Chronic Kidney Disease and Cardiovascular Risk: Time to Focus on Therapy

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Using a robust statistical analysis of a selected population of patients older than 60 years of age with isolated systolic hypertension, the article by de Leeuw et al. (1) in this issue of *JASN* demonstrates that renal impairment and proteinuria are independent predictors of cardiovascular risk (1). The finding serves to highlight further the apparent increased cardiovascular risk associated with even mild levels of chronic kidney disease (CKD).

Although it has been suggested that CKD may merely reflect an increase in severity of cardiovascular disease (2), it has been demonstrated to be an independent predictor of adverse outcome in many recent reports in population-based samples, such as the Framingham study (3) and the National Health and Nutrition Epidemiological (NHANES) Survey (4), and also in populations with preidentified increased cardiovascular risk, such as the Hypertension Optimal Treatment (HOT) study (5), the Heart Outcomes and Prevention Evaluation (HOPE) study (6), and the Hypertension Detection and Follow-up Program (HDFP) study (7). It has also been recently demonstrated in populations of patients with specific cardiovascular disease processes, such as those with acute coronary syndromes (ACS) (8) and those undergoing percutaneous coronary interventions (9), and in patients with congestive heart failure (CHF) (10).

Whether directly attributable to CKD or merely a surrogate of increased severity of cardiovascular disease, the perceived increase in cardiovascular risk mandates a concerted effort to improve outcomes. Unfortunately, therapeutic decision-making in patients with renal and cardiac disease is severely limited by a notable absence of data. Patients with CKD are routinely excluded, usually because of perceived increased risk of adverse outcomes but also on many occasions for reasons that are not clearly defined. The SYST-EUR study (1) reported here excluded from consideration patients with serum creatinine ≥2.0 mg/dL.

Similar findings of an increase in cardiovascular risk associated with CKD were made in a recent combined analysis of four large trials in ACS (GUSTO-IIb, GUSTO-III, PURSUIT, and PARAGON-A) despite the fact that three of the studies included in that analysis also excluded patients on the basis of renal function (8). It could be argued that increased severity of disease provides a greater opportunity for the demonstration of efficacy. If research evaluating such therapies included a more balanced consideration of competing risks and benefits, then arguably more patients with CKD should be included in cardiovascular trials.

Although GFR was derived using the Cockcroft and Gault formula for the purposes of analyzing the associations of renal function (11), the authors of this article unfortunately chose to use serum creatinine as their primary variable of interest in assessing and reporting the risk associated with CKD. The analysis might have been better served by a greater emphasis on GFR, as reporting of GFR as the primary variable representing renal function has become a welcome trend in a number of recent articles assessing the risks associated with renal impairment in a cardiovascular context (2,4,8,12,13). The new guidelines for classification of CKD offered by the NKF (14) will hopefully facilitate more uniform evaluation of these risks and, more importantly, will aid in the appropriate discussion of intervention strategies.

The controversy over renal disease as a causal factor or mere associated marker notwithstanding, given that patients with even mild renal dysfunction have been consistently demonstrated to have worse outcomes, it is extremely important that we move forward and focus our efforts on determining appropriate treatment strategies for patients with CKD. De Leeuw et al. found that treatment with nitrrendipine did not interact with serum creatinine in predicting mortality or adverse outcome (1). On the other hand, the beneficial effect of the ACE inhibitor ramipril on mortality and cardiovascular outcomes in the HOPE trial was shown to be even greater in those with mild kidney disease (6). It is apparent also that patients with ESRD probably benefit more from bypass grafting than from percutaneous coronary intervention (15,16). These findings highlight precisely why patients with CKD should be allowed to participate in clinical trials; excluding them may lead to many missed opportunities to better define targeted therapies. That we need improved therapeutic strategies in CKD is clear from studies showing that many therapies, such as aspirin and beta-blockers, are sorely underutilized in CKD (12).
There are many questions and controversies that remain in determining the most appropriate strategies for management of patients with cardiovascular and renal disease. The approach to ACS in patients with CKD is complicated by a high prevalence of asymptomatic cardiac ischemia, frequent abnormal findings with baseline electrocardiograms (17,18), and nonspecific elevation of cardiac enzymes (19,20). Pharmacokinetic data is also not clear for both established and developing antiangiogenesis strategies. With regard to unfractionated heparin for example, despite reports of impaired clearance and increased transfusion requirements (21) in CKD, standard dosing recommendations for unfractionated heparin do not recommend adjustment for abnormal renal function (22).

Other areas of concern and confusion with respect to cardiovascular interventions in CKD include the management of arrhythmias and use of antiarrhythmic drugs (23), the use and targets of lipid-lowering therapy (24), and lastly dosing strategies and indications for both thrombolytics and glycoprotein 2b/3a inhibitors.

The article by de Leeuw et al. (1) further highlights the increased risk associated with CKD in patients with cardiovascular disease. A concerted effort to answer some of the many outstanding therapeutic issues could potentially advance recent modest improvements in mortality in the ESRD population and, more importantly, could have a significant impact on the larger and increasingly apparent CKD population not receiving renal replacement therapy.

References

See related article, “Prognostic Significance of Renal Function in Elderly Patients with Isolated Systolic Hypertension,” on pages 2213–2222.