hypertension in ESRD patients. Although ultrafiltration effectively removes water and sodium concurrently through convection, there may be an additional exchange of sodium from the dialysate to the patient's plasma depending on the sodium concentration gradient between the two compartments. Directly programmable ultrafiltration enables greater convective sodium removal in shorter periods of time, but increases the risk of intradialytic hypotension related to the abrupt hemodynamic changes. Although the use of higher dialysate sodium concentrations may reduce the risk of intradialytic hypotension, it may increase the risk of hypertension.[49] In contrast, the use of individualized dialysate sodium concentrations (as opposed to standardized concentrations, which may exceed the pre-HD plasma sodium of the patient) have been associated with lower pre-HD systolic BP in the context of decreased thirst and interdialytic weight gain.[50]

The Renin-Angiotensin-Aldosterone System and Hypertension

The RAAS has local and systemic effects that control BP by altering renal sodium reabsorption and vascular resistance. Renin released from juxtaglomerular cells cleaves angiotensinogen to Ang I, which is ultimately converted to Ang II by the ACE. Ang II causes vasoconstriction upon binding to angiotensin type 1 (AT1) receptors in vascular smooth muscle cells (VSMCs). Ang II increases proximal tubular reabsorption of sodium and stimulates aldosterone release from the adrenal gland, which is responsible for further sodium reabsorption in the distal nephron. Although this proposed sequence applies to the levels and activity of RAAS components in the plasma, there is also local RAAS activity. Consequently, measurements of RAAS mediators in the plasma may not always identify a disruption of the axis at the tissue level.[51]

Early evidence for systemic RAAS activation in CKD stems from studies in patients with autosomal dominant polycystic kidney disease (ADPKD). It has been shown that PRA and plasma aldosterone were higher in hypertensive ADPKD patients compared to patients with essential hypertension, and plasma aldosterone is higher in normotensive ADPKD patients compared to healthy controls (despite similar creatinine clearance between the groups).[52] Autosomal dominant polycystic kidney disease patients also manifest an accentuated response to ACE inhibitors compared to unaffected family members, further supporting the role of RAAS in the hypertension seen in ADPKD even prior to the onset of significant renal impairment.[53] However, the findings from these studies may not be entirely generalizable to more heterogeneous groups of CKD patients because the proposed renal ischemia induced by large cyst formation in ADPKD does not necessarily apply to CKD from other etiologies. There is evidence that PRA and aldosterone are higher in hypertensive CKD patients compared to healthy controls, essential hypertension patients, or even normotensive CKD patients.[54,55] However, there is also evidence that CKD patients have lower PRA compared to healthy

controls, although the values were similar to subjects with essential hypertension and normal renal function.[56] Despite these conflicting findings, increased intrarenal RAAS activity has been described in patients with hypertension and varying etiologies of CKD, including immunoglobulin A (IgA) nephropathy, membranous nephropathy, and diabetic nephropathy.[57–59]

As mentioned previously, success in managing BP can be achieved in many ESRD patients by appropriately using ultrafiltration for volume removal.[46] However, there are HD patients who remain quite hypertensive despite achieving their estimated dry weight. Previous reports have shown both increased or normal PRA in groups of HD patients compared to controls, and PRA did not consistently correlate with BP.[60,61] However, increased PRA has been demonstrated in HD patients with hypertension that is ultrafiltration resistant compared to those whose BP responds to ultrafiltration.[61] Bilateral nephrectomy, a procedure previously used for ultrafiltration-resistant hypertension in ESRD patients, has been shown to reduce PRA, Ang I and II, along with reductions in BP in these ultrafiltration-resistant hypertensive patients.[62]

Renin and Aldosterone

Although the primary action of angiotensin converting enzyme (ACE) inhibitors and ARB is to decrease the production and action of Ang II via the inhibition of the ACE enzyme or Ang II receptor, a complete perspective on the role of RAAS in hypertension associated with kidney disease warrants a discussion of the other components of the RAAS, including aldosterone and renin. Following the use of an ACE inhibitor or ARB, serum aldosterone levels typically decrease. However, in up to 40% of patients receiving these medications, aldosterone levels can rebound to pretreatment levels through a process referred to as aldosterone escape.[63] Aldosterone increases BP via enhanced sodium reabsorption in the distal nephron, but it is also likely involved in vasoconstriction via interaction with the Ang II receptor.[64] Despite evidence that CKD patients experiencing aldosterone escape may have worse control of proteinuria, systemic BP does not seem to be different from CKD patients whose aldosterone levels remain depressed following ACE inhibitor or ARB treatment.[65,66] These studies included patients with IgA nephropathy who were normotensive and had creatinine clearance >50 mL per minute or patients with early diabetic nephropathy and hypertension; such investigations have not been performed in broader groups of CKD patients. Evidence regarding the potential benefit of mineralocorticoid receptor blockers is included in the Treatment section of this chapter.

In contrast to the expected decrease in aldosterone following ACE inhibitor or ARB use, renin levels and PRA are expected to increase as a result of the blockade in events downstream from the main actions of renin. It has been demonstrated in vivo that Ang II can be generated by enzymes other than ACE.[67] This presents a potential obstacle to complete RAAS blockade if renin levels are sufficiently elevated in the context of an ACE inhibitor or ARB administration, and the possible use of add-on therapy to ACE inhibitors or ARB with a direct renin-inhibitor is further discussed in the Treatment section.

Angiotensin Converting Enzyme 2

Understanding of the RAAS continues to expand, and attention has been drawn to another enzyme in this pathway. ACE2 is a monocarboxypeptidase homolog of ACE that decreases Ang II levels by (1) increasing the degradation of Ang II to Ang 1-7, a vasodilatory and antiproliferative mediator, and (2) converting Ang I to Ang 1-9. This latter process not only prevents the conversion of Ang I to Ang II via ACE, but the increase in Ang 1-9 acts as a substrate for additional enzymatic conversion to Ang 1-7. Infusion of human recombinant ACE2 (rACE2) does not alter BP significantly in normotensive mice.[68] However, rACE2 prevents BP increases induced by the infusion of Ang II when they are infused together. Consistent with the proposed mechanism of ACE2, Ang II levels were significantly lower and Ang 1-7 levels were higher in mice receiving Ang II plus rACE2 compared to Ang II alone. ACE2 is highly expressed in the kidney and is believed to play a role in the progression of CKD via local activity of the renal RAAS. Mice that have undergone 5/6 nephrectomy have significantly reduced renal ACE2 expression and a trend toward reduced renal ACE2 activity compared to sham-operated mice.[69] Although BP was similar in nephrectomy and sham-operated mice, there was greater proteinuria in the nephrectomy mice. The proteinuria was further increased following administration of the ACE2 inhibitor. The major implications of these studies are that there may be further opportunities to reduce Ang II levels beyond the currently implemented strategies.

Sympathetic Nervous System and Hypertension

The SNS has been studied extensively as a possible contributor to hypertension in CKD and ESRD patients. In CKD patients, there is evidence for multiple pathways that the SNS may affect to increase BP. In support of the previous discussion of the effects of salt balance on BP, renal sympathetic nerve stimulation increases proximal tubular reabsorption of sodium and water.[70] Additionally, the systemic effects of the SNS include increased cardiac output and vasoconstriction. Although evidence of activated SNS activity based on elevated catecholamine levels in CKD is inconsistent and possibly confounded by decreased renal clearance of these compounds, other estimates of SNS, such as muscle sympathetic nerve activity (MSNA), confirm the hyperactive state in CKD and ESRD. The mechanisms responsible for hyperactive SNS are thought to be related to increased renal nerve activity. The kidney possesses baroreceptors and chemoreceptors that increase renal nerve firing secondary to pressure changes or metabolites produced in response to ischemia

or uremia. Animal models of renal artery stenosis, arterial ligation causing partial renal ablation, or intrarenal phenol injection all reveal increased nerve activity.[71–73] Activation of renal nerves results in a centrally mediated hypertension via activation of the SNS, which can ultimately be interrupted by a blockade of neural signals. For example, Sprague-Dawley rats that have undergone a 5/6 nephrectomy experience an attenuation in hypertension following a dorsal rhizotomy with a concurrent reduction in the turnover of norepinephrine in the hypothalamic nuclei and locus coeruleus.[72] In humans, there is evidence for SNS activation even prior to overt renal impairment if a potential cause for renal ischemia is present. Hypertensive ADPKD patients have increased MSNA compared to controls despite preserved renal function in both groups.[74] Muscle sympathetic nerve activity was even higher in ADPKD patients with decreased GFR, but was not different between normotensive ADPKD patients and controls. Given the experimental association with bilateral renal ischemia, the possibility exists that the increased MSNA is related to increases in RAAS activation. One study confirmed the presence of increased MSNA in CKD patients, and showed that the administration of the ACE inhibitor enalapril caused a reduction in MSNA (relative to the decrease in BP it caused), whereas amlodipine increased MSNA.[75] In a small study including patients with various etiologies of nondiabetic CKD and matched control, MSNA changed similarly in the patients and controls with variability in volume status, but MSNA was persistently higher in the CKD patients.[76]

The evidence for the role of increased SNS activity in the etiology of hypertension in renal disease is best supported by the findings of Converse et al.[77] Twenty years ago it was established that ESRD patients had increased MSNA compared to healthy controls and other ESRD patients that had undergone bilateral nephrectomies. Higher mean arterial BP was also seen in the ESRD patients whose native kidneys were still present, and the hypothesis was that afferent signaling from the ischemic kidneys modulated an overall SNS response best managed by surgical removal of the kidneys. This is further supported by the fact that reversing the uremic state of ESRD patients with renal transplantation does not decrease MSNA, but a native kidney nephrectomy in the transplant recipient does.[78] The fact that nondiabetic HD patients have a normal arterial and cardiopulmonary baroreflex response weakens any suggestion that uremia-induced impairments in these reflexes might further contribute to abnormally elevated SNS activity in this population.[79]

Renalase

Adding to the evidence that CKD patients, particularly those with hypertension, have increased MSNA and circulating catecholamine levels is the recent discovery of a protein that may facilitate higher levels of catecholamines. Renalase is an amine oxidase that contributes to catecholamine degradation, which, in comparison to other common amine oxidases, can circulate in the plasma. Renalase is secreted into the circulation by the kidneys, and patients with ESRD on HD have nearly undetectable levels, supporting the role of adequate renal function to maintain its presence.[80] Although in CKD patients, there is no direct evidence how circulating renalase is responsible for hypertension, animal models demonstrate the development of hypertension following knockout of the renalase gene and a reduction in BP following the infusion of recombinant renalase in Sprague-Dawley rats.[80]

ENDOTHELIAL CELL DYSFUNCTION AND HYPERTENSION

Because the increase in peripheral vascular resistance also contributes to the elevated BP in patients with kidney disease, it is important to understand the mechanisms responsible for vasoconstriction. Blood vessels are lined with endothelial cells, which release mediators that exert their actions on VSMC receptors. The balance between vasoconstricting mediators and vasodilating mediators dictates the ultimate response of the VSMC and the amount of resistance. Endothelial nitric oxide synthase (eNOS) uses arginine as a substrate to produce the vasodilator nitric oxide (NO). This process is dependent on the presence of the cofactor tetrahydrobiopterin (BH4), and production of NO can be inhibited by the arginine analog asymmetric dimethylarginine (ADMA). One of the primary vasoconstrictive agents is endothelin-1 (ET-1), but the ultimate response of the vascular tone is dependent on which ET receptor is being bound. The interplay between all of these mediators is complex. Substances such as Ang II modify the activity of ET-1, and NO release is sensitive to the relative state of oxidative stress and inflammation.

Endothelin

ET-1 is a 21 amino acid mitogenic peptide that is produced ubiquitously, but to a large extent in vascular endothelial cells. Its original description demonstrated that it had more potent vasoconstrictive effects than other vasoconstrictive peptides including Ang II, vasopressin, and neuropeptide Y while having a longer lasting effect on vascular tone than the endothelial-derived relaxing factor NO.[81] Additionally, ET-1 has been shown to promote vascular cell hypertrophy and increase nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, resulting in oxidative stress and endothelial cell dysfunction.[82] There are two primary receptors for ET-1: ET-A and ET-B. ET-1 binding to ET-A and ET-B receptors found on VSMC causes vasoconstriction, whereas binding to ET-B receptors on the endothelial cells causes vasodilation, suggesting a mechanism for feedback inhibition to stimulation by ET-1. Because ET-1 has paracrine behavior and migrates from the endothelial cells to VSMC (away from the lumen), plasma levels of ET-1 have proven to be unreliable in establishing a clear causal relationship with hypertension. However, mRNA expression of ET-1 in the endothelium of resistance vessels is higher in patients with moderate-to-severe hypertension compared to those with mild hypertension

or controls.[83] Its role in hypertension in humans is further implicated by its effects on arterial tone. Following an infusion of ET-1, forearm blood flow decreases (increased tone) in both hypertensive and healthy humans, although the effect is greater in hypertensive patients. The pharmacologic inhibition of ET-A receptors alone or the combined inhibition of ET-A and ET-B receptors results in significant increases in forearm blood flow in the hypertensive patients, but not the healthy subjects.[84] The administration of a nonselective ET receptor blocker in a dose of >500 mg per day resulted in reductions in systolic and diastolic office and ambulatory BP as compared to placebo; the BP reduction from the drug was similar to that achieved with the ACE inhibitor enalapril.[85]

In patients with CKD, both systemic and local renal effects are proposed to contribute to hypertension in this population. Partial nephrectomy Sprague-Dawley rat models suggest that there is an imbalance of ET expression and degradation in the uremic state. In these animals, there were increased ET-1 levels (related to increased expression) in the endothelial cells of the thoracic aorta and renal cortex.[86] It was also found that the number of ET-B receptors was decreased in these locations, but there was a mild increase in ET-A receptor expression in the VSMC. Downregulation of ET-B receptors disables a mechanism for ET-1 degradation and can further contribute to the increased presence and action of ET-1.[87,88]

In CKD, there is also increased urinary and plasma levels of ET-1, independent of BP.[89,90] The renal excretion rate of ET-1 is increased in hypertensive CKD patients, but not in subjects with normal renal function who have increased plasma ET-1 levels accompanying essential hypertension. These findings suggest that renal production of ET-1 increases as renal function declines and contributes to hypertension in CKD.[91] Mechanisms through which ET-1 can increase BP include vasoconstriction, salt/water retention, and activation of the RAAS. ET-A receptor inhibitors have been shown to decrease systemic BP in CKD patients and controls.[92] They also increased renal blood flow and decreased renal vascular resistance in CKD patients, and this effect dissipated with a concurrent administration of an ET-B receptor inhibitor. These findings and the evidence that ET-A receptor antagonists reduce proteinuria in diabetic patients have already been further investigated in a clinical trial. The ASCEND study was a randomized double-blind placebo-controlled trial studying the effects of avosentan in patients with diabetic nephropathy.[93] Subjects were randomized to avosentan 25 mg daily, 50 mg daily, or placebo while being continued on current therapy with an ACE inhibitor or ARB. There were trends toward lower sitting and standing systolic BP in the low dose group, and this difference was statistically significant compared to placebo. However, the study was terminated early because of increased cardiovascular events in the avosentan group, particularly from congestive heart failure exacerbations and pulmonary edema. A smaller randomized placebo-controlled trial in 27 nondiabetic proteinuric CKD patients compared the effects of a selective ET-A receptor antagonist, sitaxsentan, with either the calcium channel blocker nifedipine or placebo.[94] Sitaxsentan significantly lowered BP and arterial stiffness compared to placebo. There was no difference in these outcomes compared to nifedipine, but proteinuria reduction was greater. Thus, the practical use of inhibiting various endothelin receptors remains to be fully established in CKD.

Nitric Oxide and Asymmetric Dimethylarginine

NO is one of the primary vasodilators released from the endothelium and counteracts the effects of the vasoconstrictors. NO also plays an important role in modifying renal blood flow and sodium excretion. Infusion of L-arginine, the substrate for NO production, decreases renal vascular tone in hypertensive patients who are either salt sensitive or salt resistant, but this effect is diminished in salt-sensitive patients with increasing sodium intake.[95] This suggests increased dietary sodium impairs NO release in salt-sensitive patients, and there is additional evidence that impaired renal response to arginine predicts an increased prevalence of end-organ damage in patients with salt-sensitive hypertension.[96] Furthermore, transition from a low sodium diet to a high sodium diet decreases plasma NO levels in salt-sensitive hypertensive patients compared to salt-resistant hypertensive patients where there was an inverse relationship between changes in plasma NO and BP changes.[97] These findings demonstrate that, in essential hypertension, there is impaired NO production and this impairment is associated with increased BP and long-term consequences related to uncontrolled BP.

Animal models of renal ablation have consistently identified a reduction in renal NO production, but not systemic NO production.[98,99] Differences in these studies may be related to the method of renal ablation and the consequential effects on systemic BP that could confound overall production of NO in the aorta.[98] In humans, total body NO production assessed by varying techniques has been noted to be lower in CKD patients and ESRD patients compared to healthy controls.[100–102] Although decreased NO synthase activity may be responsible for these findings, CKD patients were more hypertensive and had increased serum levels of the eNOS inhibitor ADMA.[101]

The association between ADMA and renal function has also been demonstrated in animal CKD models. Rats that have undergone a 5/6 nephrectomy have increased ADMA, and these levels correlate with increased BP.[103] Urinary ADMA excretion was increased in these animals, but the enzyme responsible for the metabolism of ADMA, dimethylarginine dimethylaminohydrolase (DDAH) was found to be decreased, suggesting that mechanisms beyond impaired renal excretion are responsible for ADMA accumulation in CKD. Further support for the role of ADMA in hypertension comes from evidence that transgenic mice overexpressing DDAH have lower BP and ADMA than controls, and that the administration of DDAH attenuates the increase in BP that

occurs following a 5/6 nephrectomy in animal models.[104,105] Infusion of ADMA into healthy humans causes an increase in systolic BP associated with decreased cardiac output, but increased vascular resistance.[106,107] In patients with nondiabetic CKD (IgA nephropathy and ADPKD) elevated ADMA levels can be seen even in the early stages of CKD prior to a significant reduction in GFR compared to healthy controls.[108] However, in this study, there were no significant differences in ADMA between hypertensive and normotensive CKD patients. Elevated ADMA has been confirmed in ESRD patients on HD where the increased levels were predictive of cardiac structure and function, as well as cardiovascular morbidity and mortality.[109–112] Cumulatively, these studies fail to consistently show a direct correlation with ADMA and BP in CKD and ESRD patients, but ADMA is associated with adverse events in this population.

Oxidative Stress

A common aspect related to many of the previously described mediators of hypertension in CKD is oxidative stress. Oxidative stress refers to an imbalance of reactive oxygen species (ROS) and naturally occurring antioxidant enzymes that favor an elevation of ROS. Chronic kidney disease is a state of both relative ROS excess and antioxidant depletion. Increased RAAS activity can generate ROS via the Ang II–induced activation of NADPH oxidase, which may be one explanation for the degree of oxidative stress seen in CKD and ESRD. Furthermore, it has been demonstrated that the enzyme responsible for the degradation of ADMA, DDAH, can be influenced by increased oxidative stress.[113] Following a 5/6 nephrectomy, Sprague-Dawley rats have increased BP that is attenuated by the administration of an antioxidant and lipid peroxidation inhibitor.[114] The BP increases again following withdrawal of the antioxidant. The levels of plasma malondialdehyde, a marker of lipid peroxidation, increased in the CKD animal models and correlated with BP. Again, malondialdehyde levels decreased when the animals were given the antioxidant, but increased when the antioxidant was withdrawn.

Additionally, ROS can interact with NO that has already been synthesized by eNOS and deplete the amount of NO available to induce vasodilation. This was shown in an experiment using a 5/6 nephrectomy in Sprague-Dawley rats where a diet fortified in the antioxidant vitamin E attenuated BP increases that occurred following the nephrectomy.[115] There was an increase in plasma and tissue nitrotyrosine, a measure of the effects of ROS on NO, in all CKD animals; this effect was reduced in the CKD animals receiving a diet high in vitamin E. Similarly, NO production from isolated vascular tissues was higher in the animals receiving vitamin E compared to the animals on a regular diet.

Numerous studies in humans with CKD and ESRD have aimed to determine if intervention with antioxidant therapy is capable of improving outcomes. A retrospective analysis of the Heart Outcomes Protection Evaluation (HOPE) study, which included nonproteinuric CKD subjects with serum creatinine (Cr) <2.3 mg per deciliter, found no difference in the composite of cardiovascular outcomes between subjects taking vitamin E 400 units daily or placebo.[116] Hemodialysis patients receiving antioxidants including vitamin E or N-acetylcysteine in randomized placebo-controlled trials showed improved cardiovascular outcomes, but there was no difference in mortality between these groups.[117,118]

Arginine Vasopressin

Experimental evidence suggests that vasopressin may also contribute to hypertension in CKD patients, although currently no therapy is aimed at decreasing its effects. Arginine vasopressin (AVP) is a peptide released from the hypothalamus in response to increases in plasma osmolarity. Receptors for vasopressin include the V1a, V1b, and V2 receptors. Traditionally, V1a receptors were believed to be responsible for vasoconstriction via VSMC, and V2 receptors responsible for water reabsorption through the insertion of aquaporin channels in the collecting duct of the nephron. Based on animal studies, the V1a receptor may mediate other effects on BP related to decreases in circulating blood volume, baroreflex sensitivity, and RAAS activity.[119,120] In CKD patients, AVP levels are higher and increase in response to osmolarity changes with a greater slope than in controls.[121] Vasopressin levels are also elevated in HD patients, and BP decreases following infusion of an AVP inhibitor in HD patients that have been saline loaded.[122,123]

Secondary Hyperparathyroidism

Secondary hyperparathyroidism is a complication of CKD that contributes to many comorbidities associated with CKD. The increased production and secretion of parathyroid hormone (PTH) is triggered in part as a response to the accumulation of serum phosphorus caused by decreased renal phosphorus excretion in CKD. Furthermore, in CKD, there is decreased renal 25-hydroxyvitamin D_3 1α-hydroxylase activity, which results in the reduced production of active vitamin D. Previous in vitro studies have investigated the role of secondary hyperparathyroidism in the etiology of hypertension, but recent clinical trials have added to the data available in human studies. One study in adult CKD patients demonstrated an association with increased BP and elevated serum PTH levels proposed to be related to higher cytosolic calcium in the subjects with elevated PTH levels.[124] This association was supported by the improvement in mean BP following treatment with the vitamin D analog alfacalcidol. Treatment with vitamin D also decreased PTH and cytosolic calcium levels along with the decrease in BP. It has since been demonstrated that although treatment with 1,25 dihydroxyvitamin D in spontaneously hypertensive rats (SHR) achieves a reduction in BP mediated through the attenuation of endothelium-dependent VSMC contraction, the administration of vitamin D had no effect on the amount of free cytosolic calcium,[125] suggestive of an effect downstream from the increase in calcium.

Although the exact mechanisms remain under debate, further evidence has been generated to support the use of active vitamin D treatment in CKD. The selective vitamin

D receptor activation with paricalcitol for a reduction of albuminuria in patients with type 2 diabetes (VITAL) study was a clinical trial where patients with diabetic nephropathy (mean estimated glomerular filtration rate: 39 to 42 mL per minute) were randomized to receive placebo versus 1 μg paracalcitol versus 2 mcg paricalcitol.[126] In this study there was a reduction in albuminuria following the administration of the larger dose of vitamin D compared to placebo. Additionally, there was a significant reduction in systolic BP in patients receiving vitamin D compared to placebo. The identification of inactive vitamin D deficiency and insufficiency in the general population and in CKD patients with secondary hyperparathyroidism has generated further interest in the effects of BP response to inactive vitamin D repletion/supplementation. A recent meta-analysis of the effects of vitamin D on the cardiovascular system among healthy individuals showed a trend toward reductions in systolic BP.[127]

Drug Related

Erythropoietin-Stimulating Agents

Beyond the disruption of endogenous mediators of hypertension that occurs in CKD patients, it is also important to consider the iatrogenic effects of commonly implemented interventions in this patient population. Anemia is another prevalent comorbidity in CKD. Though iron deficiency contributes to decreased hemoglobin levels in CKD and ESRD patients, the underlying erythropoietin deficiency has prompted widespread use of erythropoiesis-stimulating agents (ESAs) as commonly used therapeutic agents to correct anemia. Increases in BP in both previously hypertensive and nonhypertensive patients is one of the reported adverse effects of ESA use.[128] Despite the recognition that ESA administration increases BP, several meta-analyses have failed to consistently show significant differences in hypertension-related adverse events in ESA use versus nonuse or high or low target hemoglobin groups using ESA in CKD and ESRD patients.[129–131] Proposed mechanisms of ESA-induced hypertension include increased ET-1 release and increased sensitivity to Ang II and adrenergic stimuli.[132,133] Furthermore, acute and chronic ESA administration in pre-HD CKD patients resulted in impairment of flow-mediated dilatation as a measurement of endothelial cell function.[134] Current guidelines recommend treating hypertension that arises during treatment with an ESA as opposed to withholding ESA treatment in anemic patients.[135]

HYPERTENSION IN SPECIFIC ETIOLOGIES OF CHRONIC KIDNEY DISEASE

Because diabetic nephropathy and CKD attributed to hypertension are the two leading causes of ESRD in the United States, it is important to consider what aspects of the underlying disease processes make CKD-associated hypertension unique in these cases.

Hypertension in Diabetic Nephropathy

Diabetic nephropathy is the leading cause of ESRD in the United States. The timing of the onset of hypertension in patients with diabetic nephropathy is related to whether type 1 or type 2 diabetes is the underlying cause. The onset of hypertension correlates with the development of microalbuminuria in type 1 diabetics and is rarely present before that time. However, a "non-dipping" nocturnal BP pattern, where BP fails to decrease at night from the daytime values, predicts the onset of microalbuminuria in patients with type 1 diabetes and normoalbuminuria.[136] There is also evidence of genetic factors that determine whether hypertension will be present in type 1 diabetics because there is a higher prevalence of hypertension in the family members of patients with type 1 diabetes and microalbuminuria.[137] Conversely, hypertension is frequently already present in patients with type 2 diabetes before the onset of microalbuminuria.[138,139] The overlap between risk factors for hypertension and type 2 diabetes in patients with obesity and the metabolic syndrome may explain why hypertension occurs before renal disease in this population.

There are many similarities in the pathophysiology of hypertension in diabetic nephropathy and nondiabetic kidney disease. It should be recognized that in addition to the impact that impaired renal function has on sodium excretion, RAAS activation, SNS activation, endothelial cell dysfunction, and oxidative stress, the metabolic derangements present in diabetes further accentuate the role these factors have in causing increased vasoconstriction and BP.

Hypertensive Nephrosclerosis

Although diabetic nephropathy is the leading cause of ESRD in the United States, the second leading cause of ESRD is hypertensive nephrosclerosis, with an incidence rate of 100 per million in 2010 according to the USRDS.[3] Because hypertensive nephrosclerosis frequently presents with a normal urinary sediment and a lack of sonographic changes beyond decreased kidney size, many cases of CKD/ESRD attributed to hypertensive nephrosclerosis are never confirmed with a renal biopsy. Often, the identification of hypertension as the sole risk factor for CKD accounts for the designation of hypertension as the etiology. Kidney biopsies from nondiabetic hypertensive individuals with proteinuria and/or increased serum Cr revealed thickened and hyalinized arterioles with an exaggeration of arteriolar smooth muscle hypertrophy in excess of that typically seen from normal aging.[140] Additionally, both hypertrophic and sclerotic glomerular lesions can be seen in hypertensive nephrosclerosis with both autoregulatory dysfunction and ischemia possibly playing a role.[141] Because the number of patients in the general population who have a diagnosis of hypertension far exceeds the number of those who go on to develop kidney disease, there must be certain risk factors that predispose some individuals to hypertensive nephrosclerosis.

In particular, African Americans are more susceptible to renal disease than other races and often develop CKD at

younger ages. Additionally, the severity of hypertension does not correlate with renal function as well as in non-African American patients.[142] There are differences in the renal biopsy findings in African American and Caucasian patients with hypertensive nephrosclerosis, although the etiology of these differences remains unexplained.[143] Genetic variants that predominate in African Americans are sought after as possible explanations for the pattern of CKD in this population. An association between nonmuscle myosin heavy chain 9 (MYH9) gene polymorphisms and the pathologic diagnosis of focal segmental glomerulosclerosis and HIV nephropathy in African Americans has been detected.[144] In several cohorts of African American patients, it has also been shown that the presence of some MYH9 gene polymorphisms is associated with the presence of nondiabetic ESRD previously diagnosed as hypertensive nephrosclerosis.[145] Because MYH9 is expressed in podocytes, mesangial cells, and renal capillary beds, such evidence suggests the possibility that hypertension alone is not sufficient to cause progressive renal disease, but in fact, a genetic susceptibility that primarily affects the kidneys predisposes individuals to the onset of renal disease in the context of other inciting factors, including hypertension.

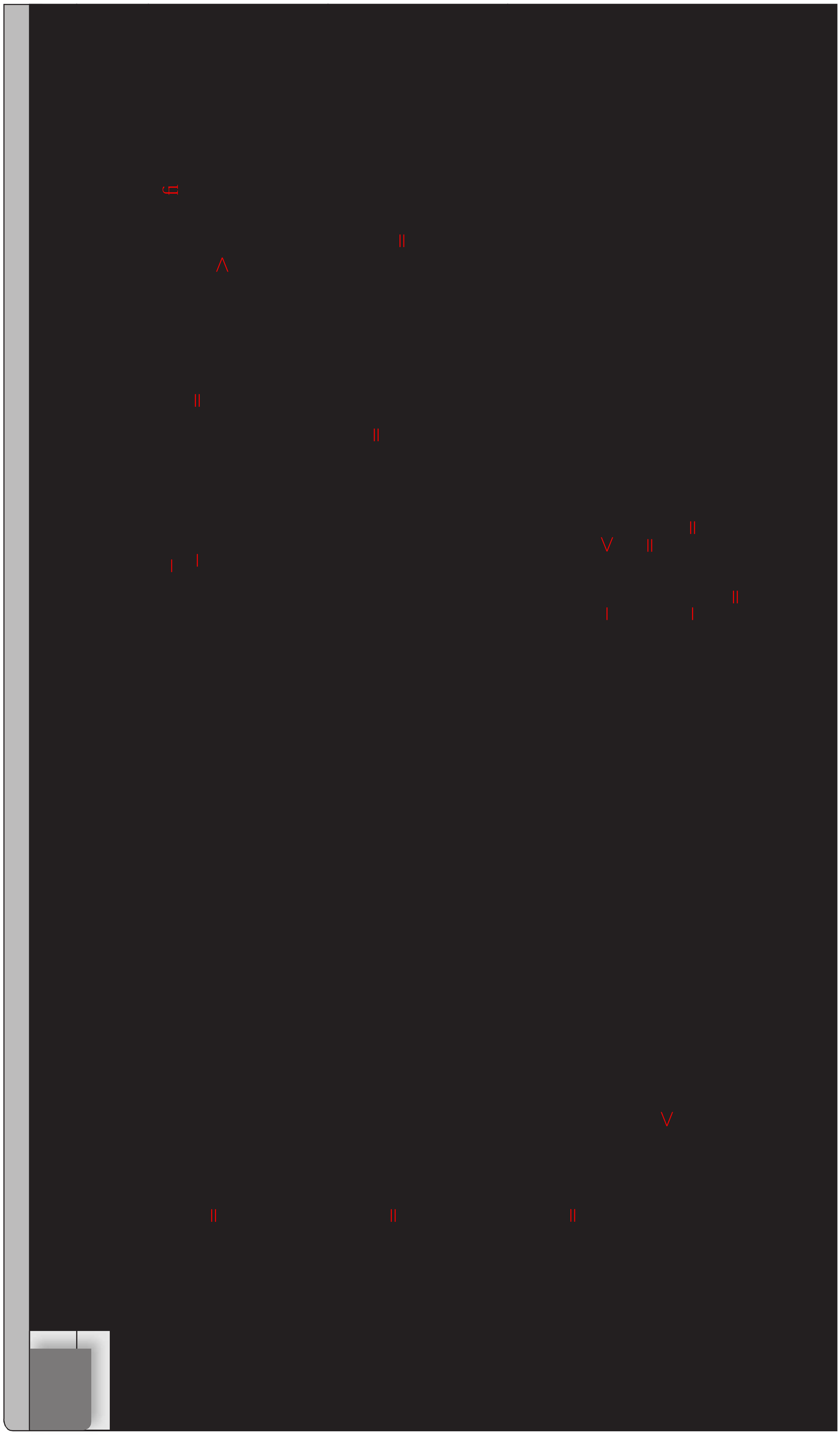
Further investigation into this topic has shown that the risk for kidney disease associated with the MYH9 gene is related to polymorphisms in another nearby location on chromosome 22q. The apolipoprotein 1 (ApoL1) gene encodes a serum factor that lyses Trypanosoma brucei rhodesiense. Case-control studies of African Americans with focal segmental glomerulosclerosis compared to African American controls reveal that the risk for renal disease was dependent on the presence of the ApoL1 alleles.[146] This has also been confirmed in African Americans patients with ESRD attributed to hypertensive nephrosclerosis.[146] This concept has important implications expanding from risk stratification of patients to expectations for managing hypertension in patients with nondiabetic kidney disease.

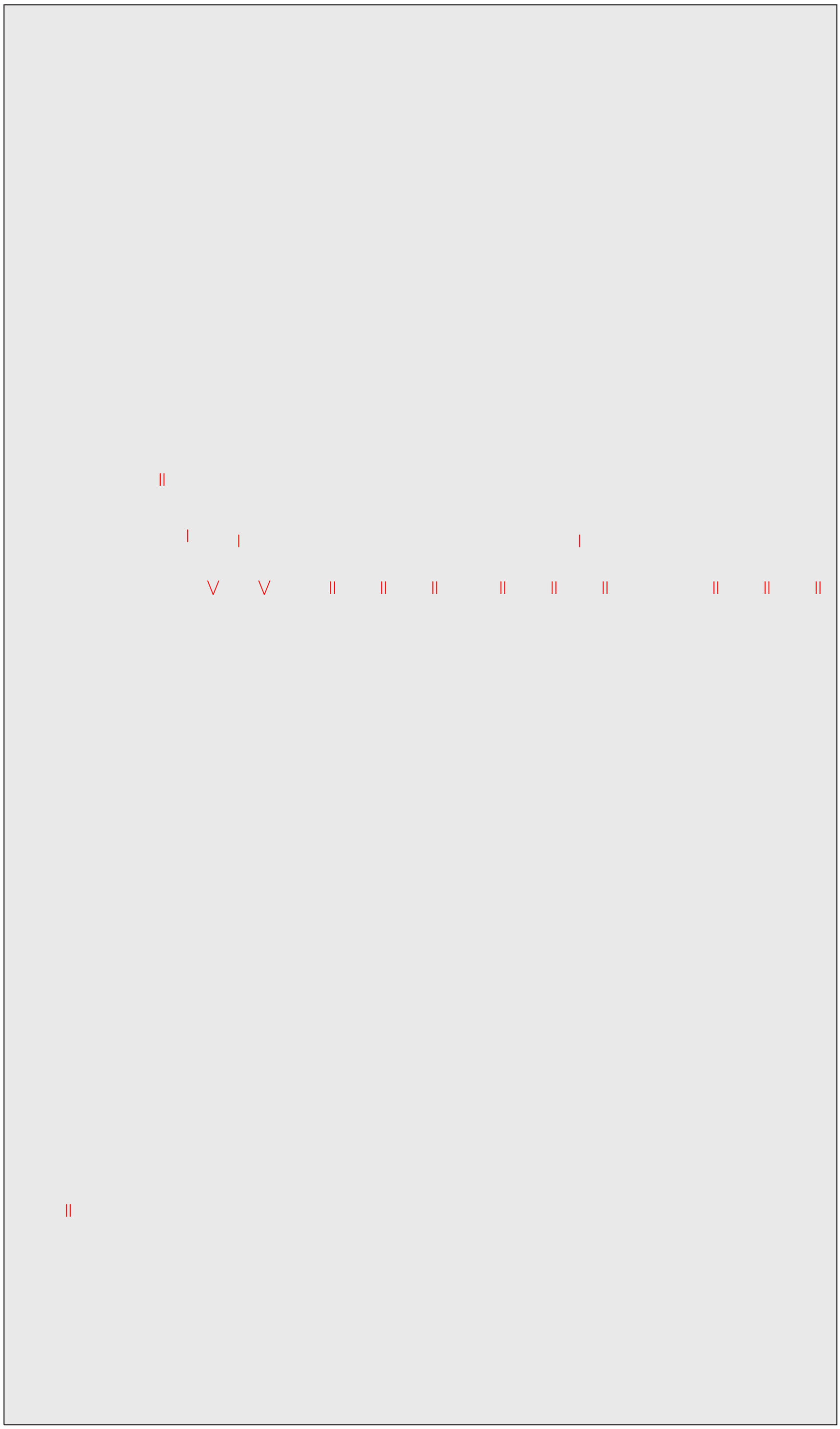
TREATMENT

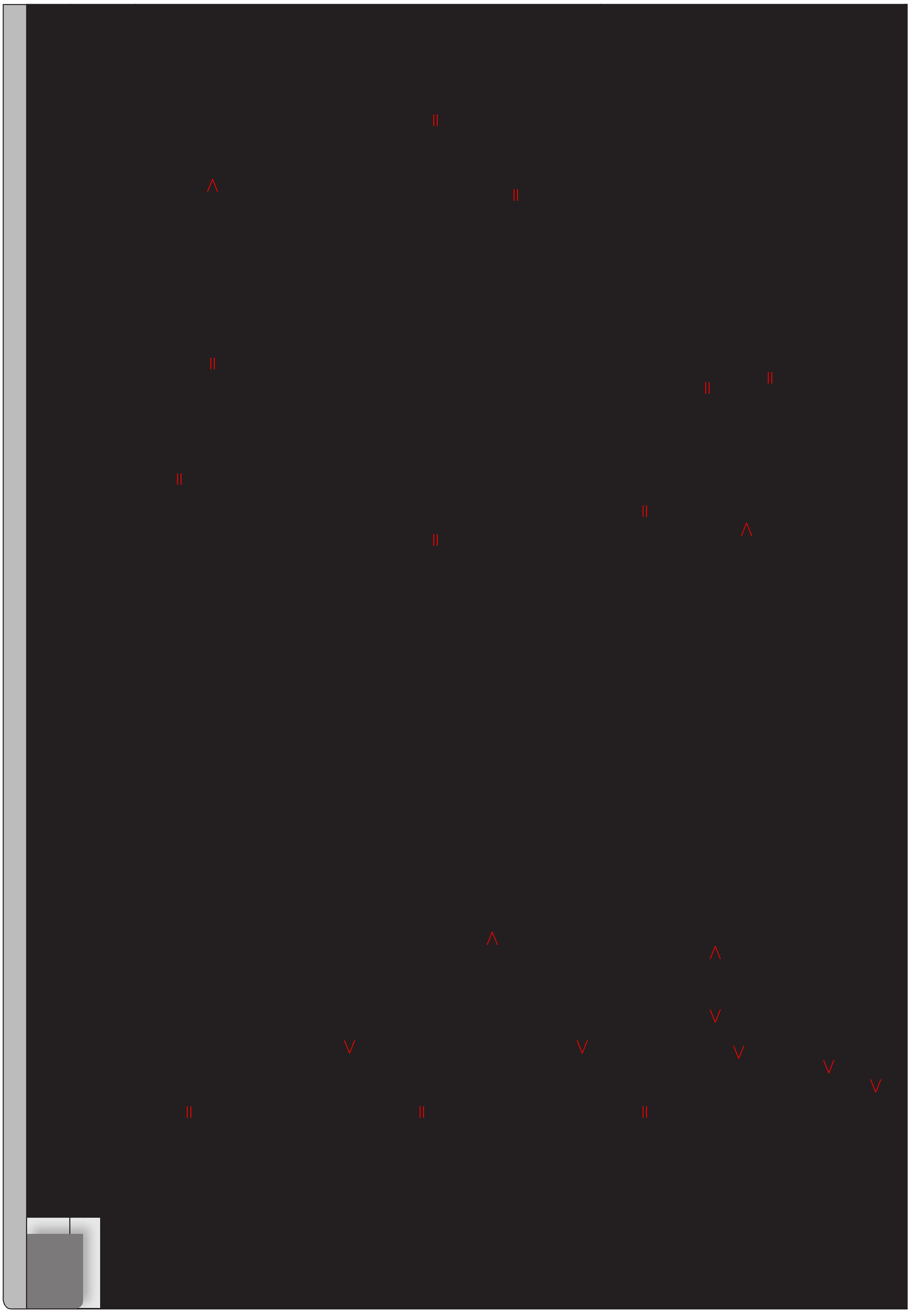
Pre–End-Stage Renal Disease

The management of hypertension in pre-ESRD CKD patients should be aimed at lowering the risk for progression to ESRD as well as reducing the risk for cardiovascular events and death. Current recommendations are to target a BP of 130/80 mm Hg in all CKD patients with consideration of a BP of 125/80 mm Hg in those with significant proteinuria.[147] These guidelines are based on the results and post hoc analyses of randomized clinical trials, which are summarized in Table 40.2. The Modification of Diet in Renal Disease (MDRD) studies randomized patients with GFR of 25 to 55 mL per minute (Study 1) and 13 to 24 mL per minute (Study 2) to a mean arterial pressure (MAP) <107 mm Hg or a MAP <92 mm Hg.[148] Although there was no difference between groups in the change in GFR with a mean follow-up of 2.2 years, a further analysis demonstrated that there was a significant reduction in GFR decline in those subjects with proteinuria randomized to the lower MAP goal.[149] The African-American Study of Kidney Disease and Hypertension (AASK) study randomized nondiabetic African American patients with a GFR of 20 to 65 mL per minute to either a MAP of 102 to 107 mm Hg or a MAP of <92 mm Hg. During the initial 3 months, there was a faster decline of GFR in the intensive BP group, but there was no difference between groups in the chronic or overall slope of GFR over time.[150] For patients with higher baseline proteinuria, there was a trend toward a slowed reduction in GFR with intensive BP control. Following the randomized study, all remaining subjects participated in a cohort study where the goal BP was set at 140/90 mm Hg. During the study, the goal BP was later changed to 130/80. For those with baseline proteinuria >0.22 g per day, there was a slower decline in GFR if they had been randomized to a MAP <92 mm Hg in the original study.[151] In contrast, the Ramipril Efficacy in Nephropathy 2 (REIN2) study randomized nondiabetic CKD patients with persistent proteinuria (1 to 3 g if the GFR <45 mL per minute, or >3 g if the GFR <70 mL per minute) to either standard BP control (diastolic BP <90 mm Hg) or intense BP control (<130/80 mm Hg). The study was halted at the first interim analysis because of similarities between BP groups in the outcomes of ESRD, proteinuria, and GFR decline despite the fact that systolic BP and diastolic BP were lower in the intensive BP group. These similarities persisted among the strata of baseline proteinuria.[152]

In summary, the following conclusions relevant to clinical practice emerge from these trials: (1) there is currently insufficient evidence from the cumulative trial data to demonstrate that, in patients with nondiabetic kidney disease, intensive BP goals (<130/80 mm Hg) slow the progression of CKD or reduce the incidence of ESRD and death, and (2) patients with proteinuria tend to have faster deterioration in renal function, but benefit the most from aggressive therapy. It is important to also acknowledge, based on studies in patients with diabetes, that renoprotection may not be synonymous with decreased overall cardiovascular risk reduction. The administration of combination therapy with perindopril and indipamide to participants with type 2 diabetes and varying levels of baseline renal disease (26% with microalbuminuria, 4% with macroalbuminuria, 19% with an estimated GFR <60 mL per minute) was associated with significantly reduced risk for the composite renal outcome of new onset microalbuminuria, new onset macroalbuminuria, new onset ESRD, or doubling of serum creatinine.[153] Achieving systolic BP <110 mm Hg offered the greatest renoprotection. Similarly, in post hoc analysis of the Irbesartan in Diabetic Nephropathy Trial (IDNT), the lowest quartiles of baseline and achieved systolic BP were associated with the lowest incidence of renal events.[154] However, the subgroup with systolic BP <120 mm Hg had a greater overall mortality than those with BP >120 mm Hg even after controlling for comorbidities. With systolic BP >120 mm Hg, cardiovascular mortality increased with each 10 mm Hg







increase, but also increased for each 10 mm Hg increment of diastolic BP lower than 85 mm Hg. Although these studies were inclusive of patients with diabetes and/or diabetic nephropathy and not completely generalizable to the whole CKD population, it is important to recognize potential limitations of overtreating BP in the context of outcomes other than renoprotection.

A large multicenter randomized clinical trial has been designed to address what the optimal BP target is for patients without diabetes mellitus in order to reduce the risk for cardiovascular events. The Systolic Blood Pressure Intervention Trial (SPRINT) will randomize almost 10,000 subjects to either an intensive BP goal (120 mm Hg) or a standard BP goal (140 mm Hg).[155] The inclusion criteria are age >55 years, hypertension, and the presence of a clinical or subclinical cardiovascular disease, excluding stroke. Inclusive in the definition is CKD with an estimated GFR of 25 to 59 mL per minute, but proteinuria >1 g will be one of the exclusion criteria. The primary outcome is the occurrence of the first major cardiovascular event, although a decline in renal function and the development of ESRD over a 6-year follow-up are some of the secondary end points. The large number of CKD patients expected to be enrolled in SPRINT will provide enough power to reach meaningful conclusions in this patient population. Given the exclusion criteria of diabetes and proteinuria >1 g per day, this study will be directly applicable to CKD patients considered at a lower risk for adverse events than some of the earlier mentioned studies.

Despite the existing debate for the ideal BP in a CKD patient, evidence shows that the majority of CKD patients fail to have BP adequately controlled.[5,10] Although most CKD patients will require more than one antihypertensive drug, all CKD patients should be prescribed a low sodium diet as the first step in managing BP. Dietary sodium intake will also affect the degree of proteinuria in CKD patients, such that increased dietary sodium intake abolishes the antiproteinuric effects of RAAS inhibition.[156] The current recommendations are to limit dietary sodium intake to less than 2.4 g per day.[147]

Inhibitors of the RAAS are the recommended first-line antihypertensive agents for most CKD patients, with the most commonly used agents being ACE inhibitors or ARBs. These agents should be titrated to the maximum recommended doses in order to achieve the greatest RAAS inhibition. Several randomized clinical trials have evaluated the efficacy of ACE inhibitors in CKD patients and, similar to the effects of implementing intensive BP lowering, show that the benefits are most appreciable in patients with higher baseline proteinuria. The African-American Study of Kidney Disease and Hypertension (AASK) and Ramipril Efficacy in Nephropathy (REIN) studies included randomization arms with different antihypertensive agents. In REIN, the ACE inhibitor ramipril decreased the risk of ESRD compared to placebo regardless of baseline proteinuria and slowed the decline of GFR in patients with nephrotic range proteinuria.[157,158] In AASK, subjects were randomized to the ACE inhibitor ramipril, the beta-blocker metoprolol, or the calcium channel blocker amlodipine. Ramipril caused a slower overall decline in GFR compared to metoprolol.[150] There was no difference in the overall decline in GFR between ramipril and amlodipine.[159] However, this was confounded by the acute increase in GFR with amlodipine because the chronic decline in GFR was slower with ramipril. Furthermore, for subjects with mild-to-moderate baseline proteinuria or renal impairment (GFR <40 mL per minute), there was a significantly slower reduction in GFR in the ramipril group. Ramipril also reduced the composite outcome of ESRD, the doubling of serum Cr, or death compared to metoprolol and amlodipine.[150,159]

The benefit of ACE inhibitors extends even to advanced nondiabetic cases of CKD. In a randomized clinical trial, patients with serum creatinine (Cr) between 3 and 5 mg per deciliter were randomized to either benazepril 10 mg twice daily or placebo, in addition to other antihypertensives.[160] Proteinuria >0.3 g per day was one of the inclusion criteria, and the mean baseline proteinuria was 1.6 and 1.7 g per day in the benazepril and placebo groups, respectively. The use of benazepril reduced the occurrence of the primary endpoint of the composite of doubling serum Cr, ESRD, or death. There was also a slower reduction in GFR and creatinine clearance over time, which was assessed as a secondary endpoint in the benazepril group. These findings occurred in the context of similar BP control between groups, and the average achieved systolic BP was <130 mm Hg in both groups.

The cumulative findings show that use of an ACE inhibitor offers benefits over other drugs even when a similar BP is achieved. In addition to these studies in nondiabetic kidney disease, there is robust evidence for BP control and RAAS inhibition in reducing renal endpoints in patients with diabetic kidney disease, specifically in the progression of overt nephropathy to composite clinical endpoints in type 1 and type 2 diabetes,[161–163] progression of microalbuminuria to macroalbuminuria in type 2 diabetes,[164] and the primary prevention of microalbuminuria in hypertensive patients with type 2 diabetes.[165,166] For CKD patients without diabetes, it should be emphasized that the benefits of RAAS inhibition are strongest in patients with the greatest risk for CKD progression. In fact, one meta-analysis confirmed that use of an ACE inhibitor was most beneficial in those with >500 mg per day of proteinuria.[167] The benefits of ACE inhibitors as first-line agents are less certain in those without proteinuria.

Additional agents are frequently required to control BP in CKD patients. Diuretic therapy addresses the impact of extracellular volume on BP and optimizes sodium balance. When GFR is significantly impaired, loop diuretics such as furosemide may be more effective than hydrochlorothiazide. It is important to dose loop diuretics at least twice daily and to consider increased doses in patients with significantly impaired GFR in order to optimize delivery of the drug to the site of action. Diuretics additionally offer the benefit of increasing renal potassium excretion in CKD patients who may be prone to hyperkalemia. Following the use of RAAS inhibitors and diuretics, the decision of which additional agents to

use will be dependent on other underlying comorbidities. Beta-blockers are recommended for patients with congestive heart failure, coronary artery disease, and arrhythmias.[147] Calcium channel blockers, vasodilators such as hydralazine and minoxodil, and clonidine may also be required if BP remains elevated. Although a post hoc analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial demonstrated that subjects with a GFR <45 mL per minute had decreased progression of CKD using the ACE inhibitor benazepril plus the calcium channel blocker amlodipine compared to benazepril plus hydrochlorothiazide,[168] it is unknown how the former combination compares to a regimen including an ACE inhibitor and a loop diuretic. A suggested approach to the selection of an antihypertensive regimen for CKD patients is provided in Figure 40.3.

Combination Renin-Angiotensin-Aldosterone System Inhibition

Because of the concerns of incomplete inhibition of the production or action of Ang II, combination therapy with both ACE inhibitors and ARB has been considered. This strategy has been shown to lower proteinuria in numerous studies of CKD patients, but it is uncertain how much of this effect is derived from additional BP lowering.[169] Because of the concerns of aldosterone escape and the non–ACE-related production of Ang II related to increased PRA in patients already receiving either an ACE inhibitor or ARB, add-on therapy using either a mineralocorticoid receptor blocker or a direct renin inhibitor has also been considered. None of these strategies is currently recommended for patients with CKD, but there is accumulating evidence of the effects of such regimens that is worth briefly discussing here.

Mineralocorticoid Receptor Blockers and Direct Renin Inhibitors. Most of the benefits of add-on therapy with a mineralocorticoid receptor antagonist (MRA) are related to a reduction in proteinuria as opposed to BP. In one clinical trial, patients with proteinuric CKD were randomized to ramipril plus dual placebo, ramipril plus spironolactone plus placebo, ramipril plus placebo plus irbesartan, or triple therapy with all three medications.[170] There were no differences in systolic BP during follow-up, but the groups receiving spironolactone as either dual or triple therapy had a clear benefit in proteinuria reduction compared to the group receiving only ramipril. Other studies involving MRA have been exclusively in patients with diabetic nephropathy and yielded similar results, suggestive of an antiproteinuric benefit from MRA,

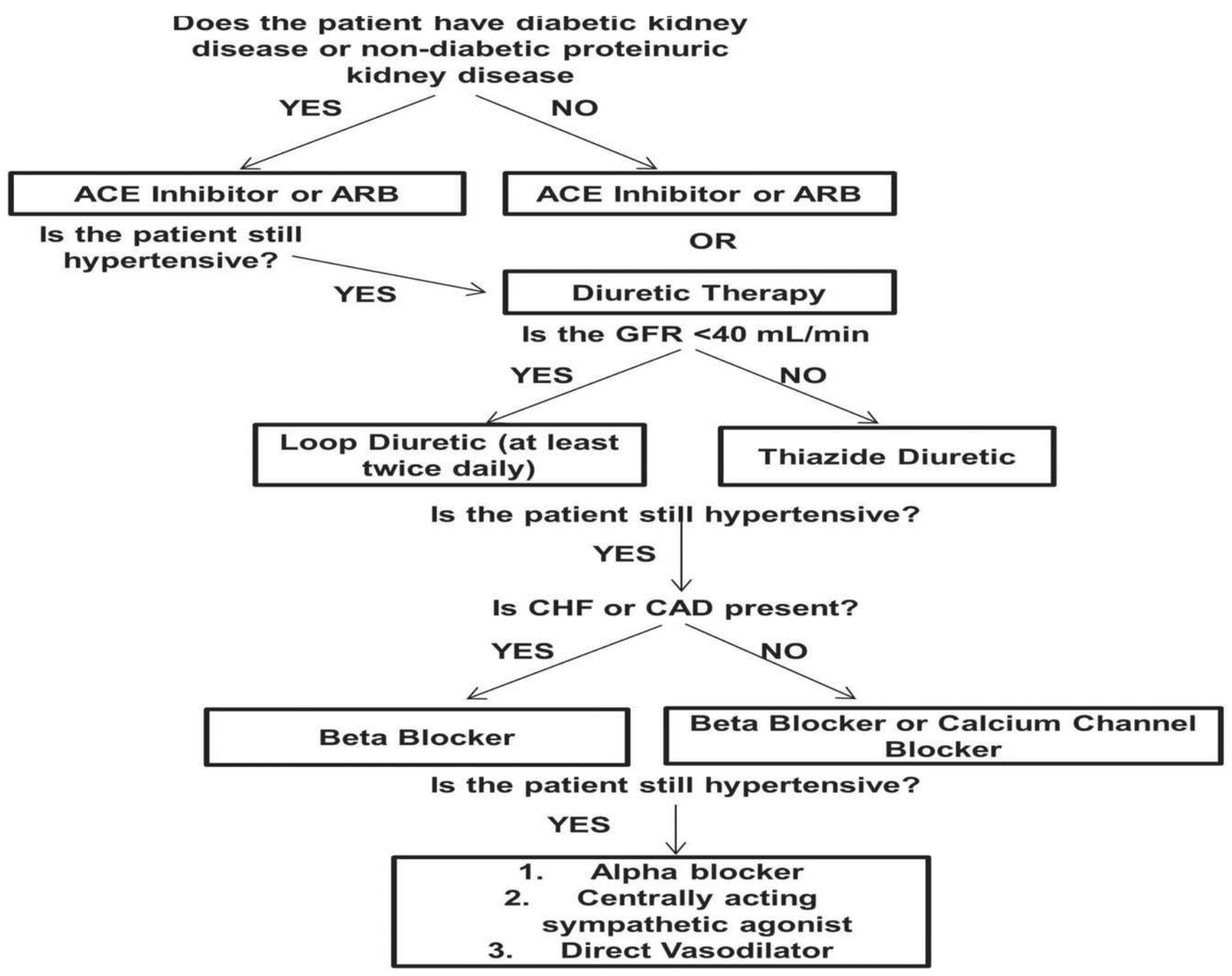


FIGURE 40.3 For chronic kidney disease (CKD) patients with diabetic kidney disease or nondiabetic proteinuric kidney disease, inhibition of the renin-angiotensin-aldosterone system (RAAS) system using either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) should be the first-line therapy. These drugs can also be used as first-line therapy in patients without proteinuria or diabetic kidney disease, but the evidence to support this decision is not as clear. Diuretics should be used to reduce extracellular volume. It is important to use a thiazide diuretic only if the glomerular filtration rate (GFR) is >40 mL per minute and to dose loop diuretics at least twice daily. For patients that remain hypertensive, those with coronary artery disease (CAD) or congestive heart failure (CHF) should receive an indicated beta-blocker, whereas for others, calcium channel blockers can be used. Finally, patients that are still hypertensive may be started on fourth- or fifth-line agents.

although BP differences have varied.[171–173] Clinical trials of the direct renin inhibitor aliskiren in CKD patients are mainly limited to diabetic nephropathy. Although the use of aliskiren as a single agent lowers BP and albuminuria,[174] the beneficial effects of combination therapy, including aliskiren compared to single agent RAAS inhibition, mainly stem from albuminuria reduction.[175,176]

End-Stage Renal Disease

The current recommendations for managing hypertension in ESRD patients is to target a pre-HD systolic BP <140 mm Hg and a post-HD systolic BP <130 mm Hg.[177] There is significant overlap in the etiology of hypertension in patients with ESRD and pre-ESRD CKD. There is increasing evidence of outcomes related to strategies aimed at targeting the underlying causes of hypertension in the HD population. Hemodialysis patients are even more vulnerable to the impact of volume overload than CKD patients because of the extremely limited ability to excrete sodium and water due to kidney failure. The mechanisms of increased vasoconstriction are also similar between ESRD and pre-ESRD CKD patients. Furthermore, the duration and timing of the weekly HD regimen may impact BP control in HD patients.

Identifying and achieving an HD patient's target dry weight are the initial steps that should be taken in managing BP. This process involves a careful clinical assessment of the patient's extracellular volume status, strict enforcement of dietary sodium restriction, and prudent application of ultrafiltration during the HD procedure. Current recommendations are to limit interdialytic sodium intake to 2 to 3 g per day in patients who appear volume overloaded.[177] In patients who remain hypertensive, there should be a consideration of a reduction in dry weight. A slow, progressive reduction in estimated dry weight over several weeks has been shown to reduce ambulatory BP in hypertensive HD patients.[48] Increasing the amount of time a patient spends on HD with either daily or nocturnal dialysis compared to thrice weekly sessions has also been shown to improve BP control. One RCT compared thrice weekly HD with a regimen consisting of six treatments per week.[178] The rates of death and a left ventricular (LV) mass were reduced after 12 months in the group randomized to more frequent HD. Pre-HD systolic BP and the number of antihypertensives required were also reduced in this group, although ambulatory BP was not measured. In an observational study, nocturnal HD has been associated with improved BP and LV mass.[179] One randomized study has demonstrated reductions in LV mass, pre-HD systolic BP, and the antihypertensive requirement in subjects converted to nocturnal HD.[180] Finally, another randomized study confirmed the improved BP with nocturnal HD, but failed to demonstrate improvement in the primary outcome of mortality and LV mass reduction.[181]

Despite the effects from dry weight reduction or more frequent HD treatments, pharmacologic treatment with antihypertensive agents is frequently required to further lower BP in HD patients. Overall, evidence from two meta-analyses supports the use of antihypertensive medications in HD patients to improve cardiovascular outcomes and mortality.[182,183] First-line recommended therapy for HD patients is the use of a RAAS-inhibiting drug.[177] In observational studies of HD patients, the use of ACE inhibitors was associated with reduced mortality.[184] However, this has not yet been confirmed in a randomized clinical trial. The Fosinopril in Dialysis (FOSIDIAL) trial randomized HD patients to either fosinopril or standard therapy and achieved a nonsignificant 8% reduction in the hazard ratio for mortality and cardiovascular death.[185] One small study that randomized hypertensive ESRD patients to one of several ARB (candesartan, losartan, valsartan) versus placebo demonstrated a reduction in both fatal and non-fatal cardiovascular events.[186] For patients that remain hypertensive after implementing a pharmacologic RAAS inhibition, other antihypertensive drugs should be prescribed based on existing comorbidities. The beta-blocker carvedilol has been shown to improve survival in patients with dilated cardiomyopathy,[187] and other beta-blockers may be used in the context of coronary artery disease. Additionally, the calcium channel blocker amlodipine has been shown to improve the composite outcome of mortality and nonfatal cardiovascular events in hypertensive HD patients already prescribed other agents, including ACE inhibitors and beta-blockers,[188] and should be considered as an add-on therapy. Fourth- and fifth-line agents, if necessary, include alpha-blockers, centrally acting sympathetic agonists (clonidine), and direct vasodilators. A suggested approach to the selection of an antihypertensive regimen for CKD patients is provided in Figure 40.4.

Despite the fact that peritoneal dialysis (PD) offers a more continuous treatment modality than intermittent HD for removing fluid and toxins, there is a high prevalence of hypertension in the PD population. In a multicenter Italian study of over 500 peritoneal dialysis patients, it was determined that the prevalence of hypertension was 88%.[189] Just as in HD patients, extracellular volume is an important determinant of BP, and both hypertensive status and the amount of sodium and fluid removal have been associated with increased mortality in PD patients.[190] Extracellular volume overload remains a primary concern in PD patients, and there is evidence using either an assessment of left atrial volume or bioimpedance analysis that PD patients are generally more volume overloaded than HD patients.[191,192] Further observational evidence, however, suggests that BP may not be as important of a predictor of the relative risk of death in the PD population.[193] Formal recommendations do not exist for the PD population as in HD patients, although attaining euvolemia in these patients remains an important goal.

CONCLUSION

Hypertension is a prevalent comorbidity associated with chronic kidney disease from the early stages to ESRD. Its existence in this population is related to multiple factors

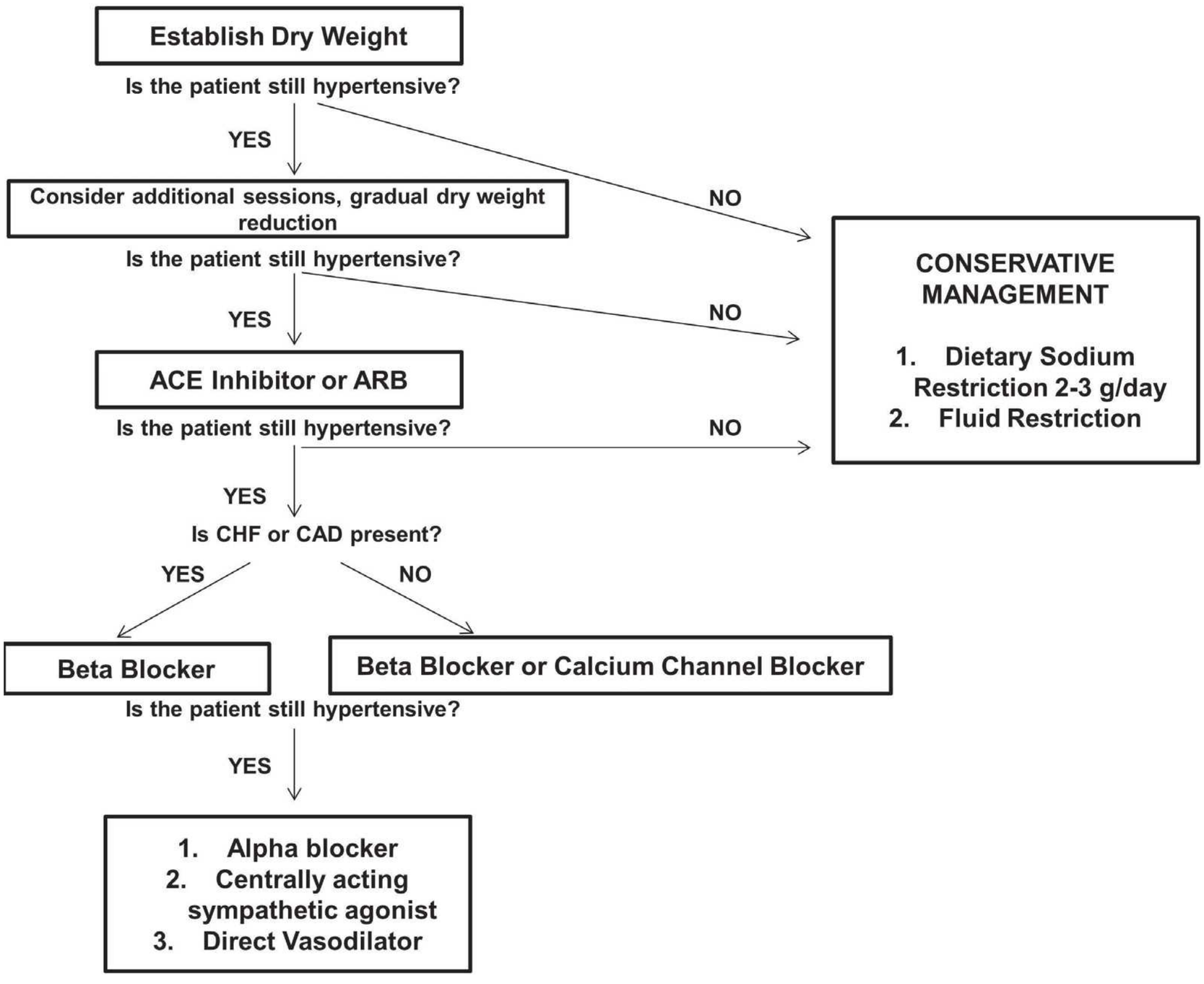


FIGURE 40.4 For hemodialysis (HD) patients, the first step in managing blood pressure (BP) should be to identify and achieve the accurate dry weight. Overtly volume overloaded patients may require additional HD treatments to achieve dry weight, and in others, a trial of gradual dry weight reduction may be possible. Inhibitors of the renin-angiotensin-aldosterone system (RAAS) (angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers) are first-line pharmacologic therapy in HD patients. As in pre–end-stage renal disease (ESRD) chronic kidney disease (CKD) patients, additional therapy may be dictated by underlying comorbidities reserving indicated beta-blockers for patients with congestive heart failure (CHF) or coronary artery disease (CAD). Calcium channel blockers can be added next for patients that remain hypertensive because there is evidence that they reduce cardiovascular end points compared to placebo in HD patients. Finally, patients that are still hypertensive may be started on fourth- or fifth-line agents (alpha-blockers, centrally acting sympathetic agonists, direct vasodilators). All HD patients should limit their interdialytic weight gain through dietary salt and water restriction to prevent extracellular volume overload.

including extracellular volume overload and increased vasoconstriction. Uncontrolled hypertension is associated with the progression of CKD to ESRD and with cardiovascular morbidity and mortality. Home and ambulatory BP measurements are currently the gold standard for predicting outcomes and assessing the overall BP burden. The target BP for CKD patients that optimally reduces the risk for both renal and cardiovascular outcomes remains unknown, but subjects with increased proteinuria derive more benefit from aggressive BP lowering. The optimal BP for patients on HD also remains unknown, but appropriate estimation and achievement of dry weight are paramount in controlling BP for most of these patients. Pharmacologic antihypertensive agents will be required for most CKD and ESRD patients, and inhibitors of the RAAS appear to be the most beneficial in CKD patients with proteinuria, with accumulating evidence that there may also be an advantage to these drugs in ESRD patients.

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