Journal of the American Society of Hypertension 3(4) (2009) 277–285

Review Article

Gauging adequacy of cardiovascular disease treatment: importance of estimating glomerular filtration rate and time-varying albuminuria

Matthew R. Weir, MD[a,*] and Raymond Townsend, MD[b]

[a]*From the Division of Nephrology, Department of Medicine, University of Maryland, School of Medicine, Baltimore, Maryland, USA; and*

[b]*Division of Nephrology, Department of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania, USA*

Manuscript received March 19, 2008 and accepted May 23, 2008

Abstract

Objective measures of cardiovascular disease (CVD) are often lacking until patients develop clinical symptomatology associated with either coronary, cerebral, or peripheral vascular disease. Estimating risk for CVD is often based on classic Framingham Heart Study criteria such as age, gender, blood pressure (BP), cholesterol, glucose levels, and family history. Moreover, there is a well-described continuous relationship between BP,cholesterol, and glucose and risk for cardiovascular events. Estimating glomerular filtration rate equations using simple formulae and screening quantitatively for albuminuria may provide an important opportunity for identifying patients at increased risk for cardiovascular events. These safe, simple, and cost-effective measures of estimating CVD risk can be used to gauge the adequacy of response to cardiovascular risk-reducing therapies. J Am Soc Hypertens 2009;3(4): 277–285.

Keywords: Cardiovascular risk; chronic kidney disease; end stage renal disease; renin-angiotensin system.

Introduction

Estimating cardiovascular disease (CVD) risk is important in clinic practice as it provides both the patient and the healthcare provider an important means for not only choosing appropriate therapeutic goals for blood pressure (BP), cholesterol, and glucose but also effective interventional strategies.[1] Often, coronary artery and cerebral vascular disease is not evident until significant clinical symptomatology occurs; thus, primary cardiovascular target organ preservation is a challenge. Consequently, more objective means of estimating CVD burden and response to therapy is needed in clinical practice.

One possibility to improve prediction of cardiovascular risk is to use estimated glomerular filtration rate (eGFR), an objective measurement of the albumin-to-creatinine ratio in the urine. The kidneys, like the heart and the brain, have direct vascular access to the aorta and central aortic pressures. Therefore, it is likely that the BPs of these 3 organ systems may not easily be predicted by brachial artery BP measurements.

One can easily and objectively assess change in eGFR or urine albumin to creatinine ratio over time. These measures may serve as an important means of not only estimating CVD, but perhaps also response to therapy.

The importance of kidney disease in predicting cardiovascular risk is underscored by an assessment of a 5% Medicare sample, where using a 1996 to 1997 cohort, one can see that the percentage of patients with chronic kidney disease (CKD) who died in a 2-year follow-up period (24.6%) was substantially higher than those who had diabetes mellitus without CKD (14.7%).[2] Moreover, those who had both diabetes and CKD were 5 times as likely (29%) to die as they were to reach dialysis (5.9%). Other epidemiological studies have clearly demonstrated the relationship between declining eGFR and increased risk of cardiovascular events.[2–4] Moreover, if one looks at the stages of CKD in the United States as defined by the National Kidney Foundation,[5] it is quite apparent that those patients with stage 4 and stage 5 CKD represent only a tiny fraction of the US population[6] (Figure 1). In large part, this is related to the competing hazard of cardiovascular death limiting the likelihood of these patients to progress to end stage renal disease (ESRD).

Why are CVD and CKD so intricately related? Classic Framingham Heart Study risk factors do not entirely explain

Conflict of interest: none.

*Corresponding author: Matthew R. Weir, MD, Division of Nephrology, Department of Medicine, University of Maryland, School of Medicine, 22 South Greene Street, Baltimore, Maryland 21201. Tel: 410-328-5720; fax: 410-328-5685.

E-mail: mweir@medicine.umaryland.edu

1933-1711/09/$ – see front matter
doi:10.1016/j.jash.2008.05.008

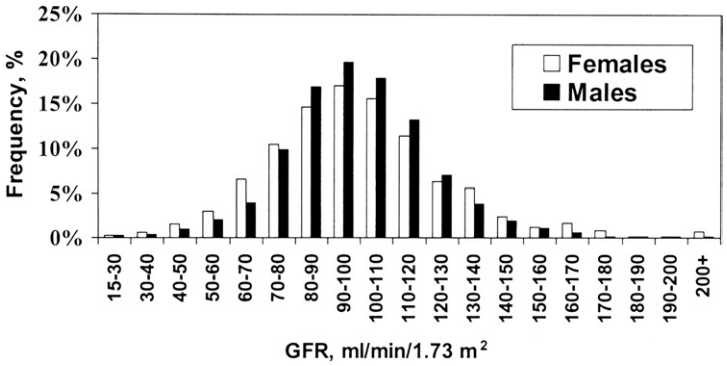

Figure 1. Millions of people affected by CKD in the US based on eGFR (from the Third National Health and Nutrition Examination Survey). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. Reproduced with permission from Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.[6]

this relationship, although they explain much of it.[7] There are both traditional and nontraditional risk factors in patients with CKD that could explain the increased propensity for cardiovascular events. Table 1 illustrates the many different traditional and nontraditional risk factors. Of the nontraditional factors, albuminuria may be one of the most intriguing to assess, both in terms of predicting risk, as well as indicating response to therapy.

An important understanding is that patients with CKD benefit as much, if not more, than patients without CKD with appropriate interventional strategies because of their increased risk for cardiovascular events. Decreased GFR has consistently been noted to be an independent risk factor for CVD outcome and all-cause mortality.[8] Consequently, eGFR and quantitating albuminuria or proteinuria are important opportunities that should not be missed in clinical practice. How best should one eGFR? The serum creatinine is a misleading guide to eGFR. There can be a 4-fold variation in measured GFR in patients with serum creatinine within 20% of 1.0 mg/dL.[9] Serum creatinine is influenced by filtration capacity, muscle mass (which is related to ethnicity and gender), and age. Thus, equations that take into account age, gender, and muscle mass are important in order to properly eGFR. Either the Cockroft-Gault equation or the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation can be used (Table 2). Neither is ideal, but the MDRD equation has been demonstrated to have important accuracy in patients with eGFR below 60 mL/min/1.73 m^2.[10] It is the patients with eGFR below 60 mL/min/1.7 $3m^2$ who fit the CKD three stage category and who have increased risk for CVD events.

Table 1
Traditional and nontraditional cardiovascular risk factors in CKD

Traditional Risk Factors	Nontraditional Factors
Older age	Albuminuria
Male gender	Homocysteine
Hypertension	Lipoprotein(a) and apolipoprotein(a) isoforms
Higher LDL cholesterol	Lipoprotein remnants
Lower HDL cholesterol	Anemia
Diabetes	Abnormal calcium/phosphate metabolism
Smoking	Extracellular fluid volume overload
Physical inactivity	Electrolyte imbalance
Menopause	Oxidative stress
Family history of CVD	Inflammation (C-reactive protein)
LVH	Malnutrition
	Thrombogenic factors
	Sleep disturbances
	Altered nitric oxide/endothelin balance

CKD, chronic kidney disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy.

Modified from Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation 2003;108:2154–69.[8]

The objective assessment of albumin or in the urine is also an important means of estimating CVD risk and the presence of kidney disease.[5] The traditional definitions of albuminuria are described in Table 3. It is important to recognize that the traditional urine dipstick is a qualitative, not a quantitative, measure of urine albumin. It does not measure other urine proteins. A more objective means for assessing for albumin or protein in the urine is to obtain a spot urine albumin or protein to creatinine ratio. In Table 3, note the gender difference in the definition of normal, micro, and clinical albuminuria or proteinuria. Since muscle mass can assumed to be constant, the urine creatinine should not vary; thus, the albumin or protein to creatinine ratio can provide an approximate assessment of daily urine albumin or protein excretion. Due to the simplicity of this test, it can be repeated longitudinally.

Microalbuminuria is an important measure of CVD risk.[11] This has been demonstrated in numerous investigations.[12,13] The relationship of cardiovascular events by degree of albuminuria was an important observation for the Heart Outcomes Protection Evaluation (HOPE) Study.[14]