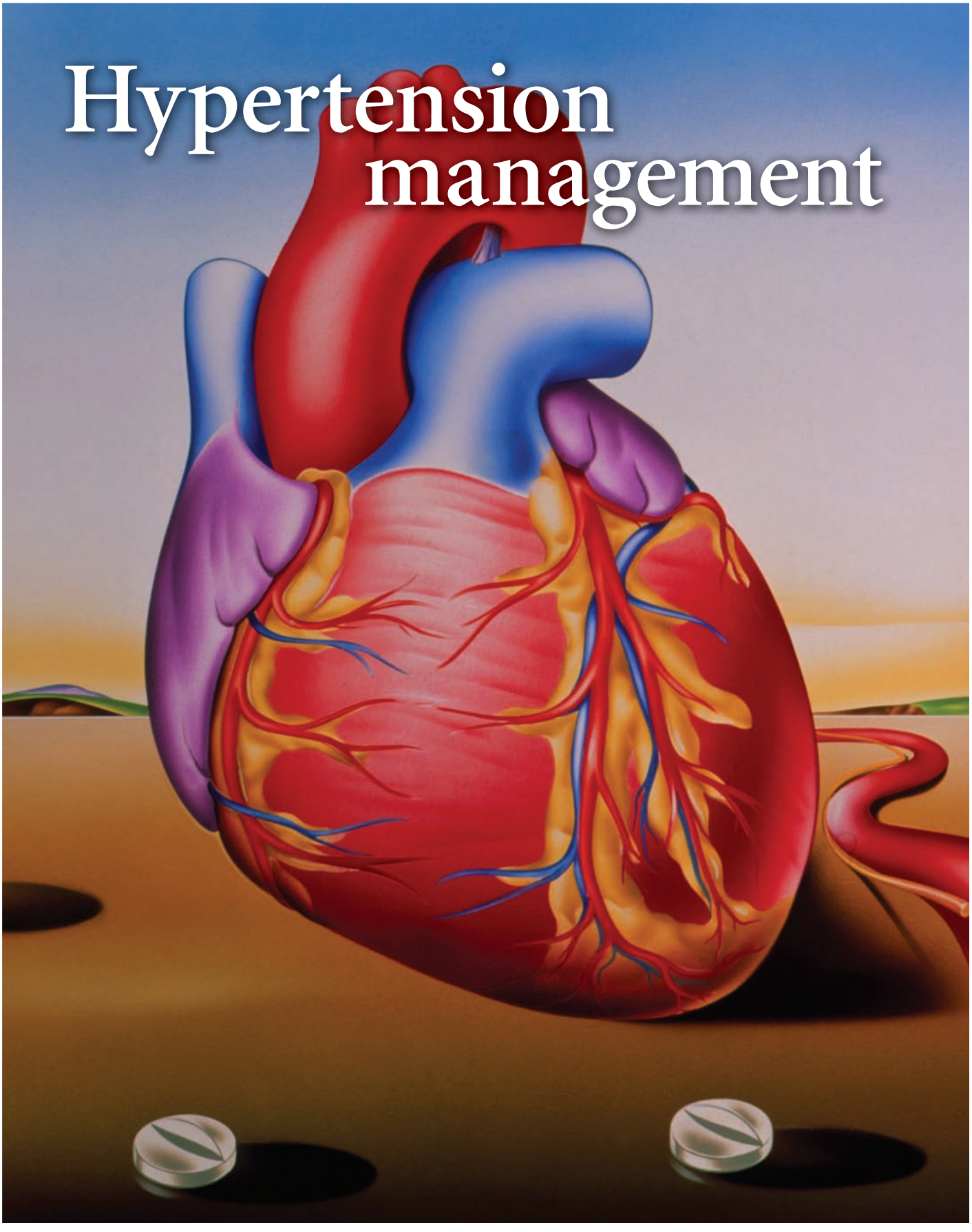
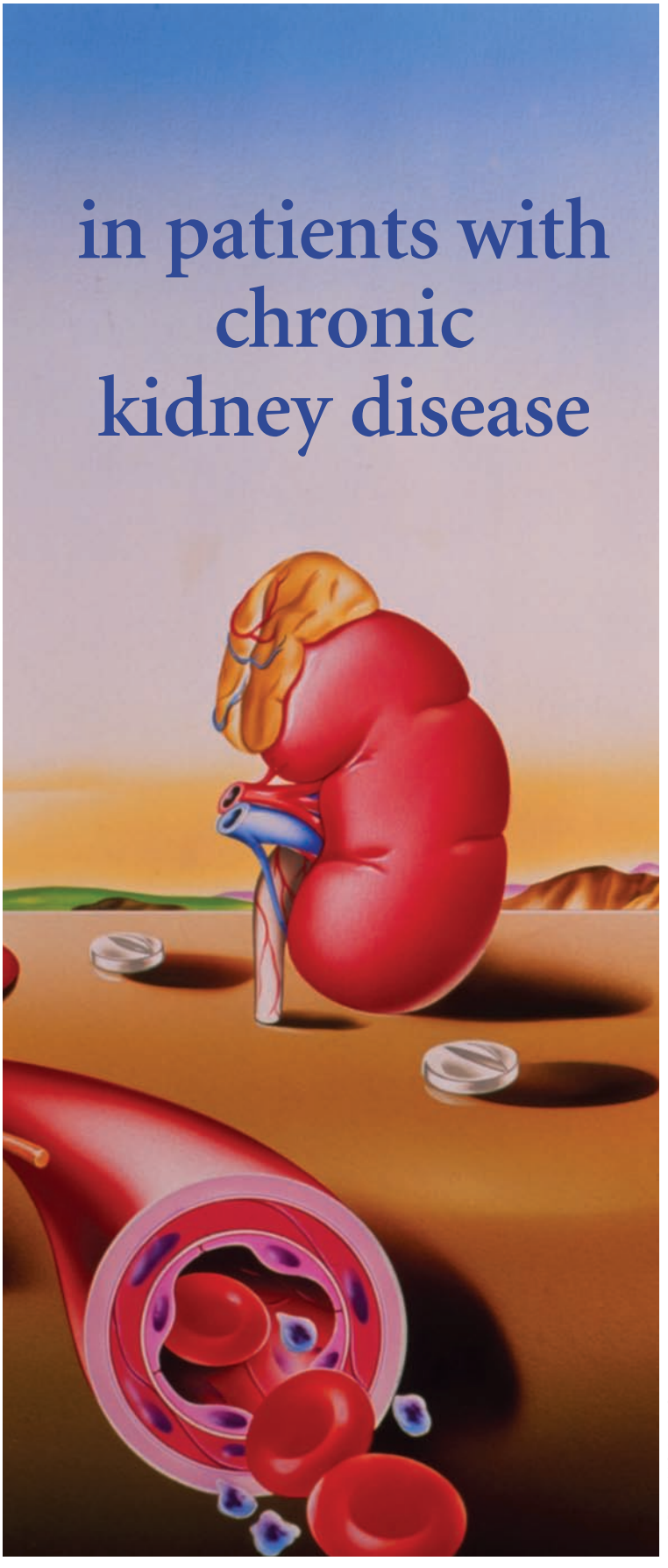
Hypertension management



in patients with chronic kidney disease



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Abstract: Managing hypertension, especially when accompanied by chronic kidney disease, is challenging. These different but related conditions are complicated by differing guidelines. NPs can safely prescribe antihypertensive treatments, which reduce hypertension and the risk of associated comorbidities, such as kidney failure, stroke, myocardial infarction, and vascular disease.

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The American College of Cardiology (ACC) and the American Heart Association (AHA) define hypertension as a BP of 130/80 or greater.[1] Hypertension affects 116.4 million American adults (46%).[1] By 2025, an estimated 1.56 billion adults worldwide will be living with hypertension.[2] Living with hypertension means patients will have to commit to lifestyle changes, including diet and exercise and taking a regimen of medications. Healthcare costs for hypertension are greater than $131 billion.[3] Patients with hypertension often have chronic kidney disease (CKD). Thirty-seven million people, 15% of the US adult population, have CKD, and 9 out of 10 are unaware they have it.[4] CKD affects patients in multiple ways, including lost work hours, hospital admissions and frequent readmissions, family stress, and disability and other societal costs. Direct costs of CKD to the US health system have been estimated by the United States Renal Data System (USRDS) to be 20% of all expenditures of Medicare.[5]

Hypertension is the second-leading cause of CKD, second only to diabetes. Although optimal BP control is important for all patients with hypertension, in patients who have comorbid CKD BP control is crucial

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to slowing the progression of CKD.[6] Early recognition of both kidney disease and hypertension may ultimately help reduce the risk of cardiovascular events and advanced kidney disease, including end-stage renal disease (ESRD) necessitating renal replacement including kidney transplant and/or dialysis. Dialysis is a costly process, both financially and in terms of its effect on individual patients. Patients receiving dialysis can have multifaceted symptoms, both physical and emotional; these include hypotension, muscle cramping, nausea and vomiting, shortness of breath and chest pain often secondary to hypervolemia, and depression/anxiety. However, most people with kidney disease will die of a catastrophic cardiovascular event before reaching ESRD.[7]

CKD is diagnosed and staged using both glomerular filtration rate (GFR) and albuminuria measurements.[8] The GFR is an estimation of kidney function derived from a mathematical formula of volume of urea cleared by the kidneys per unit of time; thus, the value depends on body size, age, and race.[9] The albuminuria measurement is a comparison of urine albumin and urine creatinine in a ratio (UACR). Albuminuria is pathognomonic for CKD, and proteinuria is an all-encompassing term that includes all types of proteins found in urine.[10] Albuminuria is a marker for kidney damage and will appear prior to a reduction in GFR or an increase in the serum creatinine.[8] A 24-hour urine collection test is the gold standard for measuring urine albumin; however, it offers challenges of inaccurate collection and time-consuming procession. A spot urine test is more accurate than a 24-hour urine and is the test of choice by the kidney community. It is also more convenient for the patient.[11]

CKD and hypertension are interrelated. Hypertension is the second-leading cause of CKD (diabetes being the first) and as CKD progresses, hypertension often worsens, becomes harder to control, and requires multiple treatment strategies. In other words, hypertension causes CKD and CKD worsens hypertension.[6] Thus, the two conditions are synergistic and commonly coexist.[11]

Pathophysiology

The pathophysiology of hypertension involves multiple factors, including reduced nephron mass, increased sodium retention and extracellular volume expansion, sympathetic nervous system overactivity, endothelial dysfunction, and activation of hormones involved in the renin-angiotensin-aldosterone system (RAAS).[11]

Within the kidneys, the RAAS regulates sodium, potassium, and blood volume, which in turn regulates BP in the arteries.[10] The two main hormones involved in the RAAS are angiotensin II and aldosterone. Angiotensin II contributes to increased circulating blood volume by the stimulation of aldosterone, an adrenal hormone that increases sodium and water retention, thus increasing BP.

In CKD, sodium modeling is altered secondary to kidney damage. This damage means the kidneys are less able to excrete sodium, causing intracellular sodium buildup leading to fluid retention and further elevation of BP.[12] Fluid retention can manifest as lower extremity edema as well as weight gain, cough, shortness of breath, distended abdomen, and/or facial swelling.

As kidney function declines, the excretion of salts and water that should occur decreases, thus contributing to hypertension, heart failure, and eventually kidney failure. Left untreated, either of the two conditions, hypertension or chronic kidney disease, by themselves can lead to disability or death.

Conflicting guidelines

In 2014, the eighth Joint National Committee (JNC8) published updated guidelines for the management of hypertension, identifying BP thresholds at which drug therapy should be initiated, BP targets during treatment, and choice of antihypertensive agents.[13] The JNC8 guideline states to start antihypertensive treatment for BPs greater than 140/90 mm Hg if the patient is under age 60. For patients older than 60, the JNC8 recommends 150/90 mm Hg as the threshold for initiation of BP therapy. For patients with diabetes and CKD, antihypertensive treatment is recommended for BPs greater than 140/90 mm Hg regardless of age. In patients with comorbid CKD, initiation of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is preferred, regardless of race or diabetes status. When hypertension is not controlled, the JNC8 recommends to either add an agent or maximize the current treatment stating that either is an acceptable option.

The goal of a BP of 140/90 mm Hg for patients with CKD was selected by the JNC8 after a review of high-quality evidence, but many in the cardiac community disagreed. In 2017, the ACC and the AHA, along with others, published a guideline on hypertension that defined hypertension as a BP greater than 130/80 mm Hg.[1] The ACC/AHA guideline recommends

nonpharmacologic management for 3 to 6 months prior to medication initiation for patients with stage 1 hypertension (130-139/80-89) who do not currently have atherosclerotic cardiovascular disease (ASCVD) and have a low risk of developing ASCVD in the subsequent 10-year period. For patients who do have outright ASCVD, for those with at least a 10% 10-year risk, and for those with stage 2 hypertension (140/90 or greater), pharmacologic treatment is recommended in addition to nonpharmacologic strategies. The ACC/AHA guideline states that an ACEI is the first-line antihypertensive choice in patients with CKD, and that an ARB may be used if the ACEI is not tolerated. International Society of Nephrology has also published a guideline Kidney Disease Improving Global Outcomes (KDIGO) focused on the treatment of hypertension in patients with CKD. This is because albuminuria is not only a marker for CKD but is often the first indication.[14] KDIGO recommends initiating ACEI or ARB therapy when a patient's BP is greater than 130/80 if albuminuria is present. If the CKD patient has no albuminuria, then the guideline recommends starting an antihypertensive agent when the patient's BP is greater than 140/90, no matter the CKD stage.

The nephrology community has published multiple papers regarding hypertension management in CKD, but these are in the nephrology literature and not often read by primary care colleagues. A recent review highlighted the need for multiple medications, often three to four, in the hypertensive patient with CKD and noted that although all guidelines encourage lifestyle management, these are not effective at reaching BP goals without medications in this subpopulation.[6] However, dietary management, especially sodium restrictions, will make hypertensive medications, particularly ACEI, ARBs, and diuretics more effective in CKD.

The 2019 Hypertension in CKD: Core Curriculum was recently published and considers the latest studies and provides expert opinion on hypertension management in CKD.[11] This article identifies a systolic BP goal of less than 130 mm Hg for the hypertensive patient with CKD. The importance of nonpharmacologic therapy (dietary and weight loss interventions) in patients with hypertension and CKD is addressed. However, for patients who will require pharmacologic therapy, ACEI or ARB therapy is identified as the best initial therapy, for those with an UACR of at least 30 mg/24 hours. Diuretics are initiated as a second-line therapy.[11]

Nonpharmacologic treatment

Dietary management is extremely important in the management of CKD. These restrictions will follow patients as they continue to lose kidney function. It is imperative to address sodium restriction to any patient who is receiving ACEIs, ARBs, or diuretics, as these medications' efficacies are blunted when high sodium load is filtered by the kidneys. Sodium has a direct relationship to hypertension and decreasing sodium intake will decrease hypertension. This feedback loop is even more important in patients with CKD. Additionally, short-term trials have shown that reducing sodium intake leads to lower BP and albuminuria.[15] KDIGO suggests limiting sodium to 2 g/day.[14] Potassium restrictions are often necessary because with declining kidney function, the excretion of potassium is altered and serum concentrations can be elevated, especially in patients on an ACEI or ARB. Some foods high in potassium are potatoes, avocados, chocolate, bananas, pineapples, and oranges as well as tomatoes. Also, it is recommended that patients stop smoking as smoking further increases both their cardiovascular and kidney failure risks. All recent hypertension guidelines endorse the importance of weight loss and exercise for BP control. In the 2019 Hypertension in CKD: Core Curriculum article by Ku and colleagues, the authors note that for every 5 kg of weight loss, BP can be reduced by approximately 5 mm Hg.[11] In addition, 90 to 150 minutes of aerobic exercise per week is recommended.[11]

Pharmacologic treatment

ACEIs and ARBs. ACEIs and ARBs are essential medications, either alone or in combination with other classes, for both hypertension and kidney disease and are often considered first-line for those with albuminuric kidney disease.[8] ARBs diminish the binding of angiotensin I receptors to angiotensin II, a potent vasoconstrictor that elevates BP. In addition to interfering with the conversion of angiotensin I to angiotensin II, ACEIs also dilate efferent arterioles in the kidneys' glomeruli thereby reducing the intraglomerular pressure.[10] ACEIs and ARBs have been shown to decrease albuminuria, an action separate from their antihypertensive effect. In the absence of albuminuria, ACEIs and ARBs have not been shown to outperform other antihypertensive classes.[11] The combination of an ACEI and an ARB increases the incident of AKI and hyperkalemia and should be avoided.[16]

Diuretics. A recent article highlighted the need to calculate dosing and use of diuretics in the hypertensive CKD patient.[17] Diuretics are an essential part of therapy for the CKD patient. Salt and water retention are major factors leading to hypertension in CKD. Even when patients may not appear on physical exam to have fluid retention, diuretics may still be indicated. Diuretics have been shown to potentiate the effects of ACEIs and ARBs; therefore, using the medications in combination can be beneficial.[18] Thiazide diuretics are recommended for CKD stages 1 through 3 (GFR ³ 30 mL/min). Loop diuretics are recommended for CKD stages 4 through 5 (GFR < 30 mL/min), including 5D (dialysis dependent).[11,19] Most nephrology professionals will prescribe loop diuretics to be taken on nondialysis days for patients undergoing dialysis, even those with low residual function.[19,20] All diuretics will require monitoring of electrolytes for hyperkalemia and hypokalemia.

Beta-blockers. Beta-blockers are not recommended as initial therapy, nor monotherapy, in patients with hypertension.[1,13] Beta-blockers have been shown to decrease cardiac events in the patients with ESRD; however, there is no available data for the majority of patients with CKD.[21] With a higher risk of adverse reactions, particularly hypotension and bradycardia, beta-blockers are not generally used in CKD unless there is an indication for a comorbid condition such as heart failure.[6]

Calcium channel blockers. In patients with CKD, calcium channel blockers (CCBs) are often second- or third-line therapy, with ACEI/ARBS as first-line therapy. There has been no evidence that show nondihydropyridine CCBs are any better at controlling BP than their counter, dihydropyridine CCBs. However, nondihydropyridine CCBs have more potential to reduce proteinuria.[14] (See *Recommended antihypertensive agents for patients with CKD*.) Large trials specifically with CKD patients and dihydropyridine medications are lacking; however, nephrology uses these medications frequently as they are extremely effective, can be used in a fluid-overloaded state, and are well tolerated.[6] The combination of an ACEI/ARB and a CCB will lower BP more than either of these medications alone.

Direct vasodilators and centrally acting alpha agonists. As the patient loses kidney function and progresses to CKD stage 4 or 5, BP becomes more difficult to control. Therefore, the use of direct vasodilators (such as hydralazine or minoxidil) and centrally acting medications (such as clonidine) is beneficial.[6] Adverse reactions from these medications include increased risk of sleepiness with clonidine to an increased risk of lupus with hydralazine. Both medications often can cause lower extremity edema. However, they are extremely effective and necessary in the armamentarium of the NP.

Case study

Mrs. J is a 34-year-old Black female with a 12-year history of diabetes and kidney disease (unknown stage or cause). She has recently relocated and is in the clinic to

Recommended antihypertensive agents for patients with CKD[11]

Medication class	Examples	CKD indications	Other considerations
RAAS Blockade			
ACEI **ARB**	lisinopril, enalapril, benazepril losartan, cozaar, irbesartan, candesartan	• Use this class of drugs as a first-line agent if albuminuria is present, delays progression of CKD. • Without albuminuria, data are more controversial, although useful in all stages of CKD.	• Monitor for cough (less likely with ARBs), angioedema, and hyperkalemia.
Diuretics			
Thiazide **Loop**	hydrochlorothiazide, chlorthalidone furosemide, bumetanide, torsemide	• Use diuretics as a second-line agent if hypervolemia is present. • Thiazide is useful in CKD stages 1-3 (GRF ≥ 30 mL/min). • Loop diuretics are recommended for CKD 4-5 (GFR < 30 mL/min).	• Monitor electrolytes, especially potassium. • Combinations of diuretics may cause adverse events as CKD progresses.
CCBs			
Dihydropyridine **Nondihydropyridine**	amlodipine, nifedipine diltiazem, verapamil	• Use CCBs as a second- or third-line therapy. • Nondihydropyridine offers greater proteinuria reduction.	• CCBs are not beneficial in reducing lower extremity swelling, as they may cause edema.

establish as a new patient. Her last appointment with a provider was 1 year ago and she has been out of BP medication for an unknown time period. She has previously taken nifedipine ER 90 mg daily and hydralazine 50 mg twice a day. Her family history includes mother with hypertension, maternal sister with hypertension, father with diabetes, and paternal grandmother with hypertension. Physical examination shows she is alert and oriented and her lungs are clear. A cardiovascular exam shows an S3 was auscultated and 3+/0-4+ bilateral pitting edema of lower extremities was noted. The patient's BP was 160/90. She weighs 170 lb (77.1 kg) and is 63 in (160 cm) tall with a BMI of 30.1. Labs were unavailable because she is a new patient. She has no known drug allergies.

There are documented medication adherence issues in this patient case. The first step is to determine why she has not taken her antihypertensive. It is the cost? Transportation? Tolerance? This answer can guide the treatment plan.

Although discussion of nonmedical management is important, this patient's provider will also need to treat her hypertension with medication at this stage. Lab testing is vitally important for evaluating for presence of albuminuria and staging for kidney disease, checking electrolytes, and evaluating for diabetes. A complete history and physical including over-the-counter analgesic must be done. The use of any over-the-counter medications that cause hypertension especially nonsteroidal anti-inflammatory drugs (NSAIDs) is often discovered.[22] NSAIDs, commonly used by patients, are nephrotoxic and can cause a decrease in GFR by causing vasoconstriction and sodium retention and should be avoided. (See *Medications that can cause hypertension*.)

Mrs. J may need to be started on an ACEI/ARB if it was discovered that she had albuminuria, however, since there are no labs available, neither are recommended at this time. Because safety should be the first consideration, restarting her nifedipine and/or hydralazine would seem to be the most prudent first step. Although neither is specifically renoprotective, decreasing the BP is renoprotective. A diuretic can be offered as a second-line medication (chlorthalidone if GFR > 30 mm/min) noting it will reduce lower extremity edema, when labs have been obtained and reviewed.

If this patient was found to have CKD with albuminuria or diabetes with albuminuria, an ACEI or ARB may be substituted or added to her present regimen along with sodium dietary restriction. The addition of a diuretic would be indicated as a second-line medication.

Medications that can cause hypertension[22]

- NSAIDs
- sympathomimetics (pseudoephedrine)
- anabolic steroids
- cyclosporin/tacrolimus
- estrogen and estrogen analogues
- methylxanthines, such as theophylline, caffeine
- cocaine
- nicotine
- ethanol
- metoclopramide

If the GFR was at least 30 mL/min, chlorthalidone would be the preferred diuretic.[1] However, an appropriately closed loop diuretic may be indicated if the patient's GFR is less than 30 and/or more volume removal is necessary to achieve BP to goal. At this time, from the minimal history obtained, it is unclear if her edema is related to CKD, albuminuria, and/or high sodium intake. Typically, loop diuretics are reserved for lower GFRs, especially if more aggressive diuresis is needed. Although this patient presently has +3 edema, with a diuretic, we may find in follow-up that her edema is less severe. When ACEIs or ARBs and/or diuretics are initiated, low sodium education should be addressed as a high sodium diet can lead to decreased efficacy of medications and/or lack of response to medications. Many patients will admit they do not like the adverse reactions and/or cost of their specific hypertension medications, and this can contribute to nonadherence. As a relationship is established, weight loss and exercise can be encouraged to help control BP further. The use of a free smart phone calorie-counting application might help educate and encourage changes in eating habits. Finally, referral to a renal dietitian can help with appropriate food choices to protect kidney function.

The patient is to be seen in follow-up in 4 weeks at which time labs will be reviewed along with a BP check and a discussion of any adherence concerns. CKD stage 1-3 is usually managed in the primary care clinic with emphasis on BP control and the lifestyle changes previously mentioned. However, CKD stage 4-5 needs referral to nephrology as late referral is associated with poor outcomes.

Conclusion

Although complex and challenging, hypertension in CKD can be effectively managed with early aggressive treatment to minimize long-term complications. The new 2019 AJKD Core Curriculum incorporates recent studies and should be used as an adjunct to the current

KDIGO and ACC/AHA guidelines.[11] KDIGO is presently developing new hypertension management in CKD guidelines that should be available in 2020. NP

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