

Lower-Extremity Peripheral Arterial Disease among Patients with End-Stage Renal Disease

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Abstract. Peripheral arterial occlusive disease (PAOD) accounts for significant morbidity and mortality among end-stage renal disease (ESRD) patients but has not been as extensively studied as other kinds of atherosclerotic disease in this population. The current epidemiology and management of PAOD in ESRD patients is here reviewed and target areas for future research are identified. The prevalence of PAOD appears to be much higher among ESRD patients than in the general population. Risk factors for disease among ESRD patients are not well understood but probably include both conventional and dialysis or uremia-associated risk factors. Standard diagnostic techniques used to identify PAOD in the general population may not be as helpful in ESRD patients because many of these tests are inaccurate in the settings of vascular calcification and

small-vessel disease. Despite the fact that this is a common disease in ESRD patients, most of these patients are not screened for PAOD. Interventions that have proven effective in the prevention and treatment of PAOD in the general population, such as smoking cessation, preventive foot care, and exercise, have not been systematically applied to ESRD patients. Furthermore, the optimal management of ischemic ulceration and gangrene in ESRD patients is quite controversial, and better algorithms for the prevention and management of PAOD in ESRD patients are needed. In conclusion, PAOD is common in ESRD patients. Future research should identify risk factors for disease in this population, and efforts should be made to develop strategies for the effective prevention and management of limb ischemia in this population.

The incidence of nontraumatic lower-extremity amputation among the United States end-stage renal disease (ESRD) population is approximately 10 times higher than that among non-ESRD patients, even controlling for diabetes mellitus (1). Although it is less common among transplant recipients than among dialysis patients, amputation is the most common vascular complication after renal transplantation, occurring in 13 to 25% of renal allograft recipients within 5 yr after transplantation (2). Peripheral arterial occlusive disease (PAOD) is the most common indication for amputation among the ESRD population. For example, amputation was listed as the diagnostic related group (DRG) code for 12,425 hospital discharges for Medicare patients with ESRD in 1998. In approximately 80% of these discharges, "circulatory system disorder" was cited as the indication for amputation (3). Furthermore, "septicemia attributable to peripheral vascular disease" was listed as one of the ten leading causes of death among patients with ESRD between 1996 and 1998 (3).

To date, PAOD has not been as extensively studied as other kinds of atherosclerotic disease, such as coronary artery and cerebrovascular disease. However, it has been demonstrated

that even patients with asymptomatic PAOD have a higher risk of death compared with the general population (4). Patients with ESRD and PAOD seem to have a similarly increased risk of death (5,6), and PAOD seems to be a risk factor for a host of adverse outcomes among patients with ESRD. For example, dialysis patients with PAOD are at increased risk for hospital admission (7), death within 6 mo after initiation of dialysis (8), and death after acute myocardial infarction (9). PAOD has recently been recognized as a risk factor for poor outcomes after renal transplantation, including prolonged hospitalization (10), poor allograft survival rates (11), and increased mortality rates (12). In combination, these findings suggest that PAOD confers substantial risks for both morbidity and death in the ESRD population.

Because so many nephrologists provide primary care for their patients (13) and because PAOD is a major cause of morbidity and death in the ESRD population, it is important that nephrologists understand how to diagnose and manage this disease. This article reviews the current management of lower-extremity PAOD in the general population and among patients with ESRD and identifies target areas for future research in this area.

Epidemiology Prevalence

Intermittent claudication, the earliest symptom of PAOD, is observed in 1 to 4% of community-dwelling men and women who are >55 yr of age (14). Estimates of the prevalence of PAOD on the basis of noninvasive diagnostic testing results range from 5.5

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Table 1. PAOD prevalence among patients with ESRD on the basis of histories and physical examination findings^a

Authors	No. of Patients	Population	Diagnostic Criteria Used					Prevalence (%)
			Prior Diagnosis of PAOD ^b	Amputation or Revascularization	Claudication	Gangrene	Decreased Pulses	
USRDS (3)	35,438	Incident dialysis	x	x	x	x	x	15
Webb <i>et al.</i> (17)	325	Prevalent dialysis			x			19
HEMO Study (16)	936	Prevalent hemodialysis	x	x	x	x		23
USRDS (3)	369	Incident transplant	x	x	x	x	x	2.4
Morrissey <i>et al.</i> (19)	39	Prevalent diabetic transplant (4 yr after transplant)		x			x	30
Kasiske <i>et al.</i> (18)	46	Prevalent transplant (15 yr after transplant)		x				15
Morrissey <i>et al.</i> (19)	65	Prevalent kidney-pancreas transplant (4 yr after transplant)		x			x	46

^a USRDS, United States Renal Data System; HEMO, Hemodialysis; PAOD, peripheral arterial occlusive disease; ESRD, end-stage renal disease.

^b Patients with claudication or abdominal aortic aneurysms were also included in this category.

to 23% (12,15). Table 1 summarizes published estimates of the prevalence of PAOD in different ESRD patient groups, on the basis of history and physical findings, and indicates the diagnostic criteria used in each study. According to 1999 United States Renal Data System data, the overall prevalence of PAOD among patients with incident ESRD was 14.9% (3). Figure 1 presents the trend in PAOD prevalence among incident ESRD patients from 1995 to 1998. Although the percent prevalence of PAOD has remained fairly stable with time, there has been an increase in the absolute number of incident ESRD patients and PAOD, which reflects expansion in ESRD program enrollment during this period. As in the general population, PAOD among new dialysis patients is more common among men (compared with women), among older age groups, and among diabetic patients (compared with nondiabetic patients) (3). There are also ethnic differences in the prevalence of PAOD among dialysis patients. The highest rates of PAOD are encountered among Native American dialysis

patients (21%), although, due to the ethnic composition of the United States dialysis patients, the vast majority of ESRD patients with PAOD are white.

It is important to note that United States Renal Data System data reflect only the prevalence of PAOD as reported on the Health Care Financing Administration’s Medical Evidence Form (Form 2728) submitted for each patient at the onset of ESRD. The Hemodialysis (HEMO) Study reported a PAOD prevalence of 23% among a sample of established hemodialysis patients (16). Webb *et al.* (17) reported a 19% prevalence of intermittent claudication among a population of 325 British patients undergoing hemodialysis. Estimates of the prevalence of PAOD among renal transplant recipients range from 15 to 30% (18,19), and rates as high as 46% have been reported for kidney-pancreas transplant recipients (19).

None of the aforementioned studies used diagnostic testing among patients without symptoms to make the diagnosis of PAOD. Therefore, these data probably underestimate the true prevalence of PAOD among patients with ESRD. Several studies have measured prevalence among patients with ESRD on the basis of noninvasive diagnostic testing results (Table 2). Estimates reported in these studies range from 16 to 48%, depending on the specific populations studied and the diagnostic techniques used. In general, estimates of the prevalence of PAOD among dialysis patients that are based on diagnostic testing results are almost double those that are based on history and physical findings alone.

Risk Factors

Established risk factors for PAOD in the general population include increased age, hypertension, hyperlipidemia, smoking, diabetes mellitus, and coronary artery disease. Several unconventional cardiac risk factors, such as lipoprotein(a) levels, homocysteine levels, and chronic inflammation, are also associated with PAOD. There have been very few attempts to

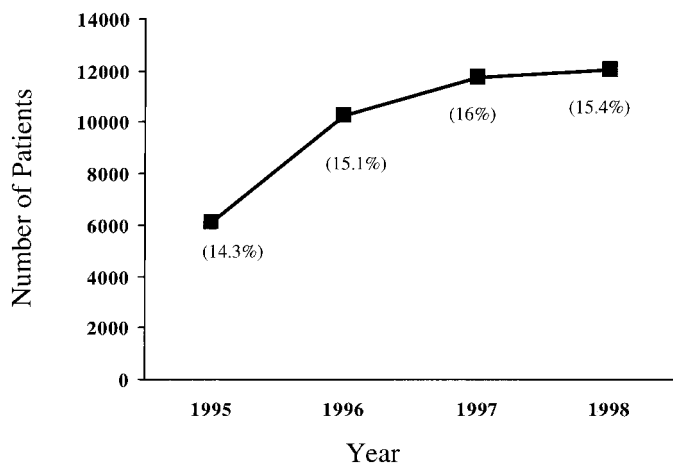


Figure 1. Numbers of patients with incident end-stage renal disease and peripheral arterial occlusive disease, 1995 to 1998 (3).

Table 2. PAOD prevalence among patients with ESRD, on the basis of diagnostic testing^a

Authors	No. of Patients	Population	Prevalence According to Diagnostic Criteria Used (%)			
			ABI < 0.9	ABI < 0.77	TBI < 0.65	PVR < 5 mm
Fishbane <i>et al.</i> (5)	132	Hemodialysis (United States)	35			
Al Zahrani <i>et al.</i> (84)	60	Hemodialysis (Saudi Arabia)	38.3			
Ono <i>et al.</i> (85)	774	Hemodialysis (Japan)	16.6			
Testa and Ottavio (6)	226	Hemodialysis (France)	33			
Makisalo <i>et al.</i> (44)	129	Before transplant (Finland)		4	20	48
Aakhus <i>et al.</i> (86)	406	After transplant (Norway)	4			

^a ABI, ankle brachial index; TBI, toe brachial index; PVR, pulse volume recording by impedance plethysmography.

identify PAOD risk factors among patients with ESRD. The HEMO Study found that diabetes mellitus and smoking were associated with PAOD among hemodialysis patients (16). Age was significantly associated with PAOD among nondiabetic patients but not among diabetic patients. Black race was negatively associated with PAOD. Other conventional cardiac risk factors, such as male gender, hypercholesterolemia, and hypertension, were not associated with PAOD in the HEMO study.

Although conventional cardiac risk factors contribute to cardiovascular morbidity and death among patients with ESRD, they cannot fully account for the excess burden of cardiovascular disease in this group (16). Preliminary evidence suggests that, as for other forms of cardiovascular disease, unconventional cardiac risk factors such as hyperparathyroidism, chronic inflammation, hyperhomocysteinemia, and apolipoprotein(a) levels may play significant roles in the development or progression of PAOD among patients with ESRD.

Vascular calcification seems to be extremely common among dialysis patients (20) and perhaps contributes to the development of PAOD. Savage *et al.* (21) observed that 75% of 24 patients with ESRD but without clinical evidence of cardiovascular disease had carotid or femoral artery calcified plaques. There is growing evidence that this phenomenon is associated with elevated serum phosphorous levels, elevated calcium and phosphorous product values, and hyperparathyroidism. Among patients with ESRD, abdominal aortic calcification seems to be correlated with increased calcium and phosphorous product levels (22), and hyperphosphatemia and hyperparathyroidism have been demonstrated to be correlated with coronary, carotid, and femoral artery atherosclerosis among dialysis patients (23,24). Goldsmith *et al.* (25) used skeletal surveys to document vascular calcification among 38 long-term hemodialysis patients. Those authors observed that calcification became more prevalent and more severe with time and that the rate of progression was determined by age, systolic BP, parathyroid hormone levels, and serum phosphorous and vitamin D levels.

Guerin *et al.* (26) recently demonstrated that the extent of vascular calcification in patients with ESRD is associated with the degree of arterial stiffness (as assessed in aortic pulse wave velocity measurements), serum fibrinogen levels, and the use of calcium-based binders. Arterial stiffening is correlated with the extent of atherosclerosis and has been demonstrated to be a powerful predictor of all-cause and cardiovascular mortality

rates among hemodialysis patients (27). These authors suggest that there may be a correlation between atherosclerotic disease burden and the degree of vascular calcification. However, the precise relationship between vascular calcification and peripheral vascular disease has yet to be fully elucidated.

There is growing evidence that chronic inflammation plays a role in the pathogenesis of atherosclerosis. Data from several prospective studies has demonstrated that elevated levels of the acute-phase reactant C-reactive protein (CRP) predicts an increased incidence of future cardiovascular events among a wide range of clinical populations, including individuals with no history of cardiovascular disease, those with angina, and those with a history of prior myocardial infarction (28). Ridker *et al.* (29) directly evaluated the relationship between CRP levels and PAOD. Those authors identified 144 healthy men, participating in the Physicians' Health Study, who subsequently developed symptomatic PAOD, and it noted that baseline CRP levels were significantly higher for that group than for a group of control subjects who did not develop PAOD. CRP levels seem to be predictive of cardiovascular mortality rates in the ESRD population, as they are in the general population (30). An association between carotid artery atherosclerosis and CRP levels among patients with chronic renal insufficiency has also been demonstrated (31). We are not aware of any studies documenting a connection between lower-limb atherosclerosis and inflammation among patients with ESRD.

Lipoprotein(a) is a genetically determined risk factor for PAOD in the general population, and dialysis patients have significantly higher levels of lipoprotein(a) and low-molecular weight apolipoprotein(a) isoforms than do individuals with normal renal function. Low-molecular weight apolipoprotein(a) isoforms are associated with the presence of carotid artery plaques among hemodialysis patients (31). However, one study of patients undergoing peritoneal dialysis noted that lipoprotein(a) levels were not correlated with the presence of peripheral vascular disease (32). Further research is needed to determine whether lipoprotein(a) confers a higher risk for the development or progression of PAOD in the ESRD population.

Hyperhomocysteinemia is a risk factor for lower-extremity PAOD and for the progression of PAOD in the general population (12). There is an extraordinarily high prevalence of hyperhomocysteinemia among patients with ESRD (33), and it has been hypothesized that hyperhomocysteinemia may con-

tribute to atherosclerosis in this population. Several studies have found that dialysis patients with the highest homocysteine levels exhibit a higher prevalence of PAOD, compared with patients with the lowest homocysteine levels (34,35).

Diagnosis

Most patients with PAOD do not exhibit symptoms. The earliest symptom of PAOD is intermittent claudication. Asymptomatic PAOD and intermittent claudication are collectively referred to as “noncritical ischemia.” More advanced disease is signaled by the onset of rest pain, ischemic ulceration, and eventually gangrene (in increasing order of severity). Patients with any of these findings are said to have “critical ischemia.”

History and physical examinations are insensitive indicators of the presence of PAOD (36). Therefore, diagnostic testing is essential for establishing this diagnosis. A commonly used diagnostic test is measurement of the ankle brachial index (ABI), *i.e.*, the ankle/arm systolic pressure ratio (37). This test exploits the fact that PAOD results in selective decreases in lower-extremity systolic pressure. ABI values of ≤ 0.9 have estimated sensitivity and specificity values of 95 and 100%, respectively, for PAOD detection (38,39). However, ABI values can be falsely elevated among patients with lower-extremity vascular calcification, because heavily calcified arteries tend to be incompressible (40). Ankle pressure is also a poor measure of perfusion among patients with extensive pedal or digital arterial disease. The sensitivity of ABI measurements for detection of PAOD among patients with ESRD has not been tested, but this technique is probably less sensitive than in the general population, because of the high prevalence of arterial calcification in this population. Therefore, it is likely that estimates of the prevalence of PAOD that are based on ABI testing underestimate the true prevalence of PAOD in the ESRD population (Table 2). Other noninvasive screening tests for PAOD, such as toe brachial index (TBI) measurements (41), transcutaneous partial pressure of oxygen (TCPO₂) readings (42), and toe pulse volume recordings (PVR) (43), are not affected by calcification of lower-leg vessels (although TBI and PVR values may be affected by digital vessel calcification, which is also observed in this patient group). TBI, PVR, and TCPO₂ tests are probably more appropriate than ABI tests for screening patients with ESRD for PAOD. However, we are aware of only one study in which alternative techniques of this type have been used in the ESRD population (Table 2) (44). In that study of patients undergoing renal transplant evaluation, toe PVR values of ≤ 5 mm and TBI values of ≤ 0.65 were much more sensitive than ABI values of ≤ 0.9 for PAOD detection. Although ABI measurements can be performed in the primary care setting with hand-held Doppler instruments (45), more specialized techniques, such as TBI, toe PVR, and TCPO₂ testing, require referral to a vascular laboratory.

After PAOD has been detected in screening tests, the site of arterial occlusion can be localized by duplex scanning or by angiography, if a surgical intervention is planned. Increasingly, CO₂ angiography and three-dimensional peripheral magnetic resonance angiography are used instead of contrast angiogra-

phy for patients with chronic renal insufficiency, because these techniques do not cause nephrotoxicity (46,47).

Treatment

Noncritical Ischemia

General Considerations. In the general population, only approximately one-third of patients with claudication develop critical ischemia. Therefore, the treatment of noncritical ischemia is a quality-of-life issue for most patients. Interventions such as preventive foot care, smoking cessation, and exercise can be extremely beneficial. When these interventions fail to relieve symptoms, patients are usually offered revascularization and/or medications.

Preventive Foot Care. Meticulous foot care is critical for the prevention of amputation. Foot care programs have been demonstrated to be extremely effective in reducing foot complications among diabetic patients without ESRD (48). One preventive foot care program for diabetic renal transplant recipients produced reductions in the numbers of episodes of digital gangrene and major amputations and increases in the rate of foot ulcer healing (49). Instruction in diabetic foot care has not figured prominently in nephrology nursing, and most dialysis units do not have a foot care program (40). Efforts should be made to establish routine clinic-based or dialysis unit-based foot care programs for patients with ESRD and to raise physician awareness regarding the importance of preventive foot care among patients with PAOD (50).

Smoking Cessation. One controlled nonrandomized study of smoking cessation among patients with intermittent claudication reported significant improvements in walking distance among patients who stopped smoking (40). Smoking cessation may also slow the progression of disease and reduce the risk of amputation. The incidence of tobacco use among patients with ESRD is quite high. For example, of the first 1000 hemodialysis patients enrolled in the HEMO study, 52% smoked cigarettes at the time of entry into the study or had a history of tobacco use (16). Despite the high prevalence of tobacco use among the ESRD population, we were unable to find any literature reports of smoking cessation programs for this group. Organized efforts to help patients with ESRD stop smoking are needed to lower overall morbidity and mortality rates, as well as those associated specifically with PAOD.

Exercise. Exercise seems to be the most effective treatment for patients with intermittent claudication. A recent meta-analysis of 10 prospective randomized trials of exercise among patients with intermittent claudication found a weighted mean difference of 6.51 min (95% confidence interval, 4.36 to 8.66 min) in maximal walking time for the exercise group, compared with the no-treatment group (51). Exercise produced significant improvements in maximal walking time, compared with angioplasty, at 6 mo (weighted mean difference, 3.3 min; 95% confidence interval, 2.21 to 4.39 min) and did not differ significantly from surgical treatment. There have been no studies of exercise for the treatment of claudication among patients with ESRD, but there is growing evidence that exercise is beneficial in this population (52).

Medications. Although a wide variety of medications have been used to treat PAOD, few have any proven benefit. Pentoxifylline has been widely used to treat intermittent claudication but did not produce clinically significant improvements in walking distance, compared with placebo (40). Pentoxifylline is renally excreted and can accumulate during moderate to severe renal insufficiency (53). Cilostazol is a new cAMP phosphodiesterase inhibitor that has improved absolute claudication distances in randomized, double-blind, placebo-controlled trials (54,55). However, cilostazol is probably not safe for use in ESRD, because of altered protein binding. Although lipid-lowering agents are effective in the primary prevention of coronary artery disease (56), there is no evidence that these medications are effective in either prevention or treatment of PAOD. A recent meta-analysis of seven prospective randomized trials of lipid-lowering agents among patients with existing PAOD noted no significant improvements in pain, ABI, or skin necrosis (57). Despite the lack of efficacy in PAOD treatment, most clinicians would prescribe lipid-lowering agents for patients with PAOD because of their proven benefits in reducing coronary artery and cerebrovascular disease in this high-risk patient group. Some data suggest that the use of aspirin alone or aspirin plus dipyridamole results in less progression of PAOD, as measured angiographically; however, there is no evidence for improved clinical outcomes (40). Although vitamin E, steroid sex hormones, defibrotide, garlic, and ginkgo biloba have been used to treat PAOD, they have no proven benefit and cannot be recommended at this time.

Angioplasty. Angioplasty is indicated for select patients with intermittent claudication. However, trials comparing angioplasty with exercise suggest that, although angioplasty may result in short-term improvements in walking distance, this benefit is not sustained with time (58). Angioplasty of intermittent claudication has not been studied in patients with ESRD.

Surgical Revascularization. Although critical ischemia is the only clear indication for surgical bypass, most bypass operations are performed because of intermittent claudication. For example, intermittent claudication was the indication for intervention for 73% of patients enrolled in Veterans Cooperative Study 199, a prospective randomized trial of percutaneous transluminal angioplasty (PTA) *versus* surgery to treat PAOD (59). There are currently no data to support the use of surgical bypass, rather than exercise therapy, for the treatment of intermittent claudication in the general population. Most centers do not routinely offer revascularization procedures for patients with ESRD and claudication, but several surgical series investigating revascularization among patients with ESRD have included small numbers of patients with intermittent claudication (60–63).

Critical Ischemia

General Considerations. Each year, approximately 150,000 patients develop critical limb ischemia in the United States. The treatment of choice is a limb-salvage procedure, such as vascular reconstruction, percutaneous angioplasty, thrombolysis, or thrombectomy. However, approximately 40%

of patients are not candidates for a reopening procedure. Approximately one-half of these patients undergo primary amputation. The remaining patients either receive no treatment or, usually as a last resort, are offered nonsurgical limb-salvage therapies such as spinal cord stimulation (SCS) or intravenous prostaglandin infusion. The percentage of patients who ultimately require amputation is even higher in the ESRD population, because many of these patients are not candidates for limb-sparing procedures in the first place and many of those who do undergo revascularization subsequently require amputation.

Limb-Sparing Procedures. Surgical Revascularization. The current trend is to offer limb-sparing surgery to patients with critical ischemia. This approach consists of surgical bypass, which may be performed in concert with limited amputation (below the tarsal-metatarsal joint) in an attempt to avoid major amputation. The management of limb-threatening ischemia among patients with ESRD poses some unique challenges. Both dialysis and transplant patients are often at high surgical risk because of the existence of comorbid conditions. Furthermore, many surgeons have anecdotally observed that the vessels of patients with ESRD are heavily calcified, rendering lower-extremity bypass technically difficult (64). In addition, these patients often heal poorly and have high rates of wound infections, even in the presence of a patent bypass graft.

There have been no prospective trials comparing surgical bypass with other modalities for the treatment of critical ischemia among patients with ESRD, but at least 15 retrospective surgical case series have been reported in the literature. All of those studies used graft patency, limb salvage, and patient survival rates as study end points. Six of those studies included data for non-ESRD control groups. Table 3 presents the results of surgical revascularization studies among patients with ESRD and demonstrates that there was considerable variation in outcomes among those studies. For example, 1-yr graft patency rates ranged from 53 to 90%, 1-yr limb salvage rates ranged from 56 to 91%, 2-yr patient survival rates ranged from 32 to 67%, and 30-d operative mortality rates ranged from 0 to 13%. Amputation in the presence of a patent bypass graft seems to be more common among patients with ESRD (65–68) and among patients with chronic renal failure (69). Graft failure is most common in the setting of frank gangrene. Differences in individual study outcomes may reflect differences in the study populations (*i.e.*, percentages of diabetic patients, smokers, and transplant recipients), in the surgical procedures performed (*i.e.*, percentage of revascularization procedures with distal anastomosis below the popliteal artery), and in the indications for surgery (*i.e.*, the percentage of patients for whom the indication for surgery was gangrene). Table 4 presents outcome data for the non-ESRD control groups included in six of the aforementioned case series. Comparisons of outcomes weighted according to the number of patients and procedures demonstrated that patients with ESRD exhibited significantly higher 30-d operative mortality rates and lower graft patency, limb salvage, and patient survival rates, compared with control subjects without ESRD.

These observations have led to disparate recommendations

Table 3. Outcomes of retrospective studies of limb revascularization among patients with ESRD^a

Authors	No. of Patients	No. of Limbs	1-yr Graft Patency Rate (%)	1-yr Limb Salvage Rate (%)	2-yr Patient Survival Rate (%)	30-d Mortality Rate (%)
Leers <i>et al.</i> (87)	34	41	62	56	52	2.4 (3wk) ^b
Mills <i>et al.</i> (65)	12	14	NR	59	67	NR
Hakaim <i>et al.</i> (68)	23	30	53	63	52 (1yr) ^b	0
Lumsden <i>et al.</i> (61)	27	34	64	65	60	5.9
Simsir <i>et al.</i> (60)	44	52	NR	67	72 (1yr) ^b	13
Korn <i>et al.</i> (73)	23	33	65	67	47	6
Beale <i>et al.</i> (88)	44	57	71	70	52	9
Johnson <i>et al.</i> (89)	53	69	78	75	38	10
Sanchez <i>et al.</i> (90)	47	69	76	71.4 (2yr) ^b	45.6	13
Edwards <i>et al.</i> (70)	19	25	85	76	18 (3yr) ^b	NR
Whittemore <i>et al.</i> (74)	12	16	67	76 (2yr) ^b	32	13
Taylor <i>et al.</i> (67)	55	71	80	82	NR	NR
Harpavat <i>et al.</i> (63)	20	25	82	86	39	10
Chang <i>et al.</i> (91)	24	32	90	90	62	6
Harrington <i>et al.</i> (62)	39	52	77	91	47	12
Total with outcome ^c	524	671	554	535	358	356
Weighted mean ^c			73.9	74	48.6	9.48

^a NR, not reported.

^b Times in parentheses represent alternative lengths of follow-up.

^c Weighted means were calculated for all outcomes by using only studies for which there were data for the particular outcome. Values for limb salvage and graft patency rates were obtained by weighting each study according to the number of limbs reported. Values for patient survival and 30-d operative mortality rates were obtained by weighting each study according to the number of patients included. The total numbers of limbs or patients used in the calculations for weighted means are indicated.

in the literature. Some authors, recognizing the tremendous morbidity associated with repeated unsuccessful surgical interventions, have recommended that patients with ESRD and critical ischemia should undergo primary amputation rather than revascularization (70). Others have suggested avoiding surgical intervention and allowing autoamputation among patients with stable gangrene who are poor surgical candidates, on the basis of data indicating poor outcomes with both surgical bypass and amputation (71). At the opposite end of the spectrum, some authors have suggested early revascularization for patients with ESRD, on the basis of the fact that outcomes are extremely poor when ischemia is advanced (65). Current practices fall somewhere in the middle of this spectrum. In the absence of frank gangrene extending above the foot, patients with ESRD and critical ischemia are generally offered revascularization when it is technically possible. Amputation is usually recommended when gangrene has extended above the middle of the foot, particularly if the patient has significant comorbidity and a sedentary lifestyle (71). However, there is considerable clinical practice variation among individual surgeons and among centers.

There is also disagreement regarding the management of failed bypass grafts among patients with ESRD. The authors of one recent surgical series of secondary interventions for failed pedal bypass grafts recommended that patients with renal insufficiency not undergo graft revision (72). This recommenda-

tion was based on their observation that all patients with renal insufficiency who underwent revision required major amputation within 1 yr. Cost is also a consideration. If successful, revascularization is cheaper than amputation because rehabilitation costs are more modest. However, the cost and length of the hospital stay increase markedly when subsequent amputation or graft revision becomes necessary. Korn *et al.* (73) estimated an average cost of approximately \$44,000 per year of limb salvage for patients with ESRD. This figure is approximately twice the estimated cost of limb salvage for non-ESRD patients (\$18,000 to \$22,000/yr of limb salvage). However, the cost was much lower among patients with ESRD who experienced sustained benefits from revascularization, compared with those who did not (\$23,538 *versus* \$110,000 per year of limb salvage). Unfortunately, it has proven difficult to predict which patients with ESRD will develop complications after bypass and ultimately require revision or amputation (74). Korn *et al.* (73) observed that patients undergoing peritoneal dialysis and patients with extensive tissue loss at the time of revascularization experienced poor outcomes after revascularization. The considerable patient morbidity and expense related to failed revascularization procedures underscore the importance of patient selection for aggressive interventions. More research is clearly needed to identify patients who are at highest risk for revascularization failure and who might be better served by primary amputation.

Table 4. Outcomes of retrospective studies of limb revascularization among non-ESRD control patients^a

Authors	No. of Patients	No. of Limbs	1-yr Graft Patency Rate (%)	1-yr Limb Salvage Rate (%)	2-yr Patient Survival Rate (%)	30-d Mortality Rate (%)
Taylor <i>et al.</i> (67)	443	540	92	97	72	2.3 ^c
Edwards <i>et al.</i> (70)	238	279	89	95	66 (3yr) ^b	NR
Mills <i>et al.</i> (65)	41	42	84 (2yr) ^b	92	81 ^d	3.6 ^d
Whittemore <i>et al.</i> (74)	40	43	86 (2yr) ^b	90 (2yr) ^b	66	9
Harpavat <i>et al.</i> (63)	173	199	83	86	87	4
Hakaim <i>et al.</i> (68)	58	70	82	84	90 (1yr) ^b	2
Total with outcome ^e	908	1161	1088	1121	697	755
Weighted mean ^e			88.9	93.6	75.9	3.1

^a NR, not reported.

^b Times in parentheses represent alternative lengths of follow-up.

^c Three-week operative mortality rate.

^d Values are for entire group (ESRD and non-ESRD patients).

^e Weighted means were calculated for all outcomes by using only studies for which there were data for the particular outcome. Values for limb salvage and graft patency rates were obtained by weighting each study according to the number of limbs reported. Values for patient survival and 30-d operative mortality rates were obtained by weighting each study according to the number of patients included. The total numbers of limbs or patients used in the calculations for weighted means are indicated.

Angioplasty. Percutaneous transluminal angioplasty (PTA) is used when arterial disease is localized to a vessel segment <10 cm in length. PTA of the iliac arteries produces better outcomes than does PTA of more distal arteries. Two prospective clinical trials comparing angioplasty with surgical bypass in the general population failed to demonstrate convincing differences in mortality, patency, and amputation rates between the two groups to 48 mo (58). However, long-term follow-up monitoring in the Veterans Cooperative Study did demonstrate significantly higher 5-yr morbidity and mortality rates for the surgically treated group, compared with the angioplasty-treated group (75). These results should be interpreted with caution; patients undergoing angioplasty may not be strictly comparable to those undergoing surgical bypass, because only a small subset of patients are candidates for angioplasty. Although some centers have experience with lower-extremity angioplasty among patients with ESRD, there have been no controlled studies of the use of angioplasty to treat PAOD among patients with ESRD, as there have been for non-ESRD patients. Furthermore, there are anecdotal reports that patients with ESRD are poor candidates for angioplasty, because of the relatively high incidence of diffuse distal lesions in this population and because of vascular calcification (76).

Spinal Cord Stimulation. SCS has been used widely in Europe to treat persistent severe ischemic pain and ulcers in patients with critical limb ischemia not amenable to medical or surgical therapy (77). SCS is thought to improve microcirculation by stimulating the autonomic nervous system and has been shown to increase tissue oxygenation in ischemic limbs. SCS is most effective when ulcers are small and pain control is a priority. SCS has not been systematically studied among patients with ESRD, but anecdotal reports are discouraging. For example, one study reported that all four patients with ESRD and critical ischemia who were treated with SCS eventually required amputation (78).

Prostaglandins. Prostaglandins have been used in the treatment of both critical and noncritical ischemia, and they were demonstrated to be superior to placebo in promoting ulcer healing in several prospective, randomized, clinical trials (79). The use of prostacyclin for dialysis patients may be problematic. Although prostacyclin has been successfully used as an extracorporeal anticoagulant for intermittent hemodialysis, careful dose adjustment is required when prostacyclin is administered in a continuous infusion because its clearance is reduced approximately fourfold in dialysis patients. The efficacy of prostacyclin among patients with ESRD was recently called into question by a prospective, double-blind, crossover, placebo-controlled trial in five patients with ESRD and intermittent claudication. Prostacyclin had no more effect on pain relief or walking distance than did placebo, and it was noted that prostacyclin did not produce vasodilation in these patients, as it does in non-ESRD patients (80).

Amputation. Limb amputation is usually performed as a last resort, when conservative measures and/or revascularization have failed or when the patient is not a candidate for revascularization. Dialysis patients exhibit extremely high rates of nontraumatic lower-extremity amputation resulting from all causes, compared with the general population (1). A total of 35,898 amputations were performed in the Medicare ESRD program between 1991 and 1994. In 1994, the crude amputation rate was approximately 4.3/100 person-years for all patients with ESRD and 13.8/100 person-years for diabetic patients with ESRD. The rate of amputation in all groups increased during the period of 1991 to 1994. Amputation rates were fivefold higher for diabetic patients than for nondiabetic patients, and men were 23% more likely to undergo amputation than were women.

Poor survival rates for patients with ESRD after amputation have been well documented (1,81). In the Medicare ESRD population, survival rates after amputation were only 32.7% at

2 yr (1). The presence of gangrene, age of >55 yr, and below- or above-knee amputation (compared with toe amputation) were associated with significant increases in the risk of death after amputation. Dossa *et al.* (81) noted increased hospital mortality rates and decreased long-term survival rates after amputation for patients with ESRD, compared with non-ESRD patients. For their group of 85 patients with ESRD, they recorded a hospital mortality rate of 24% and a 2-yr survival rate of 27%, compared with 7 and 79%, respectively, for the 375 non-ESRD patients studied. Both studies noted significantly lower amputation rates for transplant recipients, compared with dialysis patients. Patients with the highest risk of amputation after transplantation are those with coronary artery disease (82), those undergoing dialysis before transplantation (83), and those with abnormal TBI and PVR values at the time of transplantation (44).

Conclusions

PAOD is more prevalent in the ESRD population than among the general population and is responsible for significant morbidity and death in the ESRD population. Future research efforts should focus on the development of an optimal screening strategy for patients with ESRD. Effective screening would allow us to identify patients who are likely to benefit from interventions such as preventive foot care, smoking cessation, and exercise programs, which are of proven value in the treatment of noncritical ischemia in the general population. Researchers should also try to identify ESRD-specific risk factors that could be targeted in efforts to prevent or slow the rate of progression of PAOD. Finally, if poor outcomes with surgical intervention are to be improved, it is essential that we develop strategies to distinguish between patients who are good candidates for limb-salvage therapy and those who are not and might be better served by early primary amputation. (84–91)

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