Hypertension in CKD: Core Curriculum 2019

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Hypertension and chronic kidney disease (CKD) are closely interlinked pathophysiologic states, such that sustained hypertension can lead to worsening kidney function and progressive decline in kidney function can conversely lead to worsening blood pressure (BP) control. The pathophysiology of hypertension in CKD is complex and is a sequela of multiple factors, including reduced nephron mass, increased sodium retention and extracellular volume expansion, sympathetic nervous system overactivity, activation of hormones including the renin-angiotensin-aldosterone system, and endothelial dysfunction. Currently, the treatment target for patients with CKD is a clinic systolic BP < 130 mm Hg. The main approaches to the management of hypertension in CKD include dietary salt restriction, initiation of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretic therapy. Uncontrolled hypertension can lead to significant cardiovascular morbidity and mortality and accelerate progression to end-stage kidney disease. Although intensive BP control has not been shown in clinical trials to slow the progression of CKD, intensive BP control reduces the risk for adverse cardiovascular outcomes and mortality in the CKD population.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Hypertension is common in patients with chronic kidney disease (CKD). The prevalence ranges from 60% to 90% depending on the stage of CKD and its cause. The mechanisms of hypertension in CKD include volume overload, sympathetic overactivity, salt retention, endothelial dysfunction, and alterations in hormonal systems that regulate blood pressure (BP). Hypertension remains a leading attributed cause of end-stage kidney disease (ESKD) in the United States. Uncontrolled hypertension is also associated with higher risk for cardiovascular (CV) morbidity and mortality. In this Core Curriculum, we review the pathophysiology, diagnosis, and management of hypertension in patients with CKD.

Pathophysiology of Hypertension in CKD

Question 1: All of the following mechanisms have been implicated in the development of hypertension in patients with CKD except (choose 1):

a) Sympathetic nervous system (SNS) overactivity
b) Increased intracellular calcium level
c) Sodium retention
d) Reversal of hypoxia-induced vasodilation
e) Increased activity of the renin-angiotensin-aldosterone system (RAAS)
f) None of the above; all these mechanisms have been implicated

For the answer to this question, see the following text.

Several putative mechanisms contribute to elevated BP in patients with CKD, including neural and hormonal changes that often act in concert to disrupt appropriate BP regulation (Fig 1).

CKD is associated with increased activity of the RAAS. There is reduced blood flow in peritubular capillaries downstream of sclerosed glomeruli. As a result of this reduced effective (perceived) blood flow, glomeruli in these regions hypersecrete renin, thereby increasing circulating angiotensin II levels. Angiotensin II has a direct vasoconstrictor effect, which increases systemic vascular resistance and BP. Because there are fewer functioning glomeruli in CKD, each remaining glomerulus must increase its glomerular filtration rate (GFR): increasing systemic arterial pressure helps bolster perfusion pressure and GFR.

Angiotensin II also promotes sodium reabsorption in the proximal tubule and (through aldosterone) the collecting duct. Moreover, net loss of overall GFR impairs sodium excretion, which also leads to sodium retention. Sodium retention causes hypertension through volume-dependent and volume-independent mechanisms. Excess extracellular volume leads to increased perfusion of peripheral tissues, which stimulates vasoconstriction, increases peripheral vascular resistance, and therefore increases BP. Extracellular volume expansion also leads to the production of ouabain-like steroids that induce vasoconstriction and therefore increase peripheral vascular resistance. Volume-independent mechanisms include increased vascular stiffness

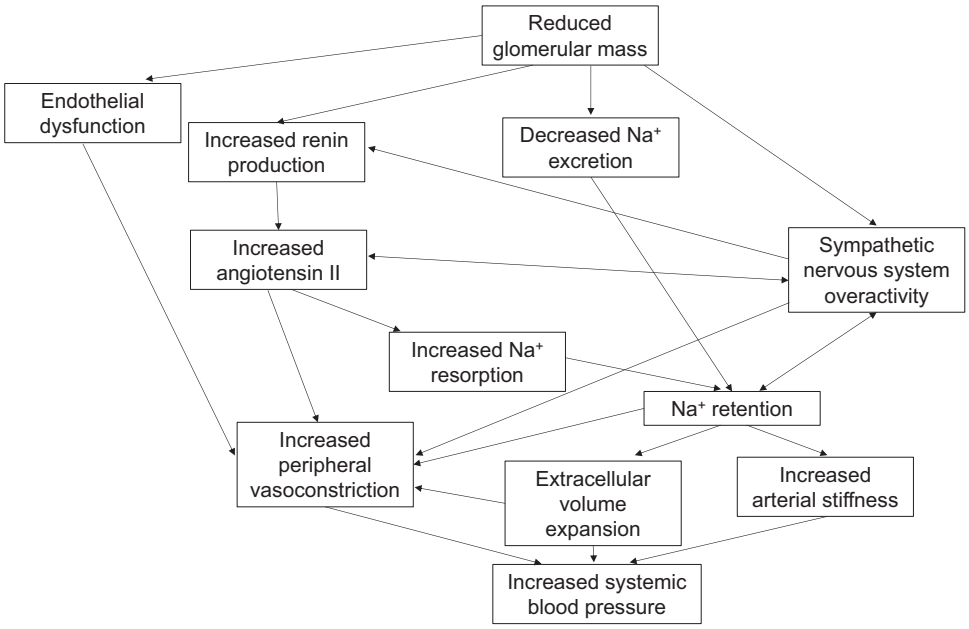

Figure 1. Pathophysiologic mechanisms of hypertension in chronic kidney disease.

and increased central sympathetic outflow (a direct sequela of increased extracellular sodium).

Overactivity of the SNS in CKD stimulates renin production by the renal juxtaglomerular cells. Beyond SNS activation by sodium retention, renal ischemia also leads to renal afferent nerve excitation through adenosine. Finally, experimental and clinical studies suggest that angiotensin II levels (which are higher in patients with CKD as detailed above) directly stimulate SNS activity.

Endothelial dysfunction (including impaired nitrous oxide production), oxidative stress, and elevated endothelin levels are also implicated in the pathogenesis of hypertension in patients with CKD.

Several factors related to CKD complications may also contribute to the high prevalence of hypertension among patients with CKD. In anemic patients, treatment with erythropoietin and erythropoiesis-stimulating agents can reverse hypoxia-induced vasodilation as hemoglobin concentration increases. There is also evidence that these agents may acutely cause vasoconstriction, even before anemia is corrected. Furthermore, secondary hyperparathyroidism increases intracellular calcium levels, leading to vasoconstriction. Because progressive CKD is associated with vascular calcification, isolated systolic hypertension that is resistant to antihypertensive therapy is relatively common. Finally, uremia may impair vasodilation by inhibiting nitric oxide synthase.

While CKD contributes to the development of hypertension, hypertension is also a major factor in the progression of CKD. Normally, the glomerular capillary loops are shielded from elevated systemic arterial pressures by a process called autoregulation. Afferent arteriole caliber changes in response to systemic pressure (myogenic reflex) and sodium chloride delivery to the macula densa (tubuloglomerular feedback) are part of the autoregulatory process that helps maintain intraglomerular pressure and therefore GFR. However, in hypertensive patients, chronically elevated systemic arterial pressures cause remodeling of the afferent arteriole and reduce its ability to constrict and dilate. Over time, elevated systemic arterial pressures transmitted to the kidney lead to glomerular hypertension, nephrosclerosis, and progressive loss of kidney function.

As the discussion shows, multiple mechanisms have been implicated in the development of hypertension in CKD. Therefore, the correct answer to question 1 is (f).

Additional Readings

- Neumann J, Ligtenberg G, Klein II, Koomans HA, Blankestijn PJ. Sympathetic hyperactivity in chronic kidney disease: pathogenesis, clinical relevance, and treatment. *Kidney Int.* 2004;65:1568-1576.
- Rodriguez-Iturbe B, Romero F, Johnson RJ. Pathophysiological mechanisms of salt-dependent hypertension. *Am J Kidney Dis.* 2007;50:655-672.

Defining Normal and Abnormal BP in CKD

Question 2: A 54-year-old woman with a medical history of stage 3 CKD and dyslipidemia presents to the clinic. BP readings taken in triage are 138/78 mm Hg and 134/80 mm Hg. Which of the following would be the best next step:

a) Repeat the BP in the clinic after 5 minutes of quiet rest
b) Initiate therapy with an angiotensin-converting enzyme (ACE) inhibitor
c) Order a 24-hour ambulatory BP monitor
d) Tell the patient her BP is appropriate for age

Question 3: The 24-hour ambulatory BP monitoring (ABPM) is considered a preferred metric of BPs because:

a) Clinical trials have shown that lowering ambulatory BPs reduced the risk for CV events
b) White coat hypertension is considered to be completely benign and should never be treated
c) ABPM measurements are more strongly associated with risk for adverse outcomes compared with clinic BP measurements
d) Home BP measurements are usually not performed correctly by patients and are not associated with risk for adverse outcomes

For the answers to these questions, see the following text.

Accurate BP measurement is critical to the diagnosis and management of CKD. Most clinical BP measurements are obtained in the office and these measurements are commonly used during treatment decisions, although 24-hour ABPM is preferred for the confirmation of abnormal BPs. Office BP measurements should be obtained in standardized fashion after 5 minutes of quiet rest using a validated device that is routinely calibrated. The cuff should be placed on the arm at the level of the atrium with the correct cuff size (the bladder of the cuff should encircle 80% of the arm), and the patient should be sitting with feet flat on the ground and back supported by a chair. At least 2 readings should be obtained in the office. Caffeine and exercise should be avoided 30 minutes before BP measurement. BP measurement errors are common in routine clinical practice, so accurate assessment of BP is critical during the diagnosis and monitoring of hypertension. All major adult clinical trial data related to the effect of BP treatment on renal and CV outcomes have used BPs obtained in the clinic setting under standardized protocols with serial measurements.

Ambulatory BP Monitoring

Because of the stronger association between BPs obtained from ABPM with CV and renal outcomes, 24-hour ABPM has been considered the preferred metric of BP in both the general population and patients with CKD. During 24-hour ABPM, an appropriate-size BP cuff is worn for 24 hours, with measurements taken every 15 to 20 minutes during the daytime and every 30 to 60 minutes during sleep. Thus, an advantage of ABPM is the provision of readings during sleep that allows for assessment of appropriate nocturnal physiologic dipping (BP should decrease by >10% during sleep) and BP variability. The presence of masked hypertension (defined as normal office BPs but elevated out-of-office BPs) has been associated with higher risk for CV disease in patients with and without CKD. Both nocturnal hypertension and nondipping status have also been associated with higher risk for adverse CV outcomes, as well as CKD progression.

A substantial proportion of patients with CKD have white coat (10%-20%) and masked hypertension (10%-30%), which would not be detected in the absence of ABPM (Table 1). However, ABPM is not widely available and reimbursement for its performance is poor. When available, elevated BPs obtained using an appropriate technique in the clinic can be confirmed with 24-hour ABPM, especially in settings of suspected white coat or masked hypertension. ABPM can also be useful for confirmation of BP control and help detect hypotension that may be occurring outside the office setting in symptomatic patients.

Home BP Monitoring

Out-of-office BP measurements (eg, home BP monitoring) are more practical than ABPM and can be a useful tool for monitoring BPs during therapy. Automated devices that have been validated should be used, and individuals should be trained to measure BP in the appropriate fashion (as for office BP measurements). Two readings should be taken at each sitting, twice a day. Although the evidence is less robust than 24-hour ABPM, home BP measurements have also been associated with risk for adverse outcomes in a similar fashion as ABPM and can be a useful adjunct for improving BP control, especially if combined with telehealth counseling.

BP Classification and Correlations Between BPs Taken in Different Settings

Based on the most recent American Heart Association/American College of Cardiology (AHA/ACC) guidelines,

Table 1. Definitions of Normal and Abnormal BP Based on the 2017 AHA/ACC Guideline in Patients With CKD

BP Classification[a]	Office BP	Daytime ABPM or Home BP
Normal or elevated BP	<130/80 mm Hg	<130/80 mm Hg
Sustained hypertension	≥130/80 mm Hg	≥130/80 mm Hg
White coat hypertension	≥130/80 mm Hg	<130/80 mm Hg
Masked hypertension	<130/80 mm Hg	≥130/80 mm Hg

Difficult-to-Control BP	Definition
Resistant hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a diuretic, without adequate BP control
Refractory hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a thiazide-type diuretic and another of which is spironolactone, without adequate BP control

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHA/ACC, American Heart Association/American College of Cardiology; BP, blood pressure; CKD, chronic kidney disease.
[a]As recommended by 2017 ACC/AHA guideline (Whelton et al. *J Am Coll Cardiol.* 2018;71(19):2199-2269).

an office BP < 120/80 mm Hg is considered to be normal, and office BPs in the range of 120- to <130/<80 mm Hg are considered to be elevated. An office BP ≥ 130/80 mm Hg would meet the threshold for hypertension. Although the Systolic BP Intervention Trial (SPRINT) found that assignment to a systolic BP treatment goal < 120 mm Hg lowered the risk for CV events and death, given that the BPs measured in routine clinic visits are unlikely to be obtained in the same standardized approach as in trials such as SPRINT (eg, unobserved using an automated device), routine clinic BPs could be 5 to 10 mm Hg higher than BPs obtained in clinical trials such as SPRINT. Thus, treatment to a systolic BP target < 120 mm Hg based on BPs obtained in routine clinical practice could potentially lead to overtreatment of BP.

An office BP of 140/90 mm Hg is thought to correlate with an ABPM 24-hour average BP of 130/80 mm Hg (135/85 mm Hg daytime and 120/70 mm Hg nighttime mean BPs) and a mean home BP of 135/85 mm Hg. The appropriate classification of BPs using a combination of office and ambulatory BPs (when available) are shown in Table 1.

Resistant and refractory hypertension (Table 1) in CKD are common, especially in CKD stages 4 to 5, for which multiple classes of complementary antihypertensive agents are frequently needed to achieve BP control.

Because the majority of clinical trials in patients with and without CKD have targeted office-measured BPs, most guidelines (including KDIGO) continue to recommend treatment of hypertension based on office-measured BPs in adults with CKD. To date, there have been no large clinical trials of adults with CKD that have targeted 24-hour ABPM-derived BPs. Because of the logistical complexity associated with routine ABPM performance and lack of solid evidence to support ABPM-based BPs, we currently recommend routine treatment of hypertension based on office BP measurements ascertained using standardized protocols. However, in our opinion, in the setting of resistant or refractory hypertension, symptoms of orthostasis or hypotension among those receiving antihypertensive therapy and concern for autonomic dysfunction or white coat hypertension, ABPM- or home-based BPs should be obtained to help further guide treatment of hypertension in patients with CKD. Home BP monitoring may be especially useful for achieving appropriate BP control among patients with CKD.

In the scenario raised in question 2, the patient's BP of 137/78 mm Hg is only mildly elevated. It is also a single visit reading and therefore it is best to repeat this reading several months later before any treatment is considered. Therefore, the correct answer is (a).

Regarding question 3, because multiple studies have shown that ABPM more strongly correlates with adverse outcomes compared to office BP, the correct answer is (c).

Additional Readings

- Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. *Kidney Int.* 2006;69:1175-1180.
- Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med.* 2018;378:1509-1520. ★ **ESSENTIAL READING**
- Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation.* 2005;111:697-716. ★ **ESSENTIAL READING**
- Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Soc Hypertens.* 2018;12:579 e571-579 e573. ★ **ESSENTIAL READING**

Hypertension Workup and Differential Diagnosis in CKD

Question 4: A 42-year-old woman with stage 3 CKD and previously well-controlled hypertension for 10 years has required escalation of antihypertensive therapy from 1 to 4 medications in the last few months. She is asymptomatic. She does not have a family history of hypertension. BP measured in the clinic is 160/90 mm Hg in both arms and legs. On laboratory evaluation, she has metabolic alkalosis but has never been hypokalemic. Kidney sizes on renal ultrasound are normal and symmetric. What is the most appropriate next step?

a) Doppler ultrasound
b) Check aldosterone-to-renin ratio
c) Echocardiogram to evaluate for coarctation of the aorta
d) Check serum metanephrine levels
e) Reduce dietary sodium intake

Question 5: All of the following are indications for workup of secondary hypertension in patients with CKD except:

a) Onset of elevated BP before puberty but after the development of CKD
b) Hypertension unresponsive to 3 antihypertensive medications, including a diuretic
c) Acute worsening of previously well-controlled hypertension
d) Persistent hypokalemia off diuretic treatment
e) Concomitant development of tremors and palpitations
f) Flash pulmonary edema

Question 6: The STAR, ASTRAL, and CORAL trials suggest that renal angioplasty with stenting may not be superior to medical therapy for renal artery stenosis. As a result, workup for renovascular hypertension should be reserved for patients who are more likely to improve their BP with revascularization. Which of the following patient characteristics suggests a higher probability of improvement in BPs after revascularization?

a) Resistant hypertension
b) Flash pulmonary edema
c) Abrupt onset of hypertension
d) a) and c) only
e) a), b), and c)

For the answers to these questions, see the following text.

As both a cause and consequence of CKD, hypertension is highly prevalent among patients with CKD. Additional workup for other causes of hypertension is warranted if there are reasons to suspect a secondary cause of hypertension (Box 1). In general, further evaluation is recommended in patients with CKD if the onset of elevated BPs occurred before puberty (and preceded the development of CKD), severe or malignant hypertension that is out of proportion to the degree of CKD is present, sudden worsening of BP control occurs in a previously hypertensive patient with good BP control, or resistant hypertension is present (Table 1). Workup and prioritization of testing should be guided by cause-specific signs or symptoms.

For example, patients with spontaneous or diuretic-induced hypokalemia should be screened for primary aldosteronism using aldosterone-to-renin ratio. In addition, compared with other causes of hypertension, primary aldosteronism is characterized by more severe hypertension, increased risk of CV events, and a higher incidence of end-organ damage. Although hypokalemia is more frequent in primary aldosteronism, it is detected in <50% of patients with primary aldosteronism. Thus, the absence of hypokalemia should not deter providers from screening for primary aldosteronism if there are other reasons to justify this evaluation. Hyperaldosteronism may occur as often in patients with CKD as in the general population.

Box 1. Causes of Secondary Hypertension

- Renovascular hypertension (atherosclerosis, fibromuscular dysplasia)
- Coarctation of the aorta
- Primary aldosteronism
- Pheochromocytoma
- Polycystic ovary syndrome
- Cushing syndrome
- Hyperthyroidism, hypothyroidism
- Obstructive sleep apnea
- Chemical or medication induced
  - Caffeine, coffee
  - Alcohol
  - NSAIDs
  - Oral contraceptives
  - Steroids
  - Calcineurin inhibitors
  - Chemotherapeutic agents (gemcitabine, VEGF receptor inhibitors)
  - Illicit drugs (amphetamines, cocaine)
- Monogenic disorders
  - Liddle syndrome
  - Syndrome of apparent mineralocorticoid excess
  - Glucocorticoid-remediable hypertension (familial hyperaldosteronism type I)
  - Familial hyperaldosteronism type III
  - Gordon syndrome
  - Subtypes of congenital adrenal hyperplasia

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; VEGF, vascular endothelial growth factor.

BP measurements in all 4 extremities should be compared to rule out coarctation of the aorta. Patients with episodic severe hypertension (with or without headache or flushing) or a family history concerning for genetic predisposition should have serum metanephrine levels checked to rule out pheochromocytoma.

Asymmetric kidney sizes, worsening estimated GFR (eGFR) with ACE inhibition or angiotensin receptor blockade, presence of an abdominal bruit, or flash pulmonary edema may suggest the presence of renovascular hypertension. The initial screening test for renal artery stenosis is Doppler ultrasonography, and peak systolic velocity in the main renal artery is the best parameter for the detection of significant stenosis. To detect ≥60% reduction in renal artery diameter, a peak systolic velocity cutoff of 180 to 200 cm/s has been proposed.

Three randomized trials comparing medical therapy and renal angioplasty with stenting in patients with atherosclerotic renal artery stenosis did not demonstrate differences in mortality, CV events, or progression of CKD: the STAR (Stent Placement in Patients With Atherosclerotic Renal Artery Stenosis and Impaired Renal Function), ASTRAL (Angioplasty and Stenting for Renal Artery Lesions), and CORAL (Cardiovascular Outcomes With Renal Atherosclerotic Lesions) trials. Although selection bias may have led to underestimation of the therapeutic benefits of angioplasty, based on these results, only patients with a higher likelihood of improvement in BPs with revascularization should be evaluated for renovascular hypertension because angioplasty is not without risks and medical management would otherwise be the primary approach to treatment. Patient factors that may increase the chances of improving BP control with revascularization include recent onset/progression of hypertension, resistant hypertension, and flash pulmonary edema. In addition, patients with a solitary kidney and renal artery stenosis or bilateral renal artery stenosis with worsening kidney function could also be considered for revascularization.

In the vignette described in question 4, the patient has resistant hypertension with poor control despite the use of 4 antihypertensive medications. It is therefore important to consider secondary causes of hypertension. The key finding is persistent metabolic alkalosis despite CKD. Although she is not hypokalemic, it is important to rule out primary hyperaldosteronism. The correct answer is therefore (b).

Regarding question 5, although hypertension in the pre-pubescent period is an indication for further workup, hypertension after the development of CKD in this period

is common and in itself should not trigger further workup. All other options require further workup. Therefore, the correct answer is (a).

Relevant to question 6, multiple studies have shown a correlation between the presence of resistant hypertension, abrupt onset of severe hypertension and flash pulmonary edema, and higher likelihood of responding to revascularization. Therefore, the correct answer is (e).

Additional Readings

- ASTRAL Investigators; Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med.* 2009;361:1953-1962.
- Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med.* 2014;370:13-22.
- Textor SC, Lerman LO. Reality and renovascular disease: when does renal artery stenosis warrant revascularization? *Am J Kidney Dis.* 2014;63:175-177. ★ ESSENTIAL READING

Management of Hypertension

Question 7: Which of the following dietary or behavioral modifications has not been shown to improve BP control, especially in patients with CKD?

a) A <2-g/d sodium diet
b) Reduction in alcohol intake
c) Weight loss
d) High-potassium diet
e) Diet low in unsaturated fats

Question 8: A 60-year-old man with CKD, diabetes, and hypertension is on treatment with a maximum-dose ACE inhibitor, but both his BP and proteinuria are still not at therapeutic targets. Which of the following would be the best choice for antihypertensive therapy, assuming that additional proteinuria reduction is a goal and the same BP target could be achieved with any of these agents?

a) Add an angiotensin receptor blocker (ARB)
b) Add clonidine
c) Add amlodipine
d) Add diltiazem
e) Add hydralazine

For the answers to these questions, see the following text.

Nonpharmacologic Therapy

Dietary and Behavioral Modification

Nonpharmacologic therapy should be the first step to the treatment of hypertension, even among patients with CKD, and the mainstays of nonpharmacologic therapy are dietary interventions. Diets rich in fruits and vegetables and low in saturated or unsaturated fats (such as the DASH [Dietary Approaches to Stop Hypertension] diet) can lead to moderate declines in BP by ~10 mm Hg in hypertensive patients. Increasing potassium intake to 3 to 4 g/d and reducing sodium intake to <1.5 g/d can also lead to reductions in BP by ~5 mm Hg with both interventions in hypertensive patients, although a high-potassium intake may be difficult to maintain without provoking hyperkalemia in patients with more advanced CKD (eg, stage 4 or 5). It is unknown whether a higher potassium diet would lower BP in patients with CKD. Limiting alcohol intake to no more than 2 drinks per day in men and 1 drink per day in women can also help improve BP control. Reducing sodium intake also has the added benefit of reducing proteinuria.

Weight loss can reduce BP by ~5 mm Hg for every 5-kg weight loss, and bariatric surgery may be a potential option in those deemed to be suitable candidates for this procedure. For those with sleep apnea, treatment with continuous positive airway pressure may also lead to modest improvements in BP. In addition, both aerobic and isometric resistance exercise can improve BPs in patients with hypertension. Currently, 90 to 150 minutes of aerobic exercise is recommended per week. Use of over-the-counter medications such as nonsteroidal anti-inflammatory pain medications should be avoided because they may increase BP and also adversely affect kidney function.

Renal Denervation

Renal denervation involves radiofrequency ablation of the network of nerves that innervate the renal artery. The role of renal denervation for the treatment of resistant (or refractory) hypertension among patients with CKD is unclear. Although the procedure itself appears to be safe, early randomized trials initially failed to demonstrate the superiority of renal denervation over sham procedures among patients with resistant hypertension and normal or mildly reduced eGFRs (>45 mL/min/1.73 m^2) in terms of reducing office or ambulatory BPs 6 months postintervention. However, more recent trials have shown more promising results, including the SPYRAL HTN-ON MED trial, which demonstrated that renal denervation was effective in reducing office systolic BPs by ~7 mm Hg compared to a sham procedure among patients with elevated BPs who were receiving pharmacotherapy at baseline. A small study of patients with CKD also showed remarkable reductions in BP (>30 mm Hg) after renal denervation in more advanced CKD (stages 3-4), and some studies have shown reductions in albuminuria and slower progression of CKD with renal denervation. However, no device is currently approved in the United States for routine clinical use.

Baroreceptor Activation

Pacing of the carotid baroreceptors to increase their activity and therefore reduce SNS activity has also been attempted as a treatment strategy for resistant hypertension. However, this method has not been shown to be efficacious. No device is currently approved in the United States, and there are no data on the effectiveness of such devices in patients with CKD.

Pharmacologic Therapy

In general, for patients with CKD, ACE inhibitors and ARBs are considered first-line antihypertensive agents by most guidelines, especially in the presence of concurrent albuminuria (albumin excretion > 300 mg/d). Evidence to support their benefit over other classes of antihypertensive agents in those without proteinuria is less robust. ACE inhibitors and ARBs induce efferent arteriolar vasodilation, which leads to reductions in intraglomerular pressure and therefore suppresses proteinuria. This renal benefit is applicable to both patients with and without diabetes. However, the combination of ACE inhibitors with ARBs has not been shown to be effective at slowing the progression of CKD or reducing CV events in patients with CKD (with or without diabetes). Because this combination may predispose to hyperkalemia and acute kidney injury, dual blockade with ACE inhibitors and ARBs has generally fallen out of favor. Similarly, although there is some evidence to support the use of ACE inhibitors or ARBs with aldosterone antagonists in certain conditions such as heart failure, patients with CKD receiving this regimen need to be monitored carefully for hyperkalemia.

There is less consensus regarding the optimal second-line class of antihypertensive agents in patients with CKD, but diuretics are a reasonable choice for most patients with CKD, especially in the setting of volume overload. Whereas loop diuretics may be preferred as GFR declines, especially if there is evidence of volume overload, there is evidence that thiazide and thiazide-like diuretics are effective antihypertensive agents, likely through indirect vasodilatory mechanisms. Of the loop diuretics, bumetanide or torsemide may be preferred due to its superior bioavailability. Torsemide also has a longer half-life than furosemide and bumetanide and can be administered once daily. Diuretics may be less optimal as the antihypertensive agent of choice for patients with CKD due to polycystic kidney disease if they trigger volume depletion and vasopressin release, which may contribute to cyst enlargement. Nondihydropyridine calcium channel blockers (eg, diltiazem or verapamil) may also have antiproteinuric effects and may be useful in patients with CKD and proteinuria. Among patients with cardiac disease, there may be indications for other classes of antihypertensive agents, such as β-blockers.

For resistant hypertension, regimens that include a diuretic or spironolactone may be considered. When BP is thought to be resistant, confirmation of the accuracy of BP measurements and adherence to BP medications is important because often BPs are "pseudo-resistant" due to measurement error or nonadherence to therapy. For patients who report symptoms of hypotension while receiving antihypertensive therapy, ABPM may be useful to confirm whether these symptoms are related to decreases in BP that may not be detected in the office.

There has been some suggestion that moving the timing of once-daily antihypertensive therapy from morning to nighttime may be beneficial for reducing CV risk, purportedly by restoring physiologic nocturnal dipping and the circadian rhythm of BP variation. However, the effect of changing only the timing of antihypertensive medications remains controversial in terms of its long-term CV benefits. In a Cochrane Review of this issue conducted in 2011 that included mostly studies of patients without CKD, bedtime dosing of antihypertensive medications was associated with better BP control, but not with a decrease in risk for adverse CV or mortality outcomes.

Table 2 provides recommendations regarding antihypertensive therapy selection among patients with CKD. In general, ACE inhibitors and ARBs are preferred first-line agents in patients with albuminuria or proteinuria, and diuretics may be useful in combination with ACE inhibitors and ARBs to balance the risk for hyperkalemia and enhance albuminuria or proteinuria reduction. In the absence of albuminuria or proteinuria, the optimal first-line agent for patients with CKD is debated and may be selected based on concurrent indications, including the cause of hypertension, need to treat hyperkalemia, or fluid overload.

More recently, a new class of antihyperglycemic medications, the SGLT2 inhibitors, has been shown to be effective in reducing risk for adverse CV and kidney disease outcomes. They also possess antihypertensive effects that do not appear to be related to glucosuria.

Medication nonadherence is one of the major reasons for inadequate BP control in patients with CKD. More than 50% of patients with CKD require 3 or more medications to control their BP, and many patients with CKD have a high pill burden because of concurrent treatment needed for metabolic acidosis, hyperphosphatemia, and other sequelae of CKD. It is important to assess for nonadherence to medications as a cause of uncontrolled BPs and to simplify regimens when possible.

In terms of question 7, although higher potassium intake is associated with decreased BP in healthy individuals, it is not known whether a high-potassium diet has the same effect in patients with CKD. The correct answer is therefore (d).

Regarding question 8, the nondihydropyridine calcium channel blocker diltiazem has been shown to have an antiproteinuric effect. Therefore, the best answer is (d).

Additional Readings

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- Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014;370:1393-1401.

Table 2. Selected Indications and Considerations in the Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Diuretics					
Thiazide (eg, hydrochlorothiazide, chlorthalidone, metolazone)	Fluid overload; may improve proteinuria if used in combination with RAS inhibitors	Kidney stone prevention (hypercalciuria); Gordon syndrome; NDI	Hyperuricemia; hypercalcemia; hyponatremia; hypokalemia; hyperglycemia (with long-term use)	Gout; hypercalcemia	May be less effective when eGFR is <30 although some studies have shown these agents remain effective even with low eGFR
Loop (eg, furosemide, bumetanide, torsemide)	Fluid overload	Heart failure; hypercalcemia	Hearing loss; hypokalemia; hypocalcemia; hyponatremia	Gout; sulfonamide-related hypersensitivity	Bumetanide and torsemide have better intestinal absorption than furosemide
Potassium-sparing (triamterene, amiloride)	Fluid overload; hypokalemia	Refractory hypomagnesemia; lithium toxicity/NDI	Hyperkalemia; metabolic acidosis	Pregnancy	
RAS Blockade					
ACEi (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Heart failure with reduced ejection fraction; post–myocardial infarction	Cough; angioedema; hyperkalemia; leukopenia; anemia	Pregnancy; bilateral renal artery stenosis	
ARBs (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Uric acid lowering (losartan) or gout; similar to ACEi	Cough (less than with ACEi); angioedema; hyperkalemia	Pregnancy; bilateral renal artery stenosis	
β-Blockers					
Selective (metoprolol, nebivolol)		Heart failure; atrial fibrillation; migraines; essential tremors; anxiety disorders; angina	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	Asthma; COPD; 2nd or 3rd degree heart block	
Combined α-β (carvedilol, labetalol)		Heart failure; atrial fibrillation	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	2nd or 3rd degree heart block	May be better tolerated in lung disease than selective β-blockers
Calcium Channel Blockers					
Dihydropyridine (amlodipine, nifedipine)		Raynaud, esophageal spasms	Lower-extremity edema; gingival hypertrophy		May worsen proteinuria
Nondihydropyridine (diltiazem, verapamil)	Proteinuria reduction	Atrial fibrillation	Constipation; gingival hyperplasia	2nd or 3rd degree heart block	↑ calcineurin and mTOR inhibitor levels
Other					
α-Blockers		Benign prostatic hypertrophy; kidney stone passage	Orthostasis		
Central α-adrenergic agonists (clonidine)			Sedation; bradycardia; dry mouth; rebound hypertension	Depression	
Vasodilators (minoxidil, hydralazine)			Headache; tachycardia; lupus-like syndrome (hydralazine); edema; pericardial effusion	Post–myocardial infarction; heart failure	
Direct renin inhibitors (aliskiren)	Proteinuria reduction; if not tolerating ACEi or ARB			Bilateral renal artery stenosis	Not recommended for use in combination with ACEi or ARBs

(Continued)

Table 2 (Cont'd). Selected Indications and Considerations in the Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Aldosterone antagonists (spironolactone, eplerenone)	Proteinuria reduction	Cirrhosis with ascites; polycystic ovarian syndrome; hyperaldosteronism	Hyperkalemia; metabolic acidosis; gynecomastia		May be useful in addition to ACEi or ARB for proteinuria reduction

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (in mL/min/.173 m^2); mTOR, mammalian target of rapamycin; NDI, nephrogenic diabetes insipidus; RAS, renin-angiotensin system.

► Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet.* 1999;354:359-364. ★ ESSENTIAL READING

Effect of Hypertension Treatment on Outcomes and Treatment Targets

Question 9: Tight BP control (to systolic BP < 120 mm Hg) has been shown to:
a) Reduce the risk for death from any cause
b) Reduce the risk for heart failure
c) Reduce the risk for CKD progression
d) Improve quality of life
e) Both a) and b)

Question 10: Largely as a result of SPRINT, the current AHA/ACC- recommended BP goal for patients with nondiabetic nonproteinuric CKD is:
a) <130/80 mm Hg
b) <130/90 mm Hg
c) <135/85 mm Hg
d) <140/80 mm Hg
e) <140/90 mm Hg

For the answers to these questions, see the following text.

There is strong observational evidence that uncontrolled hypertension is associated with worse renal and CV outcomes across all age groups. Regardless of the cause of CKD, uncontrolled (and potentially severe) hypertension accelerates loss of GFR. However, whether intensive lowering of BP slows GFR decline is less clear. Patients with CKD are at elevated CV risk, and hypertension is one of the leading risk factors for CV events and stroke. Several randomized trials have compared the effects of varying BP goals on renal and CV outcomes. As a result of these studies, BP treatment targets for patients with CKD have evolved over the last 2 decades.

Three large randomized controlled trials of patients with nondiabetic CKD (the MDRD [Modification of Diet in Renal Disease] Study, AASK [African American Study of Kidney Disease in Hypertension], and the REIN-2 [Ramipril Efficacy in Nephropathy 2] trial) that assigned BP targets of approximately <130/80 mm Hg failed to demonstrate a benefit for renal (eGFR decline or ESKD risk) or CV outcomes compared with BP targets in the range of <140/90 mm Hg. However, in the MDRD Study, assignment to the lower BP goal slowed GFR decline among the subset of patients with urinary protein excretion > 1 g/d. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, which included patients with diabetes (but excluded patients with CKD stage 4 or 5), lowering of systolic BP to <120 mm Hg was not superior compared to a <140 mm Hg target for either CV outcomes or kidney disease progression, although the majority of patients enrolled did not have CKD. The HALT-PKD (HALT Progression of Polycystic Kidney Disease) trials randomly assigned more than 500 hypertensive patients with autosomal dominant polycystic kidney disease (baseline eGFR ≥ 60 mL/min/1.73 m^2) to a low BP target (95/60-110/75 mm Hg) versus standard BP target (120/70-130/80 mm Hg) groups. During follow-up periods ranging from 5 to 8 years, the lower BP group had a 14.2% slower annual increase in total kidney volume, but there were no differences in change in eGFR. As a consequence, for many years the recommended BP target for patients with CKD without significant proteinuria was <140/90 mm Hg; this changed with the recent publication of SPRINT.

In SPRINT, 9,361 participants (~2,600 with stage 3 CKD) were assigned to a systolic BP target <120 mm Hg versus <140 mm Hg. SPRINT participants were older than 50 years and the subset with CKD had mildly to moderately decreased GFRs. Patients with significant proteinuria or ESKD were excluded from the study. This study population differed from that of the MDRD Study and the REIN-2 trial, which recruited patients with more advanced CKD and greater degrees of proteinuria. Overall, patients assigned to the lower BP treatment target had lower risk for CV events (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from CV causes) and all-cause mortality, although no difference in CKD progression was noted. The trial was stopped prematurely because of the benefit of intensive BP lowering on CV events. In a subset of SPRINT participants, those assigned to lower BP targets were also noted to have lower risk for mild cognitive impairment and dementia. Largely as a result of data from this trial, in 2017, the AHA/ACC released new guidelines recommending a <130/80 mm Hg BP target for patients with CKD given the CV benefits from this threshold, regardless of the degree of proteinuria present. However, the appropriate BP target for patients with CKD who do not fit the SPRINT inclusion criteria (including those with diabetes mellitus)

remains a subject of debate. Overall, individualized BP targets should be set only after weighing potential risks and benefits of treatment.

For question 9, SPRINT showed that tight control was associated with a decrease in all-cause mortality and CV events but had no effect on progression of CKD; thus, the answer to this question is (e). For question 10, the current AHA/ACC recommendation is BP < 130/80 mm Hg, so the correct answer is (a).

Additional Readings

- Cheung AK, Rahman M, Reboussin DM, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol.* 2017;28:2812-2823. ★ ESSENTIAL READING
- Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575-1585. ★ ESSENTIAL READING
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Treatment of Hypertension in Special Populations With CKD

Question 11: For which of the following groups is ABPM recommended routinely during the assessment and treatment of hypertension?

a) Children and adolescents
b) Patients with a functional allograft
c) Patients older than 65 years
d) Pregnant women

Question 12: The BP treatment target for a kidney transplant recipient is:

a) Systolic BP < 120 mm Hg
b) Systolic BP < 130 mm Hg
c) Systolic BP < 140 mm Hg
d) Dependent on the age of the patient

For the answers to these questions, see the following text.

Children and Adolescents

Approximately 1% of all patients with CKD are children and adolescents. Hypertension is found in a considerable proportion of pediatric patients with CKD and ESKD, ranging from 50% to 80% depending on the stage of disease. Currently, thresholds for the diagnosis of hypertension do not differ for children with or without CKD. Because there are physiologic increases in BP with growth, the threshold for normal BP changes with age and depends on the sex and height of the patient. As in adults, hypertension and proteinuria are strong predictors of CKD progression in children. Hence, adequate BP control remains an important focus of CKD management in children.

BP evaluation should be performed at every clinical encounter for pediatric patients with CKD. However, even if clinic BP measurements are within the normal range, more than one-third of children and adolescents with CKD have masked hypertension. White coat hypertension is also common in children and affects approximately half the children with elevated office BPs. Thus, the American Academy of Pediatrics (AAP) recommends the performance of 24-hour ABPM at least annually for the detection of white coat and masked hypertension in all children with CKD (Table 3). These recommendations differ from those for adults, for whom ABPM is not routinely recommended as in the AAP guidelines.

The overall goal for treating hypertension in childhood is to reduce the risk for target organ damage. The KDIGO and AAP clinical practice guidelines currently recommend that a child with CKD begin antihypertensive therapy when BP measurements are consistently above the 90th percentile for the child's age, sex, and height or ≥130/80 mm Hg.

Lifestyle and dietary modifications for the treatment of hypertension are similar for children as they are for adults. Initial antihypertensive medications for children with CKD and hypertension is either ACE inhibitors or ARBs unless there are contradictions to the use of these agents. If a pediatric patient is not responding to the preferred agents, other antihypertensive treatments such as α-blockers, β-blockers, calcium channel blockers, or direct vasodilators can be used. Lifestyle modifications

Table 3. Hypertension Classification in Children and Adolescents With CKD

	BP Measurements	
HTN Classification	Children (1-<13 y)	Adolescents (≥13 y)
Hypertension	≥95th percentile for age, sex, and height or ≥130/80 mm g, whichever is lower	≥ 130/80 mm Hg
Stage 1 hypertension	≥95th percentile to <95th percentile + 12 mm Hg, or 130-139/80-89 mm Hg, whichever is lower	130-139/80-89 mm Hg
Stage 2 hypertension	≥95th percentile + 12 mm Hg, or ≥140/90 mm Hg, whichever is lower	≥ 140/90 mm Hg

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; HTN, hypertension.
Based on information in Flynn et al (Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017;140[3]:e20171904).

should be sustained in combination with pharmacologic treatments. Repeat ABPM should be conducted at least annually to reassess hypertension treatment response.

In the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Pediatric Patients) trial, 385 children taking ACE inhibitors were randomly assigned to 2 BP targets: intensified (24-hour mean arterial BP < 50th percentile by ABPM) or conventional (mean arterial BP from 50th-95th percentile). The intensified treatment arm had slower progression of their CKD. Hence, tight BP control to a 24-hour mean arterial BP < 50th percentile by ABPM using ACE inhibitors as the first-line antihypertensive agent is currently recommended.

Additional Readings

- Flynn JT, Kaelber DC, Baker-Smith CM, et al; Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140: e20171904. ★ ESSENTIAL READING
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- Mitsnefes M, Flynn J, Cohn S, et al; CKiD Study Group. Masked hypertension associates with left ventricular hypertrophy in children with CKD. *J Am Soc Nephrol.* 2010;21:137-144.
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Older Patients

Although the Joint National Committee 8 (JNC 8) guidelines set a higher BP treatment target of <150/90 mm Hg for older patients, with the recent publication of SPRINT, it is now the recommendation that BP be <130/80 mm Hg in adults 65 years and older in the community who are ambulatory. Most trials that have included patients 65 years and older have consistently shown CV benefits to tighter BP control. However, current AHA/ACC guidelines note that individualization of BP treatment targets may be reasonable depending on comorbid conditions, life expectancy, and the presence of cognitive impairment. These recommendations do not differ for elderly patients 65 years and older who also have concurrent CKD.

Race and Ethnicity Considerations in the Treatment of Hypertension

The prevalence of uncontrolled hypertension in CKD varies considerably by race or ethnicity and is more prevalent in blacks, Hispanics, and Asians. Blacks develop hypertension at an earlier age than non-Hispanic whites, have a 4-fold higher rate of hypertension-related ESKD, and have a higher prevalence of resistant hypertension. These differences may be attributable to genetic and physiologic differences observed in blacks, including the presence of the high-risk apolipoprotein L1 (*APOL1*) gene variant, vitamin D deficiency, greater degree of sympathetic overactivity, different dietary patterns, and higher prevalence of obesity and metabolic syndrome.

Currently, BP treatment targets do not vary by race or ethnicity, but there are known significant racial and ethnic disparities in hypertension control. Nonpharmacologic treatment for all patients regardless of race and ethnicity remains the first step to therapy. Lifestyle modifications are especially important for the black and Hispanic populations, but adoption of these lifestyle changes is often difficult due to social and financial barriers in these at-risk populations.

Both the AHA/ACC and JNC 8 guidelines recommend ACE inhibitors or ARBs as initial pharmacologic treatment for hypertensive patients with CKD regardless of race or ethnicity. However, it should be noted that there is a slightly higher incidence of angioedema with ACE inhibitors in blacks and higher incidence of ACE-induced cough in Asian Americans.

Additional Readings

- Duru OK, Li S, Jurkovitz C, et al. Race and sex differences in hypertension control in CKD: results from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis.* 2008;51:192-198.
- Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA.* 2002;288:2421-2431.

Women and Pregnancy

Although the definition of normal BP differs by sex in children, in adults, no sex-specific BP treatment targets have been developed and the effect of BP treatment on outcomes has not been shown to differ by sex. Women planning to become pregnant should avoid ACE inhibitors or ARBs due to their teratogenic potential, especially if these agents are continued beyond the first trimester of pregnancy.

The optimal BP target for pregnant women with CKD is unclear. The goal of antihypertensive therapy is to prevent severe hypertension and its sequelae. Agents acceptable for use during pregnancy for the control of BP include nifedipine, labetalol, and methyldopa. RAAS inhibitors are contraindicated during pregnancy. Calcium channel blockers and β-blockers may potentially reduce the risk for preeclampsia during pregnancy.

BP Treatment After Kidney Transplantation

There have been no large-scale randomized controlled trials of alternate BP targets in patients with functional allografts. In general, both KDIGO and the ACC/AHA guidelines currently recommend a BP target < 130/80 mm Hg, although whether lower BP targets would slow the progression of CKD or reduce CV risk remains unclear. One observational study of the association between baseline BPs of participants from the FAVORIT (Folic Acid for

Vascular Outcome Reduction in Transplantation) trial suggested higher risk for CV disease and mortality with every 20–mm Hg increase in systolic BP, whereas every 10–mm Hg lower diastolic BP (if diastolic BP was <70 mm Hg) was associated with higher risk for CV disease and mortality.

In terms of antihypertensive agent selection, no specific first-line agents are recommended. Although the use of ACE inhibitors and ARBs may be reasonable as first-line agents in the kidney transplant population, especially if there is proteinuria, risk for hyperkalemia and acute kidney injury may be high with concurrent calcineurin inhibitor use. Small-scale trials that randomly assigned patients with functional allografts to ACE-inhibitor or ARB therapy versus placebo have not shown definitive benefit on pathologic changes, kidney disease progression, or death in this population.

Returning to question 11, children and adolescents with CKD have a high rate of both masked and white coat hypertension. The AAP has recommended that ABPM be performed annually in this group; thus, the best answer is (a). For question 12, although no large-scale randomized studies have been performed in kidney transplant recipients to define the best BP level in transplant recipients, the KDIGO and AHA/ACC guidelines both recommend a target of <130/80 mm Hg; thus, the best answer is (b).

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