The Stages of Chronic Kidney Disease and the Estimated Glomerular Filtration Rate

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INTRODUCTION

The ability to assess kidney function properly has important health implications; chronic kidney disease (CKD) is progressive, most often irreversible, and associated with multiple comorbidities and adverse outcomes. This is particularly true in regard to the risk of cardiovascular disease and cardiovascular events, which increases with worsening renal function. More than 50% of deaths in patients with end-stage renal disease (ESRD) are due to cardiovascular complications.[1] Any degree of kidney dysfunction—not just the most severe—can hasten the onset and progression of cardiovascular disease, and dramatically worsen prognosis.[2,3] Accurate and early detection of CKD, along with appropriately aggressive interventions, may help retard the progression of both of these interrelated diseases.

KIDNEY DISEASE OUTCOMES QUALITY INITIATIVE (KDOQI)

An estimated 20 million Americans are living with some degree of kidney disease ranging from mild damage to ESRD requiring transplantation, hemodialysis, or peritoneal dialysis. This latter group constitutes the smallest proportion of CKD patients, but consumes a staggering proportion of healthcare resources. (This small subset is easier to track than the generalized CKD population, and most economic data are therefore based on ESRD care.) In 2001, an estimated $22.8 billion were spent on ESRD care—more than 6% of the entire Medicare budget.[4] During the same year, the annual mortality rate in this relatively small group of patients exceeded 20%.[4] Over the course of 1, 2, 5, and 10 years, the survival rates of dialysis patients are 80%, 67%, 40%, and 18%, respectively.[5] Because of these poor survival rates, the National Kidney Foundation (NKF) initiated the Kidney Disease Outcome Quality Initiative (KDOQI) to help all clinicians identify, stage, and treat kidney disease. To date, NKF has published 10 sets of guidelines. The centerpiece of the program is the 2002 CKD guidelines,[6] which provide definitions of CKD, and recommend an estimated glomerular filtration rate (GFR) as the best overall measure of kidney function.

IDENTIFYING CKD

The KDOQI guidelines define CKD as kidney damage of 3 or more months' duration caused by structural or functional abnormalities with or without a decreased GFR. Pathological markers, abnormalities in the blood or urine, or imaging tests, may reveal kidney dysfunction. CKD may also be defined as a persistently low GFR of <60 mL/min/1.73m^2 for 3 or more months, with or without identifiable kidney damage.

The best available method to estimate GFR is the equation from the Modification of Diet in Renal Disease (MDRD) study (Figure 1). The equation was developed in 1999 based on data from 1,628 men and women with CKD (average GFR 40 cc/min). The MDRD equation adjusts for 4 variables: body-surface area, race, gender, and age. GFR is expressed as mL/min/1.73m^2; race is categorized as either black or not black. Based on estimated GFR, the NKF guidelines categorize CKD into 5 stages, which are reflective of kidney function regardless of the underlying pathological cause of dysfunction. (Table 1)

BENEFITS AND LIMITATIONS OF THE MDRD EQUATION

In clinical practice, the MDRD equation has several advantages over other approaches to measuring kidney function. First, in the MDRD study, the formula was accurate when compared to GFRs measured with nuclear medicine techniques, which are considered the gold standard for measuring kidney function, though they are rarely available, and are difficult to perform. Moreover, unlike measures of creatinine or urea clearance, the MDRD equation does not require 24-hour urine collection, which is prone to errors and is inconvenient for patients. Instead, the simplified 4-variable MDRD equation relies entirely on determination of serum creatinine, and provides computer-generated estimates of GFR.

TABLE 1. THE 5 STAGES OF CHRONIC KIDNEY DISEASE DEFINED BY ESTIMATED GLOMERULAR FILTRATION RATE.

Stage	Description	GFR (mL/min/1.73 m^2)	Prevalence*	
			N(1000s)	%
1	Kidney damage with normal or ↑ GFR	≥90	5,900	3.3
2	Kidney damage with mid ↓ GFR	60–89	5,300	3.0
3	Moderate ↓ GFR	30–59	7,600	4.3
4	Severe ↓ GFR	15–29	400	0.2
5	Kidney failure	<15 (or dialysis)	300	0.1

* Data for Stages 1–4 from NHANES III (1988–1994)[1]. Population of 177 million adults age ≥20 years. Data for Stage 5 from USRDS (1998)[2] include approximately 230,000 patients treated by dialysis, and assume 70,000 additional patients not on dialysis. GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For Stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio >17 mg/g in men or >25 mg/g in women on two measurements.

Sources: National Kidney Foundation. Available at: http://www.kidney.org/professionals/KDOQI/guidelines.cfm. Accessed June 11, 2006. Printed with permission from the National Kidney Foundation, Inc.

The MDRD equation compares favorably with the other widely used equation, the Cockcroft-Gault Formula (Figure 1). This equation was developed in a relatively small population of 249 men and does not produce an actual estimated GFR, but rather an estimate of creatinine clearance, which is inherently less accurate since it contains a component of tubular secretion.

Despite its advantages, however, the MDRD equation has several important limitations. If improperly understood, these limitations may lead physicians to misjudge kidney function. The MDRD equation adjusts for many, but not all, of the major variables that affect individual creatinine levels. For example, differences in muscle mass not attributable to intrinsic aging processes and race, such as pathological muscle wasting and accelerated muscle growth (e.g., weightlifting), are excluded. The equation may be inaccurate in amputees, frail patients, stroke victims, and those with unusual diets (e.g., vegetarians, vegans, high-protein or low-protein dieters).[7] It also loses

FIGURE 1: ESTIMATING EQUATIONS.

ORIGINAL MDRD STUDY EQUATION

$$GFR = 186 \times (S_{CR})^{-1.154} \times (AGE)^{-0.203} \times 0.742 \text{ (IF THE PATIENT IS FEMALE) OR } \times 1.212 \text{ (IF THE SUBJECT IS BLACK)}$$

2005 RE-EXPRESSION*

$$GFR = 175 \times (\text{STANDARDIZED } S_{CR})^{-1.154} \times (AGE)^{-0.203} \times 0.742 \text{ (IF THE PATIENT IS FEMALE) OR } 1.212 \text{ (IF BLACK)}$$

COCKCROFT-GAULT

$$C_{CR} = [\ (140\text{-AGE}) \times \text{WEIGHT}/\ ]\ (72 \times S_{CR}) \times 0.85 \text{ (IF THE PATIENT IS FEMALE)}$$

CREATININE CLEARANCE (C_{CR}) IS EXPRESSED IN MILLILITERS PER MINUTE, AGE IN YEARS, WEIGHT IN KILOGRAMS, AND SERUM CREATININE (S_{CR}) IN MILLIGRAMS PER DECILITER.

*ADJUSTED FOR USE WITH STANDARDIZED SERUM CREATININE ASSAY THAT PRODUCES VALUES THAT ARE 5% LOWER THAN PREVIOUS ASSAYS.

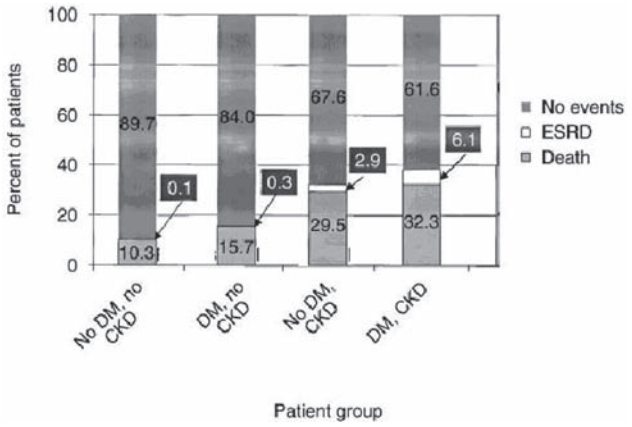
accuracy when applied to populations with a near normal GFR. Thus, specific levels are reported only for GFRs below 60 cc/min, and the nonspecific result ">60 cc/min" is used for patients with higher levels of function.

Medication use also requires consideration. Many drugs such as cimetidine and trimethoprim interfere with creatinine tubular secretion and thus elevate serum creatinine levels. The result is a decrease in estimated GFR even though there has been no real effect on renal function. Likewise, fluctuating kidney function will produce unreliable estimated GFRs, since a steady state must be achieved before the GFR can be estimated.[9] Finally, it is important that laboratories use the same calibration used to develop the equation, since different calibrations will produce different results. The error introduced by noncalibrated creatinine is mainly seen at near normal GFRs, which are already reported as a generalized >60 cc/min. A national initiative is underway to make uniform laboratory calibration a reality.

CKD AND CARDIOVASCULAR DISEASE

ESRD is not the most likely outcome of CKD. Rather, CKD patients have an elevated risk for acute and chronic cardiovascular disease, other comorbidities, and death. (Figure 2)[8,9]

Figure 2: Outcomes for Medicare patients during 2-year follow-up: risk of death or endstage renal disease.
CKD = chronic kidney disease; DM = diabetes mellitus; ESRD = endstage renal disease



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Cardiovascular disease worsens with worsening CKD. In the Atherosclerotic Risk in Communities study, a prospective cohort study with more than 15,000 patients, the risk of ischemic cardiovascular events was 38% higher in CKD patients with Stage 3 or 4 disease than in those with Stage 1 disease.[10] All-cause mortality among patients with a GFR of 15-59 mL/min/1.73m^2 was 29%, compared to 7.7% among those with a GFR of 90-150 mL/min/1.73m^2.[10] Likewise, in the 5,135-patient Cardiovascular Health Study, the risk of cardiovascular events was 31% among patients with a GFR of 15-59 mL/min/1.73m^2, and the risk of all-cause mortality 47%.[10] The most common cardiovascular complications of CKD are recurrent heart attack, stroke, and congestive heart failure. (Figure 3)[10]

Similar findings were observed in the Kaiser Permanente of Northern California Renal Registry,[11] which enrolled 1,120,295 adults (≥20 years) between 1996 and 2000. In the unadjusted analysis, a GFR of ≥60 mL/min/1.73m^2 was associated with an annual mortality rate of 1.1% and cardiovascular event rate of 2.8%. These rates increased to 24.8% and 51.8%, respectively, among those with a GFR <15mL/min/1.73m^2. The risk of both adverse outcomes increased in a linear fashion across the five stages of CKD. When the analysis was adjusted for sociodemographic and clinical characteristics, there continued to be an elevated risk (Figure 4).[11]

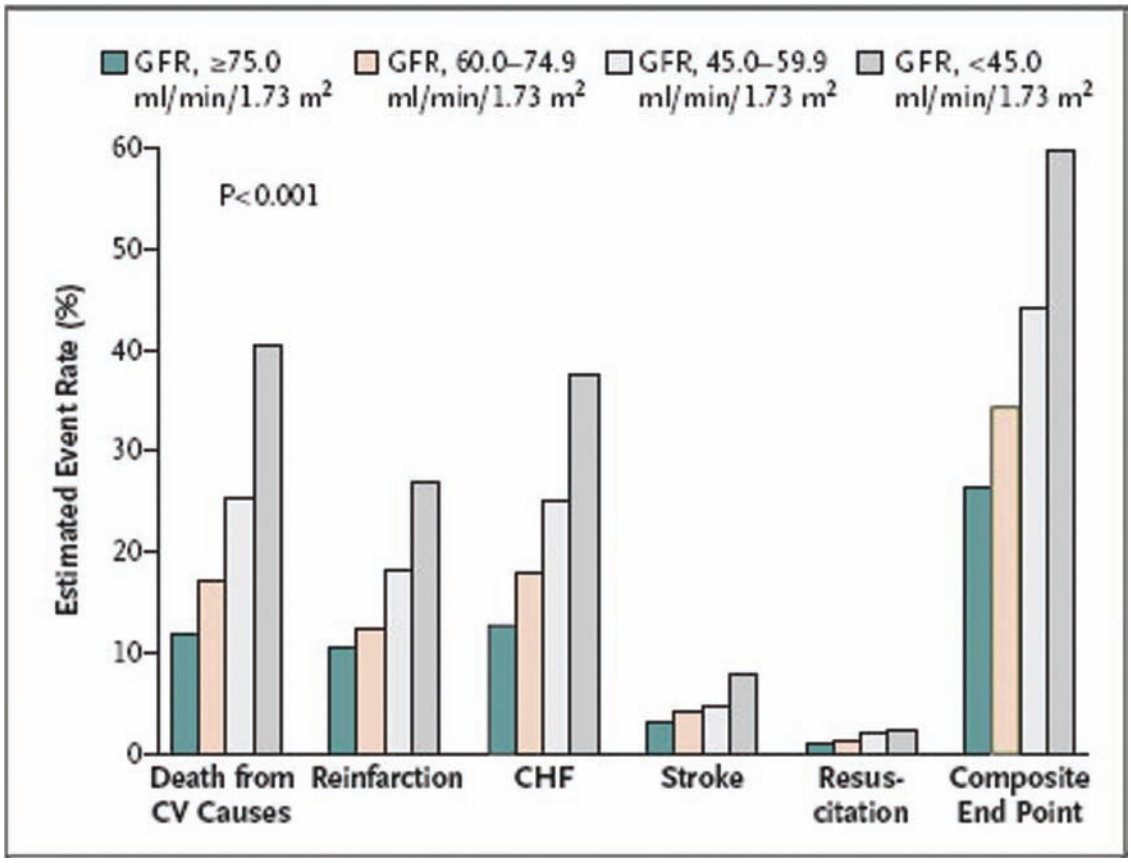
The causal relationship between cardiovascular disease and CKD has not been fully elucidated. Investigators hypothesize that impaired renal function increases arterial calcification, endothelial dysfunction, arterial stiffness, inflammation, and thrombogenesis, and that CKD patients with cardiovascular disease are less aggressively treated than those with normal function.[11] Nevertheless, that there is a relationship is clear: progressive declines in kidney function of any degree generate or accelerate cardiovascular disease. This progression may be slowed by accurately staged CKD, and early intervention.

EARLY INTERVENTIONS

Several clinical markers may be used to identify kidney dysfunction and for individualized risk stratification. Interventions that address these risks should be implemented early, and before patients are referred to a nephrologist.

Hypertension—Hypertension worsens CKD, and blood pressure should be maintained at less than130/80 mm

Figure 3: Kaplan–Meier Estimates of the Rates of Death at Three Years from Cardiovascular (CV) Causes, Reinfarction, Congestive Heart Failure (CHF), Stroke, Resuscitation after Cardiac Arrest, and the Composite End Point, According to the Estimated GFR at Baseline.
Data on patients with noncardiovascular events were censored. The P value is from the Cox model.



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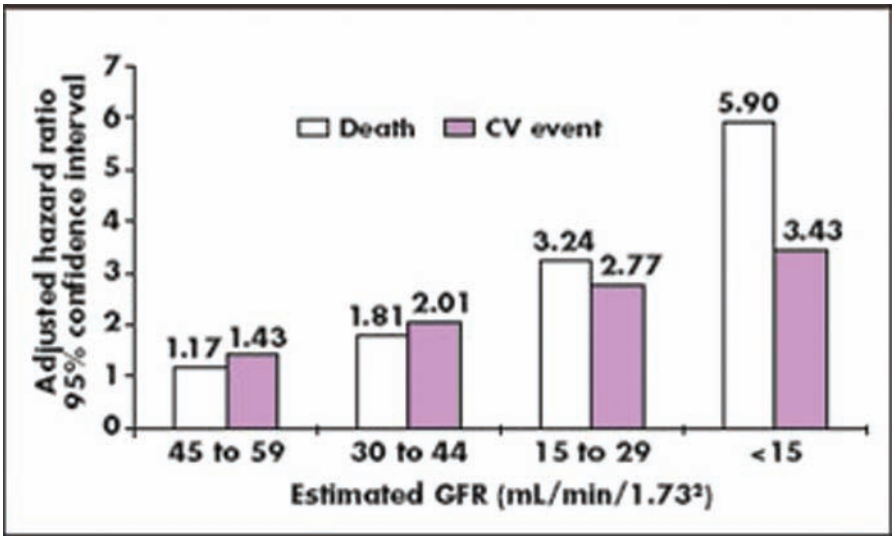
Hg in CKD patients. Among those with a gram or more of proteinuria per day (or >1 gram of urine protein per gram of creatinine on a spot urine specimen), blood pressure should be even lower (120/80 mmHg or less).[12] Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are the first-line therapeutic choices. Diuretics and salt restriction potentiate the effects of these agents. Three to four drugs are usually required to achieve these blood pressure goals. ACE inhibitors and ARBs (and even aldosterone antagonists) may be combined for optimal lowering of proteinuria, but such combinations may increase the risk of hyperkalemia.

Proteinuria—Trace amounts of protein in the urine are normal. However, persistently elevated levels (proteinuria), are associated with progressive CKD. Even small amounts—microalbuminuria—are widely appreciated as a marker of "endothelial mischief" in patients with type 2 diabetes and/or hypertension. All patients with even trace amounts of proteinuria should be considered candidates for cardiac stress testing, and further workup.

Dyslipidemia—Dyslipidemia is associated with progressive CKD. Statin therapy can help decrease proteinuria, and is cardioprotective. LDL cholesterol should be less than 100 mg/dL in CKD patients.

Diabetes—Diabetes is a common complication of CKD that requires aggressive management. HgbA1C should be reduced to less than 7%. Higher levels are associated with CKD progression.

Figure 4: 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.



Source: Go AS, HSU CY. Chronic Kidney Disease and Risk of Adverse Outcomes. Nephrology Rounds Aug/Sept 2005;3(7):1-6. Available at: http://www.nephrologyrounds.org/cgi-bin/templates/framesets/nephrologyRoundsUSA/fs_snell.cfm. Accessed June 13, 2006. Permission granted by Snell Medical Publications.

Tobacco use—Discourage smoking in all patients.

Concomitant medications—Avoid or curtail nephrotoxic drugs (e.g., use non-steroidal antiinflammatory drugs intermittently and for short durations).

Urinalysis—Urinalysis for active sediment (red blood cell casts and dysmorphic red cells) is important, even in early disease stages. Positive tests may indicate kidney and/or systemic inflammation. Renal biopsy and specific therapy may be required in such patients.

Anemia—As patients progress to Stage 3 and beyond, regularly screen for anemia. Initiate iron replacement therapy and erythropoietic stimulating agents when appropriate.

Bone mineral abnormalities—Bone mineral abnormalities become more common in Stage 3. Hyperparathyroidism is usually the first indication of a problem. Treatment involves restoring vitamin D deficits (measure 25 OH vitamin D), and/or prescribing activated vitamin D to maintain a parathyroid hormone level of 35-70 pg/mL in Stage 3 disease, and 70-110 pg/mL in Stage 4.

NEPHROLOGY REFERRAL

Referral to a nephrologist is needed as patients approach Stage 4. At this point, pre-ESRD education regarding treatment modality is provided (hemodialysis or peritoneal dialysis), an arteriovenous fistula is placed (they require months to mature), and patients are evaluated for transplantation. Nationwide, only approximately 60% of patients see a nephrologist prior to starting dialysis. Late referrals (i.e., fewer than 6 months before dialysis) results in higher costs and worse outcomes.[13] Patients with active sediment, high-grade proteinuria, and refractory blood pressure need referral sooner.

Elderly Patients

Beginning in the third decade of life, the GFR begins to decrease approximately 10 cc/min per decade in many individuals. Consequently, normal GFR in patients aged 70 years or older may be 60 cc/min or less; this is an indication of declining kidney function, but not necessarily the onset of progressive CKD. To distinguish between simple aging processes and the onset of intrinsic renal disease, an evaluation of the individual's risk of CKD is necessary. The identification of risk factors for progression, such as proteinuria or hypertension above

the goal of 130/80, would be a cause for concern and possible referral.

CONCLUSIONS

CKD is a major public health problem, and places an enormous burden on the healthcare system. Patients with CKD are at risk for multiple comorbidities, most notably cardiovascular disease. A proper understanding of the methodologies used to estimate GFR can help alert physicians to needed interventions, and help slow disease progression.

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