

Recognizing the Link Between Chronic Kidney Disease and Cardiovascular Disease

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Abstract

The prevalence of chronic kidney disease (CKD) is rising in the United States, and cardiovascular disease (CVD) is increasingly recognized to occur at elevated rates in patients with CKD compared with the general population. The impact of CVD in patients with CKD is significant, inversely related to the level of kidney function, and exaggerated when compared with matched patients without CKD. CKD is associated with an increased risk of CVD, CVD events, and death, but the prevalence of traditional CVD risk factors is also increased compared with the general population. Proteinuria, hypertension, dyslipidemia, and diabetes are common in patients with CKD and contribute directly to CVD events. CKD-related factors (eg, disorders of electrolyte and mineral metabolism, anemia, and vascular calcification) also contribute to mortality associated with CKD.

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For author information and disclosures, see end of text.

Chronic kidney disease (CKD) is characterized by decreased kidney function, as determined by the glomerular filtration rate (GFR), or kidney damage (with or without proteinuria). CKD is staged according to the level of GFR, with stage 1 representing the highest level of kidney function (GFR >90 ml/min/1.73 m²) and stage 5 representing the lowest level of kidney function (GFR <15 ml/min/1.73 m²). Recent evidence indicates that the prevalence of CKD is increasing in the United States.¹ Coresh and colleagues evaluated the National Health and Nutrition Examination Surveys data and were able to demonstrate that the prevalence of albuminuria and decreased GFR increased from 1988 to 1994 and from 1999 to 2004.¹ Furthermore, the prevalence of CKD (stages 1 to 4) increased from 10% (95% confidence interval [CI], 9.2%-10.9%) in 1988-1994 to 13.1% (95% CI, 12%-14.1%) in 1999-2004. The mean serum creatinine was also higher in the second cohort.¹ Although increased serum creatinine is an indicator of reduced kidney function, it is not a sensitive measure, since GFR (which directly impacts serum creatinine) is dependent on other factors, such as age, sex, body weight/body mass index, and race. Since routine measurement of GFR is impractical (due to complexity, expense, and involved time), clinicians routinely estimate GFR, using equations such as the Modification of Diet in Renal Disease (MDRD) and more recently, the CKD-Epi formula, to stage CKD.² These equations include serum creatinine, age, sex, and race to estimate GFR with very good precision.² It is important to note that many cardiovascular trials have excluded patients with known CKD, usually by establishing a serum creatinine level cutoff. As such, data on CKD have been inferred from these trials, usually by post hoc analysis based on GFR estimates among patients who were included in the trial.

End-stage renal disease (ESRD) is loosely defined by signs and symptoms of kidney failure, a GFR less than 15 mL/min/1.73 m², and the requirement for renal replacement therapy (usually dialysis).³ The leading cause of death in patients with ESRD has long been recognized as cardiovascular disease (CVD), which occurs in more than 50% of patients.⁴⁻⁶ CVD is also the leading cause of hospitalization among patients with ESRD.⁴⁻⁶ Evidence also suggests that other stages of CKD are associated with increased car-

■ **Table 1.** Stages of Chronic Kidney Disease and Cardiovascular Disease Risk⁶

Stage	Description	GFR (mL/min/1.73 m ²)	Cardiovascular Risk (Odds Ratio, Univariate)
1	Kidney damage with normal or increased GFR	≥90	Depends on the degree of proteinuria
2	Kidney damage with mildly decreased GFR	60-89	1.5
3	Moderately decreased GFR	30-59	2 to 4
4	Severely decreased GFR	15-29	4 to 10
5	Kidney failure	<15 or dialysis	10 to 50
End-stage renal disease	Dialysis or transplantation required	Dialysis or transplantation	20 to 1000

GFR indicates glomerular filtration rate.
Adapted from Schiffrin EL, Lipman ML, Mann JFE. *Circulation*. 2007;116:85-97.

diovascular risk, and this article will examine the relationship between CVD and CKD.^{5,6} This supplement will describe the link between CKD and CVD, the treatment of CVD in CKD, and the impact on managed care.

Associations Between CKD and CVD

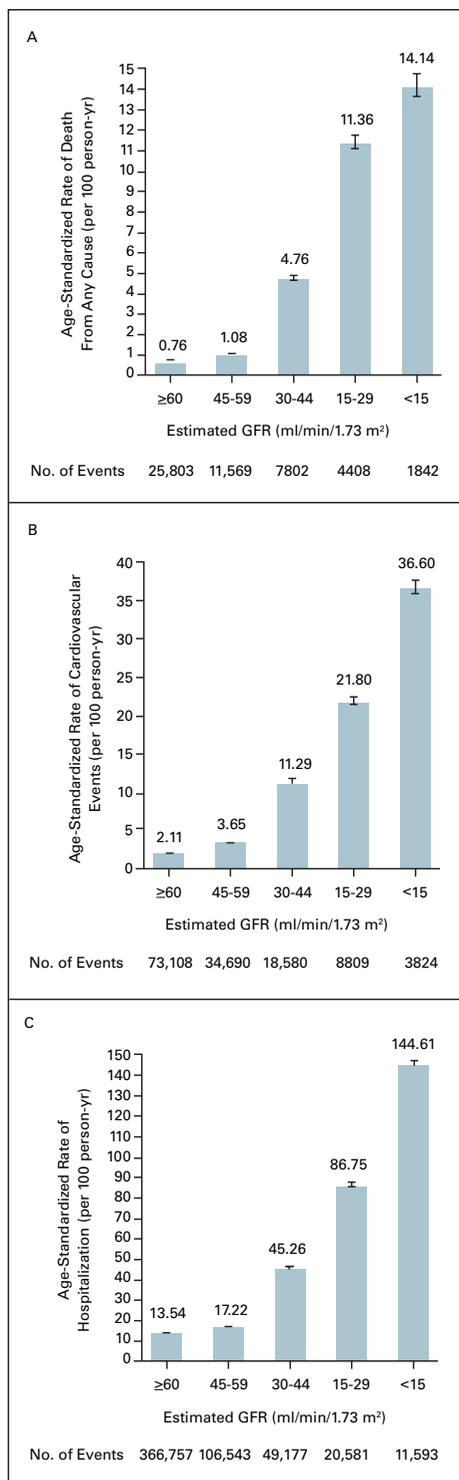
A recent publication correlated the stages of CKD to the approximate odds ratios (ORs) of CVD based on a thorough literature review (Table 1).⁶ As shown in Table 1, compared with a population without CKD, a graded inverse relationship between CKD and CVD was identified, where the lower the degree of kidney function, the higher was the risk of CVD. This relationship was noted to be approximate and affected by patient age.⁶ A review of results from several of these studies is warranted, since the relationship between CVD and CKD is varied across populations, and CVD is a broad term with multiple potential contributing factors.

One landmark study evaluated 1,120,295 subjects (from a database owned by Kaiser Permanente) for age-standardized death, cardiovascular events, and hospitalization per 100 person-years relative to various levels of GFR over approximately 3 years.⁵ Cardiovascular events were defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease; results appear in Figure 1. For all studied events, a clear association between the age-standardized rate of outcome and degree of kidney function was noted. As GFR fell below 60 mL/min/1.73 m², the rate of death, cardiovascular events, and hospitalization increased in graded fashion.⁵ Another study compared pooled data from community-based trials (including the Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study) among patients with a GFR of 15 to 59 mL/min/1.73 m² to those with a GFR of at least 60 mL/min/1.73 m² over 10 years.⁷ The composite outcome (myocardial infarction [MI]/

fatal coronary heart disease [CHD], stroke, or all-cause mortality) occurred in 30.1% of patients in the lower GFR group and in 13.2% of those in the higher GFR group. Moreover, all components of the combined end point were more frequently experienced in the lower GFR group (MI/fatal CHD, 10.1% vs 5.3%; stroke, 7.5% vs 2.8%; all-cause mortality, 23% vs 8.1%). The risk of MI/fatal CHD or all-cause mortality, but not stroke, was higher in African Americans than in Caucasians.⁷

In a secondary analysis of a 15-year follow-up of the Framingham Heart Study, CVD and mortality was evaluated in male patients with baseline serum creatinine value of 1.5 to 3 mg/dL, and in female patients with baseline serum creatinine value of 1.4 to 3 mg/dL (reduced GFR), and compared with patients with lower (“normal”) serum creatinine levels.⁸ The rates of CVD events and mortality were higher in men than women, but the rate of CVD (adjusted for body mass index, systolic blood pressure, hypertension treatment, diabetes, smoking, total cholesterol, prevalent CVD, cardiac medications, and left ventricular hypertrophy on electrocardiogram) did not differ between men and women relative to the “normal” serum creatinine groups. Adjusted all-cause mortality was higher in men with reduced GFRs versus “normal” serum creatinine values, but this effect was not demonstrated in women. Interestingly, the prevalence of hypertension, diabetes, elevated total cholesterol, low high-density lipoprotein (HDL) cholesterol, and body mass index at or above 27.8 were statistically higher in women with reduced GFRs versus those with “normal” serum creatinine values. Only the prevalence of diabetes, low HDL cholesterol, and body mass index at or above 27.3 were statistically higher in men with reduced GFRs versus those with “normal” serum creatinine values. Smoking was less prevalent in women and men with reduced GFRs, as compared with those with “normal” serum creatinine values.⁸ The results

Figure 1. Age-Standardized Death, Cardiovascular Events, and Hospitalization According to GFR⁵



A cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral artery disease. Error bars represent 95% confidence intervals. The rate of events is listed above each bar. GFR indicates glomerular filtration rate. Reprinted with permission from Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. *N Engl J Med.* 2004;351:1296-1305.

of this study suggest a high prevalence of CVD risk factors among patients with CKD, but also point out the potential pitfalls of using serum creatinine values as a marker for kidney function.⁸

Disease Factors Contributing to CVD in CKD

Microalbuminuria/Proteinuria

Urinary albumin excretion, an indicator of kidney damage and a risk factor for progression of kidney disease, is known to be associated with an increased risk of CVD events in the general population,⁹ and in patients with hypertension,^{10,11} diabetes,¹¹⁻¹³ and established atherosclerotic disease.¹⁴ A prospective, population-based cohort study of 16,958 patients conducted in Iceland compared patients with estimated GFRs of at least 90, 75 to 89, and 60 to 74 mL/min/1.73 m² without proteinuria (no CKD) to patients with proteinuria and GFRs of at least 90 (stage 1 CKD) and 60 to 89 (stage 2 CKD), and patients with CKD and GFRs of 45 to 59 (stage 3a), 30 to 44 (stage 3b), or 15 to 29 mL/min/1.73 m² (stage 4).¹⁵ The primary end point of CHD or nonvascular mortality was adjusted for age, sex, smoking status, diabetes, total cholesterol, triglycerides, systolic blood pressure, and body mass index. The risk/hazard ratios were compared with the reference group (GFR 75-89 mL/min/1.73 m² without proteinuria). Although the highest risk of CHD was present in patients with stage 3b and 4 CKD, there was a significant 1.55-fold increase in the risk of CHD in those with a GFR of at least 90 mL/min/1.73 m² with proteinuria (stage 1 CKD), and a significant 1.72-fold increase in risk of CHD in those with a GFR of 60 to 89 mL/min/1.73 m² with proteinuria (stage 2 CKD), relative to the reference group without proteinuria. Nonvascular mortality increased significantly only in those with stage 3b or 4 CKD.¹⁵ An evaluation of the Third Copenhagen City Heart Study linked CHD or death at 7 to 9 years follow-up to a baseline overnight urinary albumin excretion rate. Urinary albumin excretion of greater than 4.8 µg/min during the overnight sample (or about 6.4 µg/min during daytime) was a strong predictor of CHD or death independent of renal function, hypertension, or diabetes.¹⁶ Taken together, these results further highlight the important role of CVD in patients with CKD, and the direct impact of albuminuria/proteinuria. Proteinuria is usually assessed in practice by urine albumin to creatinine ratio or urine protein to creatinine ratio.^{17,18}

Hypertension

The Joint National Committee 7 report on blood pressure regards microalbuminuria or an estimated GFR less than 60 mL/min/1.73 m² as risk factors for CVD, and CKD as a target-

■ **Table 2.** Summary of the Incidence of Selected CVD Event Risk Factors at Baseline in Selected Community Studies^{5,7,8}

Risk Factor	Incidence (%)
Hypertension	15.4-62.1
Diabetes mellitus	3.8-31.1
Dyslipidemia	0.6-41.9
Tobacco smoking	12.4-36.2
Heart failure	1-20.8
Coronary artery disease	4.5-24.5

CVD indicates cardiovascular disease.

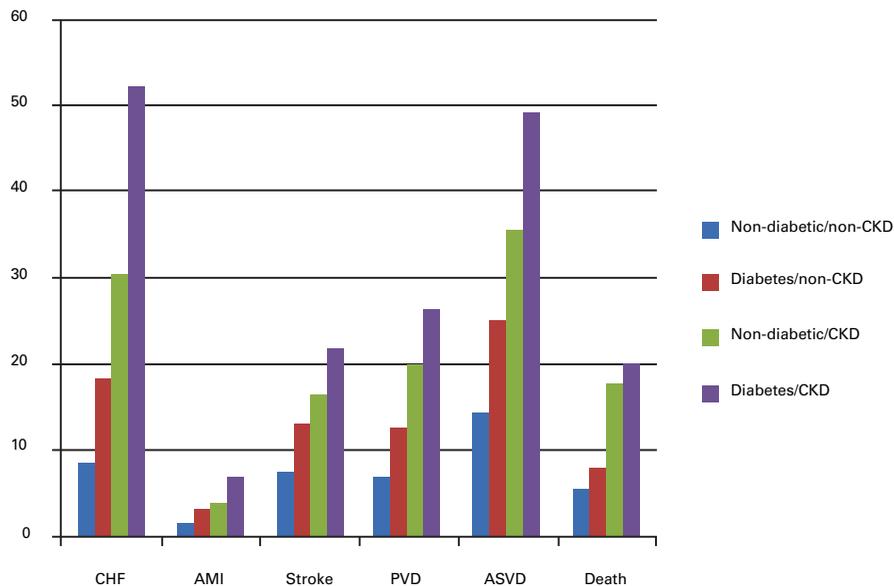
organ consequence of hypertension.¹⁹ Fluid retention and other factors may contribute to hypertension in CKD, and hypertension contributes to development of left ventricular hypertrophy, MI, angina, heart failure, stroke, and peripheral arterial disease.¹⁹ Assessment of the baseline incidence of risk factors for CVD, such as hypertension, in community-based studies is an important way to determine their frequencies in the population (**Table 2**).^{5,7,8} According to 2008 data from the US Renal Data System (USRDS), hypertension was present in 91.4% of patients with advanced CKD, and was more common in African Americans (96%) than in Caucasians (90.7%).⁴ Elevated serum creatinine levels in patients with hypertension have long been recognized as a significant risk factor for death.²⁰ A post hoc analysis of the Heart Outcomes and Prevention Evaluation (HOPE) trial also evaluated cardiovascular outcomes according to baseline serum creatinine value and presence or absence of hypertension.²¹ In the placebo group, the primary outcome (cardiovascular death, MI, or stroke) was affected by serum creatinine concentration at study entry. Compared with hypertensive individuals having a serum creatinine value less than 1.4 mg/dL, hypertensive patients with a serum creatinine value of at least 1.4 mg/dL had higher primary cardiovascular end point rates (approximately 45 events per 1000 person-years vs 65 events per 1000 person-years). The respective rates in normotensive subjects were approximately 35 events and 60 events per 1000 person-years. Interestingly, the rates of CVD events were similar in the higher serum creatinine level group regardless of the presence of hypertension at baseline.²¹ A post hoc analysis of the Hypertension Optimal Treatment study evaluated cardiovascular events in hypertensive patients according to baseline serum creatinine value and GFR.²² Major cardiovascular events (defined as nonfatal MI, nonfatal stroke, and all cardiovascular deaths) were evaluated according to serum creatinine value (≤ 1.5 mg/dL or >1.5 mg/dL) and creatinine clearance (>60 mL/min or ≤ 60 mL/min). Major cardiovascu-

lar events, cardiovascular mortality, and total mortality were predicted by serum creatinine values greater than 1.5 mg/dL (vs ≤ 1.5 mg/dL). However, major cardiovascular events, cardiovascular mortality, total mortality, and stroke were seen with lower GFRs. These results highlight the differences in outcomes when assessing kidney function through GFR estimation versus serum creatinine level.²²

Diabetes

According to USRDS 2008 data, diabetes mellitus is prevalent in patients with CKD, occurring in 48.2% of patients with stage 1 or 2 disease and in 49.4% of those with stage 3 to 5 disease.⁴ A post hoc analysis of the previously mentioned HOPE trial also evaluated cardiovascular outcomes according to baseline serum creatinine level and presence or absence of diabetes.²¹ In the placebo group, the primary outcome (cardiovascular death, MI, or stroke) was affected by serum creatinine concentration at study entry. Compared with diabetic individuals having a serum creatinine less than 1.4 mg/dL, those with a serum creatinine of at least 1.4 mg/dL had higher primary end point rates (approximately 45 events per 1000 person-years vs 85 events per 1000 person-years, respectively). The respective rates in nondiabetic subjects were approximately 35 events and 50 events per 1000 person-years.²¹ When compared with the outcomes based on the presence or absence of hypertension noted in the section above, patients with diabetes and a higher serum creatinine level tended to have worse outcomes than those with hypertension and a higher serum creatinine level. However, among patients with lower serum creatinine values, those without diabetes and hypertension appeared to have similar risk.²¹ A study involving a 5% sample (N = 1,091,201) of the US Medicare population evaluated the impact of diabetes in CKD on CVD and death, by comparing patients with and without CKD and diabetes over 2 years.²³ The CVD outcomes included congestive heart failure, acute MI (AMI), cerebrovascular accident/transient ischemic attack (stroke), peripheral vascular disease (PVD), death, and atherosclerotic vascular disease, which was a combined end point of AMI, stroke, and PVD. As shown in **Figure 2**, patients without CKD and diabetes had the lowest incidence per 100 patient-years for all events. Diabetics without CKD had numerically higher rates of the events, but rates were less than those found in nondiabetics with CKD. The highest rates of all events were observed in patients with CKD and diabetes.²³ In fact, these patients were 5 times as likely to die from CVD as they were to reach ESRD. These findings demonstrate the important interaction between diabetes and CKD in regard to increased rates of CVD. The third report of the National Cholesterol Education Program (NCEP) consid-

Figure 2. Incident CVD Events per 100 Patient-Years From a US Medicare Population²³



AMI indicates acute myocardial infarction; ASVD, atherosclerotic vascular disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular disease; PVD, peripheral vascular disease.

ers diabetes a CHD equivalent, so it is interesting that CKD had a higher impact than diabetes on CVD in the Medicare population study.^{23,24}

Dyslipidemia

Dyslipidemia is a common comorbidity observed in both diabetes and CKD. The National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative guideline for management of dyslipidemia in diabetes and CKD identifies these patients as being at high risk for CVD.²⁵ The NKF and NCEP recommend aggressive treatment and maintaining a goal low-density lipoprotein (LDL) cholesterol level of 100 mg/dL or less.^{24,25} The effect of various stages of CKD on the lipid profile was recently reviewed, so it will not be discussed in detail.²⁶ In brief, HDL cholesterol level tends to decrease with declining renal function, while LDL cholesterol level tends to remain neutral or increase in CKD stages 1 through 4, and remain neutral or decrease in stage 5 disease. A tendency toward increased triglyceride levels has also been noted in CKD.²⁶ Data from the placebo group of the Justification for the Use of statins in Prevention, an Intervention Trial Evaluating Rosuvastatin (JUPITER), was used to compare cardiovascular events in patients with an estimated GFR at least 60 mL/min/1.73 m² to those with a GFR less than 60 mL/min/1.73 m².²⁷ Although JUPITER was not specifically a dyslipidemia trial, the baseline LDL cholesterol level was approximately 109 mg/dL, and above the goal (100 mg/dL) set by guidelines. JUPITER’s primary end point (nonfatal MI, non-

fatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed cardiovascular death) occurred more commonly in the lower GFR group (hazard ratio [HR] 1.54, 95% CI 1.23-1.92, P = .0002). After adjusting for baseline differences in age, sex, smoking, and drugs, patients with reduced renal function remained at risk (HR 1.54, 95% CI 1.22-1.96, P = .0004). Patients with lower GFRs were also at increased risk of MI, stroke, and cardiovascular death (HR 1.44, 95% CI 1.08-1.92, P = .02) or arterial revascularization (HR 1.53, 95% CI 1.13-2.08, P = .008).²⁷ These results highlight the significant impact of dyslipidemia on CVD in the presence of CKD.

Smoking

Tobacco smoking in patients with CKD without established CVD is associated with a 59% increase in heart failure and 68% increase in PVD compared with nonsmokers over 2.2 years.²⁸ Compared with other CVD risk factors in patients with CKD, the effects of smoking are less well studied. The effect of smoking on cardiovascular mortality appears to be equivocal, but patients who smoke actively have a 43% higher risk of all-cause death compared with lifelong nonsmokers. Former smokers have a 26% higher risk of death; however, when this analysis was adjusted for baseline comorbidities, the effect was no longer observed. Despite the relative lack of data regarding its effects on CVD in CKD, smoking remains one of the most modifiable risk factors in patients with CKD.²⁸

Kidney Disease–Related Complications

A number of kidney-related factors increase cardiovascular burden as kidney function declines. The kidney is known to secrete erythropoietin, which stimulates the bone marrow to produce red blood cells. In one systematic review of patients with CKD or ESRD, low hemoglobin (due to no use of erythropoiesis-stimulating agents [ESAs]) versus a hemoglobin target of 11 to 12 g/dL (with ESA use) resulted in a

1.14-fold increase in the OR of death. Interestingly, a hemoglobin target of greater than 12 g/dL in patients with CKD or ESRD versus a target of 9 to 10.9 g/dL was associated with a 1.12-fold increase in the OR of death. These results highlight the need to carefully manage hemoglobin levels with ESAs within a recommended range of 9 to 11 mg/dL.²⁹

Evidence suggests that coronary artery calcification occurs very early in ESRD.³⁰ Vascular calcification is thought to occur due to kidney disease–related disorders in calcium and phosphate metabolism, which increases the risk of CVD-related mortality.³⁰ Deficiency of vitamin D, associated with declining kidney function, also contributes to calcium and phosphate abnormalities, independently increasing the risk of mortality.³¹ The mortality risk associated with vitamin D deficiency may be partly related to vitamin D therapy and its resultant effects on left ventricular hypertrophy.³² The incident structural heart disease associated with CKD and the electrolyte abnormalities encountered as GFR falls may further lead to arrhythmias, contributing to CVD morbidity and mortality.³³

Established Cardiovascular Disease

The incidence and impact of ventricular hypertrophy, which occurs frequently in up to 70% to 80% of dialysis patients, was recently reviewed in detail.^{32,34} The concept of cardiorenal syndrome reflects a bidirectional effect of the kidney on heart function and vice versa.³⁵ Cardiorenal syndrome is particularly reflective of ventricular hypertrophy and heart failure, and the related effects on or by renal function.³⁵ Table 2 demonstrates that heart failure was present in 1% to 20.8% of patients at enrollment in community-based studies, suggesting that this cardiovascular complication is common in CKD.^{5,7,8} In a recent review of pooled data from studies examining mortality in patients with heart failure and moderate or severe CKD, the hazard ratio was 1.3 to 2.9 compared with a non-CKD population.³⁶ CVD, in the absence of heart failure, is also a commonly encountered complication in CKD. Coronary artery disease was also common in community studies.^{5,7,8} Cardiac troponin (cTn) levels are often used to establish the presence of acute coronary syndrome (ACS); however, cTn may be chronically elevated in the absence of ACS in patients with CKD, conferring an increase in CVD event risk. Baseline elevation of cTn may complicate assessment of ACS, but it is nevertheless important to determine whether ACS has occurred and to treat it appropriately.³⁷ Based on assessment of patients with mild (GFR >60 mL/min/1.73 m²), moderate (GFR 30-60 mL/min/1.73 m²), or severe (GFR <30 mL/min/1.73 m²) renal impairment, the Global Registry of Acute Coronary Events determined that as estimated GFR declined, the rate

of mortality and bleeding complications associated with ACS increased in a graded manner. There was no clear association with in-hospital MI or stroke.³⁸ Using different definitions of renal function, Anavekar and colleagues demonstrated an increased risk of CVD events and death after MI, even at a GFR of 60 to 74 mL/min/1.73 m² (relative to a GFR >75 mL/min/1.73 m²).³⁹ Taken together, these results highlight the importance of even mild reductions in GFR among patients with established CVD.

Conclusion

CKD is an increasing public health concern in the United States. In patients with CKD, CVD is highly prevalent and is a leading cause of death. The risk of CVD events and mortality among patients with CKD appears to exceed that of matched controls, suggesting a direct effect of CKD on CVD. It is also evident that traditional cardiac risk factors, complications attributable to kidney disease, and established CVD contribute to the adverse CVD outcomes experienced by patients with CKD. Because many patients with elevated serum creatinine levels were excluded from major cardiac trials, risk is inferred from results of community-based studies or data from placebo groups in interventional trials, and treatment benefits are often inferred from post hoc analyses. The difficulties in managing this population are also highlighted by the challenges in providing treatment, which may be complicated by difficulties in dosing medications or enhanced risk of complications (eg, bleeding).

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