

Central and peripheral arterial diseases in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.

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Chronic kidney disease (CKD) affects about 10% of all populations worldwide, with about 2 million people requiring dialysis. Although patients with CKD are at high risk of cardiovascular disease and events, they are often underrepresented or excluded in clinical trials, leading to important knowledge gaps about how to treat these patients. KDIGO (Kidney Disease: Improving Global Outcomes) convened the fourth clinical Controversies Conference on the heart, kidney and vasculature in Dublin, Ireland, in February 2020, entitled Central and Peripheral Arterial Diseases in Chronic Kidney Disease . A global panel of multidisciplinary experts from the fields of nephrology, cardiology, neurology, surgery, radiology, vascular biology, epidemiology, and health economics attended. The objective was to identify key issues related to the optimal detection, management, and treatment of cerebrovascular diseases, central aortic disease, renovascular disease, and peripheral artery disease in the setting of CKD. This report outlines the common pathophysiology of these vascular processes in the setting of CKD, describes best practices for their diagnosis and management, summarizes areas of uncertainty, addresses ongoing controversial issues, and proposes a research agenda to address key gaps in knowledge that, when addressed, could improve patient care and outcomes.

In February 2020, Kidney Disease: Improving Global Outcomes (KDIGO) convened a clinical Controversies Conference in Dublin, Ireland, titled Central and Peripheral Arterial Diseases in Chronic Kidney Disease . The rationale for this conference was the recognition that although cardiovascular events account for a majority of deaths among persons with chronic kidney disease (CKD) and kidney failure, these individuals have a much higher risk of both atherosclerosis and arteriosclerosis. Atherosclerosis affects the intima of the vessels and is characterized by formation of lipid- and calcification-rich plaques that reduce the capability of arteries to transport blood to all parts of the body. The process of arteriosclerosis affects mainly the media, especially of larger vessels, and increases arterial stiffness, thereby reducing the elastic function of arteries. 1 Furthermore, these noncardiac vascular diseases often cause substantial morbidity and have a major impact on quality of life in the CKD population. Despite these consequences, they have received less attention than heart disease. The objective of the conference was to identify key issues related to the optimal detection, management, and treatment of cerebrovascular diseases, central aortic disease, renovascular disease, and peripheral artery disease (PAD) in the setting of CKD. Conference details are posted on the KDIGO website: <https://kdigo.org/conferences/central-peripheral-arterial-disease/> .

There are strong associations between CKD and cerebrovascular disease that increase with declining kidney function. 2 , 3 The incidence of stroke in CKD is 13.4 per 1000 person-years, 4 rising to 25.3 per 1000 person-years in patients requiring dialysis, 5 and it remains elevated at 6.0 per 1000 patient-years even after receipt of a kidney transplant. 6 Risk appears to be greater for patients treated with hemodialysis, compared with those on peritoneal dialysis. 7 Patients with proteinuria also represent a high-risk subgroup, with a previous meta-analysis showing that such individuals were at a 71% higher risk of stroke compared with those without proteinuria. 8 Recent data suggest that proteinuria may be a better predictor of stroke risk in CKD than estimated glomerular filtration rate (eGFR), possibly as an indicator of microvascular disease. 9 CKD is also associated with worse stroke outcomes, greater likelihood of institutionalization, 10 and higher short- and long-term mortality. 10 , 11

Multiple mechanisms for the high risk of stroke in CKD have been proposed, 12 including shared risk factors (e.g., diabetes, hypertension), nontraditional risk factors arising as secondary consequences of kidney dysfunction (e.g., inflammation, abnormal calcium–phosphorus metabolism, accumulation of uremic toxins), 13 enhanced apoptosis by decreased adenosine monophosphate (AMP) kinase phosphorylation, and increased activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) pathway, 14 dialysis-specific factors (e.g., cerebral “stunning,” dialysis-induced dysregulation of cerebral blood flow 15), and other systemic

conditions that cause stroke and CKD (e.g., systemic lupus erythematosus or Fabry's disease). 2 , 16

Hemodialysis-specific factors likely play a role, as hemodialysis has been shown to induce a significant reduction in global and regional cerebral blood flow. 17 Intradialytic hemodynamic instability is associated with ischemic white matter changes 18 as well as cognitive dysfunction. 19

In an analysis of nearly 700,000 patients from the Get With The Guidelines–Stroke program, patients with CKD were less likely to receive “evidence-based therapies” compared with those without CKD, 20 including thrombolysis and antiplatelet agents and preventive treatments, such as statin therapy and smoking cessation.

Most randomized controlled trials (RCTs) of i.v. thrombolysis excluded patients with advanced CKD, resulting in limited data on its safety and efficacy in this group. In a meta-analysis of 7 observational studies, CKD patients treated with thrombolysis had a higher risk of symptomatic intracranial hemorrhage and mortality than those without CKD. 21 In contrast, in a post-hoc analysis of the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study), patients with CKD who received thrombolysis had higher risk of mortality (attributable to nonvascular causes) but not of disability or intracranial hemorrhage. 22 We concur with the American Heart Association/American Stroke Association guidelines recommending the use of thrombolysis in otherwise-eligible CKD patients without restriction, including hemodialysis patients with a normal partial thromboplastin time (PTT). 23

Few thrombectomy trials have enrolled participants with advanced CKD, 24 , 25 and limited observational data are inconsistent regarding outcomes. 26 , 27 Despite the paucity of data, we would not withhold thrombectomy in CKD patients judged to be suitable candidates for interventional treatment.

Dialysis therapy is challenging in acute stroke. An increase in brain water content with intermittent hemodialysis, possibly related to osmotic shift due to acute urea reduction, 28 may lead to increases in intracranial pressure (ICP); subclinical cerebral edema during intermittent hemodialysis has been observed even in hemodynamically stable patients. 29 Blood pressure (BP) and volume fluctuations also have the potential to extend the penumbra in acute stroke, as global cerebral blood flow declines acutely by about 10% during hemodialysis. 17 Systemic anticoagulation during hemodialysis may exacerbate hemorrhage. 30 Unfortunately, there is no evidence to guide best clinical practice in this scenario. 31 , 32 Figure 1 summarizes our dialysis prescription recommendations.

Patients with moderate-to-severe CKD were excluded from most clinical trials evaluating efficacy and safety of antiplatelet therapy. 33 In a meta-analysis of 3 trials, antiplatelet therapy for primary prevention of stroke in patients with CKD increased the risk of major bleeding events without reducing major cardiovascular events or mortality. 34 For secondary prevention in CKD, studies show a reduction in the risk of myocardial infarction, but not stroke, with antiplatelet therapy. 35 However, despite a paucity of CKD-specific data, given the large benefits of aspirin in doses ranging from 50 to 325 mg/d demonstrated in the general population, 36 its use for secondary prevention in patients with CKD should be considered. 33 , 37 , 38

A secondary analysis of the COMPASS (Cardiovascular Outcomes for People using Anticoagulation Strategies) trial revealed promising results for patients with CKD G1-G3b. 39 COMPASS was a doubleblind RCT that compared low-dose rivaroxaban with or without aspirin in patients with a history of chronic coronary disease or PAD. The risk of stroke was reduced with dual blockade therapy. Although there was no excess relative risk of bleeding in patients with CKD, the absolute risk was higher. It may be reasonable to consider low-dose rivaroxaban and aspirin for the prevention of stroke in patients with an eGFR of 30–59 ml/min per 1.73 m² and a prior history of coronary artery disease or PAD, after careful assessment of bleeding risk.

The efficacy of statin therapy for the primary prevention of stroke in patients with CKD was demonstrated in the Study of Heart and Renal Protection (SHARP) trial, which demonstrated a 25% reduction in ischemic stroke in patients with CKD treated with a combination of simvastatin plus ezetimibe. 40 However, in a meta-analysis of data from 28 trials, the efficacy of statins in CKD appeared to diminish with advancing kidney disease ($P = 0.008$ for trend), and there was little evidence of benefit for patients receiving dialysis (rate ratio: 0.94; 99% confidence interval: 0.79–1.11). 41 According to a previous KDIGO guideline, 42 all individuals over 50 years of age with CKD should be started on statin with or without ezetimibe therapy. Statins may be continued in patients on dialysis who are already taking them, but the guideline does not recommend starting statins in this age group. 42

The KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in CKD has recommended a systolic BP target of <120 mm Hg in CKD for primary and secondary prevention when tolerated, using standardized office BP measurement. 43 This recommendation was influenced by subgroup analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), in which targeting a systolic BP <120 mm Hg compared with <140 mm Hg reduced rates of major cardiovascular events and all-cause death in patients with CKD. 44

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the only large RCT of carotid interventions that reported results according to kidney function. 45 Surgery was highly effective for patients with CKD with symptomatic high-grade stenosis, resulting in a risk reduction of 82.3% compared with 50.8% for patients without CKD. Rates of perioperative cardiac complications were higher in the CKD group, but perioperative death rates were not. We therefore agree with guidance from the Society for Vascular Surgery recommending carotid endarterectomy for symptomatic patients with CKD with high-grade stenosis. 46

There is a strong association between CKD and cerebral small vessel disease. 47 , 48 Silent cerebral infarction (SCI) is prevalent in as many as 56.5% of asymptomatic patients in cross-sectional analyses. 49 , 50 Several mechanisms for this association have been proposed, including the kidneys' and brain's shared anatomic and physiological susceptibility to hypertensive vascular injury, 51 common vascular risk factors, 48 and shared genetic susceptibility. 52 The presence of SCI in CKD appears to have implications for future stroke risk, cognition, gait, and stability. 50 , 53 The American Heart Association/American Stroke Association have issued a scientific statement with suggestions for the clinical care of patients with SCI in the general population, 54 which we have used to develop modified consensus recommendations on management of SCI in CKD (Table 1 43 , 55).

There is a high incidence of stroke in patients with CKD that is mostly attributable to traditional risk factors. Inequities in stroke care exist at every step from presentation and diagnosis to treatment and prevention. The importance of admission to an acute stroke unit with expert, multidisciplinary care cannot be overstated. Tables 2 33 , 37 , 38 , 42 , 43 , 56 and 3 highlight key conference recommendations for primary and secondary prevention of stroke in CKD, and the critical research priorities.

Preliminary evidence suggests that the prevalence of AAA is up to 30% higher among individuals with CKD than it is in the general population. 57 In a recent, large observational study, an eGFR <75 ml/min per 1.73 m^2 and a urine albumin–creatinine ratio (ACR) ≥ 10 mg/g (1 mg/mmol) were independently associated with a higher risk of incident AAA over a median follow-up of 13.9 years. 58 CKD is also associated with AAA outcomes. Several observational studies have shown that CKD (eGFR <60 ml/min per 1.73 m^2) before surgery is associated with greater post-operative eGFR decline 59 and higher odds of eGFR loss $>20\%$ during long-term follow-up. 60 , 61 Similarly, CKD has been associated with higher 30-day and long-term mortality, higher risk of cardiovascular events, and longer length of hospital stay after AAA surgery (Figure 2). 62 , 63

Duplex ultrasonography, computed tomographic angiography, and magnetic resonance angiography are commonly used for diagnosis of AAA. 64 , 65 Usually, a gray-scale ultrasound

(B-mode imaging) is sufficient for the initial evaluation and follow-up of an AAA (size measurement and aneurysm extent); additional information (e.g., presence and extent of mural thrombus) can be obtained by color Doppler ultrasound. 66 However, ultrasound alone is not sufficient for procedural planning, and computed tomographic angiography is commonly needed. 64 , 65

Routine follow-up imaging is also required to monitor for complications after endovascular aneurysm repair (EVAR), such as endoleak, device migration, or continued aneurysm expansion requiring repeat intervention, whereas open repair does not require further imaging in the absence of clinical signs or symptoms. The traditional protocol for post-EVAR imaging includes computed tomographic angiography at 1 month, 6 months, 1 year, and then annually, paired with duplex ultrasound imaging.

Open surgical repair and EVAR decrease AAA-specific mortality, but they both can have post-operative complications, including acute and chronic kidney dysfunction. Indications for elective and emergent AAA treatment do not differ based on the presence of CKD. 67 However, CKD is associated with higher risk of post-surgery acute kidney injury (AKI), long-term eGFR decline, cardiovascular events, and mortality.

EVAR has superior short-term outcomes compared with open surgery and has become the treatment of choice for many patients. 67 Given the lack of RCTs comparing EVAR with open surgery in patients with CKD, anatomic and other patient-related parameters should be considered when deciding on treatment. Depending on the anatomy, open AAA repair can be performed with suprarenal or infrarenal aortic clamping; the former is associated with higher morbidity and AKI rates 68 due to longer kidney ischemia time. Endovascular repair for a standard infrarenal AAA can be performed with infrarenal or suprarenal fixation (e.g., use of bare stents or hooks to decrease the chance of device migration and endoleak).

In older studies, the incidence of AKI after elective AAA surgery ranged widely, due to variation in criteria for defining AKI. 69 In recent years, however, studies that have used standardized criteria for AKI have reported an incidence of AKI after EVAR for infrarenal AAA of 9%–21% (Table 4). 70 – 81 Open repair is associated with a 1.6- to 2-fold higher risk of AKI but better long-term preservation of kidney function 59 , 80 , 82 than EVAR. Juxtarenal, suprarenal, or thoraco-abdominal aneurysms cannot be treated with standard “off the shelf” EVAR devices and require individualized fenestrated EVAR (fEVAR) or branched EVAR devices (Figure 3), which are associated with considerably higher rates of AKI. 80 Studies also suggest that EVAR with suprarenal fixation is associated with greater long-term eGFR decline than EVAR with infrarenal fixation or open repair. 59 , 83 , 84 AKI after AAA surgery is independently associated with faster loss of kidney function, as well as with cardiovascular events and mortality. 61 , 73 , 74 It is unclear whether AKI is mechanistically involved in acceleration of cardiovascular disease or is a marker indicating that patients have a higher occult burden of cardiovascular disease. 69 There is currently no single strategy proven to reduce the risk of AKI or long-term eGFR decline following open AAA surgery or EVAR. Prevention of adverse kidney outcomes post-AAA surgery has not been studied specifically in patients with CKD. 69 Current guidance for patients at high risk for AKI is based on extrapolation from studies of cardiac catheterization and includes perioperative i.v. administration of crystalloid solutions for those with an eGFR <40 ml/min per 1.73 m² or with a transplanted or solitary native kidney. 85

In previous reports, the prevalence of CKD was estimated as being 8.5%–10% of patients with acute aortic dissection. 86 , 87 In a recent registry report of patients with acute aortic dissection type A (i.e., involving ascending aorta; n = 14,911) and type B (without ascending aorta involvement; n = 5622) in Germany, 19.3% of patients with type A and 20.4% of patients with type B dissections had CKD. 88

In the German registry study, although CKD was not associated with mortality in patients with type A dissections, it was significantly more common among non-survivors of type B dissection than among survivors. Post-operative AKI occurred frequently, and 24.6% of patients with type A

dissection, and 8.2% of patients with type B dissection, required kidney replacement therapy. 88 A retrospective study of 478 patients with acute type B dissection undergoing intervention showed that 53% experienced AKI (27% stage 1, 15% stage 2, and 11% stage 3) that was associated with longer hospital stay and higher long-term mortality. Preoperative CKD was an independent predictor of AKI and mortality. 87 In another analysis of 1034 patients with acute aortic dissections, AKI developed in 18% and was an independent mortality predictor. 86

Currently, there are no data supporting differences in treatment of aortic dissection for patients with versus without CKD. Type A dissections are almost always treated surgically. Type B dissections are mostly treated with open surgical or endovascular repair, especially if visceral or renal arteries are compromised, leading to critical ischemia. 89 Medical treatment with aggressive BP lowering is recommended for uncomplicated type B dissections and patients with a prohibitively high surgical risk profile. Patients with advanced CKD and advanced age or extensive preexisting comorbidities may be considered high risk and may be more likely to be treated with medical management. 89

Although the association of central aortic disease with CKD or AKI has been explored in recent years, there are still limitations of existing evidence and important areas for future research, as summarized in Table 5 .

While the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) 90 and Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) 91 trials failed to demonstrate benefits of renal artery stenting with respect to the key outcomes of kidney function, cardiovascular events, and mortality, at least in CORAL a consistent modest difference in systolic BP favoring the stent group was found. However, as a result, the medical community is now reluctant to contemplate revascularization for ARVD. Optimal medical therapy is therefore paramount, as is consideration of remaining uncertainty regarding revascularization.

Patients with ARVD usually have polyvascular disease, and many are first identified during investigation of nonrenal vascular disease, including aortic, coronary, cerebral, and PAD, and heart failure. After an ARVD diagnosis, rates of vascular events are high, and annual mortality is many times higher than the risk of kidney failure requiring kidney replacement therapy. 92 As a result, high-dose statin therapy (e.g., atorvastatin 80 mg daily) is essential, and guidelines recommend antiplatelet therapy (e.g., aspirin) as part of vasculoprotective treatment.

Control of BP to optimal targets (systolic BP <120 mm Hg when tolerated, using standardized office BP measurement) is the goal, 43 but this may be achieved in only the minority of patients. Despite concerns regarding reduced glomerular filtration pressures associated with renin–angiotensin–aldosterone system (RAAS) blockers (i.e., angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) in patients with bilateral renal artery stenosis or with renal artery stenosis in a solitary functioning kidney, RAAS blockers are the most logical antihypertensive agents, given the role of RAAS upregulation in the ischemic kidney. 93 , 94 RAAS blockers should be introduced in all patients with ARVD. Although a fall in eGFR may occur, we consider the recommendation to withdraw RAAS therapy if this occurs to be too cautious. 95 However, major reductions in eGFR (e.g., > 4 ml/ min per year) 96 in patients with high-grade (>75%) renal artery stenosis should prompt consideration of renal revascularization.

The pathophysiology of the ischemic kidney beyond a high-grade renal artery stenosis has been evaluated in swine models and includes vascular rarefaction, RAAS-induced inflammation and oxidative stress, and eventual loss of functioning nephrons with fibrotic replacement. 97 , 98 The human ARVD situation is often complicated by hypercholesterolemia, diabetes, smoking, hypertension, and genetic predisposition to vascular disease, and there is a limited correlation between renal artery stenosis severity and kidney dysfunction. At some point in the natural history of ARVD, the systemic inflammatory response triggered by chronic subclinical ischemia may take precedence over reduced blood flow as the driver of reduced kidney function. Identifying kidneys with renal artery stenosis that have yet to reach the “point of no return” (irreparable damage) is of critical importance. It is accepted that revascularization does not improve kidney function in the

setting of atrophic kidneys or those with thin cortices. Proteinuria and a high Doppler ultrasound resistive index are additional markers of poor outcome because they are indicative of severely damaged renal parenchyma (Table 6). Additional markers of viability of kidney parenchyma will be needed to determine whether to intervene with future novel therapies (e.g., vascular endothelial growth factor [VEGF], endothelin antagonists, or stem cells) or with selected revascularization in appropriate patients.

Many patients enrolled in the ASTRAL 90 and CORAL 91 trials had lower-risk phenotypes, and some had physiologically insignificant renal artery stenosis. Patients with higher-risk features were often managed with revascularization outside of the RCT setting. Additionally, there are numerous reports of patients who appear to have had major clinical benefits from stenting. Key patient subgroups who were not well represented in these RCTs and for whom a positive response to revascularization may be more likely include those with high-grade bilateral renal artery stenosis or renal artery stenosis affecting a solitary kidney who present with AKI, marked reductions in eGFR with RAAS blockers, acutely decompensated heart failure, or the combination of progressively deteriorating CKD and uncontrolled arterial hypertension (Table 7). 96 Percutaneous renal artery revascularization is the intervention of choice in the majority of patients selected for revascularization; open surgical revascularization should be reserved for patients with congenital disease, or with complex anatomy (e.g., multiple stenoses) and those refractory to or with multiple restenosis events after endovascular intervention.

There is a clear link between ARVD and various heart failure phenotypes. 99 Up to 30% of patients with chronic heart failure may have renal artery stenosis, 99 and there are multiple case reports and observational case series describing the benefits of renal revascularization in patients suffering acute decompensations. The term “flash pulmonary edema” has become widespread to describe sudden onset (within minutes) of pulmonary edema in patients with no previous history of myocardial or coronary artery disease, and this presentation is highly suggestive of a renal artery stenosis etiology. Flash pulmonary edema is an accepted indication for renal revascularization in patients with high-grade renal artery stenosis. 100 Revascularization may also be indicated for decompensated chronic heart failure, 101 although clinical trial evidence for this approach is still lacking.

Recognizing the heterogeneous nature of ARVD, clinicians evaluating patients for possible revascularization should consider renal artery stenosis severity, the viability of the kidney beyond the renal artery stenosis, and the presenting clinical syndrome. Key aspects of the clinical presentation that might signal a potential benefit of revascularization include AKI, RAAS-induced functional decline, acute heart failure, and progressive CKD with severe arterial hypertension. Areas in need of further research are enumerated in Table 8 .

The prevalence of PAD is higher among persons with CKD than among those without, varying from 12% to 38% among people with CKD and those receiving dialysis. 102 , 103 These variations can be attributed in part to variability in the methods used to ascertain PAD but also partially to differences in age, hypertension control, and diabetes of the patients in the distinct studies. Several studies have shown that the risk for severe PAD, including amputation, is markedly increased even in CKD G2 and G3. In a large population study, Bourrier et al . 103 found high event rates in this population compared with those without CKD. In another large cohort from Germany, the amputation-free survival after 1 year was only about 80% among individuals with CKD G2-G3 and PAD, 104 which may be due in part to underdiagnosis and undertreatment of these patients.

The Rose, 105 Edinburgh, 106 and San Diego 107 claudication questionnaires are designed to detect symptomatic PAD but have not been validated in persons with CKD. The ankle-brachial index is a first-line diagnostic tool for PAD but has limitations among patients with CKD. 100 , 108 , 109 Notably, the risk of amputation is also exceedingly high among patients receiving dialysis. 104 , 110

Data regarding PAD in patients who have received a kidney transplant are sparse but suggest that transplant recipients have lower risk of PAD compared with those receiving maintenance dialysis. 111 The presence of PAD is associated with poor allograft and overall mortality in transplant recipients. 112

Traditional risk factors such as diabetes and hypertension play an important role in the pathophysiology of PAD in CKD, and a history thereof may be a more important PAD risk determinant than age alone. However, vascular calcification, inflammation, oxidative stress, uremic toxins, and microvascular disease may also contribute to the elevated risk of PAD among patients with CKD. 113

Vascular calcification can manifest as intima arterial calcification or medial arterial calcification (MAC). 114 Atherosclerosis is the main cause of intima arterial calcification, whereas aging and cellular senescence play pivotal roles in MAC. CKD accelerates the aging process and increases the risk of MAC. Although atherosclerosis and intima arterial calcification are known to be central to the development and progression of PAD, the role of MAC is less clear. Nonetheless, it is clear that MAC can lead to false-normal or increased ankle-brachial index, even in the setting of severe PAD, which can pose diagnostic challenges.

Inflammation and oxidative stress contribute to the development of atherosclerotic disease in CKD. Some studies have shown that anti-inflammatory agents and antioxidants may reduce the risk of cardiovascular outcomes. 115 Elevated levels of several uremic toxins, such as p-cresol, p-cresyl sulfate, and indoxyl sulfate, have been associated with increased risk of cardiovascular outcomes. 116 – 118 To date, there are no established therapies to reduce these uremic toxins, except kidney replacement therapy. In this regard, gut microbiota may be an interesting potential therapeutic target, 119 as they produce these uremic toxins and could be manipulated through dietary modifications, medication, or fecal transplantation.

Although PAD has been considered a large artery disease, recent studies have indicated that microvascular disease contributes to the progression of PAD and associated serious complications such as chronic limb-threatening ischemia and lower-extremity amputation. 120 – 122 These observations raise further concern about using the ankle-brachial index as a diagnostic test for PAD, because it does not measure microvascular disease.

Diagnostic testing for PAD is indicated in symptomatic patients but may also be appropriate in asymptomatic patients to ascertain the need to start a secondary preventive therapy, with statins or platelet inhibition, for example. Symptoms and signs of PAD are often not solicited by healthcare providers or volunteered by patients. Given that PAD is not often spontaneously discussed and has a high prevalence in the CKD population, a reasonable approach is to implement a systematic screening strategy using questionnaires 107 to identify intermittent claudication in patients with CKD. Also, it is reasonable to perform routine foot examinations in patients on dialysis, given their high risk of critical limb ischemia and the feasibility of visual examination during hemodialysis.

The ankle-brachial index is the first-line diagnostic test for PAD. However, because MAC is common among patients with CKD and can lead to false negative results of ankle-brachial index screening, we advocate for simultaneous measurement of toe-brachial index in CKD populations. 123 Regarding imaging modalities, duplex ultrasound is a gold standard diagnostic modality for PAD. Computed tomographic or magnetic resonance angiography may be helpful in planning leg revascularization procedures for selected patients.

Lifestyle modifications, including smoking cessation and supervised exercise programs, have proven benefits beyond the management of PAD 124 , 125 and should be offered to all affected patients, including those with CKD. The benefit of antiplatelet agents in the setting of symptomatic PAD is unequivocal. 126 In the COMPASS trial, 39 the use of rivaroxaban plus aspirin was associated with a lower risk of major adverse cardiovascular events (MACE), compared with aspirin

alone, among 6276 participants with a GFR <60 ml/min per 1.73 m². Importantly, no increased risk of bleeding was noted among those with CKD.

Statin therapy decreases MACE among patients with CKD not treated with dialysis, including those with PAD. 127 Further, the benefit of statins in improving amputation-free survival among persons with PAD has been documented in a large observational study of over 150,000 patients, and most patients with CKD over the age of 50 years would meet recommended criteria for statin therapy based on future CVD risk. 128 Proprotein convertase subtilisin/kexin type 9 inhibitors further reduce the risk of MACE 129 and major adverse limb events among individuals with established atherosclerotic disease who are already receiving treatment with a statin. 130 Although likely to be safe and effective, use of proprotein convertase subtilisin/kexin type 9 inhibitors among patients with CKD needs further study. 131

Patients with CKD and PAD are less frequently considered for limb revascularization 132 and are at high risk of limb amputation. 133 Although revascularization in persons with CKD is associated with increased risk of post-procedure complications, 134 , 135 data suggest that it results in improved amputation-free survival and limb salvage at all severity stages of CKD. 136

A major obstacle in the development of appropriate treatment guidelines in persons with CKD and PAD is their exclusion from clinical trials. Nearly 45% of trials evaluating therapies for PAD have excluded persons with CKD. 137 Most trials do not report subgroup analysis based on CKD status, 137 and treatment strategies therefore need to be extrapolated from findings in the general population. As a result, a research agenda for the study of PAD in CKD is proposed in Table 9 . 138

CKD patients can be affected by atherosclerotic disease with various manifestations; therefore, the knowledge gaps and research needs outlined here, if addressed, could potentially improve patient care and outcomes.

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See Appendix for list of Conference Participants.

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(a) Cumulative freedom for the combined cardiovascular endpoint consisting of death, nonfatal myocardial infarction, stroke, and peripheral vascular complications, logrank $P < 0.001$. (b) Cumulative survival: logrank $P < 0.001$ ($n = 383$; group 1: eGFR >90 ml/min per 1.73 m^2 ; group 2: eGFR $60\text{--}89$ ml/min per 1.73 m^2 ; group 3: eGFR $30\text{--}59$ ml/min per 1.73 m^2 ; group 4: eGFR <30 ml/min per 1.73 m^2). Reprinted from the *Journal of Vascular Surgery*, Volume 58, Saratzis A, Sarafidis P, Melas N, Saratzis N, Kitis G. Impaired renal function is associated with mortality and morbidity after endovascular abdominal aortic aneurysm repair, Pages 879–885, Copyright © 2013, with permission from the Society of Vascular Surgery. 63

Types of endovascular aneurysm repair (EVAR), depending on the anatomy of the abdominal aneurysm (infrarenal aneurysms include a proximal aortic neck that provides an adequate landing zone for EVAR; juxtarenal aneurysms are adjacent to or include the lower margin of the renal arteries; suprarenal and thoraco-abdominal aneurysms also extend above the orifice of renal arteries).

Recommendations for the management of subclinical cerebrovascular disease in CKD

AF, atrial fibrillation; BP, blood pressure; CKD, chronic kidney disease; CMB, cerebral microbleed; CT, computed tomography; ICH, intracerebral hemorrhage; KDIGO, Kidney Disease: Improving Global Outcomes; MRI, magnetic resonance imaging; SCl, silent cerebral infarct.

Recommendations for the primary and secondary prevention of stroke in CKD

ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ASA, American Stroke Association; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2.

Research recommendations for cerebrovascular disease and CKD

Incidence of AKI in elective infrarenal EVAR using standardized AKI reporting criteria

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; EVAR, endovascular aneurysm repair; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not available; RIFLE, risk, injury, failure,

loss, end-stage renal disease.

Gaps in knowledge and research recommendations for central aortic disease and CKD

AAA, abdominal aortic aneurysm; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EVAR, endovascular aneurysm repair.

Assessment of kidney parenchyma viability in a kidney with renal artery stenosis

ACR, albumin-creatinine ratio; BMI, body mass index; PCR, protein-creatinine ratio.

Possibly consider kidney length-to-BMI ratio.

Proteinuria may be arising from an atrophic kidney.

Definite and possible indications for renal revascularization therapy in atherosclerotic high-grade renal artery stenosis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes.

Gaps in knowledge and research recommendations for renovascular disease and CKD

ARVD, atherosclerotic renovascular disease; CKD, chronic kidney disease; RCT, randomized controlled trial; VEGF, vascular endothelial growth factor.

Gaps in knowledge and research recommendations for PAD and CKD

CKD, chronic kidney disease; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9.