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Management of Peripheral Arterial Disease in Chronic Kidney Disease

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Lower extremity peripheral arterial disease (PAD) has not been examined in most prior studies of the epidemiology of cardiovascular disease among patients with chronic kidney disease (CKD) [1–5], and very few epidemiologic studies of PAD have considered CKD as a potential risk factor [6–11]. Thus, knowledge of the epidemiology, outcomes, and treatment options for PAD among patients with CKD lags behind that for other forms of cardiovascular disease. This article underlines the high prevalence and incidence of PAD as well as the considerable morbidity and mortality associated with PAD in persons with CKD. It also draws attention to the paucity of information available to guide management of PAD among patients with CKD and reviews relevant literature from the general population.

Epidemiology of peripheral arterial disease in patients with chronic kidney disease

Prevalence of peripheral arterial disease in chronic kidney disease

Prevalence estimates for PAD are highly dependent on the diagnostic method selected and population of interest [12]. In the adult population, PAD diagnosed using an ankle brachial index (ABI) cutoff of less than 0.90 has an estimated prevalence of 12%, with approximately one third of these patients having classic symptoms of claudication [13,14]. As is true for the general population, prevalence estimates among patients with CKD are much lower when PAD is defined by the presence of intermittent claudication than when it is defined using the ABI.

Prevalence of intermittent claudication

Intermittent claudication is often considered a cardinal symptom of PAD. Prior epidemiologic studies have reported the prevalence of typical intermittent claudication in the adult population to be less than 5% and in many cases less than 2% [6,16–18]. Although several studies have examined risk factors for intermittent claudication, few have included renal insufficiency as a potential correlate or have examined the prevalence of intermittent claudication among patients with renal insufficiency [9,19,20]. Webb et al [21] reported a 19% prevalence of intermittent claudication among 325 chronic dialysis patients in the United Kingdom. Leskinen et al [22] found that among 59 predialysis patients, 36 dialysis patients, 41 renal transplant recipients, and 59 control subjects in Finland the prevalence of intermittent claudication was 6.8%, 2.8%, 10%, and 0%, respectively. Both of these studies, however, focused on a small sample of patients with advanced CKD.

In the Cardiovascular Health Study (CHS), a cohort study of 5888 community-dwelling adults aged 65 years or older, the baseline prevalence of classic intermittent claudication (by the Rose Claudication Questionnaire) was 1.68% among

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patients with normal renal function and 4.46% among patients with renal insufficiency defined as a serum creatinine measurement of 1.3 mg/dL or higher among women and 1.5 mg/dL or higher among men (O'Hare et al, unpublished work based on CHS public use data). Among patients aged 45 to 64 years enrolled in the Atherosclerosis Risk in Communities (ARIC) study, the prevalence of Rose intermittent claudication was 0.68% among those with normal renal function and 1.63% among those with an estimated creatinine clearance of less than 60 mL/min (O'Hare et al, unpublished work based on ARIC public use data). In summary, the prevalence of intermittent claudication seems to be substantially higher among patients with CKD than in the general population, although the exact prevalence varies according to the population studied and may reflect the older age and higher prevalence of diabetes and hypertension in patients with CKD as well as other risk factors for claudication in this population.

Prevalence of ankle brachial index less than 0.90

In the general population, an ABI of less than 0.90 correlates well with the presence of angiographic evidence of PAD [23]. PAD prevalence estimates that are based on ABI measurement are consistently higher than those based on the presence of intermittent claudication. In community-cohort studies, the prevalence of an ABI of less than 0.90 has ranged from less than 5% among ARIC participants to as high as 12.4% among CHS participants [8,10,18,24]. Prevalence estimates among patient cohorts recruited from medical clinics tend to be considerably higher [15,25]. For example 29% of high-risk patients enrolled from primary care clinics as part of the PAD Awareness, Risk and Treatment: New Resources for Survival program had an ABI of less than 0.90 [25]. Patients eligible for this study included those over 70 years old and those between the ages of 50 and 69 years who had diabetes or a smoking history.

A small number of studies have reported ABI measurements in relation to renal function. Newman et al [24] documented an inverse association between serum creatinine level and ABI of less than 0.90 that was independent of potential confounders. Among the subset of CHS patients who underwent baseline serum creatinine measurement, 12% with renal insufficiency (defined as a serum creatinine level $\geq$ 1.3 mg/dL in women and $\geq$ 1.5 mg/dL in men) and 7% with normal renal function had an ABI of less than 0.90 [26]. Based on data from the most recent National Health and Nutrition Examination Survey (1999–2000), 24% of the noninstitutionalized civilian population aged 40 years and older with an estimated creatinine clearance of less than 60 mL/min/1.73 m^2 are estimated to have an ABI of less than 0.90, compared with 3.7% of those with a clearance of 60 mL/min/1.73 m^2 or higher [27]. As for the CHS sample, renal insufficiency was independently associated with a low ABI even after adjustment for differences in patient age, diabetes, and other potential confounders. In the small study by Leskinen [22] described previously, 15.3% of Predialysis patients, 8.3% of dialysis patients, and 2.6% of transplant patients had an ABI below 0.90, whereas none of the control patients in this study had an ABI below 0.90.

Among dialysis patients, several larger cross-sectional studies have examined the prevalence of a low ABI. With the exception of a study in Japanese dialysis patients in which 16.9% of patients had an ABI below 0.90 [28], all other studies have reported the prevalence of an ABI below 0.90 among hemodialysis patients to be in the range of 30% to 38% [29–31]. Hence, the prevalence of PAD seems to be much higher among dialysis-dependent patients than among the general population and those with milder forms of CKD.

Sensitivity and specificity of diagnostic testing for peripheral arterial disease

In the general population, claudication detected by the Rose Claudication Questionnaire has a high specificity and positive predictive value but extremely low sensitivity for detecting large-vessel PAD [12]. The Edinburgh Claudication questionnaire seems to be somewhat more sensitive [32]. A low ABI is highly sensitive and specific for the presence of more than 50% stenosis of lower extremity vessels on angiography [23].

The sensitivity and specificity for the Rose and Edinburgh claudication questionnaires are unknown among patients with CKD. There is a theoretical concern that a high prevalence of vascular calcification, particularly in patients with advanced CKD, may render an ABI below 0.90 a less sensitive measure of lower extremity PAD in this population. In support of this possiblity, Leskinen et al [22] reported an extremely high prevalence of ABIs above 1.30 among Finnish predialysis patients, hemodialysis patients, and post–renal transplant patients (23.7%, 41.7%, and 23.1%, respectively). These numbers are much higher than those reported for several larger dialysis-patient cohorts. For example, 7% among a sample of 132 United States hemodialysis patients [30] and 10.9% among a sample of 1010 Japanese hemodialysis patients had an ABI higher than 1.30. For comparison, in the latter study, 0.67% of patients in an age- and gender-matched control group of healthy volunteers had an ABI higher than 1.30 [28]. Collectively, these findings suggest that a broader range of ABI measurements may be encountered in dialysis patients than in the general population.

Incidence of peripheral arterial disease in chronic kidney disease

CKD has not traditionally been viewed as a possible risk factor for PAD, and most previous epidemiologic studies of PAD have not even included information on renal function [6–11]. Conversely, although many studies have now demonstrated that CKD is a risk factor for all-cause mortality, cardiovascular death, and cardiovascular events such as coronary heart disease and stroke [1–5], most of these studies did not examine the association of CKD with lower extremity PAD.

Among patients enrolled in the United Kingdom Prospective Diabetes Study, albuminuria was associated with the development of PAD during study follow-up in univariate but not in multivariate analysis [33]. This analysis examined only albuminuria, not renal function. Renal insufficiency, defined as a serum creatinine level $\geq$ 1.3 g/dL in women and $\geq$ 1.5 mg/dL in men, was independently associated with the development of intermittent claudication among participants in the CHS [1]. Secondary analysis of data from the Heart and Estrogen/Progestin Replacement Study showed that both moderate and severe CKD, defined respectively as an estimated creatinine clearance of 30 to 59 and less than 30 mL/min/1.73m^2, were associated with an increased risk of arriving at a predefined PAD end point (revascularization, amputation, or lower extremity sympathectomy) during follow-up [34]. This study did not adjust for the baseline prevalence of PAD among study participants. Thus, although patients with even moderate CKD are at risk for PAD events, it is unclear whether this risk simply reflects a higher baseline prevalence of subclinical PAD in this population (as described previously) or whether CKD is a true risk factor for PAD.

Risk factors for peripheral arterial disease among patients with chronic kidney disease

Established risk factors for PAD include male sex, older age, diabetes, smoking, hypertension, dyslipidemia (low HDL and high LDL and triglyceride levels), lipoprotein (a), hyperhomocysteinemia, and chronic inflammation, whereas alcohol intake and physical activity seem to be protective [6–11,35–43]. Among dialysis patients, many of the risk factors for PAD are the same as for the general population, but there also seem to be associations that are unique to dialysis patients. Webb et al [21] reported that among 325 hemodialysis patients, intermittent claudication was associated with older age, smoking, hypertension, and hypertriglyceridemia. Among a subgroup of patients enrolled in the HEMO study, Cheung et al [44] reported cross-sectional associations of baseline PAD with smoking, older age, diabetes, and non-black race. In this study, hypertension and cholesterol were not associated with PAD. Among patients enrolled in Waves 1, 3, and 4 of the United States Renal Data System's (USRDS) Dialysis Morbidity and Mortality Study (DMMS), coronary artery disease, cerebrovascular disease, smoking, lower diastolic blood pressure, left ventricular hypertrophy, lower serum albumin, malnourished status, lower parathyroid hormone level, and longer time since initiation of dialysis were associated with baseline PAD, in addition to age, gender, diabetes, and race as reported for the HEMO study [45]. The lack of association of PAD with either hypertension or dyslipidemia in these last two studies is striking. A limitation of these studies is that they were cross-sectional in nature and did not define PAD using objective measures of lower extremity perfusion such as the ABI. There is currently a paucity of studies examining risk factors for PAD among patients with CKD who are not receiving dialysis.

Few longitudinal analyses have examined risk factors for incident (rather than prevalent) PAD among patients with CKD. In a study of the association of smoking with cardiovascular end points among patients enrolled in DMMS2, active smokers had an increased risk of peripheral arterial events [46]. This outcome, however, was defined broadly to include arterial aneurisms, Raynaud's phenomenon, and arterial embolic events in addition to lower extremity atherosclerotic disease. On the other hand, smoking was not a risk factor for lower extremity amputation among hemodialysis patients enrolled in DMMS 3 and 4 [47] (although the study outcome was not restricted to amputations performed for PAD), nor was it a risk factor for amputation following revascularization among dialysis patients enrolled in DMMS 1, 3, and 4 [48]. No studies have examined risk factors for the development of PAD among CKD patients.

Impact of chronic kidney disease on peripheral arterial disease outcomes

In the general population, patients with intermittent claudication are at increased risk for death and for cardiovascular events, although the course of their lower extremity disease is often benign [49,50]. In fact, even patients with subclinical PAD are at increased risk for all-cause and cardiovascular mortality along with myocardial infarction, stroke, and peripheral arterial events [18,24,51–57]. Furthermore, although most of the aforementioned studies have focused on the prognostic value of a low ABI, it has recently been shown that the presence of a high ABI (>1.40)—generally indicative of arterial incompressibility—is also predictive of mortality [58]. Finally, in addition to its well-documented associations with mortality and cardiovascular events, lower extremity PAD is also associated with lower extremity functional impairment [29,59–62] and with depression [63,64].

Although the natural history of claudication in the general population is characterized by high cardiovascular mortality but relatively benign lower extremity outcomes, it is unclear whether this is also the case in CKD. Relatively more information is available on the prognostic importance of a low ABI in patients with CKD. Several studies have now reported an association between an ABI below 0.90 and increased risk of both cardiovascular and all-cause mortality among hemodialysis patients [28,29,31]. In fact, in one study, patients with a high ABI (>1.30) and those with a borderline low ABI (0.90–1.10) were also at increased risk for all-cause and cardiovascular mortality when compared with patients who had ABIs between 1.10 and 1.30 [28].

The ABI–mortality association has not been examined among patients with milder forms of CKD. Most information on mortality among patients with CKD and PAD comes from studies of operative outcomes among patients undergoing lower extremity revascularization (as discussed later). Furthermore, the impact of PAD on functional status and other health-related quality-of-life outcomes likewise has not been explored among patients with CKD. Compared with the general population, dialysis patients seem to have lower self-assessed physical function, demonstrate poorer physical performance [65–67], and have a high prevalence of depression [68]. The associations of PAD with physical function, physical performance, or depression among patients with CKD have not been measured, however.

Medical therapy for peripheral arterial disease

Statin therapy

Cholesterol lowering with statin therapy seems to reduce overall frequency of cardiovascular events among high-risk patients in the general population [69,70]. Thus, statin therapy is frequently recommended for patients with PAD based solely on their elevated risk of cardiovascular death, myocardial infarction, and stroke [71]. Recently, however, the Medical Research Council\British Heart Foundation (MRC\BHF) Heart Protection Study has demonstrated a specific benefit of statin therapy in reducing PAD events among those at high risk for cardiovascular events. In this trial, patients randomly assigned to receive treatment with simvastatin, 40 mg, versus placebo experienced fewer peripheral vascular events in follow-up [72,73]. This benefit was seen among participants with and without diabetes and, importantly, in patients with PAD who had no prior history of other cardiovascular disease. Furthermore, statin therapy may also be associated with improved health-related quality-of-life outcomes in patients with PAD. For example, statin therapy seems to improve pain-free walking distance in patients with claudication [74] and is associated with superior leg function in patients with PAD [75]. In an observational study of 293 patients undergoing infrainguinal bypass operations, statin therapy was associated with superior graft patency and lower amputation rates, although it was not associated with improved survival [76].

Among dialysis patients, low rather than high serum cholesterol levels seem to be predictive of mortality [77,78]. At least one observational study has shown that dialysis patients receiving statin therapy nevertheless have lower overall cardiovascular mortality [79]. Although there have been no published randomized, controlled trials of the impact of statin therapy on cardiovascular events focusing specifically on dialysis patients or patients with CKD, several larger trials have included participants with mild CKD. In the Cholesterol and Recurrent Events study, pravastatin was equally effective in reducing secondary cardiovascular events in patients with mild chronic renal insufficiency (defined as an estimated creatinine clearance $<$ 75 mL/min) as among the overall study population [80]. Peripheral arterial events were not included as an outcome in this study, however. Likewise in the MRC/BHF Heart Protection Study, a reduction in major vascular and coronary events has been documented for the 1329 participants with mild CKD, but the peripheral arterial disease outcome (noncoronary revascularization) examined in the primary analysis was not included in this subgroup analysis [73]. Therefore, it remains unclear whether statin therapy also reduces PAD events among patients with CKD; the overall frequency of these events in this cohort was fairly low, and the study was not powered to examine this outcome. The impact of statin therapy on lower extremity function also has not been studied in patients with CKD. Although patients with CKD were not specifically excluded from the study by McDermott et al [75], no information is provided on the prevalence of CKD in this cohort or on the association of statin therapy with lower extremity function in this subgroup.

Blood pressure–lowering agents

In the general population, hypertension is a risk factor for PAD. The Appropriate Blood-Pressure Control in Diabetes study was a prospective, randomized, controlled trial among persons with diabetes of the effects of intensive blood pressure control with either enalapril or nisoldipine versus moderate blood pressure control in the placebo group. In this trial, intensive blood pressure control resulted in fewer cardiovascular events among those with and without PAD [81]. Furthermore, although there was an inverse relationship between ABI and the odds of a cardiovascular event among those randomly assigned to placebo, no such relationship existed among patients randomly assigned to intensive blood pressure control [81]. Although this study demonstrates that intensive blood pressure lowering reduces cardiovascular events in patients with PAD, it does not address the question of whether tight blood pressure control can reduce the incidence of these events, because PAD events were not evaluated. Although some participants had CKD (a creatinine level above 3.0 mg/dL was an exclusion criteria), the impact of intensive blood pressure control on cardiovascular events among persons with CKD and PAD has not been reported.

In the Heart Outcomes Prevention Evaluation study, persons aged 55 years or older with prevalent cardiovascular disease were randomly assigned to receive ramipril versus placebo. All-cause and cardiovascular mortality, stroke, and myocardial infarction were decreased among participants who received ramipril. This effect was seen among participants with and without PAD at baseline [82]. Ramipril was also associated with a decreased need for lower extremity revascularization or amputation in the overall study population. In subgroup analysis, however, a statistically significant protective effect was present only for patients without clinical evidence of PAD and with an ABI higher than 0.90 [82]. Although further subgroup analysis has not been conducted among those with PAD and CKD, ramipril was equally protective against the primary outcome of stroke, myocardial infarction, or cardiovascular death among participants with and without CKD (defined as a serum creatinine level between 1.4 and 2.3 mg/dL) [83]. Finally, in an observational study of patients undergoing infrainguinal bypass, overall mortality was lower among patients who were receiving angiotensin-converting enzyme (ACE) inhibitors, but graft patency and amputation rates were similar in the two arms [76].

Smoking cessation

Current and former smoking is associated with PAD in cross-sectional analysis [10,84], and smoking increases the risk of amputation in patients with claudication [85] and decreases patency rates after lower extremity bypass [86]. Smoking cessation seems to result in an increase in exercise tolerance and in ankle pressure among patients with intermittent claudication [87]. Although these studies did not focus specifically on patients with CKD, Foley et al [46] have shown that, among dialysis patients, current smoking is predictive of future cardiovascular events, including PAD. Although smoking remains a modifiable risk factor, it is noteworthy that among several large cohorts undergoing lower extremity revascularization smoking was less common among those with CKD than among those with normal renal function [88,89].

Nevertheless, smoking cessation should be strongly encouraged in patients with CKD and PAD given their high incidence of PAD and other cardiovascular events.

Antiplatelet agents

In a meta-analysis of clinical trials using antiplatelet agents (aspirin, clopidogrel, ticlopidine, picotamide, and dipyridamole), use of any antiplatelet agent resulted in a 23% risk reduction of the chosen outcome of nonfatal myocardial infarction, nonfatal stroke, or vascular death among the subgroup of 9214 patients with PAD [90]. The benefit was similar among patients with intermittent claudication, those having peripheral grafting, and those having peripheral angioplasty. In the Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial—a randomized, blinded, clinical trial designed to assess the relative efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of a composite outcome cluster of ischemic stroke, myocardial infarction, or vascular death—there was a 23.8% risk reduction in these outcomes in the clopidogrel-treated group among the subgroup of patients with PAD at baseline [91]. The risk of amputation (a secondary study outcome) was not significantly different between treatment groups, although the study was underpowered to test that outcome. Severe renal insufficiency was an exclusion criterion for the CAPRIE trial, and subgroup analysis among patients with milder forms of renal insufficiency enrolled in the trial has not been conducted.

Cilostazol

Cilostazol is a phosphodiesterase inhibitor that has both antiplatelet and vasodilating properties. Cilostazol has been shown to increase pain-free and maximal walking distance among persons with claudication caused by PAD but does not seem to affect mortality or cardiovascular morbidity in this group [92–94]. Persons with CKD were not explicitly excluded from these trials, but no subgroup analyses are presented. Furthermore, it is unclear whether cilostazol is a safe drug for dialysis patients. It has not been tested in this population, and its metabolism may be affected by altered protein binding in dialysis patients.

Exercise

Exercise therapy is considered first-line therapy for intermittent claudication, although its value in asymptomatic PAD and critical ischemia is unknown [95]. A number of prospective studies have shown that exercise improves walking ability and quality of life in patients with claudication. A meta-analysis of studies of exercise to reduce claudication demonstrated that programs that use intermittent walking to near-maximal pain over at least 6 months are most likely to be effective [96]. The safety and efficacy of exercise therapy for claudication among patients with CKD have not been reported. A high prevalence of claudication among dialysis patients [21], documented low activity levels in this population [97], and the rarity of exercise counseling in the dialysis unit setting [98] suggest that exercise therapy could be an important area for intervention. Less is known about the activity levels and exercise counseling practices among patients with milder forms of CKD.

Surgical therapy for peripheral arterial disease

Revascularization

Lower extremity surgical or percutaneous revascularization may be performed for disabling claudication or for critical limb ischemia (rest pain, ischemic ulceration, or gangrene). Many small retrospective surgical case series have demonstrated higher mortality rates and lower limb salvage rates among patients with advanced CKD [99–105]. In larger series of patients undergoing lower extremity revascularization, postoperative and 1-year mortality seem to increase with declining renal function [88,89].

A recent retrospective study of 800 hemodialysis patients enrolled in the USRDS DMMS 1, 3, and 4 who underwent lower extremity revascularization demonstrated high mortality and amputation rates after this procedure [48]. Mortality and limb salvage rates were more favorable among study patients who underwent percutaneous rather than surgical revascularization. Although this finding may reflect selection bias, it suggests a need for randomized, controlled clinical trials to explore the possibility that lower extremity angioplasty may result in better outcomes than surgical revascularization among dialysis patients. In this study, amputation rates after revascularization were higher among black patients, those without insurance or receiving Medicaid, and those with diabetes. Although dialysis patients seem to be at singularly increased risk for limb loss after lower extremity revascularization, this does not seem to be true for patients with milder forms of CKD based on a retrospective study of lower extremity revascularization procedures performed nationally within the Department of Veterans Affairs [89].

Amputation

Amputation rates among end-stage renal disease (ESRD) patients seem to be disproportionately high, and, along with diabetes, the presence of diagnosed PAD is one of the strongest risk factors for amputation [47,106]. Based on national Medicare data, lower extremity amputation is associated with extraordinarily high mortality rates among ESRD patients. Those at greatest risk include older patients, Native American and African-American (compared with white) patients, those whose primary renal disease was diabetes or hypertension, and those undergoing dialysis (versus transplant recipients) [106]. Dialysis patients seem to be at particularly high risk for bilateral amputations [107]. In general, there has been little interest in efforts to prevent amputation among ESRD patients, although provision of preventive foot care in the dialysis unit setting does seem to be effective in lowering amputation rates among patients with diabetes [108,109].

Unfortunately, observational studies do not provide clear guidance for surgical decision making in patients with CKD and limb-threatening ischemia. The increased risk of death after amputation and revascularization attributable to CKD are quite similar [88,110]. Crude postoperative mortality rates are considerably higher after amputation than after revascularization [110], and mortality rates are lower after percutaneous than after surgical revascularization among dialysis patients [48]. These findings, however, may simply reflect the impact of selection bias. Further studies are needed to evaluate the risks and benefits of amputation over revascularization (and type of revascularization) among patients with CKD and to investigate reasons for the high mortality associated with these procedures in this population.

Impact of chronic kidney disease on surgical management of limb ischemia

Several studies have suggested that the clinical indications for lower extremity revascularization may differ for patients with normal renal function and those with CKD. In a case-control study of patients undergoing lower extremity revascularization at two surgical centers, rest pain and claudication were the most common reasons for revascularization among non-ESRD controls, whereas ulceration and gangrene were the most common reason among dialysis patients [111]. In addition, dialysis patients were more likely to undergo more distal revascularization procedures. Similar patterns existed in a national sample of veterans undergoing initial lower extremity revascularization [89]. Even after adjustment for other patient characteristics, when compared with all other veterans undergoing bypass procedures, dialysis patients were more likely to present with wound infection, gangrene, infection or ischemic ulceration, elevated white blood cell count, and preoperative sepsis at the time of initial revascularization. They were also more likely to have a preoperative hospital stay longer than 1 week, to undergo concurrent minor amputation, and to undergo a more distal procedure. These findings may indicate more rapid disease progression among dialysis patients or may reflect different referral and care patterns for this population.

Few studies have evaluated the impact of CKD on procedure choice for limb-threatening ischemia. Collins et al [112] found a higher prevalence of dialysis patients among a national sample of veterans undergoing amputation than among those undergoing lower extremity revascularization for PAD, and this finding seemed to be independent of other patient characteristics such as age or prevalence of diabetes [112]. In a smaller study of all amputations and revascularizations performed at a single medical center over a 3-ear period, Abou-Zamzam [113] also found that dialysis patients seemed to be overrepresented in the group undergoing amputation. In multivariate analysis, dialysis status was the only independent predictor of amputation versus revascularization, although this study did include patients undergoing secondary procedures.

Summary

PAD has been overlooked in many epidemiologic studies evaluating cardiovascular risk associated with renal disease. Conversely, CKD has not been evaluated as a potential risk factor in epidemiologic studies of PAD. PAD, however, seems to be more prevalent among patients with even moderate CKD than in the general population and is most common among chronic dialysis patients, one third or more of whom have a low ABI. Patients with CKD also seem to be at increased risk for developing claudication and for requiring surgical intervention for lower extremity PAD. Furthermore, even moderate CKD seems to be a risk factor for postoperative death and complications after both lower extremity amputation and revascularization procedures. Conversely, even asymptomatic PAD seems to be a risk factor for death among dialysis patients.

In the general population, statins, antiplatelet agents (particularly clopidogrel), antihypertensive agents, and ACE inhibitors all have a proven benefit in reducing cardiovascular events in patients with PAD and in some instances may also reduce PAD events. Available evidence suggests that patients with CKD also experience cardiovascular risk reduction with statin and ACE-inhibitor therapy, but these therapies have not been shown to reduce PAD events specifically in patients with CKD. Further studies are needed to identify interventions that can specifically reduce the incidence of PAD complications in patients with CKD.

Although it is clear that mortality and complication rates after both lower extremity amputation and revascularization are increased in patients with even moderate CKD, currently available observational studies do not provide clear guidance for surgical decision making in CKD patients with limb-threatening ischemia. Further studies are needed to evaluate the risks and benefits of amputation over revascularization among patients with CKD and to investigate reasons for the high mortality associated with these procedures in this patient group. Further studies are also needed to measure the impact of CKD on care processes for PAD with the goal of identifying target areas for improvement.

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