

## Cardiovascular Risk Linked to Chronic Kidney Disease—But Who Actually Has Chronic Kidney Disease?

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Recent studies reemphasize the close relationship between kidney failure and cardiovascular disease.<sup>1-3</sup> While the diagnosis of chronic kidney disease (CKD) naturally raises the concern of progression to end-stage disease, many patients with CKD die of cardiovascular disease long before needing dialysis or a transplant.<sup>4,5</sup> It could be argued that clinicians caring for patients with CKD provide the greatest benefit by pursuing aggressive preventive cardiology measures, including careful blood pressure control, lipid management, and smoking cessation. Although the benefits of risk factor intervention are well established in some high-risk subgroups, few studies directly address cardiovascular risk factors by levels of kidney function in the general population.

In this issue of *Mayo Clinic Proceedings*, Foley et al<sup>6</sup> report the prevalence of cardiovascular risk factors based on estimated kidney function. They examined data from 15,837 subjects participating in the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988 to 1994. These data were reviewed to establish the presence of 9 risk factors (current smoking, obesity, elevated total cholesterol levels, hypertension, diabetes mellitus, anemia, elevated C-reactive protein levels, elevated homocysteine levels, and albuminuria). Their data show a progressive increase in the cumulative number of risk factors with reduced levels of estimated glomerular filtration rate (GFR). Subjects with the greatest reduction of estimated GFR (<30 mL/min per 1.73 m<sup>2</sup>) had an average of 4 risk factors. More than a third of subjects in this subgroup had 5 or more risk factors.

The report by Foley et al underscores the fact that medical care in the general population during that period regularly failed to address these important conditions known to accelerate adverse cardiovascular risk. Several of these markers in fact reflect direct sequelae of kidney disease, eg, anemia, proteinuria, and hypertension. Perhaps it is not surprising that subjects with the most advanced renal dysfunction have more abnormal risk factors. Achieving better control of risk factors is a major opportunity to improve clinical outcomes and has been the target of major efforts within the nephrology community, as reflected by subspecialty task force guidelines.<sup>7,8</sup>

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Who actually has CKD? Is it possible that estimates of kidney function simply correlate with other processes associated with cardiovascular disease? Age may be an important confounder. Older age is associated with both an increased risk of cardiovascular disease and a reduced measured GFR, with the lower limit of normal being 87 mL/min

per 1.73 m<sup>2</sup> for a 20-year-old person and 60 mL/min per 1.73 m<sup>2</sup> for a 75-year-old person.<sup>9</sup>

Also of interest is that several traditional cardiovascular risk factors in the NHANES population showed a nonlinear trend (eg, glycosylated hemoglobin, body mass index, total cholesterol, blood pressure), increasing progressively with mild reductions in GFR and then leveling off or even decreasing in those with the most severe reductions in GFR. These nonlinear trends may be due to premature death of subjects with operant risk factors or to a confounding effect from the development of cardiomyopathy and malnutrition with more severe CKD.<sup>8</sup> Moreover, these nonlinear trends, as well as statistical adjustments for self-reported hypertension, diabetes, and cardiovascular disease, may explain why several traditional cardiovascular risk factors failed to predict an estimated GFR less than 60 mL/min per 1.73 m<sup>2</sup> in the report by Foley et al.

The greater concern regarding this and other recent reports<sup>10</sup> is the use of the Modification of Diet in Renal Disease (MDRD) equation to estimate the burden of reduced kidney function in the general population. The MDRD equation is a statistical model that predicts GFR on the basis of a set of variables (serum creatinine, age, sex, and race) and was developed from a referred population with clinically diagnosed CKD and a mean measured GFR (iothalamate clearance) of 40 mL/min per 1.73 m<sup>2</sup>.<sup>11</sup> With the MDRD equation, 4% of the general population (25% for those ≥70 years) has been classified as having an estimated GFR less than 60 mL/min per 1.73 m<sup>2</sup>.<sup>10</sup> These estimates are too high for the general population and reflect important inaccuracies with the equation in populations without clinically diagnosed kidney disease. Healthy persons with a high-normal serum creatinine level or an estimated GFR of 60 mL/min per 1.73 m<sup>2</sup> have a 30% to 50% higher measured GFR than estimated GFR.<sup>12,13</sup> Persons with type 1 diabetes mellitus have higher measured GFR than those obtained by these estimates.<sup>14</sup> These differences may reflect imprecision with a single measurement of serum creatinine<sup>15,16</sup> and variability in muscle mass and protein intake not adequately modeled by the MDRD equation.<sup>12</sup> Because persons without CKD are healthier, they may have more muscle mass than persons with CKD, resulting in higher serum creatinine levels at the same GFR.<sup>12,17</sup> Without a study based on measured GFR, the true burden of reduced kidney function in the general population remains uncertain.

Applying the MDRD equation to the general population produces paradoxical effects from sex and race variables on the estimation of GFR that seriously challenge its concurrent validity. According to the MDRD equation, men should have a 35% higher GFR than women, and African Americans should have a 21% higher GFR than white persons at the same serum creatinine level. However, formal measurements of GFR in healthier populations indicate that men have only a 5% to 8% higher GFR than women.<sup>12-14</sup> No difference is apparent in GFR between African Americans and white persons at the same serum creatinine level.<sup>13</sup> On the basis of the MDRD equation alone, women and white persons have a higher risk for CKD compared to men and African Americans.<sup>10,18</sup> These estimates are inconsistent with the equal prevalence of albuminuria (another marker of kidney disease) in women and men and the higher risk of albuminuria in African Americans compared to white persons.<sup>10,19</sup> Most importantly, they are also inconsistent with the increased risks of development of end-stage renal disease in men and African Americans compared to women and white persons.<sup>20</sup>

Even with these reservations, the NHANES data extend our understanding of the important overlap between cardiovascular risk factors and CKD. They reemphasize the potential for major improvements in managing conventional cardiovascular risk factors such as hypercholesterolemia and hypertension and highlight the extremely high number of risk factors in advanced CKD. However, several questions remain unanswered. Is it possible that substantial decrements in kidney function represent one more manifestation of cardiovascular disease, perhaps as a result of small vessel injury within the kidney? Is it possible that meticulous attention to glucose tolerance, blood pressure, smoking, dyslipidemia, and systemic inflammation may offer a major opportunity to slow the rate of developing CKD overall? A single examination of the US population in cross-section cannot provide definitive answers to these questions but does stimulate the generation of important hypotheses to be studied further.

The NHANES data presented by Foley et al provide an important starting point for physicians. We agree that there are major opportunities for the medical community to actively benefit patients with CKD who often have multiple cardiovascular risk factors. Our challenge going forward is to more accurately identify and classify persons in the general population who truly have CKD to better understand how cardiovascular risk factors cosegregate and interact with CKD. We hope that results from the next NHANES will reveal meaningful improvement in the management of these cardiovascular risk factors.