Cardiovascular Involvement in General Medical Conditions

Chronic Kidney Disease

Effects on the Cardiovascular System

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Abstract—Accelerated cardiovascular disease is a frequent complication of renal disease. Chronic kidney disease promotes hypertension and dyslipidemia, which in turn can contribute to the progression of renal failure. Furthermore, diabetic nephropathy is the leading cause of renal failure in developed countries. Together, hypertension, dyslipidemia, and diabetes are major risk factors for the development of endothelial dysfunction and progression of atherosclerosis. Inflammatory mediators are often elevated and the renin-angiotensin system is frequently activated in chronic kidney disease, which likely contributes through enhanced production of reactive oxygen species to the accelerated atherosclerosis observed in chronic kidney disease. Promoters of calcification are increased and inhibitors of calcification are reduced, which favors metastatic vascular calcification, an important participant in vascular injury associated with end-stage renal disease. Accelerated atherosclerosis will then lead to increased prevalence of coronary artery disease, heart failure, stroke, and peripheral arterial disease. Consequently, subjects with chronic renal failure are exposed to increased morbidity and mortality as a result of cardiovascular events. Prevention and treatment of cardiovascular disease are major considerations in the management of individuals with chronic kidney disease. (Circulation. 2007;116:85-97.)

Key Words: atherosclerosis ■ hypertension ■ kidney ■ vasculature

It is increasingly apparent that individuals with chronic kidney disease (CKD) are more likely to die of cardiovascular (CV) disease (CVD) than to develop kidney failure.1,2 A large cohort study comprising >130 000 elderly subjects showed that increased incidence of CV events could be in part related to the fact that persons with renal insufficiency are less likely to receive appropriate cardioprotective treatments.3 However, beyond the effects of lack of appropriate therapy, it is clear that accelerated CVD is prevalent in subjects with CKD. The first part of the present review will therefore focus on the epidemiological links between impairment of renal function and adverse CV events, between albuminuria and CV events, and between serum cystatin C and CVD. The second part of the present review will address the mechanisms that lead to the association of renal and CVD, which include hypertension, dyslipidemia, activation of the renin-angiotensin system, endothelial dysfunction and the role of asymmetric dimethyl arginine (ADMA), oxidative stress, and inflammation. Finally, mechanisms that are involved in vascular calcification often found in CKD and end-stage renal disease (ESRD) will be described. Additionally, ESRD is associated with several specific complications caused by the uremic state per se, which can contribute to the development and progression of CVD through volume overload with consequent hypertension, anemia, uremic pericarditis, and cardiomyopathy. However, these issues will not be addressed because the emphasis will be on CKD before ESRD is reached. In addition, the CV complications associated with dialysis will not be discussed. The different stages of CKD according to the level of glomerular filtration rate (GFR) are shown in Table 1. ESRD corresponds to the stage where patients need renal replacement therapy (ie, dialysis or renal transplantation), whereas stage 1 is mostly recognized by either albuminuria or structural renal abnormality (eg, hyperechoic renal parenchyma on ultrasound). Table 2 provides the approximate odds ratios (univariate) of CVD according to stages of CKD on the basis of the literature cited below. The increase in risk in comparison to people without CKD depends on the age of the population studied: the younger the person, the higher the relative risk. Microalbuminuria increases the CV risk 2- to 4-fold.

Epidemiological Links Between Impaired GFR and Adverse Cardiovascular Events

Evidence for the relationship between renal dysfunction and adverse CV events was perhaps first recognized in the dialysis population in whom the incidence of CV death is strikingly high. Approximately 50% of individuals with ESRD die from a CV cause,2,4,5 a CV mortality that is 15 to 30 times higher than the age-adjusted CV mortality in the general population.6 This disparity is present across all ages, but it is most marked in the younger age group (25 to 34 years...
old), where the CV mortality is 500-fold greater in ESRD patients compared with age-matched controls with normal renal function. It is therefore unsurprising that established CVD is easily demonstrable in CKD. For example, 40% of patients who have started dialysis treatments have evidence of coronary artery disease, and 85% of these patients have abnormal left ventricular structure and function.

The relationship between renal disease and CV mortality has also been shown to extend to subjects with more moderate degrees of renal functional impairment. In fact, the majority of patients with stage 3 to 4 CKD (ie, a GFR<60 mL/min per 1.73 m²) die of CV causes rather than progress to ESRD. Here too, objective evidence of structural and functional cardiac abnormalities has been demonstrated by echocardiography. Levin et al determined left ventricular mass index in a population of 115 men and 60 women with an average creatinine clearance (CrCl) of 25.5 mL/min with 2-dimensional targeted M-mode echocardiography. The population was stratified into 3 groups according to renal function. The prevalence of left ventricular hypertrophy (LVH) was 26.7% in subjects with CrCl>50 mL/min, 30.8% in those with CrCl between 25 and 49 mL/min, and 45.2% in individuals with CrCl<25 mL/min.

Tucker et al reported a similar finding in a population of 85 persons with renal insufficiency. With the same echocardiographic techniques, as well as comparable criteria for the diagnosis of LVH, these investigators found an LVH prevalence of 16% in subjects with a CrCl>30 mL/min and 38% in those with a CrCl<30 mL/min. These studies demonstrate that LVH is common in patients with renal insufficiency even before they progress to dialysis, and that the prevalence of LVH correlates with the degree of renal functional impairment.

A growing number of studies have demonstrated that the relationship between renal dysfunction and increased CV morbidity and mortality extends across the spectrum of renal dysfunction to encompass the mildest degrees of renal impairment. Moreover, this relationship appears to hold across populations with widely varying degrees of baseline CV health.

**CVD Associated With Renal Disease in the General Population**

The Framingham Heart Study was among the first to assess mild renal insufficiency and its association with death and adverse CV events in the general population. Of the 6233 participants in the study, mild renal insufficiency was present in 246 men and 270 women (serum creatinine, 1.4 to 3.0 mg/dL). Of these individuals, 81% had no prevalent CVD at entry. Over the 15-year follow-up period, there was no significant association between mild renal insufficiency and either death or adverse CV events in women. However, in men there was a trend toward more CV events with mild renal insufficiency, and a significant association was demonstrated with age-adjusted all-cause mortality (hazard ratio, 1.42). Given the relatively small number of subjects followed in this study and the low number of outcome events, these findings were suggestive but not definitive of a correlation between mild renal dysfunction and increased CV morbidity and mortality.

More recently, Go et al examined the relationship of GFR and adverse CV events in a low-risk population. They analyzed the database of a large healthcare provider in northern California and used the Modification of Diet in Renal Disease (MDRD) formula to estimate the baseline GFR from measurements of serum creatinine in >1.1 million adults, with only those who were on dialysis or who had undergone a kidney transplant excluded. The primary outcomes examined included death from any cause, CV events, and hospitalizations. The end-point information was obtained from the health-plan database and the California death registry with a mean follow-up period of 2.84 years. After adjustment for age, sex, race, coexisting illnesses, and socioeconomic status, a stepwise increase in the rate of each of the 3 primary outcomes was seen for every sequential decrease in GFR. With the best cohort (GFR>60 mL/min per 1.73 m²) as the point of reference, the adjusted hazard ratio for death from any cause and any CV event increased to 1.2 and 1.4, respec-
tively, for a GFR between 45 to 59 mL/min per 1.73 m²; 1.8 and 2.0 for a GFR between 30 to 44 mL/min per 1.73 m²; 3.2 and 2.8 for GFR between 15 to 29 mL/min per 1.73 m²; and 5.9 and 3.4 for a GFR<15 mL/min per 1.73 m². The adjusted risk of hospitalization with a reduced GFR followed a similar pattern. This large study, which incorporated a diverse population of adults, clearly demonstrated an independent and graded (inverse) correlation between decreasing levels of renal function and increasing event rates of CV morbidity and death.

CVD Associated With Renal Disease in Hypertensive Subjects

The association between renal function and mortality in the hypertensive population was evaluated by the Hypertension Detection and Follow-up Program Cooperative Group, which followed and treated 10 940 hypertensive subjects to compare stepped care to referred care.13 The primary end point of the study was all-cause mortality. Persons with a baseline serum creatinine \( \geq 1.7 \) mg/dL experienced an 8-year mortality rate that was \( >3 \) times higher than that of all other participants.

Data from the Hypertension Optimal Treatment (HOT) study support this finding. In the HOT study, 18 790 hypertensive subjects, only 10% of whom had evidence of atherosclerotic disease, were assigned to 3 diastolic blood pressure target groups and followed for a mean of 3.8 years. Persons with a serum creatinine \( >3 \) mg/dL were excluded and the Cockcroft-Gault14 equation was used to calculate baseline GFR. The adjusted relative risks for total mortality and for major CV events (nonfatal myocardial infarction [MI], nonfatal stroke, CV death) were 1.65 and 1.58, respectively, in subjects with GFR<60 mL/min compared with those with a GFR\( \geq 60 \) mL/min.15

Effect of Renal Disease on Individuals With Preexisting Stable CVD or Risk Factors for CVD

A post hoc analysis of the Heart Outcomes and Prevention Evaluation (HOPE) study examined the impact of baseline serum creatinine on the incidence of the composite primary outcome (CV death, MI, or stroke).16 The HOPE population included individuals with objective evidence of vascular disease or diabetes combined with another CV risk factor and was designed to test the benefit of add-on ramipril versus placebo in this population. Patients with heart failure or a serum creatinine concentration \( >2.3 \) mg/dL were excluded. The follow-up period was \( =5 \) years. There were 980 subjects with mild renal insufficiency (serum creatinine \( \approx 1.4 \) mg/dL) and 8307 subjects with normal renal function (serum creatinine \( <1.4 \) mg/dL). The cumulative incidence of the primary outcome was 22.2% in individuals with mild renal insufficiency versus 15% in those with normal renal function \( (P<0.001) \). The impact of renal insufficiency was independent of both the baseline CV risk factors as well as the treatment group.

A similar relationship between renal function and CV events was demonstrated in the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial.17 In PEACE, add-on trandolapril was compared with placebo in a population with chronic stable coronary artery disease and LVEF>40%. The primary end point was a composite of death from CV causes, MI, and coronary revascularization. Patients with a serum creatinine \( >2.0 \) mg/dL were excluded and the median duration of follow-up was 4.8 years. A post hoc analysis of 8280 subjects, in whom baseline renal function was separated into quartiles with the MDRD formula, demonstrated significant stepwise increases in event rates as the baseline GFR declined. Interestingly, unlike in HOPE, there was a significant interaction between GFR and treatment group with respect to CV and all-cause mortality in that the angiotensin-converting enzyme inhibitor benefited only those individuals with a GFR\( <60 \) mL/min per 1.73 m².

Effect of Renal Disease in Patients With Established Heart Failure or Postmyocardial Infarction

Hillege et al examined whether renal dysfunction was a predictor of mortality in stable patients with advanced heart failure.18 They studied 1906 subjects with New York Heart Association class III and IV heart failure and evidence of left ventricular dysfunction (LVEF<35%) who were enrolled in the Second Prospective Randomized study of Ibipamine on Mortality and Efficacy (PRIME II).19 Hillege et al correlated baseline GFR, as calculated with the Cockcroft-Gault equation, with overall mortality after a median follow-up of 277 days. The authors found that patients in the lowest quartile of GFR \( (<44 \) mL/min) had relative risk of mortality of 2.85 compared with subjects in the highest quartile \( (>76 \) mL/min). Somewhat surprisingly, baseline GFR was independent of impaired LVEF and was a stronger predictor of mortality than either LVEF or New York Heart Association class. In fact, GFR was the strongest predictor of mortality of all factors analyzed, which included parameters of neurohormonal activation.

Hillege et al also explored the prognostic ability of baseline renal function to predict the development of heart failure after an anterior-wall MI.20 Patients with a serum creatinine \( >180 \) \( \mu \)mol/L (2.0 mg/dL) were excluded. Baseline GFR was calculated with the Cockroft-Gault formula, and the 298 patients were divided into tertiles of renal function. At 1 year of follow-up the incidence of congestive heart failure by tertile of decreasing GFR was 24.0%, 28.9%, and 41.2%. Risk of de novo congestive heart failure was 1.86-fold higher in the lowest tertile \( (<81 \) mL/min) than in the highest tertile \( (>103 \) mL/min). As the mean GFR in the lowest tertile was 67.0 mL/min, the study by Hillege et al highlights the impact of even mild GFR reductions on cardiac outcomes.

In a post hoc analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT), Anavekar et al examined the relationship between baseline renal function and adverse outcomes in 14 527 subjects with acute MI complicated by clinical or radiologic signs of heart failure and/or left ventricular dysfunction.21 Subjects were randomly assigned to receive captopril, valsartan, or both, and they were followed for a mean of 24.7 months. Individuals with a serum creatinine \( >2.5 \) mg/dL were excluded from the study. The primary end point was death from any cause, and secondary end points included death from CV causes, heart failure, recurrent MI, resuscitation after cardiac arrest, stroke, and a composite of these.22 Anavekar et al stratified these subjects
into 4 groups; the investigators used the MDRD formula to estimate baseline GFR (mL/min per 1.73 m²) and found that, irrespective of treatment group, there was a progressive increase in both the primary end point as well as each of the secondary end points as GFR declined across the 4 groups. These findings remained significant even when an extensive, 70-candidate, variable model was used to adjust for higher comorbidities in patients with the poorest renal function. If the group with a GFR >75 mL/min per 1.73 m² is considered the reference point, the adjusted hazard ratio for adverse CV events was 1.10 in the GFR group between 60.0 to 74.9 mL/min per 1.73 m² and 1.49 in the GFR group <45.0 mL/min per 1.73 m². When GFR was analyzed as a continuous variable, each decrease in GFR of 10 mL/min per 1.73 m² below 81.0 was associated with a 1.1-fold increase in risk of death and nonfatal CV complications.21

**Epidemiological Links Between Albuminuria and Adverse Cardiovascular Events**

Renal disease may not only be identified by low GFR but also by the presence of abnormal quantities of albumin in the urine. In fact, the appearance of pathological albuminuria often precedes the functional deterioration that is evidenced by a decline in GFR. Importantly, albuminuria has also been shown to be a potent independent marker of CV risk in both diabetic and nondiabetic persons. Similar to GFR, the link between albuminuria and adverse CV events was first recognized in the more overt situations of macroalbuminuria (urine albumin:creatinine ratio [ACR] >300 mg/g),23,24 and then this link was extended to more modest elevations such as microalbuminuria (ACR, 30 to 300 mg/g).25 More recently, it has become increasingly recognized that CV risk begins to rise within currently defined normal levels of albuminuria (ACR<30 mg/g). Thus, urinary albumin is a continuous CV risk factor, whereas microalbuminuria is a designated threshold for renal functional deterioration in individuals with and without diabetes.

**CVD in Patients With Macroalbuminuria**

The Irbesartan Diabetic Nephropathy Trial (IDNT) enrolled subjects with type 2 diabetes, hypertension, and macroalbuminuria.26 A total of 1715 subjects with mean urine ACR of 1416.2 mg/g were randomized into 3 treatment groups that received irbesartan, amlodipine, or placebo and were followed for a mean period of 2.6 years. The primary outcome of the main trial was a renal-centric composite of serum creatinine doubling, ESRD, or death. Although irbesartan proved to be the superior treatment with respect to the primary outcome, no difference was detected between treatment groups on the secondary outcome of CV events. With this data, a post hoc analysis was performed by Anavekar et al27 to assess the relationship between baseline albumin excretion and the CV composite (CV death, nonfatal MI, hospitalization for heart failure, stroke, amputation, and coronary and peripheral revascularization). A univariate analysis revealed that the proportion of patients who experienced the CV end point progressively increased with increasing quartiles of baseline urine ACR. A multivariate analysis confirmed albuminuria as an independent risk factor for CV events with a 1.3-fold increased relative risk for each natural log increase of 1 U in urine ACR.

A similar population was studied in the Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL). Here, 1513 persons with type 2 diabetes, hypertension, and macroalbuminuria (mean baseline ACR, 1810 mg/g) were randomized to either losartan or placebo and followed for a mean of 3.4 years. The primary end point was the same as in IDNT, namely a composite of mainly adverse nephrological events (serum creatinine doubling, ESRD, or death), and, consistent with IDNT, the angiotensin antagonist provided superior nephroprotection but conferred no statistically significant benefit on the secondary CV outcomes,28 although de novo heart failure was less frequently noted in the losartan group. Nevertheless, in a post hoc analysis of RENAAL, baseline albuminuria was again shown to be a predictor of both the prespecified composite CV end point (composite of MI, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or CV death) as well as of heart failure alone. With subjects stratified into 3 groups on the basis of baseline ACR (<1500, 1500 to 3000, >3000 mg/g), comparison of the highest tertile with the lowest revealed an adjusted hazard ratio of 1.92 for the composite CV end point and 2.70 for heart failure. In multivariate analysis, baseline albuminuria was the strongest independent predictor of both these outcomes. Perhaps more significant was the finding that the change in urine albumin excretion from baseline to 6 months was the only dynamic correlate of adverse CV outcomes. A 50% reduction in baseline albuminuria translated into an 18% reduction in the composite CV end point and a 27% reduction in the risk of heart failure. Thus, albuminuria is not only a risk factor for adverse CV outcomes but may also be a therapeutic target or an indicator of therapeutic response.29

**CVD in Patients With Microalbuminuria**

Microalbuminuria also correlates with adverse CV events. In a multivariate analysis of CHD mortality in a type-2 diabetic population, Mattock et al reported that microalbuminuria was the strongest predictor of adverse CV outcomes with an odds ratio of 10.02, which outranked smoking (odds ratio, 6.52), diastolic blood pressure (odds ratio, 3.20), and serum cholesterol (odds ratio, 2.32).30

The HOPE study investigators reported on the risk of CV events associated with baseline ACR >2.0 mg/mmol (equivalent to 17.7 mg/g). This amount of albuminuria was present at baseline in 1140 (32.6%) subjects of the diabetic cohort and in 823 (14.8%) subjects of the nondiabetic cohort. In the overall population a baseline ACR >2.0 mg/mmol increased the adjusted relative risk of CV events (1.83), all-cause death (2.09), and hospitalization for congestive heart failure (3.23). The impact of microalbuminuria on the primary composite outcome (CV death, MI, or stroke) was significant in both diabetics (relative risk, 1.97) and nondiabetics (relative risk, 1.61).31

The ability of microalbuminuria to predict adverse CV events is not restricted to a high-risk population like that of the HOPE trial. In fact, Hillege et al demonstrated the ability of microalbuminuria to predict CV and non-CV mortality in
the general population. The investigators mailed medical questionnaires and a vial to collect early morning urine samples to all inhabitants of the city of Groningen between 1997 and 1998. More than 40,000 subjects responded and were followed for a mean period of 961 days. Vital statistics and the causes of death were available from government registries. The percentage of subjects who manifested baseline microalbuminuria was 22.5% in those who succumbed to CV death, 16.0% in patients who died as a result of non-CV death, and 7.0% in patients who remained alive at the end of the study period. After adjustment for other known CV risk factors, a doubling of the urine albumin excretion rate was associated with a relative risk of 1.29 for CV mortality and 1.12 for non-CV mortality. Here again, microalbuminuria outranked the predictive power of other classic CV risk factors.

CVD in Patients With Albuminuria in the Normal Range

The relationship between CV events and albuminuria has been extended further by several studies that suggest CV risk associated with increased levels of urinary albumin excretion begins to emerge at levels previously defined as normal (ACR < 30 mg/g). Here too, the association appears to apply to a wide spectrum of patient populations. Analysis of the HOPE study population supports albuminuria as a continuous risk factor for adverse CV events from an ACR as low as 0.5 mg/mmol (equivalent to 4.4 mg/g). For every subsequent 0.4 mg/mmol increase in the ratio, the adjusted hazard of major CV events increased by 5.9%.

Similarly, Klausen et al reported that the risk of CV events in the general population began to increase at urinary albumin excretion levels below the defined threshold for microalbuminuria. Klausen et al followed subjects in the Third Copenhagen City Heart Study, which included 10,200 randomly selected participants who underwent a detailed CV investigation program and provided a timed overnight urine sample. Subjects were classified into quartiles on the basis of urinary albumin with a follow-up period that ranged from 5 to 7 years. A urinary albumin excretion above the upper quartile of 4.8 μg/min (equivalent to ACR ~9 mg/g) was associated with an increased adjusted relative risk of 2.0 for CHD and 1.9 for death.

A post hoc analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study related not just baseline albuminuria to CV risk but also the impact of reduction of urinary albumin excretion on CV events.35 The LIFE study followed 8,206 hypertensive individuals with LVH for a mean period of 4.8 years. The principal finding of LIFE was that losartan proved superior to atenolol in the reduction of the composite primary end point (CV death, nonfatal stroke, nonfatal MI) for the same degree of blood pressure reduction.36 In the post hoc study by Ibsen et al, the LIFE population was stratified into 4 groups according to mean ACR at baseline (1.21 mg/mmol, equivalent to 10.6 mg/g) and at year 1 (0.67 mg/mmol, equivalent to 5.9 mg/g). The percentage of subjects who experienced an adverse CV event was reported on the basis of whether their ACR was above or below the mean values. This analysis demonstrated a statistically significant stepwise increase in the primary composite end point that started with the group with the low baseline/low year-1 group ratios (5.5%). Intermediate risk was found in the groups with low baseline/high year-1 (8.6%) ratios and high baseline/low year-1 ratios (9.4%). The highest risk group had high baseline/high year-1 values (13.5%). These results were independent of in-treatment blood pressure and indicated that reductions in urine ACR over time translated into diminished CV risk.

Epidemiological Links Between Serum Cystatin C and Adverse Cardiovascular Events

Recently, serum cystatin C has gained recognition as an excellent endogenous marker of kidney function. Cystatin C is a cysteine proteinase with a molecular weight of 13 kDa that is produced by almost all human cells and released into the blood. Cystatin C is freely filtered by the glomerulus and metabolized by proximal tubular cells, but it is not secreted into the tubules. Cystatin C does not appear to be affected by age, gender, or muscle mass, and there is evidence to suggest that it may be a more sensitive detector of incipient renal dysfunction than creatinine-based estimates of GFR such as the Cockroft-Gault or MDRD formulas. Several recent reports have indicated that cystatin C may be a better predictor of adverse CV events and all-cause mortality than either serum creatinine or creatinine-based estimating equations. Ix et al categorized a population of 990 ambulatory persons with stable coronary heart disease into quartiles on the basis of baseline serum cystatin C levels and followed these subjects for a median of 37 months. Subjects in the highest cystatin C quartile (≥1.30 mg/dL), when compared with the lowest quartile (<0.91 mg/dL), had a hazard ratio of 3.6 for all-cause mortality, 2.0 for CV events (composite of CHD death, MI, and stroke), and 2.6 for incident heart failure. These statistically significant results were adjusted for traditional CV risk factors. Potentially the most important finding in this study was that higher cystatin C levels were predictive of these adverse outcomes even among people without microalbuminuria or a diminished GFR as estimated by the MDRD formula (≤60 mL/min per 1.73 m²). Currently cystatin C is not routinely measured in clinical practice.

In summary, the presence of renal dysfunction, whether detected by GFR, urine albumin excretion, or serum cystatin C, predicts adverse CV outcomes. These relationships appear to extend to individuals with and without diabetes, those with and without preexisting CVD, and subjects with minimal to marked perturbations in their renal parameters.

Mechanisms of Cardiovascular Complications in Renal Disease

As described in the preceding paragraphs, there is growing evidence that relatively minor renal abnormalities such as a slightly reduced GFR or microalbuminuria even within the normal range may be associated with increased risk of CV events. One of the principal pathophysiological mechanisms involved in this association has been proposed to be endothelial dysfunction. Whether micro- or macroalbuminuria is an expression of generalized endothelial cell dysfunction remains to be demonstrated. However, many studies have
demonstrated the correlation of albuminuria with endothelial dysfunction as measured in peripheral blood vessels. Many of the traditional and nontraditional CV risk factors that could affect endothelial function can be found in association with CKD. Related conditions such as diabetes, obesity, and hypertension, as well as the presence of renal dysfunction per se lead to activation of the renin-angiotensin system, oxidative stress, elevated ADMA, low-grade inflammation with increased circulating cytokines, and dyslipidemia, which are all common pathophysiological mechanisms that play a role in the association of renal failure and CVD.

Hypertension
Hypertension in and of itself represents a powerful risk factor for CVD in CKD and is almost invariably present in patients with renal failure. Sodium retention and activation of the renin-angiotensin system have been considered the most important mechanisms involved in the elevation of blood pressure in subjects with kidney disease. Sympathetic nervous system activation also plays a role. Plasma catecholamine concentrations are elevated, and increased nerve sympathetic traffic has been demonstrated in renal failure. The participation of the sympathetic system has become more complex with the recent discovery of renalase, a new regulator of cardiac function and blood pressure produced by the kidney. Xu et al screened libraries of the Mammalian Gene Collection Project and identified a 37.8-kDa oxidase, which contained flavin-adenine-dinucleotide, expressed mainly in glomeruli and proximal tubules of the kidney but also in cardiomyocytes and other tissues; the investigators called this oxidase reninase. Renalase metabolizes catecholamines in the following order: dopamine → epinephrine → norepinephrine. In contrast to other oxidases, renalase is secreted into plasma and urine of healthy persons. However, it is not detectable in uremic individuals. Recombinant reninase exerts a powerful and rapid hypotensive effect on rats. To what extent the impairment of renalase production contributes to sympathetic hyperactivity and blood pressure elevation in CKD remains to be established. Also, endothelial dysfunction and remodeling of blood vessels may participate not only in vascular complications in patients with kidney disease but also in the maintenance of elevated blood pressure.

Hypertension also plays a major role in cardiac damage in CKD via LVH induction. In addition, a reduction in coronary reserve and capillary density that occurs in CKD patients exposes them to coronary ischemia, which in turn leads to worsening of ventricular dysfunction.

Endothelial Dysfunction, Nitric Oxide
Bioavailability, and ADMA in Renal Disease
Impairment of endothelial function is recognized as one of the initial mechanisms that lead to atherosclerosis. Endothelial dysfunction, which occurs in both large and small arteries, is present in renal disease. Microalbuminuria, a marker of glomerular hyperfiltration, has been correlated with and may be a manifestation of impaired endothelial function. Experimental evidence suggests that microvascular endothelial dysfunction participates in the mechanisms that lead to progression of renal disease, which in turn may exacerbate endothelial dysfunction and contribute to acceleration of atherogenesis. It has been postulated that glomerular endothelial dysfunction is an early feature of essential hypertension that may precede blood pressure elevation. Microalbuminuria may itself contribute to renal dysfunction, which progresses with uncontrolled blood pressure elevation. Endothelial dysfunction in turn may contribute to CV mortality already in mild renal insufficiency as suggested by the Hoorn Study. Reduced bioavailability of nitric oxide (NO) appears to be one of the main factors involved in chronic renal failure–associated endothelial dysfunction, in large measure because of increased oxidative stress in the vascular wall (see Dyslipidemia, Inflammation, and Oxidative Stress in Renal Disease). Prevalence of impaired endothelial function, low-grade inflammation, and dyslipidemia associated with incipient and progressive renal disease may explain the acceleration of atherosclerosis and, together with hypertension, may explain the high prevalence of coronary ischaemia and CV events in CKD. The presence of hypertension, sometimes difficult to control, in subjects with the previously mentioned risk factors may underlie the prevalence of cerebrovascular disease and stroke in patients with renal disease. Paradoxically, a recent report showed that lowest systolic blood pressure was associated with stroke in stage 3 to 4 CKD.

ADMA is a competitive inhibitor of NO synthase. ADMA is synthesized potentially in many tissues, but in the CV system it is produced in the heart, endothelium, and smooth muscle cells. It is derived from the catabolism of proteins that contain methylated arginine residues, and it is released as the proteins are hydrolyzed. The synthesis of ADMA requires the enzyme protein arginine methyltransferase type I, which methylates arginine residues, and the protein arginine methyltransferase type II forms symmetric dimethylarginine, which is a stereoisomer of ADMA and is not an inhibitor of NO synthase. ADMA and symmetric dimethylarginine enter endothelial cells through the cationic amino acid γ transporter. The activity of this transporter colocalizes with caveolin-bound NO synthase, which suggests that γ transporter activity may be a determinant of the local concentrations of ADMA. The ADMA and symmetric dimethylarginine compete with each other and L-arginine for transport into the cell. Thus, ADMA may block entry of L-arginine, with the resulting decrease in synthesis of NO. ADMA is metabolized mainly by dimethylarginine dimethylaminohydrolase and cleared by the kidney. Exogenous ADMA inhibits NO generation in vitro, and in humans it reduces forearm blood flow and cardiac output and increases systemic vascular resistance and blood pressure. Subpressor ADMA infusion increases renovascular resistance, induces intimal hyperplasia, and affects small and large vessels. Plasma concentrations of ADMA are increased in association with endothelial dysfunction and/or reduced NO production, particularly in renal failure. Increased ADMA in renal failure may result from both increased activity of protein arginine methyltransferase and decreased metabolism by dimethylarginine dimethylaminohydrolase. It is unclear whether endogenous ADMA concentrations increase sufficiently to inhibit NO production in vivo. Interestingly, plasma
norepinephrine and ADMA concentrations are closely correlated in patients with ESRD and are likely to act through common mechanisms that contribute to CV events. ADMA is now considered one of the strongest markers of atherosclerosis. Elevated plasma concentrations of ADMA are associated not only with endothelial dysfunction and atherosclerosis but predict mortality and CV complications in CKD and ESRD. In subjects with mild to advanced CKD, plasma ADMA was inversely related to GFR and was an independent risk marker for progression to ESRD and mortality. In the Mild to Moderate Kidney Disease Study, ADMA was significantly associated with progression of non-diabetic kidney disease. Elevated plasma ADMA has been shown to be a marker of CV morbidity in early nephropathy associated with type 1 diabetes. In the Ludwigshafen Risk and Cardiovascular Health Study, ADMA independently predicted total and CV mortality in individuals with angiographic coronary artery disease. Although reduced bioavailability of NO and accumulation of ADMA cause endothelial dysfunction, there is little evidence for coronary artery endothelial dysfunction in renal failure. Recently, Tatematsu et al induced renal failure in dogs and evaluated coronary vasodilator response to acetylcholine, which demonstrated blunted responses in the CKD dogs. mRNA expression of dimethylarginine dimethylaminohydrolase-II and endothelial NO synthase in coronary arteries were downregulated, which demonstrated a possible mechanism for coronary endothelial dysfunction in early stages of CKD.

Dyslipidemia, Inflammation, and Oxidative Stress in Renal Disease

Individuals with CKD become progressively malnourished, as evidenced by low levels of albumin, prealbumin, and transferrin, which has been suggested to be a mechanism for activation of inflammation. Diseases in which low-grade inflammation is found, such as diabetes and hypertension, are often associated with CKD. Thus it is difficult to conclude whether there is a direct effect of renal failure on inflammation in early CKD. Renal failure causes changes in plasma components and endothelial structure and function that favor vascular injury, which may play a role as a trigger for inflammatory response. Dyslipidemia associated with CKD contributes to the inflammatory response in renal failure. The changes in blood lipid composition and their relation to renal dysfunction and inflammation are summarized in Table 3. Hepatic apolipoprotein A-I synthesis decreases and high-density lipoprotein levels fall. High-density lipoprotein is an important antioxidant and also protects the endothelium from the effects of proinflammatory cytokines. Apolipoprotein C-III, a competitive inhibitor of lipoprotein lipase, is increased in CKD. Serum triglyceride levels increase as a result of accumulation of intermediate-density lipoprotein, which comprise very low-density lipoprotein and chylomicron remnants. These impair endothelial function and are associated with CVD.

Because dyslipidemia associated with CKD appears to play a role in the enhanced CV risk of these patients, treatment of dyslipidemia conversely should reduce proteinuria and ameliorate the progression of CKD. Indeed, statin therapy appears to reduce proteinuria modestly, and results in a small reduction in the rate of loss of kidney function, especially in populations with CVD.

The changes in lipoprotein composition and structure as well as angiotensin II–mediated alterations in endothelial function stimulate and amplify the effect of inflammatory mechanisms. Between 30 and 50% of CKD patients have elevated serum levels of inflammatory markers such as C-reactive protein, fibrinogen, interleukin-6, tumor necrosis factor-α, factor VIIc, factor VIIIc, plasmin-antiplasmin complex, D-dimer, and the adhesion molecules E-selectin, VCAM-1 and ICAM-1. Mechanisms are unclear but increased inflammatory mediators have been attributed to increased oxidative stress, accumulation of postsynthetically modified proteins, advanced glycation end products, and other agents normally cleared by the kidney. Thus, causes of inflammation may include comorbidities, oxidative stress, infections, and hemodialysis-related factors that depend on membrane biocompatibility and the dialysate. Progressive deterioration of renal function in CKD may lead to dyslipidemia or accumulation of uremic toxins, which can stimulate oxidative stress and inflammation, which in turn may contribute to endothelial dysfunction and progression of atherosclerosis.

A major contributor to the increase in circulating inflammatory biomarkers in CKD may be enhanced oxidative stress. Mechanisms of oxidative stress in uremia may involve activation of reduced nicotinamide adenine dinucleotide (NAD(P)H) oxidase, xanthine oxidase, uncoupled endothelial NO synthase, myeloperoxidase (MPO), and mito-
Calciphylaxis is the result of an elevated calcium (Ca) that can lead to life-threatening skin necrosis or acral gangrene. When angiotensin II acts through the AT1 receptor, it stimulates generation of ROS by uncoupled endothelial NO synthase as well as reduced inactivation of ROS by antioxidant systems such as superoxide dismutase also play an important role. MPO is present in neutrophils and monocytes/macrophages, and has been shown to be expressed to a significant degree in human atheroma. It may thus play a role in the accelerated atherosclerosis of renal failure. It has recently been reported that a single nucleotide polymorphism in the promoter region of the MPO gene associated with reduced expression of MPO is accompanied by a lower prevalence of CVD in ESRD patients. Active MPO is released from white blood cells during hemodialysis, and this could be a mechanism whereby MPO plays a role in vascular injury in subjects with ESRD.

**Renin-Angiotensin System**

Activation of the renin-angiotensin system occurs in many forms of renal disease. Angiotensin II stimulates NAD(P)H oxidase, which leads to generation of superoxide anion and contributes to endothelial dysfunction and vascular remodeling and growth. Mechanisms whereby the renin-angiotensin system may be activated by kidney disease are multiple and beyond the scope of the present review, but such mechanisms may in part depend on the adaptation to loss of renal mass that results in changes in renal hemodynamics. When angiotensin II acts through the AT1 receptor, it stimulates generation of ROS by NAD(P)H oxidase and other enzymes systems, which leads to upregulation of inflammatory mediators, which include cytokines, chemokines, adhesion molecules, and plasminogen activator inhibitor 1, and superoxide scavenging of NO. These events, together with the mechanisms already mentioned, promote endothelial dysfunction, vascular remodeling, and the progression of atherosclerosis.

**Vascular Calcification, Inducers and Inhibitors of Calcification, and the Role of Phosphate in Renal Failure**

Accelerated calcifying atherosclerosis and valvular heart disease occur with high frequency in CKD. A recent study showed that 40% of patients with CKD and a mean GFR 33 mL/min exhibited coronary artery calcification compared with 13% in matched control subjects with no renal impairment. Calcification can be found in atherosclerotic plaques and in the vascular media, smooth muscle cells, and elastic laminae of large elastic and medium muscular arteries as well as in cardiac valves. Subjects with renal failure who exhibit medial calcification are typically middle-aged and have been dialyzed for some time, although some individuals may already have calcified vessels before dialysis. There is a specific dialysis-related type of vascular calcification called calciphylaxis, or calcific uremic arteriopathy, that is characterized by diffuse calcification of the media of small to medium arteries and arterioles with intimal proliferation and thrombosis that results in skin ulcers and can lead to life-threatening skin necrosis or acral gangrene. Calciphylaxis is the result of an elevated calcium (Ca) × phosphate (P) product without presence of an active osteogenic process, and it must be differentiated from other forms of calcification of the skin that do not affect blood vessels and from medial calcific sclerosis, which affects larger vessels. It is a rare complication of renal failure present in up to 4% of hemodialysis patients, typically in obese diabetic females, associated often with secondary hyperparathyroidism, hypercalcemia, hyperphosphatemia, malnutrition, and sometimes with warfarin therapy or hypercoagulability. However, although warfarin and hypercoagulability have both been implicated, the latter on the basis of an association of protein C deficiency and calciphylaxis, some studies suggest that neither hypercoagulability nor warfarin play a role in this rare condition. Similarly, parathyroidectomy has been reported to lead to the resolution of the skin ulcers of calciphylaxis in some series but not all.

Mechanisms involved in vascular calcification in CKD include passive precipitation of Ca and P in the presence of excessively high extracellular concentrations, effects of inducers of osteogenic transformation and hydroxyapatite formation, and deficiency of calcification inhibitors. Table 4 summarizes some of the inducers and inhibitors of vascular calcification that induce an osteoblast phenotype in vascular smooth muscle cells. Patients with ESRD often have severe changes in their Ca×P product, which induces a trend toward ectopic calcification. Aortic stiffening associated with calcification will cause LVH, which results in increased CV risk. Increased phosphate levels are also a source of increased CV risk, probably as a result of worsening vascular calcification. Precipitation associated with a raised Ca×P product may contribute to soft-tissue calcification, but calcification of the media of blood vessels appears to involve active transport through the Na-P cotransporter PiT-1 which occurs in part as a result of a phenotypic switch of vascular smooth muscle cells into osteoblast-like cells as a consequence of high intracellular Ca and P, which induce osteogenic differentiation of smooth muscle cells. In an in vitro model, elevated Ca or P induced human vascular smooth
muscle cell calcification, which was initiated by release of membrane-bound matrix vesicles and apoptotic bodies. Vesicles released by cells exposed to Ca and P calcified to an important degree, but those released in the presence of serum were minimally calcified and were found to contain the calcification inhibitors fetuin-A and matrix Gla protein (MGP) (see next paragraph). Thus, vascular calcification is a cell-mediated process regulated by calcification inhibitors, functional impairment of which leads to accelerated vascular calcification.

Among the inhibitors of calcification, fetuin-A (α2-Schmid Heremans glycophorin; molecular weight, 60 kDa), which is produced by the liver and circulates in blood, appears to be of prime importance. Fetuin-A has a transforming growth factor-β receptor II–like domain and may function as a soluble transforming growth factor-β antagonist that interferes with insulin receptor autophosphorylation and tyrosine kinase activity. It forms stable colloidal spheres with Ca and P (calciprotein particles) and is the main component of a high molecular mass complex that contains Ca, P, and MGP. Low serum fetuin-A levels in subjects with CKD have been associated with enhanced vascular calcification and increased CV mortality. MGP belongs to a family of N-terminal γ-carboxylated (Gla) proteins that require a vitamin K–dependent γ-carboxylation for their biological activation and prevent bone morphogenetic protein (BMP)-2/BMP receptor-2 (BMPR2) interactions. The γ-carboxylated MGP, but not the non–γ-carboxylated MGP, is carried in plasma by fetuin-A. Mice that lack MGP develop spontaneous calcification of arteries and cartilage. Elevated concentrations of MGP may be found in the vicinity of atherosclerotic plaques and have been shown to be associated with calcification of vascular smooth muscle cells in vitro. MGP levels in blood have been reported to correlate negatively with coronary artery calcification.

Osteoprotegerin regulates osteoclast activation. It acts as a soluble decoy receptor that prevents the binding of the osteoclast stimulator receptor activator of nuclear factor-κB ligand to its receptor. Osteoprotegerin deficiency in mice leads to vascular calcification, but its mechanism of action has not been elucidated. Osteoprotegerin levels are elevated in ESRD, correlate with vascular calcification, and predict mortality in hemodialysis patients, in particular in individuals with high C-reactive protein levels. Interestingly, lower soluble receptor activator of nuclear factor-κB ligand concentrations were associated with better outcomes.

Elevated pyrophosphate (PPI) concentrations prevent hydroxyapatite crystal formation and calcification. PPI is synthesized by the rate-limiting enzyme nucleotide pyrophosphatase phospho-diesterase-1. Mice that lack nucleotide pyrophosphatase phospho-diesterase-1 develop PPI deficiency, which results in an altered vascular smooth muscle cell phenotype and vascular calcification. The cellular PPI exporter ankyrin, which is encoded by the transmembrane transporter progressive ankylosis locus, mediates PPI exit from cells. Vascular calcification may also result from enhanced activity of the membrane-bound tissue-nonspecific alkaline phosphatase, which degrades PPI to P. PPI deficiency may occur in ESRD as a consequence of removal of PPI during hemodialysis, which may be one of the mechanisms that contribute to accelerated vascular calcification in hemodialysis patients.

BMPs are important regulators of bone formation. They are members of the largest subclass of the transforming growth factor-β superfamily and have been localized in areas of vascular calcification. BMP-2 is generated from a 60-kDa precursor, which is processed to an 18-kDa monomer that associates with another monomer to form the active homodimer, which then binds to its receptor. The BMPR is a heterodimer that consists of types 1 and 2 serine/threonine kinases. BMPR2 phosphorylates BMPR1, which in turn phosphorylates the Smad 1/5/8 complex, which, with Smad 4, then modulates target gene expression. Of the different BMPs, BMP-2 or BMP-4 may induce osteogenic differentiation of vascular smooth muscle cells through induction of transcription factors Cbfal, osterix, and the msh homeobox homolog MSX-2. Other effects of BMP-2/BMP-4 that contribute to calcification of the vasculature are the triggering of apoptosis and inhibitory effects on MGP. In addition, BMP-4 has been shown to exert vascular effects that lead to increased oxidative stress and impaired endothelial function, and to what extent these effects are related to media calcification remains to be established. BMP-7 on the other hand inhibits vascular calcification by upregulation of α-smooth muscle actin expression via induction of p21 and upregulation of Smad 6 and 7. BMP-7 is expressed mainly in the kidney, and its expression decreases with progression of renal failure, which results in reduction of its ability to inhibit calcification. Lowering of BMP-7 affects bone metabolism with consequent increase in serum phosphate levels, which adversely affects the Ca×P product and induces phenotypic changes in vascular smooth muscle cells, which leads to metastatic calcification.

Increased leptin levels may participate in the process of vascular calcification in CKD because serum leptin concentrations are increased in renal failure as a result of reduced leptin excretion. Leptin induces heterotopic calcification via its receptors in the hypothalamus that induce an increased leptin excretion. Leptin increases bone marrow stem cell differentiation into an osteoprogenitor phenotype and may act on vascular smooth muscle cells to induce calcification, in part by an increase in ROS generation and induction of BMP-2.

In summary, BMP-2/BMP-4 binds the BMPR1/BMPR2 receptor complex and phosphorylates the regulatory Smads, which then signal downstream to upregulate the expression of transcription factors Cbfal, osterix, and MSX-2. BMP-4 also stimulates generation of ROS. Cbfal expression is also enhanced by ROS, leptin, vitamin D, high phosphate levels, and PIT-1. The result is a phenotypic change in vascular smooth muscle cells to an osteogenic phenotype. These cells express alkaline phosphatase and produce hydroxyapatite crystals. Calcification inhibitors such as fetuin-A, MGP, osteoprotegerin, osteopontin, BMP-7, and Smad 6 antagonize BMP-2/BMP-4 signaling and metastatic calcification (Figure).
Mechanisms depicted here are some of those involved in vascular calcification in chronic kidney disease. Activation of the renin-angiotensin system results in stimulation of AT1R, which stimulates reduced NAD(P)H oxidase, the main source of vascular ROS. BMP-2/4 binds the BMP receptor BMPR1/BMPR2 receptor complex and phosphorylates the Smad 1/5/8 complex, which, with Smad 4, signals downstream to upregulate expression of transcription factors Cbfa1, osterix, and MSX-2. Cbfa1 expression is also enhanced by ROS, leptin, vitamin D, increased Ca x P product, or high PO4 levels induced by Pit-1, the sodium-phosphate cotransporter, activated in part as a result of the phenotypic switch of VSMCs into osteoblast-like cells. VSMCs that have acquired an osteogenic phenotype express ALP and produce hydroxyapatite crystals. Calcification inhibitors such as PPi inhibit hydroxyapatite precipitation, whereas fetuin-A, MGP, OPG, OPN, BMP-7, and Smad 6 antagonize BMP2/4 signaling and calcification. AT-R indicates angiotensin AT receptor; NAD(P)H, nicotinamide adenine dinucleotide; ROS, reactive oxygen species; BMP, bone morphogenetic protein; PO4, phosphate; VSMC, vascular smooth muscle cells; ALP, alkaline phosphatase; PPI, pyrophosphate; MGP, matrix Gla protein; OPG, osteoprotegerin; and OPN, osteopontin.

Conclusion

The present review underlines the CV risk to which patients with CKD are exposed and summarizes some of the mechanisms that lead to the increased risk of adverse CV events. It is also clear that some of this risk is modifiable and can be improved with currently available therapy by reduction of blood pressure according to guidelines, aggressive treatment of dyslipidemia, control of protein intake, minimization of bone resorption, optimization of Ca and P metabolism, and combat of hypercoagulability, with the caveat that warfarin may be implicated in calciphylaxis of the latter. Therapeutic aspects that may require new approaches include management of the increased oxidative stress and low-grade inflammation, as well as development of novel strategies to increase the concentrations of inhibitors of calcification and to moderate the agents that promote calcification.

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Disclosures

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