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The Cardiorenal Syndrome: Nontraditional Cardiovascular Risk Factors in Patients with Renal Disease

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Cardiovascular disease (CVD) is the leading cause of death among patients with end-stage renal disease (ESRD). Patients with ESRD have cardiovascular (CV) mortality rates 10- to 20-fold higher than the general population. This increase in CV risk for patients with chronic kidney disease (CKD) and ESRD is multifactorial. Important factors include dysregulation of calcium-phosphorous metabolism and extraskeletal calcifications, anemia, and heightened systemic inflammation. This issue of *Nephrology Rounds* reviews the risk factors connecting CVD and renal disease.

Background

CVD is the leading cause of death among patients with ESRD. In fact, an analysis of the United States Renal Data System (USRDS) revealed that mortality from CVD accounted for 42.2% of the 17.9 deaths/100 patient-years at risk.¹ In a prospective study of 4024 patients initiating dialysis between 1996 and 1997, >50% had overt CVD at the time of initiation.² Patients with ESRD have CV mortality rates 10- to 20-fold greater than the general population.³⁻⁵ This increased risk rises steeply to ≥ 65 -fold in the 45- to 54-year-old subgroup.^{3,6} Even patients with milder degrees of renal insufficiency have significant elevations in CV risk, ie, approximately 3-fold compared with the general population.^{3,7}

The Framingham Study was pivotal in determining "risk factors" for disease; it provided a set of measurable conditions or markers that, when evaluated, could predict the risk of disease, in particular, a series of risk factors relevant to the development of CVD in the general population. The list included the "traditional" risk factors of age, sex, blood pressure (BP), dyslipidemia, diabetes, and smoking. However, the dramatic comparative increase in CV risk for patients with renal disease led to a search for additional, "nontraditional" CV risk factors in these patients (Figure 1).

Anemia

Anemia is usually observed in patients with glomerular filtration rates (GFRs) < 60 mL/min/1.73m². Anemia prevalence rates are approximately 25% in patients with creatinine clearance (CrCl) > 50 mL/min,⁸ and approximately 44% in those with GFRs in the 15-29 mL/min/1.73m² range (anemia defined as a hemoglobin (Hb) of < 12 g/dL in men and < 11.0 g/dL in women). By stage 5 CKD, approximately 90% of patients are anemic.⁹⁻¹¹ Several studies suggest that anemia is a major risk factor contributing to poor CVD outcomes, including left ventricular hypertrophy (LVH), worsening congestive heart failure (CHF), and myocardial ischemia.

In a 1999 cross-sectional study,¹¹ LVH prevalence was 26.7% (as detected by echocardiography) in patients with CrCl > 50 mL/min, 30.8% in those with CrCl at 25-49 mL/min, and 45.2% in those with CrCl < 25 mL/min. In multivariate analyses by the same investigators, Hb concentration was found to be an independent risk factor for the development of LVH, with a 32% increased risk for LVH for every 0.5 g/dL decrease in Hb.¹⁰ Similarly, CrCl was also found to be associated with an increased risk of LVH development, with a 3% increase in risk of LVH for every 5 mL/min decline in GFR ($P=0.0168$). In fact, at initiation of dialysis, only 15% of patients possess normal LV structure and function, and they have 20- to 40-fold higher rates of CV mortality than the general population.^{12,13} These findings suggest that patients are anemic long before they develop ESRD. A study based on data from Medical Evidence Forms (Health Care Financing Administration 2728, now the Centers for Medicare and Medicaid Services - CMS),¹⁴ found that erythropoietin treatment given prior to dialysis initiation was associated with survival improvement as compared with nontreated patients. A study of 11 patients with CKD^{15,16} demonstrated that partial improvement of anemia was associated with a significant decrease in LV mass index (LVMI), from 178.2 ± 20.6 g/m² to 147.3 ± 20.6 g/m², and a trend towards decreased LV thickness. Another study by Hayashi et al¹⁷ found reductions in LVMI with partial correction of anemia (hematocrit [Hct] $32.1\% \pm 1.8\%$) at 4 months (from baseline of 140.6 ± 12.1 g/m² to 126.9 ± 10.0 g/m² after partial correction), and a further decrease in LVMI with normalization of Hct at 12 months (Hct $39.1\% \pm 2.4\%$), to 111.2 ± 8.3 g/m². A retrospective analysis of 89 193 Medicare patients with ESRD¹⁸ found that predialysis erythropoietin treatment was associated with higher Hct at dialysis initiation and a lower risk of mortality at 1 year.



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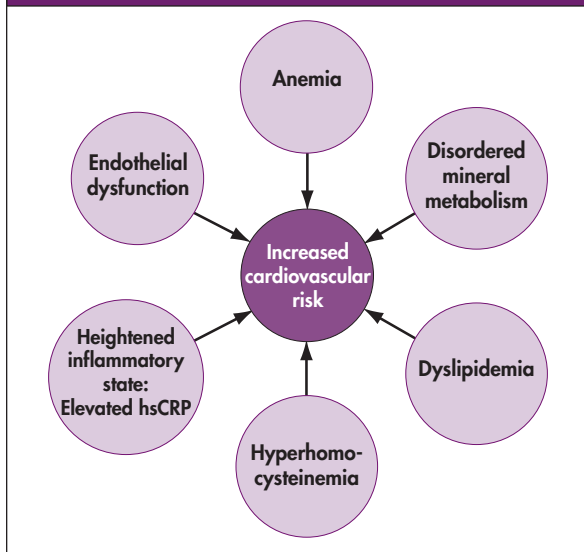
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Figure 1: Additional risk factors for cardiovascular disease in patients with renal disease



hsCRP = high-sensitivity C-reactive protein

Several studies, however, have also suggested that normalizing Hct results in unfavorable outcomes. In the U.S. Normal Hematocrit Study,^{19,20} 1233 hemodialysis (HD) patients with either ischemic heart disease or CHF were assigned randomly to Hct targets of 30% or 42%. The trial was preemptively terminated due to a trend towards a higher risk in the primary endpoint, death or first nonfatal myocardial infarction (MI) in the normal Hct group (relative risk [RR] 1.3; 95% CI, 0.9-1.9). The open-label Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) study²¹ randomized 1432 CKD patients to either an Hb of 13.5 g/dL or 11.3 g/dL, with a primary endpoint composite of death, MI, CHF hospitalization, and stroke. In the resulting 222 composite events, 125 were in the higher Hb group and 97 were in the lower Hb group ($P=0.03$; hazard ratio [HR] of 1.34; 95% CI, 1.03-1.74). There was also a significantly higher rate of serious adverse events in the higher Hb group.

Disordered mineral metabolism

In the past decade, calcium-phosphorous management in CKD has shifted to concerns about significant increases in CV risk associated with extraskeletal calcification, particularly in the coronary vasculature. A study in ESRD patients²² assessed valvular calcifications by electron beam computed tomography (CT), and found aortic and mitral calcification rates of 55% and 59%, respectively. Later, Block et al²³ found that a serum product of calcium and phosphorous (CaP) >55 was associated with a significant increase in mortality. Those individuals in the highest quintile of CaP (>72) had an increased risk of death (RR = 1.34) compared with those with a CaP in the 42 to 52 range. A study²⁴ evaluating the presence of coronary calcification in 39 young patients on dialysis and 60 normal subjects, found that 14 of the patients on dialysis had coronary calcification compared with only 3 normal subjects. Furthermore, patients with calcification were found to be older (26 ± 3 vs 15 ± 5 years, $P<0.001$) and had been on dialysis for a longer duration (14 ± 5 vs 4 ± 4 years, $P<0.001$). In addition, elevated CaP and the use of calcium-based phosphate binders were both found to be associated with increased risks of calcification. In a follow-up CT scan of a subgroup

($n=10$) of the patients with calcification, the calcification score increased nearly 2-fold (125 ± 104 to 246 ± 216 , $P=0.02$), over a mean interval of 20 ± 3 months.²⁴ A large observational study²⁵ of 40 538 patients on HD found that serum phosphorous >5.0 , higher adjusted serum calcium concentrations, and moderate-to-severe hyperparathyroidism (parathyroid hormone [PTH] ≥ 600 pg/mL) were associated with an increased RR of death. The population-attributable risk percentage for disordered mineral metabolism taken collectively was 17.5% (largely due to the high prevalence of hyperphosphatemia).

Dyslipidemia

The Framingham Study essentially established the key role of dyslipidemia in the development of CVD; however, lipid profiles in patients with kidney disease, particularly with ESRD, are different from those in individuals without kidney disease. Total and low-density lipoprotein cholesterol (LDL-C) levels are often within the normal range, while high-density lipoprotein cholesterol (HDL-C) levels are decreased and plasma triglycerides are increased.²⁶ In addition, patients with renal disease also have greater oxidative stress, resulting in higher levels of oxidized glutathione and advanced glycation end products, as well as increased oxidation of lipoproteins.²⁷⁻³⁰ In fact, the oxidative change in LDL may be the initial and requisite step in the development of atherosclerosis. It results from the ingestion of oxidized LDL by scavenger monocytes, the subsequent enrichment of these cells with cholesterol esters, and the consequent formation of foam cells, the primary step in atherosclerosis.³¹⁻³³ Oxidized LDL may play a role in atherogenesis through other pathways as well, including an increase in leukocyte-endothelial interactions and monocyte chemotaxis, as well as endothelial cell toxicity and the stimulation of platelet-derived growth factor (PDGF).³³ Chronic HD patients have increased titers of auto-antibodies to oxidized LDL relative to age-matched controls;^{30,34} thus, LDL-C, the lipid parameter most often followed in the general population, may not be an optimal marker in patients with renal disease.²⁶

Given the increased atherogenesis in patients with renal disease, even in the presence of normal levels of LDL-C, several investigators^{26,35} evaluated the use of non-HDL-C, calculated by subtracting HDL-C from total cholesterol, as a potential marker for CV risk in patients with ESRD. Schreier et al³⁵ assessed triglyceride, intermediate-density lipoprotein (IDL)-C, HDL-C, and non-HDL-C levels in 50 patients with ESRD and 20 healthy controls. They found that the patients with ESRD had higher triglyceride levels, IDL-C, and very low-density lipoprotein (VLDL)-C than control subjects, but lower levels of HDL-C; however, there were no statistically significant differences in non-HDL-C between the groups. In receiver operator curve (ROC) analyses to evaluate which of the lipid parameters was the most useful biomarker for CVD risk, they observed that IDL-C and VLDL-C had the best ROC curves, while non-HDL-C had a curve close to the 45° line and, thus, was a poor marker for CVD risk. Nishizawa et al²⁶ assessed lipid variables as they relate to CV outcome data using multivariate Cox models and, in contrast to the findings of Schreier et al, found that non-HDL-C was an independent predictor of CV mortality in 525 patients on maintenance HD. As a result, although lipid abnormalities remain a key risk factor in the development of CV disease, a new set of standards must be established for patients with renal disease compared with disease-free individuals.

Hyperhomocysteinemia

Homocysteine (Hcy) is a sulfur-containing amino acid that is produced as a result of the transmethylation of methionine. Initial evidence suggested that elevations in plasma Hcy levels were associated with increased risks of ischemic heart disease or stroke. This evidence was based on retrospective case-control studies indicating higher Hcy levels in subjects with these disorders than in their age-matched controls.³⁶⁻³⁸ In 1995, an initial meta-analysis of observational studies on Hcy levels and CV disease reported that a 5 $\mu\text{mol/L}$ elevation in plasma Hcy resulted in a 70% increased risk of ischemic heart disease and an 80% elevation in stroke risk.³⁸ Since then, numerous prospective studies have examined the association between Hcy and CVD. A 5-year prospective study of 14 916 physicians revealed a 3.4-fold increased risk for MI in men with elevated Hcy levels.³⁹ The Homocysteine Studies Collaboration Group subsequently performed a meta-analysis of a number of prospective studies to evaluate the role of Hcy in populations that were apparently healthy at the time of enrollment.⁴⁰ A 25% decrease in plasma Hcy levels ($\sim 3 \mu\text{mol/L}$) was associated with an 11% (95% CI, 4% to 17%) reduction in risk of ischemic heart disease and a 19% (95% CI, 5% to 31%) reduction in stroke risk after adjustments for age, sex, systolic BP, total cholesterol, and the study in question. Elevations in plasma Hcy levels are a common metabolic consequence of renal failure and elevations of Hcy levels 2- to 3-fold are found in patients with renal dysfunction.⁴¹⁻⁴⁵ In fact, systemic Hcy concentrations increase with incremental decreases in GFR and this is observed not only among patients with established renal dysfunction,⁴¹⁻⁴⁵ but also in those with normal⁴⁶⁻⁴⁸ and supranormal⁴⁹ GFRs as well. The Oxford Healthy Aging Project⁵⁰ studied 1200 subjects ≥ 65 years old and found that, after adjusting for age, sex, and serum folate and vitamin B12 levels, a 1% difference in serum Cr was associated with a 1% difference in Hcy level. Prospective studies of patients with renal dysfunction suggest that such increases place these patients at an increased risk of CV events.^{51,52} A 10 $\mu\text{mol/L}$ increase in plasma Hcy concentrations — a level commonly seen in renal dysfunction — has been associated with a 1.8-fold increased risk of CV events.³⁸ The mechanism linking hyperhomocysteinemia to CV disease remains somewhat obscure; however, it appears to include direct endothelial injury,^{53,54} an increase in the oxidation of LDL,⁵⁵ an increase in thromboxane-mediated platelet aggregation,⁵⁶ a decrease in thrombomodulin expression and protein C activation,⁵⁷ and an increase in smooth muscle cell (SMC) proliferation.⁵⁸

Inflammation: high sensitivity C-reactive protein (hsCRP)

The association between inflammation, as measured by hsCRP, and atherosclerosis has been demonstrated through numerous prospective clinical trials.⁵⁹⁻⁶³ As a prognostic marker, hsCRP has proven useful in the setting of acute coronary syndromes, both for short-term, inpatient prognostication and for long-term outcome prediction, and as a primary-prevention screening tool for CV risk assessment.^{59,64-67} The CV effects are implicated by CRP mechanisms such as complement activation;^{68,69} induction of adhesion molecule expression (including vascular cell adhesion molecule-1 and selectin);^{68,70} an increase in the endothelial cell expression of plasminogen activator inhibitor-1;^{68,71} augmentation of T-cell-mediated damage to endothelial cells;^{68,70,72} stimulation of macrophages;^{68,73} reduction in nitric oxide (NO) generation;^{68,74,75} and inhibition of angiogenesis. Elevations of CRP are reported in >70% of patients receiving HD.

Wang et al⁷⁶ demonstrated an increased prevalence of coronary valve calcifications in ESRD patients with elevated CRP levels compared to those with decreased levels. The association between inflammation and calcification may be an inflammatory cell-mediated promotion of alkaline phosphatase activity in osteoclast-like cells found in the vascular beds that was demonstrated *in vitro*.^{77,78}

In conjunction with elevated cardiac troponin T (TnT) levels, hsCRP has an additive prognostic value.⁶⁷ A prospective multicenter trial of 224 hemodialysis patients by DeFilippi et al⁷⁹ assessed the predictive value of TnT and hsCRP levels for the long-term risk of all-cause mortality. They found that progressively higher levels of both biomarkers were associated with increased mortality compared with the lowest quartiles. After choosing arbitrary cutoff points for high and low levels of both biomarkers, they divided patients into 4 groups based upon whether they had low levels of both biomarkers, high levels of both, or 1 of the 2 was high, but the other was low. Over the study period, a 2.5-fold (95% CI, 1.5-4.0) increase in mortality was found in patients with high levels of both biomarkers compared with patients having low levels of both. In patients with elevations in only 1 of the 2 biomarkers, the increase in mortality risk was between the low-low and high-high groups. Furthermore, in patients with low levels of hsCRP, low and high levels of TnT did not result in a significant increase in mortality (63% vs 42% respectively; $P=0.22$), while among patients with high levels of hsCRP, high levels of TnT were associated with significantly higher mortality than those with low TnT (33% vs 65% respectively; $P=0.03$). In stratifying these findings by positive or negative family history and by white race, no interaction was indicated between these factors and the levels of the 2 biomarkers. Multivariable modeling revealed that both hsCRP and TnT were independent predictors of all-cause mortality along with age, white race, presence of diabetes, and body surface area, with no interactions detected between any of these variables and the levels of either biomarker.

Apple et al⁸⁰ investigated hsCRP concentrations in 399 patients with ESRD on HD and found an increase in mortality in those with hsCRP levels $\geq 1 \text{ mg/L}$. Mortality at 2 years was 18% for the group with normal hsCRP, in contrast to 44% in those with hsCRP $\geq 1 \text{ mg/L}$ ($P<0.001$). Their results revealed that hsCRP was an independent predictor of survival and the best biomarker for predicting all-cause mortality in comparison with cardiac troponin I (TnI) and TnT levels.

Bayes et al⁸¹ evaluated CRP levels in 94 patients with ESRD on HD receiving folic acid and vitamin B complex supplements. CRP was a significant predictor of mortality ($P=0.03$) and patients with CRP $<3 \text{ mg/L}$ had greater survival than those with higher CRP ($P=0.01$). Even after adjustment for age and anti-oxLDL antibody titre in a multivariate analysis, CRP continued to be a significant risk factor for mortality (odds ratio [OR] 3.1; 95% CI, 1.04-9.25; $P=0.04$).

Endothelial dysfunction: The role of nitric oxide (NO)

NO is an inhibitor of vascular smooth-muscle cell proliferation, platelet aggregation, and monocyte endothelial adhesion, all of which are critically involved in the development of atherosclerosis. NO is also a potent vasodilator and therefore a key regulator of blood flow.^{82,83} NO is synthesized by oxidation of the terminal nitrogen of the amino acid L-arginine by nitric oxide synthase (NOS). Asymmetric dimethyl L-arginine (ADMA), an analog of L-arginine, blocks the active site of

NOS and suppresses the synthesis of NO.^{82,83} Plasma concentrations of ADMA increase early in the course of renal disease, even in the presence of a normal GFR.⁸⁴ A 2.7 $\mu\text{mol/L}$ increase in plasma levels (ie, the average difference in concentration between patients with CKD and normal subjects), is associated with a >3-fold increase in risk for CV events.⁸⁵ *In vitro* evidence from endothelial cell cultures suggests that physiologic concentrations of ADMA (2-10 $\mu\text{mol/L}$) result in inhibition of NOS, with subsequent reductions in NO production.^{82,83} In addition, administration of ADMA to experimental animals results in systemic vascular resistance and increased BP.⁸⁶ Cultured endothelial cells treated with blood from patients with renal disease (with ADMA concentrations 4-fold higher than healthy controls) resulted in significant *ex vivo* inhibition of NO synthesis, giving further evidence to the physiologic relevance of this pathway.^{87,88} A cross-sectional study in patients without renal disease suggested that higher levels of ADMA were associated with increasing age, higher mean arterial pressures, and also with increasing thickness of the intima-media of the carotid arteries.⁸⁹⁻⁹¹ Several clinical studies have demonstrated increased levels of ADMA in patients with renal dysfunction.^{84,85,92-94} Given that this increase is seen even in patients with renal disease and a normal GFR (measured by inulin clearance), the mechanism is thought to be secondary to a disturbance of ADMA degradation by renal dimethylarginine dimethylaminohydrolase rather than decreased renal excretion.⁸⁴ Furthermore, in one study with ESRD patients, those with evidence of atherosclerotic disease had significantly elevated ADMA levels compared with the nonatherosclerotic group, suggesting that the ADMA levels were related to the presence of atherosclerosis.⁹³ New evidence suggests that increasing ADMA levels, and thus decreasing levels of NO, may play a role in the progression of renal disease.⁹⁵ With these findings, studies now are focused on therapies to restore endothelial cell function in patients with renal disease. Some research suggests that L-arginine, but not D-arginine, results in restoration of function in patients with ESRD.⁹⁶ In patients with peripheral vascular disease, L-arginine administration resulted in increased endogenous NO synthesis and ameliorated symptoms of intermittent claudication compared with healthy control patients.⁹⁷

Lipoprotein a

Lipoprotein a (Lp[a]; a similar lipoprotein to LDL, but with the addition of a glycosylated protein, apolipoprotein) has been linked with the development of atherosclerosis and elevated levels are found in the ESRD population.⁹⁸⁻¹⁰² Studies indicate that there are up to 6-fold higher levels in patients with severe nephrotic syndrome and up to 4-fold higher concentrations in dialysis patients, compared with healthy controls.¹⁰⁰⁻¹⁰⁹ In addition, Cressman et al¹⁰⁸ found a significant association between elevated levels and mortality from CVD in HD patients. Lp(a) levels have been shown to decrease by 45%-75% in patients who have undergone renal transplantation, further supporting an association with renal disease.^{98,110} The 2 postulated mechanisms for this increase in Lp(a) are: hepatic overproduction of albumin and other proteins produced by the liver (eg, apolipoproteins), secondary to reduced oncotic pressure stimulation

resulting from hypoalbuminemia; or, alternatively, a reduction in catabolism if, in fact, the kidney plays a role in this process.

Other mechanisms possibly play a role in the development of atherosclerotic plaque mediated by Lp(a). Lp(a) is ingested by macrophages, resulting in the formation of foam cells, and it can be oxidized, which increases its atherogenicity. Lp(a) also impairs the activation of plasminogen, resulting in enhanced vascular SMC proliferation.^{108,111-113}

Numerous studies have evaluated the role of Lp(a) in CV risk stratification.^{60,114-116} Bostom et al¹¹⁷ demonstrated the link between Lp(a), Hcy, fibrinogen, and CVD in patients with renal disease. *In vitro* experiments by Harpel et al¹¹⁸ suggested 1 mechanism for this link between these biomarkers, indicating that, in physiologic concentrations, Hcy in its reduced form changed the structure of Lp(a) to expose lysine-binding sites located on the apolipoprotein (a) segment, thus causing an increase in Lp(a) binding to fibrinogen.

Conclusions

CVD is the major cause of mortality in patients with renal disease.¹¹⁹ Numerous current investigations focus on risk stratification to identify and treat individuals at a high risk for disease. In renal disease, the search for risk factors and biomarkers of disease must assess the important confounders introduced by renal failure, ie, the effect of reductions in renal clearance. Elevations in substances usually cleared by the kidney may suggest CVD, but may also simply be a reflection of decreased renal clearance.

The link between inflammation and CVD has been demonstrated in numerous studies, and several substances (eg, TnT, CRP, and fibrinogen) reflect the degree of inflammation. Several new risk factors are under investigation to determine their exact roles and, although the understanding of cardiac risk stratification in patients with renal disease has improved, there is a great deal still to be investigated.

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