Peripheral Arterial Disease in CKD: Disease Burden, Outcomes and Interventional Strategies

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Disease Burden

Peripheral arterial disease (PAD) has been described as the "global pandemic" of our time [1]. In comparison to the 30 million individuals living with HIV, peripheral arterial disease far outnumbers many other chronic diseases. Studies comparing the trend of peripheral arterial disease prevalence have revealed that approximately 200 million individuals were living with peripheral arterial disease in the year 2010. This indicates a dramatic rise in prevalence, with an additional 40 million individuals compared to the year 2000 when the prevalence was estimated to be around 160 million [2]. In the United States, conservative estimates place the figure in the range of at least 8–10 million individuals suffering from peripheral arterial disease [3, 4].

The reasons for increasing prevalence of peripheral arterial disease can be explained by the alarming rise of other conditions such as hypertension, diabetes and hypercholesterolemia [2]. Peripheral arterial disease was traditionally believed to be more common in men when compared to women. However, recent studies show that the prevalence of PAD in men and women is almost equal in the high income regions of the world, and the prevalence is higher in women compared to men in the low and mid income regions [2]. Other studies have showed a similar prevalence between men and women in the US [5]. The prevalence of peripheral arterial disease also rises with increasing age. While the prevalence is roughly around 4% for individuals older than 40 years, it sharply increases to 15% for individuals over 70 years of age [6]. The American College of Cardiology and the American Heart Association recommends the use of an Ankle brachial index (ABI) as the diagnostic test of choice for evaluating lower extremity peripheral arterial disease. An ABI of 1 is considered normal and an ABI of less than 0.9 is considered abnormal. When the ABI is abnormally high (greater than 1.4) (such as in CKD) it is recommended to use the Toe Brachial index (TBI) to establish the diagnosis in individuals with high clinical suspicion [7].

Chronic kidney disease (CKD) is defined by the National Kidney Foundation as a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m^2 for greater than 3 months. CKD is listed by the Centers for Disease Control (CDC) as one of the most prevalent chronic illnesses, with one in seven adults living in the United States with some degree of CKD [8, 9]. CKD is closely intertwined with PAD, with individuals with kidney disease being twice as likely to have peripheral arterial disease compared with those preserved kidney function. In addition, there is a linear relationship between the severity of CKD and the severity of peripheral arterial disease. The National Health and Nutrition Examination survey estimates at least 1 million individuals above the age of 40 with even mild to moderate CKD suffer from peripheral arterial disease defined as Ankle Brachial Index (ABI) less than 0.9 [10]. CKD is also associated with abnormally high ABIs, in particular ABIs greater than 1.4 which inherently is a marker for arterial stiffening and or calcification [11]. When the ABI is abnormally high (greater than 1.4), it is recommended to use the Toe Brachial index (TBI) to establish the diagnosis in individuals with high clinical suspicion [12]. In those individuals who have end stage kidney disease (ESKD), as many as 20–30% have coexistent peripheral arterial disease [13]. The other risk factors strongly associated with peripheral arterial disease include the traditional cardiovascular risk factors namely hypertension, smoking, hypercholesterolemia and diabetes [6].

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The disease burden estimated for peripheral arterial disease, albeit staggering, may still not represent the true prevalence, since many of the studies did not utilize toe brachial index or duplex ultrasound in addition to ABI to detect peripheral arterial disease [1]. In addition many other forms of peripheral arterial disease go misdiagnosed or remain under diagnosed. The prevalence of renal artery disease ranges from 20 to 60% in individuals diagnosed with PAD, whereas literature on mesenteric artery disease is largely lacking [8]. The prevalence of abdominal aortic aneurysms ≥ 3 cm in diameter is approximately 3–4% [14].

Impact of PAD and CKD

Peripheral arterial disease is associated independently with increased mortality [15–17]. Patients with peripheral arterial disease have increased risk of cardiac events during the course of their life [18–20]. There is also a trend towards increased occurrence of stroke and cerebrovascular events in the PAD patient population [21]. Patients with PAD are plagued by lower quality of life and limited mobility [22]. Similarly, CKD currently ranks among the top 10 causes of mortality in the United States and is an important cause of disability and years lost to life [23].

From a health care economic perspective, analysis of Medicare data in the United States reveals that roughly 7% of the beneficiaries were treated for PAD. The average spending per person with PAD was close to $2000 dollars per year. The overall cost of managing PAD based on just the Medicare data from 2001 was roughly around 4.4 billion dollars [24]. This compounds the fact that the expenditure for management of all forms of CKD including ESKD was an astounding 87 billion dollars in 2012 [25].

Clinical Presentation and Management of PAD

Aorto Iliac Disease

Clinical Presentation

Aortoiliac disease can result in buttock claudication, infra-inguinal claudication symptoms of thighs and or calves and vasculogenic erectile dysfunction. Aortoiliac disease can worsen other coexisting lower extremity arterial disease by decreasing arterial inflow.

Non-interventional Management

Smoking cessation is universally recommended. Control of risk factors like hypertension and diabetes along with exercise forms the cornerstone of non-interventional management [26]. Interestingly supervised exercise has been shown to be superior to medical therapy alone [27].

Once symptomatic aorto iliac peripheral arterial disease is identified, medical therapy with low dose aspirin should be initiated [24]. In addition, symptomatic peripheral arterial disease of any bed would be considered as clinically significant atherosclerotic cardiovascular disease. Hence dyslipidemia in this setting should be managed with high dose statin therapy according to the most recent American College of Cardiology cholesterol guidelines [28]. In cases of aspirin intolerance, clopidogrel 75 mg a day is an alternative [24].

Interventional Management

The Trans-Atlantic Inter Society consensus (TASC) group categorizes aorto-iliac and femoral popliteal lesions into A, B, C and D based on anatomy and lesion complexity [24]. (Table 32.1)

For TASC A aorto iliac lesions, endovascular therapy is the treatment of choice. For type B and C lesions endovascular therapy is the preferred option. Surgery can be an alternative in a suitable risk patient [24]. In patients with TASC D lesions, surgery has been the gold standard but percutaneous strategies are now equivalent [29].

Surgical techniques for aorto-iliac disease include aorto-iliac thromboendarterectomy, aorto bifemoral bypass surgery and extra anatomic bypass surgery. Extra anatomic bypass surgery includes axillo-femoral and femorofemoral techniques. Extra anatomic bypass has the advantage of avoiding an open abdominal procedure and thereby the morbidity associated with it however long term patency rates are lower compared with the other approaches [27].

Endovascular therapy with angioplasty and stents has comparable outcomes to surgical techniques with less morbidity and mortality. Stents for aorto-iliac lesions can be self-expandable, balloon expandable or covered stents (stents that are covered with materials such as polytetrafluoroethylene PTFE, Goretex etc.). Calcified focal lesions commonly seen in CKD requiring higher radial force are better managed by balloon expandable stents whereas larger diameter lesions are better served with self-expandable stents. For aorto-iliac disease in general, covered stents are used in situations where rupture of the vessel is likely (neocarinal formation, calcified lesions and aneurysmal lesions). Primary patency rates for stents in the aortoiliac location are very promising with 1 and 4 year rates approaching 100 and 80% respectively. Also, covered stenting of the iliac artery has specifically shown to decrease the need for repeat interventions. For bifurcation aortic disease involving aorta and the iliacs, the preferred technique is by way of "aorto-iliac" kissing stents [26].

Intravascular ultrasound (IVUS) has been used as an alternative to contrast angiography in endovascular aortic repair with comparable outcomes without the risk of compromising renal function [30, 31]. More recently intracardiac

Table 32.1 Trans-Atlantic Inter Societal Consensus (TASC) classification of aorto-iliac and femoral popliteal lesions

	Aorto-iliac lesions	Femoral popliteal
TASC A	Unilateral or bilateral stenoses of CIA Unilateral or bilateral single short ($\leq$3 cm) stenosis of EIA	Single stenosis $\leq$10 cm in length Single occlusion $\leq$5 cm in length
TASC B	Short ($\leq$3 cm) stenosis of infrarenal aorta Unilateral CIA occlusion Single or multiple stenosis totaling 3–10 cm involving the EIA not extending into the CFA Unilateral EIA occlusion not involving the origins of internal iliac or CFA	Multiple lesions (stenoses or occlusions) each $\leq$5 cm Single stenosis or occlusion $\leq$15 cm not involving the infra geniculate popliteal artery Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass Heavily calcified occlusion $\leq$5 cm in length Single popliteal stenosis
TASC C	Bilateral CIA occlusions Bilateral EIA stenoses 3–10 cm long not extending into the CFA Unilateral EIA stenosis extending into the CFA Unilateral EIA occlusion that involves the origins of internal iliac and/or CFA Heavily calcified unilateral EIA occlusion with or without involvement of origins of internal iliac and/or CFA	Multiple stenoses or occlusions totaling $\geq$15 cm with or without heavy calcification Recurrent stenoses or occlusions that need treatment after two endovascular interventions
TASC D	Infra-renal aortoiliac occlusion Diffuse disease involving the aorta and both iliac arteries requiring treatment Diffuse multiple stenoses involving the unilateral CIA, EIA and CFA Unilateral occlusions of both CIA and EIA Bilateral occlusions of EIA Iliac stenoses in patients with AAA requiring treatment and not amenable to endograft placement or other lesions requiring open aortic or iliac surgery	Chronic total occlusions of CFA or SFA ($\geq$20 cm, involving the popliteal artery) Chronic total occlusion of popliteal artery and proximal trifurcation vessels

CIA Common Iliac Artery, *EIA* External Iliac Artery, *CFA* Common Femoral Artery, *AAA* Abdominal Aortic Aneurysm, *SFA* Superficial Femoral Artery

echocardiography (ICE) catheter which is used for intracardiac imaging has been used similar to IVUS in endovascular repair of abdominal aortic aneurysm. ICE catheter use is associated with minimal or no use of contrast in the patients who underwent the procedure [32]. Whether used solely or in conjunction with contrast angiography these are valuable tools in reducing the need for iodinated contrast in patients with CKD or those who are intolerant to iodinated contrast media.

Infrainguinal Peripheral Arterial Disease

Clinical Presentation

Symptomatic infra inguinal peripheral arterial disease manifests as claudication of the thighs, calves, non-healing ulcers of lower leg following trauma and critical limb ischemia. Critical limb ischemia is defined as chronic rest pain, ulcers, gangrene that is attributable to arterial occlusive disease.

Non Interventional Management

For both asymptomatic and symptomatic lower extremity PAD, smoking cessation is universally recommended. Supervised exercise programs consisting of at least 30 min of walking, at least 3 times a week lasting at least for 12 weeks is a Class I recommendation for patients with claudication symptoms. For those individuals who are unable to participate in a supervised program, a home based program can be a suitable alternative. For symptomatic PAD, low dose aspirin and statin therapy in addition to aggressive management of risk factors like hypertension, diabetes, dyslipidemia is recommended [26].

In situations where aspirin is not tolerated, clopidogrel 75 mg once a day is an alternative [33]. For patients with intermittent claudication and without any contraindications, a trial of oral cilostazol 100 mg twice daily is recommended. In those patients who cannot tolerate cilostazol, a trial of oral pentoxifylline 400 mg three times daily is recommended [26].

Interventional Management

For individuals with ongoing lifestyle limiting symptomatic lower extremity peripheral arterial disease who have failed all non-interventional measures, surgical revascularization or endovascular therapy is recommended [26].

For TASC A femoral popliteal lesions, endovascular therapy is the treatment of choice. For TASC B and C lesions, endovascular therapy is the preferred modality with surgery being an option if the surgical risk is good [24]. For TASC D lesions surgery has historically been the treatment of choice, but with improved equipment and procedural technique, this is more equivocal [27]. Endovascular strategy includes plain balloon angioplasty, bare metal stents, PTFE covered stents and drug-coated stents [27]. Finally drug coated balloons are emerging as a superior alternative to plain balloon angioplasty [34].

For infrapopliteal disease, revascularization is recommended primarily where there is critical limb ischemia. Surgical techniques are available with autologous venous conduits from femoral or popliteal to the pedal or tibial arteries. Synthetic grafts are only a second choice if autologous veins are not available since veins offer higher patency rates compared with synthetic material [26]. Endovascular therapy for infra popliteal lesions primarily involves use of balloon angioplasty with bare metal stents being used as bailout if necessary. Paclitaxel coated balloon angioplasty has showed promise in infra popliteal disease by significantly decreasing rates of restenosis and amputation [35, 36]. Small series of drug coated coronary stents have also showed promise, but would require more robust studies to validate. Notably, limb salvage rates for endovascular therapy and surgery for infra popliteal disease are comparable (80–85%) [37].

For patients with infra inguinal peripheral arterial disease and CKD requiring percutaneous interventions, carbon dioxide angiography is an alternative to iodinated contrast angiography [38]. The use of carbon dioxide has been studied as a sole agent or supplementary agent along with iodinated contrast in individuals with CKD. Carbon dioxide angiography has proven to reduce the amount of contrast exposure, radiation time while preserving renal function [39, 40].

Extra Cranial Carotid Artery Disease

Clinical Presentation

Extracranial carotid artery disease is responsible for 15% of ischemic strokes. Symptomatic or clinically significant carotid artery disease is defined as focal disease associated with stroke, transient ischemic attacks (TIA) or transient mono-ocular blindness (amaurosis fugax) [28].

Non Interventional Management

Medical therapy for symptomatic extracranial carotid artery disease is similar to management of PAD in other arterial beds and involves management of risk factors namely, hypertension, diabetes, smoking cessation, statin therapy. Aspirin, clopidogrel or the combination of aspirin-dipyridamole is recommended for individuals who have symptomatic disease [28].

Interventional Management

Carotid artery endarterectomy is recommended in individuals with extra cranial carotid artery stenosis greater than 70% by non-invasive imaging or greater than 50% by catheter angiography who have experienced non disabling stroke, TIA or amaurosis fugax and who are at low to average risk for surgical complications. Similarly, carotid artery stenting can be considered in the above situation if the risk of stenting is low to average [28]. In patients with stroke or a TIA carotid artery revascularization with either stenting or surgery can be performed within 2 weeks of the index clinical event [28].

In the asymptomatic individual with carotid artery stenosis greater than 70%, recent data from ACT-1 [41] and CREST [42] showed that outside the peri-operative period, there was no difference in the rate of ipsilateral late stroke after endarterectomy or stenting. This however does not help resolve the vexing question of how best to treat the asymptomatic patient, especially in centers with less angiographer experience. It is hoped that with Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial (CREST-2), data will emerge on outcomes with both interventions as well as optimal medical management.

Carotid artery revascularization is not recommended when the stenosis is less than 50% or if the artery is known to be chronically occluded [28].

Vertebral Artery Disease

Clinical Presentation

Vertebral artery disease results in symptoms related to the posterior circulation (dizziness, vertigo, diplopia, perioral numbness, blurred vision, tinnitus, ataxia, bilateral sensory deficits, and syncope). Vertebral artery disease is estimated to be responsible for roughly 20% of posterior circulation strokes [28].

Non Interventional Management

Non interventional management is similar to extracranial carotid artery disease which involves management of vascular risk factors, anti-platelet therapy and statin.

Interventional Management

Asymptomatic vertebral artery disease does not require any interventions. Even when vertebral artery disease is identified, interventions are not commonly done due to the presence of 2 vertebral arteries and most patients remain asymptomatic and unrecognized [43]. Compounding the above factors is the paucity on data on the subject. Surgical correction of vertebral artery disease or angioplasty is rarely performed. There is also a paucity of data on the subject [44].

Peripheral Arterial Disease Outcomes in the CKD Population

As mentioned previously, PAD is associated with an increased risk of future major adverse cardiac events and mortality (Fig. 32.1) [13–19].

Even in asymptomatic individuals with abnormal ABIs, the relative risk of 10-year all-cause mortality has been shown to be twice as high and cardiac mortality, four times as high compared with individuals with normal ABIs [45]. Patients with stable peripheral arterial disease also have a high incidence of acute limb ischemia and acute visceral ischemia defined as arterial events of less than 2-week duration resulting in symptoms. The prognosis after acute peripheral vascular events is very poor with significantly high disability and mortality (about 70%) at 1 and (90%) at 5 years [46]. Individuals with CKD frequently have more severe grades of peripheral arterial disease. CKD as a risk factor on its own increases the chance of future cardiovascular outcomes and worse mortality. There is a linear relationship between the severity of CKD measured by decline in GFR and the risk of death or cardiovascular event [47]. This is shown in Table 32.2.

CKD also doubles the lower extremity amputation rate in PAD patients compared to those without it. Co existent CKD tends to increase the propensity for hospital acquired infections and patients with CKD and PAD are twice as likely to have sepsis [48]. Chronic kidney disease greatly affects outcomes in peripheral arterial disease (Table 32.3). In patients with lower extremity arterial disease, death rates are roughly 3–5 times higher compared with people with normal renal function [51]. The presence of both CKD and PAD increases mortality to a greater degree than the presence of either one alone (Fig. 32.2) [52].

Repair and treatment of peripheral arterial disease is also complicated by the presence of CKD. In the case of peripheral lower extremity interventions, the presence of CKD increased the likelihood of requiring interventions for multiple vessels. The presence of severe CKD increased the likelihood of death or amputation at 30 days by three times. Also severe CKD increased the risk of requiring repeat intervention in infra inguinal arteries with previous angioplasty [53]. In individuals undergoing aorto iliac stenting however, there has not been conclusive data to show that CKD decreases stent patency or increases repeat

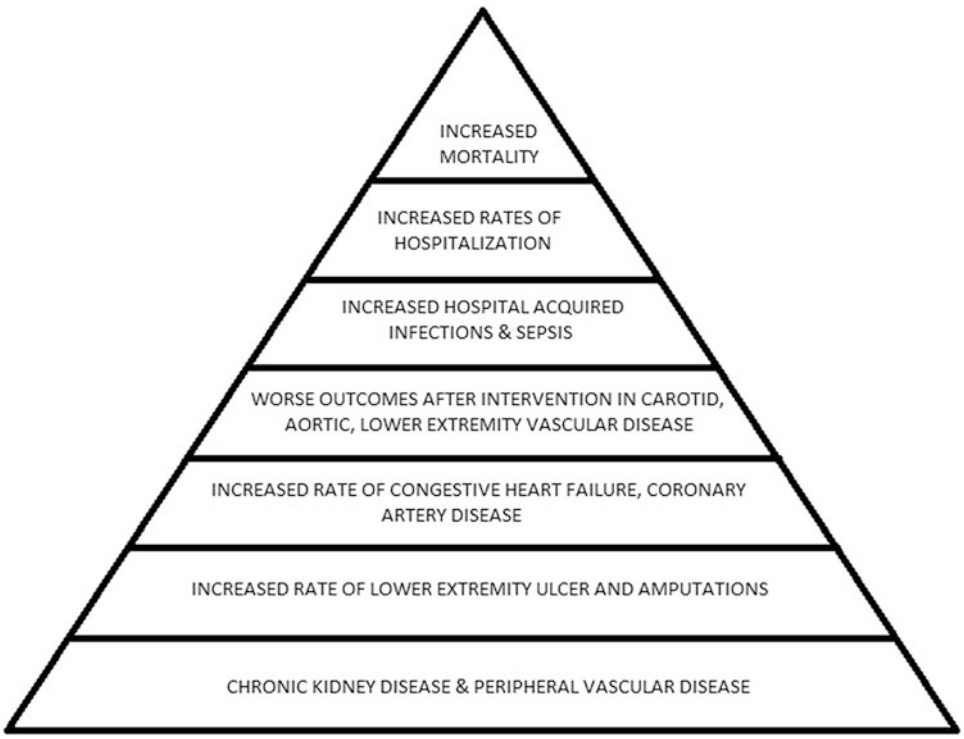

Fig. 32.1 Association of adverse outcomes with the presence of both chronic kidney disease and peripheral vascular disease

Table 32.2 Showing adjusted hazard ratio for any cardiovascular even and all cause mortality among 1,120,295 ambulatory adults stratified by estimated GFR

Estimated GFR in ml/min/1.73 m^2	Cardiovascular event	All cause mortality
≥60	1.00	1.00
45–59	1.4	1.2
30–44	2.0	1.8
15—29	2.8	3.2
<15	3.4	5.9

The group with GFR ≥ 60 served as the reference group
Adapted with permission from Ref. [47]

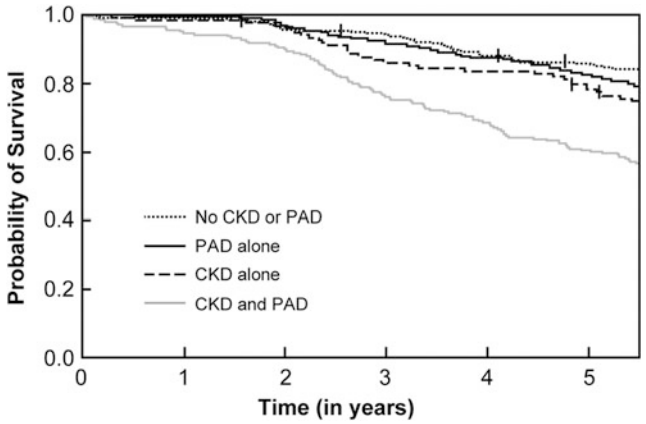

Fig. 32.2 Kaplan–Meier plot of survival probability over time stratified by presence or absence of CKD and PAD. *CKD* Chronic Kidney disease, *PAD* Peripheral arterial disease. Log-rank test for overall difference $P < 0.0001$ (With permission from Ref. [52])

interventions [54]. In individuals undergoing lower extremity bypass surgery as a means of revascularization, severe CKD worsens mortality and amputation free survival [55].

In the case of abdominal aortic aneurysms, the risk of complications and cardiovascular events associated with open or endovascular repair rise in proportion to the severity of CKD. (Refer to Table 32.4) The 30-day mortality is twice as high in individuals with severe CKD (6 vs. 3%; $P = 0.0081$) compared with milder disease [56, 57] and patients with severe CKD who underwent open repair of AAA had a 30-day mortality rate of 10% and a 40% rate of any complication [43]. While it is clear that acutely there is an increased association of morbidity and mortality in individuals undergoing surgical repair of abdominal and infra inguinal arterial disease, data specifically on graft patency rates in this population is still unclear.

Similar to other peripheral disease in other arterial beds, carotid artery disease in conjunction with CKD appears to fare worse (Table 32.5). The impact of CKD on patients undergoing carotid interventions has been examined. In more than 20,000 patients undergoing carotid endarterectomy, moderate CKD (GFR 30–60 ml/min/1.73 m^2) increased the risk of cardiac events (1.7 vs. 0.9% for controls, $P < 0.001$) and pulmonary complications (2.1 vs. 1.3% control; $P < 0.001$) without an increase in mortality. However, severe CKD (GFR less than 30 ml/min/1.73 m^2) had a significantly increased mortality (3.1 vs. 1.0% control, $P < 0.001$) [59]. GFR less than 60 ml/min/1.73 m^2 has also been identified as a risk factor for poor 5-year survival in individuals undergoing carotid endarterectomy for asymptomatic carotid artery disease [60]. The trend appears to be the same in patients undergoing carotid artery stenting. There does not appear to be a significant difference in mortality in individuals with moderate CKD (GFR 30–60 ml/min/1.73 m^2) compared with those having GFR greater than 60 ml/min/1.73 m^2. However, once GFR declines to the range of severe CKD, the 30-day mortality climbs up to roughly 5 times. (0.66% normal renal function, 1.15% moderate renal insufficiency, and 5.45% severe renal insufficiency; $P = 0.005$) [61]

Table 32.3 Pad outcomes stratified by stages of CKD

Study	Outcome	GFR estimation	CKD stratification				Length of follow up	*P* value
			eGFR > 90	eGFR 60–89	eGFR 30–59	eGFR < 30		
Lacroix et al. [49]	Amputation	MDRD	53/219 (24.2%)	80/344 (23.3%)	98/325 (30.1%)	52/122 (42.6%)	1 year	0.0003
Lacroix et al. [48]	Mortality	MDRD	35/219 (16.0%)	62/344 (18.0%)	103/325 (31.7%)	54 (44.3%)	1 year	<0.0001
Otte et al. [50]	Foot ulceration rate per 1000 patients per year	MDRD			29	98		0.02

MDRD Modified Diet and Renal Disease, *eGFR* estimated Glomerular Filtration Rate

Table 32.4 AAA outcomes stratified by stages of CKD

Study	Outcome	GFR estimation	CKD stratification				Length of follow up	*P* value
			eGFR > 90	eGFR 60–89	eGFR 30–59	eGFR < 30		
Patel VI et al. [43]	Mortality after EVAR	MDRD		2.6% (n = 746)		5.7% (n = 370)	30 days	0.0081
Patel VI et al. [43]	Mortality after open AAA repair	MDRD		4.1 (n = 367)		9.9 (n = 202)	30 days	0.0057
Saratzis et al. [43]	Non fatal MI after EVAR	CKD EPI	0.5% (1/173)	3% (3/110)	5% (5/80)	30% (6/20)	34+/ 12 months	<0.001
Saratzis et al. [44]	Non fatal stroke after EVAR	CKD EPI	0% (0/173)	0% (0/110)	10% (8/80)	5% (1/20)	34+/ 12 months	<0.001
Saratzis et al. [44]	Mortality after EVAR	CKD EPI	0.5% (1/173)	2% (2/110)	12% (10/80)	35% (7/20)	34+/ 12 months	<0.001

CKD EPI Chronic Kidney Disease Epidemiology Collaboration formula, *EVAR* Endovascular Abdominal Aortic Aneurysm Repair, *AAA* Abdominal Aortic Aneurysm

Table 32.5 Carotid artery disease outcomes stratified by stages of CKD

Study	Outcome	GFR estimation	CKD stratification			Length of follow up	*P* value
			eGFR > 60	eGFR 30-59	eGFR < 30		
Sidawy AN et al. [45]	Mortality following CEA	MDRD	% (n = 13,965)	1.4% (n = 6423)	3.1% (n = 511)	30 days	<0.05
Protack CD et al. [47]	Mortality following CAS	MDRD	1.02% (n = 604)	3.33% (n = 262)	15.39 (n = 55)	30 days	0.02
Protack CD et al. [47]	Stroke following CAS	MDRD	4.08% (n = 604)	3.33% (n = 262)	23.08% (n = 55)	30 days	0.01
Avgerinos et al. [58]		MDRD	5/868 0.6%	5/414 1.2%	2/60 3.3%	30 days	<0.05

CEA Carotid Endarterectomy, *CAS* Carotid Artery Stenting, *MI* Myocardial Infarction

Conclusion

The management of PAD and CKD both independently and together is an arduous task. CKD increases the chance of adverse cardiovascular and cerebrovascular outcomes. It also increases the risk of interventional strategies currently available. Clinicians need to be cognizant of this so as to provide optimal management strategies to patients and also to avoid the burden of cost that these two conditions impale on the healthcare system. Hence management of these conditions requires a thorough understanding of their pathophysiology and relationship. Management of these complex conditions will require a multi-disciplinary team approach involving cardiologists, nephrologists, vascular surgeons, podiatrists, and wound care experts to integrate all aspects of care in these complex patients.

References

1. Hirsch AT, Duval S. The global pandemic of peripheral artery disease. Lancet. 2013;382(9901):1312–4.
2. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet. 2013;382 (9901):1329–40.
3. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the medicare population. Vasc Med. 2008;13(3):209–15.
4. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18–209.
5. McDermott MM, Liu K, Criqui MH, Ruth K, Goff D, Saad MF, et al. Ankle-brachial index and subclinical cardiac and carotid

disease: the multi-ethnic study of atherosclerosis. Am J Epidemiol. 2005;162(1):33–41.
6. 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. 2004;110(6):738–43.
7. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. 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 (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654.
8. Hoerger TJ, Simpson SA, Yarnoff BO, Pavkov ME, Rios Burrows N, Saydah SH, et al. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. Am J Kidney Dis. 2015;65(3):403–11.
9. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. 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 (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654.
10. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. Circulation. 2004;109(3):320–3.
11. Ix JH, Katz R, De Boer IH, Kestenbaum BR, Allison MA, Siscovick DS, et al. Association of chronic kidney disease with the spectrum of ankle brachial index the CHS (Cardiovascular Health Study). J Am Coll Cardiol. 2009;54(13):1176–84.
12. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. 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 (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463–654.
13. Stack AG. Coronary artery disease and peripheral vascular disease in chronic kidney disease: an epidemiological perspective. Cardiol Clin. 2005;23(3):285–98.
14. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, et al. The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. Arch Intern Med. 2000;160(10):1425–30.
15. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326(6):381–6.
16. Newman AB, Sutton-Tyrrell K, Vogt MT, Kuller LH. Morbidity and mortality in hypertensive adults with a low ankle/arm blood pressure index. JAMA. 1993;270(4):487–9.
17. Vogt MT, Cauley JA, Newman AB, Kuller LH, Hulley SB. Decreased ankle/arm blood pressure index and mortality in elderly women. JAMA. 1993;270(4):465–9.
18. Criqui MH, McClelland RL, McDermott MM, Allison MA, Blumenthal RS, Aboyans V, et al. The ankle-brachial index and incident cardiovascular events in the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2010;56(18):1506–12.
19. Lee AJ, Price JF, Russell MJ, Smith FB, van Wijk MC, Fowkes FG. Improved prediction of fatal myocardial infarction using the ankle brachial index in addition to conventional risk factors: the Edinburgh Artery Study. Circulation. 2004;110(19):3075–80.
20. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. Circulation. 2004;109(6):733–9.
21. Tsai AW, Folsom AR, Rosamond WD, Jones DW. Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. Stroke. 2001;32(8):1721–4.
22. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, et al. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. Vasc Med. 2008;13(1):15–24.
23. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
24. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. Vasc Med. 2008;13(3):209–15.
25. Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2015;66(1 Suppl 1):Svii, S1-305.
26. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33(Suppl 1):S1–75.
27. Murphy TP, Cutlip DE, Regensteiner JG, Mohler ER III, Cohen DJ, Reynolds MR, et al. Supervised exercise, stent revascularization, or medical therapy for claudication due to aortoiliac peripheral artery disease: the CLEVER study. J Am Coll Cardiol. 2015;65(10):999–1009.
28. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. J Vasc Surg. 2015;61(3 Suppl):2S–41S.

29. Ruggiero NJ II, Jaff MR. The current management of aortic, common iliac, and external iliac artery disease: basic data underlying clinical decision making. Ann Vasc Surg. 2011;25 (7):990–1003.
30. von Segesser LK, Marty B, Ruchat P, Bogen M, Gallino A. Routine use of intravascular ultrasound for endovascular aneurysm repair: angiography is not necessary. Eur J Vasc Endovasc Surg. 2002;23(6):537–42.
31. Hoshina K, Kato M, Miyahara T, Mikuriya A, Ohkubo N, Miyata T. A retrospective study of intravascular ultrasound use in patients undergoing endovascular aneurysm repair: its usefulness and a description of the procedure. Eur J Vasc Endovasc Surg. 2010;40(5):559–63.
32. Belenky A, Atar E, Orron DE, Litvin S, Knizhnik M, Almog M, et al. Endovascular abdominal aortic aneurysm repair using transvenous intravascular US catheter guidance in patients with chronic renal failure. J Vasc Interv Radiol. 2014;25(5):702–6.
33. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. J Am Coll Cardiol. 2011;57(8):e16–94.
34. Rosenfield K, Jaff MR, White CJ, Rocha-Singh K, Mena-Hurtado C, Metzger DC, et al. Trial of a Paclitaxel-coated balloon for femoropopliteal artery disease. N Engl J Med. 2015;373(2):145–53.
35. Fanelli F, Cannavale A, Corona M, Lucatelli P, Wlderk A, Salvatori FM. The "DEBELLUM"—lower limb multilevel treatment with drug eluting balloon—randomized trial: 1-year results. J Cardiovasc Surg (Torino). 2014;55(2):207–16.
36. Liistro F, Porto I, Angioli P, Grotti S, Ricci L, Ducci K, et al. Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia. Circulation. 2013;128 (6):615–21.
37. Steering Committee TASC, Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). Vasc Med. 2015;20(5):465–78.
38. Scalise F, Novelli E, Auguadro C, Casali V, Manfredi M, Zannoli R. Automated carbon dioxide digital angiography for lower-limb arterial disease evaluation: safety assessment and comparison with standard iodinated contrast media angiography. J Invasive Cardiol. 2015;27(1):20–6.
39. Palena LM, Diaz-Sandoval LJ, Candeo A, Brigato C, Sultato E, Manzi M. Automated carbon dioxide angiography for the evaluation and endovascular treatment of diabetic patients with critical limb ischemia. J Endovasc Ther. 2016;23(1):40–8.
40. Stegemann E, Tegtmeier C, Bimpong-Buta NY, Sansone R, Uhlenbruch M, Richter A, et al. Carbondioxide-aided angiography decreases contrast volume and preserves kidney function in peripheral vascular interventions. Angiology. 2016;67(9):875–81.
41. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. N Engl J Med. 2016;374(11): 1011–20.
42. Brott TG, Howard G, Roubin GS, Meschia JF, Mackey A, Brooks W, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. 2016;374 (11):1021–31.
43. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32(14):1769–818.
44. Coward LJ, McCabe DJ, Ederle J, Featherstone RL, Clifton A, Brown MM, et al. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. Stroke. 2007;38(5):1526–30.
45. Kornitzer M, Dramaix M, Sobolski J, Degre S, De Backer G. Ankle/arm pressure index in asymptomatic middle-aged males: an independent predictor of ten-year coronary heart disease mortality. Angiology. 1995;46(3):211–9.
46. Howard DP, Banerjee A, Fairhead JF, Hands L, Silver LE, Rothwell PM, et al. Population-based study of incidence, risk factors, outcome, and prognosis of ischemic peripheral arterial events: implications for prevention. Circulation. 2015;132 (19):1805–15.
47. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004 09/23; 2016/01; 351 (13):1296–1305.
48. Luders F, Bunzemeier H, Engelbertz C, Malyar NM, Meyborg M, Roeder N, et al. CKD and acute and long-term outcome of patients with peripheral artery disease and critical limb ischemia. Clin J Am Soc Nephrol. 2016;11(2):216–22.
49. Lacroix P, Aboyans V, Desormais I, Kowalsky T, Cambou JP, Constans J, et al. Chronic kidney disease and the short-term risk of mortality and amputation in patients hospitalized for peripheral artery disease. J Vasc Surg. 2013;58(4):966–71.
50. Otte J, van Netten JJ, Woittiez AJ. The association of chronic kidney disease and dialysis treatment with foot ulceration and major amputation. J Vasc Surg. 2015;62(2):406–11.
51. Pasqualini L, Schillaci G, Pirro M, Vaudo G, Siepi D, Innocente S, et al. Renal dysfunction predicts long-term mortality in patients with lower extremity arterial disease. J Intern Med. 2007;262 (6):668–77.
52. Liew YP, Bartholomew JR, Demirjian S, Michaels J, Schreiber MJ Jr. Combined effect of chronic kidney disease and peripheral arterial disease on all-cause mortality in a high-risk population. Clin J Am Soc Nephrol. 2008;3(4):1084–9.
53. Patel VI, Mukhopadhyay S, Guest JM, Conrad MF, Watkins MT, Kwolek CJ, et al. Impact of severe chronic kidney disease on outcomes of infrainguinal peripheral arterial intervention. J Vasc Surg. 2014;59(2):368–75.
54. Aihara H, Soga Y, Iida O, Suzuki K, Tazaki J, Shintani Y, et al. Long-term outcomes of endovascular therapy for aortoiliac bifurcation lesions in the real-AI registry. J Endovasc Ther. 2014;21(1):25–33.
55. Owens CD, Ho KJ, Kim S, Schanzer A, Lin J, Matros E, et al. Refinement of survival prediction in patients undergoing lower

extremity bypass surgery: stratification by chronic kidney disease classification. J Vasc Surg. 2007;45(5):944–52.
56. Patel VI, Lancaster RT, Mukhopadhyay S, Aranson NJ, Conrad MF, LaMuraglia GM, et al. Impact of chronic kidney disease on outcomes after abdominal aortic aneurysm repair. J Vasc Surg. 2012;56(5):1206–13.
57. Saratzis A, Sarafidis P, Melas N, Saratzis N, Kitas G. Impaired renal function is associated with mortality and morbidity after endovascular abdominal aortic aneurysm repair. J Vasc Surg. 2013;58(4):879–85.
58. Avgerinos ED, Go C, Ling J, Makaroun MS, Chaer RA. Survival and long-term cardiovascular outcomes after carotid endarterectomy in patients with chronic renal insufficiency. Ann Vasc Surg. 2015;29 (1):15–21.
59. Sidawy AN, Aidinian G, Johnson ON III, White PW, DeZee KJ, Henderson WG. Effect of chronic renal insufficiency on outcomes of carotid endarterectomy. J Vasc Surg. 2008;48(6):1423–30.
60. Wallaert JB, Cronenwett JL, Bertges DJ, Schanzer A, Nolan BW, De Martino R, et al. Optimal selection of asymptomatic patients for carotid endarterectomy based on predicted 5-year survival. J Vasc Surg. 2013;58(1):112–8.
61. Protack CD, Bakken AM, Saad WE, Davies MG. Influence of chronic renal insufficiency on outcomes following carotid revascularization. Arch Surg. 2011;146(10):1135–41.