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In Practice

Peripheral Artery Disease and CKD: A Focus on Peripheral Artery Disease as a Critical Component of CKD Care

Pranav S. Garimella, MD, MPH,[1] Peter D. Hart, MD,[1,2] Ann O'Hare, MD,[3] Stephanie DeLoach, MD,[4] Charles A. Herzog, MD,[5] and Alan T. Hirsch, MD[6]

The incidence of peripheral artery disease (PAD) is higher in patients with chronic kidney disease (CKD) than in the general population. PAD is a strong independent risk factor for increased cardiovascular disease mortality and morbidity, including limb amputation, in persons with CKD. Diagnosis of PAD in patients with CKD may be challenging in the absence of classic intermittent claudication or the presence of atypical leg symptoms. In addition, pedal artery incompressibility may decrease the accuracy of ankle-brachial index measurement, the most common PAD diagnostic tool. Alternative methods such as toe-brachial index should be used if clinical suspicion persists despite a normal ankle-brachial index value. Aggressive risk-factor modification, including treatment of diabetes, hyperlipidemia, and hypertension and smoking cessation, should be mandatory in all patients. Treatment of all individuals with PAD should include antiplatelet medications and prescribed supervised exercise programs and/or cilostazol for individuals with claudication symptoms. Preventive foot care measures and a multidisciplinary approach involving podiatrists and vascular and wound care specialists should be used to reduce amputations. Revascularization for critical limb ischemia is associated with poor outcomes in patients with CKD with PAD. Future investigation is recommended to evaluate the benefit of earlier treatment strategies in this high cardiovascular disease risk population with CKD.
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INDEX WORDS: Peripheral artery disease; chronic kidney disease; ankle-brachial index; amputation.

CASE PRESENTATION

A 53-year-old man with end-stage renal disease (ESRD) treated with dialysis has a history of hypertension, dyslipidemia, and diabetes mellitus. He presents to his nephrologist with a 2-year history of nonspecific right-leg pain and a nonhealing ulcer on his foot. At the time of dialysis therapy initiation 3 years ago, his ankle-brachial index (ABI) was 1.2 and further testing was not pursued given the absence of an ulcer and concerns regarding gadolinium and contrast exposure. Computed tomography angiography at this presentation shows multisegmental right-leg peripheral artery disease (PAD), and revascularization is not deemed likely to be feasible. The nonhealing ulcer is now considered a contraindication to kidney transplant and immune suppression. After 6 months of wound care, analgesics, non–weight bearing, and antibiotics to treat wound infections, the ulcer fails to heal and progresses to gangrene, and the patient requires amputation of his foot.

INTRODUCTION

Persons with chronic kidney disease (CKD) have a high risk of developing generalized atherosclerosis and cardiovascular disease (CVD) compared with individuals with normal kidney function.[1] CKD is associated with more severe CVD and a worse prognosis,[2,3] such that more persons with CKD are likely to die of CVD than progress to ESRD.[4] Even in asymptomatic patients with ESRD starting dialysis therapy, more than half have CVD.[5] This most likely is related to a combination of traditional risk factors, such as diabetes, hypertension, hyperlipidemia, and smoking, and nontraditional risk factors, such as uremia, inflammation, and malnutrition.

PAD represents the progressive occlusion of peripheral arteries by atherosclerosis and is associated with a high rate of morbidity and mortality, especially in patients with CKD.[6,7] Despite the proven association of CKD with a high risk of ischemic events, such as acute myocardial infarction, stroke, and cardiovascular mortality, its association with lower-extremity PAD has been less well described. Until recently, most large PAD epidemiologic studies did not consider CKD as a PAD risk factor and did not report information about level of kidney function.[6,8,9]

In patients with CKD, data on the accuracy of office-based methods for PAD diagnosis or how CKD

From the [1]Department of Medicine and [2]Division of Nephrology, John H. Stroger, Jr Hospital of Cook County, Chicago, IL; [3]Department of Medicine, University of Washington, Seattle, WA; [4]Department of Medicine, Thomas Jefferson University, Philadelphia, PA; [5]Cardiology Division, Department of Internal Medicine, Hennepin County Medical Center, University of Minnesota; and [6]Lillehei Heart Institute and Cardiovascular Division, University of Minnesota Medical School, Minneapolis, MN.

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Address correspondence to Pranav S. Garimella, MD, MPH, Department of Medicine, John H. Stroger, Jr Hospital of Cook County, 1900 W Polk St, Chicago, IL 60612. E-mail: pranavgarimella@gmail.com

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might modify the benefit and risk of PAD care strategies are lacking. The nephrologist often is faced with a relative lack of robust diagnostic tools and treatment guidelines to be able to provide an accurate PAD diagnosis and effective medical care to these patients. In addition, many nephrologists share uncertainty about whether delivery of more aggressive PAD care would significantly improve key clinical outcomes given recent data suggesting a lack of benefit of other CVD interventions in patients with ESRD.[10-13]

The objective of this article is to review the epidemiology, ischemic risk, utility, and limitations of current diagnostic modalities and potential treatment options for PAD in patients with kidney disease. We also highlight knowledge gaps and opportunities that might guide clinical research.

EPIDEMIOLOGY OF PAD IN CKD

Prevalence and Incidence

Data from the National Health and Nutrition Examination Survey (NHANES) showed that PAD affects 15% of US adults older than 70 years.[14] In asymptomatic persons 70 years or older or 50-69 years with atherosclerosis risk factors, the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Study found PAD (defined as ABI $\leq$0.90 or history of lower-extremity revascularization) in 29% of the population, but classic claudication in only 5.5% of patients with PAD newly diagnosed and 12.6% of patients with a prior diagnosis of PAD.[15] The prevalence of both symptomatic (eg, intermittent claudication and critical limb ischemia) and asymptomatic PAD are both greater in individuals with CKD compared with the general population. Data from the NHANES 1999-2004 survey of PAD indicate that 24% of persons with creatinine clearance $<$60 mL/min/1.73 m^2 have PAD compared with 3.7% of persons with creatinine clearance $>$60 mL/min/1.73 m^2.[16] Prevalence rates of PAD are higher when using a combination of clinical and diagnostic modalities rather than clinical features alone and vary substantially according to the population studied (Table 1).

Clinical data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) and claims data for incident dialysis patients from the US Renal Data System (USRDS) reported prevalent PAD as 25%-46% of each cohort.[17,18] Smaller studies have reported similar PAD prevalence rates based on ABI criteria.[20,21] The Chronic Renal Insufficiency Cohort (CRIC) Study, a large prospective study of more than 3,000 patients with CKD stage 3 or higher, reported that 15% of participants had an ABI $<$0.9 at enrollment. However, of this defined PAD group, only 7% of patients reported a history of known PAD.[22] Based on the age and risk-factor profile common to most

Table 1. Prevalence of PAD in Patients With Kidney Disease

Study	Population	Prevalence	Diagnostic Criteria
	Patients on Dialysis		
USRDS[17]	35,438 incident dialysis patients	45.9%	Claims data
DOPPS[18]	29,873 prevalent hemodialysis patients	25.3%	Clinical[a]
HEMO[19]	936 prevalent hemodialysis patients	23%	Clinical[a]
Fishbane et al[20]	132 prevalent hemodialysis patients	35%	ABI $<$0.9
Testa & Ottavioli[21]	226 prevalent hemodialysis patients	33%	ABI $<$0.9
	Patients With CKD Stage $\geq$3		
NHANES[14]	211 participants with CCr $<$60 mL/min/1.73 m^2	24%	ABI $<$0.9
CRIC[22]	3,199 participants with eGFR $<$60 mL/min/1.73 m^2	7.4%	Self reported history of PAD
		15.9%	ABI $<$0.9
CHS[23]	648 participants with kidney disease[b]	12%	ABI $<$0.9
ARIC[24]	376 participants with eGFR $<$60 mL/min/1.73m^2	8.6 incident cases/1,000 person-years	Clinical[a] and ABI $<$0.9
CHS[25]	648 participants with kidney disease[b]	10.7 incident cases/1,000 person-years	Incident intermittent claudication

Abbreviations: ABI, ankle-brachial index; ARIC, Atherosclerotic Risk in Communities; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CCr, creatinine clearance; CRIC, Chronic Renal Insufficiency Cohort; DOPPS, Dialysis Outcomes and Practice Patterns Study; eGFR, estimated glomerular filtration rate; HEMO, Hemodialysis Study; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral artery disease; USRDS, US Renal Data System.

[a]Includes history of known PAD, amputation, revascularization, claudication, signs of critical limb ischemia, or reduced pulses on examination.

[b]Serum creatinine level $\geq$1.5 mg/dL in men and $\geq$1.3 mg/dL in women.

CKD populations, it is likely that PAD prevalence is 10%-20%.

The incidence of PAD in CKD populations is greater than in populations with normal kidney function, as seen in community-based studies such as the Heart and Estrogen/Progestin Replacement Study (HERS)[26] and the Atherosclerotic Risk in Communities (ARIC) Study.[27]

Risk Factors for PAD

As in the general population, traditional cardiovascular risk factors (eg, age, male sex, tobacco use, diabetes, and hypertension) appear to be associated with an increased risk of PAD in patients undergoing dialysis.[18,28,29] However, the heightened risk in these patients is not explained by these traditional risk factors alone.[19] Kidney disease is an independent risk factor for the development of PAD, with risk increasing with worsening kidney function.[24] Albuminuria, in the absence of decreased estimated glomerular filtration rate (eGFR), also is associated independently with the risk of developing PAD.[30-32] In addition, several nontraditional risk factors unique to patients with kidney disease, especially those on dialysis therapy, have been implicated in the development of PAD in retrospective studies. The chronic inflammatory state induced by uremia and oxidative stresses in these patients in turn can produce hypoalbuminemia, which is known to be associated with PAD.[28] Elevated levels of homocysteine[33,34] and lipoprotein(a) also are known to be associated with PAD in dialysis patients.[29] The association of elevated serum calcium, phosphate, and parathyroid hormone levels in contributing to increased vascular stiffness and/or atherosclerotic PAD is still unclear.

The presence of vascular calcification and arterial stiffness are independent risk factors for adverse CVD events and mortality in both the general population[35,36] and patients with kidney disease.[37,38] The effect of arterial stiffness on the risk of developing clinical PAD or establishing PAD diagnosis has not been evaluated extensively. In a cross-sectional analysis of patients with diabetes evaluated at a vascular clinic, Aboyans et al[39] reported an inverted J-shaped association between ABI and other measures of PAD, such as toe-brachial index (TBI) and posterior tibial artery peak flow velocity, suggesting that an elevated ABI may mask underlying limb ischemia. Similarly, Suominen et al[40] diagnosed PAD using diagnostic criteria of TBI <0.7, which was present in 60% (112/188) of patients with ABI >1.4. The presence of PAD was confirmed in all 82 patients who underwent diagnostic lower-extremity angiography (stenosis $>50\%$).[40] The mortality rate also was higher in patients with elevated ABI and PAD diagnosed by angiography and TBI compared with those with elevated ABI only. PAD often may be asymptomatic, and because the prevalence of arterial calcification increases with worsening kidney failure,[41] it is not known whether there is an additive effect of vascular calcification on atherosclerotic PAD with regard to mortality and other key CVD outcomes.

Persons with CKD and PAD have higher mortality rates than those with either of the conditions alone.[42-45] In a retrospective study, Liew et al[43] reported the highest 6-year mortality rates in patients with both PAD and CKD (45%) compared with patients with either CKD or PAD alone (26%-28%) or neither condition (18%). Similarly, a Chinese study that prospectively evaluated 938 patients with ABI <0.9 reported 38% mortality in patients with PAD and CKD compared with only 5% in those with neither disease at 3 years of follow-up.[44]

DIAGNOSIS

Detection of Asymptomatic PAD

Asymptomatic PAD in patients with CKD is a clinically relevant potent marker of a high short-term risk of cardiovascular ischemic events, including myocardial infarction or stroke.[46] Early detection may improve both patient and clinician awareness of the potential significance of future exertional leg symptoms or signs of more advanced PAD. This recognition could lead to more intensive risk-factor intervention or initiation of medical therapies to improve limb symptoms and overall cardiovascular morbidity.

Current recommendations regarding the detection of asymptomatic PAD vary by health professional organization (Box 1). PAD clinical guidelines from the Inter-Society Consensus for the Management of PAD (TASC II) and American College of Cardiology (ACC) and American Heart Association (AHA) have offered a strong recommendation for detection of asymptomatic PAD to provide an opportunity to initiate proven risk-reduction medical therapies before a first event ("facilitated secondary prevention"). These 2 guidelines do not promote screening of asymptomatic populations, but offer clinicians an opportunity to use the most cost-effective and risk-free atherosclerosis detection tool (the ABI) in a well-defined high-risk clinic-based population. The US Preventive Services Task Force evaluation was focused on the utility of true population-based screening in nonclinical settings to detect asymptomatic PAD to prevent future leg symptoms[50] and did not address the critical question of whether adverse CVD events would be prevented by early detection of PAD. This cardiovascular risk reduction goal has been tentatively endorsed by an AHA consensus conference on vascular screening[52] and currently is under evaluation.

Box 1. Current National and International Recommendations for Active Detection of PAD in Clinical Practice

KDOQI[47]

- At the time of dialysis therapy initiation, all patients should be evaluated for the presence of PAD
- Evaluation should include physical examination, including assessment of arterial pulse and skin integrity
- Further specialized studies, such as duplex studies or invasive testing, should be undertaken if abnormalities are detected upon physical examination and interventions are considered

TASC II[48]

Recommend screening for PAD in:

- Patients with exertional leg symptoms
- Patients aged 50-69 y with cardiovascular risk factors
- All patients aged ≥70 y
- Patients with a 10-y risk of a cardiovascular event of 10%-20%, determined by SCORE or Framingham Heart Association guidelines

ACC/AHA[49]

Recommend screening for PAD in:

- Patients aged <50 y with diabetes and additional CVD risk factor
- Patients ≥50 y with any CVD risk factor (smoking, diabetes, hypertension, elevated cholesterol)
- Patients ≥65 y[51]

USPSTF[50]

- Recommends against routine screening for PAD and concludes that harms of routine screening for PAD exceed benefits when used to prevent leg symptoms

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; KDOQI, Kidney Disease Outcomes Quality Initiative; PAD, peripheral artery disease; SCORE, Systematic Coronary Risk Evaluation; TASC II, Trans-Atlantic Inter-Society Consensus; USPSTF, US Preventive Services Task Force.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that all patients be evaluated for PAD at the time of dialysis therapy initiation (strength of recommendation: weak).[47] This recommendation does not address the potential benefit of detecting PAD (asymptomatic or symptomatic) in the pre-ESRD state. However, the high coprevalence of diabetes and lower-extremity comorbid conditions (osteoarthritis, infections, neuropathy, deconditioning, etc) would profoundly diminish any opportunity to detect classic claudication in a CKD population. The current recommendation seems to favor duplex ultrasonography over physiologic vascular testing and also suggests a first-line role for invasive angiography if endovascular interventions are considered. We believe the term "intervention" should be synonymous not just with invasive endovascular repair strategies, but should extend to pharmacological therapies and lifestyle changes in these patients.

Clinical Signs and Symptoms

Intermittent claudication, defined as muscle pain or discomfort brought on by exercise and relieved by rest, is the classic symptom of lower-extremity ischemia, and patients without claudication often are considered asymptomatic. However, observational studies have shown that claudication is present in <15% of individuals who have objectively defined PAD,[15,53] and this likely is true in patients with CKD and PAD.[22] Although poor lower-extremity skin and hair integrity have been used in traditional textbooks to define an increased likelihood of underlying PAD, the presence or absence of these signs is both insensitive and not specific enough to serve as useful diagnostic signs. However, the presence of abnormal pulses provides adequate data for any clinician to proceed to establish a PAD diagnosis by further objective diagnostic testing.[49,54]

Ankle-Brachial Index

The ABI is a simple, inexpensive, and accurate tool that provides diagnostic information to confirm the clinical suspicion of lower-limb PAD, defined as ABI ≤0.90.[49] In patients without CKD, sensitivity of an ABI <0.90 in detecting PAD is ~95%. Normal ABI values are >1.10, but recent data show that individuals with an ABI of 0.90-1.10 also represent a cohort with increased short-term rates of cardiovascular risk.[55] However, the well-established accuracy of the ABI in the general population has not been verified in CKD populations.

The biggest concern among renal clinicians is the low sensitivity of the ABI given artificially normal or high values in patients with CKD. The presence of elevated ABI is common in patients with CKD (23%), ESRD (41%), and kidney transplant recipients (24%) and is thought to reflect the higher prevalence of medial arterial calcification.[41] Elevated ABI values (>1.3) also are associated with increased risk of mortality and cardiovascular events.[35,36] The presence of medial arterial calcification is significantly higher in ankle arteries compared with toe arteries, especially in patients with diabetes, neuropathy, and kidney disease.[56] In patients with an abnormally high ABI >1.3, to accurately detect PAD, the TASC II and AHA/ACC guidelines recommend measuring the TBI.[49,57]

Toe-Brachial Index

Recent studies suggest that TBI may be a better tool than ABI for ruling out total arterial occlusion in patients with diabetes[58] or critical limb ischemia.[59,60] In one study, 62% of patients with an elevated ABI (>1.3) had PAD as diagnosed by TBI <0.6,[40] and in a subset of this population undergoing digital subtrac-

tion angiography, all except one patient had PAD confirmed based on >50% arterial stenosis. These investigators suggested that patients with even moderately incompressible pedal arteries may have PAD, a perspective supported by data from 475 patients with a normal ABI, of whom 25% (118) had PAD diagnosed by TBI, and confirmed by angiography in 93%. These findings provide supportive evidence for the clinical utility of the TBI.

There is some evidence to support TBI measurements in patients with CKD. Leskinen et al[41] found an increased prevalence of PAD (defined as TBI <0.7, ABI <0.9, and claudication history) and medial arterial calcification in patients with CKD requiring dialysis and recommend measuring both ABI and TBI in patients with CKD. In a cross-sectional study evaluating TBI and peak posterior tibial artery flow velocity, it was noted that both were abnormally low in patients with a low and high ABI.[39] Results from another study that included patients with CKD and ESRD showed that PAD diagnosed by TBI is associated independently with all-cause and cardiovascular mortality in patients with an elevated ABI.[61] These findings suggest that atherosclerotic PAD may be underdiagnosed in the presence of an elevated ABI, and strategies other than the ABI may be needed to establish PAD diagnosis in these high-risk groups. Test characteristics of TBI in persons with CKD with and without medial arterial calcification are unknown, and further studies are needed to better define the role of the TBI.

Contrast-Based Angiographic Diagnostic Tests

Both computed tomography and magnetic resonance angiography are important tools in the diagnosis of PAD.[49] These methods, in contrast to physiologic (ABI, TBI, and transcutaneous oxygen tension studies) or duplex ultrasound studies, are reserved for use when invasive treatments are planned and may be pertinent to only a small fraction of individuals with CKD, even if PAD is advanced. A meta-analysis evaluating computed tomography in diagnosing 50% vessel stenosis reported 95% sensitivity and 96% specificity compared with digital subtraction angiography in healthy individuals.[62] However, the accuracy of the arterial imaging technique has not been tested in advanced CKD populations, although these patient groups have the highest risk of iodinated contrast–induced nephrotoxicity. Similarly, magnetic resonance angiography has excellent accuracy in detecting lower-limb PAD.[63] However, the risk of gadolinium-induced nephrogenic systemic fibrosis limits the utility of this test in individuals with PAD on dialysis therapy. In general, contrast-based advanced imaging studies are avoided in patients with eGFR <30 mL/min/1.73 m^2 because the risks may outweigh the benefits.

THE TREATMENT OF PAD IN CKD

The literature for the treatment of PAD in patients with CKD or ESRD is scarce, and current treatment guidelines therefore are based on extrapolation of studies in the general population that unfortunately did not provide information based on level of kidney function (Table 2).

Medical Therapy

All patients with PAD require intensive medical risk-reduction treatments, encompassing the full range of proven beneficial medical interventions.

Risk-Factor Modification

Lipid-Lowering Therapy. No randomized controlled trials have evaluated the benefit of lowering lipid levels in the treatment of PAD in patients with CKD or ESRD. The Heart Protection Study compared simvastatin to placebo in more than 20,000 patients with PAD and other high-risk vascular disease, but excluded those with severe kidney disease. The study found a 22% reduction in risk of major vascular events (myocardial infarction, stroke, and vascular death) in patients with PAD, even in the absence of known coronary artery disease.[64] This and other trials with similar outcomes support the routine use of statins in patients with PAD.[71-73] Randomized trials of statins also have suggested increased pain-free walking distance in patients with PAD. However, the evidence is not robust enough to routinely support this claim.[74-77] Although past studies of statins in dialysis patients failed to show a significant mortality and morbidity benefit,[12,13] recently published data from the Study of Heart and Renal Protection (SHARP) showed a significant reduction in nonhemorrhagic stroke and any arterial revascularization in dialysis patients using simvastatin/ezetimibe.[78] Of note, although the benefit observed in SHARP provides hope that statins could decrease event rates, the lack of a consistent benefit observed in 4D[13] (Die Deutsche Diabetes Dialyse Studie) and AURORA[12] (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis) suggests ongoing uncertainty regarding the magnitude of benefit that might be achieved. Because PAD represents progressive arterial narrowing and limb ischemia rather than plaque rupture and acute occlusion, it seems likely that statins may be beneficial for patients with PAD regardless of the degree of decreased kidney function. This is an area in which further research may be warranted.

Blood Pressure Control. Hypertension is a potent risk factor for PAD.[14,15] However, there are very few data

Table 2. Selected Trials Evaluating Medical Therapy for PAD and Relevance to Patients With CKD

Trial and/or Intervention	Primary Outcome	Population Studied	Comments
Heart Protection Study; simvastatin vs placebo[64]	Myocardial infarction, coronary death, stroke, or revascularization	20,536 participants with PAD and other high-risk vascular disease	Excluded individuals with severe kidney disease or evidence of substantially impaired kidney function
Atorvastatin vs placebo[13]	Change in maximal walking time	354 patients with claudication	
UKPDS 33; intense blood glucose control in patients with type 2 diabetes[65]	All-cause mortality, adverse cardiovascular events	3,867 patients newly diagnosed with type 2 diabetes	Excluded patients with serum creatinine >2 mg/dL
Exercise training[66]	Improving walking distance	25 men with claudication	Excluded patients with diabetes due to their severe and distal PAD
Supervised exercise vs control group[67]	6-min walk test and the Short Physical Performance Battery	156 participants with ABI <0.95	Excluded patients with normal ABI
Antithrombotic Trialists' Collaboration; antiplatelet therapy vs control[68]	Nonfatal myocardial infarction, nonfatal stroke, or death from vascular cause	135,640 participants; 9,214 had PAD	No separate data for PAD patients with kidney disease
CAPRIE; clopidogrel vs aspirin[69]	All-cause & CVD mortality, nonfatal CVD events, leg amputation	19,185 participants with ischemic stroke, myocardial infarction, or symptomatic PAD	Excluded patients with severe kidney disease, uncontrolled hypertension
Cilostazol vs placebo[70]	Maximal walking distance	Meta-analysis of RCTs of 2,702 patients with claudication	

Note: The Antithrombotic Trialists' Collaboration included patients with kidney disease (2,632 patients on dialysis therapy); all other trials listed did not report including patients with kidney disease. Conversion factor for creatinine in mg/dL to μmol/L, ×88.4.

Abbreviations: ABI, ankle-brachial index; CAPRIE, Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; CKD, chronic kidney disease; CVD, cardiovascular disease; PAD, peripheral artery disease; RCT, randomized controlled trial; UKPDS, United Kingdom Prospective Diabetes Study.

to define the PAD-specific benefit of antihypertensive medications in patients with symptomatic PAD, including those with kidney disease.[79] Current PAD guidelines recommend treatment of hypertensive patients with PAD to reduce CVD morbidity and mortality,[49] and better blood pressure control has been shown to slow the progression of CKD and reduce mortality.[80] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the first-line agents to control blood pressure for patients with CKD and diabetes or proteinuria, and their use has been associated with slowing the progression of CKD,[81-83] with post hoc analysis of trials showing a survival benefit.[84,85] β-Blockers are not contraindicated in patients with PAD[86] and may improve claudication and walking distance in hypertensive patients with PAD.[87] The optimal target blood pressure in patients with CKD is an issue of debate, and results of the ongoing Systolic Blood Pressure Intervention Trial, which compares systolic targets of 120 versus 140 mm Hg in hypertensive adults at risk of CVD, should provide valuable information for the effect of blood pressure control on incident cardiovascular events and dementia.[88]

Smoking Cessation. Cigarette smoking is an important modifiable risk factor for atherosclerosis, with data indicating that the risk of PAD, heart failure, and mortality in dialysis patients who quit smoking is decreased to levels similar to those of lifelong nonsmokers.[89] Observational data also suggest that cigarette smoking is associated with progression of CKD and smoking cessation is associated with lower rates of amputation and lower incidence of ischemic pain at rest in patients with PAD.[90-92] Recent data show that prescription of individualized smoking-cessation treatment is associated with a major improvement in adjudicated quit rates at 6 months compared with usual care[93] and serves as one of the key PAD performance measures that are attributed to all clinicians who care for patients with PAD.[94] Because CVD is the leading cause of death in patients with kidney disease and smoking cessation has a beneficial effect on mortality reduction, all patients with kidney disease should be advised to stop smoking and be offered medical and counseling help to quit.

Diabetes Mellitus. Uncontrolled diabetes is a risk factor for the development and progression of both

CKD and PAD.[95-97] No studies have specifically evaluated the benefit of tight glucose control in preventing or slowing PAD in patients with CKD. Although treatment with insulin and oral hypoglycemic agents has not shown a significant benefit on the risk of PAD in patients with diabetes,[65,98] TASC II guidelines recommend aggressive glucose control to maintain hemoglobin A_{1c} levels <7.0% to prevent cardiovascular events.[48] However, several studies have shown no association between hemoglobin A_{1c} level and survival in dialysis patients,[99-101] and data from the recently published Action to Control Cardiovascular Risk in Diabetes trial show that very intense blood glucose control may increase 5-year mortality.[102] Because patients with kidney disease are prone to severe life-threatening hypoglycemia, hemoglobin A_{1c} levels that are slightly higher (hemoglobin A_{1c} of ~7%) than those recommended for the general population may be appropriate, although further studies are needed to validate this.

PAD Exercise Training (PAD Rehabilitation)

Supervised exercise rehabilitation for 30-45 minutes a day 3 times a week for at least 12 weeks is a first-line (class 1A) recommended therapy for patients with symptomatic claudication.[49] Such supervised exercise programs improve pain-free walking distance[66,103,104] in all symptomatic patients with PAD and also can improve functional status in individuals with asymptomatic PAD.[67] In randomized trials, supervised exercise has been superior, and never inferior, to an invasive treatment strategy.[105,106] To be effective, physicians must be capable of writing a PAD exercise prescription or refer patients to standardized supervised exercise programs. Although aerobic exercise programs in dialysis patients have been shown to improve peak oxygen consumption and self-reported physical functioning,[107] their benefit on PAD and CVD outcomes is unknown and further studies are needed.

Antiplatelet Medications

Antiplatelet medications are recommended in patients with PAD[48,49] to prevent myocardial infarction and strokes. There is little evidence that antiplatelet agents significantly improve PAD symptoms or outcomes. The Antithrombotic Trialists' Collaboration reported that use of any antiplatelet agent (aspirin, clopidogrel, ticlopidine, picotamide, and dipyridamole) was associated with a 23% reduction in risk of nonfatal myocardial infarction, nonfatal stroke, or vascular death even in patients with PAD.[108] In the Clopidogrel Versus Aspirin in Patients With Ischemic Events (CAPRIE) trial, which excluded patients with severe kidney disease, treatment with clopidogrel was associated with a 24% relative risk reduction of CVD outcomes compared with aspirin in patients with PAD.[69] Updated PAD treatment guidelines recommend clopidogrel as an alternative agent to reduce CVD events, including mortality, in patients with symptomatic PAD.[51] There currently are no recommendations regarding choice of antiplatelet therapy in patients with kidney disease and PAD.

Cilostazol

Cilostazol is a phosphodiesterase 3 inhibitor with both antiplatelet and vasodilator properties that improves symptoms of PAD (claudication-free walking distance) and health-related quality of life.[109,110] Thus, use of cilostazol is a class 1A recommendation as first-line therapy for individuals with PAD and claudication.[49] No prospective studies have evaluated whether this beneficial treatment impact is preserved in individuals with CKD. The starting or maintenance dose of cilostazol often is lowered in individuals with decreased kidney function (eGFR <25 mL/min/1.73 m^2), primarily to lower adverse-event rates (headache, tachycardia, or loose bowel movements). It is unknown whether such lower doses also lower claudication efficacy. In dialysis patients, there are emerging data to suggest that cilostazol may improve patency after percutaneous transluminal angioplasty for lower-extremity PAD.[111,112] Data from the USRDS indicate that prescription rates of cilostazol for PAD are extremely low in both nondialysis patients with CKD (1.2%) and those treated with dialysis (2%).[113] Although this low rate may be due in part to a high prevalence of heart failure in dialysis patients,[114,115] which is a contraindication to cilostazol therapy, lack of prescriptive experience among physicians also is a possibility.

Invasive Therapy

Revascularization

Patients who do not achieve adequate symptomatic benefit from pharmacological and exercise-based claudication interventions or those with critical limb ischemia (pain at rest, ischemic skin ulceration, or gangrene) are candidates for open surgical or percutaneous revascularization. No randomized trials have evaluated the relative benefit or risk of angioplasty versus surgery or optimal medical therapies alone for PAD in patients with CKD/ESRD or revascularization versus medical therapy in this population. Current knowledge is derived from retrospective studies and prospective registries.[116-124] This is a critical comparative effectiveness research question that is germane to nephrologists and patients with CKD and PAD.[125]

A number of case series have shown that patients with kidney disease undergoing revascularization experience

significantly higher rates of graft failure, perioperative infection, limb amputations, and mortality than those with normal kidney function.[116-118,126,127] However, there is considerable heterogeneity across studies in the severity of decreased kidney function. In dialysis patients, diabetes, African American race, and lack of insurance have been shown to be risk factors for amputation after revascularization.[128] Analyses of data from the Veterans Affairs suggest that patients receiving dialysis, but not those with earlier stages of CKD, are more likely to experience lower-extremity amputation after surgical revascularization. Of 9,932 patients who underwent their first lower-extremity surgical revascularization procedure, the incidence of lower-extremity amputation within 1 year of revascularization increased linearly from 10% to 29% with worsening kidney function.[127] In the same study, at the time of revascularization, dialysis patients were more likely to have a wound infection, lower-extremity gangrene, ischemic ulceration, preoperative sepsis, and longer hospital stay compared with all other patients undergoing this procedure. Collectively, these findings seem to suggest that there are systematic differences in clinical presentation at the time of revascularization for dialysis versus nondialysis patients. This may be due to differences in the natural history of lower-extremity PAD, with more rapid evolution of advanced PAD and procedural complications in patients receiving dialysis, or perhaps due to differences in antecedent treatment decisions (eg, delayed referral to surgery) in this population. Although patients with ESRD are more likely to require distal revascularization procedures,[129] percutaneous revascularization has been promoted as an option for patients who have more proximal stenoses and lesser anatomic PAD disease burden.[130-132] The use of each of these strategies and timing of invasive therapy has not been tested. In the absence of prospective data to define the risk and benefit of these critical invasive strategies, patient choice in selecting a treatment likely often is suboptimal.

In addition to risk of amputation after revascularization, mortality rates in patients with ESRD undergoing bypass surgery for PAD are extremely high, with >50% of patients dying within 2 years of the procedure,[117,126,133] similar to patients with critical limb ischemia who do not undergo surgery.[134] It seems likely that high mortality rates after revascularization in patients with CKD have shaped treatment practices for limb ischemia in this population. In one study, patients with critical limb ischemia and eGFR <60 mL/min/1.73 m^2 were less likely to undergo a revascularization procedure compared with those with better kidney function and instead were more likely to be managed medically or undergo amputation. Nevertheless, for all groups, including those with CKD, patients who underwent revascularization experienced lower mortality rates than the other groups.[135] Thus, prospective randomized trials comparing different strategies for managing advanced limb ischemia in patients with CKD are needed. Currently, it is unknown whether a more proactive approach to care involving earlier use of any revascularization strategy may (or may not) be beneficial in this CKD population compared with an approach based on optimal medical management and delayed surgical intervention.

Amputation

Rates of nontraumatic lower-limb amputations are approximately 4.3 events/100 persons per year for all patients with ESRD, with rates as high as 13.8 events/100 persons per year for diabetic patients with ESRD.[136] In this study, Eggers et al[136] reported high mortality rates (almost 50% and 66% at 2 and 3 years, respectively) in those undergoing amputation. Similar to other critical limb ischemia populations, patients with ESRD who are Native American or African American or have diabetes are at particularly high risk of amputation.[136,137] The presence of moderate or severe kidney disease is also a strong risk factor for bypass graft failure and amputation,[127,138] with high postamputation mortality. The requirement for amputation probably identifies patients at increased risk of death, but it also is possible that the procedure itself may confer periprocedural mortality risk in this population. Observational data suggest that preventive foot care and educational programs may reduce amputation rates in patients with diabetes and dialysis patients.[139-141] However, randomized trials are needed to assess their efficacy and economic feasibility in this population.

The Role of Preventive Foot Care

Edmonds et al[142] showed a high rate of foot ulcer healing (86%) and reduced major amputations (40%-50%) when patients with diabetes were provided access to the skills of a chiropodist, shoe fitter, nurse, physician, and surgeon to manage the distinctive lesions of the neuropathic and ischemic diabetic foot during a period of 3 years. A similar reduction in gangrene and major foot amputations was seen in patients with diabetes after kidney transplant using a multidisciplinary approach.[143] In diabetic dialysis patients, use of an intensive diabetes care education and management program in the dialysis unit was associated with a statistically lower hospitalization rate for diabetes and peripheral vascular– and infection-related admissions, with no amputations occurring in the study group compared with 5 amputations in the

control group.[141] In one retrospective study, the presence of an onsite chiropodist who provided weekly foot assessment, foot care education, and further specialist referral suggested a favorable trend toward decreased amputations, with a lower risk of death or time to first amputation in Cox regression models.[139] There is an unmet need to evaluate the economic feasibility and sustained benefit of multidisciplinary or specialist foot care in preventing amputations in patients with kidney disease and PAD.

CONCLUSIONS

PAD is an underdiagnosed and undertreated disease that is one of the most potent risk markers for cardiovascular morbidity and mortality in patients with kidney disease. Its high prevalence, combined with significant mortality, morbidity, and quality-of-life reduction associated with both diseases, highlights the need for nephrologists to understand the potential benefits of early diagnosis and aggressive management of PAD in patients with CKD/ESRD. Current clinical care guidelines are limited by the paucity of observational or randomized studies addressing PAD in this high-CVD-risk population. Existing methods of PAD diagnosis and treatment are significantly less effective in preventing amputations and death in patients with kidney disease than in those without. There thus is a growing need to identify key knowledge gaps and strategies to address these gaps. Table 3 summarizes major clinical questions regarding PAD diagnosis and treatment, including recommendations from existing guidelines and literature for patients with kidney disease. We also highlight the existing knowledge gaps and propose research possibilities. Future studies should improve the accuracy, safety, and cost-effectiveness of PAD diagnostic methods; evaluate

Table 3. Practice Recommendations, Knowledge Gaps, and Proposals for Future Research

Key Clinical Questions	Clinical Practice Recommendations	Current Knowledge Gap	Suggested Research
What is the best modality to establish the diagnosis of PAD in patients with CKD/ESRD?	Clinical history and physical examination, with targeted use of the ABI; if ABI nondiagnostic, consider other PAD physiologic or imaging tests; consider CTA or MRA if planning revascularization procedure	Questionable accuracy of the ABI value (either falsely normal or elevated in presence of noncompressible pedal pulses); limited use of contrast-based imaging modalities	Future clinical trials should define the accuracy of the ABI compared with and in combination with other physiologic PAD testing modalities (eg, TBI)
Should diagnostic tests other than ABI be used routinely in patients with CKD? At what CKD stage should ABI accuracy be questioned?	If ABI is elevated (>1.3) or pedal arteries are noncompressible, or clinical suspicion persists despite a normal ABI, consider performing exercise ABI/TBI or other imaging	Unknown rate of a falsely normal ABI in patients with CKD and ESRD; the sensitivity, specificity, and predictive values of this key test are not known in this target population	Prospective evaluation of ABI test characteristics in a cohort of CKD patients to determine the association of abnormal ABI values by eGFR; determine the predictive value of ABI to define CVD morbidity and mortality in CKD populations
Which pharmacological, exercise, risk-factor modification, or revascularization strategies of care are efficacious in patients with CKD and PAD?	Aggressive management of diabetes, lipid and blood pressure control, smoking cessation, antiplatelet therapy; prescription of supervised exercise program in patients with claudication; revascularization if CLI is present or if above interventions not beneficial	Extrapolation of results from general population to CKD patients; exclusion of patients with CKD, especially advanced stages, in all previous studies	Retrospective analysis of existing cohort or meta-analysis of drug therapy for treatment of PAD in CKD populations; RCT to evaluate efficacy of drug therapies in CKD populations
Are preventive interventions such as podiatrist evaluation and special fitting shoes useful in prevention of progression to CLI/amputations?	Consider podiatric evaluation in patients with CLI or infections to reduce risk of amputation	Limited data from studies in patients with dialysis or in diabetic patients with no known PAD	Prospective study to evaluate clinical and economic implications of measures to prevent development of CLI and progression to amputation in CKD/ESRD populations

Abbreviations: ABI, ankle-brachial index; CKD, chronic kidney disease; CLI, critical limb ischemia; CTA, computed tomography angiography; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; MRA, magnetic resonance angiography; PAD, peripheral artery disease; RCT, randomized control trial; TBI, toe-brachial index.

strategies to improve clinical outcomes in early PAD; and directly assess the magnitude of improvement achieved when PAD treatments—preventive, medical and revascularization—are applied in CKD populations.

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