Kidney International, Vol. 66, Supplement 92 (2004), pp. S11–S15

Cardiovascular risk in chronic kidney disease

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Cardiovascular risk in chronic kidney disease. National Kidney Foundation guidelines define chronic kidney disease (CKD) as persistent kidney damage (confirmed by renal biopsy or markers of kidney damage) and/or glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for greater than three months.

Patients with CKD experience higher mortality and adverse cardiovascular (CV) event rates, which remains significant after adjustment for conventional coronary risk factors. This progressive CV risk associated with worsening renal function may be explained by other factors that become increasingly important with renal decline. In this regard, more investigation of nonconventional factors that have received a lot of attention includes associations with inflammation, albuminuria, reduced vascular compliance, and homocysteine.

In addition, individuals with CKD encounter the problem of "therapeutic nihilism," in which there is a lack of appropriate risk factor modification and intervention, despite established awareness of their high cardiovascular risk. Several studies suggest that these individuals derive as much, if not more, benefit from evidence-based cardiovascular therapies and strategies. Greater educational efforts are needed to reduce this therapeutic gap.

A large population of individuals entering the transition phase toward end-stage renal disease (ESRD) is emerging. National Kidney Foundation guidelines define these individuals as having chronic kidney disease (CKD) [1]. CKD is defined as persistent kidney damage (confirmed by renal biopsy or markers of kidney damage) and/or glomerular filtration rate (GFR) <60 mL/min/1.73m^2 for greater than three months [1]. Using these criteria, current estimates account for at least 11 million individuals and rising [1].

Many community-based studies have documented that individuals with CKD have a rising prevalence of cardiovascular (CV) disease associated with progressive renal decline [2–5]. A higher rate of adverse CV events is noted among this cohort when compared with those with normal renal function [5–7]. Indeed, although there has been an appropriate emphasis on reducing the risk of progression to dialysis of patients with CKD, these individuals are much more likely to die from cardiovascular causes [8].

Key words: nonconventional risks, traditional risks, cardiovascular events, mortality.

EPIDEMIOLOGY

Evidence for increasing CVD morbidity and mortality tracking with mild to moderate renal dysfunction has mainly stemmed from community-based studies. These have included the Framingham Heart study, NHANES I, ARIC, and the Hoorn studies [8–11]. All of these studies documented an inverse relationship between renal function and risk of an adverse cardiovascular outcome [8–11].

The influence of mild to moderate renal impairment post acute coronary syndrome has been shown to increase cardiovascular mortality and morbidity at 30 and 180 days [12–15]. Longer-term outcome data related to a broader spectrum of renal dysfunction have been limited, partly related to smaller cohorts and exclusion of individuals with renal dysfunction. Studies that have examined the relationship between renal function and cardiovascular outcomes among high CV risk cohorts with left ventricular dysfunction with longer follow-up have included the Studies of Left Ventricular Dysfunction (SOLVD), Trandolapril Cardiac Evaluation (TRACE), Survival and Ventricular Enlargement (SAVE), and Valsartan in Acute Myocardial Infarction (VALIANT) trials [16–18] (Table 1). Although these studies excluded individuals with baseline serum creatinine of ≥2.5 mg/dL, approximately a third of patients had CKD based upon National Kidney Foundation estimated glomerular filtration rate (eGFR) criteria [1]. In all of these studies, reduced renal function was associated with significantly higher mortality and adverse CV event rates independent of other comorbidities, with an especially marked rise in event rates below an eGFR of 60 mL/min/1.73m^2 (Fig. 1); any short-term risk conferred at baseline also persisted in the longer term following acute myocardial infarction (AMI).

Why increased cardiovascular risk in chronic kidney disease?

Mechanisms as to why renal dysfunction portends increased CV risk are still being elucidated. Several

Table 1. Influence of baseline renal function on cardiovascular outcomes in cohorts with left ventricular dysfunction

Trial	Year	Number of patients	Hazard ratio for CV events for every 10 mL/min/1.73m^2 decrease in baseline eGFR
Studies of Left Ventricular Dysfunction (SOLVD)	2001	6635	1.1
Trandolapril Cardiac Evaluation (TRACE)	2002	6252	1.2
Survival And Ventricular Enlargement (SAVE)	2003	2184	1.5
Valsartan in Acute Myocardial Infarction Trial (VALIANT)	2003	14527	1.1

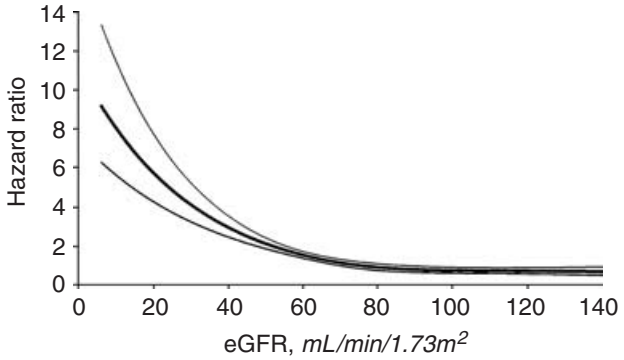

Fig. 1. Hazard ratio for CV events with declining eGFR in VALIANT. From Anavekar et al, *N Engl J Med*, 2004.

explanations have been provided, inclusive of high proportions of coronary risk factors and comorbidities [2, 19]. Increasing expression of nonconventional risk factors that may be acting alone or synergistically with existing coronary risks, and lack of appropriate risk factor modification and intervention are all considered to be contributing factors.

Traditional coronary risk factors

Individuals with renal impairment usually have complex medical histories consisting of multiple comorbidities, and several studies have documented an increasing prevalence of traditional coronary risk factors with reduced renal function [4, 12, 13]. Atherosclerotic disease in those with CKD appears to be markedly accelerated, with more extensive anatomic disease present at younger ages consistent with a cardiovascular risk similar to older aged non-CKD counterparts.

Many coronary risk factors, particularly diabetes mellitus and hypertension, are well-established predictors for renal disease progression [20]; a bilateral relationship exists in which conventional coronary risk factors contribute to renal disease, and this decline in renal function appears to close the loop on a vicious cycle whereby progressive renal decline heightens the potency of traditional and novel risk factors promoting accelerated atherosclerosis (Fig. 2). Although CV risk attributed to CKD has been found to be independent of various comorbidities, the significant CV risks associated with diabetes and hypertension still persist among those with CKD [4].

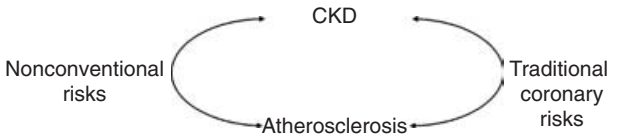

Fig. 2. Relationship between atherosclerosis and CKD.

Dyslipidemia is a common finding among CKD cohorts [21]. Worsening CKD is associated with changes in lipid profiles. In mild to moderate stages of CKD, low high-density lipoprotein (HDL) levels, increased triglycerides, and increased levels of intermediate density lipoproteins are often noted [8, 22]. As CKD approaches ESRD, there appears to be increased oxidation of low-density lipoprotein (LDL), with progressive lowering of total cholesterol levels. The influence of dyslipidemia upon CV outcomes appears to demonstrate a "U"-shaped relationship, with increased CV event rates seen among those with severe CKD (i.e., ESRD) having low cholesterol levels [8]. Explanations for this "low cholesterol paradox" have been attributed to the effects of chronic malnutrition and inflammation, which become increasingly important with severe CKD [4, 23, 24]. In this context, the "U"-shaped relationship of cholesterol level for CV outcomes probably reflects the interplay of two mechanisms: at mild to moderate stages of CKD, high cholesterol levels are a contributing factor toward atherosclerosis [4], while in severe CKD, low cholesterol levels are probably identifying malnourished individuals with a high burden of chronic inflammatory activity [23] and already established atherosclerosis. This paradox in ESRD has raised the question of utility of lipid-lowering therapy. However, recent data confirms higher risk of moderate CKD in statin trials and similar CV risk reduction [25, 26].

Nonconventional risk factors

Conventional coronary risk factors alone cannot explain the significantly elevated CV risk and predisposition for adverse CV outcomes. Evidence for this stems from documented discrepancies between calculated Framingham coronary point scores, which seem to underestimate CV risk, compared with actual CV event rates [11, 27]. Following adjustment for conventional coronary risk factors, reduced renal function has consistently been associated independently with significantly higher mortality and adverse CV event rates [28, 29]. Progressive cardiovascular risk associated with worsening renal function unexplained by known risk factors requires a broader

Table 2. Proposed factors associated with increased CV risk with worsening CKD

Conventional
Age
Male gender
Hypertension
Diabetes
Dyslipidemia
Smoker
Uremic
Lower creatinine clearance or eGFR
Albuminuria
Lower serum albumin
Anemia
Vascular
Reduced vascular compliance
Other
Homocysteine, inflammation, oxidative stress
Ca^{2+} $PO4^{3-}$ procoagulation

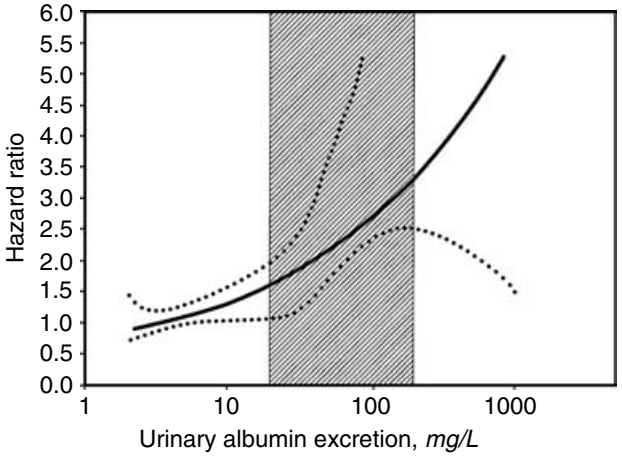

Fig. 3. Increasing risk for CV death with worsening albuminuria. From Hillege et al, *Circulation*, 2002.

understanding of other factors that become increasingly important with renal decline (Table 2). Nonconventional factors that have received a lot of attention include associations with inflammation, albuminuria, anemia, reduced vascular compliance, and homocysteine.

Inflammation. Atherosclerosis is an inflammatory disorder [30]. Several large cross-sectional studies have identified C-reactive protein (CRP) as an independent risk factor for cardiac disease [31]. CRP levels provide an overall measure of systemic inflammatory activity; they increase dramatically in response to cytokine-mediated stimuli and appear to have fairly constant fractional clearance rates among normal subjects [32].

Several studies have documented increases in proinflammatory cytokines, elevated CRP levels, increased oxidative stress, reduced clearance of proinflammatory substances such as advanced glycosylation end products and products of carbonyl stress [33, 34] among both predialysis and dialysis patients [23, 35]. These have all been strongly and independently linked with increasing rates of cardiovascular morbidity and mortality [35]. CRP is a particularly attractive candidate of augmenting CV risk in CKD because it has been implicated as not just a marker, but as an actual promoter of atherosclerotic disease progression [36].

In addition, inflammation has also been linked to alterations in protein metabolism. Many individuals with severe CKD suffer from malnutrition, which is partly explained by excessive protein losses coupled to an elevated catabolic state [37]. Malnutrition as reflected by low serum albumin levels have been shown to strongly predict adverse outcomes among individuals with CKD, particularly those receiving renal replacement therapies [38]. Additionally, independent of nutritional status, albumin is also a negative acute phase protein whose synthesis decreases during inflammation [39].

Anemia. Anemia is an independent predictor for renal disease progression because it may reflect progressive erythropoietin deficiency and the negative influence of increasing uremic factors upon erythropoiesis with renal decline [40]. Chronic anemia has been demonstrated to be an independent risk factor for adverse CV outcomes, particularly in patients with kidney disease and in patients with heart failure [41]. Anemia is associated with left ventricular (LV) dilatation, left ventricular hypertrophy (LVH), and death in patients with CKD [41]. The mechanism for this association is unclear; however, it has been postulated that the presence of anemia may be signifying an acute phase response and systemic inflammatory activity rather than a direct effect, per se [41], in addition to the augmentation in cardiac workload.

Albuminuria. Several retrospective and prospective studies have consistently demonstrated that worsening albuminuria is paralleled by increasing cardiovascular complications [42–44]. A plausible explanation for these findings is that albuminuria not only reflects glomerular damage, but is also a sensitive indicator of generalized atherosclerotic-mediated capillary vasculopathy [43, 44]. Albuminuria has been shown to cluster with a number of vascular risk factors inclusive of hypertension, renal dysfunction, dyslipidemia, hyperhomocysteinemia, and several inflammatory markers [42]. After adjustment for these factors, albuminuria is an independent predictor for adverse CV events, and this risk increases in a continuous fashion [45]. The precise mechanism underlying this is currently unknown; several derangements in the fibrinolysis and coagulation systems have been noted favoring a thrombogenic state [45].

Vascular compliance. Individuals with CKD are noted to have evidence of reduced vascular compliance [46]. Reduced vascular compliance, as evidenced by elevated aortic pulse wave velocities, has been demonstrated to be a significant predictor for adverse CV events [47, 48], and several studies have also shown that widened

pulse pressure is also an independent predictor for cardiovascular and all cause mortality, both of which have been shown to progressively worsen with renal decline [49]. In a study involving 1290 untreated hypertensive patients with mild to moderate CKD, an inverse correlation with renal function independent of blood pressure and other traditional coronary risk factors was seen with aortic pulse wave velocity [50]. The effect of calcium on CV risk in individuals with ESRD has been studied and contributes to reduced vascular compliance [51]. Elevations in the calcium-phosphate product associated with secondary hyperparathyroidism lead to vascular calcification [51]; this has not been demonstrated in individuals with CKD, who usually have normal calcium/phosphate homeostasis. Mechanisms as to why vascular compliance is reduced and/or arterial stiffness progressively increases with worsening renal function are still being elucidated.

Homocysteine. The metabolism of homocysteine and other sulfur-containing amino acids has been shown to be abnormal with renal decline [52]. Among patients with severe CKD, every 1 μmol increase in plasma homocysteine levels has been shown to be independently associated with a 1% risk for vascular events [52]. The mechanism by which elevated homocysteine levels cause vascular disease is unknown; it may be related to endothelial dysfunction, platelet hyper-reactivity, and/or abnormalities involving the coagulation cascade [3]. Among individuals with hyperhomocysteinemia and vascular events, but without CKD, lowering of homocysteine levels is associated with reduced risk for further CV events. However, the same relationship does not seem to hold true among those with severe CKD; in particular, these patients seem to be resistant to conventional homocysteine-lowering therapies, and among those where the level is reduced, only marginal benefits in reducing CV events have been noted [3].

Underuse of risk modifying strategies

Despite the higher risk of major CV events and death, the proportion of individuals with CKD receiving appropriate risk factor modification and/or interventional strategies is lower than the general population, a concept termed "therapeutic nihilism" [2]. This reduced use of proven therapies must be considered as a significant iatrogenic factor contributing to their increased CV risk. Several databases and registries have consistently observed a reduced use of proven therapies with worsening renal function [12, 53, 54]. In patients with severe CKD who are known to be at extreme CV risk, less than 50% are on the combination of aspirin, β-blocker, ACE inhibitors, and statins [55]. Potential explanations, whether justified or not, include concerns of worsening existing renal function, and/or therapy-related toxic effects due to low clearance rates [2, 56]. Bleeding concerns with the use of platelet inhibitors and anticoagulants are especially important with reduced renal function and appear to contribute to the decreased likelihood of patients with severe CKD to receive aspirin and/or clopidrogrel [54]. However, several studies have shown that when appropriately titrated and monitored, cardiovascular medications and coronary revascularization used in the general population can be safely administered to those with renal impairment, and with similar benefits [55, 57].

CONCLUSION

Chronic kidney disease is a potent harbinger for adverse cardiovascular outcomes, incorporating both conventional and nonconventional cardiovascular risk factors. Ironically, although awareness of this high risk is being appreciated, application of strategies for reducing their cardiovascular morbidity and mortality seem to be limited when compared with non-CKD cohorts. CKD patients seem to derive as much, if not more, benefit from such established cardiovascular therapies and strategies. Greater efforts are needed to reduce this therapeutic gap.

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