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REVIEW

The Impact of Chronic Kidney Disease on Peripheral Artery Disease and Peripheral Revascularization

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Abstract: Chronic kidney disease (CKD) is a clinical condition characterized by high morbidity and mortality. Globally, CKD is also increasing in prevalence and incidence. The two principal kidney measures namely estimated glomerular filtration rate (eGFR) and albuminuria have been found to be predictors of renal and cardiovascular (CV) endpoints including peripheral artery disease (PAD). The prevalence of PAD was increased in CKD patients and, particularly, in patients with more severe CKD stages. Despite the fact that revascularization strategies are suitable in CKD patients in similar fashion to non-CKD patients, few CKD patients underwent these procedures. In fact, if it is true that revascularization improves prognosis in PAD patients irrespective of baseline eGFR, it was also demonstrated that CKD patients, who underwent revascularization, were at higher risk for amputations, mortality, re-intervention and perioperative complications. With the present review article, we have examined the association between CKD, PAD and peripheral revascularization highlighting data about epidemiology, pathophysiologic mechanisms, and results from previous observational and intervention studies. We have also examined the future perspectives and challenges of research around the association between CKD and PAD.

Keywords: chronic kidney disease, CKD, peripheral artery disease, PAD, ESKD, amputations, albuminuria

Introduction

Chronic kidney disease (CKD) is a chronic condition that can be diagnosed through the presence of a reduction in estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m^2 and/or an increase in urine albumin excretion, namely albuminuria >30 mg/g or 30 mg/24h and/or by the presence of abnormalities in kidney structures persisting for at least 3 months.[1,2] The eGFR is considered the principal measure of kidney function, whereas albuminuria is a well-assessed marker of kidney damage, being expression of alterations that may occur in any kidney structure, such as the glomerulus or the renal tubule.[3] The presence of CKD exposes patients to an enhanced risk of several "hard" outcomes, so defined because they are associated with a major change in the patients' quality of life and in their long-term prognosis. CKD patients have, indeed, an increased risk for CKD progression to the End-Stage-Kidney-Disease (ESKD), which is the most severe phase of CKD requiring the recurrence to substitutive treatments, such as dialysis or kidney transplantation, and have an increased risk for cardiovascular (CV) events too.[4] Several studies have explored the risk factors for CKD progression/ESKD and reporting

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that, among others, albuminuria, eGFR, serum phosphate levels, presence of diabetes, hemoglobin levels, age and male gender are strong predictors of the CKD outcomes.[5] In the past few decades, preclinical and clinical research had also focused on assessing the risk factors and determinants for CV risk in CKD patients.[6] Overall, the previous studies have prompted the Scientific Community to implement the development and validation of reliable biomarkers of CV risk in patients with CKD, testifying that the risk stratification of CKD patients in terms of CV prognosis has not completely achieved yet.[7–10] The major problem is represented by the fact that CV endpoint can encompass a wide spectrum of events, including fatal and non-fatal myocardial infarction (MI), heart failure (HF), stroke, arrhythmias, and peripheral artery disease (PAD). The pathogenesis, underlying these endpoints, varies between events, CKD stage and even between patients. Hence, prediction of CV risk in CKD still remains a great challenge for research. Furthermore, CKD affects the long-term prognosis of patients with coronary artery disease undergoing revascularization, which represents a non-negligible percentage of patients with CV damage.[11] The aim of the present review article is to examine, among the listed CV events, the onset of Peripheral Artery Disease, given the importance, which is gaining, due to the novel acquisitions on both the pathogenetic pathways and therapeutic strategies.

Global Dimension and Cardiovascular Risk in Patients with Chronic Kidney Disease

The prevalence and incidence of CKD are both displaying an increasing trend over time. According to the Global Burden of Disease, the global prevalence of CKD increased by 86.95% from 1990 to 2016 and, similarly, the incidence of CKD rose by 88.76% in the same time frame.[12] This increasing trend was found in all categories of socio-demographic index (SDI), albeit being higher in the low-SDI countries. National Registries reported a variable prevalence of CKD. In the United States (US) population of the National Health and Nutrition Examination Survey (NHANES), prevalence of CKD was of 13.1% overall and a prevalence ≥10% was also reported in Canada, Australia, China and the Netherlands.[13] When taken together, these data show a non-trivial prevalence of CKD in the general population. Moreover, the severity of the problem is even enhanced by the prevalence and incidence of CV disease in CKD patients. In several insurance-based US population, mainly including elderly subjects suffering from CKD and diabetes, the incidence of atherosclerotic events and death overcame the one of ESKD.[14,15] Among the population of CKD patients referred to Nephrologist, a tertiary care setting, the prevalence of history of CV disease (defined as the positive anamnesis for an episode of MI, stroke, HF, PAD) rose from 30% to 50% in the cohort of MASTERPLAN, Chronic Renal Impairment in Birmingham (CRIB), African Americans Study (AASK) and Italian CKD-Multicohort.[16–19]In the CKD-Multicohort, which enrolled 3.957 CKD patients from multiple diagnoses referred to 128 Italian Renal Clinics, 34% of them had CVD with the following distribution: 15.0% MI, 6.0% stroke, 15.1% PAD, 6.5% HF and 10.0% arrhythmias.[19] On the Global Scale, an analysis of the Global Burden of Disease targeted CKD cohorts found that more than half of the total deaths' amount in these subjects were due to CV fatal events.[20]

In a meta-analysis of more than 600.000 subjects of general population and high-risk populations derived from the CKD-Prognosis Consortium (in this large population, high-risk subjects were those with diabetes or CKD), Matsushita and colleagues found that the two principal parameters used to diagnose CKD, ie, albuminuria and eGFR were significantly associated with the development of CV events (defined as CV mortality, coronary heart disease, stroke and HF).[6] Intriguingly, the prediction ability of those parameters was equal or stronger than that provided by traditional CV risk factors, such as smoking habit or blood pressure levels or LDL cholesterol levels. Several hypotheses have been claimed to explain the cause–effect relationship between kidney measures and CV risk. Albuminuria is considered a biomarker of endothelial dysfunction.[6,21] Across the endothelium, albuminuria causes both structural (mainly to the endothelial glycocalyx) and functional alterations, such as the increase in vascular pressure. Across the kidney, albuminuria exerts alterations of the glomerulus and also has a direct toxic effect on renal tubules, amplifying pro-inflammatory and pro-fibrotic pathways that lead to kidney impairment over time. Moreover, as a vicious circle, the development of CKD per se contributes to increase CV risk via the presence of risk factors, such as inflammatory stimuli, volume expansion and uremic milieu.[22] Thus, it has been hypothesized that those pathophysiological mechanisms are shared between CKD and CV disease.

Peripheral Artery Disease in Chronic Kidney Disease

With respect to PAD, several studies have demonstrated that patients with CKD have an increased risk of

developing PAD.[23,24] Peripheral artery disease is defined as the atherosclerotic lesions of peripheral arteries and differs from the acronymous PVD (peripheral vascular disease) which refers to the atherosclerotic lesions occurring in different vascular territories.[25] Data from the US NHANES have reported that prevalence of PAD in patients with diabetes was 3-fold higher than those without diabetes, whereas the risk of PAD increased by 6.5 times in patients with eGFR <60 as compared with eGFR ≥60 mL/min/1.73m^2.[26] The risk of PAD increases for both patients with severe CKD and for those with mild-moderate CKD. Peripheral artery disease is defined as a chronic pathologic process due to atherosclerosis, which involves mainly the arteries providing flow to lower extremities.[27] Risk of PAD in patients with CKD was confirmed even after adjusting the association for potential cofounders.[28,29] In the Atherosclerosis Risk in Communities (ARIC) cohort, enrolling patients who were likely to develop CKD or with CKD, incidence of PAD, defined as ankle-brachial index <0.9, new intermittent claudication, or PAD-related hospitalizations, was higher in CKD patients after accounting for age, gender, race and presence of CV risk factors.[29] Likewise, to other CV clinical events, the onset of PAD is strongly associated with the individual levels of eGFR and albuminuria. In a large meta-analysis of more than 800.000 subjects included in the CKD-Prognosis Consortium, risk for developing PAD increased, using the threshold of 95 mL/min/1.73m2, by 22% for eGFR of 45 mL/min and by 2-fold for eGFR of 15 mL/min.[30] The risk trend showed a similar magnitude when the effect of increasing albuminuria was tested. In fact, as compared with an albuminuria level of 5 mg/g, risk raised by 50% for albuminuria of 30 mg/g and by about 2-fold for albuminuria of 300 mg/g. All these data lead to think that there is an exponential association between decreasing eGFR/increasing albuminuria and PAD. Other traditional risk factors play an additional role in determining PAD in CKD patients. Among them, smoking habit and arterial hypertension have shown to have a wide and consistent relationship with vascular diseases and PAD.[31,32] Furthermore, the incidence of PAD in CKD patients was associated with age, with a 28% risk increase by 10 years of age.[33] Among the traditional correlates of PAD, male gender remains a significant predictor of PAD in patient with CKD.[34] Being male conferred a 40% increased probability of developing PAD in this population. The presence of PAD affects individual prognosis and quality of life over time. In an observational study enrolling more than 400.000 patients referred at the Manitoba Centre for Health Policy in Manitoba (Canada), the presence of PAD was more common in patients with CKD than in those without it, and the combination of PAD and CKD characterized the subgroup of patients at highest risk for lower-limb complications, CV events and mortality.[35] Even more importantly, the presence of PAD alone was associated to a poorer prognosis, as compared to the presence of other CV diseases (eg, stroke, MI) without PAD.[36] All these evidences can demonstrate the importance of an early detection and treatment of PAD in CKD patients. A further effort should be aimed at improving awareness of PAD among both clinicians and patients.[37]

Revascularization for Peripheral Artery Disease: State of Art

PAD is traditionally classified with two principal systems: the Rutherford classification, which is based on 7 risk categories (from 0 to 6), and the Fontaine classification, this latter being graded from Stage I to IV (Table 1).[38,39] Both classifications include stages of increasing clinical and prognostic PAD severity. Another classification that is rapidly supplanting the Rutherford and Fontaine scores particularly in CKD patients undergoing renal replacement therapy.[40] In fact, the WIfI classification provides more insights into the outcomes associated to each operative treatment.[41] The WIfI classification attributes a score to wound (W), ischemia (I), foot infection (f) and a combination of these scores allows to reach a unique categorization into meaningful clinical stages (depicted in Table 1). The initial therapeutic strategy of PAD consists in reinforcing preventive measures against adverse CV events.[42] In particular, smoking cessation and exercise training have shown to have a good influence in stabilizing or even relenting the progression of claudication symptoms.[43] Other measures are the improvement of antihypertensive, lipid-lowering and antiplatelet treatments as well as the reduction in patient's body weight. Several specific medications are indicated in CKD patients at increased risk for PAD. Antiplatelet treatments such as aspirin or clopidogrel have shown to reduce cardiovascular events in CKD and are thus recommended in absence of contraindications.[44,45] Lipid lowering agents, namely statins and/or ezetimibe have shown to reduce cardiovascular risk and PAD risk in CKD patients, irrespective of the basal level of LDL-cholesterol and should be started in these high-risk

Table 1 Rutherford, Fontaine and WIfI Classifications of PAD

Grade	Category	Rutherford	Grade	Fontaine	WIfI		
0	0	Asymptomatic. Absence of hemodynamically significant occlusive disease	I	Asymptomatic, incomplete blood vessel obstruction	Risk of amputation	Proposed clinical stages	WIfI spectrum score
	I	Mild claudication	II	Mild claudication, limb pain	Very low	Stage 1	W0 I0 fI0,1 W0 I1 fI0 W1 I0 fI0,1 W1 I1 fI 0
I	2	Moderate claudication	IIA	Claudication > 200 meters	Low	Stage 2	W0 I0 fI2 W0 I1 fI1 W0 I2 fI0,1 Wo I3 fI0 W1 I0 fI2 W1 I1 fI1 W112fi0 W2 I0 fI0/1
	3	Severe claudication	IIB	Claudication < 200 meters	Moderate	Stage 3	W0 I0 fI3 W0 I2 fI1,2 W0 I3 fI1,2 W1 I0 fI3 W1 I1 fI2 W1 I2 fI1 W1 I3 fI0,1 W2 I0 fI2 W2 I 1 fI0,1 W2 I2 fi0 W3 I0 fi0,1
II	4	Ischemic rest pain	III	Rest pain, particularly in the feet	High	Stage 4	W0 I1,2,3 fI3 W1 I1 fI3 W1 I2,3 fI2,3 W2 I0 fi3 W2 I1 fI2,3 W2 I2 fi1,2,3 W2 I3 fI0,1,2,3 W3 I0 fI2,3 W3 I1,2,3 fI0,1,2,3
III	5	Minor tissue loss. Nonhealing ulcer, focal gangrene with diffuse pedal ischemia	IV	Limb necrosis and/or gangrene			
	6	Major tissue loss namely extending above trans-metatarsal level, functional foot no longer salvageable					

patients.[46,47] If the medical therapies and physical exercise can begin in the first stages of PAD, they warrant a durable stability of PAD.[48] The intermediate step, recommended for patients who have not experienced any improvement in their clinical symptoms, is the treatment with cilostazol. Cilostazol is a phosphodiesterase inhibitor that acts by suppressing platelet aggregation. It also has a direct arterial vasodilator.[49] In previous trials, cilostazol showed to be able to significantly increase maximal walking distances and pain-free walking distances in patients with moderate-to-severe claudication.[50] Nevertheless, in several cases, conservative treatment does not represent the best choice. In fact, patients, who do not respond adequately to medical treatment/exercise training as well as patients with claudication symptoms impact the quality of life, are eligible for revascularization (Figure 1). Revascularization for PAD should be executed via surgical or percutaneous techniques or via combination of both of them. Surgical revascularization encompasses bypass grafts and endarterectomy, whereas percutaneous treatment should be executed via angioplasty, atherectomy and stenting in the most cases. The choice of the type of intervention is influenced by multiple factors. To facilitate clinical decision making, the Inter-Society Consensus for the Management of Peripheral Artery Diseases (TASC II) has provided a classification of PAD based on the differential outcomes after percutaneous or surgical treatment.[24] The factors considered for risk stratification have mainly been the location and extent of obstructive lesion and the patient's baseline risk profile. Overall, TASC II classification comprises four types of lesions (namely A, B, C, D) foriliac, femoral, and popliteal lesions. Type A and B lesions have an excellent prognosis after endovascular treatment. Conversely, type C lesions have a more favorable outcome after surgical open intervention and thus surgery should be preferred unless the baseline risk contraindicates this procedure. Type

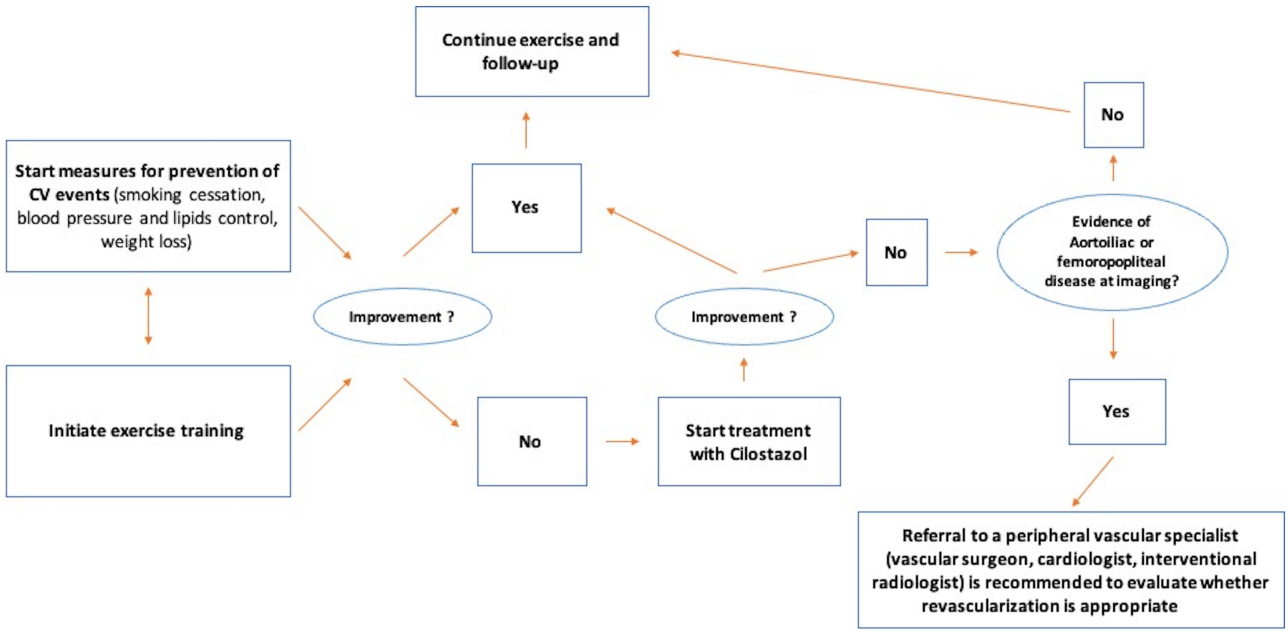

Figure 1 Algorithm for the management of PAD in CKD patients.

D lesions are not well treated by endovascular procedures and are therefore must be referred for surgical repair, even if, due to the improvement of techniques and materials, percutaneous approach to complex lesions has shown good mid- and long-term results.[51] The location of occlusive lesions is another important element to consider during treatment selection, since endovascular treatment is associated with better outcomes when the occlusion is located in aorto-iliac rather than infra-inguinal portion.[52] With respect to baseline individual risk, several risk factors should be carefully evaluated, including presence of coronary heart disease, diabetes, kidney function impairment and evaluation of nutritional status. Several risk factors predict poor prognosis of PAD in patients with CKD. Among them, the African American race has been found associated with an increased risk for failure after lower limb revascularization.[53] Several risk prediction models, computing the in-hospital and long-term individual risk, have been also developed.[54,55]

Why Does CKD Affect the Management and Prognosis of PAD?

One of the crucial points of the link between CKD and PAD is that the frequency of PAD increases as the severity of CKD increases.[56] The prevalence of PAD exceeded 30% in patients with stage 5CKD in several studies.[57,58] Such a trend has a reflection from a "public health" perspective, since patients with CKD and PAD showed an increase in both length of in-hospital stay and health care costs. CKD patients with PAD are also at increased risk for in-hospital death, independently on the severity of PAD.[59] Furthermore, it has been demonstrated that CKD is associated with the onset of a more severe stage of PAD, such as chronic limb ischemia (CLI).[59] Hence, the assessment of an early diagnosis of claudication as well as the prevention and treatment of CLI represents very important steps in CKD patients. Following the current recommendations, indications for revascularization in CKD patients with PAD did not differ from those applied to patients without CKD.[60] Such an attitude is compatible with the result of a large study enrolling 351 patients who underwent either surgical or percutaneous revascularization for CLI.[61] This analysis has been assessed on patients with different levels of renal function impairment and showed that revascularization conferred benefits in terms of amputation-free survival and limb salvage in both CKD and non-CKD patients. Many other studies, specifically carried out in CKD populations, reported that endovascular and surgical revascularization are both effective in reducing patients' mortality and amputation rate, with the surgical strategy being more advantageous in the long term (beyond 2 years follow-up).[62,63] What can be considered as a "clinical paradox" is that, despite the high prevalence of PAD in CKD patients, these high-risk patients undergo fewer revascularization procedures as compared to patients

without CKD. In a report of the Veterans Affairs National Patient Care Database, patients with eGFR between 30 and 59 mL/min/1.73m2 had a lower probability (16%) to undergo revascularization, being this probability reduced of about 50% in patients with an eGFR of 15–29 mL/min/1.73m2 and even of about 70% in CKD patients in ESKD.[64] Similar findings were extrapolated from a European database, thus testifying that this trend is generalizable, irrespective of the geographic area.[65] This low tendency in referring CKD patients to intensive care treatments for PAD can be interpreted considering other studies suggesting high risk for complications and worse outcomes after revascularization.[42] In patients with ESKD the risk for limb loss after surgical revascularization was about 5-fold higher when compared to those with an earlier stage of CKD, despite a similar revascularization rate.[66] Similarly, an augmented risk of amputation and reintervention has been reported in ESKD patients undergoing percutaneous revascularization.[67] Another factor that may influence treatment decisions is the patients with both PAD and CKD, who undergo revascularization, are also subject to develop Contrast-induced acute kidney injury (C-AKI). The risk of C-AKI is mainly caused by the fact that patients are selected for revascularization practice angiography before the procedure. Furthermore, in the vast majority of cases, this diagnostic exam is not executed together with measures that prevent C-AKI, such as the use of low contrast volume, the introduction of statins or n-acetylcysteine and the meticulous control of intravascular volume in order to avoid.[68–70] The presence of C-AKI and CKD, and particularly the concomitant presence of both conditions, was associated with about a 3-fold higher risk of death in CKD patients after revascularization.[60] With respect to perioperative complications, CKD patients were found at increased risk of respiratory insufficiency, intubation, bleeding and infectious.[60,71]

Potential Links Between CKD and PAD

CKD is a chronic condition, which can be caused by many disparate etiologies.[2] Moreover, albeit several risk factors are able to predict the future outcomes in patients with different degrees of renal impairment, the prognostic weight of each factor varies between CKD stages and even between patients with similar severity of kidney function impairment.[72] This means that the CKD status perfectly fits the concept of "heterogeneity" with regard to both etiology and prognosis. Notwithstanding, CKD shows, regardless of the different etiologies, common pathophysiologic patterns. First of all, CKD is associated with pro-inflammatory and pro-fibrotic stimuli.[73] Tissue expression as well as circulating levels of inflammatory mediators, such as interleukins (IL-1, IL-6), tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (MCP-1), C-reactive protein and kidney injury molecule-1 (KIM-1), are altered in patients with CKD.[74] Among inflammatory markers, some of them, such as MCP-1 and KIM-1, have shown to improve prediction of CKD progression beyond considering traditional risk factors.[75] The inflammatory status in CKD worsens both the vascular calcification and endothelial dysfunction.[76] The vascular-endothelial dysfunction in CKD has been widely investigated and described in previous studies.[77,78] It consists of a mosaic of alterations, including increased intima-media thickness and vascular stiffness that is determined by inflammation, oxidative stress and other risk factors typical of CKD (eg, hyperphosphatemia).[78] Imbalances of extracellular matrix (ECM) also contribute to the inflammatory status and to the development of PAD in CKD patients. Experimental and human studies testified that both blood and urine levels of matrix metalloproteinases (MMPs) are enormously unregulated in CKD patients.[79] Matrix metalloproteinase-3 (MMP-3), MMP-7 and MMP-9 have a direct pro-inflammatory effect by increasing mononuclear cell activation and proliferation.[80,81] Furthermore, MMP-3 promotes epithelial-to-mesenchymal transition, the process through which epithelial cells acquire the fibroblastic phenotype that anticipates tissue fibrosis.[82] The imbalance in MMPs has also been associated with the development of PAD. A number of MMPs (MMP-1, -2, -3, -9, -14 and the tissue inhibitor of metalloproteinase-1 also called TIMP-1) have shown to accelerate the atherosclerotic process.[83] In the context of atherosclerotic plaque, MMPs regulate the formation of the fibrous cap and increase the amount of inflammation too.[84] Increased plasma levels of MMP-1 and −8 have been associated to an increased risk for amputation in patients undergoing surgical revascularization for PAD.[85] Additionally, CKD is characterized by the reduced excretion of substrates that can damage various cells and systems and that are thus defined "uremic toxins". The indolic uremic toxins indoxyl sulfate and indoxyl acetate have a prothrombotic effect that is determined by their effect on both extrinsic coagulation pathway and on platelet activation.[85,86] β2-microglobulin, a protein expressed on the surface of immune cells, has shown to improve the prediction of CV events in CKD patients even after

accounting for their eGFR levels and, in particular, it has been linked to the onset of PAD in these patients.[87–90] Thus, it can be hypothesized that the link between CKD and PAD is a mix of multiple factors, including the inflammation, oxidative stress, imbalance in ECM composition that are associated with PAD and amplified by the concomitant presence of CKD. This can partially explain the results of an autoptic study demonstrating that the severity of atherosclerotic disease increases going from mild to severe CKD stages independently of other CV comorbidities and even in absence of diabetes.[91] Nevertheless, future mechanistic studies are needed to shed light on the exact molecular mechanisms leading from CKD to PAD. A summary of the main key-messages of the previous sections of the manuscript is reported in Table 2.

Peripheral Artery Disease in Chronic Kidney Disease: Future Challenges

The management of CKD patients has always been focused on slowing CKD progression and reducing CV and all-cause mortality risk too. To this aim, the past two decades have been signed by the implementation of clinical trials testing the efficacy of novel drugs on cardiovascular and renal protection in CKD patients.[72] This was a really great effort in clinical research. A first crucial step was the demonstration that drugs inhibiting the Renin-Angiotensin-Aldosterone-System (RAASi) are effective in reducing both the eGFR decline over time and CV risk.[92,93] Despite the implementation of these agents in clinical practice, nowadays the residual CV risk (namely the risk that remains after the use of maximum tolerated dose of RAASi) is still very high. Reasons for this phenomenon has to be found, at least in part, in the great individual variability in response to nephroprotective treatments. A further step forward has been done in 2020 with the publication of large intervention studies, which demonstrated the strong efficacy on cardio-renal protection of other pharmacologic agents, ie the sodium-glucose -cotransporter 2 inhibitors (SGLT2is), the selective antagonists of endothelin receptors type A (ERA) and the novel nonsteroidal mineral receptor antagonists (MRA).[94–98] These novel drug classes provided encouraging findings, especially in patients with both CKD and type 2 diabetes, since they warrant a significant CV protection when added to the standard-of-care (RAASi). Moreover, the development of individual risk prediction models in CKD patients have contributed to detect with more accuracy CKD patients at high-risk for worse CV outcomes that need a stricter monitoring and intensive care. However, in the majority of cases these scores have been built considering CV outcome as a composite of multiple endpoints including MI, HF or PAD. What we have learned from the current Literature is

Table 2 Summary of the Principal Aspects of the Association Between CKD and PAD

	Key-Messages
Epidemiology	• Chronic kidney disease (CKD) is associated with an increased risk for cardiovascular (CV) diseases, including Peripheral Artery Disease (PAD). • Risk of PAD is about 6.5 fold higher in patients with CKD (eGFR<60 mL/min/1.73m^2) as compared with those without CKD. • There is an association between CKD and PAD even after adjustment for the traditional CV risk factors.
Risk factors	• Kidney measures, albuminuria and eGFR levels are significant predictors of the risk of PAD in CKD patients. • Traditional CV risk factors, such as smoking habit and increased blood pressure, play a significant role beyond the kidney measures in determining PAD in CKD patients. • Risk of PAD is increased in more severe stage of CKD (ie Stage 4 and 5).
Pathogenesis	• CKD is a condition characterized by an inflammatory status which exacerbates vascular damage. • Alterations of extracellular matrix, which are present in CKD, contribute to impair inflammation and accelerate atherosclerotic process. • Uremic toxins play a direct role in determining vascular damage and PAD.
Management and Prognosis	• Revascularization is indicated in patients with CKD and severe PAD with symptomatic and limiting claudication • Both percutaneous and surgical revascularizations improve the prognosis of CKD patients in term of amputation rate and their mortality. • CKD patients show higher risk for perioperative complications after revascularization as compared with non-CKD patients.

that each of this CV outcome has a proper risk profile. This is particularly true when considering that CKD is per se an heterogeneous condition. Hence, CV risk prediction remains suboptimal. In the specific context of PAD, improving risk stratification of patients, that is translated in clinical practice into finding CKD patients at high risk of developing PAD, is an urgent need, indeed. Recently, the International Society of Nephrology (I.S.N.) has started a program entitled "closing the gaps" with the aim of encouraging the implementation of novel biomarkers of CV risk in CKD.[10] The I.S.N. outlined two important points, namely the need to find biomarkers for specific CV endpoints and to build large international databases that allow to generalize the results to different races and patients. The final result may be the redefinition of guidelines for PAD management in CKD. In fact, if it is clear that revascularization improved outcomes irrespectively of CKD severity, it has been also demonstrated that CKD patients are more likely to develop both short-term and long-term complications after revascularization. Hence, the careful detection of CKD patients at increased risk for PAD would be extremely important for their management and prognosis. Similarly, the current management of PAD cannot differentiate the indications for percutaneous versus surgical revascularization among CKD and non-CKD patients. However, PAD in CKD is characterized by its more distal localization and is associated to a greater degree of vascular calcification and stiffness. For this reason, research should also focus in the future in realizing devices specific for lesions present in CKD patients. Furthermore, it should be emphasized that the observed limited benefit for CKD patients differs from that observed in patients without CKD. Hence, the risk benefit ratio for a given procedure may be different although this is not yet well demonstrated. The decision to proceed with limb-preservation strategies therefore hinges upon the ability to properly risk-stratify patients. This risk stratification may in fact be different for patients suffering from CKD and chronic limb threatening ischemia. Thus, clinical trials comparing the outcome of these different intervention strategies, specifically conducted in CKD setting, are eagerly expected.[99] Further experimental studies should also flank the clinical research by revealing more molecular and pathophysiologic mechanisms of PAD in patients with different degrees of kidney impairment.[42] Another important step for research, and for clinical practice as well, is represented by the need for a multidisciplinary approach to the patient with CKD and PAD. In this case, the multidisciplinary model of care, which may encompass Vascular Surgeon, Nephrologist, Cardiologist, Radiologist may help to reach a better and earlier care for these high-risk patients.

Conclusions

In conclusion, CKD is associated with a wide spectrum of CV diseases including PAD. The prevalence of PAD is high in CKD patients and increases moving from mild to severe degrees of kidney function impairment. The surgical or percutaneous revascularizations have shown to improve prognosis in CKD patients. Novel studies would be very helpful to both refine risk stratification of patients with CKD and PAD and help clinicians decide which type of intervention may be the best for each patient.

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All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

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