

## REVIEW

## Cardiovascular disease in chronic kidney disease – a review of risk factors

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### ABSTRACT

Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD), such that the risk of cardiovascular mortality is greater than the risk of progression to end-stage kidney disease. Despite the increased prevalence of traditional and non-traditional cardiovascular risk factors, patients with kidney disease have been mostly under-represented in previous cardiovascular outcome studies, thereby resulting in a paucity of data on the evidence-based management of CVD in CKD. In this review, we explore the evidence on the burden of CVD and its risk factors in patients with CKD, highlight various inflammatory biomarkers for predicting CVD and provide an overview on novel biomarkers for CVD.

**Keywords:** chronic kidney disease; cardiovascular disease; cardiovascular disease risk factors.

### INTRODUCTION

Ever since the link between chronic kidney disease (CKD) and cardiovascular disease (CVD) was established about two decades ago, several epidemiological studies have confirmed and even extended this finding. Patients with CKD are more likely to develop CVD than their age-matched counterparts in the general population, so much so that the risk of death from CVD is much higher than the risk of eventually requiring dialysis [1]. Sarnak et al. [2] showed that CKD is a strong predictor of CVD and suggested that it should be recognized as a coronary disease risk equivalent, like diabetes mellitus. Declining renal function represents a continuum of cardiovascular risk and in those individuals who reach end-stage kidney disease (ESKD) the risk of suffering a cardiac event is extremely high [3].

Even though increased frequencies of traditional and non-traditional risk factors have been well documented in CKD patients, those with kidney disease have been

mostly under-represented in previous cardiovascular outcome studies, thereby resulting in a paucity of data on the evidence-based management of CVD in CKD. In this review we explore the evidence on the burden of CVD and its risk factors in CKD patients, highlight various inflammatory biomarkers for predicting CVD and provide an overview on novel biomarkers for CVD.

### OVERVIEW OF CVD IN CKD

The various forms of CVD that may affect patients with CKD are listed in Table 1. A study that evaluated the pattern of cardiac lesions among haemodialysis patients in Cameroon found high frequencies of cardiac lesions including left ventricular hypertrophy (60%), valvular calcifications (38%), cardiac failure (36%) and conduction abnormalities (33%) [4]. These findings probably represent the tip of the iceberg because CVD was defined on the basis of electrocardiographic and echocardiographic

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**Table 1.** Spectrum of cardiovascular diseases in chronic kidney disease.

<b>A. Peripheral and cerebrovascular disease</b>
Arterial hypertension
Atherosclerosis causing limb ischaemia
Stroke
<b>B. Myocardial disease</b>
Myocardial ischaemia and infarction
Left ventricular hypertrophy
Cardiomyopathy
Myocarditis
<b>C. Pericardial disease</b>
Uraemic pericarditis
<b>D. Others</b>
Arrhythmias
Cardiac autonomic dysfunction
Sudden cardiac death

abnormalities; subclinical lesions such as increased carotid intimal media thickness (CIMT) and atherosclerotic plaques were not captured. Among black CKD patients receiving care in a tertiary health facility in South Africa, we reported a higher prevalence of carotid atherosclerotic vascular disease (AsVD) in stage 3 CKD and ESKD patients compared to controls. AsVD was more prevalent among peritoneal dialysis (PD) patients compared to haemodialysis (HD) and CKD stage 3 patients [5]. In a previous study, we also reported an increased prevalence of left ventricular hypertrophy (LVH) among kidney transplant recipients compared to controls [6]. Heart failure, a common CVD in CKD patients, may present as acute left ventricular failure or congestive cardiac failure (CCF). It may present as diastolic dysfunction, less often as systolic dysfunction, or as a combination of both. A study that evaluated elderly CKD patients found that the relative risk of developing heart failure was 1.45 and 1.68 in CKD stages 1–2 and 3–5, respectively [7]. The prevalence of peripheral arterial disease (PAD) is high in patients with CKD and inversely related to kidney function [8]. Sudden cardiac death (SCD) is an entity with complex pathophysiological mechanisms including structural and electrophysiological remodelling in the heart, CKD-related inflammation, sympathetic activation, myocardial ischaemia, metabolic acidosis, altered nitric oxide levels and dialysis-related factors such as electrolyte shifts across cell membranes and hypotension. According to the United States Renal Data System (USRDS), one-quarter of all-cause mortality among dialysis patients was attributed to cardiac arrest [9].

## EPIDEMIOLOGY OF CVD IN CKD

In a previous study, we evaluated the prevalence of AsVD and its predictors among Black patients with stage 3 CKD or ESKD on continuous ambulatory peritoneal dialysis (CAPD) or HD. AsVD was most prevalent among CAPD patients, occurring in 70%, compared to 47.5% among HD patients and 17.1% among controls [5]. Similarly, Go et al. [10] reported an association between lower GFR and CVD. The adjusted hazard ratio increased from 1.4 in CKD stage 3 to 3.4 in patients with ESKD. Liu et al. [11] reported an association between CAD and CKD among patients who underwent coronary angiography; 18.8% of patients with CAD had CKD compared with 5.4% without CAD. The term cardiorenal syndrome (CRS) is increasingly being used to define a pathophysiological condition in which cardiac and renal dysfunction coexist. A single-centre retrospective cohort study of 1,087 patients admitted to an internal medicine ward in Italy had a CRS prevalence of 17.5% [12].

## RISK FACTORS FOR CVD IN CKD

In 1961, the Framingham Heart Study group introduced the concept of CVD risk factors by linking the presence of previously identified clinical conditions to the development of future CVD [13]. The risk factors in patients with CKD are categorised as traditional or non-traditional (Table 2).

**Table 2.** Risk factors for cardiovascular disease in CKD.

Traditional	Non-traditional
Hypertension	Inflammation
Diabetes mellitus	Endotoxaemia
Smoking	Oxidative stress
Older age	Hyperhomocysteinaemia
Males	Anaemia
Obesity	Abnormal calcium–phosphate metabolism
Higher LDL cholesterol	Lipoprotein (a) and apolipoprotein (a) isoforms
Lower HDL cholesterol	Advanced glycation end products (AGES)
Family history of CVD	Asymmetric dimethylarginine (ADMA)
Menopause	Malnutrition
Physical inactivity	Proteinuria
LVH	Extracellular fluid volume overload Renin angiotensin system overactivity Endothelial dysfunction Pro-thrombotic state Elevated fibroblast growth factor 23 (FGF-23) levels

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; CVD, cardiovascular disease; LVH, left ventricular hypertrophy.

Certain traditional risk factors may be aggravated by CKD. Patients with CKD also have additional risk factors such as inflammation, oxidative stress, endothelial dysfunction, anaemia, and calcium–phosphate abnormalities that are related to the uraemic milieu.

## TRADITIONAL RISK FACTORS

### Hypertension

Hypertension is a risk factor for mortality in CKD patients. The blood pressure–mortality association is J-shaped, suggesting an ideal blood pressure that is neither too high nor too low. Isolated raised systolic blood pressure (and wide pulse pressure) appears to increase long-term mortality risk and low BP (mean and diastolic) predicts early mortality [14]. The Action to Control Cardiovascular Risk in Diabetes BP trial (ACCORD BP), which evaluated 4,733 hypertensive diabetic patients, showed that lowering BP to below the standard target of 140 mmHg reduced the risk of stroke by about 40% [15].

### Diabetes mellitus

Diabetes mellitus is a cardiovascular risk equivalent and diabetic patients are at increased risk of cardiovascular mortality, with a 2-fold risk of death from cardiovascular causes compared to those without diabetes [16].

### Cigarette smoking

Smoking increases the risk of CVD in kidney disease patients and may accelerate the progression of kidney disease. Evidence has demonstrated the beneficial effects of stopping smoking among cohorts of male smokers followed up for 50 years [17]. Current smokers had a 2-fold increased risk of CKD compared to former smokers, and the number of cigarettes smoked daily predicted the likelihood of having CKD. Guidelines have recommended stopping or complete avoidance of smoking as an integral part of a CKD management strategy.

### Age

The association of blood pressure variation with ageing was clearly demonstrated in the Framingham study, and age has been shown to be an important predictor of cardiovascular events. A cross-sectional study of CVD risk factors among Black Africans with CKD found a positive correlation between CIMT and age [18].

### Obesity

Increased waist–hip ratio was shown to be associated with fatal cardiovascular events among stages 3 and 4 CKD patients pooled from the Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study [19]. This study concluded that the cardiovascular risk

related to obesity may be underestimated by body mass index [19].

### Dyslipidaemia

Dyslipidaemia is one of the traditional CVD risk factors that is worsened by CKD. Elevated triglyceride levels may be due to delayed catabolism of triglycerides from down-regulation of the gene for lipoprotein lipase or an increase in lipoprotein lipase inhibitor [20]. Furthermore, the dialysis modality used in ESKD could have procedure-dependent effects on serum levels of triglyceride, although this remains a subject of controversy. In addition to increasing hepatic lipoprotein output, massive proteinuria increases gene expression for the enzymes hydroxyl-3-methylglutaryl-CoA reductase (HMG-CoA reductase) and cholesterol 7 $\alpha$ -hydroxylase, which are rate-limiting steps in cholesterol biosynthesis and catabolism to bile acids [21]. This strengthens the need for early commencement of anti-proteinuric therapy with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB). Reduction of LDL-C with statin therapy has been shown to significantly reduce CVD in CKD patients [22]. The JUPITER study showed that rosuvastatin prevented major atherosclerotic events in apparently healthy men and women, thus justifying subsequent evaluation of the effect of statins on CVD in high-risk groups such as CKD patients. Similarly, among kidney transplant recipients, a randomised controlled trial, Assessment of Lescol in Kidney Transplantation (ALERT), showed that fluvastatin reduced cardiac death and non-fatal myocardial infarction (relative risk 0.65) compared to placebo [23]. Furthermore, a landmark multicentre trial, the Study of Heart and Renal Protection (SHARP), recruited over 9,000 CKD patients and evaluated the cardiovascular effect of lowering LDL-C with a combination of simvastatin and ezetimibe compared to placebo [22]. The study demonstrated a reduction of 17% in the first major atherosclerotic event including non-fatal myocardial infarction or coronary death, non-haemorrhagic stroke or arterial revascularisation in the treatment group [22].

### Sex

Males are more predisposed to cardiovascular disease. In a South African study with 7,188 participants, the prevalence of ischaemic heart disease was higher among males (18.4% vs 13.1%) [24].

### Physical activity

There is consistent evidence suggesting an association between physical activity and reduced CVD morbidity and mortality, with reports from several population studies showing that there is a 2-fold rise in the risk of CAD in individuals with a sedentary lifestyle compared to those

who were active [25]. The risk associated with sedentary lifestyle is comparable to that conferred by hypertension, cigarette smoking or hypercholesterolaemia.

### Left ventricular hypertrophy

Levin et al. [26] showed that the prevalence of LVH increases with advancing renal failure; LVH was present in 26.7% of patients with GFR greater than 50 mL/min, 30.8% of patients with GFR between 25 and 49 mL/min, and 45.2% of patients with GFR of <25 mL/min. Left ventricular mass index (LVMI) was inversely associated with GFR; LVMI in CKD patients with GFR >50 mL/min, 25–50 mL/min and <25 mL/min were 97.5 g/m<sup>2</sup>, 100.8 g/m<sup>2</sup> and 114.4 g/m<sup>2</sup>, respectively. Uraemia causes remodelling of the heart muscle, leading to LVH, fibrosis and left ventricular dysfunction [27].

## NON-TRADITIONAL RISK FACTORS

### Declining GFR

Reduced GFR is closely related to the presence of cardiovascular disease. In a study that assessed the predictors of CAD among 800 patients with CKD, significantly lower eGFR was found among participants who had CAD compared to those without [28].

### Proteinuria

Meta-analysis of cohorts with cardiovascular events showed a graded increase in the risk of CAD with elevated proteinuria [29]. Moderately elevated albuminuria was associated with a 50% increase in the risk of CAD (HR = 1.47), whereas the risk is doubled in patients with macroalbuminuria (HR = 2.17). Schmieder et al. [30] showed that elevations in proteinuria predicted mortality among patients with vascular disease but normal GFR.

### Anaemia

Anaemia is associated with LVH, is present in approximately 75% of patients initiating dialysis and is a major predictor of cardiovascular morbidity and mortality [26]. In dialysis patients, every 1 g/dL reduction in haemoglobin was associated with left ventricular dilatation (OR 1.46), heart failure and mortality [31]. Although the role of hypoxia inducible factors (HIF) in erythropoietin production have been described in CKD, there are no data on the relationship between HIF and atherosclerosis.

### Calcium–phosphate abnormalities and secondary hyperparathyroidism

Alterations in the serum levels of calcium, phosphate, vitamin D and parathyroid hormone (PTH) are frequently

encountered in CKD. A robust association has been established between hyperphosphataemia and LVH and cause-specific mortality in patients on haemodialysis [32, 33]. Hyperphosphataemia is associated with increased coronary artery calcification in haemodialysis patients. Apart from the contribution of calcium–phosphate abnormalities to vascular calcification, alterations in the levels of the physiological regulators of vascular calcification such as fetuin-A, osteoprotegerin and matrix-GLA protein, significantly influence vascular calcification in CKD patients. Among HD patients, plasma levels of osteoprotegerin predicted all-cause (RR 2.67) and cardiovascular (RR 3.15) mortality [34].

### Chronic inflammation and inflammatory biomarkers

The aetiology of chronic inflammation in ESKD patients is multifactorial, arising from immune dysregulation and inflammatory activation, including decreased renal clearance and increased production of cytokines, intestinal dysbiosis with increased translocation of gut bacteria into the systemic circulation, periodontal disease, increased pro-inflammatory and oxidative stress from uraemic toxins, metabolic acidosis, vitamin D deficiency-associated immune dysfunction and dialysis-related factors [35]. The relationship between elevated C-reactive protein (CRP) and CVD in ESKD patients was documented among maintenance HD patients in South Africa [36]. The available evidence suggests a link between chronic inflammation and accelerated atherosclerosis. In support of this finding, we demonstrated that circulating endotoxaemia was common among South African CKD patients, and was associated with left ventricular mass index [37]. In another study, we showed that endotoxaemia was associated with a 4-fold increased risk of atherosclerosis [38]. Taken together, this evidence suggests that chronic inflammation may be a mediator of accelerated atherosclerosis in CKD patients.

### Oxidative stress

Oxidized LDL, a marker of oxidative stress, has been shown to play a crucial role in the pathogenesis of CAD, hypertension and atherosclerosis [39]. Oxidative stress depletes endogenous nitric oxide, resulting in endothelial dysfunction, which triggers the process of left ventricular remodelling and fibrosis, and oxidation of lipoproteins.

### Endothelial dysfunction

Nitric oxide is produced by endothelial NO synthase (eNOS), which has vasodilator, antiplatelet, anti-proliferative, anti-adhesive, permeability-decreasing and anti-inflammatory properties. Impaired function or non-availability of NO will induce immune activation and systemic inflam-

mation, ultimately leading to atherosclerosis and CAD. Asymmetric dimethylarginine (ADMA), a naturally occurring inhibitor of NOS, has been shown to accumulate and contribute to the CVD burden in CKD patients [40].

### Hyperhomocysteinaemia

Lower levels of homocysteine are associated with reduced risk of cardiovascular events, and a meta-analysis of studies that investigated the association between the methylenetetrahydrofolate reductase gene (MTHFR) and risk of coronary heart disease further suggested that this association is causally related [41].

### Adiponectin

Adiponectin is a major risk factor for type 2 diabetes, obesity, insulin resistance, metabolic syndrome, visceral adiposity, and atherosclerosis [36]. In addition, a negative correlation has been established between eGFR and adiponectin levels [36]. Even though it is thought that excretion of adiponectin in ESKD patients may be impaired, it remains to be seen whether elevated levels of adiponectin in CKD patients are due to impaired clearance or a compensatory mechanism militating against increased cardiovascular risks in CKD patients.

### Fibroblast growth factor 23

Fibroblast growth factor 23 (FGF-23) plays a key role in calcium–phosphate metabolism and is directly related to kidney function. In CKD patients, FGF-23 is a predictor of myocardial hypertrophy, and pharmacological reduction of FGF-23 through blockage of the FGF-23 receptor resulted in improvement of LVH, further suggesting that FGF-23 antagonists may be a potential therapeutic strategy to reduce CVD in CKD [42].

### Genetic susceptibility to cardiovascular disease

Many genetic polymorphisms have been examined for their role in modifying CVD risk in CKD patients. Polymorphisms in the Apolipoprotein L1 (APOLI), interleukin-6 (IL-6), fibroblast growth factor (FGF-23) and hypoxia-inducible factor (HIF) genes, to mention but a few, have been associated with increased risk for CVD in CKD. The Jackson Heart Study (JHS) and Women's Health Initiative (WHI) study evaluated associations between APOLI high-risk genotypes and renal and cardiovascular diseases. They showed that the APOLI G1/G2 variants, that decrease autophagosome functions, removal of pro-atherosclerotic cells and clearance of oxidized LDL, significantly increased the burden of atherosclerotic CVD in African Americans (JHS and WHI combined, odds ratio, 2.12), suggesting a genetic component to CVD disease in CKD patients of African ancestry [43]. In support of this finding, we recently

showed that Black South African CKD patients who are carriers of at least one APOLI risk allele had a 3-fold increased risk of subclinical atherosclerosis (odds ratio 3.19), and the presence of high-risk APOLI risk variants was strongly associated with increased oxidized LDL levels [44]. Furthermore, the association between maternal APOLI genetic variants and pre-eclampsia, an important risk factor for hypertension, CKD and CVD, was explored in pregnant women of African ancestry. These same high-risk APOLI variants were associated with early-onset pre-eclampsia [45].

Inflammation plays a crucial role in atherosclerosis and other manifestations of CAD. Genetic polymorphism (−174G/C) on the IL-6 gene is associated with atherosclerotic CVD in dialysis patients [46]. Corroborating this finding, we recently reported an association between IL-6 gene polymorphism and IL-6 levels as well as atherosclerosis among Black South African CKD patients [47].

FGF-23 has been identified as an independent cardiovascular risk marker in multiple patient populations. Schwantes-An et al. [48] reported an association between polymorphisms in the FGF-23 gene and cardiovascular (CV) mortality and heart failure in haemodialysis patients. FGF-23 rs11063112 was associated with a 32% and 37% increased risk of CV mortality and heart failure, respectively, in patients of European ancestry, and 31% and 51% among patients of African ancestry.

The chromosomal region 14q23.2 contains the gene for the alpha subunit of the transcription factor HIF-1, a key factor in the adaptation to ischaemia/hypoxia. Genetic variants are associated with acute myocardial infarction and intradialytic hypotension in haemodialysis patients [49].

Genome-wide association studies have yielded strong evidence that the 9p21.3 locus is associated with CAD in diverse populations. Akan et al. [50] demonstrated associations between 9p21.3 polymorphisms and CAD risk among Tanzanian patients; the GG genotypes (rs10757274 and rs10757278) were associated with a 3-fold and 4-fold increased risk of CAD, respectively. It remains to be seen how CKD will impact on the association between chromosome 9p21 variants and CAD risk factors in African populations.

## CONCLUSIONS

The burden of CVD in CKD patients is huge and multifactorial in nature, with contributions from traditional as well as non-traditional risk factors. Cardiac and vascular insults stem from ventricular remodelling, endothelial dysfunction, uraemia, anaemia, inflammation and vascular



calcifications. Ethnically diverse patterns of cardiovascular disease suggest that, at least in part, there are genetic factors which influence these complications in patients with CKD.

The huge morbidity and mortality associated with coexisting CKD and CVD highlights the importance of early identification and treatment of cardiovascular risk factors in at-risk individuals. The public-health implications of early detection of CVD are enormous, particularly in sub-Saharan Africa where resources for health are inadequate. Improved governmental support for the early detection and treatment of patients with CKD is imperative. This must include prompt identification of CVD risk factors and appropriate therapeutic interventions.

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