Review Article

Waiting List and Kidney Transplant Vascular Risk: An Ongoing Unmet Concern

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Keywords

Chronic kidney disease · Waiting-list · Kidney transplantation · Atheromatosis · Arteriosclerosis · Vascular calcification · Cardiovascular disease · Mortality

Abstract

Background: Chronic kidney disease (CKD) is an important independent risk factor for adverse cardiovascular events in patients waitlisted for kidney transplantation (KT). Although KT reduces cardiovascular risk, these patients still have a higher all-cause and cardiovascular mortality than the general population. This concerning situation is due to a high burden of traditional and nontraditional risk factors as well as uremia-related factors and transplant-specific factors, leading to 2 differentiated processes under the framework of CKD, atherosclerosis and arteriosclerosis. These can be initiated by insults to the vascular endothelial endothelium, leading to vascular calcification (VC) of the tunica media or the tunica intima, which may coexist. Several pathogenic mechanisms such as inflammation-related endothelial dysfunction, mineral metabolism disorders, activation of the renin-angiotensin system, reduction of nitric oxide, lipid disorders, and the fibroblast growth factor 23-klotho axis are involved in the pathogenesis of atherosclerosis and arteriosclerosis, including VC. **Summary:** This review focuses on the current understanding of atherosclerosis and arteriosclerosis, both in patients on the waiting list as well as in kidney transplant recipients, emphasizing the cardiovascular risk factors in both populations and the inflammation-related pathogenic mechanisms. **Key Message:** The importance of cardiovascular risk factors and the pathogenic mechanisms related to inflammation in patients waitlisted for KT and kidney transplant recipients.

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Introduction

Growing evidence suggests that chronic kidney disease (CKD) is an important, independent risk factor for major adverse cardiovascular events (MACE). In particular, patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² have 2–16 times higher risk of MACE than patients with an eGFR >60 mL/min/1.73 m² [1–4]. Likewise, the rate of developing MACE is significantly higher than that of developing end-stage renal disease (ESRD) [3]. Cardiovascular risk varies greatly among ESRD patients. A priori, patients who are listed for transplantation represent a healthier ESRD population than patients who are never listed for transplantation. Indeed, a higher number of hospitalizations related to cardiac events is observed in patients who were never waitlisted for transplantation compared with waitlisted patients [5]. However, longitudinal studies have demonstrated that overall mortality in waitlisted patients is also significantly higher than in transplanted patients, regardless of the type of transplant and cardiovascular risk, especially in the older population [6–9]. In fact, the number of elderly patients on the waiting list for kidney transplantation (KT) has risen significantly in recent years and older waitlisted patients have a higher death risk than age-matched KT recipients [10]. Undoubtedly, this is a frustrating situation given the great efforts made to manage cardiovascular disease (CVD) in both the general population and uremic patients [11].

Although KT improves cardiovascular outcomes and quality of life in the ESRD population, these patients still have a significantly higher cardiovascular mortality than the age- and gender-matched general population, even in the best initial condition as is living donor transplantation [12–16]. Taken together, this high cardiovascular mortality cannot be fully explained by classical risk factors, suggesting that both traditional and nontraditional risk factors plus community-based health indicators and transplant-specific risk factors concur in waitlisted and transplanted patients, leading to early CVD and death (Table 1).

Arteriosclerosis (alterations in the medial layer) and endothelial dysfunction-related atherosclerosis (alterations in the intimal layer) are both considered systemic diseases with many shared risk factors, including inflammation, which may precede the appearance of both entities [17, 18]. Indeed, endothelial dysfunction and inflammation are universal phenomena in uremic patients, involving activation of T cells and macrophages, plus proliferation and migration of smooth muscle cells (SMCs). In addition, vascular calcification (VC) is common in patients with kidney disease, including KT recipients, and it usually fails to revert after KT, thereby increasing posttransplant cardiovascular mortality [19]. Finally, the binomial arteriosclerosis-atherosclerosis (A/A) may be present simultaneously in the nonuremic general population (A/A-non-CKD) in CKD patients (A/A-CKD) and in KT recipients (A/A-KT). Table 2 synthesizes a few clinical, epidemiological, histological, and biomarker differences between these 3 groups of patients derived from animal and human studies.

Therefore, understanding the pathogenic mechanisms of the vascular lesions in waitlisted patients and KT recipients could be crucial in order to optimize the management and outcomes in both populations. This review will focus on the consequences of a stressed cardiovascular system leading to A/A-CKD and A/A-KT, as well as on some potential mechanisms involved in the acceleration of both processes in these patients. Given the breadth of the topic, this review is not intended to be exhaustive, but it may set the stage for the current understanding of this very continuing concern both in patients on the waiting list as well as KT recipients.

Table 1. Traditional and nontraditional risk factors plus transplant-specific risk factors and community risk factors for CVD in waitlisted patients and kidney transplant recipients

Traditional risk factors	Age, gender, race, family history, obesity/sedentary, glucose metabolism disorders, hypertension, dyslipidemia, smoking, hypercoagulability, left ventricular hypertrophy
Nontraditional risk factors	Albuminuria/proteinuria, hyperhomocysteinemia, C-reactive protein/inflammatory markers, nitric oxide inhibitors, increased endothelin, increased adhesion molecules, endothelial dysfunction, oxidative stress, increased fatty acids, advanced glycation end products, reduced adiponectin/increased leptin, reduced vitamin D, increased asymmetric dimethylarginine, increased natriuretic peptides
CKD-related risk factors	Albuminuria/proteinuria, reduced GFR, increased PTH, increased calcium/phosphate product, reduced vitamin D, increased FGF-23/klotho deficiency, reduced fetuin A, vascular calcification, volume overload, anemia, acidosis, increased asymmetric dimethylarginine
Transplant-specific risk factors	Immunosuppression, inflammation, viral infections, post-transplant hypertension, diabetes and dyslipidemia, allograft dysfunction, albuminuria, left ventricular hypertrophy, vascular calcifications
Community-based risk factors	Low birth weight, smoking, physical inactivity, poverty, preventable hospital stay rate, poor physical health days, poor mental health days, potential life years lost, self-reported days in fair or poor health

CKD, chronic kidney disease; FGF-23, fibroblastic growth factor-23; GFR, glomerular filtration rate; CVD, cardiovascular disease.

Clinical Consequences: Epidemiological Data

Waitlist

Many ESRD patients, including young adults and waitlisted patients, start dialysis with uremia-related comorbidities, which are associated with mortality while remaining on dialysis [20–22]. This is currently a concerning health issue given the significant increase in the proportion of incident ESRD patients with CKD secondary to high-risk comorbidities such as diabetes and hypertension, which can increase mortality on the waitlist [23]. In addition, the significant and growing disparity between the demand for KT and the supply of organs may augment mortality in this particular population. This may also limit access to KT, especially in high-risk patients [24]. Indeed, the annual mortality in candidates for KT ranges from 5 to 10% worldwide, though it increases greatly in the older population (>50 years) [8]. A large observational study performed in Spain in waiting list patients showed an overall mortality of 24% after a median follow-up of 22 months [21].

The leading cause of death in patients with ESRD during their first year of dialysis is CVD secondary to A/A-CKD, specifically ischemic heart disease (IHD), ventricular dysfunction, and stroke, after which is complications resulting from infection [11, 23]. As an example, the cumulative 3-year incidence of myocardial infarction in waitlisted patients ranges from 8.7 to 16.7% [25], and CKD patients are more likely to have a positive cardiac stress test compared with patients without CKD [1, 26]. In addition, the incidence and severity of obstructive coronary artery disease (CAD) increase as renal function declines [27, 28]. In other words, cardiovascular morbidity and mortality are inversely and independently associated with kidney function, mainly when GFR <15 mL/min/1.73 m² [29–31].

Similarly, the prevalence of congestive heart failure (CHF) increases with declining renal function. Indeed, the prevalence of CHF in patients who are on dialysis is 13–36 times great-

Table 2. Clinical, epidemiological, histological, and biomarker characteristics in A/A-non-CKD and A/A-CKD patients as well as A/A-KT recipients driven from human and experimental studies

Characteristics	GP without CKD (A/A-non-CKD)	CKD patients (A/A-CKD)	KT recipients (A/A-KT)	Comments
Clinical and epidemiological risk factors	Population-based risk factors including community-based risk factors, LVH and hypercoagulability	Increased traditional risk factors plus community-based risk factors, nontraditional risk factors, and uremia-related risk factors	Increased traditional risk factors plus community-based risk factors, nontraditional risk factors, and transplant-associated risk factors	A greater number of CV risk factors in renal patients explain a greater number of CV events in these patients compared with the GP
Histological lesions	Affecting tunica intima (atheromatosis) and/or involving tunica media (arteriosclerosis) leading to VC	Indistinguishable lesions from the GP, but augmented in this population	Similar lesions to CKD patients	Both lesions may coexist and are universal under uremic environmental
Carotid ultrasound data	c-IMT and atherosclerotic plaques in arteries	Similar findings to the GP with a greater extension of vascular lesions in renal patients	Similar findings to CKD patients	A greater amount of major VC and c-IMT are found in A/A-CKD and A/A-KT compared with the GP
Vascular calcification by angiography/ultrasound/CT	Increasing with aging	25% in CKD-stage 3, 35% in CKD-stage 4, and 50% at starting dialysis	25–30% at the time of KT and VC do not revert after KT	VC increase significantly mortality in renal patients compared with the GP.
Inflammation-related mechanisms: Atheromatosis: major role T cells and macrophages Arteriosclerosis: major role vascular SMC	CRP, proinflammatory cytokines (TNF, IL-1β, IL-6, MCP-1) and adhesion molecules (ICAM-1 and VCAM-1), VEGF, NFκB in wall arteries and plaque-infiltrating macrophages activating the osteogenic cascade	Overexpression of inflammation-related mechanisms compared to the GP, including the osteogenic cascade	Similar inflammation-related mechanisms to CKD patients, but to a lesser extent	Given that endothelial dysfunction and inflammation are universal phenomena in renal patients, overexpression of proinflammatory cytokines, adhesion molecules, and activation of the osteogenic cascade are seen in AA-CKD and AA-KT
Biomarkers of A/A	Endothelial dysfunction: NO, ADMA, chemokines, ICAM-1, VCAM-1, E-selectin, ROS, endothelial microparticles, oxLDL, AI; Procoagulant state: PAI-1, IL-1β, IL-6, CRP, NFκB; Adipokines (leptin, adiponectin), klotho deficiency, AGEP , pro-inflammatory cytotoxic CD4+CD28null T cells	Similar to the GP and increased expression of osteogenic cascade biomarkers deficiency (BMP-2, BMP-4, and Msx2 gene expression), hypomagnesemia	Similar to CKD patients but to a lesser extent	Increased levels of biomarkers are seen in A/A-CKD and A/A-KT compared with A/A-non-CKD

A/A-non-CKD, atheromatosis/arteriosclerosis in nonuremic individuals; A/A-CKD, atheromatosis/arteriosclerosis in kidney transplant recipients; All, angiotensin II; ADMA, asymmetric dimethylarginine; AGEP, advanced glycation end protein; CKD, chronic kidney disease; c-IMT, carotid-artery intima and media thickness; CRP, C-reactive protein; CT, computerized tomography; CV, cardiovascular; GP, general population; KT, kidney transplantation; LVH, left ventricular hypertrophy; NO, nitric oxide; ROS, radical oxygen species; SMC, smooth muscle cell; VC, vascular calcification; BMP, bone morphogenetic proteins; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6; NFκB, nuclear factor-κB; oxLDL, oxidized low-density lipoprotein.

er than that for the general population [32, 33]. CHF is also associated with a high mortality in many ESRD patients, especially when left ventricular hypertrophy (LVH) or diastolic dysfunction is present [34]. LVH is very prevalent in ESRD patients (50–100%) [35]. The development of uremia-associated cardiomyopathy related to hemodynamic factors (from pressure and volume overload), nonhemodynamic factors (oxidative stress, inflammation, profibrogenic factors, renin-angiotensin system, and growth factors), plus VC may be relevant for the appearance of LVH. In addition, pulmonary hypertension is a major comorbidity in ESRD patients, including waitlisted patients, increasing mortality in these patients [36–38].

Valvular heart disease (VHD) evidenced by echocardiographic studies is very common in CKD patients and appears to be more prevalent as eGFR declines [39]. Clinical conditions contributing to VHD in these patients include accelerated VC, LVH, and increasing cavity size owing to increased volume.

The relative risk of stroke in ESRD patients is estimated to be 5–10 times than that of the age-matched general population, with an overall stroke rate of approximately 4% per year [40, 41]. Most strokes in CKD patients are ischemic, and the stroke mortality rate is nearly 3 times higher than that for non-CKD patients.

Peripheral vascular disease (PVD) is a stronger predictor of morbidity and mortality in dialysis patients, including patients waitlisted for KT [42, 43]. An observational study by our group in KT candidates showed greater all-cause mortality in PVD patients in comparison with patients that did not have PVD (45 vs. 21%), and the presence of PVD at entry to waitlist resulted in a 1.9-fold increased risk of all-cause mortality during follow-up using standard methods for survival analysis and a competing risk analysis [44]. This study found that the prevalence of PVD was similar to that already noted for this population [45].

CKD patients have a high prevalence of VC, which has been associated with cardiovascular events [46, 47]. Notably, the onset of VC occurs during the initial stages of CKD (25% in stage 3 and 35% in stage 4) and can be detected in over 50% of patients who initiate dialysis [48]. In KT candidates, conventional radiologic techniques show that up to 25% of patients have VC in major arteries (aorta or iliac arteries), and these vascular lesions do not regress after KT [19].

CKD patients, including waitlisted patients, have an increased risk of atrial fibrillation, which is the most common arrhythmia in these patients (6%) [49, 50]. In addition, sudden cardiac death (SCD) is highly prevalent in ESRD patients [51]. Indeed, the annual mortality rate in ESRD patients due to SCD is 5% and SCD explains about one-fourth of dialysis patient deaths [4, 23]. Moreover, SCD accounts for 20–26% of overall mortality [52–54]. There exists an inverse linear relationship between renal function and the risk of SCD, as seen in a large cohort of CKD patients with important CAD [2, 51]. However, the true prevalence of SCD in waitlisted patients is currently unknown.

Finally, the intima media thickness of the common carotid artery (c-IMT) is an early marker of subclinical atheromatosis. This thickness has been associated with a higher risk of CVD and death in uremic patients as well as in the general population [55, 56]. In a prospective observational cohort study, 33% of KT candidates were found to be in the tertile with the highest c-IMT (>0.7 mm). Likewise, a greater degree of luminal narrowing was observed in the histopathological analysis of the inferior epigastric artery among patients in the highest tertile, as well as a greater frequency and seriousness of calcification in the medial layer of the artery [57]. Figure 1 shows A/A lesions evidenced by carotid artery ultrasound in individuals with and without renal disease.

Kidney Transplant Recipients

Although a combination of noncardiovascular causes of mortality, specifically infections plus malignancy, exceed cardiovascular risk mortality, the differences are small and CVD,

Fig. 1. Sagittal ultrasound and Doppler of carotid artery demonstrating lesion suggestive of carotid plaque (arrow) in a patient without renal disease (**A**), and increased carotid intima-medium thickness (*) and calcified carotid plaque (arrow) in a patient with CKD (**B**, **C**). Data obtained by our research unit.

particularly A/A-KT disease, is the major contributor to posttransplant death [16]. The main phenotypes of CVD, including IHD, CHF, VHD, pulmonary hypertension, and arrhythmias, can all occur in KT recipients. As a consequence, cardiovascular events in KT, including cardiovascular mortality, still occur more often than in the age-matched general population. Because a reduced eGFR (<60 mL/min/1.73 m²) is very usual after KT (40%), and this is related to MACE posttransplantation, KT patients have a high prevalence of CVD. Indeed, compared to the general population, these patients experience up to 10 times the rate of cardiac death and the yearly rate of cardiovascular events (fatal or nonfatal) can be 50 times greater [58, 59]. In the European population, a MACE can occur in up to 40% of KT recipients during the first 10 years posttransplantation [60]. A common complication after KT is IHD, occurring in 4.7–11% of recipients within 3 years of transplantation, resulting in a 2.6-fold increase in the risk of death after KT [61–63]. Indeed, the mortality rate due to IHD in KT recipients is 25% at 1 year and 45% at 5 years after the episode. However, after the initial posttransplant period, the likelihood of IHD is slightly less than its demographic-adjusted incidence in waitlisted patients [61]. Diabetic patients who received medical optimization before the transplant and eventually renal replacement therapy with KT experienced a marked reduction in IHD-related hospitalizations [64]. Moreover, KT recipients who have a myocardial infarction are more likely to survive than waitlisted patients who have the same event, as are KT recipients who undergo coronary revascularization compared to dialysis patients [14, 65].

Few reports exist of SCD in KT recipients, and no useful data exist to be able to compare the incidence of SCD in KT recipients with that in waitlisted patients. Ventricular arrhythmias are increased after KT, and the risk of SCD in KT recipients can reach 15% [66, 67]. Likewise, little clinical information is available to compare the incidence of CHF in KT recipients with that in patients waitlisted for KT, especially in patients who have IHD [65]. The ejection fraction improves over time in most KT recipients, suggesting that partial recovery of renal function and return to a more favorable uremic environment could be important to restore myocardial function in KT recipients who have preexisting uremic cardiomyopathy [68, 69]. Nevertheless, large observational studies have reported the detrimental effect on KT outcome of preexisting and de novo heart failure [70].

Pulmonary hypertension has also emerged as a major prognostic factor posttransplantation, as evaluated by right heart catheterization or transthoracic echocardiography [36, 71].

Neither is it known whether KT reverses valvular calcification nor whether VHD progresses more slowly after KT. Nevertheless, KT recipients are likely to experience worsening of their VHD with time, especially those with allograft dysfunction [72, 73].

Fig. 2. Combination of traditional and nontraditional risk factors, plus community-based risk factors and transplant-specific risk factors leading to a stressed cardiovascular system, CVD, and premature death in waitlisted patient and kidney transplant recipients. CVD, cardiovascular disease.

KT recipients are more likely to have a stroke than the age- and gender-matched general population. Indeed, nearly half of the cardiovascular mortality after KT is due to stroke [74, 75], with ischemic stroke being more frequent than hemorrhagic stroke posttransplantation, though the latter is associated with higher mortality [76, 77]. Nevertheless, stroke is less likely to occur in KT patients than waitlisted patients, with KT recipients having a reduction of 34% in cerebrovascular accidents compared with waitlisted patients [74].

PVD is very common after KT, particularly among high-risk populations like diabetics, and these patients have a significantly higher mortality after KT [45, 78]. In addition, among KT recipients with PVD there is a high incidence of CHF, IHD and stroke, which may impair outcomes in these patients [78].

Lastly, successful KT may not completely decrease significant preexisting subclinical vascular atheromatosis evidenced by an increased pretransplant c-IMT. In an observational study by our group, a high c-IMT either remained or worsened in almost half the KT recipients 1 year posttransplantation and individuals were more likely to die if their c-IMT remained high or increased [57].

Risk Factors for CVD

Traditional risk factors for CVD cannot wholly explain the high incidence of CVD or increased cardiovascular mortality in patients waitlisted for KT or in KT recipients. This suggests that a merger of traditional risk factors, nontraditional risk factors such as uremic-related and transplant-specific risk factors, plus community-based risk factors are all involved in the development of CVD and cardiovascular death (Fig. 2).

Waitlist

Few clinical entities comprise so many risk factors as uremic status [11]. Multiple evidence suggests a higher burden of A/A-CKD compared to A/A-non-CKD [1, 79, 80]. For instance, CKD patients are more likely to have a positive cardiac stress test than non-CKD patients [26, 81]. Likewise, a worse cardiovascular profile, evidenced by older age, smoking, diabetes, and higher systolic blood pressure, has been observed in KT candidates with subclinical atheromatosis and a high c-IMT [57]. Moreover, many CKD patients present albu-

minuria, which has been identified as a significant predictor of MACE [82]. Epidemiological studies in CKD patients have shown an inverse relationship between magnesium levels and VC and cardiovascular mortality [83]. Regardless of uremia-related risk factors and other emerging risk factors not directly related with uremia, age and traditional risk factors, for example, diabetes and hypertension, play a crucial role in the increased risk for death. Indeed, data from registry studies have shown that older patients with high comorbidity, such as diabetics, have a significantly higher risk of CVD and death while remaining on dialysis, particularly those returning from transplantation [84, 85]. In addition, age and diabetes are also strong independent risk factors for stroke and PVD [41, 86–88]. Other sociodemographic factors such as race, employment status, smoking, and cardiovascular comorbidity (IHD, stroke, PVD) are risk factors independently associated with mortality in dialysis patients, including KT candidates [89]. Indeed, large observational studies have shown that PVD conferred an increased risk of cardiovascular mortality, particularly in the diabetic population [45, 90].

Similarly, in the European dialysis population, these same factors, together with psychiatric disorders, previous cancer and age >60 years, have been associated with a significantly lower survival than for younger patients [91, 92]. A large observational study of KT candidates from Spain used competing risk models to assess the importance of baseline comorbidities when starting dialysis on survival of patients waitlisted for KT, using the Charlson comorbidity index and other comorbidities related with uremia [21]. Overall mortality was 24% due, mainly, to CVD and older age (>50 years), Charlson comorbidity index score >3, a central venous catheter, and unemployed status at dialysis entry, which were significantly associated with mortality. A composite risk model including these factors showed that the risk of death increased significantly with increasing risk levels. Additionally, the presence of PVD at list entry is an independent risk factor for mortality in southern European KT candidates, indicating that PVD may reflect progression of atherosclerotic disease, especially in the older population with a higher burden of diabetes and cardiovascular disorders [44]. Moreover, a competing risk analysis showed that KT candidates on the waiting list who had had a previous KT experienced increased mortality after listing. This suggests that a failed KT may still cause low-chronic inflammation, itself a recognized risk factor for death while on dialysis [85, 93]. In this sense, a hypercatabolic inflammatory state has been suggested to have a relationship with mortality in waitlisted patients with a significant weight loss (<5 kg) or a body mass index of <23 kg/m² [94].

Candidates for a KT may well have suboptimal health indicators such as low birth weight, smoking, obesity, physical inactivity, mental disorder, or low income. Accordingly, these poor health indicators together could have a negative and prominent impact on survival in waitlisted patients [95].

Finally, other sociodemographic factors, such as non-Caucasian individuals, living in rural areas or far from a transplant center, unmarried patients, or individuals without adequate health coverage economically, may represent barriers for successful access to KT [96–100], which may prolong waiting list time and favor the onset of life-threatening comorbidities while remaining on the list. In any case, dialysis patients who are on the waiting list may well share many of the same risks as those who are not. As a result, many dialysis patients not included on the waiting list show a higher survival than some patients who are waitlisted early while in their first dialysis year [89].

Kidney Transplantation

Although the treatment of choice for many ESRD patients is KT, cardiovascular mortality among KT recipients is significantly greater than among the age- and gender-matched general population, as shown in observational studies [13, 23]. It is plausible that this high mortality

Fig. 3. Cardiovascular, infectious and neoplastic disorders in kidney transplant recipients that share common causal factors within the framework of immunosuppressive treatment, leading to premature death.

among KT recipients may be due to the interplay between comorbid CVD, infections, and cancer, all of which can be conditioned by immunosuppressive treatment (Fig. 3). Indeed, risk factors for A/A-KT and CVD that already exist in recipients of a KT are worsened by new cardiometabolic disorders after KT; risk factors that include the metabolic side effects of immunosuppressants, obesity, posttransplant diabetes, dyslipidemia, hypertension, and allograft dysfunction [63]. A large multicenter database involving 23,575 adult KT recipients from 14 transplant centers worldwide showed that pretransplant diabetes, new onset posttransplant diabetes, prior pre- and posttransplant CVD, and eGFR were strong predictors of CAD [63]. In fact, KT patients have a high prevalence of preexisting CVD risk factors as well as new-onset risk factors for CVD, such as hypertension (40–90%) [101, 102], diabetes (24–40%) [103–105], dyslipidemia (50%) [106], and smoking (about 40%) [107]. However, in the field of atherosclerotic CVD, the most important cardiovascular risk factors in patients receiving immunosuppression are diabetes, hypertension, dyslipidemia, and smoking. For every 10 mm Hg increase in the systolic blood pressure, the risk of graft failure and death is increased by 5% [101]. The use of calcineurin-inhibitors (CnIs) and steroids is related with a high prevalence of posttransplant hypertension; this is especially so with cyclosporine, which induces a greater endothelial dysfunction-mediated vascular resistance than tacrolimus [108]. Pancreatic beta cell function is affected by CnIs, with randomized controlled studies showing that tacrolimus increases the likelihood of posttransplant diabetes compared with cyclosporine [109–111]. By contrast, a systematic meta-analysis of 6 randomized controlled trials found that belatacept is associated with lower rates of posttransplant diabetes compared to CnIs [112]. KT recipients are very likely to experience posttransplant dyslipidemia, and this may be exacerbated by obesity, diabetes, proteinuria, and immunosuppressive agents such as the mammalian target of rapamycin. Cigarette smoking has been associated with an increased cardiovascular risk, and its negative impact on patient survival is similar to that of diabetes [107]. As a result, a worse cardiovascular profile (diabetes, smoker, and higher systolic blood pressure) and a greater amount of major VC were found in KT recipients with the highest c-IMT tertile after a median follow-up of 68 months, and these high-risk patients were more likely to die in comparison to the patients in the middle and lower c-IMT tertiles (23.7 vs. 13.2 vs. 2.6%, respectively) [57]. In fact, glucose metabolism disorders, including prediabetic alterations, may play an important role in developing subclinical atheromatosis posttransplantation [113]. Notably, in nondiabetic KT patients, there was an association between HbA1c levels and a c-IMT in the upper tertile. Moreover, lower levels of adiponectin, a protective hormone against the development of diabetes, have been related with subclinical atheromatosis and a greater risk of all-cause and CVD mortality. This suggests that adiponectin might be a marker of A/A-KT [114, 115]. In this line, long-term European cohort studies

have found an increased incidence of cardiovascular events and higher mortality associated with diabetes, both pre- and post-KT, where diabetes is an independent risk factor for the development of life-threatening cardiovascular complications owing to A/A-KT [116]. This may be due to a worse metabolic and vascular profile in patients who develop post-KT diabetes compared to patients who do not, evidenced by increased systolic and diastolic blood pressure levels plus higher serum cholesterol and triglyceride levels [117]. In fact, after adjusting for other confounding variables, posttransplant hypertension is associated with a significantly increased risk of death and graft loss [101]. Likewise, dyslipidemia may also increase the risk for progression of A/A-KT and development of CVD during long-term follow-up [106]. Eventually, cardiovascular risk factors may be worsened by immunosuppressive drugs, thereby contributing to greater rates of CVD and mortality in this population.

The high prevalence of emergent and transplant-specific risk factors such as inflammation, proteinuria, chronic anemia, hyperhomocysteinemia, kidney failure, LVH, klotho deficiency, and viral infections all result in an anomalous relationship between KT and CVD in these patients, increasing the risk of the entire spectrum of CVD [16, 118–130]. For instance, proteinuria plus allograft dysfunction are known to be independent risk factors for posttransplant mortality and graft loss [131, 132]. As a result, the risk of IHD after KT, coupled with hypertension, diabetes or dyslipidemia is significantly greater in this population in comparison with the general population after applying the Framingham risk score [133, 134]. Finally, similarly to waitlisted patients, KT recipients may have many indicators of poor health, including low birth weight, obesity, smoking, mental worsening, lack of physical activity, or low income, as previously described [135]. In this setting, the combination of these indicators of poor health could raise the mortality risk in these patients.

Taken together, all of these risk factors mechanistically might converge in several inter-related processes. First, a process of accelerated atheromatosis, including subclinical atheromatosis, can result in an increased risk of cardiovascular events. Second, anomalous cardiac remodeling can lead to LVH and ventricular dysfunction [35, 130]. Lastly, calcification of the tunica media (arteriosclerosis) increases life-threatening complications. The final consequence is heart failure and premature death of these patients.

Potential Pathogenic Mechanisms for Atherosclerosis and Arteriosclerosis

Given the high burden of CVD in waitlisted patients and KT recipients, it is plausible to think that other potential mechanisms such as endothelial dysfunction or atheromatosis-related inflammation could hasten both A/A processes, leading to worse survival. In fact, both of these may share pathogenic mechanisms (inflammation, diabetes, lipid disorders, klotho deficiency, etc.) under a uremic environment, leading finally to VC at 2 sites in the arterial wall, either the tunica intima (atherosclerosis) or the tunica media (arteriosclerosis). Intimal VC is a late event in the atherosclerotic process (plaque calcification) and osteochondrogenesis is probably a secondary phenomenon of primary inflammation processes in the plaque or its surroundings. Medial VC involves differentiation of vascular SMCs (VSMCs) toward osteoblast-like cells, which is a more proximal event, with subsequent mineralization of the tunica media (arteriosclerosis). Calcification of both atherosclerotic plaque and the medial layers of the arteries is accelerated by CKD [31], especially in ESRD patients with diabetes [136]. Although KT may partly correct the multiple uremia-related processes and inflammation leading to reduction of cardiovascular events with respect to uremia, these entities (atherosclerosis and arteriosclerosis) rarely regress after KT.

Interestingly, both calcification of the tunica intima (atherosclerosis) and calcification of the tunica media (arteriosclerosis) may coexist in renal patients, including KT recipients [19,

137] and share overlaps in their risk profile and signaling pathway, especially inflammatory processes [138] (Table 2). Indeed, both types of VC are associated with low-grade inflammation. However, while atherosclerosis is a classic inflammatory disease in which activation of T cells and macrophages is involved plus the proliferation and migration of SMCs resulting in endothelial dysfunction, the SMCs have a crucial role in the arteriosclerotic process, whereas the immune cells appear to have a minor role. Indeed, VSMCs are considered the main mediators of medial calcification [1]. In other words, the relationship between calcification in the tunica intima and inflammation is more relevant than what happens in the calcification of the medial layer, but still dependent on infiltrating cells into the early atheromatous lesion, such as VSMCs and macrophages. In addition, this phenomenon is directly related with the degree of inflammation. But, how does VC start and how does it develop in the process of atheromatosis and arteriosclerosis?

Atherosclerosis

Inflammation-related endothelial dysfunction is related to both A/A-non-CKD and A/A-CKD, including A/A-KT recipients [57, 139, 140]. Atheromatosis is an active inflammatory process affecting the artery wall. Mechanistically, endothelial dysfunction is the initial stage in the pathophysiology of this mottled process. Impairment of the endothelium may be evidenced by expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), the monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), which are strongly expressed in the endothelium affected by atherosclerotic lesions [57, 141, 142]. These proteins are also closely related with infiltration and proliferation of atheromatosis-related inflammatory cells. Research is increasingly showing that inflammation commonly antecedes calcification, in both the intimal layer and the tunica media of the arterial wall, where inflammation-related molecules (e.g., IL-1, IL-6, tumor necrosis factor [TNF]- α , MCP-1), adhesion molecules (ICAM-1 and VCAM-1), and nuclear factor- κ B (NF κ B) are crucial for stimulating the cell response to free radicals, cytokines, and oxidized low-density lipoprotein (oxLDL), among other stimuli, in addition to the differentiation of mesenchymal cells to osteoblastic cells [143]. Indeed, NF κ B is a ubiquitous transcription factor that regulates the inflammatory response. In the process of atherosclerosis, NF κ B generates the transcription of VCAM-1, ICAM-1, MCP-1, and E-selectin in VSMCs and endothelial cells. This pathogenic mechanism might be more relevant when multiple risk factors are present, as occurs in renal patients, including KT recipients (Fig. 4).

Indeed, a prospective observational study of 115 KT candidates detected a higher vascular expression of VCAM-1 in the inferior epigastric artery of ESRD patients with the highest c-IMT tertile [57]. In addition, this study also found a high correlation among vascular inflammatory markers (IL-6, MCP-1, ICAM-1, and VCAM-1). Similarly, circulating proinflammatory markers have also been associated with subclinical atheromatosis in KT recipients [140]. Additionally, as patients in the highest VCAM-1 tertile have a poor survival after KT, the production of vascular VCAM-1 may be suggestive of the development of A/A-KT and cardiovascular events. A common pathogenic mechanism accounting for the role of adhesion molecules in the A/A-CKD process (including KT recipients) seems likely. Under a uremic environment, the clustering of traditional risk factors and uremia-related risk factors results in endothelial activation and the release of proinflammatory cytokines in the artery wall, upregulating adhesion molecules (VCAM-1 and ICAM-1) on the cell surface by SMCs in the intima layer with a synthetic phenotype. These molecules would participate in the interaction between cells and the recruitment of additional inflammatory cells (e.g., macrophages), leading to the development of atherosclerosis. As a consequence, adhesion molecules, especially VCAM-1, induce migration of SMCs to the neointima and the switching from a contractile to synthetic SMC, leading to more severe vascular lesions and higher production of proinflammatory cytokines

Fig. 4. Interactions among inflammation, atherosclerosis, arteriosclerosis, and multiple risk factors, including uremia-related factors and transplant-specific factors. VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; IL-6, interleukin-6; NFκB, nuclear factor-κB; TNF, tumor necrosis factor.

and adhesion molecules, as reported [144]. This may explain the correlation observed in human studies between the severity of vascular lesions and VCAM-1 levels [57, 145]. In animal models of atheromatosis, VCAM-1 plays a predominant role at the site of the vascular lesion, with histological lesions showing that ICAM-1 immunostaining is stronger in the endothelium and weaker in intimal cells than VCAM-1, staining of which is much more restricted to lesions and abundant in neointimal cells [146]. The fact that soluble VCAM-1, but not ICAM-1, remained the only predictor of subclinical atheromatosis in patients with hypertension and PVD [147] supports this theory. Last, activation of these proinflammatory cytokines and adhesion molecules promotes fibrosis as the consequence of a final pathway, preserving the inflammation in the atherosclerotic vascular lesions.

As occurs in calcification of the tunica media primarily driven by differentiation of VSMCs toward osteoblast-like cells, calcification of atherosclerotic lesions is also dependent on humoral factors (e.g., bone morphogenetic protein 2), which enhance plaque calcification, worsened by factors released from infiltrating macrophages. Furthermore, infiltrating macrophages downregulate matrix Gla-protein (MGP), thus decreasing the defense against crystallization. Given that microcalcification also induces inflammation [148], this could attract macrophages into atherosclerotic plaques, possibly boosting and perpetuating this process [148, 149]. Later, calcified atherosclerotic plaque may generate local biomechanical forces (e.g., wall shear stress) initiating inflammatory signaling pathways, thus playing a crucial role in the natural history of atherosclerosis in different vascular beds [150].

Diabetes mellitus could trigger inflammatory mechanisms leading to the development of atheromatosis and VC, mainly when a uremic environment is present. Indeed, NFκB overexpression has been noted in the artery wall of patients where the 2 risk factors (uremia and diabetes) coincide [151]. As a result, a higher expression of IL-6, MCP-1, and VCAM-1, in addition to greater activation of NFκB p65, has been observed in the artery wall of type 1 diabetic patients with uremia. Accordingly, a significant correlation between MCP-1 levels and p65 nuclear translocation has been found in the artery wall of this particular population, suggesting that MCP-1 is possibly regulated in a NFκB-dependent fashion when a proinflammatory state like type 1 diabetes is present [145, 152]. Additionally, these factors have also been related with severe vascular lesions and a greater c-IMT [145]. These findings support the important role of this transcription factor in the atheromatous process of diabetic patients

via an increase in proinflammatory cytokines. Finally, receptors for advanced glycation end-products have been found in human atheromatosis lesions, suggesting an important role of these molecules in the atheromatous process [153].

Nitric oxide (NO) is one of the principal vasodilating substances released by the endothelium and, thus, a critical regulator of arterial elasticity, decreasing arterial stiffness in animals and humans [154]. NO impedes growth and inflammation and has antiplatelet aggregation effects. Asymmetric dimethylarginine (ADMA) is one of the products of the protein metabolism process which is elevated in CKD. ADMA can reduce the production of NO in endothelial cells contributing to progression of atherosclerosis [155]. Thus, a reduction in NO in the presence of impaired uremia-related endothelial function seems likely. Indeed, CKD is a situation of NO deficiency as a result of a decrease in renal NO production or an increase in bioinactivation of NO, principally by reactive oxygen species and inflammation mechanisms and mediators, like C-reactive protein (CRP) [156, 157]. In vitro studies have found that CRP reduces both basal and stimulated release of NO by downregulating transcription of endothelial NO synthase [158]. In humans, an inverse association between CRP and endothelium-dependent vasoreactivity has been reported [159], contributing to the development of inflammation-related atheromatosis. Reduction of ADMA levels is also observed after KT [160].

Inflammation and oxidative stress have also been linked to the pathogenesis of atheromatosis, and angiotensin II can cause oxidative stress in the cardiovascular system via the production of reactive oxygen species. This leads to the release of proinflammatory cytokines, adhesion molecules, and chemokines through NF κ B activation [161, 162]. Additionally, angiotensin II raises blood pressure and promotes renal and myocardial fibrosis [1]. In theory, thus, pharmacologic blockade of the renin-angiotensin system (e.g., angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) might result in beneficial cardiovascular effects, as reported in observational studies of uremic patients and KT recipients [163–165]. In any case, whether these drugs have a beneficial effect on proinflammatory cytokine production in the artery wall is still undetermined.

Inflammation in association with lipid disorders, particularly increased levels of oxLDL, has also been found to provoke cardiovascular events in CKD patients [166]. Thus, given the crucial role of oxLDL in the atheromatous-associated inflammatory response in the artery wall, statins could, a priori, ameliorate this dynamic and complex process by modulating the vascular inflammation.

Finally, klotho is a transmembrane protein produced mainly in renal tubular cells that has antiaging, antiapoptotic, and nephroprotective actions. CKD has been found to be a condition of klotho deficiency in animal models of CKD, demonstrating reduced expression of the klotho gene, lower klotho concentrations in kidney tissue, and lower circulating soluble klotho [167–169]. Systemic and local inflammation decreases renal tissue expression and soluble α -klotho levels, and patients with low serum soluble klotho levels have significantly higher cardiovascular and all-cause mortality rates [170, 171]. Under a uremic environment, thus, a relationship between klotho, inflammation, and cardiovascular risk could be expected in renal patients, including KT recipients [129]. Indeed, serum klotho was related to systolic blood pressure, pulse pressure, increased c-IMT, CRP, carotid atherosclerotic plaque quantity, and atherosclerosis in hemodialysis patients [172].

In CKD patients, inflammation-related endothelial dysfunction may possess 2 roles. First, it is a critical step for developing CVD. Coronary microvascular dysfunction has been linked to adverse cardiovascular outcomes in CKD patients. Second, dysfunction and apoptosis of endothelial cells may lead to CKD progression [173]. Although multiple risk factors are implicated in this process of endothelial dysfunction and disintegration (Table 1), the competing twin risks of patients with CKD and/or CVD have not yet been elucidated. In other words,

Fig. 5. Factors potentially involved in the development of VC in renal patients. VC, vascular calcification; FGF-23, fibroblast growth factor 23.

currently it is unknown why some patients progress to ESRD without significant CVD, while others die from CVD without reaching ESRD. This concern may also be extended to KT recipients.

Arteriosclerosis

Multiple evidence points to different processes in the sequence of events in the calcification of the tunica media compared to the intima layer. Local inflammation is the secondary prominent feature in the calcification of the medial layer, not the primary event [46]. The osteochondrogenic transdifferentiation of VSMCs is orchestrated by a complex intracellular signaling network, which has been assessed *in vivo* and *in vitro* [174]. Atherosclerotic plaque-infiltrating macrophages are a prime feature in the calcification of the tunica media. First, macrophages release proinflammatory cytokines (IL-6 and TNF- α), which may activate bone morphogenetic proteins (BMP-2 and BMP-4) and *Msx2* gene expression, starting the osteogenic cascade, promoting calcification via paracrine *Wnt* signals and nuclear activation and localization of β -catenin. This molecule is a coregulator of transcription factors (Runx2-Cbfa 1, osterix and Sox9) involved in the conversion of VSMCs. Likewise, TNF- α -induced stimulation of endothelial cells boosts BMP-2 expression and the production of endothelial microparticles, resulting in VC and osteogenic differentiation. VSMCs, thus, can transform to osteoblast-like cells with ensuing mineralization by beginning the osteogenic cascade, regulated by favoring promoters (e.g., high extracellular phosphate and calcium concentrations) plus metabolic toxicities, including oxLDL and free radicals. The final result is either VSMC apoptosis or NF κ B stimulation and activation of inflammatory mediators and macrophages, thus closing the vicious circle [175].

VC of the tunica media is not therefore just the result of simple calcium phosphate deposition in the artery wall. An extensive description of the mechanisms involved in medial calcification is beyond the scope of this review, but some of the key factors appear to be the parallel occurrence of a phenotype switch of VSMCs and local inflammation, in an environment of calcification-regulating humoral factors. In fact, several uremia-related factors and unusual levels of bone-related proteins have been identified in CKD patients and in animal models as possibly responsible for the mechanism underlying VC. Phosphate, fibroblast growth factor 23/klotho, osteopontin, MGP, osteoprotegerin, vitamin D-PTH axis, fetuin-A, magnesium, and sclerostin are humoral factors potentially responsible for the VC [46, 137, 176–178] (Fig. 5). For example, high serum phosphate has been related to VC, valvular calcification, and death in CKD patients [46, 178]. The active form of vitamin D stimulates the absorption of calcium and phosphate, contributing to greater VC [178]. Vitamin D depletion, however, is related with aortic stiffness in ESRD patients and the progression of atheromatosis in an animal model [179, 180]. *In vitro* and *in vivo* studies have shown an inverse relationship between magnesium levels and VC in renal patients and in experimental

Table 3. Clinical interventions and proposed effects on the principal traditional risk factors associated with the clinical consequences of atheromatosis and arteriosclerosis in the general population and renal patients, including kidney transplant recipients

Risk factor/intervention	Proposed effect on athero-matosis and/or arteriosclerosis	General population	CKD patients	KT recipients	Ref.
Hyperlipidemia/lipid-lowering agents (statins and ezetimibe) and PCSK9 inhibitors	Reduction of total cholesterol and LDL-cholesterol, prevent vascular lipid deposition, reduction of CV events, and reduction of inflammation, apoptosis of CD4+CD28null cells	*Reduction of total and LDL cholesterol and reduction of major CV events (13–17%) in high-risk individuals *Alirocumab reduced CV events vs. placebo (HR 0.85, 95% CI 0.78–0.93)	*Reduced the risk of a first major CV event by 21% in mild-to-moderate CKD patients (meta-analysis) *Reduction of major CV events by 20% in nondialysis CKD patients; however, no compelling evidence exists for statins use in ESRD, but might be beneficial in diabetic patients	*Statins may reduce CV events in KT recipients although treatment effects are imprecise (meta-analysis) *One RCT showed reduction of cardiac death or MI by 30–35%	[184–194]
Hypertension/antihypertensive drugs, (focused on RAS blockers and beta-blockers)	Blockade of RAS, reduction of blood pressure (<140/90 mm Hg), reduction of proteinuria, antiproliferative effects, cardiac remodeling, improving cardiac function, prevention of atheromatosis, reduction of CV events	*HR for all-cause mortality in hypertensive patients with eGFR >45 mL/min/1.73 m ² is 1.24 (95% CI 1.1–1.4) *Overall, intensive lowering of blood pressure in hypertensive patients is associated with a lower rate of CV events. *Reduction of all-cause mortality (HR 0.73; 95% CI 0.60–0.90) in the intensive treatment (SBP <120 mm Hg) *Reduction of major CV events with losartan vs. atenolol (RR 0.87, 95% CI 0.77–0.98) *In diabetic patients, control of diastolic pressure is associated with reduced risk (51%) of CVD	*HR for all-cause mortality at eGFR <15 mL/min/1.73 m ² is 3.62 (3.19–4.11) *Reduction of CV events and cardiac mortality by 49% with candesartan or valsartan *Beta-blockers improved all-cause mortality (RR 0.72, 95% CI 0.64–0.80) and CV mortality (RR 0.66, 95% CI 0.49–0.89) in CKD patients with heart failure	*Each 10 mm Hg rise in SBP increases risk of death by 18%. Posttransplant LVH regression per se reduces CV events (HR 0.41, 95% CI 0.22–0.79) *ACEI therapy resulted in reduction of major CV events at 10 years (HR 0.209, 95% CI 0.068–0.636) in one RCT *RAS blockers are associated with reduction of all-cause mortality (HR 0.629, 95% CI 0.41–0.97) in observational studies. However, other studies, supporting the use of RAS inhibitors are inconsistent	[16, 101, 163, 164, 195–203, 205]
Hyperglycemia/hypoglycemic drugs, including novel oral hypoglycemic agents (SGLT2 inhibitors, GLP-1 agonists, and DDP-4 inhibitors)	Control of glucose levels and HbA1c % plus reduction of CV events	*HR for all-cause and CV mortality in diabetics with GFR >100 mL/min/1.73 m ² is 1.21 (95% CI 1.06–1.39) *Overall intensive glucose control reduces the risk for CV disease (RR 0.90, 95% CI 0.83–0.9) *Intensive glucose control is associated with a lower risk of microvascular disease (24%), myocardial infarction (15%), and death from any cause (13%) *SGLT2 inhibitors and GLP-1 agonists are associated with the reduction of CV events (14–17%)	*HR for all-cause and CV mortality in diabetics with GFR <15 mL/min/1.73 m ² is 14.5 (95% CI 8.2–23.8). However, intensive glycemic control has not demonstrated substantially improved CV outcomes in CKD patients *SGLT2 inhibitors (empagliflozin) reduced the risk of cardiovascular death by 29% vs placebo (HR 0.71, 95% CI 0.52–0.98) *GLP-1 agonists (liraglutide) reduces CV death (HR 0.67, 95% CI 0.50–0.90) and CV outcomes occur in a lower proportion than placebo (15.4 vs. 21.4%)	*Increased risk of CV mortality in diabetics (HR 1.80, 95% CI 1.10–2.96) *Early basal insulin therapy decreases PTDM *Belatacept decreases risk of PTDM (OR 0.43) *DPP-4 inhibitors are safe and efficient in KT *SGLT2 inhibition is feasible and well tolerated in diabetic KT recipients. Whether SGLT2 inhibition or GLP-1 are able to reduce CVD is undetermined yet	[103, 112, 204, 206–214]
Obesity/reduction of weight (caloric restriction diet, lifestyle changes, drugs, bariatric surgery)	Reduction of weight and obesity-associated medical complications	*Obese individuals have a 68% increased odds of developing stage 3 CKD, CV disease, and diabetes *Modest weight loss (8%) improves aortic stiffness *Lorcaserin (selective serotonin 2c receptor agonist) facilitated sustained weight loss (2.0% per year during 3 years) *Bariatric surgery reduces weight, hypertension, and diabetes in obese patients *An intensive lifestyle increased weight loss but did not reduce consistently the rate of CV events in overweight or obese adults with type 2 diabetes	*Weight loss interventions have potential beneficial effects in CKD patients, improving glycemic control, blood pressure, and dyslipidemia *Caution should be exercised in using drugs for reduction of weight	*Obesity at the time of KT is associated with both increased mortality and death-censored graft loss *Lifestyle changes should be strongly encouraged *Bariatric surgery following KT has also been associated with favorable clinical outcomes, notably improvements in glycemic and BP control	[215–221]

Table 3 (continued)

Risk factor/intervention	Proposed effect on athero- matosis and/or arteriosclerosis	General population	CKD patients	KT recipients	Ref.
Sedentary/exercise training	Reduction of overweight and potential reversible mechanisms involved in arteriosclerosis and inflammation	<p>*Prolonged sedentary lifestyle is associated with deleterious health outcomes</p> <p>*Higher levels of physical activity are associated with a lower rate of CV disease</p>	<p>*Physically active individuals with CVD risk factors had a lower risk of CV events (HR 0.76, 95% CI 0.61–0.95)</p> <p>*There is evidence for significant beneficial effects of regular exercise on physical fitness, walking capacity, cardiovascular dimensions (e.g., blood pressure and heart rate), health-related quality of life and some nutritional parameters in adults with CKD</p>	<p>*RCTs in adult SOT recipients demonstrated that exercise-training improved exercise capacity and was associated with lower limb muscle strength, and health-related quality of life</p>	[215, 222–226]
Smoking/cessation smoking	Smoking cessation and reduction of CV events	<p>*Negative impact of cigarette smoking on survival is similar to diabetes</p> <p>*Among quitters, the 5-year risk of stroke, MI, or death was 15.7% compared to 22.6% for patients who continued to smoke (HR 0.66, 95% CI 0.48–0.90)</p> <p>*Varenicline was efficacious for smoking cessation in this high-risk patient population</p>	<p>*Smoking cessation decreases aortic stiffness, urine albumin excretion and diabetic nephropathy progression in CKD (observational studies)</p> <p>*Similarly to the GP a beneficial effect on CV events might be expected in CKD patients</p>	<p>*Smoking increases relative risk of CV events of 1.56</p> <p>*There are limited data on the impact of smoking cessation post-KT, but it is plausible to suppose that the KT recipient will also benefit from smoking cessation like the GP</p>	[16, 107, 227–230]
Thrombotic events associated with AF and atherosclerotic lesions/antiplatelet agents	Prevention of thrombotic events, especially in patients with AF and atherosclerotic lesions	<p>*Aspirin reduces major CV events by 15% and all myocardial infarction by 36% in hypertensive patients</p> <p>In diabetic patients it reduces risk of CV events (RR 0.88, 95% CI 0.79–0.97)</p>	<p>Benefits for antiplatelet therapy among CKD patients are uncertain and are potentially outweighed by bleeding hazards</p>	<p>Although AF is also associated with an increased risk of death (HR 3.2, 95% CI 2.9–3.6), no beneficial effect has been demonstrated with the use of aspirin or novel anticoagulants in KT</p>	[195, 231–234]

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; CKD, chronic kidney disease; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1 receptor; GP, general population; HR, hazard ratio; KT, kidney transplantation; LVH, left ventricular hypertrophy; MI, myocardial infarction; PTDM, posttransplant diabetes mellitus; RAS, renin-angiotensin system; RCT, randomized clinical trial; RR, relative risk; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2; SOT, solid organ transplantation; PCSK9, proprotein convertase subtilisin-kexin type 9.

models [83, 181]. In clinical studies, osteoprotegerin is related to VC. Circulating levels of sclerostin have been related with VC in ESRD patients [177]. Finally, increased fibroblast growth factor 23 in uremic patients (up to 20 times greater than in a healthy population) and reduced klotho levels have been related with aortic calcification and peripheral VC in dialysis patients [176, 182]. Klotho is also an important defense mechanism against this pathological process [183].

Whether the control of these risk factors for VC may reverse VC in renal patients, including KT recipients, is currently undetermined. Moreover, apart from MGP, no VC biomarker contemplated in this review has sufficient discriminant power to be considered a valid predictor of cardiovascular events [176, 177]. Further longitudinal studies are still needed to elucidate this concern.

Therapeutic Approaches

Similar to the general population, clinical interventions on some of the most intensively studied classical risk factors may contribute to minimizing the clinical consequences in A/A-CKD and A/A-KT patients, but therapeutic approaches targeting the renal population are limited, and many clinical studies are inconsistent [16, 49, 101, 103, 112, 163, 164, 184–234] (Table 3). Indeed, clinical intervention on serum lipids, glucose levels, high blood pressure, obesity, and smoking have demonstrated beneficial effects on CVD in the general population, and these effects might be extended to renal patients, including KT recipients. Additionally, other potential treatments of VC have emerged from animal models and human trials. These include spironolactone [235], bisphosphonate [236], magnesium supplementation [237], zinc [238], low-dose active vitamin D, calcimimetic agents [239], noncalcium-containing phosphate binders [240–242], or vitamin K supplementation [243] among others, but no compelling evidence is yet available. Further research is required for new therapeutic strategies according to detailed mechanisms contributing to the process of VC in both the A/A-CKD and A/A-KT populations.

Conclusions

Waitlisted patients and KT recipients have an increased vascular risk compared with the general population. This important concern is due to a high burden of traditional and nontraditional risk factors plus uremia-associated factors and transplant-specific factors participating in atheromatosis, including subclinical atheromatosis and arteriosclerosis. Although therapeutic approaches used in the general population might be extended to both waitlisted and KT patients, the detailed knowledge of the pathogenic mechanisms in both processes, including inflammation-related endothelial dysfunction and VC, could contribute to the design of future therapeutic strategies to improve the management and outcomes in these patients.

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Author Contribution

D.H.: writing – original draft preparation. J.A.-T., A.M.A.-P., V.L., M.C., E.S., L.F., E.G., T.V., T.J., P.R.-E., M.G.-M., and D.H.: writing – review and editing D.H.: funding acquisition.

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