Patients with chronic kidney disease (CKD) experience serious adverse cardiovascular (CV) consequences. Cardiovascular disease is the leading cause of morbidity and mortality in patients with CKD, being secondary not only to an increased prevalence of traditional CV risk factors, but also to the presence of a wide array of nontraditional risk factors unique to patients with CKD. Pathogenesis includes both functional and structural alterations in the CV system. Those alterations give rise to a wide range of clinical CV syndromes, including ischemic heart disease, heart failure, and sudden cardiac arrest. As an increasingly prevalent disease, CKD, together with consequent CV disease, imparts major health and economic burdens to the community. In this review, we discuss traditional and nontraditional risk factors for CV disease, the pathogenesis of CV clinical syndromes, and prevention of CV syndromes in patients with CKD.

Key words
Chronic kidney disease, cardiovascular disease, risk factors, pathogenesis

Background
Chronic kidney disease (CKD) is one of the most common diseases worldwide. It is increasing in incidence and prevalence and affects at least 13% of the U.S. population (1). Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients, occurring even at the earliest stages of CKD without manifest vascular disease (2). A graded increase in CVD risk occurs with worsening renal function. The cardiovascular (CV) mortality risk is substantially higher in dialysis patients than in an age-matched general population, CVD being the leading cause of death in individuals on dialysis (3). Updated guidelines have not only recognized CKD as an independent CV risk equivalent, but have also recommended that CKD be considered the highest risk group for subsequent development of CVD (4).

The projected and actual burden of CKD has engendered controversy (5). According to the U.S. Renal Data System report published in 2013, 43% of patients with CKD and CVD had heart failure (HF), and 15% had a history of acute myocardial infarction (AMI); the equivalent proportions in non-CKD patients with CVD were 18.5% and 6.4% respectively. Among prevalent Medicare patients with CKD, 31% had HF, 11% had AMI, and 24% had atrial fibrillation. Cardiac death from arrhythmic mechanisms constituted the single largest cause of attributable mortality in both incident and prevalent patients with end-stage renal disease (ESRD).

The pathogenesis of CVD in CKD patients is in some ways similar to that in patients without kidney disease. However, uremic toxins resulting from renal dysfunction play a significant role in the development CVD (6). Recognizing that factor is very important, because prevention of CV death is achieved not only by delaying the progression of CKD, but also by modifying CV risk factors early in the course of the disease.

Discussion

CVD risk factors

GENERAL CONSIDERATIONS

Traditional Framingham risk factors include increased blood pressure (BP), cigarette smoking,
dyslipidemia, and diabetes mellitus (DM). Obesity, left ventricular hypertrophy (LVH), family history of premature coronary artery disease (CAD), and estrogen replacement therapy have also been considered in defining CVD risk (7). However, the Framingham risk model contained confounding additional CV risk that could not be accounted for. Moreover, traditional risk factors seem to carry different weight in people with CKD than in the general population (8–10). The additional CV risk might potentially be accounted for both by the quantitative and the qualitative influence of CKD over traditional CV risk factors and by the omission from the Framingham risk model of the nontraditional risk factors unique to CKD.

Uremia leads to an accumulation of organic products that are usually metabolized or excreted by the kidney. When those products are biologically active, they are a potential cause of adverse outcomes. They have been defined as nontraditional CVD risk factors based on criteria that include biologic plausibility, increased risk level with severe acute kidney disease, association with CVD, and lowered incidence of CVD outcomes with modification of the risk factor (4). These organic toxins originate from endogenous or microbial metabolism or exogenous ingestion (11). Physiochemical properties or site of origin classify these molecules into three groups: the mostly nontoxic, small (<500 Da) water-soluble molecules; the toxic middle molecules (>500 Da) that are removed only by dialysis; and the toxic protein-bound molecules. This classification is important because it determines whether the molecules can be removed during dialysis or whether a non-dialysis treatment can be of any benefit (12). Despite robust associations of the risk factors with CV outcomes, limited data support a causal association.

TRADITIONAL RISK FACTORS

**Diabetes mellitus:** In patients with CKD, a higher incidence of vascular disease is associated with DM than with any other CVD risk factor. Hypertension (HTN) is also strongly associated with DM: approximately 80% of patients with DM have an abnormally elevated BP (13). The pathogenesis of vascular disease in diabetic patients is mediated through advanced glycation endproducts (AGEs), which form as a result of nonenzymatic post-translational modification by glycation and carbamylation in the AGE–RAGE (receptor for AGE) pathway. The modification is mediated by the binding of sugar molecules with extracellular matrix or low-density lipoprotein (LDL), followed by oxidation. The AGEs deposit in the arterial wall, causing inflammation that heralds the formation of atheromata. The mechanisms behind the subsequent atherogenesis include cross-linking of proteins, modification of matrix components, increased collagen deposition, platelet aggregation, defective vascular relaxation, abnormal lipoprotein metabolism, loss of elasticity, and increased arterial stiffness (14,15). The resultant endothelial injury perpetuates a series of events including lipid permeation, recruitment of monocytes, and migration and proliferation of smooth muscle cells, leading to progression of atherosclerosis. The endothelial injury typically manifests as albuminuria.

Mortality rises tremendously with the onset of proteinuria. Standard interventions include good control of DM and proteinuria, thereby delaying the onset of diabetic nephropathy. Blockade of the renin–angiotensin–aldosterone system (RAAS) has been proved to reduce the incidence and progression of proteinuria. Trandolapril with or without verapamil lowers the incidence of microalbuminuria in patients with DM and HTN with normal albumin excretion (16). In the ADVANCE trial, a fixed-dose combination of perindopril with indapamide reduced the risk of major vascular events, including death (17). In a Japanese study, telmisartan reduced the transition from incipient to overt nephropathy and induced remission of albuminuria in patients with type 2 diabetes (18). In a different study, irbesartan was reported to have a similar beneficial effect independently of its BP-lowering effect (19). The beneficial effect of RAAS blockade is not observed once nephropathy occurs, emphasizing the importance of early intervention.

**Dyslipidemia:** Dyslipidemia—that is, higher LDL and lower high-density lipoprotein (HDL) cholesterol—is associated with atherosclerotic vascular disease and an increased risk of CVD events, including AMI. Guidelines recommend aggressive lipid-lowering therapies in patients at high risk of CVD. Although patients with advanced CKD are at high risk of CV events, there is a reluctance to use statins for several reasons. Unlike individuals in the general population, patients with CKD are at risk of malnutrition and inflammation that have a cholesterol-lowering effect. In
this subset of patients, cholesterol levels and mortality risk are inversely correlated. In contrast, a strong, graded, positive association of serum cholesterol with overall and CVD mortality has been observed in the absence of inflammation and malnutrition (20). Fibrates are contraindicated in renal failure patients because of the risk of rhabdomyolysis, leading to a reluctance to use lipid-lowering agents in patients with CKD.

Patients on hemodialysis (HD) predominantly have Frederickson type IV or III hyperlipidemias, characterized by hypertriglyceridemia because of an accumulation of very-low-density lipoprotein and intermediate-density lipoprotein, and lower levels of HDL (21). Several factors contribute to this condition:

- Decreased levels of hepatic triglyceride lipase in uremia leads to an accumulation of triglyceride-rich LDL.
- A decreased apolipoprotein CII/CIII ratio impairs the function of lipoprotein lipase, leading to accumulation of very-low-density lipoprotein (22).
- In dialysis patients, lower levels of apolipoprotein A-I (primarily because of increased catabolism) and lower levels of apolipoprotein A-II (primarily because of decreased production) lead to lowered HDL cholesterol and an abnormal HDL faction (23,24).
- Dialyzer membrane type, dialysate, and use of heparin have all been shown to play a role in the phenotype of dyslipidemia in HD patients (21).
- Use of erythropoietin and calcium and parathyroid homeostasis also seem to play a role in the genesis of dyslipidemia in patients with ESRD.

Elevated urea in patients with CKD dissociates to form cyanate, which causes carbamylation of proteins. Carbamylated LDL causes progression of atherosclerosis through endothelial cell injury, increased expression of cell adhesion molecules, and proliferation of vascular smooth muscle cells. It also causes endonuclease G activation that results in cellular injury and generation of oxidants. Elevated carbamylated LDL independently predicted an increased risk of CAD, future AMI, stroke, and death (25).

Lipoprotein(a) [Lp(a)] and apolipoprotein(a) isoforms also potentially contribute to atherogenesis. In contrast to the genetic forms, which selectively accumulate low molecular weight isoforms, the renal failure forms predominantly accumulate high molecular weight isoforms (26). Increased Lp(a) is associated with an increased risk of CAD. In a meta-analysis, the risk of CAD was increased by a factor of 1.7 in patients with higher Lp(a) levels compared with patients whose Lp(a) was in the lower range (27).

Statins were proved to have substantial CV benefits in primary and secondary prevention, including in patients with CKD stages 1–4; however, randomized controlled trials have not shown similar benefits in dialysis patients. In a German diabetes and dialysis study, atorvastatin produced no effect on the composite endpoint of CVD and nonfatal AMI or stroke in patients with DM undergoing HD (28). In the AURORA study, rosuvastatin lowered LDL cholesterol in HD patients, but had no significant effect on the composite primary endpoint of death from CV causes, nonfatal AMI, or nonfatal stroke (29). However, in the recently published SHARP trial, the combination of low-dose simvastatin with ezetimibe was demonstrated to safely reduce the incidence of major atherosclerotic events in patients with advanced CKD on dialysis (30). A recent meta-analysis provided strong evidence that in CKD, across a broad range of functional categories, including patients undergoing dialysis, statins reduce the risk of major vascular events, CV death, and all-cause death (31). In 2013, guidelines from the American College of Cardiology and the American Heart Association recommended high-intensity use of statins for all patients with CVD and CKD except dialysis patients (32). In contrast to patients on HD, patients on PD demonstrated a decline in all-cause and CV mortality with lipid-modifying medications (33). That result might be secondary to the fact that patients on PD tend to have more atherogenic lipid abnormalities, to be relatively younger, and to have higher hematocrit and albumin levels (34). The ALERT trial revealed that fluvastatin reduces CV morbidity and mortality in renal transplant recipients (35).

Hypertension: The already high prevalence of HTN in CKD increases with worsening renal function. More than 90% of patients with advanced CKD have HTN. The condition is secondary to volume expansion, sodium retention, and activation of RAAS and the sympathetic nervous system, all of which
are inevitably associated with CKD. In turn, HTN increases renovascular resistance and the filtration fraction of sodium, particularly in elderly individuals (36). With progression of renal disease, loss of the nocturnal physiologic decrease in BP, called “non-dipping,” also occurs (37). With progression of CKD, the resultant HTN gradually worsens, establishing a vicious cycle (38). Widened pulse pressure (a measure of arteriosclerosis) in HD patients is associated with an increased risk of death: the hazard ratio increases 12% with each incremental 10 mmHg elevation in post-dialysis pulse pressure (39).

In contrast to the J-curve observed between BP and CV mortality in the general population, patients on dialysis exhibit a U-curve (40). Uncontrolled HTN is strongly associated with increased CV mortality and morbidity, and itself causes kidney disease. Control of HTN has been shown to result in a reduction in CVD risk in CKD patients. Treatment of high BP was primarily achieved by RAAS blockade, because activation of RAAS is the primary abnormality in CKD patients with HTN. Moreover, aggressive treatment—as opposed to a stepped approach—was found to lower the incidence of decline in kidney function and mortality (41).

The Irbesartan Diabetic Nephropathy Trial revealed a decline in CV mortality and HF with lower achieved systolic BP (to 120 mmHg), but no difference with respect to risk of AMI was observed. Below the 120-mmHg threshold, the risks of CV death and HF events were increased. Diastolic BP less than 85 mmHg has been associated with an increase in all-cause mortality and a significant increase in AMI, but a decreased risk for stroke. Increased pulse pressure predicted increased all-cause mortality, CV mortality, AMI, and HF (42). Even minor BP reductions in patients with HTN can have a significant benefit with respect to CV outcomes (43).

Left ventricular hypertrophy: The most frequent structural cardiac abnormality in patients with CKD is LVH. The important risk factors for LVH are HTN and anemia (44). Advanced age, DM, tobacco use, serum calcium, elevated serum parathyroid hormone, hypoalbuminemia, and the presence of pericarditis have been identified as disease correlates for LVH (45). Coronary artery calcification score, widened pulse pressure, and markers of oxidant distress have also been identified as risk factors (46–49).

The prevalence of LVH increases with declining glomerular filtration rate (GFR) (50), and on commencement of dialysis, LVH is present in 75% of patients (51). In the Dialysis Mortality and Morbidity Study Wave 2, LVH was present in 17% of patients who were newly diagnosed with ESRD. In patients with CKD, LVH is associated with poorer CV outcomes. Left ventricular mass, indexed to height or body surface area (to avoid the distortion of malnutrition and fluid overload in the assessment of LVH), is a strong and independent predictor of survival and CV events in dialysis patients (52).

Cigarette smoking: Smoking, which substantially increases the risk for kidney disease, is one of the most important preventable causes of CVD. Smoking causes profound alterations in systemic and intrarenal hemodynamics through the stimulation by nicotine of postganglionic sympathetic nerve endings (53). The resultant increase in plasma epinephrine and norepinephrine causes abnormally high BP, particularly in elderly patients (54). Beta-receptor–mediated renin and angiotensin II production increases renal vascular resistance (55). Smoking also causes impaired response by the kidneys to elevated BP and increases GFR and intraglomerular pressure (56). Smoking also has non-hemodynamic effects such as endothelial dysfunction, activation of growth factors, and insulin resistance, and an association of high-normal albuminuria and microalbuminuria with the number of cigarettes smoked has been observed (57). Smokers are also exposed to substantial amounts of cadmium and lead. Smoking cessation should be an integral part of the management of patients with CKD (58).

Obesity: Visceral obesity is associated with a tripling of CV events in CKD patients (59). But, unlike the general population, dialysis patients have lower CV risk with higher body mass index (60). That paradox probably reflects the understanding that increased body mass index in dialysis patients is a general marker of better nutrition status.

Metabolic syndrome imparts an increased risk for CV events in the general population that might or might not be extrapolated to patients with CKD (data in CKD patients are lacking). Adiponectin,
an adipocyte hormone, has been implicated as a biomarker for metabolic syndrome; lower levels are associated with increased CV mortality in dialysis-dependent patients with CKD (61).

Nontraditional Risk Factors
Studies have shown that traditional risk factors are not adequate to account for the excess CVD in patients with CKD (62). Further studies in this area led to the identification of multiple nontraditional risk factors that might play a direct causal role, and of markers for pre-existing CVD or other factors that increase the risk of CVD (63).

Proteinuria: Microalbuminuria is strongly associated with CVD and its surrogate measures, including LVH, carotid intima media thickness, and myocardial ischemia (64–68). In patients with HTN and LVH, the LIFE study demonstrated that microalbuminuria is an independent risk factor for increased CV mortality and morbidity (69). The HOPE investigators found that, in patients with DM, the presence of microalbuminuria was associated with an increased risk (by a factor of 1.97) for the composite outcome of AMI, stroke, and CVD death, and (by a factor of 2.15) for all-cause mortality. Patients without DM have a 61% increased risk for the composite endpoint of stroke, AMI, or CVD death, and a doubled increase in the risk for all-cause mortality (70). Explanations for the adverse CV outcomes in DM patients with microalbuminuria suggest that these factors might be involved:

- Patients with microalbuminuria might have higher prevalence of risk factors.
- Diabetes is associated with endothelial dysfunction, vascular permeability, and abnormalities in coagulation and fibrinolysis (71,72).
- Chronic inflammation might potentially be associated with microalbuminuria (73).
- Microalbuminuria might also signify greater severity of end-organ damage.

The same factors might also be operable in non-DM patients with microalbuminuria. Microalbuminuria predicts progression to albuminuria in patients with or without DM, and those patients progress to renal insufficiency (74). That sequence is particularly important, because microalbuminuria can identify patients at risk of developing renal disease even before abnormalities of creatinine appear.

Homocysteine: Hyperhomocysteinemia was found to be associated with a higher incidence of CV mortality and atherothrombotic events in patients undergoing HD (75). High-dose folic acid, vitamin B6, and vitamin B12 supplementation did not reduce CV complications or mortality (76,77). Based on the poor benefit from intervention, evaluation for hyperhomocysteinemia and treatment of the condition are not routine in clinical practice.

Anemia: Low erythropoietin is the primary reason for the development of anemia in patients with CKD. The typical treatment for anemia is erythropoietin replacement therapy, which aims to increase hematocrit to a subnormal level. Increasing hematocrit to a normal value has been associated with increased CV mortality in HD patients with HF and ischemic heart disease (IHD) (78), primarily because of the use of intravenous iron dextran and also inadequate dialysis. Iron has been implicated in generation of oxygen-derived free radicals, and higher iron stores can cause detrimental coronary outcomes (79,80). Iron is also implicated in an increase in the risk of infection for patients on HD (81,82). Anemia is implicated in the pathogenesis of LVH in patients with CKD. In a blinded study, correction of anemia with recombinant human erythropoietin was associated with regression of LVH (83). Anemia in CKD is an inflammatory anemia that is usually normocytic. However, macrocytosis with an elevated mean corpuscular volume in patients with CKD is associated with impaired flow-mediated dilation because of endothelial dysfunction and independently predicts an increase in CV events (84).

Abnormal calcium phosphate metabolism: Hyperphosphatemia and hyperparathyroidism were found to be significantly associated with all-cause and CVD mortality in patients undergoing HD (85). Possible mechanisms of this association include vascular calcification and stiffening, increased pulse pressure, decreased coronary perfusion pressure, and LVH.

Inflammation: Increasingly, CKD is being recognized as a chronic inflammatory condition, with alterations in both adaptive and innate immunity.
Uremia creates a toxic milieu because of the accumulation of uremic toxins. Elevations in C-reactive protein (CRP), fibrinogen, interleukin 6, factor VIIc, factor VIIIc, plasmin–antiplasmin complex, D-dimer, and tumor necrosis factor α have been found in CKD patients and are postulated to be mediators of CVD (89). Dialysis, the mainstay of treatment, only partly removes those toxins. Hemodialysis exposes the patient to the risks associated with long-term indwelling catheters, membrane bioincompatibility, endotoxin leaks through back-filtration, and infections (90). Peritoneal dialysis is associated with an altered metabolic milieu because of high glucose, low pH, and glucose degradation products in dialysate (88). Patients with CKD are exposed to high levels of endotoxemia, particularly at initiation of dialysis. A high CVD burden and worsening renal function also are associated with endotoxemia, which contributes to systemic inflammation and cardiac injury, thereby reducing survival (91).

Well-studied as a marker of inflammation, CRP mediates several key processes in the pathogenesis of atherosclerosis from plaque initiation to formation and rupture (92). A major stimulus for CRP release is the interleukin 6 produced by intra-abdominal adipocytes, which explains the increased levels of CRP in patients with obesity—a common characteristic in CKD patients (93). Serum CRP increases with declining renal function, and more than one third of patients with ESRD have levels of CRP that put them in the highest-risk category for prediction of adverse outcomes (94–97). Compared with the lowest CRP tertile, the highest tertile is associated with a doubling of the risk for sudden cardiac arrest (98). Statins lower CRP levels; however, their effects on CV outcomes are controversial in patients with CKD. Rosuvastatin led to a 37% reduction in serum CRP, associated with significant reductions in CV events and all-cause mortality. In a study by Krane et al. (99), no significant difference in a composite CV outcome was observed in HD patients treated with atorvastatin; similar results with rosuvastatin were published by the AURORA study investigators (29).

Persistent inflammation leads to a malnutrition–inflammation–atherosclerosis and calcification syndrome that is associated with adverse CV outcomes (100,101). Recently, a new parameter in peripheral blood called the neutrophil-to-lymphocyte ratio has been shown to be lower in all stages of kidney disease; an increased neutrophil-to-lymphocyte ratio is independently related to impaired endothelial function and can potentially predict the occurrence of CV events (102). The finding of local neutrophil infiltration in advanced atherosclerotic plaques in patients with acute coronary syndrome has led to the hypothesis that such infiltration might degenerate the atherosclerotic plaque, thus destabilizing it (103). Elevated levels of neutrophil gelatinase–associated lipocalin was able to predict future CV events (104).

**Oxidative stress:** Uremic patients have a high oxidative burden, and the resultant oxidative stress has been implicated in atherogenesis and CV morbidity and mortality. Activated phagocytes provide a link between oxidative stress and inflammation. Retained uremic solutes such as β2-microglobulin, AGEs, cysteine, and homocysteine serve as substrates for oxidative injury (105). Results from studies conducted to reduce oxidative stress are contradictory. The HOPE study showed no benefit for CVD outcomes with vitamin E; however, the SPACE trial demonstrated a benefit with antioxidants, reporting a lower incidence of a composite endpoint consisting of fatal and nonfatal AMI, CVD death, need for coronary angioplasty or coronary artery bypass grafting, ischemic stroke, and peripheral vascular disease (106,107). Acetylcysteine, an antioxidant, was shown to reduce evidence of CVD in patients with renal failure (108).

**CVD pathogenesis**

The strong association between CKD and CVD is predictable for several reasons:

- Risk factors for CVD occur commonly in CKD.
- CKD is associated with an increased prevalence of traditional CVD risk factors (92).
- Patients with CKD manifest a variety of nontraditional CVD risk factors.
- By itself, CKD is an independent risk-equivalent of CVD (4).
- The presence of CVD predicts a faster decline in kidney function, establishing a vicious cycle (47,109).

Myocardial and arterial remodeling form the central pathway in the pathogenesis of CVD in patients with CKD. Myocardial remodeling occurs
predominantly secondary to pressure and volume overload. Pressure overload results from the frequent occurrence of HTN, aortic stenosis, arteriosclerosis, DM, and anemia, resulting in LVH. Volume overload is the result of arteriovenous shunting in dialysis, salt and water overload, anemia, IHD, HTN, and hypoalbuminemia, resulting in left ventricular dilation. The uremic environment and IHD also induce an increase in myocardial cell apoptosis that accelerates the cardiomyopathy, resulting in both systolic and diastolic dysfunction (110). Uremic cardiomyopathy was originally classified into three groups: LVH, LV dilation, and systolic dysfunction. However Mark et al. (111) showed that LVH is the predominant myocardial alteration specific to uremia; LV dilation and systolic dysfunction are usually attributable to underlying IHD.

Vascular pathology in renal disease includes accelerated atherosclerosis, arteriosclerosis, vascular calcification, and endothelial dysfunction. Vessel wall injury, HTN, dyslipidemia, prothrombotic factors, increased oxidant stress, and hyperhomocysteinemia are among the risk factors. Vascular remodeling occurs in both arterial lumen and vessel wall components, leading to atherosclerosis and arteriosclerosis respectively. Intimal fibro-fatty plaque formation is the hallmark of atherosclerosis; it is highly prevalent in CKD (112). Atherosclerotic lesions are usually fibro-atheromatous in the general population, but in patients with renal failure, they are extensive, more unstable, frequently calcified, and associated with increased medial thickness (113).

In addition to the traditional risk factors, multiple nontraditional risk factors such as albuminuria, anemia, inflammation, oxidant distress, endothelial dysfunction, homocystine, Lp(a), malnutrition, thrombogenic factors, sympathetic activity, and insulin resistance are known to be associated with atherosclerosis (110). Arteriosclerotic lesions are usually fibro-atheromatous in the general population, but in patients with renal failure, they are extensive, more unstable, frequently calcified, and associated with increased medial thickness (113).

In addition to the traditional risk factors, multiple nontraditional risk factors such as albuminuria, anemia, inflammation, oxidant distress, endothelial dysfunction, homocystine, Lp(a), malnutrition, thrombogenic factors, sympathetic activity, and insulin resistance are known to be associated with atherosclerosis (110). Arteriosclerosis is characterized by diffuse dilation and hypertrophy of the large-conduit arteries and by stiffening of the arterial walls, occurrences that are particularly secondary to pressure and volume overload and the HTN that frequently accompanies renal disease. The consequences are isolated systolic HTN leading to LVH, increased myocardial oxygen demand, and altered coronary perfusion and blood flow distribution leading to subendocardial ischemia, which is recognized as an independent predictor of overall and cardiac mortality (114).

Vascular calcification is one of the characteristic features of renal disease. Uremic toxins promote vascular smooth muscle cell proliferation; the transformation of those cells into an osteoblast-like phenotype ultimately leads to vascular calcification (115). Disorders of calcium and phosphate metabolism, hyperhomocysteinemia, AGES, and genetic factors (lower fetuin-A, matrix Gla protein, and osteoprotegerin, and loss of fibroblast growth factor 23) have been implicated in vascular calcification (116). Calcification of the atheromatous plaque (“arterial intima calcification,” an occlusive condition) frequently leads to involvement of the medial layer to form medial calcinosis (“arterial media calcification,” a nonocclusive condition) (117). Calcification of the medial layer reduces arterial elasticity, leading to macroangiopathy. It is frequently seen in elderly CKD patients and in those with diabetes. Medial calcinosis is associated with increased all-cause and CV mortality in patients on dialysis (117), and vascular calcification is associated with LVH (49).

Normal endothelial function is critical to the prevention of vascular disease, including atherosclerosis. Patients with CKD exhibit a wide range of abnormalities that can adversely influence endothelial function. Oxidative stress and chronic inflammation (with the resultant reactive oxygen species) play a main role (118). The results are inhibition of endothelial proliferation (119), a procoagulant environment at the cell surface (because of an increase in plasminogen activator inhibitor 1 and von Willebrand factor, and a decrease in tissue plasminogen activator), and dysregulation of vascular tone because of inhibition of endothelial inducible nitric oxide synthase caused by dimethylarginine, homocysteine, and oxidatively modified LDLs (120). Endothelial function—assessed by von Willebrand factor and by vascular dilation resulting from hyperemia—was abnormal even in patients with mild renal insufficiency and without any atherosclerosis.

Clinical syndromes
Cardiovascular disease is defined as the presence of IHD, HF, or LVH. Other CV conditions that are more common in CKD patients include sudden cardiac arrest, atrial fibrillation, hypotension, and cardiomyopathy. Mortality from CVD is higher by a factor of 10–30 in patients undergoing dialysis than
in the general population. This high mortality rate is attributable to a high case fatality rate and a high prevalence of CVD. High case fatality is particularly observed after AMI or HF.

**ISCHEMIC HEART DISEASE**

In CKD patients, IHD is predominantly a result of coronary atherosclerosis. With atherosclerotic involvement of the coronary arteries, the initial presentation is often acute coronary syndrome (ACS). In dialysis patients, AMI is considered a catastrophic event (more complicated and associated with higher risk of death), with dismal long-term survival. Almost 1 in 4 CKD patients experiencing AMI dies in hospital, and among the patients that survive hospitalization, the mortality rate continues to be high: 59%, 73%, and 89% at 1, 2, and 5 years respectively (121). Even in the reperfusion era, mortality continues to be high, although improvement in one outcome—the 30-day mortality after an ST-elevation myocardial infarction—was reported by the U.S. Renal Data System in 2013.

The reasons for the dismal outcomes for ACS in patients with CKD are these:

- The index of suspicion is lower and the level of inaccuracy is higher for a diagnosis of ACS in patients with ESRD on dialysis, likely because only 44% of patients with ACS have chest pain and because diagnostic EKG changes are less likely in the presence of LVH (122).
- Invasive reperfusion strategies are underutilized, and medical therapy such as antiplatelet agents, beta-blockers, and RAAS blockers are inadequately used because contraindications to those therapies are often present. Patients who received such treatments were shown to have better outcomes (123).
- Other causes include increased hemorrhagic complications after percutaneous coronary intervention and increased likelihood of post-infarction HF and cardiac arrest (122,124).
- Patients who undergo percutaneous revascularization also experience an increased incidence of stent thrombosis in the uremic milieu. Reduced GFR and proteinuria were identified as risk factors for stent thrombosis (125).
- The incidence of arrhythmias and left ventricular dysfunction is increased (126).

Research in animal models suggests that ischemic preconditioning might be the best opportunity to improve outcomes after an ACS in patients with CKD (127). Revascularization is critical for optimal outcomes in pre-dialysis patients. But the same benefits might not extend to ESRD patients because of competing risk factors.

Causes other than coronary atherosclerosis are also implicated IHD. In older studies, almost half the dialysis patients with myocardial ischemia did not have large-vessel occlusive CAD. In those patients, myocardial ischemia was attributed to LVH, volume overload, small-vessel CAD, and anemia (128). Coronary calcification, measured as a coronary artery calcification score by electron-beam computed tomography, has been extensively studied. In the general population, arterial calcification is predominantly intimal; in uremic patients, calcification is predominantly medial. A high coronary artery calcification score by electron-beam computed tomography in uremic patients estimates calcium deposition in the intima, the media, or both (113), and is an independent marker of death both in dialysis patients (129) and in diabetic patients without CKD (130). Prevention of secondary hyperparathyroidism by control of phosphorus appears to be the most important measure to take in preventing vascular calcification (131).

**HEART FAILURE**

Clinical manifestations of HF are present in about one third of new dialysis patients. Of patients with CKD, 20% experienced a worsening of HF in year 1, and LVH, GFR, and hemoglobin were associated with the HF (44). In dialysis patients with HF, survival is demonstrably very poor, the 2-year mortality being 49% in HD populations and 53% in PD populations. The mortality rate currently remains about the same as that reported by the U.S. Renal Data System in 2013. Independent positive predictors for mortality in the patients were age, male sex, DM, HTN, history of CVD, and HF (132).

**SUDDEN CARDIAC ARREST**

Sudden cardiac arrest is defined as an unexpected death from a CV cause with or without structural heart disease (133). Outcomes are invariably dismal, with only 8% of patients surviving to hospital discharge (134). Randomized trials have proved that renal disease increases the risk of sudden cardiac
arrest. In CKD patients with CV disease, the risk of sudden cardiac arrest is higher by 11% – 17% for every 10 mL/min decline in GFR (135,136). In elderly patients without CV disease, the presence of CKD was independently associated with sudden cardiac arrest (137). That association strengthened in patients on dialysis, with 22% of all deaths in dialysis patients being attributed to sudden cardiac arrest, at a rate of about 2% per year (133).

Both the substrate and the trigger—without mutual exclusivity—are necessary for arrhythmogenesis leading to sudden cardiac arrest. The presence of CKD serves as a good substrate because of the associated structural (myocardial fibrosis, LVH, vascular calcification) and electrophysiologic remodeling (alteration in the conduction velocity and repolarization). Patients with CKD are also exposed to a variety of triggers inherent both to CKD and to dialysis, including myocardial ischemia, sympathetic activation, inflammation, electrolyte shifts, and hemodynamic instability (133).

Drug therapies including beta-blockers, RAAS blockers, and statins have been widely used in renal disease and have been shown to improve CV outcomes. However, data to evaluate their role in prevention of sudden cardiac arrest are insufficient. Randomized trials of their use have reported widespread evidence for the prevention of sudden cardiac arrest in patients with CV disease, but those trials excluded patients with advanced kidney disease. Based on retrospective analysis of the randomized trials, early-stage CKD patients (compared with advanced CKD and dialysis patients) appear to experience a reduction in mortality with implantation of a cardioverter defibrillator. The reduced response to ICD in the more advanced patients might be related to metabolic derangement, higher defibrillation thresholds (138), and an increased infection rate requiring extraction of the device (139). In contrast, implantation of a cardioverter defibrillator for secondary prevention in patients with ESRD appears to be beneficial (140). However, the exact indications for such implantation in patients with ESRD remain uncertain.

Summary

By itself, CKD is a major health burden, and its presence alone imparts a disproportionately high risk for CV disease. Being asymptomatic, CKD often goes undiagnosed. The presence of renal dysfunction also limits several valuable preventive and therapeutic strategies that are used to improve CV outcomes in patients without renal disease. The increased prevalence of traditional and nontraditional CV risk factors in patients with CKD has resulted in an exponential increase of CV disease in that population. Recognition of this association is imperative if CV outcomes in these patients are to be improved.

Disclosures

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References


Corresponding author:
Kul Aggarwal, MD, University of Missouri–Cardiology, One Hospital Drive, CE306, Columbia, Missouri 65212 U.S.A.
E-mail:
aggarwalk@health.missouri.edu