**Glomerular Filtration Rate**

**Proteinuria Trumps GFR in Predicting Kidney Disease Progression in Type 2 Diabetes**

By Daniel M. Keller

A lbuminuria is a stronger predictor of renal disease progression and cardiovascular (CV) morbidity and mortality than is glomerular filtration rate (GFR), said George Bakris, MD, in his talk at the two-day program “CKD and CVD from the Vascular Viewpoint: Merging Basic and Clinical Sciences to Optimize Treatment” at Renal Week. Bakris stressed the need to monitor and reduce proteinuria to maximize risk reduction and said that blood pressure control is a key element in the therapy.

Bakris, professor of medicine and director of the Hypertensive Diseases Unit at the University of Chicago Pritzker School of Medicine, cited a study of 4421 Chinese patients with type 2 diabetes but no macrovascular disease or end stage renal disease at study entry who were followed for a median of 39.4 months (1). Patients were stratified into quartiles of estimated GFR (<90, 60–89, 30–59, and 15–29 mL/min/1.73 m²).

"Even if you have absolutely normal kidney function, if you have albuminuria your risk for cardiovascular events dramatically increased, and if you don’t have albuminuria, you’re fine," Bakris said.

In the highest estimated GFR quartile, the risk of a CV endpoint (CV death, new admission for angina, myocardial infarction, stroke, revascularization, or heart failure) increased 85 percent if albuminuria was present versus not present.

Similarly, albuminuria was a strong predictor of renal endpoint (reduction in estimated GFR >50 percent, progression to stage 5 estimated GFR, dialysis, or renal death). The hazard ratio for a renal endpoint was 2.62 with albuminuria compared to no albuminuria in the group with the highest estimated GFR (P<0.007). Although a lower estimated GFR at the beginning of the study did not predict the likelihood of a renal endpoint, albuminuria did. Albuminuria in the group with the lowest estimated GFR conferred a 90-fold risk of a renal endpoint, compared with no albuminuria in the group with the best estimated GFR.

The findings in the Chinese study were supported by the results of several other trials. The African American Study of Kidney Disease (AASK) involving non-diabetic kidney disease patients (2), the Captopril Trial, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study, and the Irbesartan in Diabetic Nephropathy Trial (IDNT) found an increased time to dialysis associated with a reduction in proteinuria of at least 30 to 35 percent. In the arms of the AASK and IDNT trials that did not achieve a reduction in proteinuria, there was no change in time to dialysis.

When “looking for progression of kidney disease, you’re better off looking at changes in proteinuria than you are looking at changes in GFR,” Bakris said. In people with advanced kidney disease “unless you have a reduction in proteinuria of 30 to 35 percent with blood pressure reduction, you’re not going to get maximal benefit out of slowing kidney disease progression.” Tight control of blood pressure is essential to reducing proteinuria. One factor is sodium intake, and dietary history is a simple and inexpensive way to determine a patient’s sodium intake. A 24-hour urinary sodium test may more accurately reveal intake, especially if the patient-reported history does not point to excessive intake. “Increases in sodium increase oxygen stress, isoprostanes, and as a result, increase proteinuria and blunt the effects of ACE inhibitors and angiotensin receptor blockers (ARBs),” Bakris said. “Sodium intake is very powerful in terms of what it can do if there’s a little bit of injury already.” He explained that sodium intake >6 g/day reduces the antiproteinuric effects of blockade of the renin-angiotensin system. The use of thiazide diuretics only partially restores the effect.

Ambulatory blood pressure monitoring (ABPM) is a good indicator of blood pressure control throughout the day and night. In the AASK study, many of the African-Americans studied did not show a characteristic dip in systolic blood pressure, “which gives you an overall quote ‘higher blood pressure load’ . . . over a 24-hour pe- riod,” he said. Obese people and those with sleep apnea may also tend not to dip at night. Some patients may have normal blood pressures in the office but abnormal patterns at night. Others may have “masked hypertension” with normal office readings but elevated pressures at other times. “Having masked hypertension is as bad as having true hypertension,” Bakris said, but a clinician will not detect the problem without doing ABPM. As many as 25 percent of patients may have masked hypertension, which was probably the reason for the inability to stop kidney disease progression in AASK, Bakris said.

To slow the progression of kidney disease, systolic blood pressure needs to be reduced as soon as possible to limit injury to arteries. Multiple drugs are usually necessary, starting with an ACE inhibitor or an ARB and possibly adding a calcium channel blocker or thiazide diuretic. Updated guidelines of the European Society of Hypertension [Raijlope L et al. Blood Press. 2007; 16(2):72-9] and the American Society of Hypertension (ASH) Diabetes Consensus Update. J Clin Hypertens. Sept. 2008) provide good algorithms for multidrug therapy and treatment monitoring.

Bakris advised having all patients monitor their blood pressures at home once a day. “It makes them an active partner in their own management . . . [and] in many cases it motivates them,” he said. Patients may learn what causes their blood pressures to change, and the readings may help the physician change the timing or dose of drugs.

References
2. Updated AASK trial data: Hypertension, in press

**New Equation Provides Better Estimates of CKD Prevalence**

A newly developed equation provides more accurate estimates of glomerular filtration rate (GFR) than do other measures, according to new research. The equation is relatively imprecise and can underestimate GFR, and a participant in the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). They cautioned that GFR estimates are not as accurate as GFR measurements. More accurate GFR is likely to reduce the frequency of false-negative diagnosis of CKD and to refine the classification by stage in patients with CKD.

When applied to a representative sample of 16,000 Americans, the CKD-EPI equation yielded an estimated prevalence of CKD in the general population of 12.2 percent; CKD prevalence estimated with the MDRD equation was 13.3 percent. Among those with CKD, the proportion with stage 1 and 2 CKD was 17 percent and 21 percent, respectively, with the CKD-EPI equation, versus 13 percent and 24 percent, respectively, with the MDRD Study equation.

The investigators suggested that the CKD-EPI equation could replace the MDRD Study equation. They cautioned that GFR estimates are not as accurate as GFR measurements and that the CKD-EPI equation may not be accurate for all populations of patients.

The study, “A New Equation to Estimate GFR from Serum Creatinine Improved Accuracy and Updated Estimates of Prevalence of Chronic Kidney Disease in the United States,” was part of the Renal Week session on “Effects of Traditional and Non-traditional Risk Factors on Cardiovascular Risk in Chronic Kidney Disease and End Stage Renal Disease.”

The resulting CKD-EPI equation was more accurate than the MDRD Study equation, especially at higher levels of kidney function, when compared against actual GFR measurements. More accurate GFR is likely to reduce the frequency of false-negative diagnosis of CKD and to refine the classification by stage in patients with CKD.

The MDRD Study equation, developed from data on approximately 8000 patients in 10 studies. They then validated the equation by using data on 3896 patients from 16 studies.