

# Chronic Kidney Disease: A Risk Factor for Cardiovascular Disease

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Chronic kidney disease (CKD) is a poorly recognized but important risk factor for cardiovascular disease (CVD). Evidence has demonstrated that persons with CKD are more likely to die of events related to CVD than from consequences of progression in renal failure per se [1,2] and CVD is the main cause of death in patients with CKD. Almost half of all deaths in patients with CKD are caused by cardiovascular events, particularly congestive cardiac failure, acute myocardial infarction (AMI) and sudden cardiac death.

During the past 10 years, the burden of CVD-related morbidity and mortality in the general population has improved remarkably, thanks to well-designed randomized, controlled trials that have unequivocally shown that treatment of targeted risk factors decreases cardiovascular and all-cause mortality. CVD-related morbidity and mortality in patients with CKD has remained almost unchanged, however, perhaps because of poor recognition of the impact of CKD on the biology of CVD and, to some extent, the lack of well-designed prospective studies to define the role of treatment of targeted risk factors in patients with CKD.

A recent analysis of a managed care database showed that, in persons with advanced CKD, death before the initiation of renal replacement therapy is twice as likely to occur than initiation

of dialysis therapy [3]. In 1998, the National Kidney Foundation established a task force on CKD and CVD, which recommended that patients with CKD be considered in the highest risk group for the onset and progression of subsequent events related to CVD. The task force recommends that patients with CKD should be evaluated thoroughly for the risk factors for CVD and that treatment recommendations for CVD risk stratification should consider the highest-risk status of patients with CKD [1].

## Stages of chronic kidney disease

The National Kidney Foundation published clinical practice guidelines (K/DOIQ) on evaluation, classification, and risk stratification of CKD [4]. These guidelines, define CKD in five different stages as (Table 1)

1. Kidney damage for more than 3 months determined either by kidney biopsy or the presence of markers of kidney damage, with or without a decrease in estimated glomerular filtration rate (eGFR). The markers of kidney damage include proteinuria (albumin/creatinine ratio or total protein/creatinine ratio, in an untimed spot urine sample), abnormal urinary sediment, abnormalities on kidney imaging studies, or a combination of these markers.
2. eGFR of more than 60 but less than 89 mL/min/1.73m<sup>2</sup> is considered mild CKD.
3. eGFR of more than 30 but less than 59/mL/min/1.73m<sup>2</sup> for 3 months or longer with or without markers of kidney damage is considered moderate CKD.

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Table 1  
Stages of chronic kidney disease and prevalence in the general population

Stage	Description	GFR mL/min/1.73m <sup>2</sup>	Prevalence	
			N (1000)	%
1 <sup>a,b</sup>	Kidney damage with normal or increased GFR	≥90	5900	3.3
2 <sup>a,b</sup>	Kidney damage with mildly decreased GFR	60–89	5300	3.0
3 <sup>a</sup>	Moderately decreased GFR	30–59	7600	4.3
4 <sup>a</sup>	Severely decreased GFR	15–29	400	0.2
5 <sup>c</sup>	Kidney failure	<15 or dialysis	300	0.1

Abbreviation: GFR, glomerular filtration rate.

<sup>a</sup> Data for stages 1–4 from National Health and Nutrition Examination Survey III (1988–1994). Population of 177 million aged 20 years or more.

<sup>b</sup> For stages 1 and 2, kidney damage was assessed by spot albumin/creatinine ratio greater than 17 mg/g (men) or 15 mg/g (women) on two measurements.

<sup>c</sup> Data for stage 5 include approximately 230,000 patients treated by dialysis and assumes 70,000 additional patients not receiving dialysis. Percentages total more than 100% because the National Health and Nutrition Examination Survey III may not have included patients receiving dialysis. GFR estimated from serum creatinine using MDRD study equation based on age, gender, race, and calibration for serum creatinine (*Data from US Renal Data System.USRDS 1998 annual data report. Bethesda, National Institutes of Health National Institute of Diabetes; 1998.*)

From National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1–266; with permission from the National Kidney Foundation.

4. eGFR of more than 15 but less than 29 mL/min/1.73m<sup>2</sup> for 3 months or longer with or without markers of kidney damage is considered severe CKD.
5. eGFR of less than 15 mL/min/1.73m<sup>2</sup> is considered indication for renal replacement therapy (dialysis or renal transplantation).

This categorization is arbitrary and to some extent is based on the results of small observational studies that have demonstrated inevitable progression in the decline of eGFR in persons with eGFRs of less than 60 mL/min/1.73m<sup>2</sup>. The GFR estimation is based on the Modification for Diet and Renal Disease (MDRD) formula, taking into consideration serum creatinine level, age, race, and body size to avoid inadvertent mistakes in quantifying GFR based on the serum creatinine level alone [5–7]. The National Kidney Foundation GFR calculator (MDRD equation) is

available at <http://www.kidney.org/professional/doqi/index.cfm> (Table 2).

The stages of CKD are based on the severity of impairment in the levels of GFR. As of 2000, 20 million adults in the United States adult population (10.8% of the population) had various stages of CKD. Although there are several different etiologic factors for the development of CKD, these can be broadly classified as diabetic and nondiabetic in nature, because these two categories have different rates of progression of CVD and different associated comorbidities [7,8].

**Early stages of chronic kidney disease and its impact on cardiovascular biology**

Onset of CKD is associated with an increased predilection for the development of CVD-related events [9,10]. Persons with CKD are predisposed

Table 2  
Equations to predict glomerular filtration rate based on serum creatinine

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

Abbreviations: C<sub>Cr</sub>, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; S<sub>Cr</sub>, serum creatinine in mg/dL.

<sup>a</sup> Age is given in years and weight in kilograms.

From Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of CVD. *Hypertension* 2003;42:1050–65; with permission.

to three types of CVD—atherosclerosis, arteriosclerosis, and cardiomyopathy—when compared with age- and gender-matched persons with normal kidney function.

Atherosclerotic disease in CKD patients is somewhat different from that in the general population with atherosclerosis. In both groups, atherosclerosis is an intimal disease characterized by the presence of atheromatous plaques. In patients with CKD and in dialysis-dependent patients, however, this atherosclerotic burden is further complicated by an increased frequency of calcific lesions, an increase in medial thickness and calcification involving medium- to large-sized blood vessels.

In addition, CKD patients have an increased prevalence of arteriosclerosis and remodeling of large arteries [11]. Remodeling of large arteries is caused by a combination of factors such as pressure overload leading to wall hypertrophy and an increased wall/lumen ratio resulting from flow overload. There is also a proportional increase in arterial diameter and wall thickness with a reduction in arterial compliance as determined by aortic pulse wave velocity and impedance measurements.

These vascular processes work in concert to result in a significant loss of vessel wall compliance, decreased aortic compliance, and increased pulse pressure, and these factors are independent risk factors for CVD [12]. The loss of compliance is often associated with an increase in systolic blood pressure and pulse pressure, resulting in accelerated left ventricular hypertrophy (LVH), decreased coronary artery functional reserve, and coronary perfusion and hence could jeopardize myocardial microcirculatory reserves.

### Chronic kidney disease is a risk factor for cardiovascular disease

The burden of CVD in early CKD before the need for renal replacement therapy has been demonstrated by prospective and retrospective population-based epidemiologic studies. Although small studies have refuted an association between CKD and CVD, several different studies indicate that onset of CKD is associated with an increased risk for events caused by CVD. Even if the association is now strongly established, the biologic reasons for this association remain poorly understood.

#### The Hoorn study

The Hoorn study was a population-based cohort study of glucose tolerance and other cardiovascular risk factors in a white population

aged 50 to 75 years. Baseline measurements were obtained from 1989 to 1992 and were followed until January 1, 2000 (N = 631). The eGFR by the MDRD formula ranged from 16.8 to 116.9 mL/min/1.73m<sup>2</sup>. During the follow-up of 10.2 years, 117 subjects died, 50 (43%) from cardiovascular causes. Renal function was inversely associated with all-cause and cardiovascular mortality across a range of serum creatinine levels. Within this range of eGFR, a decrease in eGFR by 5 mL/min/1.73m<sup>2</sup> was associated with a 26% increase in risk of cardiovascular death. These associations persisted even after adjustments for baseline hypertension, diabetes mellitus, age, sex, and other traditional risk factors for cardiovascular disease [13]. Based on eGFR tertiles, the lowest survival rate was noted in the cohort with worst renal function, although it is not clear from the study description whether survival was confounded by the initiation of renal replacement therapy (Fig. 1).

#### The Cardiovascular Health Study

The Cardiovascular Health Study was a prospective, population-based study of persons older than 65 years with a median follow-up of 7.3 years. Renal insufficiency was defined as serum

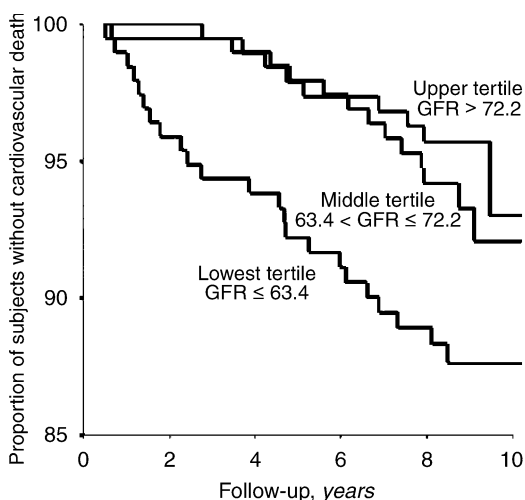


Fig. 1. Cardiovascular survival (Kaplan-Meier) according to tertiles of glomerular filtration rate (GFR), estimated by the Modification of Diet in Renal Disease equation and expressed in mL/min/1.73m<sup>2</sup>. (From Henry RMA, Kostense PJ, Bos G, et al. Mild renal insufficiency is associated with increased cardiovascular mortality: the Hoorn Study. *Kidney Int* 2002;62:1406; with permission.)

creatinine level of 1.5 mg/dL or higher in men and 1.3 mg/dL or higher in women. In patients with renal insufficiency, the rates of all-cause mortality and CVD mortality were almost twice those in persons with lower creatinine levels. In addition, there was a linear increase in the risk of CVD, peripheral vascular disease, and congestive heart failure with an increasing serum creatinine level [14]. In the same cohort of patients, Shlipak et al [15] reported that the prevalence of clinical and subclinical cardiovascular disease was 64% in patients with renal insufficiency, as compared with 43% in those with normal renal function.

#### *Subgroup analyses of Heart Outcome and Prevention Evaluation (HOPE Study)*

Mann et al [16] studied the subset of subjects with renal insufficiency (serum creatinine  $\geq$  1.4 mg/dL; N = 980) from the enrollees of Heart Outcome and Prevention Evaluation and compared the outcome with 8307 persons with serum creatinine levels below 1.4 mg/dL. Cumulative incidence of each primary outcome measure (cardiovascular death, myocardial infarction, or stroke) was higher in patients with renal insufficiency than in persons with normal creatinine levels (22.2% versus 15.1%;  $P < 0.001$ ; 11.4% versus 6.6%;  $P < 0.001$ ; and 17.8% versus 10.6%,  $P < 0.001$ , respectively). The use of an angiotensin-converting enzyme (ACE) inhibitor (ramipril) was associated with similar reductions in the incidence of these primary outcomes in patients with and without renal insufficiency.

#### *British population-based study*

The relationships between serum creatinine concentration and the risk of major events related to ischemic heart disease and stroke and all-cause mortality were examined in a prospective study in a general population of middle-aged men (aged 40 to 59 years) drawn from 24 British towns who have been followed for an average of 14.75 years (N = 7690). There were 287 major stroke events, 967 major ischemic heart disease events, and 1259 deaths from all causes during the follow-up. Stroke risk was significantly increased at serum creatinine levels above 116  $\mu\text{mol/L}$  (1.3 mg/dL, 90th percentile) even after adjustment for a wide range of cardiovascular risk factors (relative risk [RR], 1.6). Risk of a major ischemic heart disease event was significantly increased at serum creatinine levels at or above 130  $\mu\text{mol/L}$  (1.5 mg/dL, 97.5 percentile), but this risk was attenuated after

adjustments for age and diabetes mellitus (RR, 1.2). An increased creatinine concentration ( $\geq$ 116  $\mu\text{mol/L}$ , 1.3 mg/dL) was associated with a significant increase in stroke in both normotensive and hypertensive men. Both all-cause mortality and overall cardiovascular mortality were significantly increased in those with serum creatinine levels above 1.5 mg/dL (97.5 percentile), and no significant association was seen with cancer or other noncardiovascular mortality. It was concluded that even a borderline increase in the serum creatinine concentration is a marker for increased risk of cerebrovascular disease in both normotensive and hypertensive persons [17].

#### *Framingham Offspring community study*

The Framingham Offspring community-based study followed a cohort of 6233 subjects for 15 years. CVD was almost twice as prevalent in persons with mild-to-moderate CKD (based on serum creatinine levels) as in those without underlying renal disease [18].

#### *Second National Health and Nutrition Examination Survey mortality study*

The association between renal insufficiency and increased CVD-related and all-cause mortality rates during 16 years of follow-up was examined among participants in the second National Health and Nutrition Examination Survey Mortality Study (NHANES II). Study subjects were 30 to 74 years of age at the baseline examinations from 1976 to 1980, with proteinuria (n = 8786) or serum creatinine levels of 3.0 mg/dL or lower (n = 6354); GFR was estimated by using the MDRD formula. CVD-related mortality rates were 6.2, 17.9, and 37.2 deaths/1000 person-years among subjects with urinary protein levels of less than 30, 30 to 299, and 300 mg/dL or higher, respectively. There were 4.1, 8.6, and 20.5 deaths/1000 person-year among participants with eGFRs of 90 or higher, 70 to 89, and 70 mL/min or lower, respectively. After adjustment for potential confounders, in this representative sample of the United States general population, renal insufficiency was independently associated with increased CVD-related and all-cause mortality [19].

#### *Managed care group database analysis*

A recent retrospective study from 1996 to June 30, 2001, of a managed care database with 27,998 enrollees with eGFR of less than 90 mL/min/1.73m<sup>2</sup> until renal replacement therapy, death,

disenrollment from the health plan, or the last date of follow-up. Only 3.1% of persons with stage 2 to stage 4 CKD progressed and required dialysis; whereas 24.9% of this cohort died before the need for dialysis therapy. Another important finding was that patients with CKD had a significantly increased frequency of comorbidities during the follow-up period as compared with those without CKD. During the follow-up period, persons with CKD were at greater risk of developing other comorbid conditions than those with an eGFR of 90 mL/min/1.73m<sup>2</sup> or higher. Comorbidities included coronary artery disease (11.5% versus 7.4%), congestive heart failure (10.4% versus 5.2%), and anemia (24.5% versus 0.1%). These results indicate that CKD is a strong risk factor for the development of different spectrums of cardiovascular disease and anemia (Table 3) [3].

#### *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial*

Rahman et al [20] analyzed the data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which enrolled 42,418 high-risk hypertensive participants aged 55 years and older with more than one risk factor for CVD at the time of enrollment. A total of 40,514 subjects had a baseline serum creatinine measured at the time of randomization in the study. Based on the MDRD equation and the practice guidelines promulgated by the Dialysis Outcome Quality Initiative (K/DOQI), 15.1% had normal or increased eGFR ( $\geq 90$  mL/min/1.73m<sup>2</sup>), 56.7% had a mild reduction in eGFR (60–89 mL/min/1.73m<sup>2</sup>), 17.2% had a moderate decrease in eGFR (30–59 mL/min/1.73m<sup>2</sup>),

and 0.6% had severe of CKD ( $\leq 29$  mL/min/1.73m<sup>2</sup>). A history of previous AMI and stroke was present in 19.2%, 23.4%, 28.7%, and 26.9% of persons with stage 2, 3, 4, and 5 CKD, respectively. A history of coronary bypass surgery or angioplasty or other revascularization procedure was noted in 9.2%, 13.6%, 17.2%, and 14.4% of patients with stage 2 to 5 CKD, respectively. A history of CHD was present in 21.2%, 26.4%, 31.3%, and 28.7% of patients with stage 2 to 5 CKD strata, respectively. At the time of enrollment, EKG criteria for LVH were noted in 3.9%, 4.2%, 6.0%, and 11.2% of patients with stages 2 to 5 CKD, respectively (Fig. 2).

Although patients with a serum creatinine level of 2.0 mg or higher were excluded from enrollment in the ALLHAT study, the prevalence of moderate CKD (following the definition of K/DOQI practice guidelines: eGFR < 60 mL/min/1.73m<sup>2</sup>) was present in 18% of the cohort at the time of randomization, as compared with 4.6% in NHANES III cohort of the general adult population. This inconsistency is explained mostly by the overall greater age and the presence of more than one risk factor for CVD in the ALLHAT participants at the time of enrollment in the study.

#### **Conclusions from the prospective and retrospective studies of chronic kidney disease**

These observational data suggest a strong association between even a modest decrease in eGFR and an increased prevalence of clinical and subclinical CVD and different degrees of LVH. The association between renal function and CVD may reflect an unmeasured risk factor associated with impaired renal function. These putative factors

Table 3

Changes in the prevalence of comorbidities in patients with chronic kidney disease and controls matched for age and sex\*

Comorbidity	Patients with chronic kidney disease (n = 27998)		Control patients (n = 27998)	
	Baseline	Change	Baseline	Change
None	44.4	−24.1	73.7	−26.6
Coronary artery disease	13.1	11.5	6.2	7.4
Congestive heart failure	6.0	10.4	1.8	5.2
Hypertipidemia	13.6	14.1	7.4	10.5
Hypertension	37.4	21.2	16.8	19.3
Diabetes	15.8	9.2	5.3	5.7
Anemia	8.6	24.5	2.1	0.1

\* Values are given as percentage.

Modified from Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with CKD in a large managed care organization. Arch Intern Med 2004;164(6):659–63; with permission.

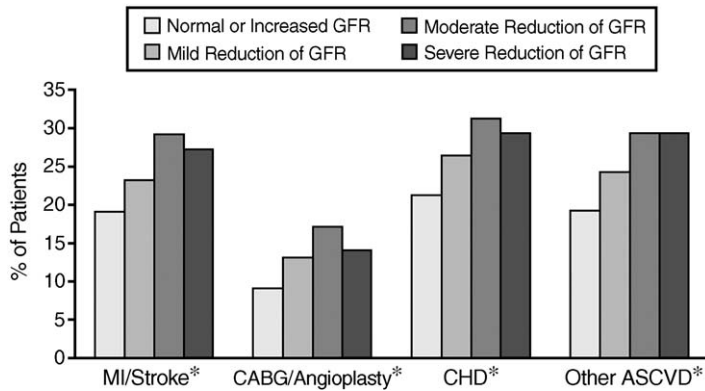


Fig. 2. History of cardiovascular disease at baseline in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Participants stratified by glomerular filtration rate (GFR). ASCVD, arteriosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CHD, coronary artery disease; MI, myocardial infarction. (From Rahman M, Brown CD, Coresh J, et al. The prevalence of reduced glomerular filtration rate in older hypertensive patients and its association with cardiovascular disease: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Arch Intern Med* 2004;164:972; with permission.)

may cause CVD or be an outcome of an underlying pathologic process that affects both GFR and the risk factors for CVD [1]. Whether an association between moderate renal insufficiency and CVD demonstrated in these retrospective and observational studies is caused by the co-occurrence of renal insufficiency with traditional cardiovascular risk factors or whether renal insufficiency per se is an independent risk factor for CVD events and cardiovascular mortality remains an interesting question.

Lack of association between CVD and CKD: Culleton et al [18] reported results from 6233 adult participants of the Framingham Heart Study with mild CKD based on serum creatinine levels of 1.5 to 3.0 mg/dL in men and 1.4 to 3.0 mg/dL in women. At baseline, 8.7% of men ( $n = 246$ ) and 8.0% women ( $n = 270$ ) had chronic renal impairment. During 15 years of follow-up, there were 1000 CVD events and 1406 deaths. After adjusting for covariates other than coexisting CVD (eg, diabetes, hypertension), mild renal impairment was not associated with either an increased risk of CVD events or all-cause mortality in either men or women. Garg et al [21] studied the cohort of participants in NHANES I (1974–1975) and NHANES I Epidemiologic Follow-up Study (18-year follow-up, 1992). The primary analysis was limited to 2352 adults with complete data, without baseline CVD and an approximate GFR of 30 to 60 mL/min/1.73m<sup>2</sup> (defined as moderate renal insufficiency). Supplementary analyses included participants with marked renal impairment and

baseline CVD. Moderate renal insufficiency was not identified as an independent risk factor for CVD after adjusting for traditional cardiovascular risk factors.

These variable results from different retrospective studies could be caused by multiple factors, particularly because Culleton et al [18] and Garg et al [21] used narrower definitions of renal impairment and used serum creatinine alone as the measurement of renal function. In addition, CVD-event data were captured after the actual event and could have been a major confounder in the final analysis. Most of the prospective cohort studies, on the other hand, consistently demonstrated an inverse association between the degree of renal function and cardiovascular morbidity and mortality.

The pathologic basis for the increased risk of CVD in patients with CKD can result from several factors, these can be summarized as follows [22]:

1. Associated comorbidities such as hypertension and diabetes mellitus that are almost always present in patients with CKD.
2. An abnormal milieu that could result in accelerated atherosclerotic burden presence of traditional and nontraditional risk factors and the presence of microinflammatory state in patients with CKD.
3. Poor use of primary preventive measures in patients with CKD because of the lack of prior randomized studies (Multicenter studies

usually have excluded patients with a serum creatinine level of 2 mg/dL or higher from the randomized studies.)

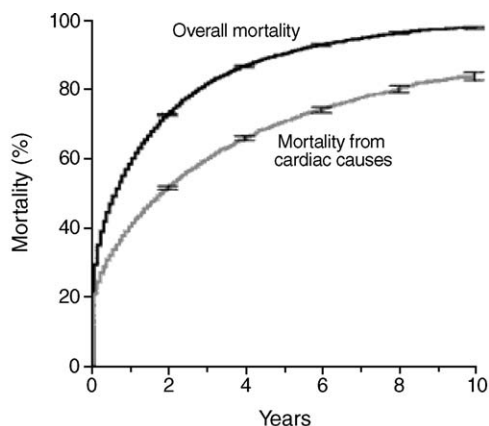
4. Unexpected or underreported toxic effects following therapeutic and diagnostic studies in patients with CKD.
5. The concept of reverse epidemiology, a paradoxical association of the triad of increased blood pressure, cholesterol, and body mass index with improved survival in dialysis patients, in contrast to the poor outcomes in the presence of any of these three factors in the general population.

### Cardiovascular disease in patients with end-stage renal disease and renal replacement therapy

Despite advances in the understanding of the dynamics of dialysis therapy, including use of the biocompatible membranes and nonacetate dialysate, and of the physiologic principles governing the adequacy of dialysis, CVD remains the most important cause of death in patients receiving maintenance dialysis therapy. CVD accounts for almost 44% of overall mortality in long-term dialysis patients [23].

Acute coronary syndrome leading to AMI in patients receiving dialysis has a malignant course. An analysis of the United States Renal Data System (USRDS) revealed that almost 60% of all patients receiving dialysis between 1990 and 1995 had an AMI. The in-hospital mortality for this group was 26%. These data also revealed an early risk of acute coronary syndrome soon after initiation of dialysis, with 29% of AMIs occurring during the first year and 52% of AMIs developing within first 2 years after initiation of dialysis therapy. During the period from 1977 to 1995, 34,189 patients receiving maintenance dialysis experienced an AMI. The 1-year and 2-year survival rates were 41% and 27%, respectively (Fig. 3).

In addition, even during the era of reperfusion therapy from 1990 to 1995, overall mortality rates at 1 year and 2 years were 61% and 74%, respectively. Two-year mortality from cardiac causes was 50% in patients with an AMI between 1977 and 1984 and 52% for patients experiencing an AMI between 1990 and 1995 (the era of reperfusion therapy). This increased mortality (all-cause mortality and mortality from cardiac causes) was noted in patients with or without diabetes mellitus, but the overall risk of death (18%) and risk of death from cardiac causes (19%) was lower in African American than in white patients [24].



No. at risk 34,189 6753 2284 834 304 105

Fig. 3. Estimated cumulative mortality after acute myocardial infarction among patients receiving dialysis. (From Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998;339(12):801; with permission.)

In view of these catastrophic outcomes after AMI in maintenance dialysis patients, every effort should be made to evaluate the presence of atherosclerotic coronary artery disease (CAD) during the early stages of the evolution of CKD.

Cardiac disease also remains an important cause of death in recipients of kidney transplantation. Among recipients of kidney transplants from 1977 to 1996, there were approximately 79,000 patients with a functioning graft, and 4250 of these had a first AMI, with an estimated in-hospital mortality of 11.5%. The overall mortality at 2 years was 30.4%, and mortality from cardiac causes was 11.5%. African American transplant recipients had no survival advantage after AMI as was described in African American dialysis patients following AMI. On the other hand, Native American renal transplant recipients had a twofold-increased risk for cardiac death. In contrast to the dialysis population, there was a significant (almost 50%) reduction of all-cause and cardiac mortality after AMI in recipients of kidney transplants in the era from 1990 to 1996 as compared with the years from 1977 to 1984. This reduction in mortality suggests a benefit of reperfusion therapy in the recipients of a functioning renal transplant.

The American Society of Transplant Physicians recommends that all potential candidates for transplantation (except those at the lowest possible cardiac risk) should have pretransplant

screening for CAD [25]. There are no such established guidelines in the United States or in Europe concerning the evaluation of CAD in patients receiving maintenance dialysis. In view of the catastrophic outcome after the onset of AMI, it is prudent to recommend that all high-risk CKD patients be screened for the presence of CAD before the initiation of dialysis therapy.

### **Cardiac valvular abnormalities and valve replacement in patients with chronic kidney disease**

Different published series have demonstrated that dialysis-dependent patients are at an increased risk for valvular sclerosis and valvular calcification. Premature aortic valve calcification and mitral valve calcification are common in dialysis patients. The precise mechanisms for ectopic calcification in patients with CKD are not well known. The accumulation of calcium phosphate (hydroxyapatite,  $\text{Ca}_3[-\text{PO}_4]_2 \cdot x \text{Ca}[\text{OH}]_2$ , containing 40% of elemental calcium in weight) precipitates in ectopic places including coronary arteries and cardiac valves. Several factors, such as an abnormal calcium-phosphate product, hyperparathyroidism, intake of calcium-based phosphate binders, increased mechanical stress, and as yet unknown factors, have been implicated in the pathogenesis of ectopic calcification including valvular calcification [26]. Several studies suggest that the presence of vascular calcification is associated with an increased risk of cardiac events in uremic patients [27].

In a small but important group of patients receiving long-term dialysis, premature valve calcification can progress to hemodynamically significant aortic stenosis or, less frequently, mitral stenosis. Cardiac valvular disease is a common complication in hemodialysis patients, with a prevalence of up to 9%. The estimated annual incidence of valvular heart disease that leads to significant hemodynamic effects and requires valve replacement was reported to be 1.5 to 1.9 cases per 1000 dialyzed patients between 1988 and 1992 [28].

In dialysis patients, cardiac surgery, including valve replacement and coronary artery bypass grafting, is fraught with increased mortality. The reported perioperative mortality was 17.0% for aortic valve replacement only, 22.4% for mitral valve replacement only, 24.5% for combined coronary artery bypass grafting and aortic valve replacement, and 36.8% for combined coronary artery bypass grafting with mitral valve

replacement. Similar observations were reported on the retrospective analysis of USRDS database in dialysis patients requiring valve surgery.

In addition, an analysis of the USRDS database revealed, contrary to the previous belief, that bioprosthetic valves in dialysis-dependent patients function as well as the nonprosthetic (metallic) valves (Fig. 4). Undoubtedly, long-term survival in dialysis patients after cardiac valve replacement is poor, but this poor outcome does not seem to be related to the type of the prosthetic valve. There is currently a debate as to whether the American Heart Association Task force should upgrade the use of bioprosthetic valves in dialysis-dependent patients to class II status from the current class III status [29].

### **Pathophysiology of accelerated cardiovascular disease in patients with chronic kidney disease**

#### *Traditional modifiable risk factors in patients with chronic kidney disease*

##### *Hypertension*

Early CKD is associated with an increase in diastolic and, to a lesser extent, systolic blood pressure. With the onset of CKD, already existing hypertension may worsen, or new-onset hypertension could develop because of an increase in plasma volume (salt and water retention), increased activity of the renin-angiotensin-aldosterone system and sympathetic activity, and accumulation of circulating endogenous vasoactive substances.

Without effective control of hypertension and salt-water retention, blood pressure gradually worsens and causes further progression in renal damage, thereby triggering a vicious cycle. Although the impact of different degrees of hypertension in patients with CKD has not been studied, observational studies from the general population have demonstrated a linear relationship between diastolic, systolic, and pulse pressure and the development of CAD, congestive heart failure, and stroke. Such an association could be substantially higher among young individuals who develop CKD at an early age.

##### *Proteinuria or microalbuminuria*

Microalbuminuria is associated with an increased risk of CAD, LVH, and myocardial infarction in patients with hypertension and without diabetes mellitus [30,31]. The presence of proteinuria during the 6 years of follow-up was consistently associated with an increased all-cause, CVD, and coronary heart disease mortality, even after

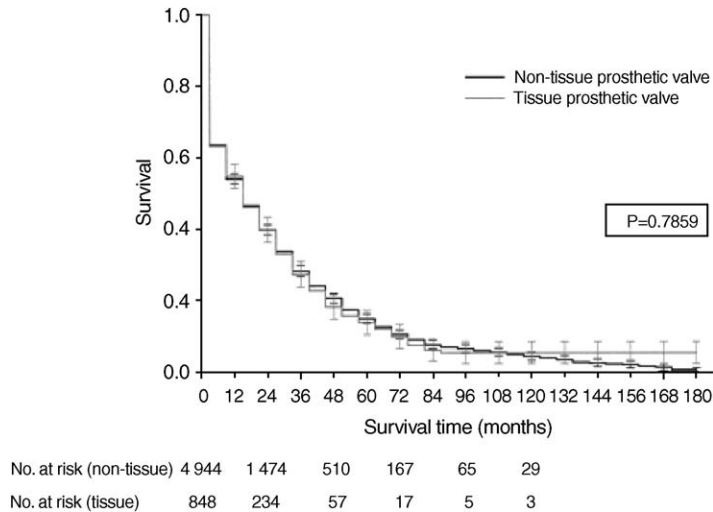


Fig. 4. Estimated all-cause survival of dialysis patients after heart valve replacement surgery with tissue and nontissue prosthetic valves. (From Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? *Circulation* 2002;105:1338; with permission.)

adjusting for other risk factors. Proteinuria was an independent risk factor for CVD mortality [32]. Similar observations were noted in the analysis of the fifteenth biennial examination of the Framingham Heart Study [33].

Proteinuria could be the result of different types of glomerular injury, but the downstream effect is uniformly similar, whatever the nature of the glomerular injury. Proteinuria of any magnitude and of any cause results in tubular injury, which, in turn, is almost invariably associated with progression of renal failure [34,35].

Microalbuminuria of any cause results in increased vascular permeability, endothelial dysfunction, and increased levels of the markers of oxidative stress [36–38]. Different types of interventions in different stages of microalbuminuria, in particular the use of angiotensin-receptor blockers [40] and blockage of the aldosterone axis [41], are associated with improved outcome of renal function and cardiovascular morbidity and mortality [39].

#### Diabetes mellitus

Diabetes mellitus (particularly type 2 diabetes) is a common cause of CKD; between 40% and 45% of the current dialysis patients in the United States have diabetes mellitus. The presence of diabetes is an independent risk factor for CVD. The combination of diabetes and CKD is perhaps additive with regard to the onset and progression

of CVD in patients receiving renal replacement therapy and recipients of organ transplantation. Recipients of solid-organ transplantation and bone marrow transplantation can develop new-onset diabetes (posttransplant diabetes mellitus [PTDM]) and complications caused by the development of insulin-resistant syndrome in such patients with PTDM. The effects of PTDM on CVD remain to be elucidated.

The microvascular complications of type 1 and type 2 diabetes can be modified or prevented modified by intensive glycemic control [42,43]. It is well established that tight glycemic control prevents end-organ damage and prevents progression in CVD and CKD. The use of angiotensin-receptor blockers in patients with diabetes mellitus can delay the progression of CKD and the need for renal replacement therapy [44].

The optimal glycemic control meeting the American Diabetes Association's defined goal of glycosylated hemoglobin levels is essential to prevent new-onset atherosclerotic disease and to ameliorate the progression of atherosclerosis in patients with diabetes mellitus and CKD.

#### Dyslipidemia in chronic kidney disease

During the progression of CKD, dyslipidemia is characterized by an accumulation of partially metabolized triglyceride-rich particles resulting in the production of predominantly very-low-density lipoprotein and intermediate-density

lipoprotein remnants, either because of abnormal lipoprotein lipase levels or its function, resulting in hypertriglyceridemia and significantly reduced high-density lipoprotein (HDL) cholesterol levels [45]. Several prospective studies in the general population have demonstrated that the relationship between the risk of CAD and blood cholesterol is almost log-linear. The minimum threshold below which a lower total cholesterol is not associated with a risk of atherosclerosis is not known. On the contrary, recent evidence has demonstrated that a low-density lipoprotein (LDL) cholesterol goal should be approximately 70 mg/dL in patients with established CAD [46,47].

Microalbuminuria and macroalbuminuria are associated with increased cholesterol, and the combination of microalbuminuria and early renal impairment is usually associated with an increase in LDL [48]. Most often, nephrotic-range proteinuria (ie, proteinuria of > 3 g/24 hours) further accentuates the increase in LDL cholesterol [49]. In addition, accurate estimation of LDL cholesterol in patients with CKD with or without a microinflammatory state may be hampered by the presence of other unmeasured and unknown lipid abnormalities (eg, the presence of a high proportion of small, dense LDL particles, an increase in the levels of oxidized-LDL [50], and increased fragments of lipoprotein (a) as a part of total LDL cholesterol) [51].

There are no known randomized, controlled, interventional studies to test the hypothesis that dyslipidemia is directly related to atherosclerosis in patients with CKD or receiving renal replacement therapy. Seliger et al [52,53] in a retrospective, observational study, however, analyzed the USRDS database and identified a cohort of 3716 patients who were placed on dialysis in 1996. Patients receiving statin therapy had better CVD outcomes and a reduced rate of all-cause mortality during the follow-up. The major caveat of this retrospective study was that patients receiving statins might have had other favorable factors that prevented them from developing accelerated atherosclerosis and that could not be recognized in the final analyses.

An inverse association between blood cholesterol and all-cause mortality or cardiovascular mortality has been termed reverse causality [54]. The paradoxical association of lower cholesterol and increased mortality (the so-called “U-shaped curve”) in dialysis patients is partly explained by the presence of markers of malnutrition, systemic

inflammation, and concurrent illness [55,56]. In a cohort of 1167 hemodialysis patients, Iseki et al [55] demonstrated low serum cholesterol levels and decreased serum albumin levels were associated with increased all-cause mortality. In patients with normal serum albumin levels, the opposite was true: high serum cholesterol was associated with increased mortality. Increased levels of C-reactive protein and other markers of inflammation, such as serum ferritin, interleukin-6, and tumor necrosis factor alpha, are associated with low serum cholesterol levels [56]. Hence, low total cholesterol is often associated with microinflammation, malnutrition, or the combination of these factors.

Nevertheless, these observations support the notion that there is a paradoxical association (reverse epidemiology) between low serum cholesterol and increased mortality in hemodialysis patients. These observations do not refute the hypothesis that dyslipidemia is important in the pathogenesis of atherosclerosis. Rather, it is more likely that high cholesterol levels impart the same degree of risk for atherosclerosis in patients with CKD as in the general population and that other conditions, such as systemic inflammation, infection, and poor nutritional intake, account for the increased mortality in patients with low cholesterol levels.

Because of the lack of prospective studies, the K/DOQI work group for dyslipidemia in CKD evaluated the prevalence of dyslipidemia in a large cross-section of 1047 hemodialysis patients enrolled in the Dialysis Morbidity and Mortality study. Based on National Cholesterol Educational Program, Adult Treatment Panel III definitions, 20% of patients had a normal lipid profile, 62% had dyslipidemia that would warrant therapy, 56% had LDL levels of 100 mg/dL or higher, and another 6% had triglyceride levels of 200 mg/dL or higher, and non-HDL cholesterol (total cholesterol–HDL cholesterol) levels of 130 mg/dL or higher in the presence of LDL cholesterol levels of less than 100 mg/dL. Also, based on these definitions, the prevalence of dyslipidemia that would need treatment was slightly higher in peritoneal dialysis patients (73%); another 6% had triglyceride levels of 200 mg/dL or higher and non-HDL cholesterol levels of 130 mg/dL, respectively, in the presence of LDL levels of less than 100 mg/dL [57].

Several studies have demonstrated the impact of dyslipidemia on cardiovascular morbidity and mortality after kidney transplantation [58,59]. The effects are almost similar to the observations in the general population. Only one prospective,

randomized study has evaluated the role of statin therapy on CVD-related events in the recipients of kidney transplantation [60].

#### *High-density lipoprotein cholesterol*

Low levels of HDL cholesterol are associated with an increased risk of arteriosclerotic cardiovascular disease (ASCVD), independent of LDL cholesterol levels. Based on the results of a meta-analysis of observational studies in the general population [61], patients with early renal disease (progressive CKD) demonstrate a significant decrease in HDL cholesterol in the early stages of the disease [62]. These low levels of HDL cholesterol persist in more than 50% of patients receiving dialysis [63–65] and in more than 20% of patients in the posttransplant period [58,59,66].

The crucial questions, however, are:

1. The optimal dose and the type of statin that is safe and effective as a lipid-lowering agent in patients with CKD (in early-stage disease, after initiation of dialysis therapy, and after transplantation);
2. The dose and type of statin that could decrease the levels of different fractions of cholesterol, including LDL cholesterol and triglyceride levels have not been studied so far;
3. Whether such therapy could prevent the progression and ameliorate the burden of atherosclerosis in patients with CKD and in patients receiving renal replacement therapy yet to be proven [67].

#### *Nontraditional modifiable factors in patients with chronic kidney disease*

A study by Fathi et al [67] showed the lack of improvement in the burden of CVD with the use of statin therapy, despite an appropriate response to lipid-lowering agents with reduction in lipid levels. This finding suggests that other factors (so-called “nontraditional factors”) may be involved in the development and progression of ASCVD in patients with CKD [68].

Several nontraditional risk factors, such as increased levels of C-reactive protein, lipoprotein (a), homocysteine, and fibrinogen, have been associated with an increased risk for CVD in the general population [69–71].

Muntner et al [68] analyzed the NHANES III database and demonstrated that the lowest level of kidney function was associated with increased levels of apolipoprotein B, lipoprotein (a), homocysteine, fibrinogen, and C-reactive protein in

patients with CKD and associated CVD. The prevalence of these risk factors was directly proportional to the decrease in kidney function. Similarly, observational studies have demonstrated an increase in the levels of C-reactive protein, lipoprotein (a), fibrinogen, and homocysteine, and increased mortality in dialysis patients [72].

As in the general population, the biologic and clinical significance of these nontraditional risk factors in patients with CKD is uncertain. These risk factors may be merely an epiphenomenon or may be etiologically related to the onset and progression of ASCVD. Other studies have also demonstrated similar association of CKD with increased levels of markers of inflammation and oxidative stress. Thus, an important triad (inflammation, oxidative stress, and the presence of other traditional risk factors) could play a significant role in the pathogenesis of the complex syndrome of ASCVD in patients with different degrees of CKD [73].

#### *Cardiovascular Health Study and markers of inflammation*

Shlipak et al [74] studied the association of renal insufficiency with inflammatory and procoagulant markers as potential mediators both for CVD and kidney disease. Several inflammatory and procoagulant factors were evaluated using baseline data from the Cardiovascular Health Study, a population-based cohort study of 5888 persons aged 65 years or older. C-reactive protein, fibrinogen, factor VIIc, and factor VIIIc levels were measured in nearly all participants; interleukin-6, intercellular adhesion molecule-1, plasmin–antiplasmin complex, and D-dimer levels were measured in nearly half of the participants. Renal insufficiency was defined as a serum creatinine level of 1.3 mg/dL or higher in women and 1.5 mg/dL or higher in men. Based on these criteria, renal insufficiency was present in 647 participants in the study (11%). After adjustment for baseline differences, levels of C-reactive protein, fibrinogen, interleukin-6, factor VIIc, factor VIIIc, plasmin–antiplasmin complex, and D-dimer were significantly higher among persons with renal insufficiency ( $P < 0.001$  for each risk factor). The positive associations of renal insufficiency with these inflammatory and procoagulant markers were similar regardless of CVD status (clinical, subclinical, or no CVD disease) at baseline. Therefore, renal insufficiency is independently associated with increased levels of these biomarkers (putative risk factors) and may be an important link between CVD and CKD.

### *Uremia-related risk factors for arteriosclerotic cardiovascular disease*

The effects of uremia may be independent of established traditional and nontraditional risk factors. CKD is generally considered to be a vasculopathic state [75]. The factors that may contribute to this increased risk for CVD because of progressive decline in renal function could be: such as anemia, left ventricular hypertrophy and increased left ventricular mass index, chronic microinflammation, increase oxidative stress, vascular calcification, and increased levels of biomarkers of myocardial damage or stress.

### *Anemia*

Anemia is a frequent complication of CKD. Anemia resulting from a deficiency of erythropoietin (EPO) is present in the majority of patients when the eGFR is less than 60 mL/min. Levin et al [76] reported that even in early stages of kidney disease (creatinine clearance rate > 50 mL/min), approximately 25% of patients have anemia. The decrease in hemoglobin begins as early as the onset of stage 2 or 3 CKD and continues to progress with progression in CKD. Anemia is an important risk factor for CVD, because its presence is associated with LVH in the general population [77]. Anemia is an important and the most common manifestation of end-stage renal disease (ESRD) and continues to remain an important and the most common feature (in >40% of patients) following kidney transplantation. In one cross-sectional study, an estimated creatinine clearance rate below 50 mL/min was associated with a threefold increased risk of anemia in women and a fivefold increased risk in men [78].

The effect of milder decreases in kidney function on hemoglobin levels was analyzed in a population-based sample of 15,419 participants aged 20 years and older in the NHANES III conducted from 1988 to 1994. There was a strong correlation between decreased kidney function and hemoglobin level. The prevalence of anemia (hemoglobin level < 12 g/dL in men and < 11 g/dL in women) increased from 1% at an eGFR of 60 mL/min/1.73m<sup>2</sup> to 9% at an eGFR of 30 mL/min/1.73m<sup>2</sup> and to 33% in men and 67% in women at an eGFR of 15 mL/min/1.73m<sup>2</sup> [79]. The burden of anemia in these patients was independent of the iron stores and the markers of chronic inflammatory state.

A prospective study of 446 subjects (86% white) with a mean duration of renal disease of

6.6 years and a mean creatinine clearance rate of 36.3 mL/min without an arteriovenous fistula and without previous exposure to EPO therapy. Follow-up at 12 months showed that LVH increased from the baseline with a decrease in hemoglobin (odds ratio [OR], 1.32) for every 0.5 g/dL decrease in hemoglobin. Systolic blood pressure increased (OR, 1.11) for every 5 mm increase in hemoglobin. The use of ACE inhibitors had no impact on either the baseline or follow-up LVH. The progression in LVH was associated with worsening of cardiac symptoms (15%) and increased rate of hospitalization (22%), and both of these were related to cardiac causes in such a short period of follow-up [80]. It is possible that in the presence of less-than-optimal hemoglobin values, ACE inhibitors and angiotensin-receptor blockers are unable to exert left ventricular remodeling effect.

Similarly, in patients receiving dialysis, a decrease in hemoglobin concentration by 1 g/dL was associated with about 1.3-fold greater incidence of congestive heart failure [81]. Correction of anemia in dialysis patients has been shown to reduce left ventricular mass and the incidence of congestive heart failure [82].

LVH is present in 80% of incident dialysis patients. Because hemoglobin decreases in the early stages of the evolution of CKD, and because anemia is a leading cause of progression in LVH, treatment with EPO in the early stages of the CKD might be more effective in preventing the development and progression of LVH and growth.

A recently published study in patients with CKD reported a significant improvement in hemoglobin levels and in quality of life with the use of EPO therapy administered every week. This study did not evaluate the effects of an increase in hemoglobin level on the progression of LVH [83,84].

### *Other advantages of the use of erythropoietin therapy*

Several studies have demonstrated that anemia is common in patients with congestive heart failure and is associated with worsening of symptoms and decreased survival. When anemia in these patients is treated with EPO, a significant improvement in cardiac function, skeletal muscle function, and symptoms has been observed [85,86]. Although it was originally believed that EPO acted specifically on hematopoietic cells, recent evidence has demonstrated several nonhematopoietic effects of

erythropoietin therapy. Ischemia/reperfusion experiments on the heart [87] and brain [88,89] in rat models showed a significant reduction in infarct size when treated with EPO therapy. Other effects of EPO are related to its proangiogenic effects on endothelial cells, which could be of potential value in patients with ischemic heart disease [89,90]. These preclinical findings suggest that EPO may have potential effects in cardiovascular disease well beyond the correction of hemoglobin levels [82,89].

#### *Left ventricular hypertrophy or Increase in left ventricular mass index*

LVH is present in more than 80% of incident dialysis patients. It is assumed that the LVH develops early and gradually worsens with the progression of CKD.

A prospective study evaluated 146 hemodialysis patients who achieved the target hemoglobin level of 10 g/dL (versus 13 g/dL). Follow-up EKGs in 48 weeks showed that achieving the target hemoglobin of 13 g/dL did not lead to regression of established concentric LVH or left ventricular dilation. EPO therapy, however, prevented new-onset left ventricular dilation and was associated with improved quality of life [91]. The follow-up of this study, however, was very short, only 48 weeks.

#### *Left ventricular hypertrophy and cardiac events*

The impact of LVH on mortality was studied in ESRD patients enrolled in the Dialysis Morbidity and Mortality Study Wave 2. EKG data about the presence and absence of LVH were analyzed in 64% (n = 2584) of the entire cohort. The prevalence of LVH was 16.4%. Multivariate analysis showed that progression in LVH was dependent on age, presence of hypertension, diabetes mellitus, hyperparathyroidism, and hypoalbuminemia. The effect of LVH on subsequent mortality was highest in the first 6 months of follow-up, and the event rate became less pronounced thereafter [92].

In ESRD patients, hypertension is also a leading cause of LVH, but structural left ventricular changes and myocardial fibrosis could be caused by nonhemodynamic factors, such as increased levels of angiotensin II, parathyroid hormone, endothelins, and aldosterone and increased sympathetic nerve activity with increased plasma catecholamine levels [93].

Anemia management, volume control, and the use of ACE inhibitors and angiotensin-receptor blockers are the cornerstones of preventing the

progression of LVH and making possible the regression of LVH in patients with CKD either before or after the initiation of dialysis [94]. A Brazilian study demonstrated that renal transplantation resulted in resolution of systolic dysfunction, regression of LVH, and improvement of left ventricular dilatation. The reduction of LVH was dependent on optimal renal function and, to a greater extent, dependent on the degree of blood pressure control as assessed by ambulatory blood pressure monitoring [95].

#### *Left ventricular hypertrophy and sudden cardiac death*

The mortality of dialysis patients is almost 3.5 times higher than the age matched healthy controls. Analysis of USRDS data base revealed that nearly 60% of all cardiac deaths in dialysis population is due to cardiac arrest [96].

The relative contribution of prevalent cardiovascular risk factors for sudden cardiac death is not known, and the relative importance of these risk factors for increased risk for death have not been studied or are poorly understood. In a small study of 123 hemodialysis patients followed for 10 years with annual echocardiographic examination, Paoletti et al [97] demonstrated that progressive LVH (defined by delta-left ventricular mass index [LVMI]) was associated with increased risk of sudden cardiac death.

Another study followed the LVMI in 161 hemodialysis patients with repeated EKG examinations. An increase in LVMI was associated with an increased risk of cardiovascular events. The cardiovascular event-free survival in patients with changes in LVMI below the 25th percentile was significantly higher ( $P = 0.004$ ) than in those with changes above the 75th percentile. An increase in LVMI by  $1 \text{ g/m}^{2.7}$  per month was associated with a 62% increase in the incident risk of fatal and nonfatal cardiovascular events (hazard ratio, 1.62; 95% CI, 1.13–2.3;  $P = 0.009$ ) [98].

#### *Chronic microinflammation and increased oxidant stress*

Acute or chronic microinflammation results in the production of acute-phase proteins. C-reactive protein, fibrinogen, and interleukin-6 are positive acute-phase proteins; albumin and cholesterol are negative acute-phase proteins. Increased levels of C-reactive protein, fibrinogen, and interleukin-6 are associated with an increased risk for cardiovascular events in both the general population and in dialysis-dependent persons. The precise

mechanism by which hypoalbuminemia and increased levels of C-reactive protein are associated with increased risk for CVD remains unclear. An acute-phase response could lead to hypoalbuminemia caused by decreased synthesis of albumin or to an increase in the level of C-reactive protein. Increased levels of C-reactive protein have been shown to predict all-cause mortality and increased morbidity in hemodialysis patients (Fig. 5) [99].

Fibrinogen is another acute-phase protein, and hyperfibrinogenemia is a nontraditional risk factor for CVD. Fibrinogen has an important modulating effect on coagulation and increases blood viscosity. Several prospective studies in the general population have shown increased mortality with increased levels of fibrinogen [71]. The fibrinogen levels tend to increase in the early stages of CKD, and even higher levels are seen in patients with CKD, without or with associated proteinuria [100]. Although there are genetic variations in the synthesis of fibrinogen [101], Prinsen et al [102] demonstrated by using isoptic methods that in vivo absolute fibrinogen synthesis rate is increased in the early stages of CKD and in patients receiving peritoneal dialysis.

A meta-analysis of prospective studies in the general population has demonstrated that an increase in the fibrinogen level of about 0.1 mg/dL results in almost 1.8-fold increased the risk of cardiovascular events [71]. If there is a cause-and-

effect relationship between increased levels of fibrinogen and cardiovascular events (because early renal insufficiency is often associated with similar degrees of increase in fibrinogen levels), an increase in fibrinogen level could portend a similar degree of risk for CVD-related events in patients with CKD.

Increased levels of fibrinogen are independently associated with concentric LVH and systolic dysfunction in ESRD patients [103]. The exact mechanisms of how increased fibrinogen levels result in an increased left ventricular mass remain unclear. The increased left ventricular mass could be secondary to the microinflammatory state. These relationships may contribute to the negative prognostic effect of elevated fibrinogen levels in ESRD. Chronic inflammation could be the mechanism of cardiovascular damage in dialysis patients, because interleukin-6 polymorphism has been shown to be different in patients with and without LVH [104].

Biomarkers of increased oxidative stress accumulate in patients with CKD and in dialysis-dependent patients. These markers include advanced glyoxidation products, lipid peroxidation products and oxidized LDL, and advanced protein oxidation products. In addition, increased oxidative stress is associated with nitric oxide (NO) dysregulation and increased diathesis for vascular injury [105].

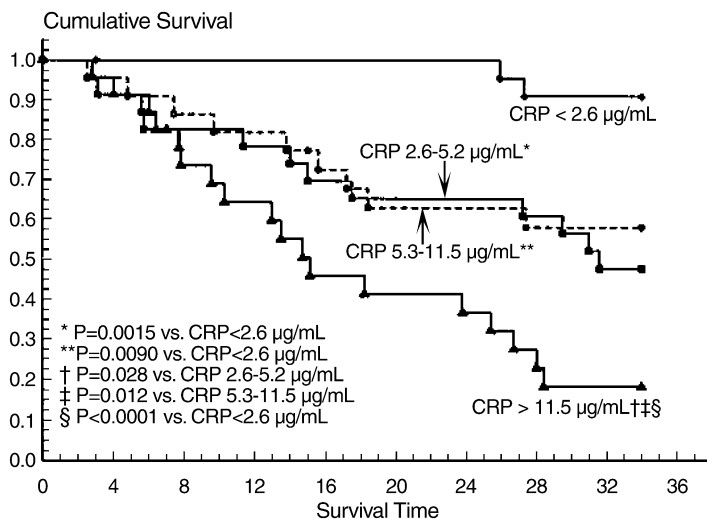


Fig. 5. Kaplan-Meier estimate of survival in hemodialysis patients with serum C-reactive protein (CRP) levels in the highest quartile, middle two quartiles, and lowest quartile. (From Yeun JY, Levine RA, Mantadilok V, et al. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 2000;35:472; with permission.)

The endogenous inhibitor of NO, asymmetric dimethylarginine (ADMA), is a strong predictor of adverse cardiovascular outcomes in patients with ESRD. Interaction of ADMA with the NO system results in the decreased availability of NO, thus resulting in the altered vascular relaxation, and may be an important factor in the pathogenesis of LVH and vascular calcification in CKD patients. The relationship between plasma ADMA and left ventricular geometry and function was studied in a cohort of 198 hemodialysis patients. Plasma ADMA levels were significantly higher in patients with significant LVH and increased LVMI. In addition, ADMA levels were inversely related to left ventricular ejection fraction. How increased levels of ADMA affect left ventricular remodeling and left ventricular dysfunction remains poorly understood. It could be another marker of a microinflammatory state [106] or an epiphenomenon.

#### *Vascular calcification*

Ectopic calcification is common in patients receiving dialysis therapy. The exact mechanism for the process of calcification within the arterial wall in patients with CKD and in dialysis-dependent patients is not known. Coronary artery calcification in the general population represents the burden of atherosclerotic disease and has been shown to predict cardiovascular outcomes [107]. Soft tissue, coronary, and valvular calcifications are relatively common in patients receiving maintenance dialysis. Calcification in the vessel wall can be either intimal calcification (a hallmark of atherosclerosis, this process starts as early as in childhood and adolescence) or medial calcification. Medial calcification (Mönckeberg's medial calcinosis) is relatively more common in patients with diabetes mellitus and CKD. The progression in coronary artery calcification in the general population has been associated with both traditional and nontraditional risk factors for CAD. The progression of coronary artery calcification in patients with CKD is further confounded by the duration of dialysis (dialysis vintage), duration and degree of hyperphosphatemia and its associated complications such as hyperparathyroidism, and the use of calcium-containing phosphate binders. The picture is complicated further by the presence of other atherogenic factors such as increased oxidative stress and the degree of associated microinflammation. The major caveat is the unpredictability of the severity of coronary

artery calcification as measured on electron beam CT and the degree of occlusive CAD [108]. Some studies have demonstrated that mere presence of coronary artery calcification is associated with increased all-cause mortality [109,110]. The most optimistic observations, however, suggest that the degree of coronary artery calcification in dialysis patients can be ameliorated with the use of non-calcium-containing phosphate binders (sevelamer) [111]. Also, lipid-lowering therapy has resulted in a significant decrease in the degree of coronary artery calcification in the general population [112] and in the dialysis population [113].

#### **Increased levels of cardiac troponin I and T as biomarkers of myocardial stress or damage**

Troponin I and T, identified as cardiac troponins (cTnT and cTnI), have emerged as new markers of cardiac ischemia and infarction and follow similar kinetics of release from the myocardium after AMI. After an AMI, levels of both troponins are elevated within 3 to 6 hours. Troponin T tends to peak at 12 hours, and troponin I peaks closer to 24 hours; both remain elevated for up to 5 days. These biomarkers may remain detectable up to 2 weeks after the ischemic event.

cTnT levels are useful in risk stratification of patients with suspected acute coronary syndrome. Its role in patients with CKD remains questionable, because cTnT is excreted by the kidneys.

Aviles et al [114] studied the impact of positive cTnT (third-generation recombinant human cTnT assay) in the patients enrolled in the Global Use of Strategies to Open Occluded Coronary Arteries IV trial. They included patients with decreased creatinine clearance rates (measured by Cockcroft and Gault formula, with adjustment for gender) in four different groups: abnormal creatinine clearance and detectable or increased cTnT levels (n = 950), abnormal creatinine clearance only (n = 783), abnormal cTnT levels only (n = 2695), and normal creatinine clearance and cTnT levels (n = 2605). Based on the quartiles of creatinine clearance (first to fourth: <58.4 mL/min, 58.4–76.9 mL/min, 77.0–98.6 mL/min, and >98.6 mL/min, respectively), cTnT levels were independently associated with the risk of death or myocardial infarction within 30 days (primary outcome) across a wide range of creatinine clearance rates. The odds ratio for short-term outcome (30 days) actually rose with declining creatinine clearance rates (Fig. 6). There were, however, only 11 patients with a creatinine

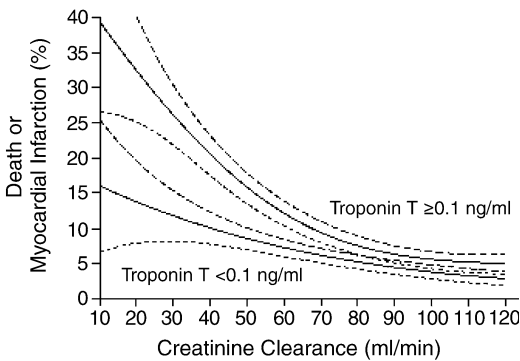


Fig. 6. Incidence of the primary end point of death or myocardial infarction, according to the baseline troponin T level and creatinine clearance rate. (From Aviles RJ, Askari AT, Lindahl B, et al. Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med* 2002;346:2050; with permission.)

clearance rate of less than 10 mL/min; therefore the value of positive cTnT in establishing the diagnosis and prognosis in dialysis patients was not clarified by this study. The value of increased cTnT level in asymptomatic patients with CKD using the third-generation troponin assay is not known at present [115].

DeFilipi et al [116] measured cTnT and C-reactive protein in patients with ESRD and assessed the combined value of these markers to predict outcomes and associated cardiac pathology. A prospective cohort of patients receiving maintenance hemodialysis ( $n = 224$ ) was enrolled in this study with a mean follow-up of more than 2 years. Increased quartiles of both C-reactive protein and cTnT predicted increased risk of death compared with the lowest quartiles, and this risk was independent of other potential confounders for cardiovascular disease. In addition, increased levels of cTnT, but not C-reactive protein, were a predictor of diffuse CAD, and the prevalence of multivessel CAD was significantly higher in the group with highest quartiles of cTnT levels. It also became evident from this study that neither troponin nor C-reactive protein could predict the presence of LVH and reduced left ventricular ejection fraction ( $<40\%$ ) [116].

A similar observation was reported in a cross-sectional study by Iliou et al [117,118]. They measured cTnT and performed EKGs in asymptomatic maintenance hemodialysis patients. Almost 19% of patients had increased levels of cTnT at the time of enrollment into the study. Increased

levels of predialysis cTnT levels were associated with LVH, all-cause mortality, and major cardiovascular events (cardiac death, myocardial infarction, or unstable angina).

Although the spectrum of increased cTnT in patients with CKD is still evolving, it is unclear from the observational studies whether increased levels of these biomarkers are perhaps an expression of underlying myocardial hypoxia-ischemia or microinfarction. Whether troponin assays will offer a new tool for risk stratification of underlying CVD in patients with CKD remains to be proven.

## Summary

The goal of risk stratification of CVD in patients with CKD is to lead to effective and early intervention and to prevent the adverse outcomes associated with this complex multisystem disease that is characteristic of growing number of patients with CKD in the general population [119] and of patients receiving dialysis therapy or kidney transplantation [120]. By 2030, there will be 2.24 million patients with ESRD in the United States, and approximately 1.3 million of these cases of ESRD will be caused by diabetes mellitus. Thus, CVD in this high-risk population presents a challenge for the nephrology and the cardiology community.

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