

Kidney Disease as a Risk Factor for Development of Cardiovascular Disease

A Statement From the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention

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Chronic kidney disease¹ (CKD) is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. The number of individuals with kidney failure treated by dialysis and transplantation exceeded 320 000 in 1998 and is expected to surpass 650 000 by 2010.^{1,2} There is an even higher prevalence of earlier stages of CKD (Table 1).^{1,3} Kidney failure requiring treatment with dialysis or transplantation is the most visible outcome of CKD. However, cardiovascular disease (CVD) is also frequently associated with CKD, which is important because individuals with CKD are more likely to die of CVD than to develop kidney failure,⁴ CVD in CKD is treatable and potentially preventable, and CKD appears to be a risk factor for CVD. In 1998, the National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of CVD in CKD.⁵ This report showed that there was a high prevalence of CVD in CKD and that mortality due to CVD was 10 to 30 times higher in dialysis patients than in the general population (Figure 1 and Table 2).^{6–18} The task force recommended that patients with CKD be considered in the “highest risk group” for subsequent CVD events and that treatment recommendations based on CVD risk stratification should take into account the highest-risk status of patients with CKD.

The major goal of this statement is to review CKD as a risk factor for development of CVD. As background, we shall also review the definition of CKD and classification of stages of severity of CKD, the spectrum of CVD in CKD and differences from the general population, and risk factors for CVD in CKD.

Definition and Classification of Stages of Severity and Types of CKD

In 2002, the NKF published clinical practice guidelines on evaluation, classification, and risk stratification in CKD.³ In these guidelines, CKD is defined as either (1) kidney damage for ≥ 3 months, as confirmed by kidney biopsy or markers of kidney damage, with or without a decrease in glomerular filtration rate (GFR), or (2) $\text{GFR} < 60 \text{ mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^2$ for ≥ 3 months, with or without kidney damage (Table 1).

Kidney damage is ascertained by either kidney biopsy or markers of kidney damage, such as proteinuria, abnormal urinary sediment, or abnormalities on imaging studies. The finding of proteinuria not only defines the presence of CKD but also has important implications for diagnosis of the type of kidney disease and is associated with a worse prognosis for both kidney disease progression and the development of CVD. Proteinuria is variously defined (Table 3).^{3,19–21} Measurement of albumin-to-creatinine ratio or total protein-to-creatinine ratio in untimed “spot” urine samples is recommended for assessment of proteinuria.³

$\text{GFR} < 60 \text{ mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^2$ is selected as the cutoff value for definition of CKD because it represents a reduction by more than half of the normal value of $\approx 125 \text{ mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^2$ in young men and women, and this level of GFR is associated with the onset of laboratory abnormalities characteristic of kidney failure, including increased prevalence and severity of several CVD risk factors. Estimation of GFR from serum creatinine and prediction equations including age, sex, race, and body size is recommended to avoid the

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TABLE 1. Stages of CKD

Stage	Description	GFR, mL · min ⁻¹ per 1.73 m ²	US Prevalence, 1000s	US Prevalence, %
1	Kidney damage with normal or increased GFR	≥90	5900	3.3
2	Kidney damage with mildly decreased GFR	60–89	5300	3.0
3	Moderately decreased GFR	30–59	7600	4.3
4	Severely decreased GFR	15–29	400	0.2
5	Kidney failure	<15 or dialysis	300	0.1

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Data for stages 1–4 from NHANES III (1988–1994), based on population of 177 million with age ≥20 years. Data for stage 5 from United States Renal Data System (1998)¹ include ≈230 000 patients treated by dialysis and assume 70 000 additional patients not on dialysis. GFR estimated from serum creatinine by abbreviated Modification of Diet in Renal Disease Study equation based on age, sex, race, and calibration for serum creatinine. For stages 1 and 2, kidney damage was assessed by spot albumin-to-creatinine ratio >17 mg/g (men) or >25 mg/g (women) on 2 measurements.

misclassification of individuals on the basis of serum creatinine alone^{3,22–24} (Table 4 and NKF GFR calculator available at <http://www.kidney.org/professionals/doqi/index.cfm>).

Kidney failure is defined as GFR <15 mL · min⁻¹ per 1.73 m² or treatment by dialysis. Approximately 98% of patients beginning dialysis for CKD in the United States have an estimated GFR of <15 mL · min⁻¹ per 1.73 m².²⁵ This definition is not synonymous with end-stage renal disease, which is an administrative term in the United States signifying eligibility for coverage by Medicare for payment for dialysis and transplantation.

Among individuals with CKD, the stage of severity is based on the level of GFR (Table 1). The prevalence of kidney failure (≈300 000, or 0.1% of the US adult population) is considerably less than the prevalence of earlier stages of CKD (≈20 million, or 10.8% of the US adult population).

Diagnosis of CKD is traditionally based on pathology and etiology. A simplified classification, which we shall use in this article, emphasizes diseases in the native kidney, which can be broadly divided as diabetic and nondiabetic in origin, and kidney diseases in the transplant.^{3,26,27}

Spectrum of CVD in CKD and Differences From the General Population

In this section, we consider arterial vascular disease and cardiomyopathy as the primary types of CVD (Table 4). In CKD, it is useful to consider 2 subtypes of arterial vascular disease, namely, atherosclerosis and large-vessel remodeling or arteriosclerosis. Atherosclerosis is an intimal disease characterized by the presence of plaques and occlusive lesions.²⁸ There is a high prevalence of atherosclerosis in CKD.^{29,30} Atherosclerotic lesions in kidney failure are frequently calcified, as opposed to fibroatheromatous, and have increased media thickness compared with lesions in the general population.³¹ Surrogates of atherosclerosis include both intima-media thickness of the carotid wall that is detectable by ultrasound and inducible myocardial ischemia that is detectable by coronary stress tests. Electron-beam computed tomography is a sensitive method to detect vascular calcification but may not be an ideal method to detect atherosclerosis in CKD, because it is unable to distinguish between intimal calcifications of atherosclerosis and medial calcification that is common in CKD. Clinical presentations of atherosclerosis include ischemic heart disease, namely,

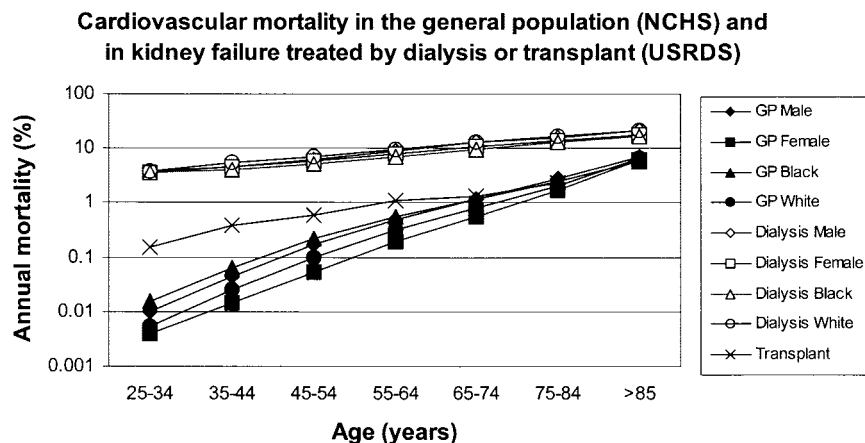


Figure 1. Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary edema in general population (GP; National Center for Health Statistics [NCHS] multiple cause of mortality data files International Classification of Diseases, 9th Revision [ICD 9] codes 402, 404, 410 to 414, and 425 to 429, 1993) compared with kidney failure treated by dialysis or kidney transplant (United States Renal Data System [USRDS] special data request Health Care Financing Administration form 2746 Nos. 23, 26 to 29, and 31, 1994 to 1996). Data are stratified by age, race, and sex. CVD mortality is underestimated in kidney transplant recipients owing to incomplete ascertainment of cause of death. Reproduced and modified with permission from Foley et al.⁶

TABLE 2. Approximate Prevalence of CVD in the General Population and CKD

	Ischemic Heart Disease (Clinical)	LVH (Echo)	Heart Failure (Clinical)
General population	8–13*	20†	3–6‡
CKD stages 3–4 (diabetic and nondiabetic kidney disease)	NA	25–50 (varies with level of kidney function)§	NA
CKD stages 1–4 (kidney transplant recipients)	15	50–70¶	NA
CKD stage 5 (hemodialysis)	40#	75**	40#
CKD stage 5 (peritoneal dialysis)	40#	75**	40#

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NA indicates not available. Values are percentages.

*Age 55–64 years. The higher percentage is for men. Data are from NHANES III, American Heart Association statistical Web site.⁷

†Data from Levy et al.⁸

‡Age 55–64 years. The higher percentage is for men. Data from NHANES III, American Heart Association statistical Web site.⁷

§Data from Levin et al.⁹

||Data from Kasiske.¹⁰

¶Data from Parfrey et al.,¹¹ Hernandez et al.,¹² Peteiro et al.,¹³ Huting et al.,¹⁴ and Himelman et al.¹⁵

#Data from Dialysis Morbidity and Mortality (Wave 2). United States Renal Data System Annual Data Report, 1997.^{16,17}

**Data from Foley et al.¹⁸

angina, myocardial infarction, and sudden cardiac death, which is common in CKD, and cerebrovascular disease, peripheral vascular disease, or heart failure (Table 5).

Stress imaging is an important modality for testing for myocardial ischemia. A recent meta-analysis reveals that stress imaging is of value in predicting CVD morbidity and mortality in kidney transplantation candidates treated by dialysis.³² It remains unknown, however, whether the diagnostic accuracy of these tests, as defined by a “gold standard” of angiographic obstructive coronary artery disease, is different from the general population. Furthermore, it remains unknown whether stress nuclear or stress echocardiographic testing is more accurate in patients with CKD.

Dialysis patients with ischemic heart disease may not necessarily have large-vessel coronary disease. In one study, up to 50% of nondiabetic dialysis patients with symptoms of myocardial ischemia did not have large-vessel coronary

artery disease (defined as luminal narrowing of >50% of major coronary vessels).³³ The authors hypothesized that the patients may have ischemia secondary to the combined effects of volume overload and left ventricular hypertrophy (LVH), which causes increased oxygen demand, and small-vessel coronary disease, which causes decreased oxygen supply. It needs to be acknowledged, however, that the latter study was performed in the pre-erythropoietin era, during which hemoglobin levels were lower, which also may have contributed to ischemia; therefore, the results may not be generalizable to current practice.

Patients with CKD also have a high prevalence of arteriosclerosis and remodeling of large arteries.²⁸ Remodeling may be due either to pressure overload, which is distinguished by wall hypertrophy and an increased wall-to-lumen ratio, or flow overload, which is characterized by a proportional increase in arterial diameter and wall thickness. Remodeling

TABLE 3. Definitions of Proteinuria

Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total protein			
24-Hour excretion (varies with method)	<300 mg/d	NA	≥300 mg/d
Spot urine dipstick	<30 mg/dL	NA	≥30 mg/dL
Spot urine protein-to-creatinine ratio (varies with method)	<200 mg/g	NA	≥200 mg/g
Albumin			
24-Hour excretion	<30 mg/d	30–300 mg/d	>300 mg/d
Spot urine albumin-specific dipstick	<3 mg/dL	>3 mg/dL	NA
Spot urine albumin-to-creatinine ratio (varies by sex*)	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

NA indicates not applicable.

*Sex-specific cutoff values are from a single study.¹⁹ Use of the same cutoff value for men and women leads to higher values of prevalence for women than men. Current recommendations from the American Diabetes Association define cutoff values for spot urine albumin-to-creatinine ratio for microalbuminuria and albuminuria as 30 and 300 mg/g, respectively, without regard to sex.²⁰

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TABLE 4. Equations to Predict GFR Based on Serum Creatinine

Cockcroft-Gault equation ²⁴	$C_{Cr}(\text{mL}/\text{min}) = \frac{(140 - \text{Age}) \times \text{Weight}}{72 \times S_{Cr}} \times (0.85 \text{ if female})$
Abbreviated MDRD Study equation ^{22,23}	$\text{GFR}(\text{mL} \cdot \text{min}^{-1} \text{ per } 1.73 \text{ m}^2) = 186 \times (S_{Cr})^{-1.154} \times (\text{Age})^{-0.203} \\ \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

C_{Cr} indicates creatinine clearance; MDRD, Modification of Diet in Renal Disease; and S_{Cr} , serum creatinine in mg/dL.

Age is given in years and weight in kilograms.

often accompanies a reduction in arterial compliance, which can be detected through measurement of aortic pulse wave velocity and characteristic impedance.^{34,35} Noncompliant vessels may result in increased systolic blood pressure, increased pulse pressure, LVH, and decreased coronary perfusion. Both decreased aortic compliance^{35–37} and increased pulse pressure³⁸ have been found to be independent risk factors for CVD in dialysis patients.

Patients with CKD also have a high prevalence of cardiomyopathy (Table 2).¹⁸ Hypertension and arteriosclerosis result in pressure overload and lead to concentric LVH (increased wall-to-lumen ratio), whereas anemia, fluid overload, and arteriovenous fistulas result in volume overload and primarily lead to left ventricular dilatation with LVH (a proportional increase in left ventricular mass and diameter). These structural abnormalities may lead to diastolic and systolic dysfunction and may be detectable by echocardiography. Clinical presentations of cardiomyopathy include heart failure and ischemic heart disease, even in the absence of arterial vascular disease.

Diagnosis of heart failure may be challenging in dialysis patients because salt and water retention may be treated by ultrafiltration during dialysis, often leaving other signs and symptoms, such as decreased blood pressure, fatigue, and anorexia, as the only clues to its presence. On the other hand, salt and water retention may reflect inadequate ultrafiltration rather than heart failure or a combination of both heart failure and inadequate ultrafiltration. Indeed, one of the major causes of inadequate ultrafiltration during dialysis is hypotension, which may be a manifestation of heart failure. Regardless of the cause, heart failure is a powerful risk factor for adverse outcomes in dialysis patients, which suggests that it is usually a manifestation of advanced CVD.³⁹ Left ventricular mass

index is dependent on volume status; therefore, there is a need for standardized assessments of left ventricular function in hemodialysis patients.⁴⁰

CVD Risk Factors in CKD

In subjects with CKD, for the purposes of this discussion, we classify CVD risk factors as either “traditional” or “nontraditional” (Table 6),⁴¹ and we define traditional risk factors as those in the Framingham Heart Study that have been used to estimate the risk of developing symptomatic ischemic heart disease.^{42,43} Most of the traditional CVD risk factors, such as older age, diabetes mellitus, systolic hypertension, LVH, and low high-density lipoprotein (HDL) cholesterol, are highly prevalent in CKD. The cardiovascular risk conferred by many traditional risk factors, such as diabetes,⁶ older age,² and LVH,⁴⁴ largely parallels the relationships described in the general population, although some important differences have been noted with regard to other risk factors. For example, U-shaped relationships exist between all-cause mortality and both blood pressure and cholesterol levels in dialysis patients (Figure 2).^{45–48} The increased risk at lower levels of blood pressure and cholesterol may reflect confounding from cardiomyopathy and malnutrition, respectively, although this has not been proved. In support of the latter, hypertension was a risk factor for the development of LVH, heart failure, and ischemic heart disease but not mortality in a Canadian cohort of dialysis patients.⁴⁹

Several cross-sectional studies have suggested that the Framingham risk equation is insufficient to capture the extent of CVD risk in subjects with CKD.^{17,50,51} There are 2 interpretations for these findings. First, other factors (nontraditional risk factors) that are not included in Framingham risk equations may play an important role in promoting ischemic

TABLE 5. Spectrum of CVD in CKD: Differences From the General Population

Types of CVD/Pathology	Surrogates	Clinical Presentations of CVD
Arterial vascular disease		
Atherosclerosis	Inducible ischemia, carotid IMT, EBCT (may be less useful than in the GP for atherosclerosis because of medial rather than intimal calcification), ischemia by ECG	IHD (myocardial infarction, angina, sudden cardiac death), cerebrovascular disease, PVD, HF
Arteriosclerosis: dilated and noncompliant large vessels	Aortic pulse wave velocity, calcification of the aorta, LVH (indirectly), increased pulse pressure	IHD, HF
Cardiomyopathy		
Concentric LVH and LV dilatation with proportional hypertrophy	LVH, systolic dysfunction, and diastolic dysfunction by echocardiogram. LVH by ECG	HF, hypotension, IHD

IMT indicates intima-media thickness; EBCT, electron-beam computed tomography; GP, general population; ECG, electrocardiogram; IHD, ischemic heart disease; PVD, peripheral vascular disease; HF, heart failure; and LV, left ventricular.

TABLE 6. Traditional and Nontraditional Cardiovascular Risk Factors in CKD

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male sex	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
LVH	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. Reproduced and modified with permission from Sarnak et al.⁴¹

heart disease in subjects with CKD. Second, traditional risk factors may have a qualitatively and quantitatively different risk relationship with CVD in CKD compared with the general population. For example, individuals with CKD may have had a longer and more severe exposure to hypertension than subjects without CKD. In addition, subjects with CKD may have been treated for hypertension, and the Framingham risk equation does not take into account dose or years of treatment with antihypertensive medications.⁵²

To define a nontraditional factor as a risk factor, all of the following conditions ideally should be met: (1) biological plausibility as to why the factor may promote CVD risk; (2) demonstration that the risk factor level increases with severity of kidney disease; (3) demonstration of an association be-

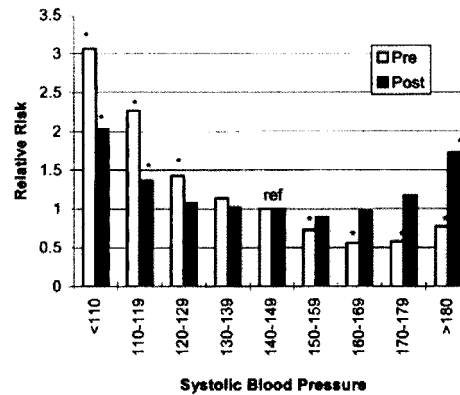


Figure 2. Mortality vs systolic blood pressure in hemodialysis patients. Dialysis Clinic, Inc prevalent cohort (1992 to 1996; n=5433). Cox regression analysis including age, race, sex, and diagnosis as baseline covariates and predialysis (Pre) or postdialysis (Post) systolic blood pressure, albumin, and Kt/V as time-dependent covariates. Reproduced with permission from Zager et al.⁴⁶

tween the risk factor and CVD in CKD in observational studies; and (4) demonstration in placebo-controlled clinical trials that treatment of the risk factor decreases CVD outcomes. Although conditions 1 and 2 are met for the most part when one considers the nontraditional risk factors listed in Table 6, there remain many gaps in the CKD literature regarding condition 3, and particularly condition 4. This is, therefore, an active area of research.

Several nontraditional factors, such as hyperhomocysteinemia, oxidant stress, dyslipidemia, and elevated inflammatory markers, are associated with atherosclerosis,⁵³⁻⁶⁰ and 2 recent reviews suggest that oxidant stress and inflammation may be the primary mediators or the “missing link” that explains the

TABLE 7. Microalbuminuria as a Risk Factor for CVD Outcomes in Subjects With Diabetes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Stehouwer, 2002 ⁹⁵	Type 2 DM; age <66 y	363	NA	NA	+
Gerstein, 2001 ⁸⁰	DM plus another CVD risk factor	3498	Composite: MI, stroke, CVD death	+	+
Agewall, 1997 ⁸⁸	DM and treated hypertension	94	CVD mortality	+	+
Stephenson, 1995 ⁸⁴	Type 1 DM	1188	CVD mortality	+	+
Stephenson, 1995 ⁸⁴	Type 2 DM	3234	CVD mortality	+	+
Dinneen, 1997 ⁹⁰	Type 2 DM: pooled odds ratios of 11 cohort studies	2138	Composite: CVD morbidity and mortality	+	+
Mogensen, 1984 ⁹¹	Type 2 DM; age 50-75 y	76	NA	NA	+
Valmadrid, 2000 ⁹⁷	Type 2 DM; mean age 68 y	840	CVD mortality	+	+
Miettinen, 1996 ⁹³	Type 2 DM	1056	Composite: stroke, IHD, and PVD	+	NA
Messent, 1992 ⁹²	Type 1 DM	63	CVD mortality	+	-
Rossing, 1996 ⁹⁴	Type 1 DM	939	CVD mortality	+	+
Gall, 1995 ⁸⁹	White with type 2 DM	328	CVD mortality	-*	+
Uusitupa, 1993 ⁹⁶	Incident type 2 DM	133	CVD mortality	-	NA

DM indicates diabetes mellitus; NA (no data available), the outcome was not evaluated in the study; MI, myocardial infarction; IHD, ischemic heart disease; PVD, peripheral vascular disease; +, the author concluded that microalbuminuria was an independent risk factor for the outcome after adjustment for all other CVD risk factors; and -, the author concluded that microalbuminuria was not an independent risk factor for the outcome after adjustment for all other CVD risk factors.

*Macroalbuminuria but not microalbuminuria was an independent risk factor.

All subjects are considered highest risk in this table because by definition, subjects had diabetes. Only prospective studies are considered.

tremendous burden of CVD in CKD.^{61,62} Other factors such as anemia are associated with cardiomyopathy,^{9,63} whereas abnormal calcium and phosphorus metabolism is associated with vascular remodeling and development of noncompliant vessels.⁶⁴

As mentioned above, although many of these putative risk factors are associated with increased risk for either all-cause mortality or CVD in various stages of CKD,^{56,57,65–68} for the most part, their causal relationship to CVD has not yet been proved in clinical trials. However, 3 important clinical trials include the following. The Normal Hematocrit Trial enrolled ≈1300 hemodialysis patients with ischemic heart disease or heart failure and randomized them to a predialysis hematocrit goal of either 30% or 42% with the use of erythropoietin.⁶⁹ The higher hematocrit group had a higher (although not significantly) incidence of all-cause mortality and myocardial infarction, the primary end point. The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE) Study randomized 196 hemodialysis patients with CVD to 800 U of vitamin E or placebo. The vitamin E group had a lower incidence of the primary end point, which was a composite of myocardial infarction (both fatal and nonfatal), ischemic stroke, peripheral vascular disease, and unstable angina.⁷⁰ Finally, a recent controlled trial randomized 134 hemodialysis patients to either 600 mg of oral acetylcysteine (an antioxidant) twice per day or placebo.⁷¹ Those patients randomized to acetylcysteine had a lower incidence of the primary end point, which was a composite of fatal and nonfatal myocardial infarction, CVD death, need for coronary angioplasty or coronary artery bypass surgery, ischemic stroke, and peripheral vascular disease manifested by either amputation or need for angioplasty. Although the latter 2 studies should be interpreted with caution because they were small and are not consistent with studies in the general population,⁷² it is important to recognize that dialysis patients have higher levels of oxidant stress and inflammation than the general population; therefore, the results are provocative and need to be followed up in larger trials.

CVD in Kidney Failure

CVD mortality is ≈10 to 30 times higher in patients treated by dialysis than in patients in the general population, despite stratification for sex, race, and the presence of diabetes.⁶ After stratification for age, CVD mortality remains ≈5-fold higher in dialysis patients than in the general population, even at the extremes of age (Figure 1). The high mortality rate is likely due to both a high case fatality rate and a high prevalence of CVD.

A high case fatality rate in dialysis patients has been observed after acute myocardial infarction and in patients with heart failure. Mortality 1 and 2 years after myocardial infarction was 59% and 73%, respectively, in dialysis patients (Figure 3),⁷³ which is much higher than after acute myocardial infarction in the general population, even in subjects with comorbid conditions such as diabetes. For example, in the Worcester Heart Attack Study, approximately three fourths of diabetic men and two thirds of diabetic women discharged after an acute myocardial infarction were still alive 2 years

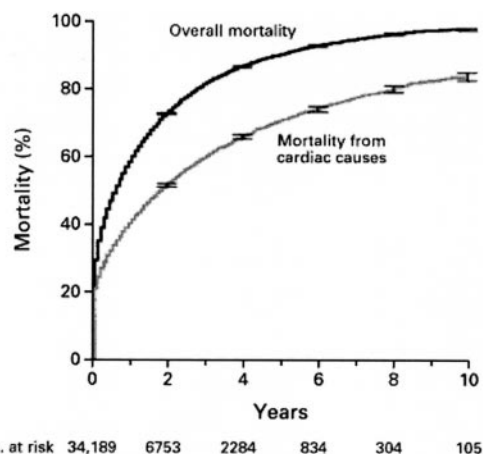


Figure 3. Estimated cumulative mortality after acute myocardial infarction among patients on dialysis. Reproduced with permission from Herzog et al.⁷³

later.⁷⁴ In another study in dialysis patients, median survival was only 18 months after development of de novo heart failure, which is also far higher than observed in the general population.³⁹

The prevalences of atherosclerosis, heart failure, and LVH are extremely high in hemodialysis patients (Table 2).⁶ Approximately 40% of incident hemodialysis patients have clinical evidence of ischemic heart disease or heart failure. In addition, the prevalence of LVH in incident dialysis patients is high. In the Canadian Prospective Cohort Study of 433 incident dialysis patients, 74% had LVH at baseline, 44% had concentric LVH, 30% had hypertrophy with left ventricular dilatation, and 15% had systolic dysfunction.¹⁸

CVD in Kidney Transplant Recipients

CVD accounts for 35% to 50% of all-cause mortality in kidney transplant recipients,^{75–77} and CVD mortality rates are at least twice as high as in an age-stratified sample of the general population but significantly lower than an age-stratified dialysis population (Figure 1).^{6,77} The 2 most likely explanations for the reduced risk in kidney transplant recipients compared with dialysis patients are selection bias for those undergoing transplantation and removal of the hemodynamic and uremic abnormalities associated with dialysis in those who receive transplants.

CVD morbidity is also higher in transplant recipients than in the general population even in comparisons with population samples with similar age and sex distributions. The prevalence of coronary artery disease is ≈15%,¹⁰ the prevalence of LVH is 50% to 70%,^{11–15} and the incidence of CVD is at least 3 to 5 times that of the general population.^{6,10}

Risk factors for CVD in kidney transplant recipients are multiple. They include traditional CVD risk factors, such as hypertension, diabetes, hyperlipidemia, and LVH, which are highly prevalent, and nontraditional risk factors associated with reduced GFR, such as hyperhomocysteinemia or factors unique to transplantation itself, including the direct effects of immunosuppression or rejection. It has recently been demonstrated that although the Framingham risk equation predicts ischemic heart disease after kidney transplantation, it tends to

TABLE 8. Proteinuria as a Risk Factor for CVD Outcomes in Patients Without Diabetes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Highest-risk population					
Gerstein, 2001 ⁸⁰	Vascular disease	5545	Composite: MI, stroke, CVD mortality	+	+
Diercks, 2002 ¹¹²	Subjects with ST-T-wave changes	7330	CVD mortality	+	+
High-risk populations					
De Leeuw, 2002 ¹¹¹	Systolic hypertension and age ≥ 60 y	4695	Composite: fatal and nonfatal CVD (stroke and IHD)	+	+
Ljungman, 1996 ¹¹⁵	Hypertensive and nonhypertensive men	120	Composite: IHD, stroke, and PVD	+	NA
Agewall, 1997 ⁸⁸	Treated hypertension	345	CVD mortality	–	–
Damsgaard, 1990 ¹¹³	Age 60–74 y	216	NA	NA	+
Grimm, 1997 ¹¹⁴	Men in the upper 15% of coronary heart disease risk	12 866	CVD mortality	+	+
Yudkin, 1988 ¹²⁴	Diabetic screening project	187	NA	NA	+
Culleton, 1998 ¹¹⁰	Men with mean age 68 y	1045	CVD mortality	–	+
Culleton, 1998 ¹¹⁰	Women with mean age 69 y	1541	CVD mortality	+	+
Jager, 1999 ¹¹⁷	Age 50–75 y stratified by glucose tolerance	631	CVD mortality	+	+
Roest, 2001 ¹²¹	Postmenopausal women	561 cases, 557 controls*	CVD mortality	+	NA
Kuusisto, 1995 ¹²⁰	Mean age 68 y	1069	IHD death and nonfatal MI	+	NA
Ordonez, 1993 ¹²²	Nephrotic syndrome	142 cases, 142 controls*	Composite: MI, angina and coronary insufficiency	+	+
Low-risk populations					
Hillege, 2002 ¹¹⁶	City of Groningen	40 458	CVD mortality	+	+
Miettinen, 1996 ⁹³	Finnish cohort	1375	Composite: IHD, stroke, and PVD	+	NA
Wagner, 1994 ¹²³	White men aged 45–74 y, NHANES I	6588	CVD mortality	+	+
Wagner, 1994 ¹²³	White women aged 45–74 y, NHANES I	6588	CVD mortality	–	+
Muntner, 2002 ¹¹⁹	NHANES II	6534	CVD mortality	+	+
Kannel, 1984 ¹¹⁸	Framingham men	5209	CVD mortality	+	+
Kannel, 1984 ¹¹⁸	Framingham women	5209	CVD mortality	–	–

+ indicates that the author concluded that proteinuria was an independent risk factor for the outcome after adjustment for all other risk factors; –, the author concluded that proteinuria was not an independent risk factor for the outcome after adjustment for all other risk factors. All other abbreviations as in Table 7.

*Case-control studies. All the rest of the studies in the table are prospective studies.

Populations were considered highest risk if they had CVD, other vascular disease, surrogates of CVD, or diabetes; high risk if subjects were selected on the basis of having a traditional CVD risk factor such as hypertension or increased age; and low risk if the population was a community study.

underestimate the risks, especially the risk associated with diabetes.⁷⁸ The latter effect is probably due to more severe diabetic vascular disease in patients with diabetic kidney disease.

CVD in Diabetic Kidney Disease

In this section, we primarily focus on microalbuminuria, because it is the earliest sign of kidney disease in diabetes. We define all patients as being in the highest risk group for future CVD events because of the presence of diabetes.

Microalbuminuria is associated with an increased prevalence of CVD risk factors. Although blood pressure may be normal in subjects with type 1 diabetes, a pattern of “nondipping” at night is frequently observed by 24-hour ambulatory blood pressure monitoring and may precede the development of microalbuminuria.⁷⁹ Nondipping is a well-recognized CVD risk factor. Dia-

betic subjects with microalbuminuria also have an increased prevalence of dyslipidemia, poor glucose control, and increased blood pressure compared with diabetic patients without microalbuminuria.^{80,81}

There is a strong association between microalbuminuria (albuminuria) and CVD in cross-sectional analysis. This relationship has been found for surrogate measures, such as carotid intima-media thickness⁸² and LVH,^{83,84} and different clinical presentations of CVD, such as coronary artery disease^{81,84} and peripheral vascular disease.⁸⁵ The relationship between microalbuminuria (albuminuria) and clinical CVD has been confirmed in diverse racial/ethnic groups, including Koreans, American Indians, and Asian Indians.^{81,86,87} Although the relationship is present in both type 1 and type 2 diabetes, the relationship is generally stronger in type 2 diabetes because of the older age of individuals with this disease.

TABLE 9. Decreased GFR as a Risk Factor for CVD Outcomes

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Highest-risk populations					
Dries, 2000 ¹⁴⁹	Ejection fraction \leq 35%	5834	Pump failure mortality	+	+
Kearney, 2002 ¹⁵⁰	Ambulatory patients with chronic HF	553	Mortality due to progressive HF	+	+
McClellan, 2002 ¹⁵²	HF by ICD 9 code	665	NA	NA	+
Hillege, 2000 ¹⁵¹	Class III and IV NYHA HF and LVEF $<$ 35%	1906	NA	NA	+
Mahon, 2002 ¹⁵³	HF	585	NA	NA	+
McCullough, 2000 ¹³⁹	CCU	9544	Arrhythmias, conduction problems, HF, shock, mitral regurgitation	+	+
Soman, 2002 ¹⁴¹	CCU	9544	Arrhythmias	+	NA
Matts, 1993 ¹⁴²	MI	417	CVD mortality	+	+
Walsh, 2002 ¹⁴³	MI	483	NA	NA	+
Beattie, 2001 ¹⁴⁶	MI	1724	NA	NA	+
Shlipak, 2002 ¹⁴⁸	Elderly and MI	130 099	NA	NA	+*
Wright, 2002 ¹⁶¹	MI	3106	NA	NA	+
McCullough, 2002 ¹⁴⁰	Emergency department with possible MI	808	Composite: all-cause mortality, MI, HF	+	NA
Al Suwaidi, 2002 ¹⁵⁷	Acute coronary syndromes	37 925	Composite: all-cause mortality and MI	+	+
Freeman, 2003 ¹⁷³	Acute coronary syndromes	889	NA	NA	+
Wison, 2003 ¹⁷⁴	Acute coronary syndromes	2503	CVD mortality	+	NA
Januzzi, 2002 ¹⁶⁰	Non-ST-elevation coronary syndrome	1570	Composite: all-cause mortality, MI, and refractory ischemia	+†	NA
Best, 2002 ¹⁵⁸	PCI	5327	NA	NA	+
Shaw, 2002 ¹⁶⁸	PCI	100 253	CVD mortality	–	+
Rubenstein, 2000 ¹⁴⁴	PCI	3334	Composite: all-cause mortality, MI, CABG, and repeat PCI	+	+
Reinecke, 2003 ¹⁷⁷	PCI	1049	NA	NA	+
Szcech, 2001 ¹⁵⁴	CABG or PCI	59 576	NA	NA	+
Szcech, 2002 ¹⁵⁵	CABG or PCI	3608	CVD mortality	+	+
Gruberg, 2002 ¹⁵⁶	Coronary stents	5084	NA	NA	+
Gruberg, 2003 ¹⁷²	PCI with saphenous vein grafts	1265	NA	NA	+
Anderson, 1999 ¹⁷⁶	CABG	3902	Composite: cardiac arrest and HF	+	+
Beddhu, 2002 ¹⁵⁹	Coronary angiography	8600	MI	+	+
Hemmelgarn, 2001 ¹⁴⁵	Coronary angiography	16 989	NA	NA	+
Shlipak, 2001 ¹⁴⁷	Postmenopausal women with coronary disease	2763	Composite: IHD and stroke	+	NA
Mann, 2001 ¹³²	Vascular disease or diabetes combined with another CVD risk factor	9287	Composite: CVD mortality, MI, and stroke	+	+‡
Anderson, 2000 ¹⁷⁵	Valve surgery	834	Composite: cardiac arrest and low cardiac output	+	+
High-risk populations					
Fried, 1998 ¹⁶²	Age \geq 65 y	5201	NA	NA	+
Manjunath, 2003 ¹³⁷	Age \geq 65 y	4893	Composite: HF, IHD, PVD, stroke, and CVD mortality	+	+
Manolio, 1996 ¹⁶³	Age \geq 65 y	5201	Stroke	+	NA
Gottdiener, 2000 ¹⁶⁴	Age \geq 65 y	5888	HF	+	NA
Ruilope, 2001 ¹³⁴	Hypertension	18 597	Composite: CVD death, MI, and stroke	+	+
Schillaci, 2001 ¹⁶⁶	Whites with hypertension	1829	Composite: IHD, TIA, stroke, HF, and symptomatic aortoiliac disease	+	–
De Leeuw, 2002 ¹¹¹	Isolated systolic hypertension and age \geq 60 y	4695	Fatal and nonfatal CVD (stroke and IHD)	+	+
Henry, 2002 ¹⁶⁵	Age 50 to 75 y and 27% DM by design	631	CVD mortality	+	+
Flack, 1993 ¹⁶⁷	Hypertensive men	5524	CVD mortality	–	–
Shulman, 1989 ⁴	Hypertension	10 940	CVD	+	+
O'Brien, 2002 ¹⁶⁹	General surgery; mean age 60 y	49 081	Cardiac arrest	+	+
Low-risk populations					
Garg, 2002 ¹⁷⁰	NHANES I	2352	CVD mortality	–	–
Muntner, 2002 ¹¹⁹	NHANES II	6534	CVD mortality	+	+
Culleton, 1999 ¹³¹	Men	2837	Composite: CVD death, HF, IHD, and stroke	–	+
Culleton, 1999 ¹³¹	Women	3386	Composite: CVD mortality, HF, IHD, and stroke	–	–

TABLE 9. Continued

First Author, Year	Inclusion Criteria	n	Definition of CVD	Author Conclusion re: CVD	Author Conclusion re: All-Cause Mortality
Manjunath, 2003 ¹³³	Age 45–65 y	15 350	Composite: CVD mortality, stroke, and IHD	+	NA
Wannamethee, 1997 ¹⁷¹	Men 40–59 y	7690	Stroke	+	+
Wannamethee, 1997 ¹⁷¹	Men 40–59 y	7690	IHD	–	+

HF indicates heart failure; ICD 9, International Classification of Diseases, 9th revision; NA (no data available), the outcome was not evaluated in the study; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CCU, coronary care unit; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; IHD, ischemic heart disease; PVD, peripheral vascular disease; TIA, transient ischemic attack; DM, diabetes mellitus; +, the author concluded that decreased GFR was an independent risk factor for the outcome after adjustment for all other risk factors; and –, the author concluded that GFR was not an independent risk factor for the outcome after adjustment for all other risk factors.

*Positive for 6-month follow-up and negative for 1-year follow-up.

†Not adjusted.

‡Adjusted only for center.

Studies whose primary goal was to evaluate whether CKD is a risk factor for acute kidney failure are not included in this table. Only prospective studies are considered in this table. Populations were considered highest risk if they had CVD, other vascular disease, surrogates of CVD, or diabetes; high risk if subjects were selected on the basis of having a traditional CVD risk factor; and low risk if they were community studies.

Longitudinal studies also document that microalbuminuria is an adverse prognostic indicator for clinical CVD outcomes and all-cause mortality in subjects with diabetes (Table 7).^{80,84,88–97} For example, in the Heart Outcomes Prevention Evaluation (HOPE) Study (subjects with vascular disease or diabetes plus another traditional risk factor at baseline), those with microalbuminuria and diabetes had a 1.97-fold (95% confidence interval 1.68 to 2.31) and 2.15-fold (95% confidence interval 1.78 to 2.60) increased risk for a composite outcome of myocardial infarction, stroke, or CVD death, as well as all-cause mortality, respectively, compared with subjects with diabetes without microalbuminuria.⁸⁰ A recent pooled analysis of type 2 diabetes in 11 cohort studies (2138 patients followed up for a mean of 6.4 years) showed that microalbuminuria was associated with an adjusted overall odds ratio for all-cause mortality of 2.4 (95% confidence interval 1.8 to 3.1) and for cardiovascular morbidity and mortality of 2.0 (95% confidence interval 1.4 to 2.7).⁹⁰

There are several potential explanations for why the presence of microalbuminuria may be a risk factor for outcomes in diabetes. First, as discussed above, subjects with microalbuminuria have a higher prevalence of traditional risk factors than diabetic subjects without microalbuminuria. However, even after adjustment for other risk factors, the presence of microalbuminuria remains an adverse prognostic indicator (Table 7). Second, microalbuminuria may reflect generalized endothelial dysfunction and increased vascular permeability or abnormalities in the coagulation and fibrinolytic systems.^{98,99} Third, microalbuminuria may be associated with inflammatory markers.¹⁰⁰ Fourth, microalbuminuria may denote the greater severity of end organ damage. Therefore, even if one adjusts for the presence of clinical CVD, the subject with microalbuminuria likely has more advanced disease.

CVD in Nondiabetic Kidney Disease

In this section, we focus on proteinuria and reduced GFR as manifestations of CKD. We consider proteinuria rather than microalbuminuria alone because studies have evaluated microalbuminuria, albuminuria, dipstick proteinuria, or ne-

phrotic range proteinuria. Nephrotic syndrome in diabetic and nondiabetic individuals is associated with a number of disorders that have been implicated in CVD, such as extreme dyslipidemia and hypercoagulability, and is reviewed elsewhere.^{101,102} The goal of this review is to highlight the importance of lower levels of proteinuria.

We define a highest-risk population as one that is selected for already having CVD, other vascular disease, surrogates of CVD (such as LVH), or diabetes. An intermediate-risk population is one that is selected for having a traditional risk factor for CVD, such as increased age or hypertension. A low-risk population was defined as a community study.

Proteinuria

As in subjects with diabetes, nondiabetic persons with microalbuminuria have a higher prevalence of CVD risk factors (including dyslipidemia, increased blood pressure by 24-hour ambulatory blood pressure monitoring, heavier body size, insulin resistance, and a history of smoking) than subjects without microalbuminuria.^{103–105} There is a strong association between microalbuminuria and CVD in cross-sectional analysis. For example, microalbuminuria is associated with surrogates of CVD, such as increased intima-media thickness of the carotid artery in hypertensive subjects,¹⁰⁶ more frequent concentric LVH in hypertensive men,¹⁰⁴ abnormal left ventricular geometry and mass in subjects with hypertension and LVH,^{107,108} and electrocardiographic evidence of myocardial ischemia.¹⁰⁹ Subjects with microalbuminuria also have a higher prevalence of clinical CVD than those without microalbuminuria.¹⁰⁵

As in subjects with diabetic kidney disease, the presence of proteinuria in nondiabetic individuals is, for the most part, independently associated with an increased risk for CVD events in longitudinal studies (Table 8).^{80,88,93,110–124} Microalbuminuria in nondiabetic subjects in the HOPE study was associated with a 61% increased risk of the composite end point of stroke, myocardial infarction, or CVD death and a 2-fold increase in risk for all-cause mortality.⁸⁰ In low-risk populations, however, the results have been less consistent. For example, in the Framingham Heart Study, the relative

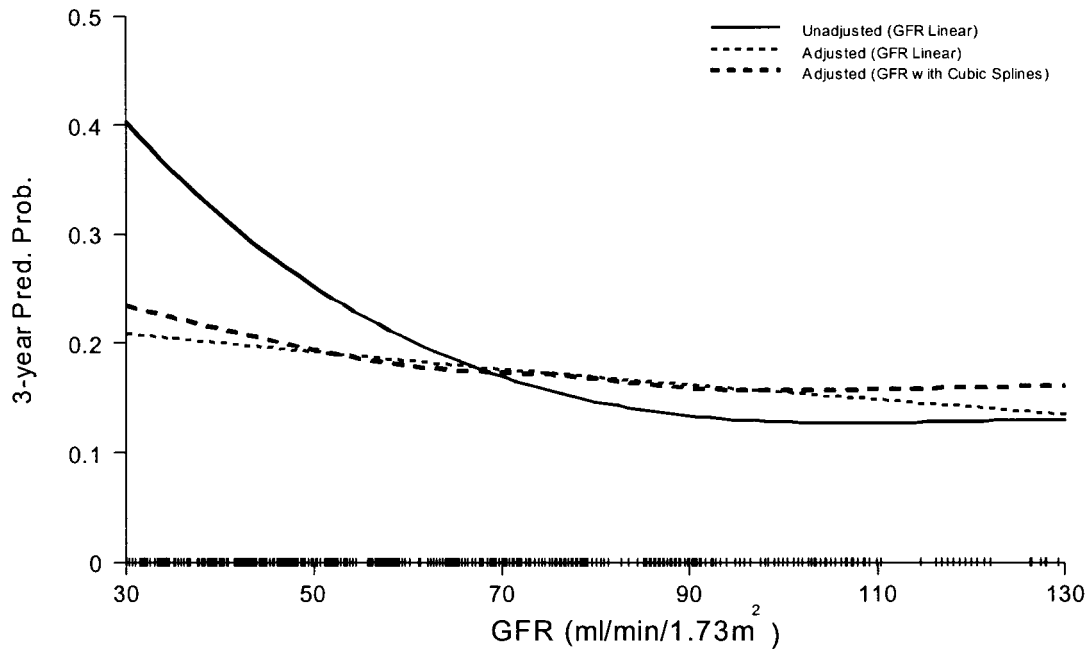


Figure 4. Smoothed 3-year predicted probability (Pred. Prob.) of developing CVD by level of GFR in the Cardiovascular Health Study. Unadjusted curve shows risk incorporating each individual's value for other covariates. Adjusted curve shows average risk in population if everyone had GFR value shown on x-axis. Linear model includes GFR as continuous variable in Cox regression, whereas cubic spline includes cubic transition between linear segments with knots (at 0.05, 0.275, 0.5, 0.725, 0.95 quantiles of GFR) corresponding to GFR values of 45.3, 64.0, 76.2, 88.5, and 107.3 $\text{mL} \cdot \text{min}^{-1}$ per 1.73 m^2 , respectively. Tick marks along the x-axis indicate GFR values for individual participants with events (marks form solid bar in GFR regions with many events). Lower GFR cutoff of 30 $\text{mL} \cdot \text{min}^{-1}$ per 1.73 m^2 was chosen because only 37 subjects had GFR values between 15 and 30 $\text{mL} \cdot \text{min}^{-1}$ per 1.73 m^2 ; therefore, data were less precise in latter range. Reproduced and modified with permission from Manjunath et al.¹³⁷

risk for CVD death or all-cause mortality for dipstick-positive proteinuria in women was similar to that in the HOPE study, but there was no significant independent association between dipstick-positive proteinuria and these outcomes in men.¹¹⁰ Conversely, in the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study, a community study in the Netherlands, a doubling of urine albumin concentration was associated with a 29% increase in relative risk for CVD mortality.¹¹⁶ As in diabetic kidney disease, the presence of microalbuminuria in nondiabetic individuals may reflect generalized endothelial dysfunction^{125–129} or abnormalities of the fibrinolytic and coagulation pathways, may be a marker of inflammatory status,¹³⁰ or may denote the greater severity of the target end-organ damage.

Reduced GFR

Reduced GFR is associated with a high prevalence of CVD risk factors and a higher prevalence of CVD surrogates and clinical CVD. For example, several studies across a broad spectrum of populations, such as the HOPE study, the Cardiovascular Health Study (CHS), the Hypertension Optimal Treatment (HOT) Study, the Framingham and Framingham Offspring Studies, and the Atherosclerosis Risk In Communities (ARIC) Study, have shown that levels of systolic blood pressure and total cholesterol and the percentage of subjects with low HDL cholesterol are greater in subjects with decreased GFR. In addition, the percentages of subjects with diabetes, electrocardiographic LVH, ischemic heart disease, and heart failure are higher in those with

decreased GFR.^{131–135} More recently, it has been demonstrated that the level of kidney function is also associated with the extent of demonstrable angiographic coronary disease. For example, in women with chest pain who undergo angiography, an elevated creatinine of 1.2 to 1.9 mg/dL is an independent predictor of significant angiographic coronary disease, as defined by a luminal narrowing of 50%.¹³⁶

The prevalence of LVH is also inversely related to the level of GFR. In one study, the prevalence of LVH, as measured by echocardiography, was 45%, 31%, and 27% in patients with creatinine clearance of <25, 25 to 50, and >50 mL/min, respectively.⁹ These percentages contrast sharply with the <20% prevalence of LVH in similar-aged patients in the general population.⁸

Reduced GFR is also associated with clinical CVD outcomes in prospective studies. It is important initially to consider the effect of reduced GFR on CVD outcomes without adjustment for other risk factors for 2 reasons. First, decreased GFR may be associated with other CVD risk factors and therefore may be useful for risk stratification in and of itself. Second, the adjusted analyses may inappropriately reduce the association between level of GFR and outcomes. That is, reduced GFR may result in more severe hypertension and dyslipidemia, and therefore one may overcorrect for effects if factors in the causal pathway of lower GFR to CVD are included in statistical adjustments. Figure 4 demonstrates the difference in the probability of developing CVD over 3 years by level of GFR with and without adjustment for other CVD risk factors in the CHS.¹³⁷ Without

adjustment for other risk factors, a GFR of $30 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 is associated with a CVD risk of 40%, compared with 15% associated with a GFR of $130 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 . After adjustment for other CVD risk factors, a GFR of $30 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 is associated with a CVD risk of 22%, compared with 15% associated with a GFR of $130 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 . The interpretation of this finding is that although much of the risk of CKD is due to its association with other CVD risk factors, the presence of CKD in and of itself remains an important independent risk factor for CVD outcomes.

Decreased GFR has consistently been found to be an independent risk factor for CVD outcomes and all-cause mortality in the highest-risk populations (Table 9).^{*} This is true in subjects with vascular disease or diabetes plus another CVD risk factor, after coronary artery bypass, after cardiac valve surgery, after myocardial infarction, in patients undergoing percutaneous coronary interventions, in patients with unstable coronary syndromes, in patients presenting to the emergency ward with chest pain, and in patients with heart failure.[†] Furthermore, it appears that this increase in risk is present with even mild reduction in kidney function.^{174,177,178}

In high-risk populations, most but not all studies have suggested that decreased GFR is an independent risk factor for outcomes. This is true in the elderly, in whom even mild reductions of kidney function are associated with worse outcomes,¹³⁷ in studies of subjects with hypertension,⁴ in studies of populations with a higher than normal prevalence of diabetes,¹⁶⁵ and among older patients undergoing general surgery.¹⁶⁹ In the Multiple Risk Factor Intervention Trial (MRFIT), the baseline creatinine level was not independently associated with CVD outcomes or all-cause mortality. However, an increase in follow-up serum creatinine level at 6 years did predict adverse CVD outcomes.¹⁶⁷ The authors postulated that the lack of association with baseline serum creatinine may have been due to a narrow range of serum creatinine levels at baseline.

In low-risk populations or community studies, the relationship between the level of kidney function and outcomes has not been as clear. In both the Framingham Study and the first National Health And Nutrition Examination Survey (NHANES I), the level of kidney function was not an independent risk factor for CVD outcomes,^{131,170} whereas in the ARIC Study and NHANES II, it was a risk factor for both CVD and all-cause mortality.^{119,133} Potential reasons for the discrepancies in the studies include differences in the study populations (for example, blacks were part of the ARIC study but not the Framingham studies), alternate measures to ascertain level of kidney function (serum creatinine is less sensitive than estimated GFR to detect small differences in level of kidney function and therefore may be less likely to detect an association in a low-risk population), and potential type II errors due to lower CVD event rates in community studies.¹⁷⁹ Either way, it appears that the presence of reduced GFR is either not a risk factor or at most is a modest independent risk factor for CVD outcomes in low-risk populations.

There are a number of possible explanations for the independent association of reduced GFR and CVD outcomes. First, a reduced GFR may be associated with an increased level of nontraditional CVD risk factors that frequently are not assessed in many studies.^{180,181} Second, reduced GFR may be a marker of undiagnosed vascular disease or alternatively a marker for the severity of diagnosed vascular disease, especially in high- or highest-risk populations. Third, reduced GFR may be a measure of residual confounding from traditional CVD risk factors. For example, subjects with reduced GFR may have had more severe hypertension or dyslipidemia and therefore have suffered more vascular damage secondary to hypertension or dyslipidemia. Fourth, recent studies have suggested that subjects with reduced GFR are less likely to receive medications or therapies such as angiotensin converting enzyme inhibitors, β -blockers, aspirin, platelet inhibitors, thrombolytics, or percutaneous intervention than patients with preserved GFR. Perhaps as important was the fact that in the same studies, patients with reduced GFR who did receive the above interventions obtained similar benefit as patients with preserved GFR.^{140,148,161,173,182,183} Finally, decreased GFR itself may be a risk factor for progression of ventricular remodeling and cardiac dysfunction.

The results in Tables 7 through 9 may be limited for the following reasons. First, negative results may not have been submitted or published, resulting in a publication bias. Second, we did not perform a systematic review to locate all studies for which the primary goal was the evaluation of the relationship between either proteinuria (albuminuria) or reduced GFR and CVD outcomes. Third, there is a possibility that other studies of which we are not aware evaluated risk factors for CVD outcomes and included proteinuria (microalbuminuria) or level of kidney function in the multivariable analyses. Finally, we have not included studies for which the primary goal was the evaluation of risk factors for acute kidney failure—for example, after receiving intravenous contrast agents. These studies may be relevant, because reduced GFR is a strong risk factor for acute kidney failure and through this mechanism may lead to an increase in CVD events and all-cause mortality.¹⁸⁴

Unanswered Questions

There remain many unanswered questions. A few, alluded to above, include the following: Are all the potential nontraditional risk factors defined in Table 6 indeed risk factors for CVD in all stages of CKD? Is a mild decrease in GFR associated with an increased CVD risk in low-risk populations, and if so, through what mechanism? Will therapy designed specifically to reduce albuminuria/proteinuria decrease CVD events? What are the cellular mechanisms of left ventricular remodeling in CKD, and how may treatment modalities alter this process? We also expand on 2 additional questions.

First, is the presence of CKD more of a risk factor for heart failure or ischemic heart disease outcomes? There is debate in the literature whether the presence of CKD leads primarily to accelerated atherosclerosis with manifestations of ischemic heart disease or cardiomyopathy manifested primarily as heart failure. A recent study in kidney transplantation patients has shown that the incidence of de novo heart failure was

^{*}References 4, 111, 119, 131–134, 137–177.

[†]References 132, 135, 139, 140, 144–146, 149, 155, 161, 175, 176.

considerably higher in kidney transplant recipients than in the Framingham cohort, whereas the incidence of ischemic heart disease was not.¹⁸⁵ However, because most studies have not clearly distinguished between the risk of heart failure versus the risk of ischemic heart disease, this issue remains unresolved and needs additional study.

Second, is there a threshold level of GFR below which an increased risk for CVD begins or where the risk for CVD increases in a nonlinear fashion? Many studies have suggested that the relative risk for CVD increases more rapidly below a GFR of $\approx 60 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 ^{133,137,139,148,159}; however, formal statistical analyses have not had sufficient power to prove this point.^{133,137} In theory, a threshold level of GFR of $\approx 60 \text{ mL} \cdot \text{min}^{-1}$ per 1.73 m^2 may make sense, because the prevalence of many nontraditional risk factors, such as anemia and abnormalities of calcium and phosphorus metabolism, increases as GFR decreases below this range.

Summary

There is a high prevalence of CVD in subjects with CKD. The presence of CKD, whether it is manifested by proteinuria (albuminuria) or reduced GFR, appears to be an independent risk factor for CVD outcomes, particularly in higher-risk populations. These findings are consistent with the NKF task force recommendation that patients with CKD should be considered in the highest-risk group for CVD events. The seventh report of the Joint National Committee for the Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) includes CKD as a “compelling” indication, justifying lower target blood pressure and treatment with specific antihypertensive agents.¹⁸⁶ Similarly, the recently published “NKF-K/DOQI Clinical Practice Guidelines on Managing Dyslipidemia in Chronic Kidney Disease” recommend that all patients with CKD be included in the highest-risk group, justifying a lower target low-density lipoprotein cholesterol level.⁵³ By contrast, the third report of the Adult Treatment Panel of the National Cholesterol Education Program (ATP-III) does not include CKD in the list of high-risk conditions necessitating more aggressive management.¹⁸⁷ We suggest that the National Cholesterol Education Program and other groups include CKD in the highest-risk group for recommendations for prevention, detection, and treatment of CVD risk factors. In addition, these findings reinforce the recent recommendation from the NKF on the importance of early identification and treatment of CKD and its associated comorbid conditions. We suggest that the routine evaluation of patients with CVD or those at high risk for CVD include measurement of spot urine albumin-to-creatinine ratio or total protein-to-creatinine ratio and estimation of GFR by serum creatinine and prediction equations. Finally, there is an urgent need for additional randomized controlled studies to evaluate potential treatments of CVD in CKD.

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