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Original Investigation

Comparison of Measured GFR, Serum Creatinine, Cystatin C, and Beta-Trace Protein to Predict ESRD in African Americans With Hypertensive CKD

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Background: Identification of persons with chronic kidney disease (CKD) who are at highest risk to progress to end-stage renal disease (ESRD) is necessary to reduce the burden of kidney failure. The relative utility of traditional markers of kidney function, including estimated glomerular filtration rate (eGFR) and serum creatinine level, and emerging markers of kidney function, including cystatin C and beta-trace protein (BTP) levels, to predict ESRD and mortality has yet to be established.

Study Design: Randomized clinical trial followed by an observational cohort study.

Setting & Participants: 865 African American individuals with hypertensive CKD enrolled in a clinical trial of 2 levels of blood pressure control and 3 different antihypertensive drugs as initial therapy and subsequently followed by an observational cohort study.

Predictors: Quintile of measured GFR (mGFR) by iothalamate clearance, serum creatinine, serum creatinine–based eGFR, cystatin C, and BTP values.

Outcomes & Measurements: Incidence of ESRD and mortality.

Results: 246 participants reached ESRD during a median follow-up of 102 months. The incidence rate of ESRD was higher with higher quintiles of each marker. The association between higher BTP level and ESRD was stronger than those for the other markers, including mGFR. All markers remained significantly associated with ESRD after adjustment for mGFR and relevant covariates (all $P < 0.05$), with BTP level retaining the strongest association (HR for highest vs lowest quintile, 5.7; 95% CI, 2.2-14.9). Associations with the combined end point of ESRD or mortality (n = 390) were weaker, but remained significant for cystatin C ($P = 0.05$) and BTP levels ($P = 0.004$).

Limitations: The ability of these markers to predict ESRD and mortality in other racial and ethnic groups and in individuals with CKD due to other causes is unknown.

Conclusions: Plasma BTP and cystatin C levels may be useful adjuncts to serum creatinine level and mGFR in evaluating risk of progression of kidney disease.

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INDEX WORDS: End-stage renal disease; beta trace protein; cystatin C; serum creatinine; iothalamate glomerular filtration rate.

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Decreased kidney function increases the risk of end-stage renal disease (ESRD) and all-cause mortality.[1-3] ESRD in turn is associated with a substantially increased risk of mortality and morbidity.[4] Accurate identification of persons with chronic kidney disease (CKD) who are at highest risk of progressing to ESRD is critical to tailor therapy to reduce its incidence and sequelae.

Directly determining measured glomerular filtration rate (mGFR) by iothalamate clearance is considered the gold-standard method to assess kidney func-

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tion. However, this procedure is burdensome and impractical in many settings. Endogenous markers of kidney function are attractive alternatives in these settings. Serum creatinine and, more recently, serum cystatin C levels have been used most commonly to assess kidney function. However, both markers are influenced by factors other than kidney function, resulting in inaccurate estimates of GFR.[5] For example, serum creatinine levels are associated positively with greater muscle mass and dietary meat intake and inversely with concomitant illness.[5] Although cystatin C level is less sensitive to interindividual differences in muscle mass, levels of this marker are increased in persons with diabetes, inflammation, and a higher body mass index.[5]

Beta-trace protein (BTP) has been proposed as an alternative marker of kidney function.[6-8] BTP, also known as lipocalin prostaglandin D_2 synthase, is a low-molecular-weight factor that is a member of the lipocalin protein family. Serum BTP levels were correlated strongly with GFR in small studies of kidney transplant patients and patients with CKD, although data are limited in other populations.[9,10] Limited data are available for the association of BTP levels with subsequent outcomes.

We compared the ability of mGFR, serum creatinine level, estimated GFR based on serum creatinine level ($eGFR_{SCr}$), cystatin C level, and BTP level to predict ESRD and mortality in African Americans with hypertensive CKD enrolled in the African American Study of Kidney Disease and Hypertension (AASK) clinical trial and cohort study.

METHODS

Study Design

AASK was a 3×2 factorial multicenter randomized clinical trial conducted in 1995-2001. The study was designed to test the effects of 3 antihypertensive medications, an angiotensin-converting enzyme inhibitor (ramipril), a β-blocker (metoprolol), and a calcium channel blocker (amlodipine), as initial therapy in a drug regimen, and 2 levels of blood pressure control (low: mean arterial pressure ≥92 mm Hg, and usual: mean arterial pressure of 102-107 mm Hg) on progression of CKD. The study population included 1,094 nondiabetic self-identified African Americans aged 18-70 years with mGFR assessed by iothalamate clearance of 20-65 mL/min/1.73 m^2 with no identified causes of CKD other than hypertension.[11] At the conclusion of the trial, participants were invited to enroll in a cohort study that was initiated to identify factors that predict progression of kidney disease within the setting of recommended management of CKD due to hypertension (ie, use angiotensin-converting enzyme inhibitor and angiotensin receptor blocker antihypertensive drugs and low blood pressure goal [<92 mm Hg]).[10] At the end of the clinical trial, 759 participants who had not yet reached ESRD were being followed up; 689 enrolled in the cohort study.[12] Incidence of ESRD was defined as beginning maintenance dialysis therapy or receipt of a kidney transplant.[13,14] Study participants were seen in the clinic at 3, 6, and every 6 months thereafter during the clinical trial and at baseline and every 12 months thereafter during the cohort study. Details of the design of the clinical trial and cohort study have been published previously.[15]

Measurements of GFR and Endogenous Markers

Kidney function was measured twice by iothalamate clearance at baseline of the clinical trial. We used the second of these measurements for comparison to the single measurements of the other markers, and the mean of these 2 measurements for adjusted analyses. Serum creatinine, cystatin C, and BTP also were measured from samples obtained at baseline. Serum creatinine was measured in a central laboratory with the rate-Jaffé method with an alkaline picrate assay. Cystatin C and BTP were measured by particle-enhanced nephelometry (Dade/Siemens, www.medical.siemens.com). $eGFR_{SCr}$ was calculated using an equation specific to the AASK population.[16]

Other Measurements

The baseline visit consisted of a physical examination, questionnaires (including self-reporting of any history of cardiovascular disease), 24-hour urine specimen collection on the day before the first prerandomization mGFR,[14] blood pressure measurement (using Hawksley random-zero sphygmomanometers; Hawksley, www.hawksley.co.uk), and performance of a 12-lead electrocardiogram. Urinary protein excretion was expressed as urinary protein-creatinine ratio from a 24-hour urine collection.

Statistical Analysis

Correlation of log(mGFR) with the inverse of each marker was assessed. Linear or logistic regression was used to test for trends across quintiles of mGFR. Event-free survival time was defined from the time of randomization to ESRD, mortality, censoring, or administrative withdrawal at the end of the study (June 2007). ESRD was censored at death and mortality was censored at ESRD. Cox proportional hazards competing-risk models were used to account for this informative censoring.[17] Multivariate models adjusted for age, sex, prevalent coronary heart disease, total high-density lipoprotein cholesterol level, urinary protein-creatinine ratio, education, body mass index, smoking status, trial treatment group (ie, blood pressure goal and antihypertensive medication), and mean baseline mGFR. The proportionality assumption was assessed using Schoenfeld residuals and log-log plots.[18] Model discrimination was assessed using Harrell C statistic for fully adjusted models.[19]

Continuous net reclassification improvement (NRI[>0]) at 102 months of follow-up (median follow-up) was calculated from fully adjusted Poisson models and defined as the sum of those classified upward to higher risk in those with an event plus those classified downward to lower risk in those without an event less the sum of those classified downward to lower risk in those with an event plus those classified to higher risk in those without an event.[20] We also report NRI for participants with (NRI_{event}) and without an event ($NRI_{event\text{-}free}$). These models did not account for informative censoring. All analyses were conducted using Stata, version 10.1, software (StataCorp LP, www.stata.com).

RESULTS

Baseline Characteristics

Serum creatinine, cystatin C, and BTP measurements were available for 865 participants at baseline. Mean age of participants was 54.8 years, and 61% were men (Table 1). Mean mGFR was 46.5 mL/min/1.73 m^2. Lower mGFR was associated with younger age, female sex, and higher urinary protein-creatinine