Cardiovascular Disease Consequences of CKD

Alan S. Go, M.D.[*,†,‡]

Summary: Chronic kidney disease, defined as reduced glomerular filtration rate (estimated using serum creatinine- and/or serum cystatin C–based equations) or excess urinary protein excretion, affects approximately 13% of adult Americans and is linked to a variety of clinical complications. Although persons with end-stage renal disease requiring chronic dialysis therapy experience a substantially high cardiovascular burden, whether mild-to-moderate chronic kidney disease is an independent risk factor for fatal and nonfatal cardiovascular events has been more controversial. This review evaluates the current evidence about the clinical and subclinical cardiovascular consequences associated with chronic kidney disease of varying levels of severity. In addition, it discusses the predictors of adverse cardiovascular outcomes while also focusing on recent insights into the relationships between chronic kidney disease and cardiovascular disease from the Chronic Renal Insufficiency Cohort study, a large current prospective cohort study of adults from across the spectrum of chronic kidney disease.
Semin Nephrol 36:293-304 © 2016 Published by Elsevier Inc.
Keywords: Chronic kidney disease, cardiovascular disease, heart failure, myocardial infarction, risk factor

Despite many preventative and therapeutic advances, cardiovascular disease remains the leading cause of morbidity and mortality nationally, with worrisome trends in other developed and developing countries.[1,2] Importantly, however, the risk of cardiovascular complications varies across patient subgroups, including those defined by underlying renal dysfunction.[2] It is well known that patients who have end-stage renal disease (ESRD) treated with either chronic hemodialysis or peritoneal dialysis experience a particularly high rate of premature all-cause and cardiovascular mortality as well as other major adverse cardiovascular events compared with age-matched adults without ESRD.[3] However, it has been challenging to determine what component of the excess cardiovascular risk among ESRD patients is related mechanistically to the underlying kidney failure or to the potential negative effects of dialysis therapy. Over the past 2 decades, a large body of evidence strongly suggests that chronic kidney disease (CKD) not yet requiring renal replacement therapy, defined as having an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 and/or evidence of structural kidney damage, is an important risk factor for adverse cardiovascular outcomes. The relationships between measures of non–dialysis-requiring CKD and various cardiovascular events have major implications nationally given the substantially larger number of adults with stages 1 to 4 CKD compared with ESRD.[4-6] Based on data from the National Health and Nutrition Evaluation Survey (NHANES) and other sources, it is estimated that more than 20 million adult Americans (representing 13% of adults) have CKD based on either reduced eGFR or the presence of proteinuria.[7]

In this article, the link between CKD and different manifestations of cardiovascular disease (clinical and subclinical) is explored based on extensive published clinical research with a focus on the most recent insights from the prospective Chronic Renal Insufficiency Cohort (CRIC) study.[8]

CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR RISK IN THE GENERAL POPULATION

Serum Creatinine Concentration and Cardiovascular Risk

Over the past several decades, our understanding of the association between different measures of CKD and its severity with various cardiovascular outcomes has improved substantially. A brief historical review has shown the controversy about whether CKD not yet requiring renal replacement therapy was, in fact, a risk factor for fatal and nonfatal cardiovascular disease. Importantly, many of the previous studies relied only on serum creatinine concentration as the measure of

[*]*Division of Research, Kaiser Permanente Northern California, Oakland, CA.*
[†]*Departments of Epidemiology, Biostatistics, and Medicine, University of California, San Francisco, San Francisco, CA.*
[‡]*Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA.*
Financial support: Supported by the National Institute of Diabetes, Digestive and Kidney Diseases of the National Institutes of Health (U01 DK060902, U01 DK082223, R01 DK098233, and R01 DK101507) (A.S.G.).
Conflict of interest statement: Alan Go has received a research grant through his institution from Astra-Zeneca.
Address reprint requests to Alan S. Go, MD, Cardiovascular and Metabolic Conditions Section, Comprehensive Clinical Research Unit, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612-2304. E-mail: Alan.S.Go@kp.org
0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2016.05.006

kidney function, and many studies were conducted in highly selected populations using a variety of outcome definitions that collectively led to conflicting results about whether CKD was linked to cardiovascular risk. A prominent example was a report from the Framingham Heart Study, which observed that among male enrollees, a serum creatinine level of 1.5 to 3.0 mg/dL was not associated significantly with all cardiovascular events (adjusted hazard ratio [HR], 1.06; 95% confidence interval [CI], 0.79-1.43) and a serum creatinine level of 1.4 to 3.0 mg/dL in female participants also was not a significant risk factor (adjusted HR, 1.04; 95% CI, 0.79-1.37).[9] Additional studies among a middle-aged male working population[10] as well as in a cohort of older Chinese persons with hypertension[11] were consistent with this observation. On the other hand, post hoc analyses from three randomized clinical trials using crude serum creatinine concentration as a measure of kidney function reported differing results. In the Heart Outcomes Prevention Evaluation study, a baseline serum creatinine level of 1.4 mg/dL or greater was associated with a 40% higher adjusted risk of a composite cardiovascular event in a sample of participants considered to have been at high cardiovascular risk upon study enrollment.[12] Similar findings were observed in the Heart and Estrogen-Progestin Replacement Study comparing an entry serum creatinine level greater than 1.4 mg/dL with less than 1.2 mg/dL among older women with known coronary heart disease.[13] Finally, in a sample of hypertensive adults enrolled in the Hypertension Optimal Treatment study, compared with a serum creatinine level less than 1.5 mg/dL, an entry serum creatinine level of 1.5 mg/dL or greater was associated with approximately a doubling of the adjusted cardiovascular risk.[14]

Estimated GFR and Cardiovascular Risk

Although it has been well recognized that serum creatinine concentration alone was not an adequate reflection of underlying GFR, it also was clear that using more direct measures of GFR (eg, inulin clearance) was not practical to implement in clinical practice. Furthermore, equations such as the Cockcroft-Gault creatinine clearance were limited in their accuracy depending on the level of actual GFR, and limited in their applicability because certain components, including weight, are not always readily available in large populations. Collectively, these and other factors drove the emergence of various new equations to estimate GFR, combining serum creatinine concentration with demographic characteristics, and, later, serum cystatin C level. By using the four-variable serum creatinine–based equation from the Modification of Diet in Renal Disease (MDRD) study,[4,6] an analysis from the NHANES I Epidemiologic Follow-up Study did not detect an association of an eGFR between 30 and 60 mL/min/1.73 m^2 with cardiovascular death, compared with an eGFR of 90 mL/min/1.73 m^2 or greater.[15] In contrast, an analysis of NHANES II data showed that a baseline eGFR of less than 70 mL/min/1.73 m^2 was associated with a 51% higher adjusted risk of cardiovascular death compared with an eGFR of 90 mL/min/1.73 m^2 or greater.[16] Furthermore, based on data analyzed separately from the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study, an entry eGFR between 15 and 59 mL/min/1.73 m^2, compared with an eGFR of 90 mL/min/1.73 m^2 or greater, was associated significantly with a 31% and 38% adjusted higher risk of cardiovascular events, respectively.[17,18] Key limitations of these previous analyses included the small number of patients with mild to moderate CKD, reliance on only one baseline estimate of GFR, varied cardiovascular outcome definitions, and limited ethnic and racial diversity within the study populations.

Important insights to advance our understanding came from a very large community-based population receiving comprehensive care within Kaiser Permanente of Northern California, an integrated health care delivery system currently caring for more than 3.8 million members.[19] By using data from the time period 1996 through 2000, 1,120,295 adult members were identified who had outpatient measures of serum creatinine concentration obtained outside of the emergency department that were converted to eGFR using the MDRD equation. These eGFR values then were categorized using a modified National Kidney Foundation CKD staging system that specifically split the stage 3 CKD GFR range in half for more granularity to generate the following categories: 60 or greater, 45 to 59, 30 to 44, 15 to 29, and less than 15 mL/min/1.73 m^2. By using clinical and administrative data sources, patients were characterized by demographic characteristics and clinical comorbidity, along with comprehensive longitudinal ascertainment of hospitalized cardiovascular events (ischemic heart disease, stroke, heart failure, and peripheral arterial disease) and death from any cause.[19] Not surprisingly, patients with a lower baseline eGFR had a higher burden of cardiovascular risk factors at the beginning of follow-up evaluation. At an eGFR of less than 60 mL/min/1.73 m^2, the age-adjusted rate of cardiovascular events increased in a graded fashion with lower levels of eGFR. An increased risk of cardiovascular events was particularly notable with eGFR levels less than 45 mL/min/1.73 m^2 (Fig. 1). Given concerns that this observation may be confounded by other factors, there was extensive statistical adjustment for a wide range of variables, including demographic characteristics, socioeconomic status, clinical cardiovascular risk factors, proteinuria, serum albumin level, and noncardiovascular