REVIEW

Cardiovascular Pathophysiology in Chronic Kidney Disease: Opportunities to Transition from Disease to Health

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ABSTRACT

Background: Chronic kidney disease (CKD) is common, and is associated with a high burden of cardiovascular disease. This cardiovascular risk is incompletely explained by traditional risk factors, calling attention to a need to better understand the pathways in CKD contributing to adverse cardiovascular outcomes.

Findings: Pathophysiological derangements associated with CKD, including disordered sodium, potassium, and water homeostasis, renin-angiotensin-aldosterone and sympathetic activity, anemia, bone and mineral metabolism, uremia, and toxin accumulation may contribute directly to progression of cardiovascular disease and adverse outcomes.

Conclusion: Improving cardiovascular health in patients with CKD requires improved understanding of renocardiac pathophysiology. Ultimately, the most successful strategy may be prevention of incident CKD itself.

Key Words: cardiorenal syndrome, cardiovascular disease, chronic kidney disease, renocardiac syndrome

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INTRODUCTION

Cardiovascular diseases (CVD), including hypertension, currently affect 36.9% of the US population and account for $444.2 billion in direct and indirect costs per year.[1] By 2030, costs are projected to exceed $1 trillion. These costs are untenable, and sound the call for a transition in focus from treatment of disease to promotion of health.

In no population is this more relevant than individuals with chronic kidney disease (CKD). Defined by evidence of kidney damage or reduction in glomerular filtration rate for at least 3 months, CKD affects more than 1 in 6 US adults, including more than 500,000 with end-stage disease requiring renal replacement therapy. In this population, particularly those on hemodialysis, the burden of CVD is magnified, including coronary and peripheral arterial disease, atrial fibrillation, stroke, congestive heart failure (CHF), and sudden cardiac arrest (SCA). In the context of primary CKD, such incident CVD has been referred to as type 4 cardiorenal syndrome, or chronic reno-cardiac syndrome.[2]

Although overall cardiovascular mortality in patients with CKD has declined over the past 2 decades, driven importantly by reduction in mortality related to acute myocardial infarction (MI) in parallel with global advances in reperfusion therapy, antiplatelets, and quality of care, risks for death due to CHF (5%) and SCA (26%) have remained steady.[3,4] Three factors must be considered.

First, poor outcomes reflect the difficulty of treating CVD in CKD. Data to inform optimal therapy are limited, due to systematic exclusion of patients with advanced CKD from many seminal trials. Flexibility to diagnose and treat disease is reduced as a result of limitations on use of standard tools of care, such as iodinated contrast dye and gadolinium, renin-angiotensin-aldosterone (RAA) antagonists and novel anticoagulants. Avoidance of such tools may exceed true risks, as thresholds of renal dysfunction for exclusion are only loosely substantiated, and clinicians sooner tolerate sins of omission than those of commission. To a degree difficult to measure, perception of patients with CKD as doomed can become self-fulfilling prophecy by influencing withholding of tests and therapies, so-called "therapeutic nihilism."

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Second, the extent of CVD in CKD reflects a significant overlap in risk factors for atherosclerosis, in particular hypertension and diabetes mellitus. Progressive nephropathy, associated with increasing risk for cardiovascular death,[5] is also associated with increasing chronicity of hypertension and diabetes. CKD may be a marker for cumulative vascular injury, and poor outcomes the result of a greater extent and duration of disease. Overlap in risk factors appears to interact importantly with racial disparities in both incident CKD and cardiovascular death, with a disproportionate burden of both among American blacks.[6,7]

Third, on which this review focuses, it is possible that elements of the pathophysiology of CKD itself potentiate progression of CVD and adverse outcomes. Beyond traditional CVD risk factors, the consequences of progressive renal dysfunction, including disorder of sodium and water homeostasis, RAA and sympathetic nervous system activation, anemia, disorder of bone and mineral metabolism, disorder of potassium homeostasis, uremia, and toxins, may contribute directly to CVD. Understanding the relationship between these disturbances and CVD progression may inform novel approaches to therapy in patients with established CKD, and more importantly, may inspire increased emphasis on CKD prevention.

TRADITIONAL RISK FACTORS

In part, CKD is a marker for presence of traditional CVD risk factors.

Independent risk factors for coronary heart disease identified in the Framingham Heart Study—age, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood pressure, diabetes, and smoking—all have been associated with risk for CKD.[8,9] In turn, compared with the general population, individuals with advanced CKD more often exhibit diabetes, hypertension, low physical activity, low HDL-C, and hypertriglyceridemia, controlling for age, race, sex, and atherosclerotic CVD.[10]

Traditional risk factors alone cannot completely explain CVD risk in CKD. In a pooled analysis of 577 women and 357 men with CKD in the Atherosclerosis Risk in Communities (ARIC) study and Cardiovascular Health Study (CHS), Framingham scores underestimated risk for cardiac events at 5 and 10 years.[11]

An instructive example comes from experience with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) in advanced CKD. Whereas the prospective Dialysis Outcomes and Practice Patterns Study (DOPPS) suggested significant reduction in cardiovascular and non-cardiovascular death in association with statin use,[12] randomized comparisons of statin versus placebo in the Deutsche Diabetes Dialyse Studie (4D) trial[13] and the larger A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) showed no significant difference in the composite of cardiovascular death, MI, and stroke.[14] Most recently, the Study of Heart and Renal Protection (SHARP) did show a benefit of combination statin ezetimibe therapy for incidence of a first major atherosclerotic event (non-fatal MI or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).[15]

Taken together, these data suggest statins may reduce atherosclerotic events in patients with CKD, but evidence for reduction in mortality remains elusive. Multiple explanations for this may be considered. CKD may lead to cardiovascular mortality through pathways independent of statins. Statins might be expected to have less effect on incidence of SCA, which accounted for 34% of events in 4D. None of the above trials included CHF endpoints. Alternatively, CKD may attenuate or alter the physiological effect of statins. Awareness of a residual CVD risk in CKD, incompletely explained by traditional risk factor and insufficiently reduced by risk factor modification, motivates an analysis of the several facets of CKD pathophysiology contributing to CVD progression and mortality.[16]

THE KIDNEY IN HEALTH AND DISEASE

Insight into the consequences of renal dysfunction may be gleaned from review of the kidney's normal function. In health, the normal kidney shoulders several responsibilities, including regulation of salt and water homeostasis, vascular tone (via renin, activating angiotensin, and, in turn, aldosterone), oxygen-carrying capacity (via erythropoietin, stimulating bone marrow production of red blood cells), bone and mineral metabolism (via phosphate excretion and 1α-hydroxylase, activating 25-hydroxyvitamin D), potassium regulation, and elimination of drugs and toxins. Each of these pathways may contribute to CVD.

Sodium and Water Balance

Altered salt and water handling in CKD predisposes to volume retention and secondary alterations in vascular tone that together contribute to hypertension. Responsiveness to both exogenous diuretics and endogenous natriuretic peptides is reduced. When partially nephrectomized dogs or humans with stage 5 CKD are subjected to a dietary salt load, mean arterial pressure increases.[17,18] Elevation in blood pressure is initially explained by expansion of extracellular fluid volume, with a commensurate rise in cardiac output. Subsequently, however, cardiac output returns to baseline, while arterial pressure remains elevated, consistent with an increase in total peripheral resistance.[19] Augmentation in systemic vascular tone is mediated by activation of

the sympathetic nervous system and RAA system, as well as progressive imbalance of nitric oxide and asymmetric dimethylarginine.[20]

Renin, Angiotensin and Aldosterone

Activation of the RAA axis contributes significantly to abnormal vascular tone, hypertension, and nephron loss in CKD.

Renin is secreted by granular cells in the nephron's juxtaglomerular apparatus in response to multiple triggers, including hypotension, decreased detection of sodium chloride by the macula densa, and sympathetic nervous system activation. An aspartyl protease, renin cleaves circulating angiotensinogen, generating angiotensin I. Angiotensin I, in turn, is modified by angiotensin-converting enzyme (ACE) into angiotensin II, the principal effector of the RAA axis. Acting via type 1 and 2 angiotensin receptors, angiotensin II exerts multiple effects, including vasoconstriction, aldosterone synthesis, and anti-diuretic hormone (vasopressin) secretion.

In addition to these primary effects, downstream effects of angiotensin II mediated by second messengers may carry particular significance for progression of CKD and CVD. Transforming growth factor β, a mediator of interstitial fibrosis, is up-regulated by activation of the type 1 angiotensin receptor, and down-regulated in response to the angiotensin receptor blocker (ARB) losartan in animal models of cardiomyopathy and renal failure.[21,22] This pathway has been confirmed in humans and clinically applied in the context of thoracic aortic aneurysms in Marfan syndrome.[23,24]

Aldosterone promotes sodium and water retention, and also mediates increases in size and stiffness of human endothelial cells.[25] At the level of the myocardium, mineralocorticoid receptor activation contributes to extracellular matrix deposition, fibrosis, diastolic dysfunction, and alterations in cardiomyocyte calcium handling predisposing to delayed afterdepolarizations.[26] In addition to cardiovascular damage, RAA activation drives progression of CKD,[27] perpetuating a spiral of deteriorating renal and cardiovascular function.

An extensive literature, exceeding the scope of this review, has defined the cardiovascular benefits of RAA antagonism in diverse populations of patients with CVD. ACE inhibitors have been associated with improvement in mortality and symptoms across the spectrum of CHF, including New York Heart Association (NYHA) class IV,[28] symptomatic NYHA class II-III,[29] asymptomatic left ventricular (LV) dysfunction,[30] and symptomatic LV dysfunction after MI.[31-33] In high-risk individuals with vascular disease or diabetes and an additional CVD risk factor, without CHF, ACE inhibitors prevent a composite of cardiovascular events, including MI, stroke, and death.[34] ARBs have been shown to confer analogous benefits in CHF[35-37] and after MI.[38] Combination of ACE inhibitor and ARB therapies has not shown consistent benefit for hard clinical endpoints in hypertension, CHF, coronary artery disease (CAD), or CKD,[39] and current practice is to choose 1 agent.

Aldosterone antagonism with spironolactone or eplerenone has shown mortality benefit in patients with severe CHF (NYHA III-IV and LV ejection fraction [LVEF] <35%),[40] milder CHF (NYHA II and LVEF <35%),[41] and LV dysfunction and CHF after MI.[42] Additive benefit of aldosterone antagonism on background ACE inhibitor/ARB therapy may relate to "aldosterone breakthrough," a paradoxical rise in circulating aldosterone that occurs in 10% to 50% of patients within 6 to 12 months of initiation of an ACE inhibitor or ARB, possibly related to hyperkalemia.[43]

Direct inhibition of renin with aliskiren reduces blood pressure[44] and LV mass[45] in hypertensive patients with efficacy comparable to that of ARBs, albeit without additive benefit. Interest in application of direct renin inhibition to the CKD setting grew from the small Aliskiren in the eValuation of proteinuria in Diabetes (AVOID) study, in which addition of aliskiren to maximally dosed losartan in patients with hypertension and diabetic nephropathy was associated with a significant reduction in albuminuria.[46] The larger subsequent Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) study, designed to measure cardiovascular and renal endpoints in diabetic patients with CKD, CVD or both using aliskiren in addition to background ACE inhibitor therapy, was terminated prematurely due to significant increases in hyperkalemia and hypotension despite no significant difference in a composite of CVD and CKD endpoints with aliskiren compared with placebo.[47] Most recently, the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) study demonstrated no benefit of aliskiren added to a background of optimal medical therapy in patients hospitalized for CHF with LV dysfunction, with an excess of hyperkalemia, hypotension, and renal failure.[48]

Are benefits of RAA antagonism evident in patients with CKD? With respect to CHF, in the subgroup of patients with CKD in the Valsartan in Heart Failure Trial (Val-HeFT), RAA antagonism with the ARB valsartan was associated with a reduction in cardiovascular morbidity and mortality similar to that observed in patients without CKD ($P = 0.71$), and similar mild reduction in estimated glomerular filtration rate (eGFR).[49] With respect to prevention, patients with serum creatinine up to 2.3 mg/dL in the absence of significant proteinuria were included in the Heart Outcomes Prevention Evaluation (HOPE) study. Ascertaining the effects of RAA antagonism in more advanced CKD is challenging, due to systematic exclusion of affected patients from seminal trials. Potential for cardiovascular benefit in this setting must be balanced against risk for worsening renal function and hyperkalemia.

Benefits of RAA antagonism for CHF in CKD may relate importantly to the presence or absence of LV dysfunction. Common in CKD is CHF with preserved ejection fraction (HFPEF) or diastolic heart failure, for which ACE inhibitors and ARBs have not shown mortality benefit.[50-53] There remains interest in use of aldosterone antagonists for reduction in cardiovascular mortality in CKD,[54] and active investigation of aldosterone antagonism in CHF with preserved ejection fraction is under way in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) study, which will include patients with eGFR as low as 30 mL/min/1.73 m^2.[55]

The next frontier of RAA antagonism comes via an invasive procedure, renal sympathetic denervation (RSD). Accumulating data document the utility of RSD in controlling previously difficult-to-control hypertension,[56,57] and large trials for this indication are under way. For patients with CKD, in whom augmented sympathetic tone contributes to increased RAA activation,[58] RSD may prove useful for not only control of hypertension but also neurohormonal modulation in CHF and reduction in SCA. Early data suggest that RSD is safe and effective for blood pressure reduction in patients with stage 3 to 4 CKD,[59] and may be associated with reduced burden of atrial and ventricular arrhythmia.[60]

Anemia

Anemia is common in CKD, and derives from a combination of erythropoietin deficiency, iron deficiency, and erythropoietin resistance secondary to chronic disease.[61] In observational studies of patients on hemodialysis, anemia is independently associated with risk for adverse cardiovascular outcomes, including new and recurrent CHF, hospitalization, and mortality.[62,63] This risk is particularly pronounced in patients with comorbid diabetes.[64]

The mechanism of this observed association remains enigmatic. Hypothetically, anemia could be causally linked to CVD, with decreased oxygen-carrying capacity and oxygen delivery leading to tissue hypoxia, cell death, adverse remodeling, and dysrhythmia. Alternatively, anemia could be a surrogate marker for other pathways in CKD leading to CVD.

If the link were causal, we should expect correction of anemia to confer cardiovascular benefit. But this has tended to not be the case. In studies ranging from the US Normal Hematocrit Study (hemodialysis patients with CHF or CAD),[65] to Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR; nondialysis CKD patients),[66] to the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE; non-dialysis CKD patients),[67] to, most recently, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT; nondialysis CKD patients with diabetes),[68] higher hemoglobin targets in CKD have been associated with no cardiovascular benefit and, indeed, trends toward harm, in particular involving risk for stroke.

It is important to recognize that these studies evaluated the effect of a strategy to treat anemia—erythropoietin supplementation—rather than correction of anemia per se. It is possible that alternative strategies to correct anemia would improve cardiovascular outcomes. These too are limited. Serial transfusions are not only cost and resource prohibitive, but potentially harmful, promoting HLA sensitization (jeopardizing future transplantation) and introducing free hemoglobin (scavenging nitric oxide).[69,70] Excessive increase in erythrocytes by any means may confer a deleterious increase in viscosity. Although it remains possible that anemia contributes directly to progression of CVD in CKD, the association is likely complex, and more insight into the mechanisms connecting anemia to CVD is required.

Bone and Mineral Metabolism

Using serum phosphate, serum calcium-phosphate product, and intact parathyroid hormone (iPTH) levels as markers of bone and mineral dysregulation, several epidemiologic studies have identified associations with risk for death and CVD. In a nationally-representative sample of 6407 patients with end-stage renal disease (ESRD) on hemodialysis, all-cause mortality was significantly associated with the highest quintiles of serum phosphate (>6.5 mg/dL relative risk [RR] = 1.27, relative to 2.4-6.5 mg/dL) and serum calcium-phosphate product (>72 mg^2/dL^2, RR = 1.34, relative to 42-52 mg^2/dL^2).[71] Excess mortality is mainly cardiovascular in origin. In a nationally-representative sample of 7096 patients on hemodialysis, hyperphosphatemia (>6.5 mg/dL) predicted risk for death due to CAD (RR = 1.41) and SCA (RR = 1.20).[72] SCA also was associated with calcium-phosphate product (RR = 1.07 per additional 10 mg^2/dL^2) and serum iPTH level (>495 pg/mL RR = 1.25). Individual markers of bone turnover appear to be less useful in isolation than complex analysis of multiple markers. In a study of all prevalent dialysis patients in British Columbia in January 2000, with 2 years of follow-up, it was the particular combinations of high calcium-phosphate product with high (RR = 3.71) or low (RR = 4.30) iPTH that carried the highest risk for mortality.[73] Association of cardiovascular risk with elevations in serum calcium, calcium-phosphate product, and iPTH was replicated in a retrospective study of 14,829 US patients on hemodialysis.[74] Although dysregulation of bone and mineral metabolism could simply represent a marker of CKD, its plausibility as a direct contributor to cardiovascular risk is enhanced by the similar association of calcium-phosphate product elevation with cardiovascular risk in community-dwelling adults with normal or near-normal kidney function.[75]

One putative mechanism of this relationship is cardiovascular ossification, with pathological calcification of the myocardium and vasculature.[69] Patients with

advanced CKD, particularly those on dialysis, are subject to accelerated vascular calcification, as evident in findings of abnormal calcifications on noninvasive imaging of affected children and young adults.[76-78] Deposited calcium may contribute to both atherosclerosis and arteriosclerosis. Hardening and thickening of the intima and media by calcium decrease distensibility of large arteries to accommodate pulsatile blood flow, increasing systolic blood pressure and LV afterload and decreasing diastolic blood pressure and coronary perfusion.[79] Presence and extent of vascular calcification predict cardiovascular risk in patients with advanced CKD. When ultrasonography is performed for multiple vascular beds in patients on hemodialysis, the burden of calcification correlates with cardiovascular and all-cause mortality.[80]

Additional postulated mechanisms relating hyperphosphatemia to CVD include direct vascular injury via endothelial dysfunction and oxidative stress, increased levels of fibroblast growth factor 23, and inhibition of 1,25-dihydroxyvitamin D synthesis and iPTH, with associated proinflammatory and profibrotic effects.[81]

Hyperphosphatemia is alluring as a cardiovascular risk factor, in part, because it is modifiable. Phosphate-binding therapy is a mainstay of management in ESRD, with multiple oral options including calcium-based therapies (acetate and chloride), newer non—calcium-based therapies (sevelamer and lanthanum), and older aluminum-based therapies. Whether serum-phosphate reduction yields reduction in cardiovascular risk remains to be proven, however, as randomized clinical trials have yet to demonstrate a clear reduction in cardiovascular events or mortality. Recognizing that hyperphosphatemia may result from inadequate intensity or frequency of dialysis, it is plausible that observed associations with cardiovascular risk are confounded by increased severity of disease or diminished adequacy of therapy.

Closely intertwined with dysregulation of bone and mineral metabolism in CKD is the problem of vitamin D deficiency. In CKD, deficiency of 1,25-dihydroxyvitamin D is common, and may result from both deficiency of 25-hydroxyvitamin D, the vitamin's storage form, as well as deficient activity of renal 1α-hydroxylase. Several studies have explored the relationship of vitamin D deficiency to CVD in CKD.

In a series of 1108 German patients on hemodialysis followed over a median of 4 years, patients with severe 25-hydroxyvitamin D deficiency (<25 mmol/L) had significantly increased risks for cardiovascular events (hazard ratio [HR], 1.78), SCA (HR, 2.99), and all-cause mortality (HR, 1.74).[82]

Widespread expression of both the vitamin D receptor and 1α-hydroxylase by cells throughout the vascular system, including vascular smooth muscle cells, endothelial cells, and cardiomyocytes, has lent biological plausibility to the relevance of vitamin D to incident CVD.[83] Preclinical data from rodent models have pointed, in particular, to a role for vitamin D signaling in modulating ventricular hypertrophy. Vitamin D receptor knockout mice develop significant cardiomyocyte hypertrophy.[84] Conversely, supplemental 1,25-dihydroxyvitamin D attenuates cardiac hypertrophy in neonatal rats exposed to endothelin,[85] and salt-sensitive rats fed a high-salt diet.[86]

To date, randomized clinical trial data describing the effect of vitamin D supplementation on cardiovascular outcomes in the population at large have been limited and inconclusive.[87] In the particular setting of CKD, clinical trial data similarly have yet to demonstrate benefit of vitamin D supplementation.

The recent Paricalcitol Capsule Benefits in Renal Failure-Induced Cardiac Morbidity (PRIMO) trial sought to determine the effects of paricalcitol on intermediate cardiac end points, including LV hypertrophy, LV diastolic function, and cardiovascular events.[88] A total of 227 patients with stage 3/4 CKD were randomized 1:1 to paricalcitol or placebo, along with standard care for blood pressure control, with follow-up at 24 and 48 weeks. Baseline cardiac imaging showed preserved LVEF, abnormal diastolic function, and LV hypertrophy in both treatment groups. At 48 weeks, there were no significant differences in LV mass index by cardiac magnetic resonance imaging, diastolic function by transthoracic echocardiography, or all-cause hospitalizations. There were fewer cardiovascular hospitalizations in the paricalcitol group and an attenuated increase in blood levels of brain natriuretic peptide (BNP). Although small sample size may have limited the power of PRIMO to detect clinically important benefits of vitamin D supplementation, it is also possible that supplementation was too late or follow-up was too short in this population with preexisting LV hypertrophy and diastolic dysfunction.

Potassium

The kidney plays a fundamental role in maintenance of total body potassium stores. With progressive CKD, the body's capacity to maintain normokalemia in the face of alterations in potassium intake and transcellular electrolyte shifts is increasingly compromised.

CKD predicts risk for hyperkalemia and associated mortality. In a retrospective review of 2,103,422 medical records from 245,808 veterans with at least 1 hospitalization during 2005, patients with CKD had a more than 3-fold increase in risk for hyperkalemia compared with those without CKD (7.67 vs 2.30 per 100 patient-months for those on renin-angiotensin system blockers, and 8.22 vs 1.77 per 100 patient-months for those not on renin-angiotensin system blockers).[89] Among those with CKD, both moderate (5.5-6.0 meq/L) and severe (>6.0 meq/L) hyperkalemia were significant predictors of death within 1 day of the hyperkalemic event (in stage 3 CKD, adjusted odds ratio [OR], 5.35 and 19.52; in

stage 4 CKD, OR, 5.73 and 11.56; and in stage 5 CKD, OR, 2.31 and 8.02, respectively).

CKD is similarly an important predictor of hyperkalemia in patients with CHF. In the Candesartan in Heart Failure–Assessment of Mortality and Morbidity (CHARM) study, which enrolled a broadly representative sample of patients with CHF for randomization to the ARB candesartan or placebo, CKD (defined as creatinine >2 mg/dL) independently predicted risk for hyperkalemia.[90]

Hyperkalemia may contribute to cardiovascular mortality in CKD in part through direct effects on cardiac conduction. Increases in extracellular potassium decrease cardiomyocyte resting membrane potential, slowing the rate of rise of phase 0 of the cardiac action potential, slowing impulse conduction, prolonging membrane depolarization, and shortening repolarization time.[91] Progression of hyperkalemia generates the familiar evolution of the surface electrocardiogram through peaked T waves, PR prolongation, QRS widening, sinoatrial arrest, "sine wave" appearance, and ultimately, ventricular fibrillation and asystole. Bradyarrhythmias and heart block also may occur.

Some cardiovascular mortality may be driven, rather, by aggressive treatment of hyperkalemia. Studies of SCA during hemodialysis consistently identify use of a low-potassium dialysate as a predictor of death. Among the 2,793 patients with CKD and CHF in the Digitalis Intervention Group (DIG) trial, a randomized clinical trial of digoxin, hypokalemia (potassium <4 meq/L) was a significant predictor of all-cause mortality, cardiovascular and CHF mortality, and all-cause cardiovascular and CHF hospitalizations.[92]

Finally, adverse cardiovascular outcomes may result not from hyperkalemia itself, but rather the fear of hyperkalemia. Physicians routinely avoid prescribing medications to patients with CKD, even when eGFR exceeds cut-offs used in clinical trials. In a retrospective study of more than 100,000 patients with acute MI, those patients with ESRD on dialysis were significantly less likely to be treated with aspirin (67% vs 82.4%), β–blockers (43.2% vs 50.8%), or ACE inhibitors (38.5% vs 60.3%), although benefits of these therapies were similar in treated patients with and without ESRD.[93] This gap in prescribing of β–blockers and ACE inhibitors/ARBs appears to be narrowing in the most recent United States Renal data System data.[4]

Uremia and Toxins

Of final interest is the role of defective renal toxin clearance on development of CVD. Renal failure is associated with retention of a broad array of so-called uremic solutes, including advanced glycation end-products, granulocyte inhibiting protein I, β–2 microglobulin; cystatin C, Clara cell protein, retinol-binding protein, leptin, guanidines, oxalate, p-cresol, indoles, and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, among others.[94] It is postulated that toxins, in isolation or in combination, may contribute to inflammation and oxidative stress. The association of uremia with pericarditis is well described. The implications of chronic uremic solute accumulation for pathogenesis of coronary heart disease and CHF remain to be elucidated.[95]

CONCLUSION

The burden of CVD is heavy among patients with CKD, and borne by us all. Control of traditional risk factors is necessary but not sufficient to stem it, and in particular, CHF and SCA. New approaches are needed to understand and target pathways in CKD that give rise to CVD. Ultimately, the most potent strategy to accomplish this may be to prevent incident CKD.

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