

Congestive Heart Failure in Chronic Kidney Disease: Disease-specific Mechanisms of Systolic and Diastolic Heart Failure and Management

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In 2002, the National Kidney Foundation-sponsored Kidney Disease Outcomes Quality Initiative published evidence-based guidelines targeting earlier evaluation and intervention in patients who have chronic kidney disease (CKD) [1]. The cornerstone of the working group was the establishment of five stages of kidney disease (Table 1). Rather than using serum creatinine levels alone, the classification system focused on estimated glomerular filtration rate (GFR). Using the GFR allows correlation of severity of kidney function loss and the prevalence of comorbidities associated with the kidney disease. Furthermore, to aid in the understanding and communication of CKD, historical terms that are confusing and sometimes misleading (predialysis, progressive renal disease, progressive renal insufficiency) have been abolished.

Chronic kidney disease and the health care perspective

Kidney disease is a large and growing health care concern. The financial burden of caring for patients who have CKD far exceeds that for prostate or colorectal cancer in men and for breast cancer in black women [2]; the direct cost of caring for a patient receiving dialysis is more than US \$50,000 annually [3,4]. In 2001, the incidence of the population of patients who have end-stage renal disease (ESRD) receiving dialysis was greater

than 90,000 patients per United States population per year with a total prevalence greater than 290,000 patients per United States population [5]. By 2030, the number of patients who have ESRD may reach 2.24 million [5].

Although hypertension, diabetes, and cardiac disease are associated with a higher prevalence of CKD [6–8], the true prevalence of CKD has been difficult to establish, because estimates are sensitive to the definitions and methods used to identify the disease [6,9,10]. Estimates of CKD are known to be age dependent, because CKD was present in about 8% of the Framingham population at baseline and increased to 20% in the elderly [7]; this percentage, however, may be artificially increased by reliance on a single serum creatinine measurement [10]. Nonetheless, population-based studies such as the Third National Health and Nutrition Survey cross-sectional survey of 29,000 persons revealed that 3% of people over 17 years of age had serum creatinine levels above the ninety-ninth percentile for men and women aged 20 to 39 years without diabetes or hypertension [8]. Furthermore, it is estimated that approximately 8 million people in the United States have kidney disease stage III or higher [11].

Chronic kidney disease and the patient perspective

Morbidity and mortality in the dialysis population remain unacceptable despite the many advances made in the technical aspects of dialysis care. A recent analysis of data from the United States indicates that ESRD leads to more lost life-years than prostate cancer in men and almost as

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Table 1
Five stages of chronic kidney disease

GFR ^a (mL/min/1.73m ²)	Stage
> 90 ^b	I
60–89	II
30–59	III
15–29	IV
< 15 (or dialysis)	V

Abbreviation: GFR, glomerular filtration rate.

^a GFR: Estimated GFR from any one of several prediction equations using data in addition to serum creatinine alone.

^b Documented kidney damage with normal or increased GFR.

Adapted from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39(2 Suppl 2):S19.

many as breast cancer in black women [2]. The largest contributor to this mortality continues to be cardiac disease [12] as originally reported in the first cohorts of patients commencing chronic dialysis in the 1960s [13]. Furthermore, although the mortality in elderly patients who have kidney disease is a little greater than in the normal population, the cardiovascular mortality in patients who are 25 to 34 years old is several orders of magnitude higher than in normal individuals of the same age [14].

Pathophysiology

Cardiomyopathy and ischemic heart disease

Although cardiovascular disease (CVD) may be clinically generally classified into two disease entities, cardiomyopathy and ischemic heart disease, the presence of these disorders varies from patient to patient, and they frequently overlap (Fig. 1) [15]. Ischemic symptoms may result from coronary artery disease or nonatherosclerotic ischemic disease, with coronary artery disease predisposing to diastolic dysfunction and to systolic failure. Left ventricular hypertrophy (LVH) is usually present in dilated cardiomyopathy but also causes diastolic dysfunction in patients with or without normal systolic function. In a recent longitudinal study of kidney transplant recipients, a model of CKD, the rate of ischemic cardiac events was similar to that seen in the Framingham study, whereas the rate of heart failure events was substantially higher. This finding suggests that

CKD may not be simply a state predisposing to atherosclerosis but may be a milieu predisposing to cardiomyopathy [16].

Cardiomyopathy

The most common symptom of cardiomyopathy in CKD patients, as in the general population, is pulmonary edema, but cardiomyopathy may also manifest as severe exercise intolerance or, in the setting of dialysis, as sudden intradialysis hypotension. These clinical manifestations of pump failure may result from systolic dysfunction, diastolic dysfunction, or a combination of both. Echocardiography [17] may reveal the cardiomyopathy to be a consequence of

1. LVH with diastolic dysfunction: concentric LVH with normal chamber volume and impaired filling, arising from left ventricular (LV) pressure overload, such as from hypertension, arteriosclerosis and aortic stenosis.
2. Dilated cardiomyopathy and systolic failure: eccentric LV dilation with impaired wall motion resulting from left ventricular volume overload. This may occur especially in CKD patients in response to salt and water overload, anemia, and arteriovenous fistula.

Thus, hemodialysis with its associated hemodynamic stresses is the quintessential model for overload cardiomyopathy, for which the end stage is systolic dysfunction.

Because LV growth starts before the initiation of dialysis, its prevalence is inversely related to the level of declining kidney function; anemia, hypertension, and diabetes mellitus are also risk factors for progressive LV growth [18,19]. In kidney transplant recipients, there is evidence that systolic dysfunction, LV dilatation, and concentric hypertrophy present during dialysis improve after transplantation, with concomitant improvement in uremic milieu. In renal transplant recipients, however, hypertension is a risk factor for LV growth, de novo heart failure, and de novo ischemic heart disease [16,20]. Anemia and hypoalbuminemia further predispose patients to de novo heart failure [16].

Ischemic heart disease

Ischemia presents as myocardial infarction or angina resulting from decreased perfusion of the myocardium. Although symptoms of ischemic heart disease are usually attributable to critical coronary artery disease, in about one quarter of

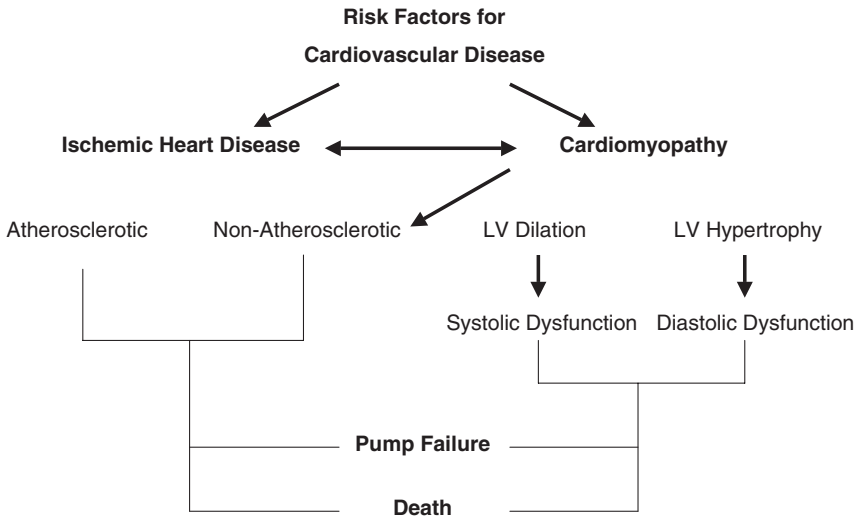


Fig. 1. The relationship of risk factors and cardiovascular disease in patients with chronic kidney disease.

the hemodialysis population these symptoms may also result from nonatherosclerotic disease, caused by small vessel disease and LV hypertrophy [21]. Symptomatic ischemic heart disease is not a significant mortality risk factor independent of congestive heart failure (CHF) [22]. Thus, the underlying cardiomyopathy predisposing the patient to heart failure is probably more prognostically important than coronary perfusion disorders, particularly in nondiabetic persons [23].

Arterial disease

Arteriosclerosis alters the structure of arteries by mechanisms other than atherogenesis. Hemodynamic overload and hypertension, common in CKD, cause intramural vascular remodeling with hypertrophy of the media and subintimal fibrosis. As a result, noncompliant vessels develop with increased stiffness and diameter. If persistent and longstanding, arteriosclerosis may adversely affect LV structure and function by increasing cardiac workload and predisposing the patient to sub-endocardial ischemia [24].

Epidemiology

The prevalence of cardiomyopathy is high in incident dialysis patients, as is the presence of ischemic heart disease and heart failure. In fact, Canadian echocardiographic data revealed only 16% of new dialysis patients have normal hearts, with LV hypertrophy present in 75%, concentric

LVH in 41%, and systolic failure in 16% [17,25]. Clinically, symptomatic ischemic heart disease was present in 38% and heart failure in 35% at first dialysis [26]. The high prevalence of CVD in patients starting dialysis suggests that the predialysis phase of CKD is a state of high cardiac risk. Indeed, earlier in the course of disease LV hypertrophy is already evident in 40% of patients who have moderate CKD [27], and admission rates for CHF are seven times greater in CKD patients than in those without CKD [5].

Risk factors

Because CVD is already well established at the onset of ESRD [28,29], it is vital to understand the interrelationship of CVD and early CKD and to recognize the importance of early intervention. Although there are limited data on the natural history of CKD in unselected populations, most patients reach ESRD secondary to chronic progressive disease (in North America, largely caused by diabetes and hypertension [5]). Most patients who have CKD do not progress to ESRD, however, either because the CKD is not progressive [30,31] or because they die first—the major contributor of mortality being CVD [7].

In 1997 The National Kidney Foundation convened a task force to examine the epidemic of CVD in chronic kidney disease [32], focusing on decreasing death rates by developing strategies to prevent disease. Specifically, the task force

considered whether strategies learned from the general population are applicable to patients who have CKD. Fortunately, interventions that retard the progression of CKD are similar to measures that reduce CVD risk. Thus, cardiac risk factor intervention in the early phases of CKD should reduce the rate of cardiac death and slow the progression of kidney disease. It is currently unknown how much of the increased prevalence of ESRD is caused by the increased prevalence of CKD [33] rather than by a reduction in mortality resulting from improved CVD management [34].

As CKD progresses, the nature of the risk factors evolves from traditional risk factors to those characteristic of chronic uremia. Recognized traditional risk factors identified in the general population include diabetes, hypertension, history of smoking, family history of coronary disease, male gender, older age, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, physical inactivity, menopause, and psychologic stress (Table 2). CKD imparts added cardiac risk through the increased prevalence of coexisting diseases such as hypertension, atherosclerosis, diabetes, and dyslipidemia. Additional excess cardiac risk may also be caused by hemodynamic and metabolic perturbations associated with CKD, including hemodynamic overload, anemia, malnutrition, hypoalbuminemia, inflammation, dyslipidemia, prothrombotic

factors, hyperhomocysteinemia, divalent ion abnormalities, vascular calcification, and hyperparathyroidism and other putative risk factors, including oxidative stress [22,35]. As CKD progresses, it is likely that the prevalence and severity of several risk factors change [36,37].

Although epidemiologic evidence indicates that CKD is a marker of high cardiovascular risk, it is not known whether CKD independently contributes to the risk of cardiovascular mortality [38,39]. It remains unclear how much of the association between kidney and vascular disease results from (1) vascular disease causing kidney disease, (2) kidney disease causing vascular disease, or (3) common underlying factors promoting the progression of both. It is likely that each of these mechanisms contributes.

Management

Hypertension

Hypertension is common in CKD, affecting about three quarters of the patients, and the prevalence of hypertension increases as the GFR declines. Treatment reduces mortality in those at risk for cardiovascular events [40–43], and achieving a target blood pressure lower than 130/80 mm Hg in patients who have CKD also slows progression of kidney disease [30,40,44–48]. Patients

Table 2
The spectrum of risk factors for cardiovascular disease

Traditional	Increased prevalence of coexisting diseases	Uremia-related
Age	Diabetes	Hemodynamic overload
Gender	Hypertension	Anemia
Race	Dyslipidemia	Electrolyte abnormalities
History of smoking	Atherosclerosis	Hyperparathyroidism
Family history	Proteinuria	Calcium/phosphate abnormalities
Physical inactivity	Left ventricular hypertrophy	Vascular calcification
Body mass index		Malnutrition
Menopause		Hypoalbuminemia
Psychologic stress		Inflammation
Fibrinogen		C-reactive protein
		Prothrombotic factors
		Hyperhomocysteinemia
		Increased oxidative stress
		Endothelial activation
		Prothrombotic factors
		Cytokines
		Advanced glycation end products
		Dialysis modality
		Acute rejection after transplantation
		Transplant immunosuppressives

who have proteinuria greater than 1 g/24 hours benefit from even lower blood pressure (<125/75) [30]. Three or four different medications are often required to reach these goals.

Interruption of the renin-angiotensin system

Angiotensin-converting enzyme (ACE) inhibitors clearly improve symptoms, morbidity, and survival in nonuremic individuals who have heart failure [49] and in patients who have CKD [50]. ACE inhibition is beneficial to those who have diastolic and systolic dysfunction [51,52]. Furthermore, the use of ACE inhibition reduces the progression of CKD, reduces proteinuria, and regresses LVH [53–55]. ACE inhibitors should also be used to prevent CHF in asymptomatic patients whose LV ejection fraction is less than 35% [56] and in postmyocardial infarction patients who have an ejection fraction of 40% or less [57]. Angiotensin-receptor blockers also reduce ESRD [58,59] and may benefit patients who have diastolic dysfunction [51,60]. ACE inhibitors and angiotensin-receptor blockers are relatively contraindicated in patients who have renovascular disease and volume depletion, and hyperkalemia in the later stages of CKD can make interruption of the renin-angiotensin system problematic.

Beta-blockers

Beta-blockade reduces morbidity and mortality in patients who have heart failure [61,62] and after myocardial infarction [63] and seems to be equally efficacious in patients who have CKD [64]. Patients who have CKD, however, and particularly in the later stages, often have conditions (sinus-node dysfunction, hypotension, and cardiac conduction abnormalities) that are contraindications to the use of beta-blockers.

Diuretics

Aside from their use as antihypertensives, diuretics have been a cornerstone of acute and chronic therapy in all patients who have cardiac failure, including those with CKD. The effects of loop diuretics are attenuated as the GFR declines, but the effects are not reduced as severely as those of thiazides. The synergistic effect of loop diuretics and thiazides on salt and water excretion and blood pressure persists, even at relatively advanced stages of CKD. Acutely, intravenous loop diuretics such as furosemide have a short-term benefit for symptomatic treatment of heart failure even in the presence of minimal or no

glomerular filtration because of their vasodilating properties. The effects of aldosterone antagonists are unpredictable in patients who have CKD. They are weak diuretics, but they are reported to be of benefit in cardiac disease or in reducing proteinuria in patients who have CKD [65,66].

Digoxin

Digoxin improves symptoms in non-CKD patients who have heart failure, and clinical deterioration may occur when it is discontinued [51,67]. There is a theoretical concern that digoxin may aggravate isolated diastolic dysfunction, because increased contractility induced by digoxin could worsen diastolic function by impairing myocardial relaxation [51]. Nonetheless, evidence suggests that patients who have heart failure and preserved ejection fraction treated with digoxin had fewer hospitalizations and improved symptoms [67]. Therefore, digoxin is recommended for use in patients who have CKD and heart failure and who have systolic dysfunction with or without atrial fibrillation. It should be used with caution in patients who have diastolic dysfunction and atrial fibrillation and if atrial fibrillation with a rapid ventricular response is present.

Diabetes management

Diabetes in patients who have moderate to severe CKD is a risk factor for cardiovascular deterioration [68]. Furthermore, in kidney transplant recipients, diabetes is an independent risk factor for ischemic heart disease [16,69,70] and heart failure [16]. Controlling diabetes has beneficial effects for early microvascular disease [71,72]. Metformin has shown benefit for macrovascular disease in obese type 2 diabetics [73] but is contraindicated in the later stages of CKD.

Smoking

Smoking status is associated independently with cardiac disease, peripheral vascular disease, and mortality but has received little attention in the CKD population [74]. Approximately 25% of patients who have CKD and more than 50% of dialysis and transplant patients have a history of cigarette use [74]. In 2003, 14% of dialysis patients in the United States continued to smoke [74]. Smoking is a potentially modifiable risk factor. Cessation reduces cardiovascular outcomes [75], may slow CKD progression [76–78], and improves quality of life [79] but may require intense intervention for maximal effect [80].

Statin therapy

Statin therapy in patients who have CKD seems to have an efficacy similar to that in patients who have CVD but do not have CKD [81–83]. The role of statin therapy, independent of lipid lowering, includes endothelial stabilization and antithrombotic and anti-inflammatory mechanisms that may modulate its effectiveness. Patients who have CKD, particularly those receiving dialysis, have increased markers of inflammation such as C-reactive protein. This inflammatory state is deemed to confer an independent increased risk of CVD through oxidative stress and resultant atherosclerosis [83]. Although statins have been shown to reduce C-reactive protein levels in patients who have normal kidney function, it is not known whether this reduction translates into clinical benefit independent of lipid reduction.

Erythropoietin

There is increasing awareness of the role of anemia in the investigation and management of CHF [84]. The combination of CKD and anemia is independently associated with an increased risk of coronary heart disease and stroke in middle-aged patients [85,86] and, in patients who have CKD stage III or greater, anemia is associated with LV growth [87]. In kidney transplant recipients, anemia is an independent risk factor for the development of electrocardiographically diagnosed LV hypertrophy [16] and of symptomatic heart failure [20]. Current CKD guidelines recommend treating anemia to achieve a hemoglobin level of 110 to 120 g/L to improve quality of life, decrease hospitalization, and potentially improve LVH [88–93]. No randomized, controlled trials have shown that normalization of anemia with erythropoietin improves cardiac disease [94–98].

Nephrology referral

Late referral to nephrology before dialysis has been recognized as a problem for many years. It is associated with increased cost and morbidity [98–101]. Published recommendations emphasize timely referral to maximize potential gains from involvement of specialized nephrology teams [102]. A minimal recommendation would be referral at GFR levels greater than 60 mL/min if the primary medical care provider cannot identify the cause of the kidney disease or requires help in the management of disease. All potential dialysis

patients who have GFR levels less than 30 mL/min should be seen by a nephrology team to ensure adequate clinical and psychologic preparation for kidney replacement therapy [102,103].

Dialysis

Ultrafiltration of extracellular fluid by dialysis is the ideal treatment for patients who have stage V CKD and acutely symptomatic CHF. In the patient receiving chronic dialysis, the goal is to use fluid removal to control both volume status and blood pressure. Unfortunately, this treatment may cause dialysis-associated hypotension that complicates the use of oral antihypertensives required for other indications (eg, beta-blockers for angina). Hemodialysis usually requires intradialysis anticoagulation, which may increase the bleeding risk of other cardiac medications such as acetylsalicylic acid.

Summary

There is a high burden of cardiac disease in the CKD population. Severe LVH, dilated cardiomyopathy, and coronary artery disease occur frequently and result in the manifestations of CHF, which is probably more important with respect to prognosis than symptomatic. Multiple risk factors for CVD include traditional risk factors and those unique to the CKD population. Furthermore, the distinctive aspects of CKD patients sometimes warrant special consideration in making management decisions. Nonetheless, interventions such as controlling hypertension, specific pharmacologic options, lifestyle modification, anemia management, and early nephrology referral are recommended when appropriate.

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