ABSTRACT

The risk of cardiovascular disease (CVD) and poor cardiovascular outcomes increases as renal function decreases. The increasing prevalence of CVD and chronic kidney disease (CKD) is fueled by the current obesity epidemic that is resulting in an increased incidence of hypertension and diabetes mellitus. Hypertension and diabetes mellitus are the 2 leading causes of CKD. It is anticipated that the recent downward trend of decreasing cardiovascular mortality will reverse directly as a result of the increased prevalence of diabetes and CKD. Observational evidence suggests that CKD is largely driven by novel risk factors that underlie traditional risk factors. The presence of global markers for acute inflammation and the increased risk of atherosclerosis and thrombosis in patients with CKD suggest that kidney disease is associated with a state of chronic inflammation similar to coronary artery disease. Anemia and depressed erythropoietin levels are important components of the "renal dysmetabolic syndrome." Patients with reduced creatinine clearance develop significant anemia, which is associated with increased cardiac output and detrimental vascular remodeling, such as left ventricular hypertrophy and thickened vessel walls. Anemia is an independent predictor of mortality in patients with CVD and is associated with an increased incidence of in-hospital mortality, 30-day mortality, 1-year mortality, and disabling strokes. Erythropoietin treatment for anemia has been shown to improve cardiac function and to reduce diuretic use and rehospitalizations. Treating anemia has clear benefit for patient quality of life. Although the association between anemia and the increased risk of cardiovascular events is strong, it is unclear whether treating anemia reduces cardiovascular risk in patients with CKD.

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kidney disease. Patients with a GFR of below 90 mL/min/1.73 m² at baseline were 3 times more likely to develop CKD than patients with a normal GFR (≥120 mL/min/1.73 m²). The odds of developing CKD steadily increased as the number of risk factors increased. The compounding nature of these risk factors—in particular, those linked with obesity—suggest that CKD has an associated dysmetabolic syndrome similar to that of diabetes mellitus. CKD appears to be driven, in large part, by novel risk factors, such as inflammation, thrombosis, and calcium-phosphate imbalances that underlie more traditional risk factors. Depressed erythropoietin levels and the resulting anemia that are prevalent in patients with CKD may have a major role in this dysmetabolic process. The outcome of what appears to be a largely obesity-driven increase in CKD will be increased cardiovascular mortality (Figure 1). The next generation of patients with CKD will likely have more severe kidney disease at an earlier age and will likely present with an increased number of confounding risk factors. This combination of factors will increase the difficulty of assessing and treating this population.

RECOGNIZING THE CARDIO-RENAL LINK

Serum creatinine level is an important indicator of kidney disease, and it has been shown to correspond with a given GFR for different age groups. In a 70-year-old man, a relatively low serum creatinine of 1.26 mg/dL may not be perceived as an indicator of impaired renal function. Nevertheless, serum creatinine level has been shown to correspond with a GFR of 60 mL/min/1.73 m², the threshold of kidney disease. As GFR falls below 60 mL/min/1.73 m², the risk of cardiovascular events increases in a consistent, graded fashion (Figure 2). This correlation suggests that physicians should use the calculation of estimated GFR to identify patients with early renal impairment who are often considered normal because of a “normal” serum creatinine and intervene aggressively before these patients reach middle- or late-stage CKD.

A study comparing patients with either normal or elevated serum creatinine (≥1.5 mg/dL for men and ≥1.3 mg/dL for women) found a higher incidence of the metabolic syndrome in those patients with elevated creatinine. Patients with kidney disease had an increased incidence of diabetes mellitus, lower levels of high-density lipoprotein, and higher levels of lipoprotein A, C-reactive protein, fibrinogen, and Factor VII. Individually, many of these markers are surrogate markers for increased risk of CVD. The presence of elevated levels of C-reactive protein and fibrinogen with CKD suggests that kidney disease is associated with a state of chronic inflammation.

Figure 1. Cardiovascular Risk Increases in the Presence of Kidney Disease


Figure 2. The Rate of Cardiovascular Events Increases with Kidney Disease Severity

Another study found that for patients presenting with acute coronary syndromes, the in-hospital mortality rates for those patients who also had renal insufficiency (creatinine clearance <60 mL/min) were 3 times higher than for patients without renal insufficiency. For patients presenting with acute myocardial infarction (AMI), in-hospital mortality rates have shown to be sharply increased for those patients whose creatinine clearance was below 60 mL/min at baseline (Figure 3). Data from the Heart and Estrogen/Progestin Replacement Study, which enrolled women with coronary artery disease (CAD) and congestive heart failure (CHF), showed that patients with creatinine clearance between 50 mL/min and 60 mL/min had sharply increased mortality risk. These studies show that kidney disease increases mortality risk from a variety of cardiovascular events, supporting the concept of a cardio-renal link.

The presence of these global markers for acute inflammation and increased risk of atherosclerosis and thrombosis suggests that CKD is associated with a chronic inflammatory state. Future research should be focused on the ill effects of this syndrome as well as conditions such as anemia which may contribute to and/or exacerbate the metabolic effects of CKD.

**THE ROLE OF ANEMIA IN THE CARDIO-RENAL LINK**

Significant anemia begins to appear in patients who have reduced creatinine clearance. CKD-related anemia is generally defined as hemoglobin (Hb) below 11 g/dL in association with reduced renal function. The anemia associated with CKD has effects on cardiac and vascular structures, leading to increases in cardiac output, as well as detrimental adaptations, including left ventricular hypertrophy (LVH) and thickening of the blood vessel walls. LVH is associated with chronic anemia and has been shown to increase mortality, perhaps because it predisposes patients to diastolic dysfunction and aggravation of coronary ischemia, thereby lowering the threshold for life-threatening arrhythmias. Clinical database analysis showed that patients with an increased Hb concentration had a reduced left ventricular mass index compared with patients whose Hb was reduced or unchanged. This indirect evidence suggests that improving anemia may have a beneficial effect on LVH. Likewise, patients with CHF have been shown to have a 13% increase in annual mortality risk per 1-g/dL decrease in Hb. Anemia’s effects on the arterial system are less well defined. However, it is reasonable to speculate that anemia could contribute to arterial hypertrophy and eventually lead to increased systemic vascular resistance.

Although the precise effects of anemia and anemia treatment need to be determined through prospective clinical trials, anemia remains a significant mortality multiplier for patients with CKD, CVD, or both.

**Table. Effect of CKD, CHF, and Anemia as Combined Risk Factors for Mortality**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>2-Year Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>16.6</td>
</tr>
<tr>
<td>CKD</td>
<td>16.4</td>
</tr>
<tr>
<td>CHF</td>
<td>26.1</td>
</tr>
<tr>
<td>CKD, anemia</td>
<td>27.3</td>
</tr>
<tr>
<td>CHF, anemia</td>
<td>34.6</td>
</tr>
<tr>
<td>CHF, CKD</td>
<td>38.4</td>
</tr>
<tr>
<td>CHF, CKD, anemia</td>
<td>45.6</td>
</tr>
</tbody>
</table>

database analysis of Medicare patients, for example, showed that patients with anemia had twice the mortality rate of the control patients. Medicare patients with heart failure, CKD, and anemia had more than 5 times the mortality risk of the control patients (Table). In a study of women presenting with symptoms of CAD, those patients with an Hb below 12 g/dL had an increased risk of cardiovascular events compared with those patients with an Hb of 12 g/dL or higher. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, which studied the impact of anemia on event rates in patients with AMI undergoing primary percutaneous coronary intervention, anemia was an independent predictor of in-hospital mortality. In this study, anemic patients were 3 times more likely to have a fatal in-hospital event, and anemia was associated with a higher incidence of 30-day mortality, 1-year mortality, and disabling strokes.

Anemia is an independent predictor of increased mortality in patients with a variety of cardiovascular presentations, and anemia may confer additional risk for many reasons, including tissue hypoxia, the induction of arrhythmia or myocardial ischemia, or the activation of the sympathetic nervous system. In patients whose anemia results from erythropoietin deficiency, adverse vascular remodeling may result from a reduced number of vascular progenitor cells, limiting the potential for vascular repair and thereby increasing the risk of a cardiovascular event. For patients with heart failure, survival is clearly related to Hb levels. Treating anemia with erythropoietin can have a positive impact on a patient’s quality of life. Erythropoietin treatment has been shown to improve cardiac function according to the New York Heart Association functional classification and reduce diuretic use and the rate of rehospitalizations.

Anemia is certainly a key link between CKD and CVD. It plays a major role in a destructive process in which these diseases appear to be propagating one another; the impact can be measured in increased cardiovascular event rates and increased cardiovascular mortality. What remains to be seen is whether eliminating traditional risk factors, and novel risk factors such as anemia, can reduce the cardiovascular risk associated with CKD.

**DISCUSSION**

**Dr Agarwal:** Dr Lepor mentioned that atherosclerosis in renal disease is more malignant. That is because it is medial sclerosis as opposed to the intimal process, isn't it? Do you think that correlates very well with the coronary disease?

**Dr Lepor:** I think the observation that you have made is correct; it is a different form of atherosclerosis. As interventional cardiologists, we are much more anxious about the care of patients with CKD in the catheterization lab. We know that complication rates, including bleeding and the development of contrast-induced nephropathy, are higher in these patients but the benefits are also much greater with revascularization. The dysmetabolic syndrome associated with CKD is analogous to the metabolic syndrome associated with insulin resistance in that there are a constellation of abnormalities, including anemia, lipid abnormalities, elevations of homocysteine levels, insulin resistance, and abnormalities of calcium-phosphate homeostasis, that are probably responsible for the heightened platelet activation and endothelial dysfunction associated with CKD. In particular, the vascular abnormalities, including endothelial dysfunction, may be related to the reduction in erythropoietin and vascular progenitor cells responsible for optimal vascular health. Dr Brinker, do you have any comments on that?

**Dr Brinker:** One message I took from your presentation was that we really know very little about the association between CKD and nonrenal death. There are a wide variety of possible influences, but it is a jump to assume a cause-and-effect relationship for any of them at this time. There are mechanisms at that we do not yet fully understand. This relationship, however, provides fuel for those who are interested in designing prospective trials because there are several straightforward ways of approaching the individual questions. For now, I am uncertain as to the clinical

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application of information arising from recent research; there appears to be myriad factors that we were essentially unaware of just 4 to 5 years ago that could be important mediators of cardiovascular disease. The question is, can we—or should we—screen for and treat any of them?

**Dr Lepor:** I think that is a very reasonable statement, but I think you can also make the analogy that CKD’s association with heart disease is not dissimilar to the association of diabetes with heart disease. Diabetes really is an umbrella for a whole host of metabolic abnormalities, very similar to what we see with CKD, and the question is, what are the major drivers in either one of those disease states that push atherosclerotic event rates?

**Dr Brinker:** Your last statement is very important. Yes, diabetes might be similar to CKD; however, cardiologists today view diabetes as a vascular disease. There seems to be some debate about the connection between blood sugar per se and cardiovascular outcomes. It seems that glucose is not the only issue; we must look deeper to insulin resistance, growth factors, and so forth. We do not completely understand these issues, but we have reached the point where we accept diabetes as a vascular disease. I am not certain that we are ready to accept CKD as a vascular disease quite yet, but I think we are now beginning to see more and more connections. Perhaps, like glucose in diabetes, the creatinine level is a surrogate for those factors accompanying CKD that adversely affect the cardiovascular system.

*For more excerpts from the faculty discussion, visit www.JHASIM.com or www.UTASIM.com.

**REFERENCES**


