Cardiovascular Issues in Dialysis Patients: Challenges and Newer Insights

Osler J. Guzon, Kevin C. Dellsperger

Cardiovascular disease is the leading cause of death among people with chronic kidney disease. In this review, we provide an update on how the association between renal dysfunction and cardiovascular disease goes beyond traditional cardiac risk factors, and we consider some of the key studies that link renal dysfunction with the development of cardiovascular morbidity and mortality. Unique challenges facing clinicians that treat patients with end-stage renal disease, particularly patients on peritoneal dialysis, are discussed. The potential relationship between endothelial progenitor cells and the renal–cardiovascular relationship are explored. We propose that moderate-to-severe renal dysfunction should be considered a coronary artery disease equivalent and that further investigation needs to be conducted to understand this key relationship.

Key words
Stem cells, cardiovascular disease, chronic kidney disease, endothelial progenitor cells

Introduction
In the United States, the number of people with chronic kidney disease (CKD) continues to climb steadily. Recent statistics from the U.S. Renal Data System (1) suggest that, although the rate of increase in the incidence of end-stage renal disease (ESRD) is slowing, an aging baby-boom population and growth of the senior demographic will increase the overall number of patients with ESRD. The number of people requiring renal replacement therapy (RRT) will also correspondingly rise. The direct and indirect impacts of these patients with CKD—particularly those on RRT—will be staggering. In this review, we identify some of the challenges facing clinicians and discuss how newer insights may lead to fundamental changes in the treatment of patients with ESRD.

Discussion

Challenges
The major cause of death in patients with ESRD, particularly those on RRT, is complications from atherosclerotic cardiovascular disease (ASCVD). Perhaps the single most important challenge for practitioners managing patients with CKD is the prevention or early diagnosis of cardiovascular disease. Recently, several key studies have linked kidney dysfunction with ASCVD. These studies not only demonstrate an association, they reveal a rather alarming relationship even at mild levels of renal dysfunction.

The first study to prospectively assess the relationship between varying levels of kidney function and risk for ASCVD was the Atherosclerosis Risk in Communities (ARIC) study (2). In this community-based study of nearly 16,000 people between 45 and 64 years of age, glomerular filtration rate (GFR) was estimated using the formula developed in the Modification of Diet in Renal Disease (MDRD) study (3). Subjects were stratified based on GFR (15 – 59, 60 – 89, or 90 – 150 mL/min/1.73 m²). After a multivariate analysis, Manjunath and colleagues showed that a GFR below 90 mL/min/1.73 m² is an independent risk factor for ASCVD and de novo ASCVD. In particular, subjects whose GFR was less than 60 mL/min/1.73 m² had an all-cause mortality nearly four times that of subjects with a normal GFR (29 events vs. 7.7 events per 1000 person–years). The authors of this study also showed that the rate of ASCVD events in subjects with a GFR less than 60 mL/min/1.73 m² was nearly three times that of subjects with a GFR greater than 90 mL/min/1.73 m² (25.6 events vs. 8.9 events per 1000 person–years).

Further corroborating the ARIC results, Go et al. (4) analyzed the Kaiser Permanente Renal Registry data...
for subjects with one or more outpatient creatinine level determinations. Approximately 1.1 million subjects passed the study’s inclusion and exclusion criteria. These were stratified according to GFR (using the formula from the MDRD study) and followed for a median of 2.84 years. Using subjects with a GFR greater than 60 mL/min/1.73 m² as the reference group, Go and colleagues found that the adjusted hazard ratio for death from any cause, for any cardiovascular event, and for any hospitalization trended upward as renal function declined, rising steeply as estimated GFR fell below 45 mL/min/1.73 m². The age-adjusted cardiovascular event rates were 2.11, 3.65, 11.29, 21.80, and 36.60 per 100 person–years for estimated GFRs of >60, 45 – 59, 30 – 44, 15 – 29, and <15 mL/min/1.73 m² respectively. Go et al. also noted that the progression to ESRD requiring either maintenance dialysis or a renal transplant was 0.31% and that 12% of subjects had a cardiovascular event during follow-up.

Based on the results of the Second National Health and Nutrition Examination Survey (5), the ARIC study, and the Kaiser Permanente Renal Registry, even mild-to-moderate renal dysfunction portends a high risk of a major adverse cardiac event (Table I). The incidence of ASCVD is similar if not greater than that for people with diabetes mellitus (6). Thus, ESRD should be considered a vascular disease equivalent, as is currently the case with diabetes mellitus.

### Potential mechanisms

The reasons that people with CKD are at an increased risk of ASCVD and death have been studied extensively. Certainly, some of the risk for development of heart disease in the dialysis population is attributable to a higher prevalence of traditional ASCVD risk factors in people with ESRD. Other influences, such as uremic dyslipidemia (7), sympathetic overactivity (8), disruption of calcium–phosphate homeostasis (9), hyperhomocysteinemia (10), hypoalbuminemia (11), inflammation (12), and malnutrition (13), play an important role in the development of clinical ASCVD in the dialysis population. Some authors have suggested that the type of renal replacement therapy has a great influence on the development of ASCVD and progression to cardiovascular morbidity and mortality.

In the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study (14), researchers compared the survival rates of patients receiving PD and those receiving HD. In this national prospective cohort study of 1041 incident dialysis patients at 81 dialysis centers in 19 U.S. states, approximately 25% of those enrolled received PD. The CHOICE authors found that, despite having a better case-mix profile at initiation of RRT, patients receiving PD had a higher risk of death than did patients receiving HD. After adjustment for demographic characteristics, clinical and treatment factors, and laboratory values, the relative risk of death in the PD patients versus the HD patients was 1.39 [95% confidence interval (CI): 0.64 to 3.06] at the 1-year follow-up and 2.34 (95% CI: 1.19 to 4.59) at the 2-year follow-up. Jaar and colleagues noted several previously described potential mechanisms that may explain the unique risk of ASCVD in patients receiving PD. Among those contributing factors is a worse lipid profile. People receiving PD have smaller, more dense low-density

### Table I Relative risk of death and cardiovascular events versus renal function

<table>
<thead>
<tr>
<th>Estimated GFR (mL/min/1.73 m²)</th>
<th>Kaiser–Permanente *</th>
<th>ARIC *</th>
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<tbody>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>CV event</td>
</tr>
<tr>
<td>≥60</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>45–59</td>
<td>1.2</td>
<td>1.4</td>
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<tr>
<td>30–44</td>
<td>1.8</td>
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<tr>
<td>15–29</td>
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<td>2.8</td>
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<tr>
<td>&lt;15</td>
<td>5.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

* GFR > 60 mL/min/1.73 m² was the index group in the Kaiser–Permanente study; GFR = 60 – 89 mL/min/1.73 m² was used as the index group in the ARIC study.

ARIC = Atherosclerosis Risk in Communities; GFR = glomerular filtration rate; CV = cardiovascular; NA = not available.
lipoprotein particles than do people receiving HD, and also more very-low-density lipoprotein particles and lipoprotein(a). Another possible explanation is the gradual loss of peritoneal integrity (13,14); this mechanism raises the possibility of inadequate dialysis and volume overload, which in turn leads to elevated blood pressure, left ventricular hypertrophy, and heart failure. Although controversial, the CHOICE study underlines the importance of elucidating mechanisms of underlying cardiovascular risk in patients with ESRD regardless of method of RRT.

Available studies suggest a higher risk of ASCVD in patients receiving PD than in those receiving HD, but truly randomized trials that compare methods of RRT are few. Initiating well-designed randomized trials would allow practitioners to better understand how the differences between PD and HD influence clinical outcome. However, given the necessary randomization, such studies are unlikely to ever be conducted.

Newer insights: endothelial progenitor cells and kidney disease

Advances in basic science and laboratory techniques are allowing scientists to understand the interaction between renal failure and cardiovascular disease better than ever before. Among the more promising nontraditional components in this renal–cardiovascular disease paradigm are endothelial progenitor cells (EPCs). Endothelial progenitor cells most frequently differentiate from bone-marrow-derived CD133+ and CD34+ hematopoietic stem cells. The EPCs have been shown to play an important role in neovascularization and endothelial repair. They are mobilized by cytokines such as vascular endothelial growth factor (VEGF), erythropoietin (EPO), and granulocyte colony stimulating factor to begin the repair process. The mechanisms of action of these cytokines are not fully understood, but it has been postulated that EPCs are attracted to areas of injury and act in ways that lead to improved clinical outcomes in patients with ischemic cardiomyopathy and in those in the peri-myocardial infarction state. The EPCs are thought to differentiate into structures of the vascular endothelium or (through paracrine effects) to promote a cytokine response favorable to cellular survival and neoangiogenesis. Epidemiologic studies have shown that lower levels of circulating EPCs are associated with a higher incidence and burden of atherosclerotic cardiovascular disease (15).

De Groot et al. (16) documented several key observations regarding the role of EPCs in patients with CKD. In their study comparing 46 patients with ESRD to 46 age-and-sex-matched controls with normal renal function, De Groot showed that plasma EPO level and absolute number of circulating EPCs per high-power field are both significantly lower in patients with uremia than in a matched control group. Second, using a multiple-regression analysis, De Groot and colleagues found CD34+ hematopoietic stem cell and plasma EPO levels to be independent predictors of the total number of EPCs in the study cohort. Finally, in complementary in vitro studies, the authors also found that uremia inhibits EPC differentiation and migration. They concluded that EPO likely plays an important role in generating an efficient EPC response, a response already blunted by uremia in patients with ESRD.

Bahlmann from the same author group examined the latter hypothesis in two studies (17,18), following 11 patients with ESRD. In those patients, plasma hematopoietic stem cell levels were measured before and after administration of darbepoetin alfa, a recombinant human EPO (rHuEPO) analog. Bahlmann et al. noted a significant increase in the number of hematopoietic stem cells after rHuEPO administration, but plasma levels of two cytokines thought to play a role in neoangiogenesis—basic fibroblast growth factor and VEGF—were unchanged. Other elegantly conducted studies have supported these findings.

For instance, Choi et al. examined 44 patients on HD who had no history of ASCVD and compared several laboratory measurements in those patients to measurements in 30 matched controls. The total number of circulating EPCs (baseline measurement), the EPC migratory capability, migratory augmentation after VEGF administration, and EPC incorporation were all significantly poorer in patients receiving HD than in the control group. Choi’s group also found 10-year coronary artery disease risk to be inversely related to the number of circulating EPCs regardless of the patient’s renal function, and showed that RRT can increase the number of EPCs to levels similar to levels seen in patients without renal failure (19).
Conclusions

Moderate-to-severe CKD is a major risk factor for the development of ASCVD and thus warrants aggressive scientific study, particularly with regard to the causal relationship between renal dysfunction and cardiovascular events. Patients with moderate or more severe renal dysfunction need to be treated aggressively to optimize lipid, hematocrit, and blood pressure values. Further investigation into the differences in clinical outcome between patients on peritoneal dialysis and those on hemodialysis should also be promoted.

Finally, recent data suggest that EPCs are critical to the renal–cardiovascular disease interaction, and a strong relationship has been demonstrated between low levels of normally functioning EPCs and poor prognosis. However, many questions regarding the application of EPCs and other stem cells for organ repair and ASCVD prevention remain unanswered. Studies evaluating the use of cytokines such as EPO and VEGF to increase EPCs in the hope of promoting vascular repair and slowing progression towards ASCVD in patients with renal disease have not been designed. More work is necessary to fully define the role of this new and emerging knowledge in the highly morbid condition of renal dysfunction.

References


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