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Peripheral Artery Disease and Chronic Kidney Disease: Clinical Synergy to Improve Outcomes

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Abstract

Persons with chronic kidney disease (CKD) are at a higher risk of developing peripheral artery disease (PAD) and its adverse health outcomes than individuals in the general population who have normal renal function. Classic atherosclerosis risk factors (e.g., age, smoking, diabetes, hypertension and hyperlipidemia) are common in CKD patients, but CKD also imposes additional unique risk factors that promote arterial disease (e.g., chronic inflammation, hypoalbuminemia and a pro-calcific state). Current nephrology clinical practice is adversely impacted by PAD diagnostic challenges, the complexities of managing two serious comorbid diseases, delayed vascular specialist referral, and slow PAD treatment initiation in CKD patients. Persons with CKD are less likely to be provided recommended ‘optimal’ PAD care. The knowledge that both limb and mortality outcomes are significantly worse in CKD patients, especially those on dialysis, is not a biologic fact, but can serve as a care delivery call to action. Nephrologists can facilitate positive change. This manuscript proposes that patients with PAD and CKD be strategically co-managed by care teams that encompass the skills to create and use evidence-based care pathways. This proposed collaborative multidisciplinary approach will include vascular medicine specialists, nephrologists, wound specialists and mid-level providers. Just as clinical care quality metrics have served as the base for ESRD and acute MI quality improvement, it is time that such quality outcomes metrics be initiated for the large PAD-CKD population. This new system will identify and resolve key gaps in the current care model so that clinical outcomes improve within a cost-effective care frame for this vulnerable population.

Keywords

Peripheral artery disease; kidney disease; clinical outcomes; collaborative care; multi-disciplinary teams

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Introduction

Cardiovascular disease (CVD) related ischemic events are more common in individuals with chronic kidney disease (CKD) than progression to end-stage renal disease (ESRD) and cause significant morbidity and mortality.^{1,2} Patients with CKD are more likely to develop atherosclerotic CVD than the general population with preserved kidney function,³ and of the three major cardiovascular disease syndromes (including both coronary artery disease and ischemic stroke), atherosclerotic peripheral artery disease (PAD) is also highly prevalent among persons with CKD.⁴ The presence of PAD in CKD patients markedly increases the short term risk of heart attack and stroke, and serves as the key cause of limb loss and mortality, with such rates being much greater than that of the general population.^{5,6} Over the last 10 years, observational studies have contributed significantly to our understanding of how decreased kidney function serves as a risk factor for PAD and its consequent adverse outcomes.^{6,7} Despite this large health impact, past randomized clinical trials (RCTs) of PAD therapies have traditionally excluded patients with severe kidney disease, even though such individuals represent the population at highest risk.⁸ As a result, current evidence-based guidelines for the evaluation and management of PAD, which might be better applied in CKD and ESRD populations, have necessarily been created by extrapolation of the risk and benefit data observed in the general population. This may contribute to the current lack of enthusiasm to apply this, otherwise strong, evidence base to inform ideal CKD care.

As there is a high CVD and PAD burden in patients with CKD, there is a need for nephrologists, cardiovascular physicians, and primary care clinicians to identify these patients, facilitate the establishment of accurate diagnoses of both CKD and PAD, and then to provide early and appropriate treatment. The objective of this article is to provide an overview of current data, spanning knowledge regarding the epidemiology, risk factors, diagnostic modalities, and potential treatment options that exist for PAD in patients with kidney disease, and to apply these data to create a new care paradigm. By highlighting gaps in current practice, we urge the creation of a new, health system-based collaborative care approach that would rely on multidisciplinary care teams dedicated to improving the health and reducing the burden of PAD, in persons with kidney disease.

The Epidemiology of PAD in CKD

In a recent meta-analysis Fowkes and colleagues estimated that as of 2010, nearly 202 million persons suffer from PAD worldwide. This large burden also represents a 25% increase in PAD prevalence over the most recent decade and is attributed, in part, to the aging population and ongoing risk factor exposure internationally.⁹ It is likely therefore that the “CKD-PAD burden” has comparably increased in both high and low-middle income nations globally. The prevalence of PAD in the U.S. is large and affects as much as 4.3% of the general adult population over 40 years of age¹⁰. Persons with CKD have higher rates of incident and prevalent PAD, due to the aggregation of traditional atherosclerosis risk factors. Population representative data from the National Health and Nutrition Examination Survey (NHANES 1999-2000) were analyzed by O'Hare and colleagues who reported that 24% of persons with CKD stage 3 or greater (creatinine clearance of <60 mL/min/1.73m²) had PAD as objectively defined by an ankle-brachial index (ABI) <0.9 .⁴ This was 6-fold higher

prevalence rate compared to persons with a creatinine clearance of >60 mL/min/1.73m² (4%). Other population cohort studies have reported PAD prevalence rates ranging from 12-15% in individuals with CKD depending on population characteristics, the degree of kidney dysfunction, and PAD diagnostic modality used.^{7,11} The actual PAD prevalence rate is likely significantly higher, as the definition of clinically significant PAD has been updated by the intersocietal American College of Cardiology/American Heart Association (ACC/AHA) Scientific Statements and guidelines. The definition of a normal ABI (no PAD) is now defined by ABI values between 1.0 and 1.4.¹² Finally PAD prevalence rates are known to be significantly higher in persons with ESRD requiring dialysis. When PAD is broadly defined by an inclusive set of clinical criteria (including known PAD, symptomatic claudication, signs of critical limb ischemia (CLI) or reduced pulses on examination, limb artery revascularization, or past ischemic amputation), PAD prevalence ranged from 23-25%.^{13,14} Use of the ABI as the key diagnostic criteria significantly increased prevalence rates to nearly 35%.^{15,16} According to recent 2010 claims data from the USRDS, nearly 46% of all dialysis patients in the U.S. were offered care that was supported by a diagnostic code for PAD.¹⁷ Thus, nephrology training programs must teach, and current nephrology clinicians simply must be adept at applying, PAD-related care strategies.

Pathophysiology and Risk Factors for PAD in CKD

Traditional risk factors for PAD are similar, but not identical, to those common to other atherosclerotic diseases (e.g., coronary and carotid artery diseases). PAD incidence has been studied to a greater extent in dialysis patients, compared to non-dialysis CKD patients to demonstrate that male sex, older age, diabetes and smoking were all found to be significantly associated with PAD.^{14,18} These findings were recently confirmed in persons with stage 3-5 CKD not on dialysis using data from the Chronic Renal Insufficiency Cohort (CRIC) study.¹⁹ A number of factors unique to persons with kidney disease may heighten their risk of PAD.

Chronic kidney disease itself is strongly and independently associated with PAD. In both the general population and select patients with CKD, the risk of PAD increases as GFR values decrease after adjusting for multiple confounding variables.^{19,20} However, a more direct causal association between kidney disease and PAD is yet to be established. It is possible that kidney disease may also be a marker of a metabolic condition associated with progressive vascular dysfunction.^{21,22} Evidence for the possibility of a direct arterial impact of CKD is derived from prior studies that have reported associations between albuminuria^{21,22}, which is a marker of generalized endothelial dysfunction and which is also a risk factor for atherosclerosis and PAD.²³ Albuminuria is also associated with medial arterial calcification (MAC) which causes elevations in ABI, leading to a “false normal” ABI value or to supranormal, high ABI measurements. It is also important to note that both atherosclerotic PAD and MAC may co-exist, thus masking the true PAD burden.²⁴

Patients who require dialysis have a unique set of biochemical and endocrine abnormalities which have been shown to be associated with PAD. The chronic uremic state is associated with systemic inflammation in dialysis patients leads to hypoalbuminemia and an increased risk of PAD.²⁵ Hyperphosphatemia is highly prevalent in dialysis patients and has been

shown to predict PAD events in a small case control study.²⁶ While vitamin D deficiency²⁷ and hyperparathyroidism²⁸ have been associated with a higher risk abnormal ABI, the associations of these less common modifiable risk factors need to be studied on a larger scale in dialysis patients. Hyperhomocystinemia²⁹ and elevated levels of lipoprotein-a (Lp-a) have also been implicated as risk factors for PAD.¹⁸ Results from the CRIC study have also shown novel associations between markers of inflammation, prothrombotic state, oxidative stress and insulin resistance with prevalent PAD among persons with CKD.¹⁹

Establishing the Diagnosis of PAD in CKD

The key rationale that underpins the call for a proactive evaluation of PAD in individuals with CKD is based on the usual assumption that an accurate assessment of cardiovascular risk will permit use of treatments to sustain quality of life by lowering this risk, will detect claudication so as to preserve independent function, and will assure that amputations are prevented. We note that a “diagnostic evaluation” is not synonymous with “screening” for PAD. There is currently no defined role for population-based PAD detection efforts in the general “low risk” population. In 2013 the United States Preventive Services Task Force (USPSTF) comprehensively reviewed the potential utility of true population-based screening of a low risk, asymptomatic community-derived pool of patients. This review assigned an “I” (indeterminate) recommendation for routine screening for PAD using the ABI, based primarily on the absence of any prospective clinical trial to precisely define benefit, risk and cost-efficacy.³⁰ While the potential benefit of establishing a PAD diagnosis is real, and the harms of the ABI test are non-existent, concern was noted that inappropriate exposure to advanced imaging or inappropriate use of non-indicated invasive leg procedures might occur, eliciting harm. In contrast, the 2005 and 2011 ACC/AHA “Guidelines for the Management of Patients with PAD” have recommended use of the resting ABI to detect PAD in individuals with 1 or more of the following factors that are known to markedly increase PAD risk: any individual with abnormal ankle pulses, the presence of exertional leg symptoms suggestive of claudication, the presence of non-healing wounds or gangrene, and specific “population tested” high risk demographic factors, including age 65 years and older, or 50 years and older with a history of smoking or diabetes.³¹ All of these “risk categories” would increase the prior prevalence of PAD to at least 25%, or higher. In these groups, specific beneficial, evidence-based care strategies would be appropriately prescribed (e.g., risk reduction medications, exercise, and care for claudication and CLI). These guidelines did not address the role of CKD as an additional known high risk cohort. It would be imperative in the CKD population that risk exposure be minimized by adherence to excellent care standards (e.g, lower exposure to iodinated contrast, gadolinium, or radiation; avoidance of invasive therapies when non-invasive therapies are available, etc.). Use of a “proactive PAD diagnostic” clinical approach in individuals with CKD provides the only hope that the process of care and outcomes might be improved. “Non-treatment” is not a treatment strategy.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that all patients should be evaluated for PAD at the time of dialysis initiation by both a vascular physical examination and use of physiologic or duplex ultrasound studies, or invasive testing as would be clinically indicated (strength of

recommendation: Weak).³² This approach also has not been evaluated in an RCT. It is presumed, but not proven, that the abysmal limb salvage outcomes that are common in dialysis patients, despite late attempts to achieve endovascular or open surgical limb revascularization, highlight the need to provide medical interventions more promptly (including lifestyle, medication or revascularization strategies) during earlier stages of kidney disease. Similarly, in 2012 the KDIGO guidelines recommended that adults with non dialysis CKD be regularly examined for signs of PAD and be considered as candidates for prescription of the evidence-based therapies (Grade 1B).³³ Acknowledging that classic claudication may not be present in all individuals with PAD, the KDIGO guidelines also supports a therapeutic strategy that promotes an earlier use of the ABI test in people at high risk of PAD. This recommendation represents an important first step in assessing the burden of PAD in pre-dialysis CKD patients.

Intermittent claudication, defined as muscle fatigue, discomfort, cramping or pain that is reproducibly induced by exercise and relieved by rest, is often considered to be the most easily recognized ischemic symptom in persons with PAD. This is not true, as classic claudication is infrequently present (< 10-15% of cases) in individuals with significant PAD, defined by an ABI < 0.9, and thus cannot be used to reliably detect PAD.³⁴ In addition, non-PAD leg symptoms are frequent in dialysis patients due to co-morbid neuropathy, pruritis, restless leg syndrome and arthritis. Thus, a clinical history alone (without objective vascular testing) is not sufficient to discern the ischemic versus non-ischemic etiology of leg discomfort in this population. In asymptomatic persons, the clinical examination cannot adequately lower the likelihood of PAD. In symptomatic patients, the presence of a cool skin, an arterial bruit and/or loss of pulses does increase the likelihood of significant occlusive disease.³⁵ Persons with CVD risk factors and any suggestive symptoms or signs of PAD should therefore be referred for further physiologic or imaging studies for diagnostic confirmation.

The ABI is a simple, inexpensive, and risk free noninvasive test with proven clinical utility in establishing the PAD diagnosis in the general population.³⁶ ABI values of <0.9 are diagnostic for PAD, yet, recent evidence also confirms that values in the range of 0.9-1.0 are “not normal”, as even individuals with these “borderline” measurements of pedal perfusion suffer an increased risk of CVD ischemic events.^{37,38} Thus, the ABI continues to represent the ideal, first line, low cost gold standard to objectively establish the PAD diagnosis in all individuals who are considered to be clinically “at risk”. The ABI is, however, limited in its sensitivity to detect PAD in the presence of MAC. Arterial wall stiffness or calcification is more frequent in older persons, those with long standing diabetes and advanced renal disease.^{39,40} As a result, ABI values may be elevated to ‘falsely normal’ or even abnormally high values (>1.4) in the presence of significant PAD. Thus, a seemingly normal ABI value should not dissuade nephrologists or other physicians from referring CKD patients, in whom the suspicion for PAD is high, for further vascular testing. This is similar to assuring that dynamic testing is offered to patients with coronary artery disease (CAD), despite the presence of a normal resting ECG. For a patient with suspected PAD and a normal or high ABI value, testing may include performance of an exercise ABI (to measure functional status and objectively document muscle symptoms), the toe-brachial index (TBI), segmental pressure recordings, or duplex ultrasonography. The TBI has been recommended as the next

diagnostic step in persons with an ABI > 1.4 as these digital arteries are usually spared from being non-compressible.⁴¹ Using a TBI cut-off of 0.7, Leskinen and colleagues have detected underlying PAD (angiographically proven) in dialysis patients characterized by an ABI > 0.9.³⁹ One study has evaluated the predictive impact of the TBI test in persons with CKD and ESRD to show that PAD confirmed by a low TBI value was associated with increased all-cause mortality.⁴² Ideally, this relationship would be confirmed in additional future studies in large CKD cohorts to validate these findings.⁴³ Similarly, while the exercise ABI is known to add valuable diagnostic and prognostic information in persons with a normal resting ABI,⁴⁴ the test accuracy would ideally be further validated in CKD patient populations.

Duplex ultrasound evaluation of arterial blood flow velocity represents an accurate diagnostic test in individuals with CKD, and can be utilized with no risk and at low cost. Advanced PAD imaging modalities, including both computed tomography and magnetic resonance angiography have shown excellent diagnostic utility.^{45,46} However, the risks of contrast-induced nephropathy (CIN) and nephrogenic systemic fibrosis limit the use of iodinated contrast and gadolinium, respectively, in persons with CKD, especially when the eGFR is below 30 ml/min/1.73m². Use of both noninvasive (CTA and MRA) and invasive conventional PAD angiography with iodinated contrast should usually be reserved for patients in whom severe claudication or CLI is not responsive to non-invasive therapies. In persons with CKD, the KDIGO guidelines recommend the use of the lowest possible dose of a low-osmolar or iso-osmolar contrast agent and volume expansion to prevent the occurrence of CIN.³³

Treatment to Improve Cardiovascular Health Outcomes for Patients with CKD and PAD

As the presence of PAD results in adverse CVD outcomes and a reduction in quality of life (QoL), the mandatory goals of all PAD therapeutic interventions are: (1) To assure delivery of evidence-based secondary prevention strategies to improve rates of heart attack, stroke and death; (2) To detect claudication in its earliest stages and to diminish these symptoms, thus improving QoL; and (3) to prevent the development of CLI, to recognize it immediately, and to prevent amputation. These goals are as important, and likely more important, in individuals with CKD as in the general population. Although persons with significant kidney disease were excluded from most past clinical trials of PAD interventions,⁴⁷⁻⁴⁹ treatment guidelines as currently formulated as an extrapolation of results from the general population, would likely be effective, and are certainly more appropriate than a “no care” or other non-evidence-based care approach. Figures 1-3 display three of seven guideline-based clinical care algorithms that support best care standards for the diagnosis and management of PAD, and that remain appropriate for CKD patients.

Secondary Prevention of CVD in Patients with PAD (with or without CKD)

The benefit of nearly all antiplatelet medications, including aspirin, clopidogrel, ticlopidine, picotamide, and dipyridamole, has been demonstrated in a wide set of studies of symptomatic individuals for whom a decreased risk of heart attack, stroke, and vascular

death has been confirmed.⁵⁰ The current AHA/ACC PAD guideline (2005 and 2011 Update) recommends low dose aspirin or clopidogrel in persons with symptomatic PAD to reduce adverse CVD events.^{31,36} Data from the Clopidogrel for Reduction of Events During Observation (CREDO) trial suggest that persons with CKD may not derive the same degree of benefit from clopidogrel therapy as those with normal renal function.⁵¹ This may in part be explained by increase platelet reactivity seen in persons with CKD leading to resistance.⁵² As well, the utility of aspirin in lowering CVD events in patients with asymptomatic PAD is unclear.^{9,19} Importantly, currently approved antiplatelet medications provide no proven benefit in reducing claudication symptoms or in preventing amputations. Large, prospective randomized trials are now in progress to evaluate the potential beneficial impact of newer antiplatelet medications, such as ticagrelor, in providing superior outcomes.⁵³ In addition, a retrospective analysis of the results of the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) study of vorapaxar have suggested a benefit of this antiplatelet medication on rates of acute limb ischemia and unplanned leg revascularization, and this medication has been Food and Drug Administration approved for use in individuals with established CAD or PAD.⁵⁴ Thus, ongoing clinical research may well expand the utility of antiplatelet medications in individuals with PAD. Therapy with an oral anticoagulant agent does not improve risk of adverse CVD events in persons with PAD.⁵⁵ Current KDIGO guidelines recommend that adults with CKD at risk for atherosclerotic events be offered treatment with an antiplatelet medication (usually low dose aspirin or clopidogrel) unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefit.⁵⁶

Smoking is a strong modifiable risk factor for the development of CVD and is known to markedly increase rates of heart attack, stroke and death. This impact is even greater for individuals with PAD and there is no risk factor that more powerfully modifies outcomes in this patient cohort. While it has been proven from data derived from the general population that individualized smoking cessation therapies are associated with improved rates of quitting, these approaches are also effective in individuals with PAD.⁵⁷ Smoking cessation has been associated with very small improvements in walking distance and some decrease in claudication symptoms; nevertheless, this is not the key benefit of smoking cessation efforts and there are certainly much more powerful treatments to improve claudication.⁵⁸ Smoking cessation is associated with lower short-term rates of heart attack and stroke, a lower need for coronary and leg invasive therapies, lower rates of progression of asymptomatic PAD to claudication, lower rates of development of CLI, lower amputation rates, and greater efficacy of PAD revascularization interventions.⁵⁹ Although these findings have not been replicated in CKD populations, given the observational benefit seen on PAD-related mortality in persons with dialysis,⁶⁰ the importance of smoking cessation therapy, including both counseling and pharmacotherapy, cannot be overstated.

Diabetes is associated with increased risk of developing PAD, CKD and adverse cardiovascular outcomes.⁶¹ Although no trials have yet demonstrated a reduced risk of PAD or CAD ischemic outcomes with intensive glucose control regimens,⁶² given the overall benefit of glucose control on microvascular complications of diabetes, a tight glucose control is been recommended in persons with PAD.⁴¹ Recent KDOQI Guidelines on the

management of diabetes in CKD have however recommended a goal HbA1C of ~7% in persons with CKD and higher goals in those at risk of hypoglycemia or those with significant co-morbidities and limited life expectancy.⁶³

Persons with PAD often have uncontrolled hypertension,²⁵ an important risk factor for progression of CKD. Although no direct effect of tight blood pressure control on reducing PAD incidence or related outcomes has been demonstrated, the additional beneficial effect of lowering blood pressure to prevent strokes, heart attacks and heart failure at the population level cannot be overstated. Renal artery stenosis is common among persons PAD and is often a cause of difficult to treat hypertension. Stenting of these lesions is not superior to maximal medical therapy with regard to improving outcomes⁴³ and is associated with unnecessary contrast exposure. There may be an advantage for PAD patients with poorly controlled hypertension and CKD to be referred to nephrologists and hypertension specialists to optimize medication use to control blood pressure. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are considered first line therapy in patients with CKD especially those with proteinuria and diabetes.⁶⁴ Similarly, due to their cardio-protective benefit, ACE-I and ARB medications are considered indicated for patients with PAD in current care guidelines.³⁶ Beta-blocker use is not contraindicated in persons with CKD or claudication, as there is no detrimental impact on claudication symptoms or limb outcomes.⁶⁵

Limited data have suggested that lipid lowering with statins might improve walking distance in persons with PAD,⁶⁶ However this is not a reliable effect, has not been studied in persons with CKD, and is not an indication for statin use. While the use of statin therapy to decrease mortality in patients with kidney dysfunction and elevated lipid levels has been controversial, and while an inconsistent benefit has been shown with statin therapy in dialysis patients,⁶⁷ there has been unambiguous evidence of statin benefit in PAD populations. Thus, given the high PAD and CAD disease burden in patients with kidney disease, statin use may be reasonable until conclusive evidence suggests otherwise.⁶⁸

Improving Limb Outcomes: Claudication and Critical Limb Ischemia Therapies

The relative benefit and harm of each potential therapeutic approach to improve claudication symptoms has been reviewed in detail.¹² Supervised exercise programs are well-proven to serve as the most effective, safest and cost effective approach to achievement of sustained improvements in PAD claudication symptoms and objective functional status (e.g., treadmill-measured walking distance).⁶⁹ This is now recommended as a Class 1A, evidence-based first line therapy for persons with PAD who seek the full range of cardiovascular risk factor and functional status benefits. This approach is not appropriate for those individuals who have other limitations, beyond claudication, that would obviate successful participation in supervised exercise (e.g., severe arthritis or orthopedic limitations, severe COPD or heart failure). While recent evidence suggests that nurse-supervised home based programs might also improve claudication and quality of life, these approaches have only been studied in research settings.^{70,71} The complete reliance on invasive therapeutic approaches (endovascular and open surgical) for nearly all individuals with claudication is not evidence-based, often voids ethical patient participation in the selection of the best long-

term claudication intervention, and is not comparably cost-effective. The comparative effectiveness of supervised exercise and endovascular care has been intensively studied in multiple prospective trials, with supervised exercise consistently demonstrating comparable or superior outcomes sustained for at least 18 months when compared to endovascular treatment.^{26,27,49} Such claudication exercise programs of care are easily created within current cardiac rehabilitative settings, and thus could be made immediately for all patients with PAD and claudication. In fact, for individuals with CKD, it is likely that the efficacy and cost-efficacy of invasive therapies is more adverse than in a healthy cohort. Unfortunately, to date no trials of supervised exercise therapy on claudication symptoms in individuals with PAD and CKD have been performed.

Cilostazol is a phosphodiesterase-3 inhibitor that has been proven to be an effective claudication medication, and has achieved a Class IA guideline-based recommendation to be the first line medical therapy individuals with lifestyle limiting claudication. Compared to placebo and pentoxifylline, cilostazol therapy was associated with significant improvements in walking time and reduction in claudication.⁷² Used twice daily, patients experience improvements in both pain free and maximal walking distance over the first 3 months of use, and this improvement is also sustained long-term, with no major adverse effects (safety has been proven in long-term follow-up). While this drug is associated with a “black box” warning not to be used in individuals with heart failure (due to a theoretical class effect of PDE-I medications when severe left ventricular systolic dysfunction is present), this contraindication is known to be relatively rare in patients with symptomatic claudication (<10% of candidates). There is documented underutilization of this effective medication, and it should be considered as a first line approach for individuals with CKD. Caution is likely reasonable in individuals with significant CKD and in dialysis patients due to the high protein binding of cilostazol and impaired excretion when creatinine clearance is <25ml/min. We suggest initial use of a lower 50 mg twice daily dose (instead of the usual 100 mg twice daily dose) for 4-8 weeks to verify drug tolerance, prior to potential up-titration. When dose-related minor adverse effects are observed (headache, palpitations, nausea, or diarrhea), a lower dose can be tried or the drug discontinued.

Patients with intermittent claudication that is not adequately improved by supervised exercise or cilostazol use should be considered candidates for advanced imaging and invasive care strategies. Similarly, individuals with CLI, defined by ischemic rest pain, non-healing wounds or ulcers, and/or gangrene, and in whom pedal or toe perfusion pressures document the ischemic etiology, are candidates for endovascular or open revascularization procedures or amputation. Data from the general population suggest that the current US national CLI standard of care is poor, as approximately half of patients with CLI receive an opportunity to undergo revascularization, while one quarter are treated by primary amputation, and the final quarter are treated by medical management alone.⁴¹ Retrospective data also indicates that persons with CLI and CKD are less likely treated with revascularization compared to persons without renal insufficiency.⁷³ This trend may however change with emerging data showing improved amputation free survival and rates of limb salvage with revascularization in persons with CLI at all levels of renal impairment.⁷⁴ An extensive review of revascularization in persons with kidney disease is beyond the scope of this article and has been discussed in detail previously.⁷⁵

While distal lesions are more common in persons with CKD (and especially ESRD), a number of case series have been published reporting successful limb salvage and decreased mortality with endovascular revascularization.^{76,77} Although initial results of endovascular treatment suggested a similar benefit and lower cost over surgical revascularization,⁷⁸ long term follow up has shown that a surgical approach was associated with greater overall survival and amputation free survival when the patient survives beyond 2 years.⁷⁹ Current AHA/ACC guidelines have stressed the fact that surgical revascularization should be considered as first line revascularization therapy in persons with a life expectancy greater than 2 years.³¹ In a meta-analysis of 28 studies, Albers and colleagues reported pooled estimates of 50%, 66% and 23% for primary patency, limb salvage and mortality respectively at 5 years in dialysis patients undergoing infrainguinal arterial reconstruction.⁸⁰ While data that describe the relative benefit and harm of open revascularization in early stages of kidney disease is limited, studies have shown that persons on dialysis have increased risk of infection, graft loss, amputations and mortality.^{6,81}

Amputation rates are very high for persons on dialysis compared to the general population with half of these patients dying within 2 years of the procedure.⁸² In a large retrospective cohort of over nearly 17,000 persons who underwent non-traumatic amputations, kidney function was inversely associated with increased risk of mortality, even among those with only moderate reduction in kidney function.⁸³ These findings underscore a number of important issues: a) current limb revascularization methods yield significantly poorer results in persons with kidney disease; b) early identification and aggressive treatment of CKD patients at high risk of PAD outcomes may provide improved opportunities to prevent limb loss and amputation (though this has not been proven); and 3) CKD patients should be included in diagnostic and therapeutic trials of PAD interventions to provide improved evidence to support future therapeutic recommendations that can be applied to this high risk population.

Improvement of Care Standards: a collaborative care approach for patients with PAD and CKD

Both PAD and CKD are common and when present together, morbidity and mortality is very high. Nephrologists often serve as the primary care or principle care provider for individuals with CKD and have demonstrated key investigational and clinical successes in fostering improvements in heart disease outcomes. PAD care is of equal importance, as rates of heart attack and stroke are highest in individuals with PAD and CKD and these individuals suffer nearly all of the amputations in CKD cohorts. Yet, the management of PAD in individuals with CKD is fraught with challenges. In addition to the PAD-specific conundrum of diagnostic accuracy, diagnostic modality, and selection of specific treatments, patients and clinicians can also quickly feel overwhelmed. These patients face a complex burden of medical, psychological and social issues that both the CKD and PAD illnesses. Ideal care almost always must span multiple healthcare specialties, necessitating a multidisciplinary approach to disease management.

Previous reports have highlighted benefits of comprehensive clinical care teams, especially in the management of patients with chronic diseases.^{84,85} Limited data and guidelines on the

use of care teams in the management of PAD exist. The NICE (National Institute for Health and Clinical Excellence) guidelines on the management of PAD have recommended that persons with CLI be managed by a multidisciplinary team.⁸⁶ Traditionally, these teams have included a vascular surgeon or physician, wound care specialist, nurse practitioners and podiatrist, but not a nephrologist. Box 1 highlights the potential clinical focus areas that would be used to charter such PAD-CKD care teams. Box 2 provides suggestions for specific care plans that nephrologists and vascular physicians could create. As well, key knowledge gaps will require a collaborative research mission and plan.

Why might these care teams be very likely to succeed in improving outcomes? Diabetic dialysis patients have nearly 3-fold increased risk of amputations compared to those without diabetes.⁸² Studies in this population have shown that the use of a multidisciplinary approach significantly reduces progression of diabetic foot ulcers and prevents need for amputation.^{87,88} The Center for Medicare & Medicaid Innovation (CMS Innovation Center) is planning on implementing a new service delivery and payment model for Medicare beneficiaries with ESRD on dialysis. One domain of this Comprehensive ESRD Care (CEC) model comprises a proposal to evaluate management of chronic diseases including foot exams, eye exam and rates of lower extremity amputation.⁸⁹ The CEC has suggested that to achieve creation of a seamless and integrated care, a comprehensive care delivery model must emphasize coordination across a full-range of clinical and non-clinical support services which may be best achieved through the establishment of an interdisciplinary care team led by a nephrologist.⁸⁹

There is indeed a large population that might benefit. Data from the REACH (Reduction of Atherothrombosis for Continued Health) registry, a large database of over 51,000 patients with at least 3 atherothrombotic risk factors or documented cerebrovascular disease, CAD, or PAD found that nearly 34% of patients had CKD defined by an eGFR of <60ml/min/1.73m².⁹⁰

Vascular physicians should therefore be aware of the magnitude of CKD burden among PAD patients and consider involving nephrologists in the management. This is especially true when invasive or contrast based imaging are planned. Judicious peri-procedure hydration in conjunction with a nephrology consultation should be considered to reduce risk of CIN. Patients with a kidney transplant are at increased risk of both CIN and wound infections due to use of immunosuppressant medications. Sirolimus, an mTOR (mammalian target of rapamycin) inhibitor commonly used to prevent allograft rejection impairs wound healing. Patients needing amputations, revascularizations or large debridement may need to have the immunosuppression changed to agents like tacrolimus to prevent post-op complications.⁹¹

In summary, current care outcomes are far from ideal. The high morbidity, suffering and costs could be diminished if PAD-CKD care teams planned to achieve the diagnostic, ischemic event reduction, claudication improvement, amputation prevention, and research goals. In an era of health care reform, the opportunity to improve care for these patients has never been better.

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Box 1**Clinical goals that might define the collaborative mission between vascular medicine and nephrology clinicians to improve care outcomes**

- Proactively recognize the burden of PAD in CKD patients and burden of CKD in PAD patients to facilitate achievement of individual health outcomes
- Facilitate appropriate use of PAD diagnostic testing (benefits and CKD-specific limitations and harms) in the CKD population. Create and implement appropriate diagnostic algorithms
- Sustain use of cardiovascular risk reduction interventions, to achieve pre-specified metrics of target goal success.
- Facilitate use of the full range of evidence-based claudication treatment strategies of care to improve functional independence and quality of life
- Facilitate use of amputation prevention care teams, including nephrology, cardiology, vascular surgery, radiology, podiatry, wound care, and vascular nursing professionals.
- Implement strategies to prevent contrast nephropathy in persons with CKD not on dialysis and those on dialysis with residual renal function
- Manage volume status and electrolytes in the peri-procedure period, for patients with PAD and CKD, especially in patients on dialysis
- Adjust medications, especially immunosuppressant medications, in patients with a renal transplant and PAD. Assure that transplantation is performed without adverse impact on PAD (iliac artery) perfusion.
- Assure that upper extremity access sites do not limit hand perfusion
- Create and measure quality care metrics in the management of dialysis patients with PAD co-morbidities

Box 2

Collaborative care opportunities to improve PAD-CKD care delivery

Focus Area	Suggestions for Nephrologists	Suggestions for Vascular Specialists
Claudication care improvement	<p>Recognize both classic claudication and atypical leg pain symptoms in patients with CKD</p> <p>Become adept at interpretation of PAD non-invasive vascular laboratory diagnostic tests.</p> <p>Utilize the claudication medication, cilostazol, with appropriate dose adjustment in patients with PAD and claudication (no PAD anatomic imaging required)</p> <p>Create and utilize supervised exercise as a primary claudication therapy in individuals with PAD and CKD (no PAD anatomic imaging required)</p> <p>Referral to vascular specialist when revascularization is required (failure of medical claudication therapies)</p>	<p>Provide full range of claudication therapies to individuals with PAD and CKD and claudication.</p> <p>Provide appropriate dose adjustment of cilostazol for patients with CKD and ESRD</p> <p>Co-lead creation of PAD claudication supervised exercise programs to assure that this modality is available</p> <p>Co-manage diabetes, lipids and hypertension, promote smoking cessation, antiplatelet therapy</p>
Amputation prevention (CLI care) improvement	<p>Active surveillance for PAD and CLI, via provision of foot examinations and evaluations for neuropathy, pedal perfusion, and foot deformities, especially in dialysis patients</p> <p>Engagement of wound care nurse or podiatry services in dialysis unit on a scheduled basis</p>	<p>Promote appropriate use of the noninvasive vascular laboratory, and use of physiologic (non-contrast) testing, and TBI/duplex techniques in patients with normal or supranormal ABI values, especially when clinical suspicion is high</p> <p>Co-develop an amputation prevention program to assess feet and wounds at regular intervals at affiliated renal clinics and dialysis units</p>
Clinical research improvement	<p>Build health system, regional or national registries of CKD patients with PAD in order to define real world outcomes, clinical failures, and to provide a platform to objectively test new care strategies. Use this platform to provide pilot data to inform PAD-CKD observational studies and prospective randomized clinical trials</p> <ul style="list-style-type: none"> Create a new PAD risk model to help identify CKD patients at high risk. Evaluate the accuracy of current PAD diagnostic testing strategies in CKD cohorts. Prospectively test the impact of diagnostic testing, medical, and invasive care strategies to prevent adverse CVD and limb outcomes <p>Refer to and enroll patients with CKD into current clinical trials of PAD treatment</p>	
Health policy and advocacy improvement	<p>Develop multidisciplinary teams of vascular specialists and nephrologists to create evidence based guidelines for management of PAD in CKD patients.</p> <p>Assure nephrology representation in all current amputation prevention clinical trials, health policy initiatives, and healthcare home initiatives.</p> <p>Create a "Call to Action" to utilize interdisciplinary health professional society leadership to foster creation of a national "PAD competent" workforce (PAD awareness would be provided to healthcare providers)</p>	

Focus Area	Suggestions for Nephrologists	Suggestions for Vascular Specialists
	and patients). Such work is best initiated in concert with nephrology leadership.

Figure 1.

ACC-AHA PAD Guideline algorithm defining the key clinical PAD syndromes that define subsequent care pathways.

Figure 2.
The ACC-AHA PAD Guideline for the assessment of claudication and systemic risk.

Figure 3.
The ACC-AHA PAD Guideline algorithm for the treatment of claudication.

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Focus Area	Suggestions for Nephrologists	Suggestions for Vascular Specialists
Claudication care improvement	<p>Recognize both classic claudication and atypical leg pain symptoms in patients with CKD</p> <p>Become adept at interpretation of PAD non-invasive vascular laboratory diagnostic tests.</p> <p>Utilize the claudication medication, cilostazol, with appropriate dose adjustment in patients with PAD and claudication (no PAD anatomic imaging required)</p> <p>Create and utilize supervised exercise as a primary claudication therapy in individuals with PAD and CKD (no PAD anatomic imaging required)</p> <p>Referral to vascular specialist when revascularization is required (failure of medical claudication therapies)</p>	<p>Provide full range of claudication therapies to individuals with PAD and CKD and claudication.</p> <p>Provide appropriate dose adjustment of cilostazol for patients with CKD and ESRD</p> <p>Co-lead creation of PAD claudication supervised exercise programs to assure that this modality is available</p> <p>Co-manage diabetes, lipids and hypertension, promote smoking cessation, antiplatelet therapy</p>
Amputation prevention (CLI care) improvement	<p>Active surveillance for PAD and CLI, via provision of foot examinations and evaluations for neuropathy, pedal perfusion, and foot deformities, especially in dialysis patients</p> <p>Engagement of wound care nurse or podiatry services in dialysis unit on a scheduled basis</p>	<p>Promote appropriate use of the noninvasive vascular laboratory, and use of physiologic (non-contrast) testing, and TBI/duplex techniques in patients with normal or supranormal ABI values, especially when clinical suspicion is high</p> <p>Co-develop an amputation prevention program to assess feet and wounds at regular intervals at affiliated renal clinics and dialysis units</p>
Clinical research improvement	<p>Build health system, regional or national registries of CKD patients with PAD in order to define real world outcomes, clinical failures, and to provide a platform to objectively test new care strategies. Use this platform to provide pilot data to inform PAD-CKD observational studies and prospective randomized clinical trials</p> <ul style="list-style-type: none"> • Create a new PAD risk model to help identify CKD patients at high risk. • Evaluate the accuracy of current PAD diagnostic testing strategies in CKD cohorts. • Prospectively test the impact of diagnostic testing, medical, and invasive care strategies to prevent adverse CVD and limb outcomes <p>Refer to and enroll patients with CKD into current clinical trials of PAD treatment</p>	
Health policy and advocacy improvement	<p>Develop multidisciplinary teams of vascular specialists and nephrologists to create evidence based guidelines for management of PAD in CKD patients.</p> <p>Assure nephrology representation in all current amputation prevention clinical trials, health policy initiatives, and healthcare home initiatives.</p> <p>Create a “Call to Action” to utilize interdisciplinary health professional society leadership to foster creation of a national “PAD competent” workforce (PAD awareness would be provided to healthcare providers and patients). Such work is best initiated in concert with nephrology leadership.</p>	