Cardio-Renal Syndrome Type 4: Epidemiology, Pathophysiology and Treatment

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Summary: Cardiovascular diseases such as coronary artery disease, congestive heart failure, arrhythmia, and sudden cardiac death represent the leading causes of morbidity and mortality in patients with CKD, increasing sharply as patients approach end-stage renal disease. The pathogenesis includes a complex, bidirectional interaction between the heart and kidneys that encompasses traditional and nontraditional risk factors, and has been termed cardio-renal syndrome type 4. In this review, an overview of the epidemiology and scope of this problem is provided, some suggested mechanisms for the pathophysiology of this disorder are discussed, and some of the key treatment strategies are described, with particular focus on recent clinical trials, both negative and positive.

Semin Nephrol 32:40-48 © 2012 Elsevier Inc. All rights reserved.

Keywords: Cardio-Renal syndrome, renocardiac syndrome, chronic kidney disease, cardiovascular disease, epidemiology, risk factors

Cardio-Renal syndrome (CRS) type 4, or chronic renocardiac syndrome, has been defined as “chronic abnormalities in renal function leading to cardiac disease” and recognizes the extreme burden of cardiovascular disease risk in patients with chronic kidney disease (CKD). CKD is divided into 5 stages according to level of dysfunction (defined by varying levels of glomerular filtration rate [GFR]) and/or presence of kidney damage (eg, diagnostic imaging and/or urinary abnormalities). With increasing levels of CKD, culminating with dialysis dependence as a component of stage 5 CKD, the relationship between CKD and cardiac disease is complex and graded. With the steady growth of CKD in the population, the expectation is that CRS type 4 will increase in lockstep with significant implications at both an individual and societal level.

EPIDEMIOLOGY

The association between CKD and increased risk for cardiac disease and events has long been recognized. In the current era, cardiovascular causes represent close to 50% of deaths in all age groups of CKD patients. Many patients progress through CKD and ultimately initiate dialysis with significant underlying cardiovascular disease, in part owing to the aging population and high prevalence of diabetes and other traditional risk factors such as hypertension and dyslipidemia. Illustrating this point, in the Hemodialysis Study, cardiovascular disease was highly prevalent, in nearly 80% of subjects, and closely related to age, diabetes, and dialysis duration. More than a third of subjects were hospitalized for a cardiovascular event, many of these were for acute coronary syndrome/coronary insufficiency. In addition, the majority of cardiac deaths were believed to be secondary to ischemia.

For lesser degrees of CKD, the risk of cardiovascular disease remains present, albeit somewhat diminished. However, the association follows a dose-response relationship, becoming increasingly evident as GFR decreases to less than 60 mL/min/1.73 m². Systematic reviews on this topic reveal significant heterogeneity in the estimates of strength of this association, largely owing to quantitative, not qualitative, differences, likely reflecting differences in study design and population. Early reports suggested that the risk related to CKD likely was accounted for by comorbid conditions, but with larger studies it has become clearer that statistical adjustment for known cardiovascular risk factors can attenuate the risk estimates somewhat, but does not negate them entirely. The risk of all-cause mortality in a meta-analysis by Tonelli et al, which included nearly 1.4 million subjects, increased significantly as GFR declined, as depicted in Figure 1. The estimated relative odds for death associated with GFR of 80, 60, and 40 mL/min/1.73 m² increased in a stepwise manner to 1.9, 2.6, and 4.4, when compared with a referent population with preserved GFR (100 mL/min/1.73 m²). In the largest single study published to date, Go et al examined more than 1.1 million adults in a population-based cohort, and identified a stepwise increase in hazard ratios for cardiovascular events (which the authors defined as hospitalization for
coronary disease, heart failure, stroke, or peripheral arterial disease) and all-cause mortality at each declining interval of GFR. These researchers performed sophisticated multivariable analyses to account for many potential confounding or influential variables, including all traditional risk factors, and still identified GFR as a strong, independent factor, as depicted in Figure 2. After multivariable adjustment, the risk of an adverse cardiovascular outcome, when compared with a referent group with preserved GFR, was increased by 43% in those with a GFR of 45 to 59 mL/min/1.73 m² and by 343% in those with a GFR of less than 15 mL/min/1.73 m². Furthermore, the mortality rate of subjects with stage 5 CKD but who were not dialysis-dependent was comparable with rates of mortality in dialysis patients.

There are a number of potential explanations for these observations. First, the persistence of the association between CKD and cardiovascular disease after multivariable analysis could be the result of residual confounding by factors that contribute to both CKD and cardiovascular disease. Second, the fact that even a mild decrease in GFR is associated with cardiovascular disease likely relates to the fact that subtle degrees of chronic vascular disease may lead to intrarenal atherosclerotic disease. In other words, declining kidney function from ischemic nephropathy may simply be the canary in the coalmine, reflective of more widespread vascular disease, in the same manner that presence of microalbuminuria has been viewed as a marker of more widespread endothelial dysfunction. Third, these observations may be suggestive that the uremic milieu contributes in a cumulative fashion to increased risk beyond that of more traditional risk factors, which by themselves do not estimate the risk of adverse cardiovascular outcomes adequately.10

Whatever the mechanism(s), the presence of CKD not only leads to an increased risk of adverse cardiovascular events, but it also influences the outcome of such events. For instance, the 2-year mortality rate after myocardial infarction in patients with CKD stage 5 is estimated to be 50%,11 which is more than double the expected 10-year mortality rate experienced by the non-CKD population suffering a myocardial infarction. Gibson et al12 analyzed more than 13,000 patients enrolled in several clinical trials of non-ST elevation acute coronary syndromes. Patients were stratified according to GFR on admission, and this was associated strongly and independently with 30-day and 6-month mortality. For every decrease of GFR by 10 mL/min/1.73 m², there was a corresponding increase in 6-month mortality by 16%, along with increases in the risk of recurrent myocardial infarction, recurrent ischemia and stroke, and hemorrhagic complications.

In addition to ischemic coronary events, functional and structural abnormalities on echocardiography are increased disproportionately in CKD and end-stage renal disease (ESRD) patients. In a groundbreaking study of patients newly started on dialysis and surviving a minimum of 6 months, investigators found a startling preponderance of abnormal echocardiographic findings, including 15% with overt systolic dysfunction, 74% with left ventricular hypertrophy, and 36% with left ventricular chamber dilatation.13,14 It is estimated that congestive heart failure is diagnosed clinically in approximately 25% of hemodialysis patients and 18% of peritoneal dialysis patients each year.10

Investigators also have discovered that lower stages of CKD are associated with the development of congestive heart failure. The Atherosclerosis Risk in Communities study investigators analyzed data from nearly 15,000 subjects enrolled in a large, population-based study of US adults and who were followed up with serial estimates of GFR.15 They excluded subjects with pre-existing heart failure at baseline, and examined the association between baseline GFR and incident heart failure, using both unadjusted and adjusted analyses. There was a marked increase in incident heart failure for subjects with a GFR less than 60 mL/min/1.73 m². Cox proportional hazards modeling yielded an adjusted relative hazard of incident heart failure of 1.10 (95% confidence interval [CI], 0.97-1.26) for cohort subjects with a GFR of 60 to 89 mL/min/1.73 m² and 1.94 (95% CI, 1.49-2.53) for those with a GFR less than 60 mL/min/1.73 m² (compared with

![Figure 1. Risk for all-cause mortality in CKD according to baseline GFR from 42 cohorts. Risks are expressed as proportions. Plotted using data from Tonelli et al.7](image1)

![Figure 2. Adjusted hazard ratios for cardiovascular events according to baseline GFR. Adjusted for multiple variables (see text). Plotted using data from Go et al.9](image2)
GFR ≥90 mL/min/1.73 m²). Despite adjustment for an extensive list of known risk factors for cardiovascular disease, a GFR consistent with stage 3 CKD or worse resulted in a doubling of the risk of new-onset congestive heart failure. Taken together, these observations are consistent with the notion that progressive kidney disease, through a variety of mechanisms, can lead to significant functional and structural changes in the heart, culminating in the clinical outcome of congestive heart failure.

An additional threat to the patient with CKD, and in particular ESRD, is posed by cardiac arrhythmias. It is estimated that as many as 30% of deaths in ESRD patients are related to cardiac arrhythmia or sudden death. In a study of more than 12,000 prevalent dialysis patients, Ganesh et al found that the highest cause of mortality was sudden death at 27%, with other cardiovascular deaths contributing an additional 20%. In lesser stages of CKD, Pun et al examined outcomes in a large study of patients undergoing cardiac catheterization, and found that for each 10-mL/min/1.73 m² decline in GFR, there was an increase in the hazard ratio of sudden cardiac death by 11% (95% CI, 6%-17%). It is easy to speculate that most causes of sudden cardiac death are caused by lethal ventricular arrhythmia. Evidence from intradialytic Holter monitoring certainly provides credence to that supposition with a high incidence of ventricular ectopy. Burton et al examined 40 prevalent hemodialysis patients who were free of significant left ventricular dysfunction, and performed both intradialytic Holter monitoring and echocardiography. They detected premature ventricular contractions in 63% of patients during dialysis, with 25% of these being classed as frequent or very frequent. In the post-dialysis phase the ectopy diminished markedly. There was an association between ectopic frequency and lower post-dialysis potassium level, as well as with a history of ischemic heart disease. Interestingly, a high percentage of subjects (67%) developed regional wall motion abnormalities on echocardiography during the dialysis treatment, and in this group the frequency of ventricular ectopy was almost doubled during dialysis compared with the post-dialysis period (0.26% versus 0.16%; P < .001).

In addition to sudden death and life-threatening ventricular arrhythmias, more recently attention has been turning to the problem of atrial fibrillation in CKD and ESRD patients. This rhythm disturbance has been shown to be prevalent, and it poses a significant risk for thromboembolic stroke and other occlusive events. By using claims data, Winkelmayer et al examined approximately 2.5 million dialysis patient observations and found an increasing prevalence of medical claims for atrial fibrillation, exceeding 10% in the most recent years, in part related to an aging dialysis population. One-year mortality in those with atrial fibrillation increased from 19.3% to 38.9%, which was significant in both unadjusted and adjusted analyses.

To examine this problem in subjects with lesser stages of CKD, the REasons for Geographic and Racial Differences in Stroke study investigators examined rates of atrial fibrillation in nearly 27,000 participants of a population-based cohort study. With increasing stage of CKD, these investigators found increasing rates of electrocardiogram-detected atrial fibrillation, reaching a prevalence of 4.2% in the CKD 4 and 5 subjects. After multivariable adjustment for a host of important confounders, the odds ratios for atrial fibrillation was increased significantly in all CKD stages (1 through 5), and reached 2.86 (95% CI, 1.38-5.92) for the CKD 4 and 5 subjects compared with subjects free of CKD. In a population of patients who were enrolled in the Chronic Renal Insufficiency Cohort by virtue of having kidney disease, investigators identified a prevalence of atrial fibrillation of 18%.

**PATHOPHYSIOLOGY**

Having identified the scope and significance of this burden of CRS type 4, it is important to examine the potential mechanisms that could be responsible for the increase in cardiovascular disease, congestive heart failure, and arrhythmia. In terms of ischemic heart disease and congestive heart failure, as mentioned before, the relationship between advancing kidney disease and heart disease may be one of shared or common risk factors, a reflection of widespread vascular disease and endothelial dysfunction, and/or the toxic effect of the uremic milieu. Furthermore, the presence of ischemic heart disease itself can contribute to congestive heart failure, and predispose to arrhythmia. Figure 3 depicts a proposed schematic whereby progressive kidney damage leads to cardiac damage through a variety of mechanisms and factors, both traditional and nontraditional, culminating in some of the unique risks that ESRD patients experience as a result of the dialysis procedure itself.

It is certainly true that individuals who are exposed to the usual constellation of what we currently view as potentially modifiable risk factors for cardiovascular disease (smoking, hypertension, dyslipidemia, age, and diabetes) also are exposed to factors that contribute to the progression of renal disease. Hence, as a group, CKD patients represent a population with a higher-than-average burden of baseline cardiovascular risk. In terms of nontraditional risk factors, a number of biomarkers show progressive increases as GFR decreases, such as troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type I, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, ischemia-modified albumin, and others. Many of these have been shown to have independent associations with subsequent vascular disease in the CKD population. For example, B-type natriuretic peptide and the related N-terminal pro-B-type natriuretic peptide both are increased significantly in CKD patients compared with age- and sex-matched subjects with normal renal function, even...
without overt heart failure. However, rather than simply attributing this to issues of reduced clearance, it is likely that these reflect the contribution of myocardial wall stress from hypertension and volume overload, ventricular hypertrophy, subclinical ischemia, cardiac remodeling, and fibrosis. In the case of C-reactive protein, this well-known biomarker for inflammation is associated so strongly with vascular disease that it has been proposed that it is not only a biomarker, but potentially causally related to vascular disease. Asymmetric dimethylarginine inhibits nitric oxide synthesis, leading to endothelial dysfunction, insulin resistance, and accelerated atherosclerosis, and was found independently to predict adverse outcomes in CKD patients.

Particular focus has been paid in recent years to the role of phosphate retention and related disorders falling under the rubric CKD mineral and bone disorder (CKD-MBD). This disorder has been characterized by early disruption of skeletal homeostasis, phosphate retention, diminished active vitamin D, and subsequent hyperparathyroidism. Of relevance to CRS type 4, vascular calcification ensues as the vasculature and cardiac valves literally undergo a phenotypic transformation and begin to ossify. Specifically, vascular...
smooth muscle cells undergo a transformation to cells that share characteristics with osteoblasts, expressing many of the same cellular markers and generating similar cellular products required for bone production and maintenance.37

The graded nature of the relationship between GFR and cardiovascular disease suggests a dose-response effect of the uremia milieu. Whether this is a direct effect of specific uremic toxins or the combined effect of a number of metabolic and physiologic derangements is unknown. Some of the potential contributors include anemia, advanced glycation end-products, calcium-phosphate product, nutrition, chronic volume overload, cardiac hypertrophy, chronic inflammation, insulin resistance, hyperhomocysteinemia, and changes to lipid metabolism.38-46 As renal function declines to the point at which uremia ensues, we begin to see the gradual accumulation of a number of toxins such as β2-microglobulin, guanidines, phenols, indoles, aliphatic amines, furans, polyols, nucleosides, dicarboxylic acids, carnitines, leptin, parathyroid hormone, erythropoiesis inhibitors, and proinflammatory cytokines.44,46-48 This primordial soup of uremic toxins is believed to result in heightened oxidant stress, inflammation, and accelerated atherosclerosis, and likely contributes to the sharp increase in cardiovascular morbidity and mortality experienced by ESRD patients.33,45,49-55

With respect to the development of congestive heart failure, a proposed mechanism includes pressure and volume overload, which increases proportionate to the decline in renal function. Hypertension, valvular heart disease, and altered compliance of the blood vessels, perhaps in part owing to CKD-MBD, contribute to pressure overload, whereas anemia, excess sodium, and, hence, extracellular fluid all contribute to volume overload. In the hemodialysis patient with a functioning arteriovenous shunt, this is a further potential contributor to volume overload.56 This increase in cardiac workload results in compensatory hypertrophy. This in turn results in excessive cardiac myocyte work relative to the supply of oxygen. Inevitably, myocyte death and fibrosis ensues, with chamber dilatation and systolic dysfunction.10,45

The increased likelihood of cardiac arrhythmias is multifactorial. With progressive decline in kidney function, maintenance of electrolyte homeostasis is impaired. High rates of coronary disease, hypertension, heart failure, and comorbid illness contribute to arrhythmia. Left ventricular hypertrophy is associated with prolongation of the QT interval, and dialysis patients show significant prolongation of the QT interval.16 Furthermore, in the ESRD population, and specifically those on hemodialysis, the rapid shifts in serum potassium and blood pressure/volume related to the dialysis procedure itself, with resultant regional wall motion abnormalities consistent with ischemia, make this a highly arrhythmogenic procedure.19 Consistent with the risk associated with the stresses of hemodialysis itself, a number of investigators have identified the pattern of increasing risk after the longer weekend interdialytic interval in patients undergoing hemodialysis three times per week, during which fluid and electrolyte shifts would be expected to be at their most extreme. In addition to these acute shifts, patients with advanced CKD also suffer from sympathetic activation and loss of vagal regulation of heart rate. In a study of more than 200 patients enrolled in the Frequent Hemodialysis Network study, Chan et al57 examined the relationship between heart rate variability and left ventricular mass, in addition to a number of other clinical and demographic variables. These investigators found a striking relationship between cardiac autonomic dysfunction and left ventricular hypertrophy, although these were cross-sectional observations, so the relative influence of one upon the other remains to be determined in longitudinal follow-up evaluation.

**TREATMENT**

The management of CRS type 4 requires a multidisciplinary, multifaceted approach. Because of the presence of so-called traditional cardiovascular risk factors, these represent an obvious target for therapy, as they would in the general population. These typically are divided into fixed factors that are inherent to the individual, such as genetic factors, sex, age, and family history, and those that are acquired and therefore may be potentially modifiable, such as lipids, lifestyle factors, and diabetes. It is noteworthy, therefore, that in a large multinational case-control study of close to 30,000 subjects, Yusuf et al58 found that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, dietary factors, alcohol, and physical activity accounted for more than 90% of the population attributable risk of myocardial infarction worldwide regardless of sex and age. These data would suggest that a significant portion of the risk faced by CKD and ESRD patients should be modifiable to some degree,59 although this typically has been a very challenging population in which to show efficacy of risk-lowering strategies.

Additional management strategies have mostly targeted those risk factors that are particular to, or exaggerated in, CKD patients such as anemia, hypertension, CKD-MBD, dyslipidemia, smoking, albuminuria, hyperhomocysteinemia, and malnutrition. A number of these, in particular anemia, homocysteine, and CKD-MBD, have held promise based on observational studies that have shown convincing associations with adverse cardiovascular risks. Sadly, few large-scale randomized controlled trials have been performed in the ESRD population, and of those most have turned out to be negative.

In terms of erythropoiesis-stimulating agents, despite a strong suggestion of benefit to anemia management in observational studies,60 a number of studies in predialysis patients yielded disappointing results. In the Correction of Hemoglobin and Outcomes in Renal Insufficiency and Cardiovascular Risk Reduction in Early Anemia Treat-
ment with Epoetin Beta studies, the targeting of a higher hemoglobin level did not improve cardiovascular outcomes. The more recent Trial to Reduce Cardiovascular Events With Aranesp Therapy study used darbepoietin to target a hemoglobin level of 13 g/dL (130 g/L) compared with “rescue” therapy once the hemoglobin level decreased to less than 9 g/dL (90 g/L) in a study of more than 4,000 type 2 diabetic patients with CKD and anemia. There was no difference in the composite primary outcome of death or a cardiovascular event, or death or a renal event, however, there was nearly a doubling of the risk of fatal and nonfatal stroke. In a study of more than 1,200 ESRD patients with known cardiac disease, the Normal Hematocrit Trial was stopped early because of a nonsignificant but worrisome increase in deaths in the group with the target hematocrit of 42%. A recent systematic review and meta-analysis of erythropoiesis-stimulating agent therapy estimated the risk of stroke associated with this therapy to be increased approximately 1.5-fold, with higher risk of hypertension, and possible increased risk of death, serious cardiovascular events, and ESRD with higher hemoglobin targets. All of these studies combined have certainly led to a careful re-examination of hemoglobin targets in this population.

Increased homocysteine has been associated consistently with adverse cardiovascular outcomes in many observational studies, particularly in the CKD population, and decades of basic science research and animal studies have supported a potential role in cardiovascular disease. Given its close inverse relationship to GFR, it has been an obvious target for intervention therapies. Furthermore, folic acid, vitamin B6, and vitamin B12 have been an obvious target for intervention therapies. Given its close inverse relationship to GFR, it has been an obvious target for intervention therapies. Furthermore, folic acid, vitamin B6, and vitamin B12 in combination are an effective and inexpensive strategy to decrease homocysteine in most populations. However, trials of multivitamins in ESRD patients have been disappointing, with negative results from a number of well-conducted clinical trials. This could be explained partly by the fact that vitamins fail to normalize homocysteine in ESRD patients, and toxicity from the vitamins themselves potentially could offset any theoretical benefit; hence, there is an interest in exploring nonvitamin alternatives to decrease homocysteine in dialysis patients. In less severe degrees of CKD, House et al conducted a randomized trial of vitamins in patients with overt diabetic nephropathy. These investigators found that the vitamin intervention led to a faster decline in kidney function, and a doubling of the composite event rate of major adverse cardiovascular event or death, with a hazard ratio of 2.0 (95% CI, 1.0-4.0; P = .04). Disheartening results of the Folic Acid for Vascular Outcome Reduction In Transplantation trial in renal transplant recipients confirmed that vitamin therapy to decrease homocysteine has no role to play in reducing cardiovascular risk in CKD patients.

CKD-MBD has been linked to the progression of cardiac disease and CRS type 4, and investigators have shown a link between even mild degrees of renal injury and vascular calcification, so strategies to control phosphate, control parathyroid hormone (PTH), and vitamin D analogues have been mainstays of therapy in this regard. In terms of phosphate binding, a recent Cochrane systematic review concluded that sevelamer hydrochloride and lanthanum carbonate were not superior to calcium salts for phosphate control, and although several of the studies showed improvements in the surrogate outcome of vascular calcification, this was not associated with any significant reduction in cardiovascular morbidity and mortality. With respect to the meta-analysis of sevelamer versus calcium salts, the risk ratio for all-cause mortality was 0.73 (95% CI, 0.46-1.16). A subgroup of patients in one study with higher cardiovascular risk by virtue of age did have an improved outcome with sevelamer. This was a subgroup analysis, and although the investigators did prespecify the analytic plan of evaluating a number of interactions with treatment, including age, they did not correct for multiple comparisons, and acknowledge that this could cast a shadow of doubt on the validity of this finding.

High PTH as a result of CKD-MBD also has been associated with adverse cardiovascular outcomes. In a health technology assessment and systematic review of cinacalcet, a calcimimetic drug that lowers PTH, the investigators found significantly lower PTH and decreased hospitalizations related to cardiovascular disease. Whether or not this approach can reduce hard cardiovascular endpoints and mortality is the objective of an ongoing large randomized trial, the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events study, whose primary outcome measures include all-cause mortality or nonfatal cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event). This study is expected to be completed by the end of 2011.

Vitamin D–receptor activation is another disorder related to CKD-MBD, and insufficient activation also may contribute to CRS type 4. Vitamin D–receptor activation is a negative regulator of the renin-angiotensin-aldosterone axis, hence vitamin D analogs theoretically could inhibit this axis while providing control of PTH and activating vitamin D receptors. This holds promise in the management of CRS type 4. A recent editorial highlighted the need to examine this strategy further with more than just surrogate outcomes.

The use of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) has been one of the greatest success stories in the primary and secondary management of cardiovascular disease risk. Two high-profile trials in ESRD patients were negative, the Die Deutsche Diabetes Dialyse Studie (4D) trial using atorvastatin and the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) using rosvastatin. However, the subsequent Study of Heart
and Renal Protection (SHARP) trial included 3,023 ESRD patients and 6,247 CKD patients not on dialysis, and preliminary results showed a significant benefit of the combination of simvastatin and ezetimibe. Treatment lowered the risk of major atherosclerotic events, with a risk ratio of 0.83 (95% confidence interval 0.74 - 0.94, \( P = .0022 \)). Consistent with the negative findings of 4D and AURORA, the subgroup of ESRD patients in SHARP seemed to experience less benefit compared with the lesser degrees of CKD, and all-cause mortality was unaffected.

In the aforementioned Frequent Hemodialysis Network study, 245 patients were randomized to three times weekly (conventional) or six times weekly (frequent) hemodialysis, and followed up for 12 months, with coprimary composite outcomes as follows: (1) death or change in left ventricular mass, as assessed by cardiac magnetic resonance imaging, and (2) death or change in the physical-health composite score of the RAND 36-item health survey. The frequent dialysis group had a significant benefit in both outcomes, and the hazard ratio for death or increased left ventricular mass was 0.61 (95% CI, 0.46-0.82). Important improvements in serum phosphate, control of hypertension, and avoidance of intradialytic hypotension also were noted in the frequent dialysis group. Although the study was underpowered to examine differences in death or major cardiovascular events, these exciting results, coupled with previous observations regarding the relationships between left ventricular mass, intradialytic hypotension, ischemia, and arrhythmia, would strongly suggest that frequent dialysis may have an important role to play in the prevention and treatment of CRS type 4.

CONCLUSIONS

Type 4 CRS or chronic renocardiac syndrome represents a burden of cardiovascular diseases under which CKD and ESRD patients suffer that is disproportionate to the risk expected based on comorbid illnesses and Framingham risk profile. Higher than expected rates of ischemic cardiac events, congestive heart failure, left ventricular hypertrophy, cardiac arrhythmias, and sudden death plague all levels of CKD, increasing steeply as kidney function declines. The pathophysiology of CRS type 4 is multifaceted, progressive, and of course bidirectional. Large randomized trials of interventions that were predicted to be fruitful based on sound observational studies have been mostly negative, or, if positive, their results have been muted compared with the general population. Although these results could be cause for a sense of cynicism, an alternative viewpoint is that CRS type 4, particularly in the ESRD population, is a complex disorder that arises over a prolonged period. As such, it is perhaps to be expected that studies of single interventions, regardless of the strength of their biological plausibility and statistical power, are largely doomed to come up short, because each targeted risk factor represents a miniscule tip of a large and deadly iceberg. One need only look to the example set by the Steno-2 investigators, who showed the significant and sustained benefits of intensive intervention with multiple drug combinations aggressively targeting known risk factors, along with behavior modification and lifestyle intervention, reducing the risk of death in high-risk type 2 diabetic patients by nearly half. It is likely for CRS type 4 that a similar approach, with aggressive management of multiple risk factors, with equally aggressive lifestyle modification, will be required to change the course of this devastating syndrome, and future trials of such multi-pronged strategies are sorely needed.

REFERENCES


