

NEPHROLOGY

Rounds™

Chronic Kidney Disease and Risk of Adverse Outcomes

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Clinical research in nephrology has historically focused primarily on patients who suffer from end-stage renal disease (ie, dialysis or kidney transplant patients) or individuals with specific disease entities (eg, membranous nephropathy). In the past several years, however, there has been burgeoning interest in studying individuals with a mildly to moderately reduced glomerular filtration rate (GFR), regardless of the underlying etiology. This issue of *Nephrology Rounds* discusses the epidemiology and outcomes of chronic kidney disease, particularly cardiovascular disease, and the relationship to reduced GFR.

The chronic kidney disease paradigm

This field of inquiry concerning GFR became more prominent following the publication of the National Kidney Foundation Chronic Kidney Disease Clinical Practice Guidelines in 2002.¹ These influential guidelines presented a new nomenclature system in which all patients with markers of kidney damage (eg, structural abnormalities or proteinuria) or reduced GFR are classified as having “chronic kidney disease” (Table 1).¹ For example, all patients with GFR consistently $< 60 \text{ mL/min/1.73m}^2$ – regardless of specific renal pathology – are classified as having Stage 3 or higher chronic kidney disease (CKD).

The CKD paradigm is based on the premise that certain complications of kidney disease are suffered by all patients with reduced GFR, eg, development of anemia and secondary hyperparathyroidism. In addition, with the CKD paradigm, important determinants for further loss of GFR are shared by all patients with kidney disease, independent of the underlying diagnosis. Prominent among these risk factors for progression are hypertension severity and proteinuria.

The epidemiology of CKD

One major reason for the attention paid to CKD is the large number of individuals who suffer from the disease. Data from the Third National Health and Nutrition Examination Survey (NHANES III) suggested that circa 1991, there were 11.2 million U.S. adults with Stage 1 or 2 CKD and 8 million persons with Stage 3 or 4 CKD.² These estimates were determined by applying the abbreviated 4-variable Modification of Diet in Renal Disease (MDRD) study equation^{3,4} to estimate GFR in a nationally representative sample. Note that these figures are 1 to 2 orders of magnitude greater than the number of individuals receiving maintenance dialysis treatment.

This study is important because it was the first to quantify the burden of CKD using a consensus definition and a nationally representative sample. To minimize potentially substantial bias due to between-laboratory differences in measured serum creatinine (SCr), a direct calibration was undertaken between the MDRD and NHANES III laboratories.⁵ Notably, the same serum sample measured at the NHANES III laboratory gave an SCr reading that was 0.23 mg/dL higher than at the MDRD study laboratory. Therefore, using uncalibrated SCr readings in NHANES III would have given an exaggerated estimate of the number of individuals with higher SCr and, hence, a lower estimated GFR.

CKD and end-stage renal disease

Many nephrologists approach patients with earlier stage CKD as potential end-stage renal disease (ESRD) patients. This “ESRD-centric” view of CKD has influenced much of

AS PRESENTED IN THE ROUNDS OF
THE NEPHROLOGY DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
BOSTON, MASSACHUSETTS



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The editorial content of *Nephrology Rounds* is determined solely by the Nephrology Division of Brigham and Women's Hospital.

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Table 1: The 5 stages of chronic kidney disease (CKD) as defined by the National Kidney Foundation.

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with normal or ↑GFR	≥90
2	Kidney damage with mild ↓GFR	60-89
3	Moderate ↓GFR	30-59
4	Severe ↓GFR	15-29
5	Kidney failure	<15 or dialysis

CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

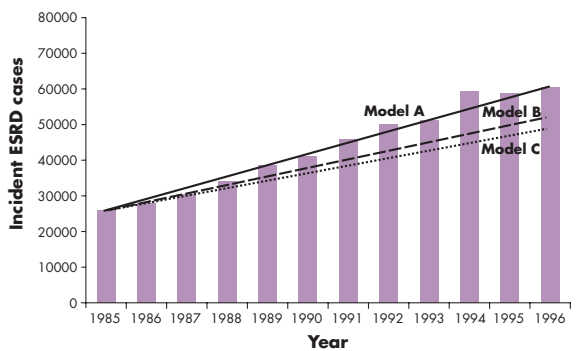
the early discourse regarding the management of CKD. For example, when the National Kidney Foundation – Dialysis Outcomes Quality Initiative (NFK-DOQI) Guidelines were upgraded to K/DOQI (Kidney Disease Outcomes Quality Initiative),⁶ several of the Guidelines, including the iron saturation and ferritin targets,⁷ were simply extended from ESRD to cover the “pre-ESRD” CKD population. However, this may not be appropriate, since CKD patients differ from ESRD patients in important ways.⁸

Similarly, many have assumed that the epidemiology of CKD closely matches the epidemiology of ESRD; however, recent data reveal that this assumption may not be valid. For example, although Blacks suffer a disproportionate burden of ESRD compared with Whites, the prevalence of Stage 3 or 4 CKD is not higher among Blacks.⁹ According to data from NHANES III, the prevalence of GFR 15 to 59 mL/min/1.73 m² was not different among Black compared with White adults (2,060 vs 2,520 per 100,000, P = 0.14). For every 100 Blacks with Stage 3 or 4 CKD in 1991, 5 new cases of ESRD developed in 1996, whereas only 1 case of ESRD developed per 100 Whites with CKD (relative risk [RR] 4.8, 95% confidence interval [CI] 2.9-8.4). The increased risk of ESRD for Blacks compared with Whites was only modestly affected after adjustment for age, sex, and diabetes.⁹ In several other community-based samples (including the Framingham Heart Study, Atherosclerosis Risk in Communities Study, and the Cardiovascular Health Study) it has been noted that Blacks are not more likely than Whites to have earlier stage CKD.¹⁰

Recent data suggest that over the past few decades, the incidence of ESRD has increased more rapidly than the prevalence of CKD.¹¹ Temporal trends in the prevalence of Stage 3 and 4 CKD and the incidence of ESRD have been compared using data from the nationally representative NHANES II (1976-80) and NHANES III (1988-94) and the comprehensive U.S. Renal Data System ESRD registry. From 1978 to 1991, the number of adults aged 20-74 years with Stage 3 or 4 CKD grew from 2.6 to 3.9 million, an increase in prevalence from 1,970 to

Figure 1: Number of new treated end-stage renal disease (ESRD) cases among blacks and white subjects aged 25-79 years in the USA from 1985-96

Bars show the number of new cases of ESRD. **Model A** is observed (unadjusted) rate of increase in incidence (8.0% per year). **Model B** is adjusted for population growth and demographic characteristics (6.9% per year). **Model C** is adjusted for population growth, demographic characteristics, and prevalence of Stage 3-4 CKD (6.1% per year). This analysis reveals that only about 10% of the growth in ESRD cases could be attributed to increase in Stage 3-4 CKD prevalence in the adult population, an effect smaller in magnitude than that attributed to simple population growth.



2,460 per 100,000. However, the increased incidence of ESRD was even greater over this period. For every 1000 adults with Stage 3 or 4 CKD in 1978, 9 new cases of ESRD developed in 1983; whereas, every 1000 adults with Stage 3 or 4 CKD in 1991 produced 16 new cases of ESRD in 1996 (RR 1.7; 95% CI, 1.1-2.7).

After analyzing these data another way, using a multi-variable Poisson model, growth in Stage 3 or 4 CKD prevalence appeared responsible for only about one-tenth of the increase in new ESRD cases (Figure 1). Data from the latest NHANES (1999-2000) confirmed continued stability in CKD prevalence through the 1990s, in contrast to ongoing increases in ESRD incidence.¹² These observations suggest that other factors besides more kidney disease per se – such as more liberal entry into ESRD treatment programs – may be important contributors to the epidemic of ESRD.

CKD, cardiovascular disease and death

It is clear from the above data that the vast majority of patients with Stage 3 or 4 CKD never progress to ESRD. Therefore, the “ESRD-centric” view of CKD – that the primary goal of care is to retard progressive loss of GFR and delay as long as possible the need for renal replacement therapy – may not be appropriate. Rather, to improve the health and well-being of all CKD patients, attention should be given to the reasons for the high rates of death associated with CKD. It is important to have good epidemiological studies of the natural history of CKD and the risk factors for adverse outcomes in this population.

In the past few years, numerous studies have reported that even modestly increased SCr levels are associated with higher rates of all-cause mortality¹³⁻¹⁹ and death attributed to cardiovascular disease (CVD)^{15,17,20-23} within selected populations at varying baseline risks for adverse events. However, whether CKD itself, rather than other associated factors, is independently responsible for an increased risk of any CVD has been controversial.^{14-17,24}

Two recruited cohorts of selected ambulatory subjects observed that reduced baseline estimated GFR was associated with the future risk of CVD.

- In the Atherosclerosis Risk in Communities (ARIC) Study, a prospective cohort study of 15,350 middle-aged adults (aged 45 to 64 years at entry), followed for a mean 6.2 years, only 444 (2.9%) had a baseline estimated GFR of 15 to 59 mL/min/1.73 m² (Stage 3 or 4 CKD).²⁵ This level of baseline GFR was associated with a 38% higher adjusted subsequent risk of ischemic cardiovascular (CV) events compared with a GFR of 90 to 150 mL/min/1.73 m², while GFR 60 to 89 mL/min/1.73 m² was associated with a 16% increased risk (borderline statistical significance).²⁵

- In the Cardiovascular Health Study (CHS), 5,135 adults aged ≥ 65 years at entry were recruited from 4 U.S. cities and among 4,893 with an estimated GFR between 15 and 130 mL/min/1.73 m², 23.4% had a baseline estimated GFR 15 to 59 mL/min/1.73 m².²⁶ Among these older subjects, compared with GFR 90 to 130 mL/min/1.73 m², a baseline GFR of 15 to 59 mL/min/1.73 m² was associated with an adjusted 31% higher risk of CV events and a 47% increased risk of all-cause mortality, while GFR 60 to 89 mL/min/1.73 m² was not significantly associated with an increased risk of adverse events.²⁶

Within 2 national surveys and the Framingham Heart Study, somewhat conflicting results were observed. Among a sample of US adults participating in NHANES II, an estimated GFR <70 mL/min/1.73 m² was associated with a 51% increased adjusted risk of CV death when compared with an estimated GFR of >90 mL/min/1.73 m².²² Interestingly, no significant association was found for all-cause (adjusted relative risk 1.2, 95% CI, 0.8 to 1.8) and CV mortality (adjusted relative risk 1.0, 95% CI, 0.8 to 1.4) in the NHANES I Epidemiologic Follow-up Study for GFR of approximately 30 to 60 mL/min/1.73 m².²³ Furthermore, an elevated SCr (defined as 1.5 to 3.0 mg/dL in men and 1.4 to 3.0 mg/dL in women) was associated with a higher risk of death in men, but not in women, and was not associated with any CV event in either gender in the Framingham Heart Study.¹⁵

Additional insights were provided from the Valsartan in Acute Myocardial Infarction Trial (VALIANT) that examined a large sample of high-risk patients with acute myocardial infarction (MI) complicated by clinical or radiologic signs of heart failure and/or left ventricular systolic dysfunction. Patients were randomly assigned within 0.5 to 12 days of their event to receive either valsartan, captopril, or both and followed for a median of 25 months.²⁷ A total of 14,527 subjects had an available MDRD estimated GFR measured an average of 5 days

after their MI, and the study examined the association between this GFR level (categorized into ≥75, 60.0 to 74.9, 45.0 to 59.9, and <45 mL/min/1.73 m²) and the subsequent risk of all-cause mortality and CV complications. Overall, 22.2% had an estimated GFR 45.0 to 59.9 mL/min/1.73 m² and 11.3% of subjects had an estimated GFR <45 mL/min/1.73 m² at entry.

Lower GFR was associated with a higher burden of comorbidity. Crude 3-year mortality rates increased with lower GFR levels (14.1% for GFR ≥75, 20.5% for GFR 60.0 to 74.9, 28.9% for GFR 45.0 to 59.9, and 45.5% for GFR <45 mL/min/1.73 m²). Compared with GFR ≥75 mL/min/1.73 m², the risk of death increased in a stepwise fashion after adjustment for baseline characteristics and clinical severity: 14% for GFR 60.0 to 74.9, 38% for 45.0 to 59.9, and 70% for GFR <45 mL/min/1.73 m². A similar trend, but with lower magnitude was observed for the composite outcomes of major CV complications.

These and other published studies were limited by inclusion of only relatively modest numbers of subjects with reduced GFR,^{13-18,21-26,28} the use of only dichotomous groups of estimated kidney function (ie, CKD vs no CKD),^{13-18,28} reliance on crude SCr values as a proxy for GFR, and non-standard cutoffs to define renal insufficiency.^{13-21,28} Furthermore, they often defined reduced kidney function using a wide range of reduced GFR (eg, 15 to 59 mL/min/1.73 m²), and used SCr measurements not directly calibrated to the MDRD laboratory. The studies lacked information on changes throughout time in GFR and relevant coexisting illnesses.^{13-21,24-28} The inclusion of only selected populations and limited race and/or ethnic diversity also limited generalizing to the broader CKD population.^{16,18,21,24,26,27}

To overcome many of these limitations, we recently examined a large, diverse sample of ambulatory adults receiving medical care within a large integrated health care delivery system to assess the independent contribution of a reduced GFR level to the risks of death and CV events.²⁹

Kaiser Permanente of Northern California Renal Registry: GFR and outcomes

The Kaiser Permanente of Northern California (KPNC) Renal Registry included all adults aged ≥20 years who had one or more outpatient determinations of SCr levels in a health plan laboratory database between January 1, 1996 and December 31, 2000. All were members of KPNC, a large integrated healthcare system insuring >35% of the San Francisco and greater Bay area adult population. The adult membership of KPNC is very similar to the local surrounding and statewide population.³⁰ Patients with treated ESRD (ie, evidence of a prior kidney transplant or receiving maintenance dialysis at study entry) were excluded.

At baseline and through December 31, 2000, GFR was estimated for each cohort member using the MDRD equation. Measurement of SCr by the Kaiser regional laboratory was calibrated against the MDRD laboratory,

which increased the validity of associations with absolute GFR levels.³¹ Each subject's start date was assigned as the date of the first GFR during the study period. Changes in GFR during follow-up were estimated from outpatient SCr determinations not associated with acute hospitalizations, since they were more likely to accurately represent stable estimates of kidney function. Renal function was categorized using a modified National Kidney Foundation CKD classification scheme¹ based on estimated GFR level: 60 or higher, 45 to 59, 30 to 44, 15 to 29, and <15 mL/min/1.73 m².

Automated health plan databases for hospitalization discharge diagnoses, ambulatory diagnoses, laboratory results, and medication prescriptions, as well as regional cancer registry data,³² were used to identify relevant comorbidity based on previously validated methods.³²⁻³⁵ Information was collected on the presence of diagnosed coronary heart disease, ischemic stroke or transient ischemic attack, chronic heart failure, peripheral arterial disease, diabetes mellitus, hypertension, dyslipidemia, chronic lung or serious liver disease, systemic malignancy, and diagnosed dementia. The presence of a serum albumin level of ≤3.5 g/dL and documented proteinuria based on outpatient urine dipstick results were found in laboratory databases. Proteinuria was defined as a urine dipstick protein result of 1+ or greater (approximately reflecting >30 mg/dL) in the absence of a possible urinary infection, which was defined as having a positive urine nitrite or esterase in the same urine sample.

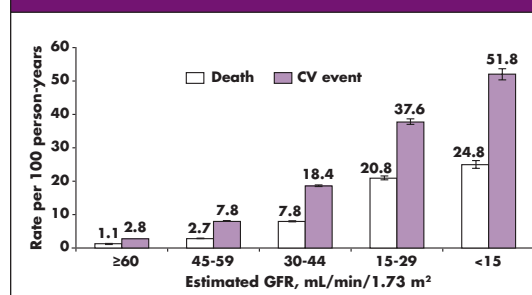
Patients were followed through December 31, 2000 until occurrence of death, end of follow-up, disenrollment from the health plan, or development of incident ESRD (defined operationally as requiring either maintenance dialysis or renal transplant). A CV event was defined as hospitalization for coronary disease, heart failure, stroke, or peripheral arterial disease. The independent effect of estimated GFR on the risk of death and CV events was examined after adjustment for other explanatory factors using Cox proportional hazard survival analysis methods with time-dependent covariates for updating changes in GFR and relevant comorbidity.

Reduced GFR is associated with increased risks of death and CV events

During the study period, 1,120,295 adult members had ≥1 outpatient SCr measurements and contributed to >3.1 million person-years of follow-up. Overall, there were 51,424 deaths and 138,291 CV events. In contrast, only 3,171 patients were started on maintenance dialysis, and 329 received a kidney transplant.

The crude rates of death and CV events increased markedly with progressively lower GFR levels (Figure 2). For death, the annual rate of all-cause mortality increased from 1.1% for GFR of

Figure 2: Crude rates of all-cause mortality and CV events among 1,120,295 adults with known kidney function from January 1, 1996 through December 31, 2000. Error bars represent 95% confidence limits.



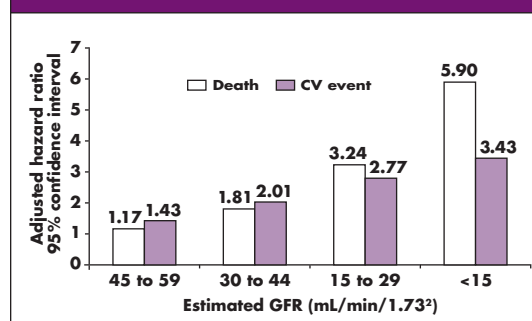
≥60 mL/min/1.73 m² to nearly 25% for a GFR <15 mL/min/1.73 m². The overall annual rate of CV events was substantially higher than for death and increased from 2.8 % for GFR of ≥60 mL/min/1.73 m² to nearly 52% for a GFR <15 mL/min/1.73 m².

In multivariable analyses adjusting for differences in socio-demographic and clinical characteristics as potential confounders, the risk of all-cause mortality increased sharply with lower GFR levels. Risk ranged from a 17% increased adjusted risk for GFR 45-59 mL/min/1.73 m² to a nearly 5-fold increased risk for GFR <15 mL/min/1.73 m² compared with GFR of ≥60 mL/min/1.73 m² (Figure 3). The adjusted risk of any CV event also increased significantly with lower GFRs, ranging from a 43% increased risk for 45-59 mL/min/1.73 m² to a nearly 2.5-fold increased risk for GFR <15 mL/min/1.73 m² (Figure 3). Of note, evidence of documented proteinuria was an independent predictor of all-cause mortality (adjusted hazard ratio 1.34, 95% CI, 1.30 to 1.38), as well as any CV event (adjusted hazard ratio 1.28, 95% CI, 1.25 to 1.32).

Implications

The strengths of this study include its large size and generalizability. It clearly demonstrates that the absolute rates of death and CV events are strikingly

Figure 3: Multivariable association between levels of estimated GFR and the risks of death and CV events. All categories of GFR are compared with GFR 60 mL/min/1.73 m²



higher than the risk for developing ESRD requiring renal replacement therapy. It is one of the few cohort studies that directly compares the rates of ESRD vs other adverse outcomes among CKD patients.³⁶ Thus, while prevention of ESRD should continue to be a major focus among patients with CKD, it is clear that interventions that are more effective are needed to reduce the much greater CVD risk among these patients.

Possible reasons for increased CV risk with CKD

Why is CKD an independent risk factor for CVD? Ongoing prospective studies such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored Chronic Renal Insufficiency Cohort (CRIC) Study involving approximately 3,000 adults with varying severity of reduced GFR will hopefully yield novel insights into this question.³⁷ Existing research suggests several possibilities.

- First, reduced kidney function may be a proxy for underlying atherosclerosis and other CV risk factors.
- Second, patients with CKD may also be less aggressively treated than their counterparts with preserved renal function. For example, secondary analysis of the VALIANT trial showed that the use of aspirin, beta-blockers, statins, or coronary revascularization procedures was lower among those patients with reduced GFR.²⁷ This may be due to (likely exaggerated) concerns about worsening renal function with these therapeutic approaches and therapy-related toxic effects secondary to reduced renal clearance.
- Finally, there are also very plausible causal mechanisms through which reduced kidney function by itself could increase CVD risk. These potential pathways include promoting accelerated arterial calcification,^{38,39} endothelial dysfunction,⁴⁰ and arterial stiffness;⁴¹ raising the levels of inflammatory factors,^{42,43} plasma homocysteine,⁴² and prothrombotic factors;⁴³ associated abnormal apolipoprotein levels;⁴² and the development of anemia⁴⁴ and associated left ventricular hypertrophy.⁴⁵ In addition to clarifying the reasons for how CKD may increase CV risk, it is hoped that future research will also identify modifiable mechanisms that may be new therapeutic targets.

Conclusions

In conclusion, the epidemiology of earlier stage CKD is not the same as the epidemiology of ESRD. However, both Stage 3 and 4 CKD and ESRD patients face a great threat from CVD. For patients with Stage 3 or 4 CKD, deaths and CV events are far more common outcomes than progression to ESRD. Widespread educational efforts targeted at primary care and subspecialty providers, as well as persons at risk for CKD, are needed to raise awareness of the

high risks of adverse outcomes in these patients and to increase appropriate screening for CKD and use of available evidence-based therapies. Discovery of novel therapeutic strategies to reduce both the risks of death and CVD, as well as prevention of ESRD in patients with CKD is needed to improve outcomes in this high-risk population.

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This publication is made possible by an educational grant from

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