Peripheral Arterial Disease: A Guide for Nephrologists

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Cardiovascular disease is a major source of morbidity and mortality for patients with chronic kidney disease (CKD). Peripheral arterial disease (PAD) is a strong predictor of coronary artery disease and a risk factor for mortality in the general population. This is of particular interest to nephrologists because the risk for PAD is increased in CKD. Often, PAD is overlooked as a source of morbidity and as a cardiovascular risk factor in this population. This review serves as an overview of the epidemiology, screening, diagnosis, and treatment of PAD with an emphasis on CKD.

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Individuals with chronic kidney disease (CKD) are at increased risk for cardiovascular diseases (CVD) (1–3), which include specific conditions such as coronary artery disease (CAD), congestive heart failure, and peripheral arterial disease (PAD). The term PAD is used to describe obstructive atherosclerosis of the lower extremities. It is traditionally defined by an ankle-brachial index (ABI) of <0.9. Nephrologists are often both primary physician and specialist for their patients with CKD, particularly those who are on dialysis. The patient population with CKD is particularly at risk for PAD; therefore, nephrologists must be knowledgeable about screening, diagnosis, and treatment strategies for this condition. Much of the literature regarding CVD in CKD has overlooked PAD (4). The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of PAD do not list CKD as a risk factor for PAD. Within the field of nephrology, the recommendations of Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for screening and management of PAD in ESRD are largely based on evidence from studies of nondialysis patients and expert opinions. Recognition of PAD is important because of its association with increased risk for cardiovascular events. PAD is common in patients with CKD, with a prevalence of 24% in one cross-sectional analysis (5). It is associated with poor prognosis and often coexists with other conditions that are associated with adverse outcomes, such as CAD and diabetes. CKD is also associated with an increased risk for PAD (5–8). Recognition of this link is growing. The latest Inter-Society Consensus for the Management of PAD (TASC II) guidelines recognized CKD as a risk factor for PAD (9). This was largely based on findings of the Heart and Estrogen/Progestin Replacement Study (HERS) in which CKD was found to be independently associated with PAD in postmenopausal women (7). PAD is also of concern because of the progressive nature of the disease and risk for amputation. For the nondialysis patient with PAD, 1 to 3% with claudication will undergo an amputation in 5 yr (9). Among patients with ESRD, amputation for PAD is more prevalent compared with the general population (10). In addition, revascularization procedures among dialysis patients are often associated with subsequent amputation (11) and high mortality at 1 yr (12). This review details the diagnosis and therapy for PAD with a particular emphasis on patients with CKD.

Epidemiology/Risk Factors

PAD affects approximately 5% of adults in the United States who are 40 yr and older (13). The incidence of PAD increases with age. Data from the National Health and Nutrition Examination Survey (NHANES) reveals that the prevalence of PAD (Figure 1) (5) in the age group 50 to 59 yr is 2.5% and increases to 14.5% in the age group of >70 yr (14). Patients with impaired renal function have a greater than two-fold risk for developing PAD (5). The NHANES 1999–2000 found 24% of adults who were older than 40 yr and had a creatinine clearance <60 ml/min per 1.73 m^2 to have an ABI of <0.9 (5). In the dialysis population, according to United States Renal Data System report, the incidence of clinical PAD is 15% (15).

Traditional cardiovascular risk factors, such as tobacco use, diabetes, hyperlipidemia, and hypertension, are also associated with PAD. Unmodifiable risk factors that are associated with PAD include black race, male gender, and age. Of the modifiable risk factors for PAD in the general population, tobacco abuse is likely the most important (16). The prevalence of PAD among those with diabetes is high, and many people's diabetes is undiagnosed (17). Dyslipidemia plays an important role in the pathogenesis of atherosclerosis and is strongly associated with PAD. Although hypertension is a risk factor for PAD, there is no clear evidence that antihypertensive medications alter disease progression.

No studies have examined risk factors for PAD specifically in patients with CKD. However, as mentioned previously, CKD itself is increasingly recognized as a risk factor for PAD. A recent study demonstrated CKD to be as significant a risk factor for PAD as compared with traditional factors, such as tobacco

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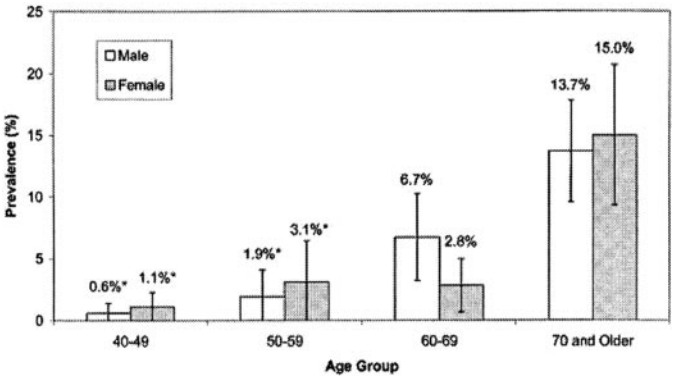

Figure 1. Prevalence of peripheral arterial disease (PAD) by age and gender, adults 40 years and older, United States, 1999 to 2000 ($n = 2174$). Error bars are 95% confidence intervals. *Estimate has relative Se >30%. Reprinted from Selvin and Erlinger (14), with permission.

use (14). Among dialysis patients, risk factors that are traditional to the general population, including diabetes and tobacco abuse, are also associated with PAD in this group (18). In ESRD, diabetes may be the most important factor for PAD risk and outcomes. Diabetes is the leading cause of kidney disease for individuals who initiate dialysis in the United State (19). Among dialysis patients, those with diabetes have the lowest survival, just 25% at 5 yr (19). The morbidity of coexistent kidney disease, diabetes, and PAD is great and often complicates PAD management for these patients.

The reasons for increased incidence of PAD in the CKD population are not entirely clear. Patients who are on dialysis may also have unique factors that predispose them to PAD. Specifically, manifestations of kidney disease, such as hyperphosphatemia, hyperparathyroidism, and chronic inflammation, are implicated in the development of PAD. Hyperphosphatemia is common in dialysis patients. Evidence suggests that elevated serum phosphorus is an independent risk factor for PAD in dialysis patients (20). Dialysis patients are in a state of chronic inflammation as a result of "uremic" factors, the dialysis techniques, and oxidative stress. Chronic inflammatory states are often associated with impaired nutrition and hypoalbuminemia. Hypoalbuminemia in ESRD has been demonstrated as a risk factor for PAD and general vascular morbidity (21,22). Homocysteine levels, which are often elevated in dialysis patients, have been associated with PAD in this group (23). Other factors that have been linked to PAD in the general population but not specifically in patients with CKD include elevated C-reactive protein (24), and lipoprotein (a). Much of the data available regarding risk factors for PAD in CKD, including those discussed in this review, are from large cross-sectional studies. Longitudinal studies are needed to characterize further PAD risk factors in CKD.

Screening

The 2006 ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease consider individuals in the following categories to be at risk for PAD: Age 70 yr and older, age 50 to 69 yr and a history of smoking and/or diabetes, age 40 to 49 and diabetes and at least one other risk factor for atherosclerosis, leg symptoms suggestive of claudication with exertion or ischemic pain at rest, abnormal lower extremity pulse examination, and known atherosclerosis at other sites (*e.g.*, coronary, carotid, or renal arterial disease) (25). Individuals with PAD have up to a six-fold increased risk for death from CAD (26). Even individuals with asymptomatic PAD are at increased risk for cardiovascular events (27). Individuals with premature PAD (diagnosed by age 60 yr) may have an accelerated course of atherosclerosis and increased risk for CAD (28).

Given the increased incidence of PAD in CKD, the K/DOQI guidelines recommend screening all patients upon initiation of dialysis. Screening for and early diagnosis of PAD in this population may be important because of its association with increased mortality in dialysis patients (29–31) (Figure 2). However, the K/DOQI guidelines in this area must be read with caution given the lack of strength in evidence supporting them. Furthermore, these guidelines address only dialysis patients and do not make specific recommendations for those with CKD that does not require dialysis. Screening is a controversial issue in this population because there is no consensus regarding optimal treatment strategies. The issues regarding cardiovascular mortality, lower limb mortality, patient's functional status, and candidacy for available medical and interventional therapies must be weighed when making the decision to screen for PAD in CKD. Patients with CKD and ESRD may not be candidates for revascularization, which would be an argument against screening in these situations. If the decision is made to screen, then an ABI should be performed. Most nephrology practices and dialysis units are not equipped for these measurements. ABI should be performed in the patient's primary care office, if offered, or in many cases, the patient should be referred to a certified vascular laboratory or a vascular medicine specialist's office. A vascular laboratory ABI is often preferred in CKD because these patients have a higher likelihood of calcified vessels, which can produced abnormally high ABI

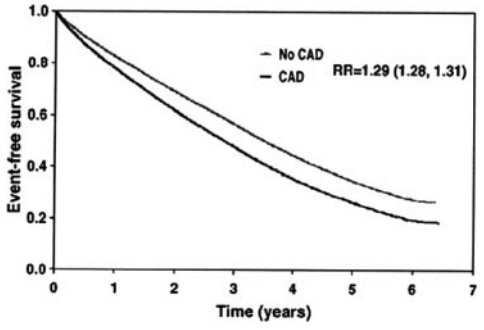

Figure 2. Adjusted survival curves for new patients who had ESRD with and without peripheral vascular disease (PVD) in the United States and who began dialysis between May 1995 and December 2000 and were followed until 2001. Relative risk (RR) is adjusted for age, gender, and race. Reprinted from Stack (31), with permission from Elsevier.

values and thus require additional testing to confirm the diagnosis (29).

Diagnosis

Diagnosis begins with a detailed review of systems in patients who are at risk for PAD, as outlined in the ACC/AHA guidelines. The medical history should focus on symptoms of claudication, rest pain, impaired ability to walk, and nonhealing lower extremity wounds. Classically, patients with PAD present with claudication, defined as reproducible muscle pain that occurs with activity and improves with rest. It results from a discrepancy in the demand for and availability of blood flow to a particular muscle group. Conditions other than lower extremity atherosclerosis can result in claudication-like symptoms, such as compartment syndromes, deep venous thrombosis, and spinal stenosis. A detailed history and physical examination should distinguish between these other diagnoses. For example, a history of trauma, edema, or back problems may point to diagnoses other than PAD. Although claudication is traditionally associated with PAD, most patients present with atypical leg symptoms. Recent studies of patients with PAD document that only 10 to 33% of individuals demonstrate classic claudication symptoms (17,32). At more advanced stages, PAD may manifest as rest pain, nonhealing leg ulcers, or gangrene. Physical examination should focus on skin integrity (*e.g.*, hair loss, presence of wounds or ulcers) and assessment of peripheral pulses. Diminished bilateral peripheral pulses, femoral bruits, and prolonged capillary refill are very specific for PAD (33).

Individuals with an appropriate clinical history and physical examination findings along with previously mentioned risk factors should undergo ABI, the standard noninvasive diagnostic test for PAD. This technique is well validated, and values are predictive of cardiovascular morbidity and mortality (26). The ABI is based on the fact that in normal circulation, the systolic BP in the leg is higher or equal to that in the arm. In PAD, lower extremity arterial lesions lower the systolic pressure in the leg, leading to an ABI <1.0. However, as with most diagnostic tests, the ABI has some limitations. There is no defined upper limit for ABI, but most studies use 1.3 as a cut point. Calcified vessels, as occurs commonly in patients with diabetes, in association with medial artery calcinosis, can result in ABI values that are supranormal or unmeasurable. Initially, it was believed that these supranormal ABI measurements were inconclusive. However, a recent study indicated that high ABI values may in fact be equally predictive of cardiovascular events and are associated with similar risk factor profiles (34).

The ABI may be difficult to interpret in patients with advanced CKD and dialysis patients, often giving very elevated measurements as a result of vascular calcifications (6). This has led some to recommend screening with alternative techniques in this population. The toe-brachial index and pulse-volume recordings have been demonstrated in one study to be more sensitive than ABI for diagnosing PAD in ESRD (35). A positive ABI often requires magnetic resonance angiography (MRA) to define better the extent of disease. Magnetic resonance imaging has been validated for precise measures of femoral artery lumen area and vessel wall calcification and detecting areas of stenosis $>50\%$ (36). However, these tests are not without adverse effects. There are now concerns that the contrast that is used for these examinations, specifically gadolinium, is associated with the development of nephrogenic systemic fibrosis (NSF) in patients with severely impaired renal function; therefore, use of MRA for patients with CKD may also be limited (37,38). A recent case series demonstrated that dialysis patients who were exposed to gadolinium from MRA developed NSF within 2 to 4 wk of exposure (38). This report and others have led to a Food and Drug Administration public health advisory for policies to limit gadolinium exposure in patients with CKD and dialysis patients. More data are needed regarding the association between gadolinium and NSF to determine whether the exposure poses significant clinical concern. However, given the current level of concern, caution is advised when ordering MRA with gadolinium in patients with GFR <30 ml/min.

Therapy

There are no randomized, controlled trial data for therapy for PAD in dialysis patients. Goals of therapy are both treatment of PAD and cardiovascular risk reduction. Measures for secondary prevention are similar to those for CAD, and PAD is now considered a CAD equivalent. Secondary preventive therapies include avoidance of smoking, use of statins, and BP control. Smoking cessation has been shown to slow disease progression in the general population as measured by increased walking times and decreased pain in those with intermittent claudication (39). There are no studies regarding impact of smoking cessation on PAD among patients with CKD. Among dialysis patients, current smoking is predictive of CVD, including PAD (40).

Lipid management is a major component of CVD risk factor modification. Patients with PAD benefit from lipid control by reducing the incidence of cardiovascular events and PAD progression. Statins are first-line therapy for hyperlipidemia, and a number of trials have examined their effects in individuals with PAD. Among patients without CKD, these agents have been shown to reduce peripheral atherosclerosis (41) and increase pain-free walking (42–44). No randomized, controlled trials have documented the effects of statin therapy in PAD among patients with CKD. Multiple trials have documented a reduction of cardiovascular events in patients who have CKD and are on statin therapy(45,46). In dialysis patients with diabetes, however, a randomized, placebo-controlled trial did not demonstrate a protective effect of statin therapy on death from cardiac causes (47). Therefore, the benefits of statin therapy in this group are unclear. Studies are ongoing to define better the benefits of lipid-lowering therapy in CKD (48).

Studies of the effects of BP control on reducing cardiovascular events such as myocardial infarction demonstrate benefits in the general population of patients with PAD. For example, a randomized, placebo-controlled trial demonstrated a reduction in cardiovascular events in patients who had PAD and were treated with ramipril (49). The impact of BP control on cardiovascular events among patients with CKD and PAD has not specifically been studied. Strict BP control is routine care for

patients with PAD. This is extended to patients with CKD and dialysis patients, who usually require BP control for management of their renal disease and cardioprotection as well.

Therapies for claudication include exercise programs and medical therapy. Exercise programs reduce claudication symptoms and increase walking times (50,51). The improvements that are gained from exercise are thought to be related to improved angiogenesis and nitric oxide release, which improves endothelial dysfunction and exercise tolerance (52–54). An exercise program should consist of lower limb aerobic activity that lasts for 45 to 60 min three or more times per week. Supervised exercise programs that are designed for PAD rehabilitation are highly recommended; however, studies of patients who engage in adequate self-directed programs also demonstrate some benefits (55). The efficacy and the safety of exercise programs for patients with CKD and dialysis patients with PAD is unknown and represents an area of much-needed study.

The evidence for medical therapies that reduce symptoms and disease progression are strongest for antiplatelet therapies (56). There may be a modest benefit with clopidogrel over aspirin. The Clopidogrel *versus* Aspirin in Patients with Ischemic Events (CAPRIE) trial found a reduced cardiovascular risk in the clopidogrel-treated group (57). Clopidogrel is more costly than aspirin, which may have an impact the prescribing decision. Severe CKD was an exclusion criterion for enrollment in the CAPRIE trial, so benefits of clopidogrel in this group are unclear. The ACC/AHA guidelines do recommend clopidogrel as an aspirin alternative (25). However, the Transatlantic Inter-Society Consensus (TASC) guidelines recommend either aspirin or clopidogrel (58).

As an antiplatelet agent, clopidogrel can pose a perioperative bleeding risk. For example, patients who received clopidogrel and underwent coronary bypass procedures were shown to experience severe bleeding that required blood transfusions and reoperation compared with patients who did not receive clopidogrel (59). The peak effects of clopidogrel with respect to bleeding time and platelet function are anywhere from 3 to 7 d. For this reason, many recommend discontinuation of clopidogrel at least 5 d before elective surgery. However, transplantation often does not allow for such planning. For this reason and the associated increased risk for bleeding, some centers will refuse transplantation in patients who are receiving clopidogrel therapy. The authors stressed the importance of weighing the benefits of clopidogrel therapy *versus* other antiplatelet agents for PAD in the patient who has CKD and is awaiting transplantation.

Patients who have inadequate relief with aspirin and exercise and who are unable to undergo revascularization or decline this may be candidates for cilostazol or pentoxifylline. Cilostazol is a phosphodiesterase inhibitor that reduces platelet aggregation and acts as a mild vasodilator. Studies have documented its efficacy in reducing claudication and increasing walking times (60–63). Use of cilostazol is contraindicated in patients with congestive heart failure, although there are no studies in this population. In addition, information in the package insert indicates that cilostazol has altered lipid binding and reduced clearance in severe renal impairment. Caution is advised for use in individuals with a creatinine clearance <25 ml/min and in dialysis patients because of concerns that the highly protein-bound drug may not be adequately cleared with dialysis. However, this drug has not been studied in dialysis patients. Pentoxifylline is less efficacious than cilostazol but is often used as an adjunctive agent. Clearance is reduced in renal failure, so dosages must be adjusted appropriately in those settings.

Severe forms of PAD often manifest in the form of critical limb ischemia. Critical limb ischemia is defined by rest pain and ischemic skin lesions such as ulcers and gangrene. In the general population, revascularization is the optimal therapy for critical limb ischemia (25,64). Revascularization *via* percutaneous transluminal angioplasty (PTA) procedures is preferred. There are no randomized, controlled trial data regarding revascularization techniques in patients with CKD and dialysis patients. A retrospective analysis of patients who had CKD and underwent lower limb revascularization found lower rates of limb loss and mortality compared with ESRD (65). Mortality rates are inversely correlated with kidney function (66). Patients with ESRD often are not good candidates for PTA because of distal disease and vascular calcifications. However, a retrospective analysis of hemodialysis patients saw lower mortality and higher limb salvage rates in those who underwent percutaneous revascularization compared with surgical revascularization (11). The findings of these retrospective analyses may reflect selection bias, and large, randomized clinical trials are needed to determine better which patients with CKD and ESRD benefit from revascularization and whether outcomes are truly superior with percutaneous compared with surgical techniques.

Individuals with lesions that are not amenable to PTA are considered for surgical revascularization. Vascular surgery is considered high risk; therefore, patients must undergo appropriate preoperative screening. Younger patients without diabetes have the best outcomes (67). Age, male gender, diabetes, and hypertension were predictors of mortality after surgical revascularization in a study of long-term follow-up in patients who underwent these procedures (68). Venous bypass grafts have high rates (25 to 30%) of stenosis within the first year. Antiplatelet agents, particularly aspirin, are the only therapy that has been shown to improve graft patency (69,70).

Patients with CKD that does not require dialysis are at high risk for postoperative mortality and cardiovascular events (66). Unfortunately, revascularization outcomes are worse in individuals with ESRD (67,71). Particularly, there is higher incidence of perioperative mortality, prolonged hospitalization, limb loss after revascularization, and delayed wound healing (11,65,71). One study found that selected dialysis patients did well with revascularization, particularly those who were ambulatory and without uncontrolled infection and extensive tissue necrosis (11). There are no prospective data to guide selection of dialysis patients for revascularization. Therefore, given the poor outcomes of revascularization in dialysis patients and the high-risk nature of these surgical procedures in patients with CKD, there must be careful consideration before pursuing these procedures. If surgery is pursued, then these patients

Table 1. PAD summary points for the nephrologist[a]

- Risk Factors
  - Modifiable
    - diabetes
    - tobacco abuse
    - CKD/ESRD
    - dyslipidemia
    - hypertension
  - Nonmodifiable
    - male gender
    - black race
    - age
- Classic Signs/Symptoms
  - Claudication
  - Rest pain
  - Leg ulcers
  - Gangrene
- Screening
  - ABI
  - TBI
- Diagnosis
  - MRI
  - CT angiography
  - CO_2 angiography
  - (must consider risks of gadolinium and contrast exposure)
- Treatment
  - Medical (no prospective studies done in CKD/ESRD)
    - antiplatelet therapy
    - smoking cessation
    - statins
    - BP and glycemic control
  - Nonmedical (must consider high risk for perioperative morbidity and mortality, eventual need for amputation)
    - percutaneous *versus* surgical revascularization
    - amputation

[a]ABI, ankle-brachial index; CKD, chronic kidney disease; CT, computed tomography; MRI, magnetic resonance imaging; TBI, toe-brachial index.

must undergo rigorous preoperative screening and should be treated with perioperative β blockade therapy. Patients with more advanced CKD, particularly those who require dialysis, may not be considered candidates for revascularization and unfortunately may be left with amputation as their ideal therapeutic option (72).

Unfortunately, amputation rates for dialysis patients are disproportionately high (10). Within this population, those with diabetes (73), older age, and black or Native American race are particularly at risk (10). After amputation, functional status is often poor. A retrospective analysis of amputees found ESRD to be highly associated with nonambulatory status after amputation (74). Mortality rates after amputation are high (75) yet similar to those after revascularization (66). Preventive strategies may offer some hope. Providing preventive foot care to patients who have diabetes and receive dialysis can lower amputation rates (76). Evidence is lacking regarding the optimal management of critical limb ischemia in CKD (Table 1).

Conclusion

PAD is an often overlooked condition and risk factor for CVD. It has an increased prevalence within the population with CKD. Screening for PAD in this population is of interest to the nephrologist because of its association with CAD and the disproportionately high rates of amputation among patients with CKD. Both the ACC/AHA and K/DOQI guidelines recommend screening individuals who are at risk. However, the evidence for screening in CKD is lacking. In addition, there is a paucity of study data for effective therapies for PAD in individuals with kidney disease, and this further complicates the decision to screen these patients. CKD increases the risk for morbidity, mortality, and limb loss after revascularization. Nephrologists and their patients must be knowledgeable of risks that are associated with therapies, as well as the increased risk for amputation. More studies are needed to determine which therapies for PAD are beneficial in patients with CKD and dialysis patients. Future research should focus on prospective analysis of preventive measures, revascularization strategies, and medical therapies for PAD in CKD.

Disclosures

None.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE: Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
2. Shilpak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, Mcclellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137: 555–562, 2002
3. Townsend RR: Cardiac mortality in chronic kidney disease: A clearer perspective. *Ann Intern Med* 137: 615–616, 2002
4. O'Hare AM: Management of peripheral arterial disease in chronic kidney disease. *Cardiol Clin* 23: 225–236, 2005
5. O'Hare AM: High prevalence of peripheral arterial disease in persons with renal insufficiency: Results from the National Health and Nutrition Examination Survey. *Circulation* 109: 320–323, 2004
6. Leskinen Y, Salenius JP, Lehtimaki T, Huhtala H, Saha H: The prevalence of peripheral arterial disease and medial artery calcification in patients with chronic renal failure: Requirements for diagnostics. *Am J Kidney Dis* 40: 472–479, 2002
7. O'Hare AM, Vittinghoff E, Hsia J, Shilpak MG: Renal insufficiency and the risk of lower extremity peripheral arterial disease: Results from the Heart and Estrogen/Progestin Replacement Study. *J Am Soc Nephrol* 15: 1046–1051, 2004
8. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD: Kidney function and risk of peripheral arterial disease: Results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol* 18: 629–636, 2007
9. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, Bell K, Caporusso J, Durand-Zaleski I,

Komori K, Lammer J, Liapis C, Novo S, Razavi M, Robbs J, Schaper N, Shigematsu H, Sapoval M, White C, White J; TASC II Working Group: Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 33: S1–S75, 2007
10. Eggers PW, Gohdes D, Pugh J: Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney Int* 56: 1524–1533, 1999
11. Jaar BG, Astor BC, Berns JS, Powe NR: Predictors of amputation and survival following lower extremity revascularization in hemodialysis patients. *Kidney Int* 65: 613–620, 2004
12. Ramdev P, Rayan SS, Sheahan M, Hamdan AD, Logerfo FW, Akbari CM, Campbell DR, Pomposelli FB Jr: A decade of experience with infrainguinal revascularization in dialysis-dependant population. *J Vasc Surg* 36: 969–974, 2002
13. Centers for Disease Control and Prevention (CDC): Lower extremity disease among persons aged ≥40 years with and without diabetes—United States, 1999–2002. *MMWR Morb Mortal Wkly Rep* 54: 1158–1160, 2005
14. Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: Results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation* 110: 738–743, 2004
15. USRDS: *United States Renal Data System Annual Data Report*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney Urologic and Hematologic Diseases, 2000, pp 339–348
16. Meijer WT, Grobbee DE, Hunink MGM, Hofman A, Hoes AW: Determinants of peripheral arterial disease in the elderly: The Rotterdam Study. *Arch Intern Med* 160: 2934–2938, 2000
17. Hirsch AT, Criqui MH, Treat-Jacobson D: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286: 1317–1324, 2001
18. Cheung AK, Sarnak MJ, Yan G, Dwyer JT, Heyka RJ, Rocco MV, Teehan BP, Levey AS: Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. *Kidney Int* 58: 353–362, 2000
19. United States Renal Data System: Excerpts from the USRDS 2003 annual data report: Atlas of end-stage renal disease in the United States. *Am J Kidney Dis* 42: S1–S226, 2004
20. Boaz M, Weinstein T, Matas Z, Green MS, Smetana S: Peripheral vascular disease and serum phosphorus in hemodialysis: A nested case-control study. *Clin Nephrol* 63: 98–105, 2005
21. Cooper BA, Penne EL, Bartlett LH, Pollack CA: Protein malnutrition and hypoalbuminemia as predictors of vascular events and mortality in ESRD. *Am J Kidney Dis* 43: 61–66, 2004
22. O'Hare AM, Hsu CY, Bacchetti P: Peripheral vascular disease risk factors among patients undergoing hemodialysis. *J Am Soc Nephrol* 13: 497–503, 2002
23. Manns BJ, Burgess ED, Hyndman ME, Parsons HG, Schaefer JP, Scott-Douglas NW: Hyperhomocysteinemia and the prevalence of atherosclerotic vascular disease in patients with end-stage renal disease. *Am J Kidney Dis* 34: 669–677, 1999
24. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 87: 425–428, 1998
25. Hirsch AT: ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): A collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines. *Circulation* 113: e463, 2005
26. Mohler ER: Peripheral arterial disease: Identification and implications. *Arch Intern Med* 163: 2306–2314, 2003
27. Dunbar RL, Mohler ER 3rd: The unsung perils of a peripheral arterial disease: A malady in search of a patient. *Prev Cardiol* 8: 108–113, 2005
28. Lane JS, Vittinghoff E, Lane KT, Hiramoto JS, Messina LM: Risk factors for premature peripheral vascular disease: Results for the National Health and Nutrition Examination Survey, 1999–2002. *J Vasc Surg* 44: 319–325, 2006
29. Fishbane S, Youn S, Flaster E, Adams G, Maesaka JK: Ankle-arm blood pressure index as a predictor of mortality in hemodialysis patients. *Am J Kidney Dis* 27: 668–672, 1996
30. Ono K, Tsuchida A, Kawai H, Matsuo H, Wakamatsu R, Maeawa A, Yano S, Kawada T, Nojima Y: Ankle-brachial blood pressure index predicts all-cause and cardiovascular mortality in hemodialysis patients. *J Am Soc Nephrol* 14: 1591–1598, 2003
31. Stack AG: Coronary artery disease and peripheral vascular disease in chronic kidney disease: An epidemiologic perspective. *Cardiol Clin* 23: 285–298, 2005
32. Mcdermott MM, Greenland P, Liu K, Guralnik JM, Criqui MH, Dolan NC, Chan C, Celic L, Pearce WH, Schneider JR, Sharma L, Clark E, Gibson D, Martin GJ: Leg symptoms in peripheral arterial disease: Associated clinical characteristics and functional impairment. *JAMA* 286: 1599–1606, 2001
33. McGee SR, Boyko EJ: Physical examination and chronic lower-extremity ischemia: A critical review. *Arch Intern Med* 158: 1357–1364, 1998
34. Resnick HE: Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality. *Circulation* 109: 733–739, 2004
35. Makisalo H, Lepantalo M, Halme L, Lund T, Peltonen S, Salmela K, Ahonen J: Peripheral arterial disease as a predictor of outcome after renal transplantation. *Transplant Int* 11[Suppl 1]: S140–S143, 1998
36. Jacoby JS, Mohler ER, Rader DJ: Noninvasive atherosclerosis imaging for predicting cardiovascular events and assessing therapeutic interventions. *Curr Atheroscler Rep* 6: 20–26, 2004
37. Marckmann P, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS: Nephrogenic systemic fibrosis: Suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 17: 2359–2362, 2006
38. Grobner T: Gadolinium: A specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis. *Nephrol Dial Transplant* 21: 1104–1108, 2006
39. Jonason T, Bergstrom R: Cessation of smoking in patients with intermittent claudication. Effects on the risk of pe-

ripheral vascular complications, myocardial infarction and mortality. *Acta Med Scand* 221: 253–260, 1987
40. Foley RN, Herzog CA, Collins AJ: Smoking and cardiovascular outcomes in dialysis patients: The United States Renal Data System Wave 2 Study. *Kidney Int* 63: 1462–1467, 2003
41. deGroot E, Jukema JW, Montauban AD: B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: A report of the Regression Growth Evaluation Statin Study (REGRESS). *J Am Coll Cardiol* 31: 1561–1567, 1998
42. Mohler ER 3rd, Hiatt WR, Creager MA: Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 108: 1481–1486, 2003
43. Mcdermott MM, Guralnik JM, Greenland P: Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation* 107: 757–761, 2003
44. Mondillo S, Ballo P, Barbati R: Effects of simvastatin on walking performance and symptoms of intermittent claudication in hypercholesterolemic. *Am J Med* 114: 359–364, 2003
45. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 360: 7–22, 2002
46. Tonelli M, Moye L, Sacks FM, Kiberd B, Curhan G; Cholesterol and Recurrent Events (CARE) Trial Investigators: Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 138: 98–104, 2003
47. Wanner C, Krane V, Marz W, Olschewski M, Mann JFE, Ruf G, Ritz E: Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 353: 238–248, 2005
48. Baigent C, Landry M: Study of Heart and Renal Protection (SHARP). *Kidney Int Suppl* 84: S207–S210, 2003
49. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S; HOPE Study Investigators: Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 25: 17–24, 2004
50. Wolosker N, Nakano L, Rosoky R, Puech-Leao P: Evaluation of walking capacity over time in 500 patients with intermittent claudication who underwent clinical treatment. *Arch Intern Med* 163: 2296–2300, 2003
51. Zwierska I, Walker RD, Choksy SA, Male JS, Pockley AG, Saxton JM: Upper- vs lower-limb aerobic exercise rehabilitation in patients with symptomatic peripheral arterial disease: A randomized controlled trial. *J Vasc Surg* 42: 1122–1130, 2005
52. Brendle DC, Joseph LJ, Corretti MC: Effects of exercise rehabilitation on endothelial reactivity in older patients with peripheral arterial disease. *Am J Cardiol* 87: 324–329, 2001
53. Gustafsson T, Kraus WE: Exercise-induced angiogenesis-related growth and transcription factors in skeletal muscle, and their modification in muscle pathology. *Front Biosci* 6: D75–D89, 2001
54. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT: Exercise training for claudication. *N Engl J Med* 347: 1941–1951, 2002
55. Mcdermott MM, Liu K, Criqui MH, Greeland P, Guralnik JM, Tian L, Schneider JR, Pearce WH, Tan J, Martin GJ: Physical performance in peripheral artery disease: A slower rate in decline in patients who walk more. *Ann Intern Med* 144: 10–20, 2006
56. Clagett GP, Sobel M, Jackson MR: Antithrombotic therapy in peripheral arterial occlusive disease. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126: 609S–626S, 2004
57. CAPRIE Steering Committee: A randomised blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 348: 1329–1339, 1996
58. Norgren L, Hiatt WR, Dormandy JA, Nehler KAH, Fowkes FGR: Inter-Society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 45[suppl 1]: S5–S67, 2007
59. Hongo RH, Ley J, Dick SE, Yee RR: The effect of clopidogrel in combination with aspirin when given before coronary artery bypass grafting. *J Am Coll Cardiol* 40: 231–237, 2002
60. Regensteiner JG, Ware JE, McCarthy WJ, Zhang P, Forbes WP, Heckman J, Hiatt WR: Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: Meta-analysis of six randomized controlled trials. *J Am Geriatr Soc* 50: 1939–1946, 2002
61. Beebe HG, Dawson DL, Cutler BS: A new pharmacological treatment for intermittent claudication: Results of a randomized, multicenter trial. *Arch Intern Med* 2041–2050, 1999
62. Mohler ER, Beebe HG, Salles-Cuhna S: Effects of cilostazol on resting ankle pressures and exercise-induced ischemia in patients with intermittent claudication. *Vasc Med* 6: 151–156, 2001
63. Reilly MP, Mohler ER: Cilostazol: Treatment of intermittent claudication. *Ann Pharmacother* 35: 48–56, 2001
64. Dormandy JA, Rutherford RB: Management of peripheral arterial disease (PAD). *J Vasc Surg* 31: S1–S296, 2000
65. O'Hare AM, Sidawy AN, Feinglass J, Merine KM, Daley J, Khuri S, Henderson WG, Johansen K: Influence of renal insufficiency on limb loss and mortality after initial lower extremity surgical revascularization. *J Vasc Surg* 39: 709–716, 2004
66. O'Hare AM, Feinglass J, Sidawy AN, Bacchetti P, Rodriguez RA, Daley J, Khuri S, Henderson WG, Johansen K: Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: Data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 14: 1287–1295, 2003
67. Zannetti S, L'Italien GJ, Cambria RP: Functional outcome after surgical treatment for intermittent claudication. *J Vasc Surg* 24: 65, 1996
68. DeBakey ME, Glaeser DH: Patterns of atherosclerosis: Effect of risk factors on recurrence and survival: Analysis of 11,890 cases with more than 25-year follow-up. *Am J Cardiol* 85: 1045–1053, 2000
69. Dorffler-Melly J: Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. *Cochrane Database Syst Rev* CD0000535, 2003
70. Collins TC, Souchek J, Beyth RJ: Benefits of antithrombotic

therapy after infrainguinal bypass grafting: A meta-analysis. *Am J Med* 117: 93–99, 2004
71. Reddan DN, Marcus RJ, Owen WF, Szczech LA, Landwehr DM: Long-term outcomes of revascularization for peripheral vascular disease in end-stage renal disease patients. *Am J Kidney Dis* 38: 57–63, 2001
72. Korn P, Hoenig SJ, Skillman JJ, Kent KC: Is lower extremity revascularization worthwhile in patients with end-stage renal disease? *Surgery* 128: 472–479, 2000
73. Speckman RA, Frankenfield DA, Roman SH, Eggers PW, Bedinger MR, Rocco MV, McClellan WM: Diabetes is strongest risk factor for lower extremity amputation in new hemodialysis patients. *Diabetes Care* 27: 2198–2203, 2004
74. Taylor SM, Kallbaugh CA, Blackhurst DW, Hamontree SE, Cull DL, Messich HS, Robertson RT, Langan EM 3rd, York JW, Carsten CG 3rd, Snyder BA, Jackson MR, Youkey JR: Preoperative clinical factors predict postoperative functional outcomes after major lower limb amputation: An analysis of 553 consecutive patients. *J Vasc Surg* 42: 227–235, 2005
75. Aulivola B, Hile CN, Hamdan AD, Sheahan MG, Veraldi JR, Skillman JJ, Campbell DR, Scovell SD, LoGerfo FW, Pomposelli FB Jr: Major lower extremity amputation: Outcome of a modern series. *Arch Surg* 139: 395–399, 2004
76. Rith-Najarian S, Gohdes D: Preventing amputations among patients with diabetes on dialysis. *Diabetes Care* 23: 1445–1446, 2000