Hypertension and Chronic Kidney Disease

5

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Before You Start: Facts You Need to Know

- Hypertension is the second leading cause of ESRD in the United States.
- Uncontrolled hypertension is associated with accelerated progression to ESRD.
- Recent genetic advances may provide more information on the cause and effect relationship of hypertension and kidney disease.
- Renovascular hypertension and ischemic nephropathy are associated with progressive chronic kidney disease but their diagnosis and treatment remain complex and challenging.
- Treatment of hypertension in CKD patients is important to delay progression of renal function loss and to protect against cardiovascular disease.
- Resistant hypertension is defined as blood pressure that remains above goal (such as 140/90) in spite of the concurrent use of 3 antihypertensive agents of different classes.

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Worldwide, hypertension is a major public health problem and is associated with morbidity and mortality due to cardiovascular and kidney diseases. In the United States, hypertension is present in approximately 80–85 % of patients with CKD and is the second leading cause of ESRD in the United States after diabetes. Uncontrolled hypertension is associated with accelerated progression to ESRD. This association was prospectively studied among 332,544 men screened for the Multiple Risk Factor Intervention Trial (MRFIT); among the 814 subjects who either died of or were treated for ESRD, it was found that elevated blood pressure was a strong independent risk factor for ESRD [1].

Although the association of hypertension and ESRD was strong, this study did not prove a cause and effect relationship. In fact, whether hypertension causes CKD or is a result of CKD or both remains debated.

The diagnosis of hypertensive nephrosclerosis is a diagnosis of exclusion; it is a clinical diagnosis based on history, physical examination, urinalysis, and laboratory testing. The diagnosis is typically made in patients with chronic kidney disease who have had long-standing hypertension and subnephrotic range proteinuria without evidence of other kidney disease (based on serologic testing and imaging tests). Few patients diagnosed with hypertensive nephrosclerosis undergo renal biopsy.

Histologic lesions of hypertensive nephrosclerosis are characterized by changes in vascular, glomerular, and tubulointerstitial structures.

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For example, vascular changes are characterized by afferent arteriolar narrowing and fibrosis, arteriosclerosis and arteriolosclerosis, and intimal fibrosis; glomerular changes by hyalinosis, global glomerulosclerosis, and segmental glomerulosclerosis; and tubulointerstitial changes by atrophy, inflammation, and fibrosis.

To examine the accuracy of the diagnosis of hypertensive nephrosclerosis, an examination of renal biopsies was performed on a subset of patients enrolled in the African American Study of Kidney Disease (AASK) Trial, a trial that was designed to examine the impact of antihypertensive therapies and two levels of blood pressure control on the rate of progression of renal dysfunction in African Americans with presumed hypertensive renal disease. The AASK pilot biopsy study of 39 patients showed 38 patients with arteriosclerosis and/or arteriolosclerosis [2]. This confirmed that renal biopsies in nondiabetic hypertensive African Americans with mild to moderate renal insufficiency in the absence of nephrotic proteinuria are likely to show changes consistent with what we call hypertensive nephrosclerosis as outlined above.

The mechanism by which hypertension causes renal dysfunction is based on animal models, which have demonstrated that autoregulation protects the glomerular microcirculation from high arterial pressures. In certain conditions, such as chronic kidney disease and diabetes, this autoregulation is impaired, which is associated with glomerular injury and glomerulosclerosis. Although some evidence from human studies support the concept of autoregulatory dysfunction at the level of the glomerular microcirculation, the evidence from animals are much stronger.

Just as hypertension may cause CKD, CKD may also cause hypertension. Why this may be so is multifactorial. These factors include sodium retention, increased activity of the renin-angiotensin system and sympathetic nervous system, and impaired nitric oxide synthesis and endothelium-mediated vasodilatation in uremic patients. Patients with CKD frequently have sleep apnea and secondary hyperparathyroidism, both of which can contribute to hypertension with the latter causing increased intracellular calcium concentration leading to vasoconstriction. Besides, the circadian variation in BP is profoundly disturbed. Ambulatory blood pressure monitoring in patients with CKD often identifies a loss of normal decline in blood pressure of 10 % during sleep, such patients are termed "nondippers," which has been associated with an increased risk of left ventricular hypertrophy and cardiovascular events [3].

The diagnosis of hypertensive nephrosclerosis has been called into question with the discovery of the association of specific genes with kidney disease. Molecular genetic advances, particularly mapping by admixture linkage disequilibrium (MALD) analyses, pointed to a cluster of polymorphisms in the *MYH9* gene on chromosome 22 that were strongly associated with African ancestry nondiabetic kidney disease. However, Genovese et al. searched an expanded risk interval and found a statistically stronger genetic association with kidney disease in *APOL1*, the gene encoding apolipoprotein L-1, which is located <20 kb from the 3′ end of *MYH9* [4].

The two *APOL1* risk allele variants, G1 and G2, have been found to be strongly associated with nondiabetic kidney disease, particularly FSGS. It is hypothesized that patients with *APOL1* risk variant alleles have a genetic predisposition to kidney disease and then suffer a "second hit" such as a gene-gene or gene-environment interaction leading to various histologic forms of nondiabetic kidney disease and perhaps many patients who are labeled as having "hypertensive nephrosclerosis" actually have an underlying genetic predisposition to kidney disease [5].

The normal in vivo functions of *APOL1* and the mechanism of kidney injury are unknown. Interestingly, however, *APOL1* risk variants likely rose to high frequency in sub-Saharan Africa due to conferring protection from African sleeping sickness caused by trypanosomes. Genovese et al. found that serum from carriers of *APOL1* risk variants demonstrated a trypanolytic

effect on *Trypanosoma brucei rhodesiense* and absence of trypanosomal killing with serum from individuals lacking *APOL1* risk variants [4]. Thus, the *APOL1* risk variants provided a likely selective advantage to carriers against African sleeping sickness, but unfortunately, possession of two *APOL1* risk variants is associated with increased risk of kidney disease. This story is similar to the protection of malaria by HgbS.

As more data emerges regarding genetic and environmental influences on the development of kidney disease, some have proposed that hypertensive kidney disease is a no longer useful term and a more generic term of arterionephrosclerosis should be used.

5.1 Renovascular Hypertension and Ischemic Nephropathy

Renovascular disease is a term used to describe several clinical syndromes resulting from reduced perfusion to the kidney including ischemic renal disease and renovascular hypertension. Ischemic renal disease occurs when renal blood flow falls below the level of renal autoregulation and leads to reduced GFR and renal atrophy. On the other hand, renovascular hypertension (RVH) is defined as a syndrome of elevated blood pressure that is produced as a result of a variety of conditions that cause renal ischemia. The most common cause of RVH is main renal artery stenosis (RAS), either by fibromuscular dysplasia or atherosclerotic renal vascular disease.

Mechanisms responsible for sustained RVH differ according to whether one or both kidneys are affected by significant stenosis. Both situations have impaired renal perfusion, which activates the renin-angiotensin system causing sodium retention. However, when there is still one functioning kidney (in experimental animals this is simulated by one clipped renal artery, with two kidneys present and is termed "two-kidney hypertension"), pressure natriuresis can occur in the functioning kidney eliminating excess sodium. This leads to a sustained decreased perfusion to the stenotic side, leading to sustained activation of the renin-angiotensin system. Hypertension in this situation is angiotensin II-dependent hypertension with secondary aldosterone excess. On the other hand when the vascular lesion involves both kidneys or affects a solitary functioning kidney (termed "one-kidney hypertension"), there is no normal kidney to counteract the increased systemic pressure. Sodium is thus retained and blood volume expanded, which feeds back to inhibit the renin-angiotensin system. However, the renin-angiotensin system activation is inappropriately activated for the degree of sodium retention.

Renovascular disease can have varied presentations. Clinical features that may alert to the presence of renovascular disease include an acute rise of serum creatinine of at least 30 % after administration of ACE inhibitor or ARB (often accompanied by hypotension), a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason, moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema, late onset of severe hypertension (after age of 55 years), or presence of an abdominal bruit.

The diagnosis of RVH requires demonstration of a critical stenotic vascular lesion affecting the renal artery. Luminal occlusion of less than 60 % rarely reduces either pressure or blood flow. RVH usually only occurs when luminal occlusion is relatively severe, usually in the 70–80 % occlusion range.

American College of Cardiology/American Heart Association (ACC/AHA) developed guidelines to assist clinicians with the diagnosis, medical treatment, and revascularization for renal artery stenosis (Box 5.1).

The gold standard for diagnosing renal artery stenosis is renal arteriography but is usually performed only after a less invasive test has increased the likelihood of an accurate diagnosis. Less invasive tests include duplex Doppler ultrasonography, CTA, or MRA. The test of choice should be based on institutional expertise and patient

Box 5.1. What the Guidelines Say You Should Do: Renal Artery Stenosis (RAS) [6]

Clinical Clues to Diagnosis

Class I Recommendations

- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of hypertension before the age of 30 years
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the onset of severe hypertension [as defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report] after the age of 55 years
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with the following characteristics: (a) accelerated hypertension (sudden and persistent worsening of previously controlled hypertension), (b) resistant hypertension (defined as the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic), or (c) malignant hypertension (hypertension with coexistent evidence of acute end-organ damage)
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with new azotemia or worsening renal function after the administration of an ACE inhibitor or/and angiotensin receptor blocking agent
- The performance of diagnostic studies to identify clinically significant RAS is indicated in patients with sudden, unexplained pulmonary edema (especially in azotemic patients)

Class IIa Recommendations

- The performance of diagnostic studies to identify clinically significant RAS is reasonable in patients with unexplained renal failure, including individuals starting renal replacement therapy (dialysis or renal transplantation)
- *Class IIb*The performance of arteriography to identify significant RAS may be reasonable in patients with multivessel coronary artery disease and none of the clinical clues or PAD at the time of arteriography
- The performance of diagnostic studies to identify clinically significant RAS may be reasonable in patients with unexplained congestive heart failure or refractory angina

Diagnostic Methods for Renal Artery Stenosis

Class I

- Duplex ultrasonography is recommended as a screening test to establish the diagnosis of RAS
- Computed tomographic angiography (in individuals with normal renal function) is recommended as a screening test to establish the diagnosis of RAS
- Magnetic resonance angiography is recommended as a screening test to establish the diagnosis of RAS
- When the clinical index of suspicion is high and the results of the noninvasive tests are inconclusive, catheter angiography is recommended as a diagnostic test to establish the diagnosis of RAS

Class III

- Captopril renal scintigraphy is not recommended as a screening test to establish the diagnosis of RAS
- Selective renal vein renin measurements are not recommended as a useful screening test to establish the diagnosis of RAS
- Plasma renin activity is not recommended as a useful screening test to establish the diagnosis of RAS
- The captopril test (measurement of plasma renin activity after captopril administration) is not recommended as a useful screening test to establish the diagnosis of RAS

Medical Treatment for Renal Artery Stenosis

Class I

- Angiotensin-converting enzyme inhibitors are effective medications for treatment of hypertension associated with unilateral RAS

- Angiotensin receptor blockers are effective medications for treatment of hypertension associated with unilateral RAS
- Calcium-channel blockers are effective medications for the treatment of hypertension associated with unilateral RAS
- Beta-blockers are effective medications for treatment of hypertension associated with RAS

Indications for Revascularization for Renal Artery Stenosis

Asymptomatic Stenosis

Class IIb

- Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS
- The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven

Hypertension

Class IIa

- Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with unexplained unilateral small kidney, and hypertension with intolerance to medication

Preservation of Renal Function

Class IIa

- Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney

Class IIb

- Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS

Congestive Heart Failure and Unstable Angina

Class I

- Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema

Class IIa

Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina

factors as radiocontrast and gadolinium are potentially harmful in patients with CKD stage 4 or 5. Captopril renal scintigraphy, selective renal vein renin measurements, and plasma renin activity are not useful as initial diagnostic tests for renal artery stenosis.

It has been suggested that calculation of resistance index by duplex Doppler ultrasonography can identify patients who are likely or not to respond to revascularization. A high resistive index was associated with a poor outcome and may indicate irreversible intrarenal vascular disease.

Once diagnosed, the optimal treatment for the patient is not clear. Patients with atherosclerotic renovascular disease have a high rate of systemic atherosclerosis and are at increased risk for adverse cardiovascular outcomes. The increased cardiovascular risk in patients with atherosclerotic renal artery stenosis may be due to mechanisms activated by the renal artery stenosis or due to the high likelihood that these patients have atherosclerosis in multiple vascular beds. Treatment should address modifiable cardiovascular risk factors, including weight loss, smoking cessation, treatment of hyperlipidemia, and blood pressure and glucose control.

There are no definitive randomized controlled trial data to guide clinicians on specific antihypertensive medical therapies in patients with RAS. It would appear that the first-line therapy should be directed at the principal mechanism thought to be responsible for the elevated blood pressure, activation of the renin-angiotensin-aldosterone system. Although blockade of the

renin-angiotensin system is considered fundamental, it is contraindicated in most patients. Antihypertensive agents that block the renin-angiotensin system remove the vasoconstrictive action of angiotensin II (AII) at the efferent arteriole. When pre-glomerular pressures are reduced for any reason, blockade of AII causes the kidney to lose its compensatory ability to preserve glomerular transcapillary filtration pressures by constricting the efferent arteriole. This can lead to "functional acute renal insufficiency." Paying particular importance to volume status and cardiac function and monitoring serum creatinine if ever agents that block the renin-angiotensin system are initiated are important in limiting renal toxicity in these patients.

Whether to treat patients with medical therapy alone or with revascularization has been evaluated in several randomized clinical trials. These trials, including the ASTRAL trial, showed a lack of benefit of revascularization using BP as an endpoint. The ASTRAL trial was a multicenter, randomized, unblinded trial of 806 patients with atherosclerotic renovascular disease assigned to undergo either revascularization in addition to medical therapy or to medical therapy alone with a primary outcome of renal function. During a 5-year period, patients in the group who underwent revascularization had a slightly slower rate of progression of renal impairment; however, the change was too small to offer clinical benefit. In addition there was no significant difference in a secondary endpoint of systolic blood pressure between the two groups. The two groups had similar rates of renal events, major cardiovascular events, and death. Given serious complications associated with revascularization occurred in 23 patients including 2 deaths, the investigators concluded that there was an increased risk but no evidence of significant clinical benefit from revascularization in patients with atherosclerotic renovascular disease. The major limitation of the ASTRAL trial was that the population enrolled only included patients who their own physician was uncertain as to whether revascularization would provide a clinical benefit leaving an unresolved question of whether some patients with severe renal artery stenosis may benefit from revascularization [8].

The CORAL trial, cardiovascular outcomes in renal atherosclerotic lesions, is an ongoing trial that was designed to answer the question if stent revascularization of hemodynamically significant atherosclerotic RAS in hypertensive patients when added upon medical therapy can prevent adverse cardiovascular and renal events. It has been proposed that atherosclerotic renal artery stenosis has many other deleterious effects throughout the body other than causing elevated blood pressure and that treating RAS with revascularization may be beneficial in ways other than lowering blood pressure. The results of this trial may provide guidance for a disease whose diagnosis and treatment remain complex and challenging at present [9].

5.1.1 BP Control in CKD

Treatment of hypertension in CKD patients is important to delay progression of renal function loss and to protect against cardiovascular disease. KDIGO clinical practice guidelines for management of blood pressure in chronic kidney disease are based on quality of evidence (Boxes 5.2 and 5.3).

BP goals should be individualized according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment. Evidence supports a goal blood pressure $\leq$140/90 mmHg for CKD patients without proteinuria defined as albuminuria <30 mg/24 h, regardless of diabetes status. Since proteinuria has been associated with worse kidney outcomes, stricter BP control is recommended with goal BP $\leq$130/80 mmHg in both diabetic and nondiabetic patients with albuminuria >30 mg/24 h.

A meta-analysis by Jafar et al. was performed to determine the levels of blood pressure and urine protein excretion associated with the lowest risk of progression of CKD using antihypertensive therapy with and without ACE inhibitors. Although the data must be interpreted with caution as the clinical trials were not designed to primarily assess this, the meta-analysis on 1860 nondiabetic patients from 11 randomized, controlled trials showed that systolic blood pressure

Box 5.2. What the Guidelines Say You Should Do: Management of Blood Pressure in Non-dialysis-Dependent CKD Patients Without Diabetes Mellitus [10]

- We recommend that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion <30 mg per 24 h whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤140 mmHg systolic and ≤90 mmHg diastolic (1B).
- We suggest that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion of 30–300 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 systolic and ≤80 mmHg diastolic (2D).
- We suggest that nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion >300 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 systolic and ≤80 mmHg diastolic (2C).
- We suggest that an ARB or ACE-I be used in nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion of 30–300 mg per 24 h in whom treatment with BP-lowering drugs is indicated (2D).
- We recommend that an ARB or ACE-I be used in nondiabetic adults with non-dialysis-dependent CKD and urine albumin excretion >300 mg per 24 h in whom treatment with BP-lowering drugs is indicated (1B).

Box 5.3. What the Guidelines Say You Should Do: Management of Blood Pressure in Non-dialysis-Dependent CKD Patients with Diabetes Mellitus [10]

- We recommend that adults with diabetes and non-dialysis-dependent CKD and urine albumin excretion <30 mg per 24 h whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤140 mmHg systolic and ≤90 mmHg diastolic [1B].
- We suggest that adults with diabetes and non-dialysis-dependent CKD urine albumin excretion of >30 mg per 24 h whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic be treated with BP-lowering agents to maintain a BP that is consistently ≤130 mmHg systolic and ≤80 mmHg diastolic [2D].
- We suggest that an ARB or ACE-I be used in adults with diabetes and non-dialysis-dependent CKD with urine albumin excretion of 30–300 mg per 24 h [2D].
- We recommend that an ARB or ACE-I be used in adults with diabetes and non-dialysis-dependent CKD with urine albumin excretion >300 mg per 24 h [1B].

of 110–129 mmHg and urine protein excretion of less than 2 g/day were associated with the lowest risk for kidney disease progression. The risk of progression increased with urine protein excretion greater than 1 g/day and systolic blood pressures greater than 120–130 mmHg. The results of the meta-analysis, which were consistent with the results of the MDRD and AASK trials, showed that lowering blood pressure is more beneficial in delaying progression of kidney disease in patients with higher levels of proteinuria [11].

Although BP control has been shown to delay progression of kidney disease, more aggressive blood pressure control has not been shown to be better. Three main randomized controlled trials, MDRD, AASK, and REIN2, evaluated lower blood pressure and cardiovascular and renal outcomes.

The Modification of Diet in Renal Disease (MDRD) study was a multicenter clinical trial designed to test the hypotheses that restricting

protein intake and controlling BP would delay the progression of chronic kidney disease. The MDRD study consisted of 2 studies. The first study randomized patients with GFR 22–55 mL/min per 1.73 m^2 to usual protein diet or low-protein diet and to a usual BP defined as MAP ≤107 mmHg or low BP defined as MAP ≤92 mmHg. The projected mean decline in GFR at 3 years did not differ significantly between the protein and blood pressure groups. In study 2, patients with GFR 13–24 mL/min per 1.73 m^2 were assigned to low-protein diet or very-low-protein diet and usual BP defined as MAP ≤107 or low BP defined as MAP ≤92. In study 2, the very-low-protein group has a marginally slower decline in GFR but no delay in the time to occurrence of ESRD or death [12].

The African American Study of Kidney Disease and Hypertension (AASK) trial randomized African Americans with hypertension, age 18–70 years old with GFR 20–65 mL/min per 1.73 m^2, and no other identified causes of renal insufficiency to one of the two mean arterial pressure goals, 102–107 mmHg or <92 mmHg, and to initial treatment with one of the three antihypertensive study drugs, metoprolol, ramipril, or amlodipine. The primary outcome measure was rate of change of GFR. Main secondary outcome was composite index of three clinical endpoints including reduction of GFR of >50 % or 25 mL/min/1.73 m^2, ESRD, or death. The study did not find a significant difference in primary or secondary outcomes or CV events or mortality between the two blood pressure groups [13].

Ramipril efficacy in nephropathy 2 (REIN-2) is a multicenter, randomized controlled trial of patients with nondiabetic kidney disease and proteinuria >1 g/day receiving ramipril 2.5–5 mg/day which randomly assigned them to either conventional BP defined as diastolic BP <90 mmHg or intensive BP control defined as BP <130/80 mmHg using add-on therapy with felodipine 5–10 mg/day. The systolic BP difference between the conventional and intensive BP groups was 4.1 mmHg and diastolic BP difference was 2.8 mmHg. The study showed no difference in ESRD rate between the two BP groups [14].

In summary, there is good evidence from the MDRD, AASK, and REIN-2 trials that aggressive BP control is not protective in regard to cardiovascular, renal, or mortality outcomes.

Once BP goals have been identified, aim should focus on the appropriate treatment plan to achieve that goal. Lifestyle modifications should be encouraged in all patients with CKD to lower BP and improve long-term cardiovascular and renal outcomes. KDIGO guidelines on lifestyle modifications are listed in Box 5.4.

Attainment of blood pressure goal generally requires multiple antihypertensive agents. A number of trials have shown that ACE inhibitors

Box 5.4. What the Guidelines Say You Should Do: Lifestyle and Pharmacologic Treatments for Lowering Blood Pressure in Non-dialysis-Dependent CKD Patients [10]

- Individualize BP targets and agents according to age, coexistent cardiovascular disease and other comorbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes), and tolerance of treatment [not graded]
- Inquire about postural dizziness and check for postural hypotension regularly when treating CKD patients with BP-lowering agents [not graded]
- Encourage lifestyle modification in people with CKD to lower BP and improve long-term cardiovascular and other outcomes
- We recommend achieving or maintaining a healthy weight (BMI 20–25) (1D)
- We recommend lowering salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated (1C)
- We recommend undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 min 5 times per week (1D)
- We suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women (2D)

or ARBs can slow the progression of diabetic kidney disease with overt nephropathy. A meta-analysis performed by Jafar et al. that included 11 randomized controlled trials comparing the efficacy of ACE inhibitors to other antihypertensive regimens that did not contain ACE inhibitors in nondiabetic patients with kidney disease showed that ACE inhibitors decreased blood pressure and urinary protein excretion, as well as slowed the increase in creatinine and reduced the incidence of ESRD. The benefit was greater in patients with higher levels of proteinuria [15]. The benefit of ACE inhibitors or ARBs on patients without proteinuria is unknown. KDIGO recommends ARBs or ACE inhibitors as first-line therapy in all CKD patients with albuminuria >300 mg/24 h.

ACE inhibitors generally reduce proteinuria by 30–35 %. The anti-proteinuric effects are generally enhanced when the patient is on a low-sodium diet or taking a diuretic since glomerular microcirculation is more dependent on angiotensin II in relative volume depletion states.

Although ACE inhibitors and ARBs may be particularly beneficial in patients with CKD as noted above, the side effects of these medications, including hyperkalemia, hypotension, and reduction in GFR, make them difficult to use in patients with CKD. Patients who become volume depleted are particularly susceptible to reduction in GFR while taking an ACE inhibitor or ARB. In response to low perfusion pressures, angiotensin II causes increased resistance at the efferent arteriole in an attempt to preserve intraglomerular pressure. This compensatory mechanism is blocked by ACE inhibitors and ARBs. Patients with reduced GFR are more susceptible to elevated potassium levels due to impaired excretion; reducing aldosterone secretion with ACE inhibitors or ARBS blocks the major hormonal stimulus for urinary potassium excretion leading to increased susceptibility to hyperkalemia in patients with CKD. Patients should have their blood pressure, potassium, and creatinine monitored within 1–2 weeks after initiating ACE inhibitor or ARB therapy. Patients at increased susceptibility for adverse effects include elderly patients and those with heart failure, potassium levels >5 mmol/L, advanced CKD with GFR <30 mL/min/1.73m^2, or on high-dose diuretics. Termination of ACE inhibitors should occur if there is a dramatic increase in serum creatinine concentration from the baseline value within the first few weeks of initiation of therapy or if patient experiences uncontrolled hyperkalemia or any other significant adverse effect.

Despite the benefit of ACE inhibitors and ARBs in previous studies, progression of CKD still occurred in a significant number of patients. Based on this finding, combination blockade of the RAAS has been evaluated in several studies to determine if dual therapy can provide additional benefit. The Aliskiren Trial in Type 2 Diabetics Using Cardiorenal Endpoints (ALTITUDE) was an international, randomized, double-blind, placebo-controlled, parallel group study which randomized a large number of type 2 diabetic patients with renal impairment to receive aliskiren 300 mg daily, a direct renin inhibitor, or placebo in addition to conventional therapy with ACE inhibitor or ARB. The study was terminated early due to lack of benefit of aliskiren over placebo in reducing cardiovascular or renal endpoints after approximately 2 years but an increased risk of adverse events including hypotension, hyperkalemia, and renal impairment [16].

The VA NEPHRON-D trial was a recently terminated multicenter, prospective, randomized, double-blind clinical trial to assess the effect of combination losartan and lisinopril compared with losartan alone, on the progression of kidney disease in diabetic patients with overt proteinuria. Those randomized to combination therapy had more adverse events leading to early termination of the trial. Publication is pending [17].

Although ACE inhibitors or ARBs are considered first-line therapy in most patients with proteinuric kidney disease, there are no specific guidelines regarding second and third agents used to control blood pressure in CKD patients. Volume expansion often plays a role in hypertensive CKD patients. Higher doses of diuretics are typically required in CKD patients due to the reduction in kidney function. There is some data that taking at least one antihypertensive at night may improve BP control in CKD patients as

many are "nondippers," which is one of the strongest predictors of adverse cardiovascular outcomes.

When treating hypertension in CKD patients, it is most important to individualize therapy.

5.1.2 Resistant HTN

According to the definition endorsed by the American Heart Association, resistant hypertension is defined as blood pressure that remains above goal (such as 140/90) in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal doses. The definition also includes patients with normal or elevated BP in the setting of four or more antihypertensive agents [18].

Resistant hypertension is common and the prevalence is increasing. It is seen among 15–30 % of treated hypertensive patients. Older age, obesity, chronic kidney disease, and diabetes are the strongest predictors of resistant hypertension.

Before diagnosing a person with resistant hypertension, pseudoresistance must be excluded. Pseudoresistance is defined as BP above goal in clinic but below goal outside of the clinic, frequently from white coat hypertension. De Nicola prospectively studied 436 hypertensive CKD patients to determine the prevalence and prognostic role of resistant hypertension in chronic kidney disease patients. The study showed that patients with true resistant hypertension were at high risk for cardiovascular and renal events; however, pseudoresistance in CKD patients is also frequent and does not increase the cardiorenal risk [3].

The best way to exclude pseudoresistance is with home blood pressure or ambulatory blood pressure readings. Home blood pressure monitoring has been shown to be useful in predicting target organ damage, CVD mortality, and CVD events. If the home BP is >135/85 mmHg, there is high probability that the ambulatory blood pressure will also be high and treatment should be started. If home BP is <125/76 mmHg, then a patient may be considered a true normotensive and no ambulatory BP is needed. The gray zone between 125–135 mmHg systolic and 76–85 mmHg diastolic requires further evaluation with ambulatory BP [7]. Agarwal and Andersen found that in patients with CKD, ambulatory blood pressures are a stronger predictor of ESRD or death compared to blood pressures obtained in the clinic [19] (Box 5.5).

Once true resistant hypertension is diagnosed, a complete history, physical examination, and laboratory studies should be done to look for contributing factors, as the etiology of resistant hypertension is commonly multifactorial. A careful history focusing on lifestyle factors such as physical activity, dietary salt intake, and heavy alcohol intake should be performed. Sodium restriction can lower blood pressure and enhance the anti-proteinuric effects of drugs that block the renin-angiotensin system in patients with proteinuria. Patients should be educated on interpreting food labels and should be provided feedback by assessing their sodium intake with a 24 h urine collection. Elderly, African Americans, and patients with CKD are particularly salt-sensitive.

A complete medication history is essential as many classes of drugs increase blood pressure including NSAIDS, erythropoietin, oral contraceptives, sympathomimetic agents such as decongestants or diet pills, stimulants, cyclosporine, and natural licorice. Physical examination and laboratory evaluation may reveal signs of organ damage such as retinopathy, cardiovascular disease, or kidney disease.

As part of their complete evaluation, patients with resistant hypertension should be screened for secondary causes of hypertension. CKD and obstructive sleep apnea are the two most common causes of secondary hypertension. Other causes include primary aldosteronism, pheochromocytoma, Cushing's syndrome, and renal artery stenosis.

Box 5.5. What the Guidelines Say You Should Do: Home and Ambulatory BP Monitoring [7]

Technical Aspects of BP Measurement

No tobacco or caffeine for 30 min preceding measurement

After 5 min of rest

With arm at heart level; back supported and feet flat on the ground

On nondominant arm (or arm with highest BP)

BP Monitor

Use a fully automated device with an upper arm cuff that has been validated by British Hypertension Society, Association for the Advancement of Medical Instrumentation, or International Protocol for the Validation of Automated BP

Measuring Devices

Monitors with memory that are able to store measurements are preferred

Training of Patients

Patients should be trained by their healthcare provider, and the monitor readings should be checked against mercury

Education content: hypertension and cardiovascular risk, BP measurement procedure, use of a validated monitor, cuff size, protocols for measuring BP, interpretation of BP readings, and monitor for their use only

Reevaluate patient technique and accuracy of the device annually

Target BP Goal

135/85 mmHg or 130/80 mmHg if patient has diabetes, coronary heart disease, or chronic kidney disease

Frequency and Schedule of Measurement

Initial values (*when patients begin HBPM at home*):

Base decisions on a 7-day measurement period with 2–3 measurements each morning and 2–3 measurements in the evening at prestipulated times (an average of 12 morning and evening values)

Exclude the first day measurements from the analyses; take advantage of these values as the reference parameter in the subsequent dose-titration phase

Dose-titration phase (*titration of initial dose and adjustment therapy*):

All measurements should be made under identical conditions and at the same times of the day and the initial values

HBPM data should be ascertained as trough values (i.e., before medication taken) in the morning and again at night

Use the average of BPs measured after 2–4 weeks to assess the effect of treatment

Long-term observation:

For stable normotensive (controlled) patients, patients should conduct HBPM a minimum of 1 week per quarter (an average of 12 morning and evening measurements under conditions described above)

Measurement should be made more frequently in patients with poor compliance.

Even after addressing lifestyle factors, contributing medications, and secondary causes of hypertension, patients often require multiple antihypertensive agents to control blood pressure. There is relatively little data addressing the efficacy of specific combinations of 3 or more drugs. In general, patients with resistant hypertension often have occult volume overload and diuretics may be particularly beneficial and are often underused. Aldosterone antagonists may provide significant antihypertensive benefit when added to other antihypertensive agents in patients with resistant hypertension. This effect may be due to lowering the elevated plasma

aldosterone levels in these patients; however, the antihypertensive effect has also been seen in patients with normal aldosterone levels. In addition, spironolactone has anti-proteinuric effects. However, extreme caution must be used when treating patients with resistant hypertension with aldosterone antagonists. These patients are at increased risk for hyperkalemia especially if they also have CKD and/or are also taking an ACE inhibitor or ARB. Given the lack of strong data, combination regimens should be chosen based on prior benefit, adverse events, comorbidities, and financial limitations.

Box 5.6. Relevant Guidelines

1. KDIGO Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease available at: http://kdigo.org/home/guidelines/blood-pressure-in-ckd/
2. ACC/AHA 2005 Practice Guidelines for Management of Patients with Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aorta) available at: http://circ.ahajournals.org/content/113/11/e463.full.pdf

Before You Finish: Practice Pearls for the Busy Clinician

- There is a strong association between hypertension and ESRD; however, the cause and effect relationship remains debated especially with the recent discovery of specific genes associated with kidney disease.
- The gold standard for diagnosing renal artery stenosis is renal arteriography. However, less invasive screening tests such as duplex Doppler ultrasonography, CTA, or MRA are typically performed first.
- There are no definitive randomized controlled trial data to guide clinicians on specific antihypertensive medical therapies in patients with renal artery stenosis. Despite previous RCT, whether revascularization is beneficial remains unclear. The CORAL trial may provide more data regarding this topic.
- BP goals should be individualized.
- Evidence supports a goal blood pressure ≤140/90 mmHg for CKD patients without proteinuria defined as albuminuria <30 mg/24 h, regardless of diabetes status.
- Since proteinuria has been associated with worse kidney outcomes, stricter BP control is recommended with goal BP ≤130/80 mmHg in both diabetic and non-diabetic patients with albuminuria >30 mg/24 h.
- Home blood pressure and ambulatory blood pressure monitoring should be used to make an accurate diagnosis of resistant hypertension.
- Treatment of resistant hypertension is typically multifactorial and should focus on a detailed history including lifestyle factors and contributing medications, physical examination, and evaluation for secondary causes of hypertension.

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